25 July 2024
EMA/CHMP/372271/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Loqtorzi

International non-proprietary name: toripalimab

Procedure No. EMEA/H/C/006120/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Loqtorzi
Applicant:	TMC Pharma (EU) Limited 7A Durands Court 45 Parnell Street Waterford X91 P381 IRELAND
Active substance:	Toripalimab
International Non-proprietary Name/Common Name:	Toripalimab
Pharmaco-therapeutic group (ATC Code):	L01FF13
Therapeutic indication(s):	Loqtorzi, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma. Loqtorzi, in combination with cisplatin and paclitaxel, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	240 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

AE – adverse event

AEX – anion exchange chromatography

ALT - alanine aminotransferase

ANC - absolute neutrophil count

aPTT – activated partial thromboplastin time

Asn - asparagine

AST - aspartate aminotransferase

BIRC – Blinded Independent Review Committee

BMI - Body Mass Index

BOR - best overall response

BTDAS – Breakthrough-Therapy-Designation Analysis Set

CEX – cation exchange chromatography

CHO – Chinese hamster ovary cells

CI - confidence interval

CPA – critical performance attribute

CPP – critical process parameter

CPS - combined positive score

CQA – critical quality attribute

CR – complete response

DCR - disease control rate

DF - diafiltration

DoR - duration of response

eCRF - electronic case report form

ECOG – eastern cooperative oncology group

ESCC/OSCC – Esophageal/Oesophageal squamous cell carcinoma

ESMO - European Society of Medical Oncology

FAS - Full analysis set subset

GMP – Good Manufacturing Practice

HCD – host cell DNA

HCP – host cell protein

HDPE – high density polyethylene

HR - hazard ratio

HRQoL - Health-Related Quality of Life

ICF - informed consent form

ICH - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IDMC - Independent Data Monitoring Committee

INR - International normalized ratio

IPC – In-process control

IPM – In-process monitoring

IRC – independent review committee

irRECIST - Immune-related Response Evaluation Criteria in Solid Tumours

ITT - Intention To Treat Population

IV - intravenous

IWRS - interactive web-based randomisation system

KPA – key process attribute

KPP – key process parameter

mAb – monoclonal antibody

MCB – master cell bank

mDOR - Median duration of response

MO – major objection

MTD – maximum tolerated dose

NPC – nasopharyngeal cancer

OC – other concern

ORR - objective response rate

OS - overall survival

PAR – proven acceptable range

PDE – permitted daily exposure

PD-1 - programmed death receptor-1

PD-L1 - programmed death-ligand 1

PFS – progression-free survival

PP – process parameter

PPAS - Per-protocol Analysis Set

PPQ – process performance qualification

PR – partial response

PRS – primary reference standard

PS - performance status

PT – Preferred term

PTAS - platinum-treated analysis set

QC – quality control

QP – qualified person

Q2W - every 2 weeks

Q3W - every 3 weeks

RECIST – Response Evaluation Criteria in Solid Tumours

RS – reference standard

SAP - Statistical Analysis Plan

SD – stable disease

SOP – standard operating procedure

SS - Safety analysis set

SUB – single use bioreactor

TP – paclitaxel and cisplatin

TPS - Tumour proportion score

UF - ultrafiltration

ULN - upper limit of normal

WBC - white blood cell

WCB – working cell bank

WRS – working reference standard

2. Background information on the procedure

2.1. Submission of the dossier

The applicant TMC Pharma (EU) Limited submitted on 13 November 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Loqtorzi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The product name was changed during the procedure from Toripalimab TMC to Loqtorzi, reference to Toripalimab TMC is made throughout the dossier.

The applicant applied for the following indication:

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.

2.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

2.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0408/2022 on the granting of a (product-specific) waiver.

2.4. Information relating to orphan market exclusivity

2.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.4.2. New active Substance status

The applicant requested the active substance toripalimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

2.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
13 October 2022	EMA/SA/0000099887	Serena Marchetti and Kristian Wennmalm

The Scientific advice pertained to the following clinical aspects:

- Justification of relevance of the data generated in pivotal trials to the EU population.

2.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Vilma Petrikaite Co-Rapporteur: Karin Janssen van Doorn

The application was received by the EMA on	13 November 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 February 2023
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	6 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	6 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 August 2023
The following GMP, GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection was performed at two investigator sites and the sponsor site, all located in China, between 11 March 2024 – 18 April 2024. The outcome of the inspection carried out was issued on:	07 June 2024
– A GMP inspection at one manufacturing site in China for active substance and finished product manufacturing and testing was carried out between 18-22 March 2024. The outcome of the inspection was positive and the corresponding GMP certificate issued and made available in EUDRAGMDP.	9 July 2024

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Loqtorzi on	25 July 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	25 July 2024

3. Scientific discussion

3.1. Problem statement

3.1.1. Disease or condition

Nasopharyngeal cancer (NPC)

NPC is a serious and life-threatening disease that differs from other head and neck cancers in terms of aetiology, treatment approach, and outcome. There are 3 histopathological subtypes of nasopharyngeal cancer, keratinising, non-keratinising, and basaloid squamous (NCCN Guidelines, 2022). Non-keratinising disease is further subdivided into differentiated and undifferentiated forms. The non-keratinising subtype is more closely associated with EBV infection and has an improved overall survival when compared to the keratinising subtype (Pan et al, 2019; Reddy et al., 1995).

Oesophageal squamous cell carcinoma (OSCC)

Oesophageal cancer, both adenocarcinoma and squamous cell carcinoma of the oesophagus, is uncommon in Europe with an ASR of 3.3/100,000 (Globocan, 2020). Squamous-cell carcinoma arises from the epithelial cells that line the oesophagus. Given the incidence of this histological subtype in the EU, to conduct a large clinical trial in a timely manner, it would be necessary to recruit the vast majority of patients from areas of the world in which OSCC is common.

3.1.2. Epidemiology

Nasopharyngeal cancer

Nasopharyngeal carcinoma is rare in the West with an age-standardized rate (ASR) of 0.44 in Europe (Globocan, 2020). 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 (Globocan, 2020; Wei et al., 2017).

Oesophageal squamous cell carcinoma

Oesophageal cancer, both adenocarcinoma and squamous cell carcinoma of the oesophagus, is uncommon in Europe with an ASR of 3.3/100,000 (Globocan, 2020). Further, in Europe, the majority of patients are diagnosed with adenocarcinoma, such that the incidence of OSCC is lower than 1.65/100,000. In China, oesophageal cancer is relatively common; ASR 13.8 with the vast majority of patients (~ 90%) developing OSCC (Globocan 2020, Li et al., 2021).

3.1.3. Aetiology and pathogenesis

Toripalimab is a humanized IgG4 kappa monoclonal antibody that binds to programmed death receptor-1 (PD-1) and blocks binding to its ligands, programmed death ligand-1 (PD-L1) and PD-L2. PD-1 is expressed on immune cells and, when engaged with its ligands, inhibits the immune response. Blockade of PD-1 binding to its ligand by monoclonal antibodies, such as toripalimab, can re-activate the anti-tumour immune response leading to tumour shrinkage and improvements in OS.

Nasopharyngeal cancer (NPC)

Latent infection with Epstein-Barr virus (EBV) is essential to the development of NPC (Tatlı Doğan et al., 2016; Huang et al., 2018) with environmental factors such as tobacco and alcohol (Du et al., 2019; Chang and Adami, 2006) playing less of a role (Xue, 2013, Chang and Adami, 2006).

Oesophageal squamous cell carcinoma (OSCC)

The primary risk factors for oesophageal cancer are alcohol ingestion and tobacco use (in any form). Other risk factors include achalasia, human papillomavirus infection, lye ingestion (resulting in stricture), sclerotherapy, oesophageal webs due to Plummer-Vinson syndrome, and irradiation of the oesophagus. Genetic causes are unclear, but 50% of patients with tylosis (hyperkeratosis palmaris et plantaris), an autosomal dominant disorder, have oesophageal cancer by age 45, and 95% have it by age 55.

3.1.4. Clinical presentation, diagnosis

Nasopharyngeal cancer (NPC)

Diagnosis is based on inspection and biopsy, with CT, MRI, or PET to evaluate extent. Treatment is with radiation, chemotherapy, and, rarely, surgery.

Oesophageal squamous cell carcinoma (OSCC)

The most common malignant tumour in the proximal two thirds of the oesophagus is squamous cell carcinoma; adenocarcinoma is the most common in the distal one third. Symptoms are progressive dysphagia and weight loss. Diagnosis is by endoscopy, followed by CT and endoscopic ultrasound for staging. Treatment varies with stage and generally includes surgery with or without chemotherapy and radiation. Long-term survival is poor except for patients with local disease.

3.1.5. Management

Nasopharyngeal cancer (NPC)

The European Society of Medical Oncology (ESMO) guidelines for the treatment of patients with recurrent or metastatic NPC recommend first-line treatment with cisplatin and gemcitabine (Bossi et al., 2021). This recommendation is based on a trial conducted solely in China that randomized 362 patients to cisplatin/gemcitabine or cisplatin/5-fluorouracil. This trial demonstrated an improvement in both overall survival (OS) and progression-free survival (PFS) with cisplatin/gemcitabine. Median OS was 22.1 months in the cisplatin/gemcitabine and 18.6 months in the cisplatin/5-fluorouracil arm; hazard ratio (HR) 0.72, p = 0.004 (Hong et al., 2020). No drugs are approved by the European Medicines Agency (EMA) for the treatment of NPC. However, there have been a number of studies of PD-1 blocking antibodies in the treatment of NPC. Published and reported trial results in the first-line treatment of patients with recurrent or metastatic NPC are included in Table 1. Note that JUPITER-02, the key trial in this submission, was the first Phase 3 trial initiated in the first-line treatment of NPC. All 3 randomised, placebo-controlled trials, which enrolled patients only at clinical sites in Asia, have demonstrated clinically important and statistically robust improvements in PFS with the addition of a PD-1 blocking antibody to cisplatin/gemcitabine;

Table 1. Trials of First-Line Treatment of Recurrent or Metastatic NPC with PD-1 Blocking Antibodies

Drug	Trial Design	N	Primary Endpoint	Primary Efficacy Results	Reference
Toripalimab (JUPITER-02) Initiated Oct-2018	Toripalimab + GC vs. Placebo + GC	289	BIRC-determined PFS	Median PFS 11.7 vs. 8.0 mos HR 0.52, p = 0.0003	Mai et al, 2021
Camrelizumab (Captain-1st) Initiated Nov-2018	Camrelizumab + GC vs. Placebo + GC	263	BIRC-determined PFS	Median PFS 9.7 vs. 6.9 mos HR 0.54, p = 0.0002	Yang et al, 2021
Camrelizumab (NCT03121716)	Camrelizumab + GC	23	ORR	91% (95% CI: 72, 97)	Fang et al, 2018
Tislelizumab (Rationale 309) Initiated Apr-2019	Tislelizumab + GC vs. Placebo + GC	263	BIRC-determined PFS	Median PFS 9.2 vs. 7.4 mos HR 0.52, p < 0.0001	Yang et al, 2021
Tislelizumab (CTR20160872)	Tislelizumab	20	ORR	20.0%[1]	Wang et al, 2019

[1]ORR is based on 3 of 15 evaluable patients reported in the abstract.
BIRC=blinded independent radiology committee; GC=gemcitabine + cisplatin; HR=hazard ratio; mos=months; NR=not reported; ORR=overall response rate; PFS=progression-free survival

Oesophageal squamous cell carcinoma

The recently updated ESMO guidelines (Obermannova et al, 2022) recommend a platinum-fluoropyrimidine doublet with a PD-1 blocking antibody for treatment of locally advanced or metastatic OSCC but note that a recent trial of a PD-1 inhibitor in combination with carboplatin/paclitaxel has been conducted. The ESMO guidelines also discuss the use of carboplatin and paclitaxel in patients with early-stage disease (van Hagen et al, 2012). In China, where OSCC is approximately 10-fold more common than in Europe, both platinum/taxane and platinum/fluoropyrimidine combinations are used. Data supporting the effectiveness of platinum/taxane combinations include results from 2 meta-analyses and 2 retrospective trials that examined hospital records.

A meta-analysis of 31 trials conducted in China, North America, Canada, and Western Europe in early disease settings found an improvement in OS, PFS, and objective response rate (ORR) when patients were treated with a taxane/platinum combination as compared to fluoropyrimidine/platinum. The HRs for the comparison of OS in the taxane/platinum and fluoropyrimidine/platinum groups were 0.57 for patients receiving neoadjuvant chemotherapy, 0.51 for chemoradiotherapy, and 0.73 for definitive chemoradiotherapy (Wang et al., 2019).

A second meta-analysis conducted in China in patients with Stage III and IV OSCC demonstrated a higher response rate with paclitaxel/cisplatin (65.6%) compared to 5- fluorouracil/cisplatin (43.8%). Only 2/22 trials provided OS data. Both showed a similar improvement in median OS in the paclitaxel/cisplatin group when compared to 5- fluorouracil/cisplatin (3.1 and 3.0 months, respectively) (Wang et al., 2017).

A retrospective analysis in China compared patients treated with paclitaxel/cisplatin to those receiving 5-fluorouracil/cisplatin. Small improvements in OS (median OS 13.5 vs. 12.7 months), PFS, and ORR were seen in the paclitaxel/cisplatin group when compared to 5-fluorouracil/cisplatin (Liu et al., 2016).

A second retrospective study conducted in China found a marked improvement in ORR (80.0% vs. 35.0%) in patients who received paclitaxel/cisplatin when compared to those receiving fluorouracil/cisplatin (Zheng et al., 2017). This data suggests that a taxane/platinum regimen may be a more or an equally effective treatment option compared to fluoropyrimidine/platinum in patients with OSCC. Further, the recent ESMO guidelines for OSCC mention the use of a carboplatin/paclitaxel combination in advanced disease, in addition to the recommendation of this combination in localized disease, as noted above. Table 2 provides information from first-line trials of patients with OSCC treated with PD-1 blocking antibodies. Note that demographic information from KEYNOTE-590 is provided for all patients (OSCC and adenocarcinoma) while efficacy findings include only patients with OSCC. Both pembrolizumab and nivolumab have been approved for the treatment of OSCC by the EMA. Nivolumab is indicated in combination with fluoropyrimidine- and platinum-based chemotherapy

and in combination with ipilimumab for the first-line treatment of unresectable advanced, recurrent or metastatic OSCC with tumour cell (TC) PD-L1 expression ≥ 1%. The HR for OS in the nivolumab arm was 0.54 in patients with high (TC ≥ 1%) and 0.98 in those with low (TC < 1%) PD-L1 tumour expression (Doki et al, 2022). Pembrolizumab, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2- negative carcinoma of the oesophagus in patients whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. The HR for OS was 0.57 in patients with high (CPS ≥ 10) and 0.99 in those with low (CPS < 10) PD-L1 tumour expression (Sun et al, 2021).

The finding that efficacy was limited to patients with PD-L1 high tumour status with both nivolumab and pembrolizumab reinforces that differential treatment effect by PD-L1 expression is unlikely to be a chance finding in patients treated with first- generation PD-1 blocking antibodies. In contrast to the data above for nivolumab and pembrolizumab, the treatment effect of toripalimab, a second-generation PD-1 blocking antibody, in OSCC does not appear to be dependent on PD-L1 expression. The HRs for OS subgroups all fall within a narrow range from 0.61 to 0.64 regardless of the level of PD-L1 tumour expression. The Applicant provided a detailed discussion of the comparability study between JS311 and other antibodies to ensure the reliability of the biomarker assay result.

Table 2. First-Line Treatment of OSCC with PD-L1 Blocking Antibodies

Trial	Trial Design	N	Region	Endpoint(s)	HR	Median
JUPITER-06 Initiated Jan-2019	Toripalimab + TP vs. Placebo + TP	514	100% Asian	OS: All pts	OS: 0.58	17.0 vs. 11.0 mos
				BIRC-determined PFS: ITT	PFS: 0.58	5.7 vs. 5.5 mos
KEYNOTE-590 (KN-590)[1] Initiated Jul-2017	Pembrolizumab + FP vs. Placebo + FP	749	Asian 53.4% White 37.1% Black 0.9% Other/Missing 8.5%	OS: ESCC, CPS ≥ 10	OS: 0.57	13.9 vs. 8.8 mos
				OS: ESCC	OS: 0.72	12.6 vs. 9.8 mos
				OS: CPS ≥ 10	OS:0.62	13.5 vs. 9.4 mos
				OS: ITT	OS: 0.73	12.4 vs. 9.8 mos
CheckMate-648 (CM-648)[2] Initiated Jun-2017	Nivolumab + FP vs. Nivolumab/Ipilimumab vs. FP	970	Asian 70%	OS: TC ≥ 1%, N + FP vs. FP	OS: 0.54	15.4 vs. 9.1 mos
				OS: TC ≥ 1%, NI vs. FP	OS: 0.64	13.7 vs. 9.1 mos
				BIRC-determined PFS: TC ≥ 1% N + FP vs. FP	PFS: 0.65	6.9 vs. 4.4 mos
				BIRC-determined PFS: TC ≥ 1% NI vs. FP	PFS: NS	
ORIENT-15[3] Initiated Dec-2018	Sintilimab +TP or FP vs. Placebo + TP or FP	659	Asian 97%	OS: ITT	OS: 0.628	16.7 vs. 12.5 mos
				OS: CPS ≥ 10	OS: 0.638	17.2 vs. 13.6 mos
ESCORT-1[4] Initiated Dec 2018	Camrelizumab + TP vs. Placebo + TP	596	Asian 100%	OS: ITT	OS: 0.70	15.3 vs. 12.0 mos
				BIRC-determined PFS: ITT	PFS: 0.56	6.9 vs. 5.6 mos
RATIONALE-306[5]	Tislelizumab + Chemotherapy[6] vs. Placebo + Chemotherapy	649	Asian 74.9% White 23.0% Other 1.2%	OS: ITT	OS: 0.66 PFS: 0.62	17.2 vs. 10.6 mos 7.3 vs. 5.6 mos

[1]Sun et al, 2021; [2]Doki et al, 2022; [3]Shen et al, 2021; [4]Luo et al, 2021; [5]Yoon et al, 2022 ; [6]Chemotherapy included the Investigator's choice of a platinum/fluoropyrimidine or platinum/paclitaxel combination; BIRC=Blinded Independent Radiology Committee; CPS=combined positive score for PD-L1 expression; FP=5-flurorouracil, cisplatin; mos=months; N=nivolumab; ITT=intent-to-treat (all randomized); NS=not significant; TP=paclitaxel, cisplatin; NI= Nivolumab/Ipilimumab; TC =tumour cell PD-L1 expression

3.2. About the product

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01FF13.

Mechanism of action

Toripalimab is a humanised IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation, cytokine production, and cytotoxic activity. Upregulation of PD-1 ligands occurs in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

<u>The applied indication is:</u>

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.

The final approved indication is:

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

Loqtorzi, in combination with cisplatin and paclitaxel, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.

The recommended dosing regimen of Loqtorzi is 240 mg every 3 weeks (Q3W) as an intravenous (IV) infusion over 60 minutes for the first infusion. If no significant infusion-related reactions occurred during the first infusion, the subsequent infusions may be administered over 30 minutes.

3.3. Type of application and aspects on development

The applicant received scientific advice from the EMA for **hepatocellular carcinoma** (EMA/SA/0000099887, 2022-10-13) and was informed about the concern for lack of applicability of the data to a European population if they did not enrol an appropriate number of EU/non-Asian patients in the studies.

3.4. Quality aspects

3.4.1. Introduction

The finished product is presented as a concentrate for solution for infusion (sterile concentrate) containing 40 mg/ml of toripalimab as active substance. One vial of concentrate for solution for infusion contains 240 mg of toripalimab.

Other ingredients are: citric acid monohydrate, mannitol, polysorbate 80, sodium chloride, sodium citrate dihydrate, water for injections.

The product is available in a type 1 neutral borosilicate glass vial capped sealed with a chlorobutyl rubber stopper and sealed with a 20 mm flip-off seal (aluminium), containing 6 mL of concentrate for solution for infusion.

3.4.2. Active substance

3.4.2.1. General information

Toripalimab is a recombinant humanised immunoglobulin G4 (IgG4)-kappa anti-programmed cell death protein 1 (PD-1) monoclonal antibody (mAb). Toripalimab is comprised of two identical heavy chains and two identical light chains joined by disulfide bonds. Each light chain contains 219 amino acids, and each heavy chain has 452 amino acids. Toripalimab has a molecular weight of 147 kDa. A serine-to-proline mutation was introduced into hinge region of the heavy chain at amino acid position 233 to increase the structural stability. Toripalimab is a glycoprotein with N-linked glycosylation at asparagine (Asn) residue 302 of the heavy chain. The oligosaccharides are predominantly G0F type. There are 11 cysteine residues in each heavy chain and 5 cysteine residues in each light chain, which form 12 intra-chain and 4 inter-chain disulfide bonds.

The information on general and structural aspects of toripalimab are adequately provided. Biological activity (mode of action) was explained.

3.4.2.2. Manufacture, process controls and characterisation

The active substance manufacturers with their respective addresses and responsibilities have been included in the dossier. A QP declaration concerning GMP compliance of all the active substance manufacturing sites was provided.

The active substance is manufactured by Suzhou Union Biopharm Co., Ltd., 999 Longqiao Road Wujiang Suzhou Jiangsu 215299 China. During the procedure, a Major Objection (MO) requesting confirmation of EU GMP for the manufacturing site Suzhou Union Biopharm Co. Ltd. was raised. The Applicant presented a valid EU GMP certificate as a proof of GMP compliance, and the MO was considered resolved.

Storage of MCB and WCB is set to be in two geographically distinct locations (China and USA) which is considered highly recommended.

Description of manufacturing process and process controls

Toripalimab is manufactured in a GMP facility using a validated process. The toripalimab active substance manufacturing process consists of cell culture (upstream) and purification (downstream) steps. The upstream manufacturing process consists of thawing one vial of the working cell bank (WCB) and expanding cells in growth medium. The host cell line used in the upstream commercial process is a serum-free CHO cells. Toripalimab is manufactured in a fed-batch process and is purified with commonly used bio-processing techniques. The downstream manufacturing process consists of protein A affinity chromatography, low pH viral inactivation, followed by cation exchange chromatography (CEX), anion exchange chromatography (AEX), and three stages of filtration: viral nanofiltration, ultrafiltration and diafiltration (UF/DF). The maximum limit for *in vitro* cell age at the end of production is set based on studies in accordance with ICH Q5D.

One vial of WCB is used to manufacture one single batch of toripalimab active substance.

Information on column dimensions (diameter and bed height) for all three chromatography systems as well as nominal value of the filters areas used for downstream process and molecular weight cut-off for UF/DF are included in the process description while information on the corresponding materials can be found in section 3.2.S.2.3.

The toripalimab active substance manufacturing process is in general adequately described. Regarding the upstream processing steps, the single production bioreactor manufacturing run is described as being a fed-batch process. The feed is performed according to a defined schedule. Reprocessing is not considered by the applicant.

Process holds have been defined.

In conclusion, the process description is at large found acceptable at a sufficient level of detail.

Control of materials

The qualitative composition of the cell culture media and process solutions used for the inoculum preparation, seed bioreactors and production bioreactor steps as well as for harvest and purification steps is provided. These do not include materials of human or animal origin. The cell culture media and process solutions are only used after release as per controlled output parameters with set in-process action limits. The qualitative composition of the media used in the active substance upstream manufacturing process have also been added to section 3.2.S.2.3.

The specifications of individual non-compendial materials are listed. Specifications, provided in section "Control of materials" are acceptable.

The resin lifetimes were initially assessed using a qualified scaled-down model and are confirmed at manufacturing scale. Membrane lifetime studies were performed. The overall data support the proposed commercial resin lifetimes. Furthermore, the materials of the disposable bags/tanks used during the purification process were identified.

The generation of the expression vector of toripalimab has been described in detail. Target sequence-bearing shuttle plasmids and the commercial expression vectors were digested using HindIII and EcoRI and then purified using standard molecular biology methods. The open reading frames (ORF) of the HC and LC were then inserted into the relevant vectors . The resulting plasmids were then digested by NotI and PvuI and ligated together to produce a single plasmid expressing the heavy and light chains.

A traditional two-tiered cell banking system of MCB and WCB was established. Two MCBs have been developed during toripalimab development. The first MCB and corresponding WCB were used to manufacture toripalimab lots used in non-clinical and phase 1 clinical studies until late 2016. The second MCB and corresponding WCBs were used to manufacture clinical and future commercial

materials. The DNA sequences of toripalimab heavy chain and light chain were the same for both MCBs. The major differences between these two MCBs are the host cell lines, and the expression vector constructions.

In conclusion, sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Control of critical steps and intermediates

Development of the process control strategy for toripalimab active substance was based on principles described in ICH guidelines related to pharmaceutical development and quality risk management. Critical and key process parameters are identified based on historical manufacturing and comprehensive process development data. Process attributes, which are monitored as in-process controls (IPCs), are also classified as critical or key and provide assurance of product quality and process performance. Definitions of process parameter (PP), key process parameter (KPP), key performance attribute (KPA), critical process parameter (CPP), critical performance attribute (CPA), critical quality attribute (CQA), and proven acceptable range (PAR) have been provided in section 3.2.S.2.4.

The toripalimab manufacturing process is controlled by process parameters with defined targets/ limits, and IPCs and in-process monitoring (IPMs) with defined acceptance criteria/expected ranges.

A listing of the IPCs and IPMs, including their acceptance criteria/expected ranges, and data obtained from PPQ batches as well as a number of historical batches are provided. For most parameters, the acceptance criteria/expected ranges show reasonable agreement with the acquired data.

Overall, the process parameters and in-process controls in combination with the other control measures are harmonised with what is described in the Process Description and appear sufficient to ensure quality and safety of toripalimab active substance as well as to monitor process consistency.

A comprehensive overview of critical IPCs and critical in-process tests performed throughout the toripalimab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Process validation

The toripalimab active substance manufacturing process was validated at the manufacturing site plant in China. The objective of the process performance qualification (PPQ) campaign was to establish that the toripalimab active substance manufacturing process consistently controls process parameters within pre-specified ranges, meets pre-established criteria for performance attributes and produces drug substance with the necessary critical quality attributes.

A total of four PPQ lots of toripalimab active substance were manufactured. A deviation in PPQ lot 2 occurred during the harvest step a turbidity excursion was found on the clarified harvest pool. Data for PPQ lot 2 were not included downstream of the harvest step. All remaining PPQ lots (PPQ lot 1, lot 3 and lot 4) met the acceptance criteria defined in the validation protocol for the upstream and downstream processes.

The deviation mentioned above was investigated, the root cause was identified and adequate measures were taken. This is accepted.

Validation of the active substance manufacturing process followed three steps: process design, process validation (also referred to as PPQ) and continued (ongoing) process validation.

Process design is stated to be the result of the product and process knowledge obtained through development used to identify the CPPs as per their impact upon the CQA of the active substance.

Process- and product-related impurity clearance to adequate levels was also demonstrated during PPQ runs or the levels were already low. Microbial control of the manufacturing process was shown to be effective as all bioburden and endotoxin IPC limits were met.

Chromatography resin lifetime has been established using data from small scale models (SSM).

Intermediate hold times were established using extended storage of PPQ batch materials. The provided results support the set hold conditions.

In each validation run, the results obtained complied with the pre-defined acceptance criteria for the performance of the active substance manufacturing process and show consistency and robustness across the PPQ batches with no observed trends.

Information with regard to leachables and extractables for the use of product-contacting, single use plastic equipment is provided in section 3.2.S.2.5.7 for the HDPE bioreactor culture bags used in steps 4 and 5 of the active substance manufacturing process. The risk assessment and provided data on leachables/extractables stated in section 3.2.S.2.5.7 and section 3.2.S.6 can be considered sufficient for all HDPE bags used in the active substance manufacturing process.

Shipping validation of the active substance has not been performed, since the active substance and the finished product manufacturing take place at the same manufacturing plant, in two adjacent buildings.

In conclusion, the toripalimab active substance manufacturing process has been validated adequately. Consistency in production has been shown on 4 full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces toripalimab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

A comparison of the new single use production bioreactor (SUB) to the original 500-L SUB has been provided. The technical comparison between the two types of SUBs do not appear to raise concerns in terms of impact on product quality.

After successful PPQ, a continued process verification will be implemented to assure that the manufacturing process remains controlled during commercial production.

The up-stream characterisation studies included thaw of working cell bank, inoculum /seed Culture preparation, production bioreactor and centrifugation and clarification. The down-stream process was divided into CEX, AEX, endotoxin removal, low pH viral inactivation, and concentration and final formulation (UF/DF).

A preliminary risk assessment was performed to determine which parameters are theoretically identified as CPPs and KPPs. Following that, manufacturing development/process characterisation studies were done to finally rank these parameters. This approach is acknowledged. Some parameters identified as CPP or KPP have not been maintained in the final control strategy and this has been satisfactorily explained and justified by the Applicant.

According to the Applicant, process development includes optimisation of unit operations and operating ranges of process parameters to ensure productivity and product quality. Conclusions about optimised conditions for upstream and downstream processes or separate unit operations were provided.

Changes introduced to the analytical methods (analytical method evolution) during the process development were described in the dossier.

Three key changes were made to the active substance manufacturing process over the course of development, resulting in four major processes used for the manufacture of toripalimab.

The process was scaled up to supply for the multiple phase 1 clinical studies. During that scale-up, a number of changes were made to accommodate the new scale, including the addition of an expansion step, and optimising feed media during cell culture. The resins for the three chromatography steps were changed to resins that function similarly but which all offer increased dynamic binding capacity and the ability to handle higher protein loads. The filter area for the UF/DF step was doubled in order to accommodate the increased process volume. There were no changes to the low pH virus inactivation and nanofiltration unit operations.

The host cell line to generate the production cell substrate was changed from an internally developed CHO cell line to a commercial serum-free CHO cell line.

Comparability between the different processes has been investigated with respect to release testing, extended characterization and stability testing at long-term, accelerated and forced degradation conditions. All results obtained were consistent across all lots of material from each of the different processes used. It can therefore be concluded that comparability is sufficiently demonstrated.

Characterisation

Toripalimab active substance has been appropriately characterised. Different active substance batches have been included in the different characterization studies. Most studies have been performed on the reference standard and on PPQ batches. An overview of the batches included in the different characterization studies has been provided.

The characterisation studies include release testing using the proposed commercial release analytical methods and extended characterization methods to assess the primary, secondary and higher order structure, as well as post-translational modifications. Physicochemical characteristics have also been sufficiently addressed. In addition, the biological and immunological characteristics have been sufficiently addressed. Forced degradation studies were conducted.

Biological activity of the active substance was analysed by measuring PD-1 binding affinity using surface resonance (Biacore SPR), by a PD-1 binding ELISA, by a competitive PD-1 blocking ELISA, and by a T-cell activation assay to demonstrate the mechanism of action (MoA) of toripalimab in vitro. Furthermore, Fc binding affinity to various Fc receptors (i.e. FcRn, FcyRI, FcyRIIa, FcyRIIIa, C1q) was also investigated using Biacore SPR. Finally, a series of cell-based assays were conducted to determine the absence of Fc-mediated effector functions (i.e. ADCC and CDC).

The impurities of toripalimab were divided into potential contaminants, process- and product- related impurities. Process- related impurities consist of protein A column leachate, host cell protein (HCP), host cell DNA, residual chemical impurities from upstream process. Data from the PPQ batches confirm sufficient clearance of the impurities during the manufacturing process. The levels detected are well below toxicology safety limits with high safety margins present. Fragments and aggregates were defined as product- related impurities.

Since the active substance contains polysorbate 80 the Applicant was advised to investigate if the active substance samples exhibit Low Endotoxin Recovery (LER). LER implies the reduced capability of Limulus Amebocyte Lysate based assays to detect a known amount of endotoxin spiked into a sample. LER is typically observed in relation to formulations containing polysorbate and a chelating agent. The Applicant has performed spike-recovery studies to investigate if the product samples exhibit LER. Spike recovery studies were performed on three batches of finished product compared to non-spiked finished product, which were kept for up to 7 days and tested periodically for sample recovery. The results met the requirements of 50-200% recovery and demonstrated that LER is not observed using the reagents, test method and sample hold conditions tested.

Leachables and extractables are evaluated separately as part of material qualification and information is provided.

In conclusion, the toripalimab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a humanized IgG4-type antibody. The analytical results are consistent with the proposed structure. Furthermore, heterogeneity of the active substance was adequately characterised by analysing size and charge variants, glycosylation and other product-related substances and impurities. Biological characterization of toripalimab indicates that this antibody has the ability to bind PD-1 with high affinity; and has capability to bind some Fc receptors (FcRn, FcyRI), a weak binding affinity to FcyRIIa, an extremely low binding affinity to FcyRIIIa, and cannot bind C1q, thus confirming that toripalimab is not expected to have ADCC or CDC activity, which can be attributed to the engineered IgG4 design. In summary, the characterisation is considered appropriate for this type of molecule.

3.4.2.3. Specification

The Applicant proposed active substance release specification, indicated applied methods and specified acceptance criteria. The release specification includes tests for identity (isoelectric point and peptide mapping); purity and impurity tests for product related impurities, process-related impurities, process additive; protein content; potency; safety (endotoxin and bioburden), and general physicochemical tests (appearance, pH, osmolality). Overall, the parameters included in the active substance specification are found adequate to control the quality of the toripalimab active substance at release.

Acceptance criteria for appearance (colour and clarity) is set based on pharmacopoeia requirements and are acceptable. The acceptance criterion for pH is based on the pH of the formulation during the active substance manufacturing process. The acceptance criterion for pH is acceptable.

The proposed acceptance criteria for acidic peaks/ basic peaks (by CE-HPLC) are considered appropriate. The proposed acceptance criterion for HCP content was initially set too wide and has been further tightened, which is considered sufficiently justified and acceptable.

Acceptance criteria for main peak and acidic peaks (by CE-HPLC) are different for release and stability specifications and these differences are justified by long-term stability data.

Toripalimab bulk active substance is filled into sterile single-use storage bags. The studies of extractables and leachables were conducted using the representative scaled down bag model. No sensitizing or genotoxic compounds at levels exceeding the safety class limits were identified. These studies support the appropriateness of the container closure. A certificate of analysis of a representative batch of the packaging material is provided to demonstrate compliance with the established in-house specification.

Analytical methods

The analytical methods used were provided in the specification table as SOP numbers. The test methods used for release and IPC testing consist of compendial and non-compendial methods which are state-of-the-art. The description of the methods is considered sufficient. The tests for appearance, pH, bioburden and bacterial endotoxins are stated to comply with Ph. Eur. and a non-detailed description is provided, which is acceptable.

For the non-compendial methods a more detailed description is provided, and it includes the method principle, operating conditions, equipment. Additionally, the system suitability criteria and representative chromatogram/electropherogram/ dose-response curve are provided. In general, the information provided is adequate. Validation results for each of the test method is provided in accordance with ICH Q2(R1) Validation of Analytical Procedures: Text and Methodology.

Regarding potency, only one test is included in the active substance and finished product specifications, i.e., the PD-1 blocking ELISA assay. It should be noted that two other potency tests have been widely used throughout process development: PD-1 binding ELISA and T-cell activation assay. These two assays have been performed for active substance characterisation, active substance and finished product batch analyses (including PPQ batches), and active substance and finished product stability studies, demonstrating consistent potency in more than toripalimab active substance and finished product batches. Based on that, it is considered acceptable to omit the PD-1 binding ELISA and T-cell activation assay from the routine active substance and finished product specifications. It is also shown by the Applicant that these assays have been properly qualified and confirmed that these assays are kept as characterisation tests in case of future process changes.

Overall, the analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch data from a number of batches manufactured according to the proposed commercial manufacturing process were provided. These batches include the eight PPQ batches and GMP batches used for method validation, stability studies and clinical and non-clinical studies. All batches meet the specification at place at time of testing. The provided batch data demonstrates adequate batch-to-batch consistency.

Reference materials

A two-tiered system consisting of a primary and a working reference standard (PRS and WRS) has been established for toripalimab. The history of the RS used during development has been provided. Both RS are requalified annually in line with a pre-defined stability protocol. Qualification data demonstrated the suitability of the primary and working RS. PRS and WRS requalification and new WRS qualification criteria are provided. The proposed acceptance criteria for future PRS and WRS have been aligned with the final DS specification limits.

3.4.2.4. Stability

The stability program of toripalimab has been developed following the principles outlined in ICH Q5C and ICH Q1B. Stability studies for toripalimab active substance are conducted under long-term recommended storage conditions, accelerated conditions, and stressed conditions including light exposure, high temperature, mechanical stress (agitation) and freeze-thaw. The parameters tested are the same as for release minus the non-stability indicating parameters: identity; impurities (residual protein A, HCD, HCP); safety (endotoxins, bioburden); and osmolality.

Long-term stability studies have been completed on clinical and PPQ batches of toripalimab active substance stored at the proposed storage long-term conditions in a single-use container made of the

same polyethylene film as used in the DS storage bag. The stability sample storage conditions represent the worst-case scenario of the commercial DS storage. The three PPQ batches will continue to be tested following the protocol described in the dossier. All the clinical and PPQ lots were manufactured using the commercial manufacturing process with minor modifications during development and the comparability data demonstrate that the changes introduced during the process development did not impact the product quality. No significant trends were observed for the quality attributes during storage. The existing stability data from 10 clinical lots support the proposed toripalimab active substance long-term stability at recommended conditions.

Accelerated stability studies were conducted for up to 6 months on the same batches of toripalimab active substance studied under long-term conditions. The samples were stored at refrigerated conditions. Overall, the results obtained indicated that the active substance is stable under these conditions up to 6 months.

Photostability testing following the ICH guideline Q1B was performed on 6 batches of toripalimab active substance. The results obtained from photostability studies demonstrate that toripalimab active substance is relative stable after exposure to light stress for up to 10 days.

Thermal stress for up to 30 days was conducted on toripalimab active substance. The results demonstrate that toripalimab active substance is sensitive to high temperature stress over 30 days.

Agitation for up to 7 days was conducted on toripalimab active substance. No degradation was observed under agitation conditions.

Freeze-thaw was conducted on toripalimab active substance. No degradation was observed under freeze-thaw condition.

Overall, the recommended shelf-life of toripalimab active substance under the proposed conditions in the proposed container is acceptable based on the provided data.

3.4.3. Finished medicinal product

3.4.3.1. Description of the product and pharmaceutical development

Toripalimab finished product is presented as a preservative-free, sterile, clear to slightly opalescent, colourless to slightly yellow concentrate for solution for infusion containing 240 mg of toripalimab active substance, which is packaged in single-use 6R type I neutral borosilicate glass vials that are sealed with chlorobutyl rubber stoppers and capped with 20 mm flip-off seals.

The composition of toripalimab finished product was provided.

The toripalimab finished product contains commonly used excipients for biologic products, which ensures necessary stability in the current formulation. All excipients used in the finished product are of Ph. Eur. grade or have been tested to comply with Ph. Eur. requirements. The provided information on the excipients is acceptable.

The toripalimab finished product contains 240.00 mg of active substance and excipient as listed in the SmPC section 6.1: citric acid monohydrate, mannitol, polysorbate 80, sodium chloride, sodium citrate dihydrate, and water for injection. The pH and osmolality are also stable. No incompatibility between the active substance and the excipients have been observed.

The formulation development study was conducted to determine the pH, buffer system and excipients by comparing the product stability under multiple conditions, such as pH, stabiliser/surfactant, temperatures and frozen/thaw. Under evaluation of pH effect on stability of the formulation it has been concluded that best thermal stability has been achieved at a specific pH and it was selected as the target pH for the formulation. Charge variants were analysed by CE-HPLC following storage at 40°C for 4 weeks, and similar % main peak content was observed in all formulations evaluated.

The stabilising effect of polysorbate 80 on toripalimab was studied. Following a four-week storage period at 40 °C, the samples were evaluated by SE-HPLC and CE-HPLC. The data indicated that toripalimab is more stable in the presence of polysorbate 80.

The toripalimab finished product formulation robustness evaluation was confirmed by a two-level fractional factorial experimental design study. The results from formulation robustness characterisation study demonstrated that the excipients within the tested ranges are adequate to stabilise the finished product. The concentration of each excipient is controlled within the tested range during buffer preparation.

There is no overage of the toripalimab finished product.

The development of manufacturing process focused on evaluation of active substance freeze/thaw process, post-thaw active substance mixing characterisation, filtration and filling characterisation. In certain cases, scaled-down models have been used.

The primary packaging is Type 1 neutral borosilicate glass vial capped sealed with a chlorobutyl rubber stopper and sealed with a 20 mm flip-off seal (aluminium), containing 6 mL of concentrate for solution for infusion. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

To demonstrate compatibility of toripalimab finished product with the designated vial and stopper, stability testing of finished product, and the extractable and leachable profile evaluation has been undertaken. Container closure integrity testing has been performed by vacuum decay method.

The DP manufacturing process underwent just a few changes in the course of development, with only one substantial change concerning the filling line. For this change, a comparability study has been conducted, and the results have been included in dossier section 3.2.P.2.3.2.3.

3.4.3.2. Manufacture of the product and process controls

The toripalimab finished product is manufactured as a sterile, single use liquid formulation in Type I borosilicate glass vials. The finished product manufacturing process consists of thawing and mixing of the active substance, bioburden-reduction filtration, sterile filtration, aseptic filling, stoppering, capping, visual inspection, labelling, packaging and storage.

No pooling of multiple active substance batches is performed during the finished product manufacturing process. Only one active substance batch is used in each active substance batch. No reprocessing is foreseen.

The process control strategy for toripalimab finished product was developed based on the identification and classification of process parameters and process attributes. Critical process parameters and IPCs have been identified.

Relevant process parameters and in-process control are provided for appropriate manufacturing steps. The toripalimab finished product intermediate is intermittently filtered through two 0.22 µm sterile PVDF filters. The pre-use post sterilisation integrity testing (PUPSIT) has been added for the sterilising filter as an IPC to the finished product manufacturing process.

The sterile finished product is filled into Type I borosilicate glass vials using a filling machine in a Grade A areawith a Grade B background. After aseptic filling, vials are stoppered with chlorobutyl rubber stoppers. The maximum fill duration is supported by filter validation and media fills.

The labelling and packaging operations are performed in an area with CNC grade. The allowable duration of room temperature exposure during labelling and packaging operation is defined.

The toripalimab finished product shipping temperature is 2-8°C. The allowable shipping duration is defined and validated.

Sterilisation and depyrogenation of primary packaging containers, closures, sterilisation of equipment and product by sterile filtration have been validated to meet regulatory guidance and industry best practices. Three consecutive full-scale batches derived from three different batches of full-scale drug substance were assessed as part of the PPQ exercise.

The finished product batch size is defined depending on the corresponding active substance batch size, and validated.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

3.4.3.3. Product specification

The finished product specification is mostly the same as that of the active substance except for impurities (process-related impurities from the active substance are not re-tested on the finished product); safety (sterility replaces bioburden at release on the finished product); physicochemical properties (particles, extractable volume, polysorbate 80, and container closure integrity testing (CCIT) are only tested on the finished product).

Overall, the parameters included in the finished product specification are found adequate to control the quality of the toripalimab finished product at release.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. Most of the specification parameters that are only tested on the finished product are compendial with Ph. Eur. except polysorbate 80 (in-house assay) and CCIT (USP <1207>), which have been adequately validated.

Characterisation of impurities

Elemental impurities were addressed in section 3.2.P.7.3 Compatibility (Extractables/Leachables). Upon request, a risk assessment on elemental impurities in accordance with ICH Q3D was performed at the finished product level and considered all potential contributors of elemental impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The risk assessment was performed according to a Failure Mode Effects Analysis (FMEA) approach and encompassed the production process, the materials used in the production process (raw materials, containers, consumables, packaging materials), cross-contamination and shared-line production. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Batch analysis

The release data from batches of toripalimab finished product which were used for toxicological study, clinical trials, comparability and forced degradation study are available and were used to set release specifications. The long-term stability data of toripalimab finished product are available and were used to set the stability specifications. All batches meet the specification at place at time of testing. The provided batch data demonstrates adequate batch-to-batch consistency.

Reference materials

The same reference standard (RS) used for the release of toripalimab active substance is used for finished product release. The analytical testing results of the RS are presented in the Section 3.2.S.5.

3.4.3.4. Stability of the product

Based on available stability data, the shelf-life of 36 months for the unopened vials stored in a refrigerator at 2°C – 8°C as stated in the SmPC is acceptable.

Stability studies were performed according to the ICH Q5C and ICH Q1B guidelines under long-term recommended storage conditions of 5 ± 3°C, accelerated conditions of 25 ± 2°C, 60 ± 5% RH, and stressed conditions (photostability, 25 ± 2°C, 60 ± 5% RH and high temperature, 40 ± 2°C, 75 ± 5%RH). Stability testing was performed on toripalimab finished product (3 of them – PPQ).

Stability data of the finished product under long term condition (5 ± 3°C) was obtained from clinical batches for up to 24 and 36 months, and PPQ batches for up to 12 months. All parameters remained within the specification. Over 36 months, there was an average slight decrease of the main peak purity with an average corresponding increase of the acidic peak and decrease of the basic peak. All other parameters remained stable over 36 months.

Stability data of the finished product under accelerated conditions (25 ± 2°C, 60 ± 5% RH) was obtained on clinical batches and PPQ batches for up to 6 months. according to the ICH guidelines were provided. Over 6 months under accelerated conditions, a slight increase in aggregates and a decrease in monomer was observed. Purity showed an average decrease of the main peak with a significant increase of the acidic peak and a slight decrease of the basic peak. This is consistent with the trends observed under long-term conditions. Overall, all parameters remained within the specification, suggesting that the finished product is stable at ambient temperature for up to 6 months.

The parameters tested for stability of toripalimab finished product is identical to the release specification except the tests for identity (isoelectric point and peptide mapping); safety (endotoxin, sterility); and some tests for physicochemical properties (osmolality, extractable volume, polysorbate 80) since these parameters are not stability indicating. For the accelerated stability testing, the

specification does not include CCIT testing but sterility, other parameters and limits are the same as in the shelf-life specification.

Photostability studies were conducted according to ICH Guidelines on finished product batches for up to 10 days. The results demonstrates that the finished product is relatively stable under light exposure for up to 10 days. An increase of aggregates and a decrease in the main peak purity was observed. The degradation products have been characterized and mostly originate from oxidation.

Thermal stress exposure under 40°C and relative humidity of 75% for up to 30 days was conducted on batches of toripalimab finished product. The results demonstrate that toripalimab finished product is sensitive to high temperature for up to 30 days. There was a slight increase by deamidation, oxidation and isomerisation modification based on characterisation results, which contribute to the increase in acidic peaks but had no apparent impact on potency.

To support the compatibility of toripalimab with administration equipment, two in-use stability studies have been performed. The first study was already submitted in the initial application and evaluated polypropylene (PP) IV bags and infusion sets. The second study has been additionally submitted and evaluated polyvinyl chloride (PVC [DEHP-containing]), polyolefin (PO) and ethylene-vinyl acetate (EVA) IV bags and PVC (DEHP-containing) or polyethylene (PE)-lined tubing infusion sets. The results of the two in-use stability studies met the pre-defined acceptance criteria. It can thus be concluded that toripalimab finished product is compatible with PP, PVC, PO and EVA IV bags as well as PP, PVC and PE-lined infusion apparatus (IV sets).

All batches have been tested using the validated methods described in Section 3.2.P.5.2. Tests included in stability protocol are identity, appearance, bioactivity and assay, impurities/degradation products. However, testing of series for the long-term stability was performed according to the older specification. For the PPQ series the specification was updated, however, the PD1-binding (ELISA assay) limit is wider than in the shelf-life specification. The applicant has explained that these limits are from the previous DP specification that were used at the time of testing, nevertheless, the results still comply with the tightened shelf-life specification provided in the updated 3.2.P.5.1 section. This is accepted. The applicant has provided missing data upon request for the total impurities of reduced CE-SDS and non-reduced CE-SDS for month 0, 3 and 6 for all PPQ series for the long-term stability studies. Testing of series for the accelerated stability was performed according to the older specification. For the PPQ series the specification was updated, however, the PD1-binding (ELISA assay) limit is wider than in the shelf-life specification. The applicant has explained that these limits are from the previous DP specification that were used at the time of testing, nevertheless, the results still comply with the tightened shelf-life specification provided in the 3.2.P.5.1 section. This is accepted.

In conclusion, the available stability data support the 36 months shelf-life of the finished product at 2–8°C.

3.4.3.5. Adventitious agents

All raw materials are subject to appropriate identification and testing prior to use. No excipients or materials of animal or biological origin are used in the toripalimab manufacturing process.

The animal derived raw materials were used during the host cell line development and have been evaluated in the relation to the risk of introducing transmitting animal spongiform encephalopathy (TSE) agents to the product and it was concluded that there is a minimal risk of contamination by TSE from these materials in the final product.

The MCB was tested for adventitious virus by both in vitro and in vivo assays. In addition, the MCB was also tested for the presence of bovine and porcine virus as per ICH Q5A. No fungal, bacterial growth or mycoplasma was detected in both MCB and WCB.

Extensive viral clearance studies were performed in accordance with the ICH Q5A to demonstrate that the downstream purification process for toripalimab is capable of removing and/or inactivating potential viral contaminants. The Xenotropic Murine leukaemia virus is the gamma retrovirus that was used as the model virus of the replication-defective virus like particles (RVLPs) that are present in CHO cells. Murine minute virus, which is approximately 18 to 24 nm in size and is resistant to physical treatments, was used as a severe challenge to the nanofiltration system. The results showed that there may be one virus-like particle (VLP) per 4.48×10^{10} doses.

Overall, adventitious agents' safety is considered sufficiently assured.

3.4.3.6. GMO

N/A.

3.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure, one major objection (MO) was raised on the GMP compliance of Suzhou Union Biopharm Co. Ltd. manufacturing site. The Applicant ultimately provided adequate evidence of GMP compliance for the site mentioned and the MO was therefore considered resolved.

All other quality issues raised as other concerns (OC) have been resolved during the procedure.

3.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

3.4.6. Recommendation(s) for future quality development

None.

3.5. Non-clinical aspects

3.5.1. Introduction

Toripalimab (also known as TAB001; JS001) is a humanized IgG4κ monoclonal antibody specifically targeting human programmed cell death protein 1 (PD-1) for the treatment of various malignancies. PD-1 is a receptor mainly expressed on the surface of T cells, whereas PD-L1 is highly expressed on tumour cells. The interaction between PD-1 and PD-L1 inhibits T-cell responses and anti-tumour activity. Binding of toripalimab to PD-1 blocks PD-1/PD-L1 interaction and thus enhances T cell

activation, and subsequently enhances T cell-mediated immune responses against tumours. Specifically, toripalimab suppresses tumour immune evasion by blocking interactions between PD-1 and its ligands (PD-L1 and PD- L2), thereby preventing inhibitory signals downstream of PD-1.

3.5.2. Pharmacology

In the non-clinical Pharmacology part of the dossier the Applicant presented data on toripalimab binding affinity, biological functions *in vitro* and *in vivo.* Assays and animal (mice and monkey) models used properly evaluated the pharmacological action of toripalimab for the intended therapeutic indication.

3.5.2.1. Primary pharmacodynamic studies

The binding affinity study determined toripalimab apparent affinity to human PD-1 of ~ 0.28 nM (as equilibrium dissociation constant (KD)), which appeared greater than comparators' (pembrolizumab or nivolumab) affinity. Quantitative sandwich ELISA demonstrated that toripalimab specifically bound to human PD-1 with EC_{50} =5.58 ng/mL (38 pM) but did not bind to other CD28 family members including CD28, ICOS and CTLA-4. ELISA studies also indicated that toripalimab binds to human and cynomolgus monkey PD-1, with EC_{50} values of 38 pM and 224 pM respectively. However, toripalimab does not cross react with mouse or rat PD-1. Flow cytometric analysis confirmed toripalimab binding to PD-1 on primary T cells (CD4+ and CD8+) of both human and cynomolgus monkeys with EC_{50} values of 3.5 nM and 4.3 nM, respectively. Competition sandwich ELISA demonstrated that toripalimab inhibited both hPD-L1 Fc (hPD-L1-Fc fusion protein) and hPD-L2 Fc (hPD-L2 - Fc fusion protein) from binding to plate-bound hPD-1Fc with IC50 values of 0.8 nM and 1.3 nM, respectively. Similarly, toripalimab blocked binding of hPD-L1 and hPD-L2 from binding to PD-1 expressed on 293T cells with IC_{50} values of 1.3 nM and 3.7 nM, respectively.

The ability of Toripalimab to enhance T cell response was examined in three *in vitro* assays:

-a NFAT-luciferase reporter gene assay in PD1 expressing Jurkat T cells cultured with CHO cells expressing PD-L1 and an anti CD3 single chain antibody. Toripalimab blocked the interaction between PD-1 and PD-L1 promoting the T cell activation in a dose dependent manner. In these studies, toripalimab inhibited PD-1/PD-L1-induced signalling in a dose dependent manner with an EC50 of 1.2-1.8 µg/ml. These experiments also demonstrated that toripalimab can block the binding between PD-L1 expressed on CHO cells and PD-1 expressed on Jurkat cells to abrogate the signalling cascade downstream of PD-1. Toripalimab blocked the interaction between PD-1 and PD-L1 promoting the T cell activation in a dose dependent manner, albeit with a lower potency than Nivolumab.

-an antigen specific recall response assay in PBMCs derived from human subjects who had been exposed to common pathogens or mixed antigens including cytomegalovirus (CMV) / Epstein-Barr virus (EBV) / flu peptides and vaccine antigen tetanus toxoid (TT). In these studies, in vitro matured dendritic cells were used as antigen-presenting cells. Compared to control antibody, toripalimab enhanced TT specific T cell proliferation with an EC50 value of approximately 100 ng/mL and a maximal effect at 300 ng/mL. The effects of toripalimab on T cell activation was also accompanied by an increase in IFN-gamma production. Toripalimab suppresses inhibitory PD-1/PD-L1 engagement and enhanced T-cell activity was also observed using CMV/EBV/flu peptides and antigens.

Whilst such results showed demonstrated enhanced T cell activation, antigen recall is not the primary mode of action of Toripalimab.

--a Mixed lymphocyte reaction assay in which T cell receptor (TCR)-dependent T cell activation was induced by co-incubating human mDC cells (mature dendritic cells) with allogeneic CD4+ T cells. Toripalimab and the positive control nivolumab effectively promoted T cell activation, leading to IL-2 and IFN-γ release in a dose-dependent manner. As IL-2 and IFN-γ are the indicators of T cell activation, these results confirm the ability of toripalimab to induce T cell activation in primary human T cells.

These assays conducted with healthy donor cells are considered sufficient for the *in vitro* POC. The absence of POC with cancer patient derived cells is supported by literature with another anti PD1 antibody.

To evaluate potential immunotoxicity the Applicant conducted cell-based assay. Toripalimab exhibited no ADCC or CDC activity against cells overexpressing PD-1, while an antibody containing the CDR region of toripalimab in a wild type human IgG1 Fc backbone showed a dose-dependent ADCC activity, and rituximab induced CDC employing Raji cells. The absence of ADCC or CDC mediated by toripalimab was confirmed in additional assays including adequate positive and negative controls.

Evaluating toripalimab biological functions *in vivo* the Applicant performed some studies in mice and monkey. Evaluation of toripalimab was first conducted in immunodeficient NSG mice following adoptive transfer of human PBMC; toripalimab treatment induced more than 2-fold increase in total T cell counts and promoted expansion of human effector / memory T cells, which are key mediators of an effective anti-tumour immune response.

Toripalimab does not cross-react with mouse PD-1. Thus, *in vivo* evaluation of toripalimab was performed in NSG mice or human PD-1 knock-in mice. Toripalimab suppressed tumour progression in 624Mel Xeno-graft Tumour Model and completely abrogated established tumour progression in a human PD-1 knock-in murine MC38 syngeneic tumour model when dosed at 10 mg/kg, twice a week for a total six doses. The estimated EC_{50} dose of anti-tumour effect is estimated to be between 0.3 mg/kg to 1 mg/kg twice a week via intra-peritoneal injection in the MC38 model.

As a pharmacodynamic readout, toripalimab receptor occupancy (RO) was evaluated in single-dose and repeat-dose toxicity studies conducted in cynomolgus monkeys. In repeat-dose toxicity studies, the half maximum RO was achieved when circulating toripalimab concentration was 0.246 μg/mL (1.67 nM). RO was >90 % when serum toripalimab concentrations reached 4.6 μg /mL (31 nM), indicating toripalimab exposure is correlated with pharmacologic activity in animals.

3.5.2.2. Secondary pharmacodynamic studies

The applicant did not submit studies on secondary pharmacodynamics and referred to toxicology studies where toripalimab other possible effects were investigated.

3.5.2.3. Safety pharmacology programme

The applicant did not perform dedicated safety pharmacology studies. Since toripalimab is a monoclonal antibody and does not belong to a class of medicinal products expected to cause cardiovascular effects, specific safety pharmacology studies were evaluated as part of the toxicology studies in cynomolgus monkeys. It is considered that for this type of product, the lack of dedicated studies for safety pharmacology is acceptable and in line with the ICH S6(R1), ICH S7A and ICH S9 guidelines.

As indicate related bridging data from toxicology studies there were no adverse cardiovascular, nervous system or respiratory system findings following IV administration of toripalimab in single-dose or repeat-dose studies using cynomolgus monkeys.

3.5.2.4. Pharmacodynamic drug interactions

No formal drug interaction studies have been performed in support of this application.

3.5.3. Pharmacokinetics

The applicant conducted non-GLP single and repeat dose studies in which the pharmacokinetic parameters were examined using naïve cynomolgus monkey.

The cynomolgus monkey was determined to be a relevant animal species because toripalimab binds to cynomolgus monkey PD-1 receptor. Since the intended route of administration in man is intravenous, toripalimab was administered IV in nonclinical pharmacokinetic studies as Test article: JS001 (Recombinant humanized anti-PD-1 monoclonal antibody injection, 240 mg/6 mL/vial,), provided by Shanghai Junshi Biosciences Co., Ltd.

Concentrations of toripalimab and its antibodies (ADA) were quantified in monkey serum using ELISA methods. For GLP studies, validated methods were used for the quantification of toripalimab in serum following standards at the time and validation reports are presented in the dossier. The analytical methods were validated for intra- and inter-day accuracy, precision and if necessary, specificity, dilution effect and storage stability. Units of measurement are clearly defined, and the same units used consistently.

The pharmacokinetic characteristics of toripalimab have been investigated in two non-GLP-compliant studies: in naïve cynomolgus monkeys following a single IV infusion at 1, 10, and 75 mg/kg and in repeat dosing at 10 mg/kg once a week for 4 consecutive times. Following single IV infusion the systemic exposure trended to increase dose proportionally, the total serum clearance after a single dose of toripalimab was low. After repeat dosing at 10 mg/kg once a week for 4 consecutive times Cmax and AUC showed that the drug exposure after last dosing was significantly lower than that after 1st dosing, likely due to the generation of anti-drug-antibody which were not monitored in the study. The half-life $t_{1/2}$ in the last dosing was only 37.6 ± 25.83 hr, and no obvious drug accumulation was observed.

The concentration of test article in serum samples of cynomolgus monkey in the 4-week toxicity study was measured using a validated ELISA assay (Study report # 2352-13163). Another validated ELISA method (Study report # S5401CySeVR and S5401CySeVR) was used for the 26-week repeat dose study. Two validated detection methods were used to detect ADA: an ECL assay on the MSD platform for the 4-week toxicity study and a Bridge-ELISA assay for the 26-week toxicity study. The toxicokinetic and anti-drug antibody samples from 26-week GLP toxicity study were analysed.

Several early development batches were used: test articlein study 2352-13086 (4-week GLP repeat dose study), test article DSin study 1348RD2 (26-week GLP repeat dose study). Based on comparability analysis the earlier drug processes are considered representative of the drug process used for the clinical batches.

In the 4-week study, monkeys were administered vehicle or 1, 10 or 100 mg/kg toripalimab by IV infusion every two weeks for a total of 3 doses whereas in the 26-week study, animals were given vehicle or toripalimab (10, 30 or 100 mg/kg) once weekly by iv bolus injection.

TK analysis of the 4-week study indicated that Cmax was typically (in 78 % of cases) reached at the end of infusion, with average Tmax values between 0.4-1.1 h. Serum concentration-time were characterized by a bi-phasic decline with time. No marked sex difference in systemic exposure was observed at any dose level. Overall, as the dosage increased from 1 to 100 mg/kg, the systemic exposure increased dose proportionally in males and females on Day 1.

The serum concentration of toripalimab declined slowly following the first and the last dose with a dose-dependent decrease in clearance at the higher doses. However, elimination was accelerated following multiple dosing, resulting in minimal accumulation observed at all dose levels. Increased elimination was related to the formation of ADA which were observed in 8/10, 8/10 and 2/10 animals in the 1, 10, 100 mg/kg dose groups, respectively. The presence of ADA persisted to the end of the recovery period. As a result of limited ADA in the high dose group, toripalimab exposure was maintained during the course of the study at the dose level of 100 mg/kg. No determination was made to ascertain if the ADA were neutralizing.

For the 26 week-study, no significant gender differences were observed (< 2-fold) between dose groups at any time point during the study. After the first dose, toripalimab had similar linear kinetics in the three dose groups with similar averaged Tmax (0.08h). Systemic exposure (Cmax and AUC) increased dose proportionally in the dose range from 10 to 100 mg/kg after the first dose.

However, after the 14th and 26th doses, toripalimab concentrations declined rapidly in the lowest dose group (10 mg/kg). The increase in clearance was correlated with the formation of ADA: 7/10, 2/10, and 3/10 animals were ADA-positive in the 10, 30 and 100 mg/kg dose groups, respectively. The accumulation ratio (AR) correlated with the duration of drug administration; the AR for SD 92 vs. SD 1 and SD 176 vs. SD 1 in the 100 mg/kg group were 1.36 (AUC0-24h) were 2.04 (AUC0-168h) and 2.45 (AUC0-168h) at the end the dosing and recovery phases, respectively.

In the 26-week study, the presentation of the means values separately for ADA positive and negative animals clearly indicated that the bulk of the variation in exposure is caused by the reduction or loss of exposure in ADA positive animals. ADA negative animals which maintained exposure throughout the study adequately represent the exposure profile of Toripalimab.

The applicant did not submit studies on distribution, metabolism and excretion.

3.5.4. Toxicology

The toripalimab toxicological program has been performed according to the ICH S6 (R1) guideline for biotechnology products and ICH S9 nonclinical evaluation for anticancer pharmaceuticals and consisted of a single dose non-GLP pilot study, and GLP 4-week and 26-week repeat-dose pivotal toxicity studies in cynomolgus monkeys. Studies of 6 months duration have generally been appropriate to support a MAA. In addition, an in vitro cytokine release assay and a GLP tissue cross-reactivity study with human tissues were conducted.

3.5.4.1. Single-dose toxicity

A non-GLP single dose toxicity study has been conducted to determine the potential toxicity and toxicokinetic profile of toripalimab when administered as single intravenous infusion for 30 minutes to male and female cynomolgus monkeys. (2 males and 2 females/groups) at dose levels of 1 or 203 mg/kg. All animals were observed for the overt sign of toxicity during a 28-day observation period.

The female administered the high dose of toripalimab showed an abrasion on the right side of the face on study day (SD) 8, greater number of fair and poor grading of food consumption. This animal was

also found to have higher serum GLU (+ 24.2%) and a higher serum CHOL (which resulted in a 34.1% higher mean value in female monkeys). The increase in glucose and cholesterol were closed to the maximal range of the historical data of the test facility. Moreover, those changes were not observed in the pivotal 4-week and 26-week repeat dose toxicity studies.

No drug-related major toxicity findings were noted when toripalimab at doses of 1 or 203 mg/kg is administered once via intravenous infusion for 30 minutes to male and female cynomolgus monkeys. The no-observed-adverse-effect level (NOAEL) of a single dose of toripalimab in this study is 203 mg/kg.

3.5.4.2. Repeat-dose toxicity

Two repeat-dose toxicity studies were performed with Toripalimab.

As toripalimab does not cross react with rodent PD-1 but binds to cynomolgus monkey PD-1 and human PD-1, the pivotal toxicity studies were done in one species only which is consistent with the ICHS6(R1) guideline.

For both repeat-dose toxicity studies toripalimab was administered by the IV route which is the intended clinical route.

4-week, toxicity with 7-week recovery period, IV, cynomolgus monkeys (2352-13086)

The purpose of this study was to determine the potential toxicity and toxicokinetic profile of toripalimab when administered intravenously every two weeks over four weeks (total of three doses) to male and female cynomolgus monkeys and to determine the persistence or reversibility of any toxic effects over a seven-week recovery period.

In this study, forty (20/sex) cynomolgus monkeys were randomly assigned to 4 groups (5 animals/sex). Animals were administered control article (1X phosphate buffered saline) or toripalimab at 1, 10, or 100 mg/kg on Study Day (SD) 1, 15, and 29 via 30-minute infusions with recovery phase extended until SD78. Daily cageside observation, food consumption, body weight, physical, ophthalmologic examination, ECG, HR, BP measurements were performed. Blood samples were collected for cytokine, immunogenicity, immunophenotyping evaluation. Also, blood and urine specimens were taken for clinical pathology.

Treatment with toripalimab at doses up to 100 mg/kg had no effect on mortality, physical examinations, cage side observations, body weights, body weight changes, food consumption, blood pressure (systolic and diastolic), heart rate, and ophthalmology.

Significantly higher body weight changes were noted in Group 3 (10 mg/kg) and 4 (100 mg/kg) males for the SD 15-22 interval and Group 4 females for the SD 29-30 interval. There was also noticed large changes in body weights from SD 29 to 36. These findings were considered unrelated to test article administration because they occurred in only one sex in that interval and did not persist to the next interval.

No toripalimab-related abnormalities in rhythm or waveform morphology were found at any dose level based on comparison of pre-dose and post-dose electrocardiographic recordings. All the electrocardiograms evaluated were qualitatively and quantitatively considered normal for cynomolgus monkeys.

Overall, there were no test article-related group or individual differences in clinical pathology (clinical chemistry, haematology, coagulation, and urinalysis). All differences in values between toripalimab-administered animals and vehicle control animals, including those that were statistically significant, were considered spurious. They showed a pattern consistent with random variation, lacked a dose-

relationship, and/or did not overlap in magnitude with relative pre-dosing values and/or absolute value seen for vehicle control animals. Furthermore, those changes lacked microscopic correlates.

No toripalimab-related adverse findings were noted/observed in macroscopic or microscopic findings. A slight increase in thyroid organ weight (1.89-, 0.26- and 1.81- fold of increase in absolute weight, organ/body weight and organ/brain weight ratio, respectively), was noted on SD 31 in males of the 10 mg/kg dosage group. However, this change is considered unrelated to toripalimab due to its minor magnitude, lack of microscopic correlations and insignificance in changes of organ-to-body weight coefficient ratio.

Individual organ weight measurements at SD31 showed increase in testes weight for dosing the 1, 10, and 100 mg/kg groups compared with control group.

No delayed effects of toxicological relevance were noted after the seven-week recovery period.

Administration of toripalimab up to 100 mg/kg every two weeks for a total of three doses did not cause proinflammatory Th1/Th2 cytokine (IL-2, IL-4, IL-5, TNF and IFN-g) increase in the serum samples acquired 24 hours after the 1st and last dose. No sign of immune adverse reaction was observed upon treatment of toripalimab in healthy cynomolgus monkeys. There was no impact of toripalimab on the frequency of T, B, NK cell subpopulations by the flow cytometry analysis of the whole blood samples, although a minor and transient increase of activated T and B cells were seen in all dosing groups on SD 8 and SD 15, but not on SD29.

Toripalimab bound to the target molecule PD-1 on activated T lymphocytes with full occupancy in all animals on SD 1 and SD 8. The full receptor occupancy was maintained until the end of study in all the animals in the high dose (100 mg/kg), and in the majority of the animals in the mid-dose (10 mg/kg). Decreased receptor occupancy (less than 80%) correlated with the clearance of toripalimab to a serum concentration below 2500 ng/mL.

The TK results of this study are reported under section 3.2.3. The NOAEL of TAB001 in male and female cynomolgus monkeys is 100 mg/kg when administered via 30 minutes intravenous infusions every two weeks over four weeks (total of three doses).

At this dose level, the mean Cmax and AUCinf on the 29th day of the dosing phase were 3.52 mg/mL and 854 mg*h/mL for males, and 3.11 mg/mL and 760 mg*h/mL for females, respectively.

<u>26-week toxicity with 66-day recovery period IV, cynomolgus monkey (1348RD2)</u>

Cynomolgus monkeys (5 animals/sex/group) were administered a vehicle (sodium chloride), 10 mg/kg, 30 mg/kg or 100 mg/kg Toripalimab weekly via IV injection for 27 doses. Three animals per group underwent a scheduled necropsy at the end of the dosing period, the remaining two animals after a 9- week recovery.

The toxicological endpoints evaluated during the study included mortality/moribundity, clinical observations, body weight, food consumption, body temperature, electrocardiogram, ophthalmology examination, clinical pathology (haematology, coagulation, clinical chemistry, immune function parameters, urinary analysis and faecal occult blood test), hormone analysis (testosterone/free testosterone), receptor occupancy, toxicokinetics, immunogenicity analysis, macroscopic examination, organ weight/ organ coefficient, histopathological examination, immune histological examination of the kidney.

One high dose female was euthanized in moribund condition on SD104, the condition was attributed to a rectocele as no prior abnormalities were noted apart from decreased food consumption from SD 99. Histopathological examination confirmed colon and rectum mucosa necrosis, bleed and inflammation. The death is considered incidental and not associated with toripalimab. In addition, increased blood urea nitrogen and creatinine associated with vacuolation in the renal tubular epithelial cell, renal

tubular enlargement and thymus atrophy and white pulp of spleen atrophy were noted. Renal tubular enlargement and interstitial inflammatory cell infiltration also occurred in several animals at all doses including controls. No specific thymus findings occurred in the remaining animals. These changes are considered incidental.

In the remaining animals, clinical observations were unremarkable and no statistically significant differences in body weight and food consumption were observed between test-article treated and vehicle control groups.

Non-adverse, body temperature increase occurred 1 h or 24 h after dosing on day 1 and on day 92 in some males administered 30 or 100 mg/kg toripalimab, mostly within the range of variations seen in the control group and with overlapping standard deviation. These changes are considered incidental.

No significant findings in the cardiovascular, ophthalmological, haematological, coagulation, immune function (lymphocytes populations, NK cells, IgG and complement), urinalysis, testosterone and in the pathological examination were noted.

Testosterone and free testosterone were evaluated in this study without a clear rationale for this assessment. No change was observed across the groups for these parameters.

As a pharmacodynamic readout, toripalimab receptor occupancy (RO) was evaluated as part of the monkey pivotal 26-week repeat-dose toxicity studies. Sustained and full receptor occupancy appeared to be found during the dosing and recovery in the mid- and high- dose treated groups (8/10 animals for each group), whilst RO was variable in the low dose group. The applicant concluded that the lower receptor occupancy seen in the low dose groups (3/10 animals) were due to the occurrence of ADAs. The overall results confirmed the inverse relationship between toripalimab RO and the presence of ADA. The TK results of this study are reported under section 3.2.3.

The NOAEL for this study was established at the high dose 100 mg/kg is endorsed. Exposure margins of 49.1x for Cmax and at least 20x for AUC are in place with the expected exposure at the clinical dose.

Overall based on both GLP repeat dose studies: toripalimab was well tolerated up to 100 mg/kg administered weekly or every two weeks. Although reduced exposure occurred in the low dose groups (up to 10 mg/kg), majority of animals at the high dose 100 mg/kg remained exposed with high receptor occupancy throughout. The exposure is considered sufficient in both studies. No significant adverse test article findings were noted in either study. This pattern of findings is expected for a PD-1 inhibitor.

Nevertheless, changes in testes and epididymis weight were noted in both pivotal repeat dose toxicity studies. When comparing data weight increased in one (4-week) study and decreased in the other one (26-week).

It is stated in the reports of the studies, that there were no adverse or notable effects in the male and female reproductive organs detected during these studies. However, data presented in 4-week repeated study report (#235-13086) shows increase in testes weight in all treatment groups at the SD31 compared with the control group and the values are 2, 3 and 10 times higher in 1 mg/kg, 100 mg/kg and 10 mg/kg dose treatment group respectively. In addition, in the 26-week study Report # 1348RD2 the decrease in testis weight in mid and high dose groups at the end of the dosing period in males is shown. These changes are considered to be related to age of the animals rather than the test article itself.

As no notable findings were observed in either the gross pathological examinations or microscopic examinations of the reproductive organs in monkeys and the reproductive toxicity is not a significant

concern for toripalimab in clinical trials, the changes in testis weights in monkeys could be considered not related to the toripalimab itself.

3.5.4.3. Genotoxicity

No genotoxicity studies were conducted.

3.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted.

3.5.4.5. Reproductive and developmental toxicity

No dedicated reproductive and development toxicity studies were conducted with toripalimab. Instead, the applicant provided a literature assessment, this is in accordance with ICH S9 and S6. The literature summary indicated that in mice inhibition of the PD-1/PD-L1 axis reduced maternal tolerance which can lead to increased foetal resorption and abortion. Similarly, to other PD-1 inhibitors already authorised the mechanism of action of toripalimab could cause embryofoetal toxicity when administered to pregnant women. No dedicated fertility endpoint assessments were included in the 4 or 26 weeks repeat dose toxicity studies. Animals in the 26-week study were 3-5 years old and 2.6 to 5.8 years old in the 4-week study. Not all animals were sexually mature. Male and female reproductive organs were examined at the end of dosing and after recovery in both studies. No significant findings were reported in female reproductive organs.

Changes in testes and epididymides weight were noted in both pivotal repeat dose toxicity studies. When comparing data weight increased in one (4-week) study and decreased in the other (26-week) study. This is discussed in repeat dose toxicity section.

Toxicity studies with juvenile animals have not been performed.

3.5.4.6. Toxicokinetic data

Toripalimab was administered at maximum dose 100 mg/kg in repeated dose toxicity study (#2352-13086) with cynomolgus monkeys. This provides a safety margin of 20.12 fold (mean value of both genders in SD1), 49.31 (mean value of both genders in SD29) in terms of AUC0-t. Toripalimab was also administered at maximum dose 100mg/kg in repeated dose toxicity study (#1348rd2) with cynomolgus monkeys. This provides a safety margin of 8.86-fold (SD1), 17.46fold (SD92), 20.58-fold (SD176) in terms of $AUC_{0\text{-}t}$.

3.5.4.7. Tolerance

Local tolerance was assessed in repeat-dose toxicity studies. No pathological findings were detected at the site of IV infusion (4-week monkey study) or IV bolus injection (26-week monkey study).

3.5.4.8. Other toxicity studies

The applicant has assessed tendency of ADA formation in repeat-dose toxicity studies in monkeys. The ADAs were detected in all dose groups in both the 4 and 26-weeks studies. The positive ratio of ADA in the serum samples decreased with dose increase, indicating that free drug in the serum interfere the detection of ADA. Decreased in toripalimab exposure and receptor occupancy correlated with the

formation of ADA. There were no ADA-mediated toxicity findings. No immune complex deposits were observed in the kidneys of animals in the 26-week study. Overall, ADA did not greatly affect the interpretation of results.

Relative to other anti PD-1 Abs and a negative control IgG4 anti-KLH, toripalimab does not induce widespread cytokine release by human PBMC when presented either in solution or immobilized forms, across a broad range of concentrations on both resting and activated PBMCs.

A GLP tissue cross reactivity assay was conducted in human tissues only. Adequate controls were included. Toripalimab produced plasma membrane and cytoplasmic staining of mononuclear cells in most human lymphoid tissues and no unexpected tissue cross-reactivity was observed.

The drug substance materials used in the nonclinical studies were different from the final proposed commercial process. The applicant states that toripalimab drug substance batches used in the toxicity studies were 99.0% to 99.9% pure and aggregates ranged from 0.1% to 1.0%. No studies on impurities were performed.

3.5.5. Ecotoxicity/environmental risk assessment

Toripalimab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), toripalimab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

3.5.6. Discussion on non-clinical aspects

Non-clinical data were submitted in accordance with the legal requirements and available guidelines. The animal species and pathology models used were considered as relevant for the intended purposes. The drug substance materials used in the nonclinical studies were manufactured using an earlier process which differed from the final proposed commercial process . A detailed description of all manufacturing process was provided in the dossier. Comparability results demonstrated that all materials from the manufacturing processes were comparable.

GLP. The lack of full TK and ADA validated results in the 26-week study can be superseded by the data of the 4-week GLP study and the clinical data.

Pharmacology. The in vitro primary pharmacodynamic studies conducted with toripalimab essentially focused on the binding properties of this antibody towards the human PD-1 target. Specificity was evidenced by the absence of binding to other Human CD28 Family receptors including CD28, CTLA-4 and ICOS. Those binding studies further confirmed that the monkey but not the rodents is a pharmacologically relevant species for the safety assessment of toripalimab.

Using Elisa and flow cytometry assays the applicant showed that toripalimab prevents the interaction between human PD-1 and its ligands, PD-L1 and PD-L2. Based on the literature data for other anti-PD1 mAbs, the applicant assumed that such an interaction will result in T cell activation, and subsequently will enhance T cell-mediated immune responses against tumours. The capacity of toripalimab to block PD1-PDL1 interaction and modulates T cell activation is shown via three in vitro assays.

Toripalimab did not mediate ADCC nor CDC.

In vivo toripalimab was found to inhibit the growth of a human melanoma cell lines (624Mel) in a Xenograft Tumour NSG mouse model with adoptive CTL transfer and to inhibit the growth of murine

colon MC38 cell line in a human PD-1 Knock-in Mouse. Those tumour models are considered adequate to show efficacy of the therapeutic approach.

Toripalimab is intended to be used in combination only, either with cisplatin and gemcitabine (for the treatment of metastatic or recurrent locally advanced nasopharyngeal carcinoma) or with platinum-based chemotherapy (for the treatment of recurrent or metastatic oesophageal squamous cell carcinoma in combination with platinum-based chemotherapy). In accordance with the Q&A document of the ICHS9 guideline the absence of dedicated non-clinical pharmacology studies with the planned combinations is agreed. A review of the scientific literature involving the combination of PD1 inhibitors with chemotherapy as well as available clinical data is supportive for a therapeutic benefit for the proposed combination.

As a pharmacodynamic readout, toripalimab receptor occupancy (RO) was evaluated as part of the pivotal toxicity studies. Sustained and full receptor occupancy appeared to be found during the dosing and recovery phases of both studies in the mid- and high- dose treated groups. The applicant concluded that the lower receptor occupancy seen in the low dose groups were due to the occurrence of ADAs. Despite high variability of ADA in the low dose group, the overall results confirmed the inverse relationship between toripalimab RO and the presence of ADA. The PK/PD profile of toripalimab in the animals is relevant for the clinic where the trough serum concentration (CtroughSS) leading to complete RO was established at ≥ 35.6 µg/mL Q2W (corresponding to ≥ 3mg/kg).

As ADA presence in cynomolgus monkeys is not predictive to human ADA formation, the uncertainties regarding the non-clinical method for ADA detection in the 26-week study could be overcome by the clinical data. It is considered that for this type of product, the lack of studies for secondary pharmacodynamics are acceptable.

The applicant did not perform dedicated safety pharmacology studies. Since toripalimab is a monoclonal antibody and does not belong to a class of medicinal products expected to cause cardiovascular effects, specific safety pharmacology endpoints were evaluated as part of the pivotal toxicology studies in cynomolgus monkeys. No adverse effects were detected. This is agreed and in line with the ICH guidelines S6(R1), S7A, and S9.

No non-clinical dedicated pharmacodynamic drug interaction studies was conducted with toripalimab, this is acceptable.

Pharmacokinetics. The pharmacokinetics of Toripalimab was assessed in a single and repeat dose PK study, and toxicokinetics in a single dose toxicity study and the two repeat dose toxicity studies (4 and 26 weeks). Exposure was generally dose proportional without any sex difference. ADA formation occurred at all doses without resulting in adverse findings. The presence of ADA reduced Cmax, AUC and receptor occupancy at low doses, whilst animals in the high dose group largely remained exposed to Toripalimab throughout. This correlated with faster clearance at low doses. Overall, ADA did not greatly affect the interpretation of results. ADA negative animals which maintained exposure throughout the study adequately represent the exposure profile of Toripalimab.

The PK profile and ADA formation appear comparable between studies and deemed classical for a mAB. Omission of distribution, biotransformation and excretion studies in this application is in line with ICH guideline requirements and is acceptable.

The applicant did not submit studies on distribution, metabolism and excretion. This is acceptable as in accordance with regulatory guidelines for biotechnology-derived pharmaceuticals (ICH S6), no tissues distribution, metabolism, excretion studies and mass balance are considered necessary.

No dedicated NC toripalimab pharmacokinetic DDI studies were presented. This is justified by the applicant and is acceptable.

Toxicology. A non-GLP single dose toxicology study included one animal per sex per group which limited the interpretation of the data. Overall, toripalimab was well tolerated. A fluctuating increase in glucose and cholesterol was seen in the sole female administered toripalimab including prior to dosing. These variations were not considered biologically relevant, the value being close to the maximal range seen in controls. Furthermore, these findings were not observed in the pivotal repeat dose toxicity studies.

The pivotal 4- and 26-week repeat dose toxicity studies in cynomolgus monkeys showed that toripalimab was well tolerated without adverse findings up to 100 mg/kg administered intravenously weekly or every two weeks. Variation in WBC counts and liver enzymes occurred at several timepoints. Those changes were not dose related and were without microscopic correlates. Therefore, those findings are considered of limited biological relevance.

When comparing the 4 and 26-week studies, opposite changes in testes and epididymides weight were noted in toripalimab treated animals. The Applicant argues that the changes in testis weights -a decrease in testis weight in mid and high dose groups at the end of the dosing period in males in 6-month toxicity study and higher testis weight was observed in the mid-dose groups at the end of the dosing period and in the low-dose group at the end of the recovery period in 4-week toxicity study - are considered to be related to age rather than the test article itself and refers to Rachel Amato's investigation. The Applicant concluded that due to the substantial variability in reproductive system development in monkeys during the age range of 3-5 years, small sample sizes in such studies may result in significant discrepancies.

The exposure levels achieved in the pivotal studies are adequate and result in sufficient safety margins (33.9-49.1 in terms of Cmax and 20-47.8 in terms of AUC) with the anticipated human exposure at the proposed therapeutic dose.

No dedicated reproductive and developmental toxicity studies have been conducted with toripalimab. Instead, the applicant provided a literature assessment, this is accepted and in accordance with ICH S9 and S6(R1). In mice inhibition of the PD-1/PD-L1 axis reduced maternal tolerance which can lead to increased foetal resorption and abortion. Human immunoglobulin G4 (IgG4) is known to cross the placental barrier; therefore, toripalimab can potentially be transmitted from the mother to the developing foetus and cause embryofoetal toxicity when administered to pregnant women. This is reflected in section 4.6 and section 5.3 of the SmPC. Embryotoxicity is also included as an important potential risk in the RMP.

Women of childbearing potential should use effective contraception during treatment with toripalimab and for at least 4 months after the last dose of toripalimab. 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.

It is known that antibodies (including IgG4) are secreted in human milk; a risk to the breast-feeding newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from toripalimab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. 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 of toripalimab.

Fertility studies have not been conducted with toripalimab. In 4-week and 26-week repeat-dose toxicology studies in cynomolgus monkeys, there were no adverse or notable effects in the male and female reproductive organs. However, those animals were unlikely sexually mature.

No studies have been performed to test the potential of toripalimab for carcinogenicity or genotoxicity which is acceptable, in line with ICH S9.

A product-specific waiver for the treatment of all conditions in the category of malignant neoplasms (except CNS, haematopoietic and lymphoid tissue and melanoma) for all subsets of the paediatric population has been approved for toripalimab. Therefore, Juvenile toxicity studies have not been performed.

Several additional toxicity studies were conducted by the applicant. No potential for additional toxicities were identified in the cytokine release assay, tissue cross reactivity assay and immunotoxicity assay.

The drug substance materials used in the nonclinical studies were different from the final proposed commercial process . No studies on impurities were performed. As degradation products do not exceed identification/qualification threshold, toxicity studies on impurities are not needed.

The applicant submitted a justification for not submitting ERA studies. The toripalimab is a natural substance the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, the toripalimab is not expected to pose a risk to the environment.

3.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical package is currently considered adequate to support the MAA of toripalimab.

3.6. Clinical aspects

3.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study	Design	Population	Dose	Primary and Secondary Endpoint	PK Sampling (Number of Patients)
CT1: A Phase 1, Open-label, Single-center, Dose Escalation Study Investigating the Tolerability and Pharmacokinetics of a Single Dose and Multiple Doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in Patients With Advanced Tumors	Dose escalation Cohort expansion	Advanced melanoma or urologic cancer refractory to standard therapy	Escalation: 1, 3, or 10 mg/kg IV Q2W Expansion: 1, 3, and 10 mg/kg IV Q2W	Safety MTD ORR PK Immunogenicity Biomarker analysis	Groups A to C: Intensive sampling; Groups D to F/G to I: Intensive + sparse sampling (N = 36)
CT2: A Phase 1a Clinical Study on the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the Use of a Single Dose and Multiple Doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in Patients With Advanced Solid Tumors	Dose escalation Cohort expansion	Advanced or recurrent solid tumours after failure of ≥1 prior systematic treatment	Escalation: 0.3, 1, 3, or 10 mg/kg IV Q2W Expansion: 1, 3, 10, and 240 mg IV Q2W	Safety MTD ORR Immunogenicity PK	Intensive + sparse sampling (N = 25)

Study	Design	Population	Dose	Primary and Secondary Endpoint	PK Sampling (Number of Patients)
CT3: A Phase 1 Clinical Study on the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of the Use of a Single Dose and Multiple Doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in Patients With Advanced Malignancies	Dose escalation Cohort expansion	Advanced solid tumours or lymphoma refractory to standard therapy	Escalation: 1, 3, or 10 mg/kg IV Q2W Expansion: 1, 3, or 10 mg/kg IV Q2W	Safety Tolerability ORR PK Immunogenicity D-R relationships Biomarker analysis	Cohorts A to C: Intensive sampling; Cohorts D to F: Intensive + sparse sampling (N = 32)
CT4: An Open-label, Multi-center, Single-arm, Phase 2 Clinical Trial Evaluating the Efficacy and Safety of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in Patients With Locally Advanced or Metastatic Melanoma After Failure of Standard Treatment	Single-arm	Locally advanced/metastatic melanoma after failure of standard of care	3 mg/kg IV Q2W	IRC-determined ORR per RECIST Safety ORR per irRECIST Immunogenicity Biomarker analysis	Sparse sampling (N = 128)
CT5: POLARIS-02: A Multi-center, Open-label, Phase 1b/2 Clinical Study to Evaluate Toripalimab (JS001 or TAB001) in Patients With Advanced Gastric Adenocarcinoma, Esophageal Squamous Cell Carcinoma, Nasopharyngeal Carcinoma, or Head and Neck Squamous Cell Carcinoma	Single-arm; multiple disease-specific cohorts	Cohorts 1 to 4 Previously treated, recurrent locally advanced or metastatic gastric cancer, OSCC, NPC, or HNSCC	3 mg/kg IV Q2W	Cohorts 1 to 4: IRC-determined ORR per RECIST v1.1 IRC-determined DoR per RECIST v1.1 Safety Immunogenicity PK	Cohorts 1 to 4 Intensive (N = 9 patients across all 4 cohorts); Sparse sampling (N = 184)
	Single-arm and multiple cohorts	Cohorts 5 to 8 First-line treatment, in combination with standard chemotherapy, of recurrent locally advanced or metastatic gastric cancer, OSCC, NPC, or HNSCC	Toripalimab 240 or 360 mg IV Q3W in combination with: XELOX for Cohort 5 TP for Cohort 6 GC for Cohort 7 TPF for Cohort 8	INV-determined ORR per RECIST INV-determined DoR per RECIST v1.1 Safety Immunogenicity PK	Intensive (N = 18 patients across all 4 cohorts); Sparse sampling (N = 48)
CT6: A Phase 1 Clinical Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in Patients With Relapsed/Refractory Malignant Lymphoma	Dose escalation	Lymphoma refractory to standard therapy	Escalation: 1, 3, or 10 mg/kg IV Q2W	Safety ORR Analysis PK Immunogenicity Biomarker analysis	Intensive + sparse sampling (N = 13)

Study	Design	Population	Dose	Primary and Secondary Endpoint	PK Sampling (Number of Patients)
CT7-1: A Phase 1 Study Investigating the Similarity of the Pharmacokinetics and Safety of a Single Dose and Parallel Comparison of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in Patients With Advanced NSCLC Prior to and After a Manufacturing Process Change	2 parallel cohorts	Advanced NSCLC refractory to standard therapy	3 mg/kg IV Q2W (28 days between the first and second doses)	Bioequivalence PK Safety INV-determined ORR Immunogenicity	Intensive sampling (N = 41)
CT7-2: A Phase I, Single-center, Open-label, Parallel-group Comparison Study to Evaluate Similarity of Fixed Dose of the Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection (JS001) Before and After Manufacturing Process Change (200L vs 500L) in Patients With Advanced Melanoma	2 parallel cohorts	Patients with advanced melanoma	3 mg/kg IV Q2W (28 days between the first and second doses)	Bioequivalence PK Safety INV-determined ORR Immunogenicity	Intensive sampling (N = 26)
CT8: A Randomized, Controlled, Multi-center Phase 2 Clinical Study Comparing Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection with High Dose Interferon as Adjuvant Therapy in the Treatment of Completely Resected Mucosal Melanoma	Randomized study	Resected mucosal melanoma	3 mg/kg IV Q2W	RFS Distant metastasis-free survival 2-year RFS OS	Sparse sampling (N = 82)
CT9: A Phase 1, Open-label, Single-center, Dose Escalation Study to Evaluate the Tolerability and Pharmacokinetics of a Single Dose and Multiple Doses of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection in Advanced Triple Negative Breast Cancer	Dose escalation Cohort expansion	Triple-negative breast cancer refractory to standard therapy	Escalation: 1, 3, and 10 mg/kg IV Q2W Expansion: 3 mg/kg IV Q2W	Safety MTD PK Immunogenicity ORR per RECIST and irRECIST	Intensive + sparse sampling (N = 20)
CT12: An Open-label, Multi-center, Single-arm, Phase II Clinical Trial Evaluating the Efficacy and Safety of Toripalimab Injection (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection, JS001) in Patients With Locally Advanced or Metastatic Bladder Urothelial Carcinoma After Failure of Standard Treatment	Single-arm	Locally advanced or metastatic urothelial cancer after ≥1 prior therapy	3 mg/kg IV Q2W	IRC-determined ORR by RECIST v1.1 IRC-determined DoR Safety Immunogenicity PK Biomarker analysis	Intensive + sparse sampling (N = 151)
CT14: A Phase Ib Clinical Trial Evaluating the Safety and Efficacy of Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection	Single-arm	NET after ≥1 prior therapy	3 mg/kg IV Q2W	Safety IRC-ORR IRC-DoR per RECIST	Sparse sampling (N = 40)

Study	Design	Population	Dose	Primary and Secondary Endpoint	PK Sampling (Number of Patients)
in Patients With Advanced Neuroendocrine Tumors After Failure of Standard Treatment				INV-assessed ORR and DoR per RECIST INV-assessed ORR and DoR per irRECIST PK Immunogenicity Biomarker analysis	
CT15: Phase III Randomized, Double Blind Study, Placebo-controlled, and Multi-center Study Comparing Toripalimab Combined With Chemotherapy Versus Placebo Combined With Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer	Randomized (1:1), double-blind, placebo-controlled, multicentre, and multinational study	First-line treatment of patients with recurrent or metastatic NPC	Toripalimab 240 mg or placebo Q3W IV × 6 cycles Gemcitabine 1000 mg/m^2 D1 Q3W× 6 cycles Cisplatin 80 mg/m^2 IV D1 Q3W× 6 cycles Toripalimab 240 mg or placebo Q3W IV alone for up to 2 years	Primary: PFS by IRC per RECIST v1.1 Secondary: OS, PFS by INV per RECIST v1.1, ORR, DCR and DoR by IRC and INV per RECIST v1.1 PFS and OS rate and 1 and 2 years PROs Safety Immunogenicity PK	Sparse sampling (N = 94)
CT21: A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center Study to Compare Toripalimab (JS001, TAB001) Combined With Standard Chemotherapy With Placebo Combined With Standard Chemotherapy in the Treatment of Advanced or Metastatic Esophageal Squamous Cell Cancer Without Previous Systemic Chemotherapy	Randomized (1:1), double-blind study comparing toripalimab + TP vs placebo + TP	Patients with advanced or metastatic OSCC who have not received systemic chemotherapy previously	Toripalimab 240 mg or placebo Q3W IV × 6 cycles Paclitaxel 175 mg/m^2 Q3W IV × 6 cycles Cisplatin 75 mg/m^2 Q3W IV × 6 cycles Toripalimab 240 mg or placebo Q3W IV alone for up to 2 years	Co-primary: PFS by BICR per RECIST v1.1 and OS Secondary: ORR, DoR, DCR, and TTR by BICR and INV per RECIST v1.1 PFS by INV per RECIST v1.1 PFS, ORR, DoR, DCR, and TTR by BICR and INV by iRECIST PFS and OS rate and 1 and 2 years PRos Safety	Sparse sampling (N = 256)
TAB001-01: A Phase 1, Multicenter, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of	Dose escalation Dose expansion	Advanced solid tumours refractory to standard therapy	Escalation: 80, 240, or 480 mg IV Q2W Expansion: 240 mg IV Q3W	Safety MTD PK ORR per RECIST	Dose escalation/ expansion: Intensive + sparse sampling (N = 184)

Study	Design	Population	Dose	Primary and Secondary Endpoint	PK Sampling (Number of Patients)
TAB001 in Patients With Advanced Malignancies		EC, gastric cancer, NET, soft tissue sarcomas, NPC, HCC, CC, and other solid tumours after ≥1 prior therapy or if intolerant to standard therapy		ORR per irRECIST Immunogenicity	

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
JS001-015-III-NPC (JUPITER-02)	35 centres in China, Taiwan, Singapore	Randomized, placebo-controlled, multi-centre, double-blind, phase 3 study	Toripalimab Arm: Induction period: Toripalimab 240 mg Day 1, gemcitabine 1000 mg/m2 on Days1 and 8, and Cisplatin 80 mg/m2 on Day 1 intravenously (IV) every 3 weeks (Q3W) for up to 6 cycles Maintenance period: Toripalimab 240 mg IV Q3W Placebo Arm: Induction period: Placebo on Day 1, gemcitabine 1000 mg/m2 on Days 1 and 8, and Cisplatin 80 mg/m2 on Day 1 IV Q3W for up to 6 cycles Maintenance period: Placebo IV Q3W	Efficacy, safety	289 induction phase: Toripalimab + chemotherapy 146, Placebo + chemotherapy 143 232 maintenance phase: toripalimab arm 114, placebo arm 118	18 October 2018 to 08 May 2022 (Cut-off Date)	The median age was 45.55 years (range: 18.9 to 72.2 years) in the toripalimab group and 50.7 years (range: 21.3 to 71.8 years) in the placebo group. Toripalimab group: 124 (84.9) male and 22 (15.1%) female Placebo group: 116 (81.1%) male and 27 (18.9%) female	Patients with diagnosed **NPC** (histologically or cytologically confirmed), metastatic (stage IVB) at diagnosis or had recurrent after treatment with curative intent, which was not amenable for local regional treatment or curative treatment	BIRC-assessed PFS (months) according to RECIST v1.1.: Toripalimab: 21.4 (95% CI: 11.73, NE) Placebo: -8.2 (95% CI: -7.03, 9.79)
POLARIS-02 JS001-1b-CRP-1.0 CT5	18 centres in China	Single-arm, multi-cohort, multi-centre, open label, phase Ib/II basket trial	Cohort 3 Toripalimab 3 mg/kg IV Q2W	Efficacy, safety	Cohort 3 190 enrolled, 124 completed at the cut-off date	Cohort 3 22 December 2016 to 19 February 2020 (Cut-off Date)	Cohort 3 The median age was 45.0 years (range: 22 to 68 years) 158 (83.2%) male and 32 (16.8%) female	Cohort 3 Patients with diagnosed NPC (histologically or cytologically confirmed), metastatic or/and advanced, who received at least two	Cohort 3 ORR of tumour based on RECIST v1.1: Per IRC assessment, ORR was 19.8% (95% CI: 14.0%, 26.6%), per investigators

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
								prior lines of treatment for advanced NPC with disease progression or who were intolerant existing treatment regimens	assessment, ORR was 19.2% (95% CI: 13.5%, 26.0%) in the BTDAS Per IRC assessment, ORR was 20.9% (95% CI: 15.1%, 27.8%), per investigators' assessment, ORR was 20.9% (95% CI: 15.1%, 27.8%) in the PTAS
	4 centres in China	Multi-centre, open-label, phase Ib/II	Cohort 7 Toripalimab 240/360 mg IV Q3W1 Cisplatin 80 mg/m2 IV Q3W Gemcitabine 1000 mg/m2 IV Days 1, 8 Q3W up to 6 cycles		Cohort 7 12 enrolled	Cohort 7 04 December 2017 to 19 February 2020	Cohort 7 The median age was 46 years (range: 30 to 55 years) 10 (83.3%) male, 2 (16.7%) female	Cohort 7 Patients with diagnosed NPC (histologically or cytologically confirmed) who have not received any systemic treatment	Cohort 7 ORR of tumour based on RECIST v1.1: per investigators assessment ORR was 75.0% (9/12, 95% CI: 42.8%, 94.5%)

3.6.2. Clinical pharmacology

3.6.2.1. Pharmacokinetics

Clinical pharmacology data in the current submission are derived from 15 clinical studies, including data from 13 clinical studies (CT1, CT2, CT3, CT4, CT5 Cohorts 1 to 4, CT6, CT7-1, CT7-2, CT8, CT9, CT12, CT14, and TAB001-01), designed to investigate the safety, pharmacokinetics (PK), and preliminary antitumour activity of toripalimab as a single agent in various cancers. The submission also contains PK data from Study CT5 Cohorts 5 to 8, which was designed to investigate the safety, PK, and preliminary antitumour activity of toripalimab in combination with platinum-based chemotherapy in NPC, OSCC, gastric cancer, and head and neck squamous cell carcinoma (HNSCC), and PK, safety, and efficacy data from Studies CT15 and CT21.

PK assays

The pharmacokinetic analyses for all studies except TAB001-01 were performed using the MSD electrochemiluminescence technology. Method S5403HuSeAP "Analytical Procedure of an MSD Method for Determination of JS001 in Human Serum" was used throughout the course of the program, except for Study TAB001-01, which employed ELISA methodology. Three amendments/revisions (AMD I, II, III) were made to the validation report (S5403PKHu/S5403PKHuVR).

Method validation report S5403PKHu (quantification of toripalimab serum levels)

The MSD assay is designed to quantify toripalimab in human serum. The assay quantitative range is from 2.560 to 2000.000 ng/mL. On the day of analysis, the samples are diluted 5-fold in assay buffer before using.

Calibration standards include a blank ("zero" point), 11 non-zero calibration standards (1.02, 2.56, 5.12, 6.40, 12.8, 32.0, 80.0, 320, 800, 1800 and 2000 ng/mL) and two anchor points (1.02 ng/mL and 2000 ng/mL) which are standards outside of the curve. Quality control samples include three concentration levels (6.00, 100 and 1500 ng/mL).

31 samples were reanalysed due to technical reasons. 2 samples were reanalysed due to inadvertent repeats. No reanalysis for PK reasons.

Incurred sample reanalysis was conducted in Study S5403PKHu. In CT1, incurred sample re-analysis was performed in 90.0% of study samples (101/1128), and 84.2% (85/101) of the samples met the pre-specified criteria (differences of at least 67% of ISR samples must be within the ± 30% range). In CT2, incurred sample re-analysis was performed in 10.9% (50/458) of study samples, and 80% (40/50) of the samples met the pre-specified criteria. ISR is not run in studies CT3-CT4-CT5-CT7-CT8-CT9-CT12 and the results referred to Pharmacokinetic Report of Study S5403PKHu (S5403PKHuCSR01 and S5403PKHuCSR02) with ISR data from previous studies.

The results of inter- and intra-accuracy and precision met the acceptance criteria for the calibration standard samples and for the quality control samples. When compared with original values, the differences of 60 (92.3%) samples were ± 30%, which met the acceptance criteria.

No “hook” effect was observed in the range of 200.000 to 200,000.000 ng/mL. Different dilution factors (2000, 500, 100, 20, and 5) did not affect the accuracy of the assay. Sensitivity, selectivity and parallelism are correctly described.

Stability tests showed that toripalimab was stable in human serum for 24 hrs or for 4 hrs post-MRD pretreatment at room temperature. The samples were stable after 5 freeze-thaw cycles. The long-term stability showed that toripalimab was stable for 9 months at -60 ~ -90°C.

Overall, the methods are considered to have been validated in accordance with the valid EMA Guideline on bioanalytical method validation.

ELISA method validation for study TAB001-01 (2352-13514)

The validation evaluated the following validation parameters: accuracy and precision, selectivity, specificity, dilutional linearity, hook (prozone) effect and analyte stability.

The standard curve range is from 1000 ng/mL to 7.81 ng/mL with a quantitation range from 1000 ng/mL to 15.6 ng/mL (LLOQ).

The results of inter- and intra-accuracy and precision met the acceptance criteria for the calibration standard samples and for the quality control samples. Of note, three of the runs (3, 4 and 15) performed by analyst 2 (JA) failed to meet intra-assay accuracy. It appears the root cause for the positive bias is likely a technical error on the part of analyst 2 during the fresh standard curve preparation; and not due to poor method performance. The justification is judged reasonable. Results from runs 13 and 14 failed due to technical error, where TAB003 drug was used to prepare the standard curve instead of TAB001.

Sensitivity, selectivity and parallelism are correctly described.

No hook effect was observed for analyte concentrations up to 6000,000 ng/mL. Dilutional linearity was acceptable for dilutions up to 1:96,000 before the MRD.

Stability tests showed that toripalimab was stable in matrix (bench top and 5°C, 21 hours). The samples were stable after 6 freeze-thaw cycles. The long-term frozen matrix stability showed that toripalimab was stable for 30 months at -80°C (addendum).

Possible reasons for reanalysis of study samples and criteria to select the value to be reported are predefined in the table on method summary and acceptance criteria in the method report 2352-13514.

Immunogenicity assays

A tiered-based assay approach was used, involving a screening assay and a confirmatory assay. Samples that were positive in the screening assay were taken forward to a confirmatory assay (by competitive inhibiton format). Titer values were only determined in later clinical studies, including TAB001, CT15, CT21 studies (not for CT5 cohorts 5-8 study). All assays (screening, confirmatory, and titer assays) used the same assay format. All ADA-positive samples from CT5 and CT15 studies have been analysed for neutralizing capacity (Nabs). All ADA-positive samples from CT21 study also were analysed for NAbs.

Methods S5403ADAHuSeAP01 and MTD081V

Anti-drug antibodies (ADAs) to toripalimab in human serum were determined using a validated solution ligand binding assay based on MSD platform. The same ADA assay methodology was validated at 2 contract research organisations (CROs): United Power Pharma Tech Co., Ltd (UP Pharma [UPP]) in China and the laboratory Smithers Pharmaceutical Development Services (Smithers) in Gaithersburg, MD, US. The methods at the 2 CROs are S5403ADAHuSeAP01 (UPP) and Method MTD081V (Smithers). S5403ADAHuSeAP01 was transferred to Smithers to enable the local analysis of ADA samples collected from TAB001-01 (completed in the US).

The validation of Method S5403ADAHuSeAP01 (report S5403ADAHuSeVR) and study analyses associated with this procedure were performed by UPP in China. Validation parameters assessed include assay precision and robustness, assay range and hook effect (no hook effect up to 100 µg/mL PC), sensitivity (1.6 ng/mL), selectivity (in normal serum samples), screening and confirmatory cut point assessment (SCP = 1.05 and CCP = 10.8%; using 54 normal human serum samples, by 2 analysts through 6 analytical runs at different incubation times, dates, plate readers, and batches of acid solution, neutralizing reagent and dilution buffer, after excluding outliers, 5% false positive rate for SCP and 0,1% for CCP), interference and specificity (human Ig G, PD-1 and TNF-α), drug tolerance (screening assay: 20 and 100 ng/mL PC can respectively tolerate 50 and 100 µg/mL of drug), as well as freeze/thaw, benchtop, and long-term stability. Robustness regarding changing lots of critical reagents (drug, capture reagent and detection reagent) was also assessed, demonstrating the methodology to be robust with respect to reagent lot changes. The initial validation report was amended to include information on critical reagents and titer validation data. In-study cut points were determined and used for studies CT4, CT5 (SCP: 1.12; from nasopharyngeal carcinoma cohort 7), CT12 and CT21 (SCP: 1.11; CCP: 11.2%; TCP: 1.21) due to either significant difference in S/N values distribution in comparison to healthy subjects or high false positive error rate in pre-dose patient samples.

The validation of Method MTD081V (report No. 2353-13516) and analysis of samples from study TAB001-01 was performed by Smithers Pharmaceuticals Development Services in US using the same positive control lot (purification rabbit anti-TAB001 lot#D2916-QJ56). The validation parameters included screening and confirmatory cut point determination (SCP = 1.64 and CCP = 48.8%; using 50 normal human serum samples analysed over four days by two analysts (12 runs) using two MSD imagers, after excluding outliers, 5% false positive rate for SCP and 1% for CCP), precision, robustness, sensitivity (2.93 ng/mL), selectivity (in normal and cancer samples), drug tolerance (10 and 100 ng/mL PC can respectively tolerate 10 and 50 µg/mL of drug; 250 ng/mL PC in presence of

100 µg/mL of drug in screening assay) and analyte stability (F/T, bench top and refrigerator stability). The in-study cut point was determined using 137 pre-dose samples from study TAB001-01 (SCP: 3.42; TCP: 3.42; excluding outliers, 5% FPR) and usd for study sample analysis. The MRD was 1:10.

A lifecycle management summary for the studies provides the validation summary for both the pre-study and the in-study validations for both methods in module 2.7.1. In addition, the method performance was summarized for each clinical trial (assay passing rate, blank, NC and PC performance).

NAB assay

A neutralizing antibody (NAb) assay was developed and validated by UPP for the detection of NAbs to toripalimab in human serum. A description of the experimental methodology is detailed in the validation report S5403MVHuSe.

In summary, toripalimab NAbs were evaluated in patient sera using an affinity capture elution method-based competitive ligand binding assay technology on the MSD platform.

Absorption
Toripalimab is administered IV [intravenously] and is 100% bioavailable, therefore no bioavailability studies were conducted.

Bioequivalence
Due to a manufacturing process change, a study to evaluate the PK equivalence of toripalimab manufactured before and after this change was conducted following a single IV infusion to patients with advanced tumours. No clinically important differences in PK were found based on the manufacturing process. The pharmacokinetics of toripalimab was not evaluated in healthy volunteers as it was developed primarily for oncology indications.

Studies S5403PKHu12 and S5403PKHu15 (CT7 1&2)

Study design

The study was an open label, parallel control, phase 1 clinical study to assess the PK equivalence of a single dose of toripalimab injection before and after the process change.

Table 3. Summary of CT7-1 and CT7-2 Study Design

Group	Drug Product, Lot#	Dose	Dosing Times	Route	Number of Patients
A (T-2-500 - old process)	JS001, 20161002	3mg/kg	1	IV	32
B (L-2-500 - new process)	JS001, 20161108	3mg/kg	1	IV	32

IV = intravenous

Note: The 32 patients included 19 NSCLC patients and 13 melanoma patients in each group.

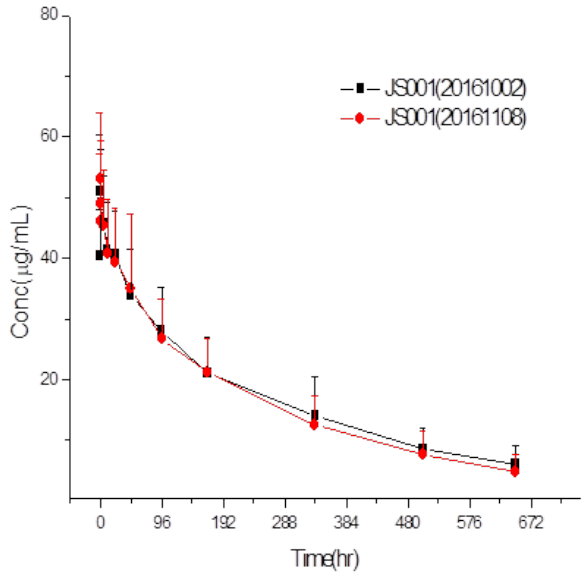
Blood samples for PK assessment were drawn at time: 0 h (within 30 minutes before drug administration), end of infusion (± 5min), 0.5 h (± 5 min), 2 h (± 5 min), 6 h (± 5 min), 12 h (± 5 min), 24 h (± 30 min), 48 h (± 30 min), 96 h (± 30 min), 168 h (± 30 min), 336h (± 30 min), 504 h (± 30 min), and 648 h (± 30 min) after the end of infusion.

Statistical analysis of PK equivalence was based on a PK dataset derived from 64 patients [38 patients with advanced NSCLC (19 patients each in new and old process groups) and 26 patients with advanced melanoma (13 patients each in new and old process groups)].

Study Results

Serum Concentrations:

Figure 1. Toripalimab Concentration-time Profile (mean ± SD) Following a Single 3 mg/kg IV Infusion to Patients with NSCLC or Advanced Melanoma



IV: intravenous; NSCLC: non-small cell lung cancer; SD: standard deviation

Serum concentrations of toripalimab declined slowly over time and measurable drug concentrations were observed till Day 27 following a single IV dose. The concentration-time profiles of two manufacturing processes were superimposable, indicating the PK comparability of these two processes.

Pharmacokinetic Analysis:

The PK parameters were estimated by non-compartmental analysis and are presented in Table 8. The PK parameters such as $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max} and clearance were comparable between two processes. The 90% CI on $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max} is presented in Table 9.

Table 4. Mean (SD) PK Parameters of Two Manufacturing Processes of Toripalimab Following a Single 3 mg/kg IV Infusion

PK Parameters	Units	Group A (old process)	Group B (new process)
		Mean ± SD (n=29)	Mean ± SD (n=27)
$t_{1/2}$	hr	254.9±83.85	216.56±81.53
#T_{max}	hr	0.00-6.00	0.00-6.00
C_{max}	μg/ml	52.33±8.63	56.04±9.73
$AUC_{(0-t)}$	hr*μg/ml	11175.62±3044.86	10719.97±2798.25
$AUC_{(0-inf)}$	hr*μg/ml	13678.72±4316.53	12486.24±3930.04
$AUC_{(t-inf)\%}$	%	16.85±8.47	12.62±7.34
Vd	ml/kg	84.22±24.39	76.64±26.23
Cl	ml/hr/kg	0.24±0.08	0.26±0.09
MRT_{inf}	hr	357.15±109.62	304.79±95.84

AUC = area under the serum curve; Cl = clearance; C_{max} = maximum serum concentration; IV = intravenous; MRT = mean residence time; PK = pharmacokinetic; SD = standard deviation; t½ = elimination half-life; T_{max} = time to reach maximum serum concentration; Vd = volume of distribution
Note: # indicated the range of individual T_{max}.

Table 5. 90% CI on the PK Parameters of Two Manufacturing Processes for Toripalimab

PK Parameters	JS001 old process		JS001 new process		Geometric mean ratio	90% CI
	n	Geometric mean	n	Geometric mean		
$AUC_{(0-t)}$	29	10783.0	27	10361.9	0.961	0.851 – 1.085
$AUC_{(0-inf)}$	29	13037.2	27	11900.1	0.913	0.792 – 1.053
C_{max}	32	52.2	32	54.4	1.043	0.963 – 1.130

AUC = area under the plasma curve; CI = confidence interval; C_{max} = maximum plasma concentration; n = number; PK = pharmacokinetic

The 90% CI on $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} in indicates the two toripalimab processes produce materials that are pharmacokinetically comparable. Bioequivalence is demonstrated between the toripalimab old process and toripalimab new process with respect to rate and extent of absorption. The 90% CIs around the point estimate are in the acceptance range of 80-125% (except 90% CI of AUC-inf with a lower limit of 79%, which is not judged clinically relevant).

The manufacturing process history is discussed along with the comparability assessment of the proposed commercial process versus historical manufacturing processes in module 3, in section 3.2.S.2.6.

Distribution

Toripalimab is primarily distributed in the plasma with a geometric mean volume of distribution at steady state of approximately 3.7 L (CV=27%). Because toripalimab is an antibody, protein binding studies were not conducted which is accepted.

Elimination

Toripalimab pharmacokinetics followed a 2-compartment model with time-varying clearance (CL). The mean CL was 14.9 mL/h (CV = 31%) after the first dose and 9.5 mL/h (CV = 36%) at steady state. Given the time-varying clearance, elimination was measured using washout (approximating 5 half-lives). At steady state, the median washout time was 4.9 months with toripalimab administered at 240 mg Q3W (Statement in the proposed SmPC). Specific metabolism studies were not conducted because toripalimab is a protein. Toripalimab is expected to be degraded into small peptides and individual amino acids by circulating phagocytic cells or by their target antigen-containing cells. Neither hepatic metabolism nor renal excretion are considered as major elimination routes. Accordingly, no active metabolites are expected.

Excretion

Based on the metabolic pathway of monoclonal antibodies, which are primarily eliminated by protein catabolism, and given that limited renal excretion is not expected due to the molecular weight of mAbs, formal organ impairment studies were not conducted and are not planned; this approach is consistent with current guidance (CPMP/EWP/2339/02, 2005; EMA/CHMP/83874/ 2014, 2015). The effects of liver dysfunction or renal dysfunction on the PK of toripalimab were analysed as covariates in the popPK model.

Metabolism

No studies were conducted on metabolism.

3.6.2.2. PK in target population

The pharmacokinetics of toripalimab was not evaluated in healthy volunteers as it was developed primarily for oncology indications.

Study S5403PKHu (CT1)

This was a single centre, Phase 1, open-label, dose - escalation study to evaluate the PK of toripalimab following up to 6 IV infusions in 36 patients with advanced solid tumours with advanced solid tumours. The patients received toripalimab at doses of 1, 3, or 10 mg/kg as IV infusions over 1 hour. Patients who received a single dose in Cohorts A to C, followed by a 28-day washout period, were allowed to receive multiple doses in Cohorts D to F if they met the eligibility criteria; multiple doses were administered Q2W.

Table 6. Summary of CT1 Study Design

Cohorts	Drug Product	Dose	Number of Doses	Route	Number of Patients
A	toripalimab	1 mg/kg	1	IV	3
B	toripalimab	3 mg/kg	1	IV	4
C	toripalimab	10 mg/kg	1	IV	3
D	toripalimab	1 mg/kg	8	IV Q2W	3
E	toripalimab	3 mg/kg	8	IV Q2W	4
F	toripalimab	10 mg/kg	8	IV Q2W	3
G[1)]	toripalimab	1 mg/kg	8	IV Q2W	12
H[1]	toripalimab	3 mg/kg	8	IV Q2W	11
I[1]	toripalimab	10 mg/kg	8	IV Q2W	3

[1] Dose expansion cohort
IV: intravenous; Q2W: every 2 weeks
Note: Cohorts D, E, and F shared patients with Cohorts A, B, and C. Patients in Groups D, E, and F received multiple doses Q2W beginning 28 days after the single administration of toripalimab in Groups A, B, and C.

Blood samples for PK study were drawn as follows:

Cohorts A to C: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96 (Day 4), 168 (Day 7), 336 (Day 14), 504 (Day 21), and 648 hours (Day 27) after the end of infusion.

Cohorts D to F: After the end of the single dose washout period, patients initiated the multiple doses period with the first dose in the multiple dosing period set as Day 29. The following are dosing time plus dosing interval.

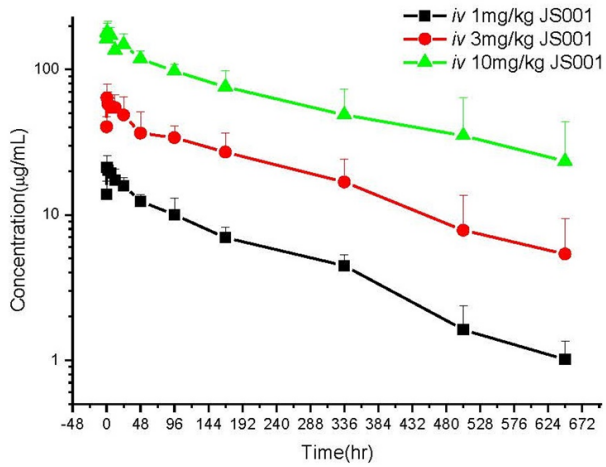
The 1st administration: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion. The 2nd, 3rd, 4th, 5th, 6th, and 8th administrations: 0 hours (within 30 minutes before drug administration) and 0.5 hours after the end of infusion. The 7th administration: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion.

Cohorts G to I: The 1st administration: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion. The 2nd, 3rd, 4th, 5th, 6th, and 8th administrations: 0 hours (within 30 minutes before drug administration) and 0.5 hours after the end of infusion. The 7th administration: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion.

Results

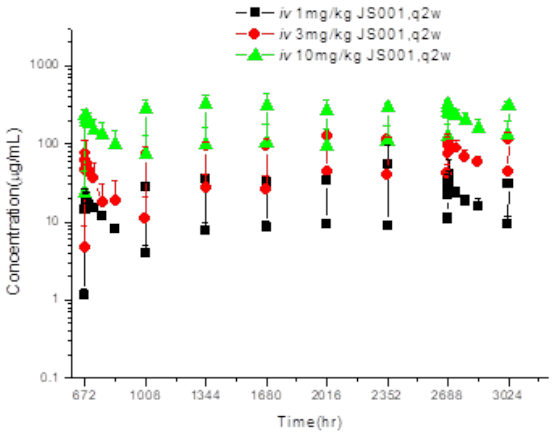
Serum concentration-time profiles of toripalimab following a single dose and following multiple doses (Q2W for 8 weeks) administered as a 1-hour IV infusion.

Figure 2. Toripalimab Concentration-Time Profile (Mean ± SD) Over 28 Days Following a Single IV Infusion to Patients With Solid Tumours (Cohorts A, B, and C) in Study CT1



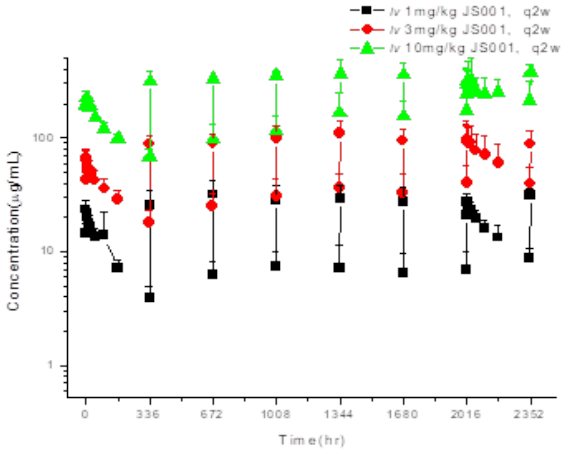
IV: intravenous; SD: standard deviation

Figure 3. Toripalimab Concentration-Time Profile (Mean ± SD) Following Multiple IV Infusions to Patients With Solid Tumours (Cohorts D, E, and F) in Study CT1



IV: intravenous; Q2W: every 2 weeks; SD: standard deviation
Note: Cohort D, E, and F shared patients with Cohorts A, B, and C. Patients in Groups D, E, and F received multiple doses Q2W beginning 28 days after the single administration of toripalimab in Groups A, B, and C.

Figure 4. Toripalimab Concentration-Time Profile (Mean ± SD) Following Multiple IV Infusions to Patients With Solid Tumours in the Expansion Phase (Cohorts G, H, and I) in Study CT1



IV: intravenous; Q2W: every 2 weeks; SD: standard deviation

Table 7. Mean (SD) PK Parameters of Toripalimab Following a Single IV Infusion (Cohorts A to C) in Study CT1

PK Parameters	Units	1 mg/kg	3 mg/kg	10 mg/kg
Number of patients		**(n = 3)**	**(n = 4)**	**(n = 3)**
T_{max}[1)]	h	0.5-2.0	0.5-6.0	0.5-6.0
C_{max}	μg/mL	22.1 ± 3.9	65.6 ± 14.4	183 ± 30.7
$AUC_{(0\text{-}inf)}$	h•μg/mL	3800 ± 658	14600 ± 4870	52900 ± 26600
$AUC_{(t\text{-}inf)\%}$	%	5.59 ± 1.47	10.1 ± 8.02	18.4 ± 17.5
$t_{½}$	h	147 ± 6.50	171 ± 88.7	276 ± 182
CL	mL/h/kg	0.27 ± 0.05	0.22 ± 0.08	0.24 ± 0.15

[1] Range reported
$AUC_{(0\text{-}inf)}$: area under the curve from 0 to infinity; $AUC_{(t\text{-}inf)\%}$: % AUC extrapolated from time t to infinity; CL: clearance: C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half life; T_{max}: time to reach maximum serum concentration
Note: PK parameters are reported to 3 significant figures where appropriate.

Table 8. Mean (SD) PK Parameters of Toripalimab in Cohorts D to F in Study CT1

PK Parameters	Units	1 mg/kg	3 mg/kg	10 mg/kg
First day of multiple dosing		**(n = 3)**	**(n = 3)**	**(n = 3)**
T_{max}[1)]	h	0.5-6.0	0.5-2.0	0.5-2.0
C_{max}	μg/mL	21.9 ± 5.12	85.4 ± 36.1	232 ± 45.2
$AUC_{(0\text{-}t)}$	h•μg/mL	3260 ± 320	8840 ± 3670	36200 ± 17100
$t_{½}$	h	150 ± 30.9	185 ± 84.9	236 ± 98.5
7th dose (Day 113)		**(n = 3)**	**(n = 2)**	**(n = 2)**
T_{max}[1]	h	0.5-6.0	0.5	0.0
C_{max}	μg/mL	47.1 ± 17.0	105 ± 32.7	324 ± 42.0
$AUC_{(0\text{-}t)}$	h•μg/mL	5680 ± 1290	19800 ± 3970	56300 ± 16800
C_{min}	μg/mL	11.0 ± 1.98	39.6 ± 7.54	127 ± 55.7
C_{avg}	μg/mL	16.9 ± 3.82	61.8 ± 12.0	176 ± 54.2
$AUC_{(0\text{-}tau)}$	h•μg/mL	5680 ± 1280	20800 ± 4030	59300 ± 18200
$t_{½}$	h	229 ± 47.4	395 ± 186	334 ± 132

PK Parameters	Units	1 mg/kg	3 mg/kg	10 mg/kg
AR		1.57 ± 0.19	2.25 ± 0.77	2.00 ± 0.54

[1] Range reported
AR: accumulation ratio calculated per the formula $\frac{1}{1-e^{-k\times Tau}}$; AUC: area under the curve; $AUC_{(0\text{-}t)}$: area under the curve from time 0 to t; $AUC_{(0\ tau)}$: area under the curve over dosing interval; C_{avg}: average serum concentration calculated per the formula $AUC_{(0\text{-}tau)}$/Tau; C_{max}: maximum serum concentration; C_{min}: minimum serum concentration; n: number of patients; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half life; T_{max}: time to reach maximum serum concentration.
Note: Cohort D, E, and F shared patients with Cohorts A, B, and C. Patients in Groups D, E, and F received multiple doses every 2 weeks beginning 28 days after the single administration of toripalimab in Groups A, B, and C.
AR is reported to 2 decimal places. All other PK parameters are reported to 3 significant figures where appropriate.

Table 9. Mean (SD) PK Parameters of Toripalimab Following the First Infusion and Following Multiple IV Infusions (Cohorts G to I) in Study CT1

PK Parameters	Units	1 mg/kg	3 mg/kg	10 mg/kg
First dose		**(n = 12)**	**(n = 11)**	**(n = 3)**
T_{max}[1)]	h	0.5-96	0.5-2.0	0.5-2.0
C_{max}	µg/mL	25.7 ± 6.06	67.6 ± 14.7	228 ± 24.7
$AUC_{(0\text{-}t)}$	h•µg/mL	3170 ± 580	10900 ± 2570	36100 ± 4260
$t_{½}$	h	153 ± 23.9	247 ± 50.7	237 ± 56.2
7th dose (Day 85)		**(n = 9)**	**(n = 8)**	**(n = 2)**
T_{max}	h	0.5-12.0	0.0-0.5	2.0-24.0
C_{max}	µg/mL	27.9 ± 5.47	107 ± 38.1	353 ± 138
$AUC_{(0\text{-}t)}$	h•µg/mL	4290 ± 1710	19700 ± 8510	91500 ± 49100
C_{min}	µg/mL	8.93 ± 4.40	37.8 ± 17.5	174 ± 95.6
$AUC_{(0\text{-}tau)}$	h•µg/mL	4810 ± 946	20700 ± 8580	82800 ± 31900
$t_{½}$	h	246 ± 50.6	286 ± 105	1690 ± 1160
AR		1.64 ± 0.20	1.80 ± 0.43	7.77 ± 4.99

[1] Range reported
AR: accumulation ratio calculated per the formula $\frac{1}{1-e^{-k\times Tau}}$; AUC: area under the curve; $AUC_{(0\text{-}t)}$: area under the curve from time 0 to t; $AUC_{(0\ tau)}$: area under the curve over dosing interval; C_{max}: maximum serum concentration; C_{min}: minimum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half-life; T_{max}: time to reach maximum serum concentration.
Note: PK parameters are reported to 3 significant figures where appropriate.

Study S5403PKHu (CT2)

This was a Phase 1a, dose - escalation study to determine the safety and PK of toripalimab following a single infusion with a 56 day washout period or following up to 6 multiple IV infusions in 25 healthy volunteers. Patients received 0.3, 1, 3, 10 mg/kg, or 240 mg (fixed dose) of toripalimab as IV infusions over 1 hour Q2W.

Table 10. Summary of CT2 Study Design

Cohorts	Drug Product	Dose	Number of Doses	Route	Number of Patients
A	toripalimab	0.3 mg/kg	6	IV Q2W	3
B	toripalimab	1 mg/kg	6	IV Q2W	7

Cohorts	Drug Product	Dose	Number of Doses	Route	Number of Patients
C	toripalimab	3 mg/kg	6	IV Q2W	6
D	toripalimab	10 mg/kg	6	IV Q2W	6
E	toripalimab	240 mg	6	IV Q2W	3

IV: intravenous; Q2W: every 2 weeks

Blood samples for PK study were drawn as follows:

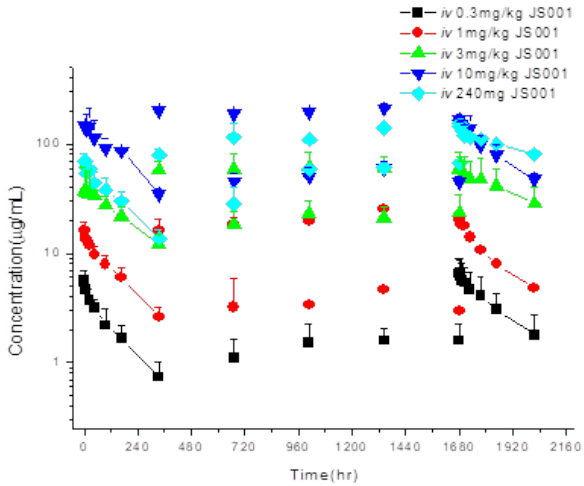
Cohort A: The 1st administration: 0 hours (within 30 minutes before drug administration) and 1, 2, 4, 8, 24, 48, 96, and 168 hours after the end of infusion. The 2nd, 3rd, 4th, and 5th administrations: 0 hours (within 30 minutes before drug administration). The 6th administration: 0 hours (within 30 minutes before drug administration); end of infusion (within 5 minutes); and 2, 6, 12, 24, 48, 96, 168, and 336 hours after the end of infusion.

Cohorts B to E: The 1st administration: 0 hours (within 30 minutes before drug administration); end of infusion (within 5 minutes); and 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion. The 2nd, 3rd, 4th, 5th administrations: 0 hours (within 30 minutes before drug administration) and end of infusion (within 5 minutes). The 6th administration: 0 hours (within 30 minutes before drug administration); end of infusion (within 5 minutes); and 2, 6, 12, 24, 48, 96, 168, and 336 hours after the end of infusion.

Concentrations of toripalimab in human serum were determined using a validated MSD-ECL assay. The lower limit of quantitation (LLOQ) was 2.56 ng/mL. PK parameters were estimated from individual concentration-time data by non-compartmental analysis using Phoenix 32 WinNonlin software (v6.4).

Results

Figure 5. Toripalimab Concentration-Time Profile (Mean ± SD) Following Multiple Infusions to Patients With Advanced Solid Tumours in Study CT2



IV: intravenous; SD: standard deviation

The PK parameters were estimated by non-compartmental analysis following the first infusion and following multiple toripalimab infusions and are presented in the table below.

Table 11. Mean (SD) PK Parameters of Toripalimab Following the First and Following Multiple IV Infusions in Study CT2PK

Parameters	Units	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	240 mg
First dose		(n = 3)	(n = 7)	(n = 5)	(n = 6)	(n = 3)

Parameters	Units	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	240 mg
				*(n = 6)		
T_{max}[1)]	h	1-2	0-2	0-96*	0-24.0	0-2
C_{max}	µg/mL	5.77 ± 1.33	16.5 ± 3.44	48.2 ± 18.9*	206 ± 35.8	71.6 ± 8.70
$AUC_{(0-t)}$	h•µg/mL	655 ± 199	2150 ± 408	7720 ± 1470*	34700 ± 6560	11400 ± 5890
t½	h	151 ± 23.9	160 ± 30.1	200 ± 36.2	212 ± 83.6	222 ± 26.9
Last dose (6th dose)		**(n = 2)**	**(n = 1)**	**(n = 4)**	**(n = 4)**	**(n = 1)**
T_{max}	h	0-2	2	0-6	0-2	0
C_{max}	µg/mL	6.58 ± 2.19	20.8	63.5 ± 21.1	258 ± 110	153
$AUC_{(0-t)}$	h•µg/mL	1100 ± 448	3160	13700 ± 6480	49400 ± 24800	34200
$t_{½}$	h	188 ± 4.93	211	338 ± 78.7	331 ± 125	525
AR		1.63 ± 0.002	1.47	1.77 ± 0.787	1.41 ± 0.446	1.92

[1] Range reported

AR: accumulation ratio calculated per the formula $\frac{1}{1-e^{-k\times Tu}}$; AUC: area under the serum curve; $AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; popPK: population PK; SD: standard deviation; t½: elimination half-life; T_{max}: time to reach maximum serum concentration

Notes: Results for 240 mg dose adjusted for body weight using median body weight from patients with evaluable PK of 64 kg (data source popPK).

PK parameters are reported to 3 significant figures where appropriate.

Study S5403PKHu03 (CT3)

This was a Phase 1, dose - escalation study to determine the safety and PK of toripalimab following a single infusion with a 56 day washout period or following up to 6 multiple IV infusions in 33 patients with advanced malignant tumours. Patients received 1, 3, or 10 mg/kg dose of toripalimab as an IV infusion over 1 hour; infusions were administered Q2W.

Table 12. Summary of CT3 Study Design

Cohort	Drug Product	Dose	Number of Doses	Route
A	toripalimab	1 mg/kg	1	IV
B	toripalimab	3 mg/kg	1	IV
C	toripalimab	10 mg/kg	1	IV
D	toripalimab	1 mg/kg	6	IV Q2W
E	toripalimab	3 mg/kg	6	IV Q2W
F	toripalimab	10 mg/kg	6	IV Q2W

IV: intravenous; Q2W: every 2 weeks

Subjects were split into cohorts and received toripalimab as follows:

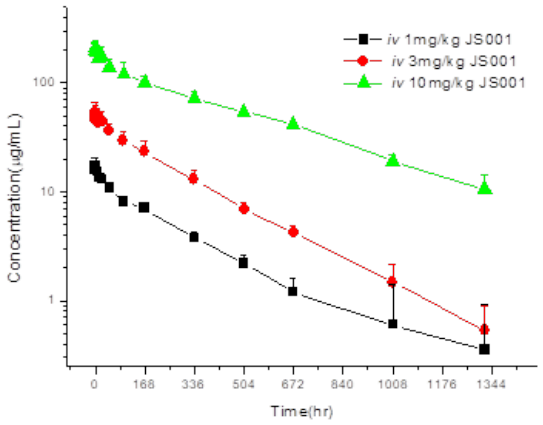
Cohorts A to C: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, 168, 336, 504, 672, 1008, and 1320 hours at the end of the infusion.

Cohorts D to F: The 1st administration: 0 hours (within 30 minutes before drug administration); end of infusion; and 2, 6, 12, 24, 48, 96, and 168 hours post-end of infusion. The 2nd, 3rd, 4th, and 5th administrations: pre-dose. The 6th administration: 0 hours (within 30 minutes before drug administration) and 2, 6, 12, 24, 48, 96, 168, and 336 hours at the end of the infusion.

Concentrations of toripalimab in human serum were determined using a validated MSD-ECL assay. The LLOQ was 2.56 ng/mL. PK parameters of toripalimab were estimated from individual concentration-time data by non-compartmental analysis using Phoenix 32 WinNonlin software (v6.4).

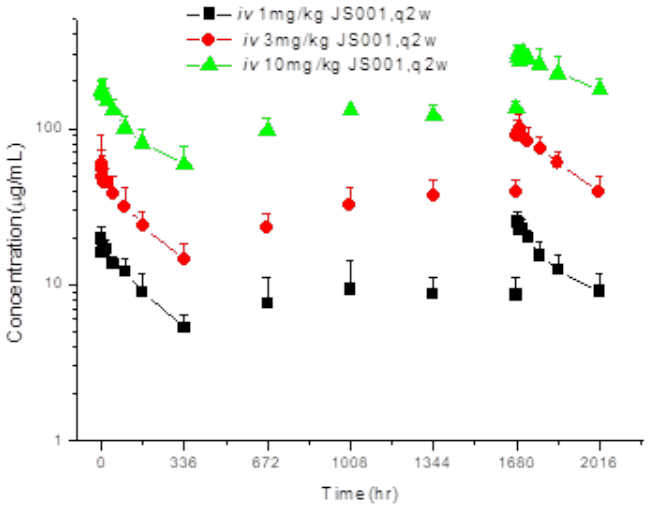
Results

Figure 6. Toripalimab Concentration-Time Profile (Mean ± SD) Following a Single IV Infusion to Patients With Advanced Malignant Tumours (Cohorts A, B, and C) in Study CT3



IV: intravenous; SD: standard deviation

Figure 7. Toripalimab Concentration-Time Profile (Mean ± SD) Following Multiple Infusions to Patients With Advanced Malignant Tumours (Cohorts D, E and F) in Study CT3



IV: intravenous; Q2W: every 2 weeks; SD: standard deviation

Table 13. Mean (SD) PK Parameters of Toripalimab Following a Single IV Infusion in Study CT3

PK Parameters	**Units**	**1 mg/kg**	**3 mg/kg**	**10 mg/kg**
First dose		**(n = 3)**	**(n = 3)**	**(n = 3)**
T_{max}[1)]	h	0.5-2	0.5-6	0-2
C_{max}	μg/mL	17.9 ± 2.58	54.0 ± 13.0	211 ± 32.0
$AUC_{(0\text{-}inf)}$	h•μg/mL	3940 ± 976	12600 ± 2590	75800 ± 4370
$AUC_{(t\text{-}inf)\%}$	%	0.05 (0.02, 9.77)[2]	1.22 ± 1.02	7.49 ± 4.85

PK Parameters	Units	1 mg/kg	3 mg/kg	10 mg/kg
$t_{½}$	h	185 ± 129	193 ± 52.2	340 ± 98.2
CL	mL/h/kg	0.26 ± 0.06	0.25 ± 0.06	0.13 ± 0.01

[1] Range reported
[2] Reported as the median as the coefficient of variation exceeded 100%.

$AUC_{(0\text{-}inf)}$: area under the curve from 0 to infinity; $AUC_{(t\text{-}inf)\%}$: % AUC extrapolated from time t to infinity; CL: clearance; C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; SD: standard deviation; t½: elimination half life; T_{max}: time to reach maximum serum concentration.
Note: PK parameters are reported to 3 significant figures where appropriate.

Table 14. Mean (SD) PK Parameters of Toripalimab Following the First and Following Multiple IV Infusions in Study CT3

PK Parameters	Units	1 mg/kg	3 mg/kg	10 mg/kg
First dose (Day 1)		**(n = 4)**	**(n = 15)**	**(n = 4)**
T_{max}[1)]	h	2-2.1	0-48	0-12
C_{max}	µg/mL	19.6 ± 4.07	72.5 ± 31.9	200 ± 17.6
$AUC_{(0\text{-}t)}$	h•µg/mL	3330 ± 680	10800 ± 3970	31700 ± 5070
$t_{½}$	h	190 ± 11.7	218 ± 69.8	343 ± 104
6th dose (~Day 71)		**(n = 3)**	**(n = 14)**	**(n = 3)**
T_{max}[1]	h	2-6	2-48	2-24
C_{max}	µg/mL	25.5 ± 4.51	92.3 ± 23.7	375 ± 98.7
$AUC_{(0\text{-}t)}$	h•µg/mL	4700 ± 925	18400 ± 4410	87300 ± 19200
$AUC_{(0\text{-}tau)}$	h•µg/mL	4700 ± 922	18400 ± 4410	87100 ± 19200
$t_{½}$	h	256 ± 8.93	290 ± 64.1	482 ± 93.2
AR		1.67 ± 0.04	1.81 ± 0.26	2.61 ± 0.39

[1] Range reported

AR: accumulation ratio based on AUC; AUC: area under the curve; $AUC_{(0\text{-}t)}$: area under the curve from time 0 to t; $AUC_{(0\ tau)}$: area under the curve over dosing interval; C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half life; T_{max}: time to reach maximum serum concentration
Note: PK parameters are reported to 3 significant figures where appropriate

Study CT4

CT4 was a single arm, open-label, Phase 2 trial conducted for detection of the occurrence of ADA, to evaluate the effect of production of the antidrug antibody on the efficacy, safety and pharmacokinetics of the study drug in patients with locally advanced or metastatic melanoma.

In the study, ADA samples were collected prior to administration of the 1st dose and within 30 minutes prior to administration (0 hour) every 4 weeks afterwards, until the end of observational period when ADA/pharmacokinetics was to be detected. 4 mL serum sample was collected prior to the first dose and prior to administration every 4 weeks afterwards from each patient to assess the possibility of anti-drug antibody (ADA) formation to explain immunogenic result.

Results

Results of anti-drug antibodies (ADA) was summarized in the following table.

Table 15. ADA results (study CT4)

Clinical Site No.	01	02	03	04	06	07
Number of samples	759	90	16	34	23	39
Number of Individuals	98	12	3	4	4	7
Number of positive samples	22	5	0	0	1	0
Number of positive individuals	19	3	0	0	1	0
Sample positive rate	2.9%	5.6%	0.0%	0.0%	4.3%	0.0%
Individual positive rate	19.4%	25.0%	0.0%	0.0%	25.0%	0.0%
Total sample positive rate	2.9%					
Total individual positive rate	18.0%					

Note: Therapeutic protein can potentially induce Anti-Drug Antibody in patients. The Anti-Drug Antibody result is highly dependent on sample collection, sampling time, patient status as well as the type, sensitivity, specificity of the analytical method. Therefore, it was inappropriate to compare directly these study results with other therapeutic proteins, otherwise it might be misleading.

As shown in the table above, positive ADA was detected in 23 patients out of a total 128 patients administered with 3mg/kg JS001. The individual ADA positive rate was 18.0%.

Study S5403PKHu04 (CT5/Cohorts 1 to 4)

This was a multi-centre, open label Phase 1b/2, study to determine the PK characteristics of toripalimab in 184 patients with advanced gastric adenocarcinoma, OSCC, NPC, or HNSCC. Toripalimab was administered to patients at a dose of 3 mg/kg Q2W for 6 doses. There were 9 patients included in the intensive PK analysis subgroup for this study.

Table 16. Summary of the PK Study Design for CT5 (Cohorts 1 to 4)

Group	**Drug Product**	**Dose**	**Dosing Frequency**	**Route**	**Number of Patients**
1	toripalimab	3 mg/kg	Q2W	IV	9

IV: intravenous; Q2W: every 2 weeks

Blood Sampling: Blood samples for PK study were drawn as follows: the 1st dose: pre-dose; end of infusion; and 2, 6, 12, 24, 48, 96, and 168 hours post-end of infusion; the 2nd, 3rd, 4th, 5th doses: pre-dose and end of infusion; and the 6th dose: pre-dose; end of infusion; and 2, 6, 12, 24, 48, 96, 168, and 336 hours post-end of infusion of.

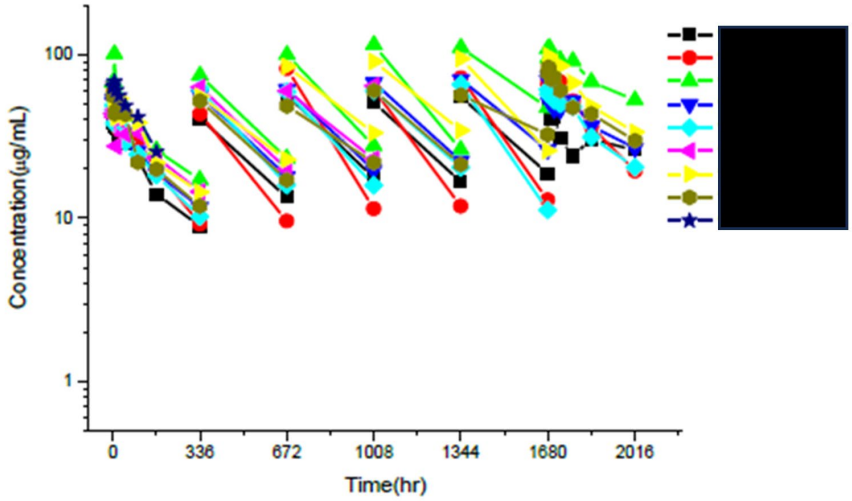
Concentrations of toripalimab in human serum were determined using a validated MSD-ECL assay. The LLOQ was 2.56 ng/mL. PK parameters of toripalimab were estimated from individual concentration-time data by non-compartmental analysis using Phoenix 32 WinNonlin software (v6.4).

Results

Serum Concentrations:

Mean serum concentration-time profiles of toripalimab are presented in the figure below.

Figure 8. Toripalimab Individual Concentration-Time Profiles Following Multiple 3 mg/kg IV Infusions to Patients With Solid Tumour in Study CT5/Cohorts 1 to 4



The PK parameters were estimated by non-compartmental analysis. The PK parameters of toripalimab on Day 1 and Day 71 are presented in the table below.

Table 17. Mean (SD) PK Parameters of Toripalimab Following the First and Following Multiple IV Infusions of 3 mg/kg Toripalimab Q2W in Study CT5/Cohorts 1 to 4

PK Parameters	Units	Values (n = 9)
First dose (Day 1)		
T_{max}[1)]	H	0-6
C_{max}	μg/mL	59.7 ± 17.8
$AUC_{(0-t)}$	h•μg/mL	8020 ± 1330
$t_{½}$	H	187 ± 41.8
6th dose (Day 71)		
T_{max}[1]	h	2-24
C_{max}	μg/mL	79.3 ± 19.7
$AUC_{(0-t)}$	h•μg/mL	15600 ± 5050
C_{min}	μg/mL	25.0 ± 12.5
C_{avg}	μg/mL	46.4 ± 14.8
$AUC_{(0-tau)}$	h•μg/mL	15600 ± 4980
$t_{½}$	h	293 ± 102
AR		1.83 ± 0.41

[1] Range reported

AR: accumulation ratio calculated per the formula $\frac{1}{1-e^{-k\times Tau}}$; AUC: area under the curve; $AUC_{(0-t)}$: area under the curve from time 0 to t; $AUC_{(0\ tau)}$: area under the curve over dosing interval; C_{avg}: average serum concentration calculated per the formula $AUC_{(0-tau)}$/Tau; C_{max}: maximum serum concentration; C_{min}: minimum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; Q2W: every 2 weeks; SD: standard deviation; $t_{½}$: elimination half-life; T_{max}: time to reach maximum serum concentration
Note: PK parameters are reported to 3 significant figures where appropriate.

Study S5403PKHu04 (CT5/Cohorts 5 to 8)

This was a multi-centre, open label, combination therapy, Phase 1b/2, study to evaluate the safety, tolerability, and antitumour activity of toripalimab in 48 patients.

In Cohorts 5, 6, 7, and 8, patients were administered toripalimab doses of 240 mg or 360 mg Q3W as IV over approximately 60 minutes in combination with disease-specific chemotherapy. Patients in Cohort 5 received XELOX (oxaliplatin and capecitabine), those in Cohort 6 received TP, those in Cohort 7 received GC, and those in Cohort 8 received TPF (docetaxel, cisplatin, and fluorouracil).

Table 18. Summary of CT5 Study Design (Cohorts 5 to 8)

Dose	Dosing Frequency	Groups	Route	Number of Patients
240 mg	Q3W	A	Intravenous infusion	14
360 mg	Q3W	B	Intravenous infusion	4

Q3W: every 3 weeks

Table 19. Study Drugs in Study CT5/Cohorts 5 to 8

Drug	Toripalimab	Oxaliplatin	Capecitabine	Paclitaxel	Cisplatin	Gemcitabine	Docetaxel	5-FU
Dosage form	Injection	Injection	Tablet	Injection	Injection	Injection	Injection	Injection
Dosage regimen	240 or 360 mg Q3W	130 mg/m^2 Q3W	1000 mg/m^2 bid, D1 to D14, Q3W	175 mg/m^2 Q3W	60, 75, or 80 mg/m^2 Q3W	1000 mg/m^2 D1 and D8, Q3W	60 mg/m^2 Q3W	750 mg/m^2 D1 to D5, Q3W
ROA	IV	IV	Oral	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion

Bid: twice daily; Dx: Day x; IV: intravenous; Q3W: every 3 weeks; ROA: route of administration

Blood Sampling Times:

Cycle 1: Pre-dose; end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, 168, and 336 hours after the end of infusion.

Cycles 2 to 5: Pre-dose and 0.5 hours after the end of infusion.

Cycle 6: Pre-dose; end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, 168, and 336 hours after the end of infusion.

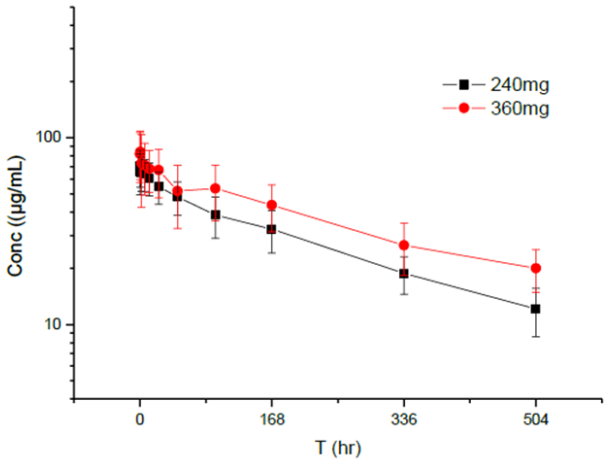
Cycle 7: Pre-dose and 0.5 hours after the end of infusion.

Cycle 9 and every 4 subsequent cycles: Pre-dose, 0.5 hours after the end of infusion, and 60 days after the last administration.

Concentrations of toripalimab in human serum were determined using a validated MSD-ECL assay. The LLOQ was 2.56 ng/mL. PK parameters of toripalimab were estimated from individual concentration-time data by non-compartmental analysis using Phoenix 32 WinNonlin software (v6.4).

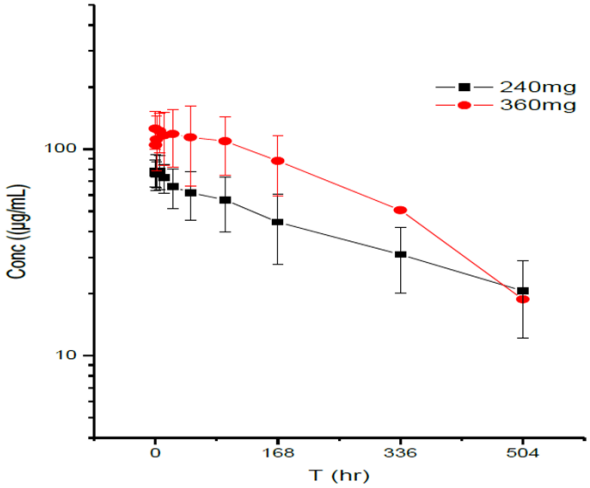
Results

Figure 9. Serum Concentration-Time Profile of Toripalimab After the First Dose in Study CT5/Cohorts 5 to 8



Conc: toripalimab concentration; T: time post-dose

Figure 10. Serum Concentration-Time Profile of Toripalimab After the Sixth Dose in Study CT5/Cohorts 5 to 8



Conc: toripalimab concentration; T: time post-dose

Table 20. Pharmacokinetic Parameters of 240 and 360 mg Toripalimab Dose After the First Dose in Study CT5/Cohorts 5 to 8

PK Parameters	Unit	Mean	SD	Mean	SD
		240 mg (n = 13)		360 mg (n = 4)	
T_{max}[1)]	h	0.00 (0.00, 12.00)		0.50 (0.50, 2.00)	
C_{max}	μg/mL	71.0	14.7	85.2	24.4
$AUC_{(0-t)}$	μg/mL•h	13700	3080	18100	6490
$t_{½}$	h	259	66.7	273	43.2

[1] Median (range) reported

$AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; n: number of patients; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half-life; T_{max}: time to reach maximum serum concentration.
Note: T_{max} was reported to 2 decimal places. All other PK parameters are reported to 3 significant figures.

Table 21. Pharmacokinetic Parameters of Multiple 240 and 360 mg Toripalimab Doses (Sixth Dose) in Study CT5/Cohorts 5 to 8

PK Parameters	Unit	Mean	SD	Mean	SD
		240 mg (n = 11)		360 mg (n = 2)	
T_{max}[1)]	H	1.97 (0.00, 6.00)		23.98 (0.00, 47.97)	
C_{max}	μg/mL	84.9	11.2	128	28.6
$AUC_{(0-t)}$	μg/mL•h	20100	5690	32600	14500
$t_{½}$	H	347	158	322	88.7
AR		1.46	0.390	1.54	1.02

[1] Median (range) reported

AR: accumulation ratio calculated per the formula $\frac{1}{1-e^{-k\times Tau}}$; AUC: area under the curve; $AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; n: number of patients; PK: pharmacokinetic; $t_{½}$: elimination half-life; T_{max}: time to reach maximum serum concentration

Note: T_{max} is reported to 2 decimal places. All other PK parameters are reported to 3 significant figures.

Study S5403PKHu11 (CT6)

This was a single-arm, single-centre, open-label, monotherapy, multiple dose escalation, Phase 1 clinical study in 13 patients to evaluate safety, tolerability, and PK parameters of toripalimab at doses of 1, 3, or 10 mg/kg IV Q2W as 1-hour IV infusions.

Table 22. Summary of the CT6 Study Design

Cohort	Drug Product	Dose	Dosing Interval	Route	Number of Patients
1	toripalimab	1 mg/kg	Q2W	IV	4
2	toripalimab	3 mg/kg	Q2W	IV	3
3	toripalimab	10 mg/kg	Q2W	IV	6

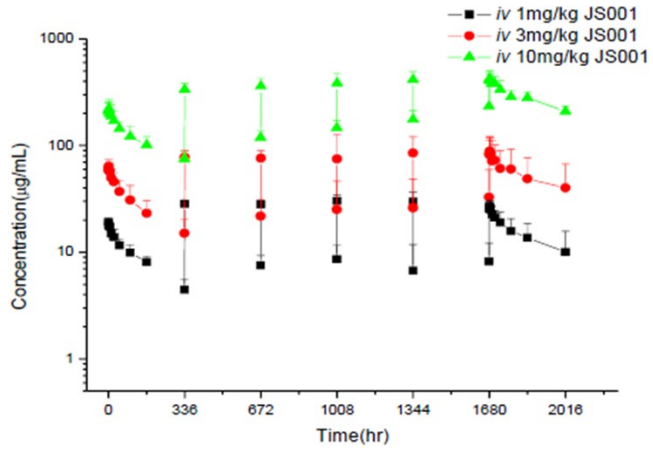
IV: intravenous; Q2W: every 2 weeks

Blood Sampling: The 1st administration: 0 hours (within 30 minutes before administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion. The 2nd, 3rd, 4th, and 5th administrations: 0 hours (within 30 minutes before administration) and at the end of infusion. The 6th administration: 0 hours (within 30 minutes before administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, 168, and 336 h after the end of infusion.

Concentrations of toripalimab in human serum were determined using a validated MSD-ECL assay. The LLOQ was 2.56 ng/mL. PK parameters of toripalimab were estimated from individual concentration-time data by non-compartmental analysis using Phoenix 32 WinNonlin software (v6.4).

Results

Figure 11. Toripalimab Concentration-Time Profile (Mean ± SD) Following Multiple Infusions to Patients With Advanced Malignant Tumour in Study CT6



IV: intravenous; SD: standard deviation

Table 23. Mean (SD) PK Parameters of Toripalimab Following the First and Following Multiple IV Infusion in Study CT6

PK Parameters	Units	Toripalimab Dose Level (Q2W)		
		1 mg/kg	3 mg/kg	10 mg/kg
First dose (Day 1)		**(n = 3)**	**(n = 3)**	**(n = 6)**
T_{max}[1)]	h	0-6	0.50	0.00-2.00
C_{max}	μg/mL	19.9 ± 0.170	63.8 ± 10.0	223 ± 46.4
$AUC_{(0-t)}$	h•μg/mL	2980 ± 271	9050 ± 2610	37600 ± 7020
$t_{½}$	h	208 ± 68.9	243 ± 36.2	429 ± 270
6th dose (Day 71)		**(n = 3)**	**(n = 3)**	**(n = 6)**
T_{max}[1]	h	0.50-6.00	2.00-6.00	0.50-6.00
C_{max}	μg/mL	27.3 ± 3.37	89.5 ± 32.1	445 ± 68.6
$AUC_{(0-tau)}$	h•μg/mL	4950 ± 1640	17800 ± 9710	94400 ± 12500
$t_{½}$	h	395 ± 229	428 ± 226	434 ± 94.3
AR		2.26 ± 0.95	2.40 ± 0.94	2.41 ± 0.39

[1] Range reported

AR: accumulation ratio calculated per the formula $\frac{1}{1-e^{-k\times Tau}}$; AUC: area under the curve; $AUC_{(0-t)}$: area under the curve from time 0 to t; $AUC_{(0\ tau)}$: area under the curve over dosing interval; C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; Q2W: every 2 weeks; SD: standard deviation; t½: elimination half-life; T_{max}: time to reach maximum serum concentration

Note: PK parameters are reported to 3 significant figures where appropriate.

Studies *S5403PKHu12 and S5403PKHu15* (CT7-1 and CT7-2) are described in the Clinical Pharmacology, Bioequivalence section.

CT8 study

This was a randomized, controlled, multicenter, phase II clinical study to investigate the recombinant humanized anti-PD-1 monoclonal antibody (toripalimab) versus high-dose interferon as adjuvant therapy in patients with completely resected mucosal melanoma PK samples were collected from a total of 82 patients in this study, with a total of 676 samples collected. Seventy-three patients were included in the statistical analysis, with a total of 662 samples. The other 9 patients were from the active comparator group, whose samples were collected by mistake, with patient numbers as follows. This involved a total of 14 samples.

Table 24. Descriptive statistics of drug trough concentration at different time points

Visit	Statistic	Trough concentration (μg/mL)
Before administration in Cycle 1	N (missing)	73 (0)
	Mean (SD)	0.0003 (0.0011)
	Median	0.0000
	Min, Max	0,0.00623
Day 29 in Cycle 1	N (missing)	69 (4)
	Mean (SD)	28.950 (7.4142)
	Median	29.390
	Min, Max	5.39, 51.67
Day 57 in Cycle 1	N (missing)	63 (10)
	Mean (SD)	41.001 (12.1512)
	Median	40.670
	Min, Max	6.51, 69.08
Before administration in Cycle 2	N (missing)	58 (15)
	Mean (SD)	42.921 (12.6927)
	Median	42.140
	Min, Max	11.11, 78.63
Day 29 in Cycle 2	N (missing)	56 (17)
	Mean (SD)	43.888 (13.8108)
	Median	44.310
	Min, Max	8.42, 84.54
Day 57 in Cycle 2	N (missing)	54 (19)
	Mean (SD)	44.015 (14.9766)
	Median	42.955
	Min, Max	7.7, 88.56
Before administration in Cycle 3	N (missing)	46 (27)
	Mean (SD)	48.233 (14.0579)
	Median	48.350
	Min, Max	14.36, 90.59
Day 29 in Cycle 3	N (missing)	45 (28)
	Mean (SD)	48.494 (15.5031)
	Median	46.550
	Min, Max	14.93, 89.87
Day 57 in Cycle 3	N (missing)	43 (30)
	Mean (SD)	51.921 (16.7078)
	Median	49.440
	Min, Max	21.3, 107.02
Before administration in Cycle 4	N (missing)	37 (36)
	Mean (SD)	52.020 (15.3913)
	Median	50.190
	Min, Max	20.37, 95.47
Day 29 in Cycle 4	N (missing)	32 (41)
	Mean (SD)	52.611 (14.2514)
	Median	52.750
	Min, Max	19.15, 80.3
Day 57 in Cycle 4	N (missing)	31 (42)
	Mean (SD)	53.130 (14.4662)
	Median	52.450
	Min, Max	24.5, 84.54
Before administration in Cycle 5	N (missing)	27 (46)
	Mean (SD)	54.217 (11.3373)
	Median	52.600
	Min, Max	30.45, 76.33
Day 29 in Cycle 5	N (missing)	28 (45)
	Mean (SD)	53.874 (13.2254)
	Median	52.970
	Min, Max	27.49, 84.75

The occurrence of ADA in the experimental group was tested to evaluate its effects on the efficacy, safety, and pharmacokinetics of toripalimab. In the study, samples were collected within 30 min before the first dose and every 4 weeks thereafter until the end of the observation period for ADA/pharmacokinetics analyses.

Results

The study results showed that the trough concentration was maintained, in most patients, between 40 and 55 μg/mL from C1D57 to C5D29, suggesting that the blood drug concentration was, roughly, at a steady state after C1D57.

Study S5403PKHu02 (CT9)

This was an open-label, single-centre, dose escalation, Phase 1 study to investigate the tolerability and PK of toripalimab after a single and multiple administrations in 20 patients with advanced triple-negative breast cancer. The study comprised two parts: a dose-escalation portion with sequential enrolment of 3-6 patients into dose cohorts of 1, 3 or 10 mg/kg toripalimab followed by a dose expansion portion with enrolment of up to 12-15 patients into the 3 mg/kg cohort. Patients received the first dose of toripalimab with a 28-day interval between the 1st and 2nd dose and administration Q2W beginning with the 2nd dose in the original version of the study; after revision on 28 Feb 2017, all patients were to receive toripalimab every 2 weeks (removal of DLT observation period). There was a total of 20 patients enrolled in the study.

Table 25. Summary of CT9 Study Design

Dose	Dosing Frequency	Route	Number of Patients
1 mg/kg	Single dose, then Q2W	IV	6
3 mg/kg	Single dose, then Q2W	IV	8
10 mg/kg	Single dose, then Q2W	IV	6

IV: intravenous; Q2W : every 2 weeks

Blood Sampling Times Following the First Dose: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, 168, 336, 504, and 648 hours after the end of infusion.

Blood Sampling Times Following Multiple Doses: The 1st administration of multiple dosing: 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion. The 2nd, 3rd, 4th, 5th, 6th, and 8th administrations: 0 hours (within 30 minutes before drug administration) and at the end of infusion. After the 7th administration, blood samples were taken at time 0 hours (within 30 minutes before drug administration); end of infusion; and 0.5, 2, 6, 12, 24, 48, 96, and 168 hours after the end of infusion. Beginning with the 9th administration, trough samples were collected before every other administration.

Concentrations of toripalimab in human serum were determined using a validated MSD-ECL assay. The LLOQ was 2.56 ng/mL. PK parameters of toripalimab were estimated from individual concentration-time data by non-compartmental analysis using Phoenix 32 WinNonlin software (v6.4).

Results

Serum concentration-time profiles of toripalimab following a single dose and following multiple doses are presented in the figures below.

Figure 12. Serum Concentration-Time Profile Following 1 mg/kg Dose in Study CT9

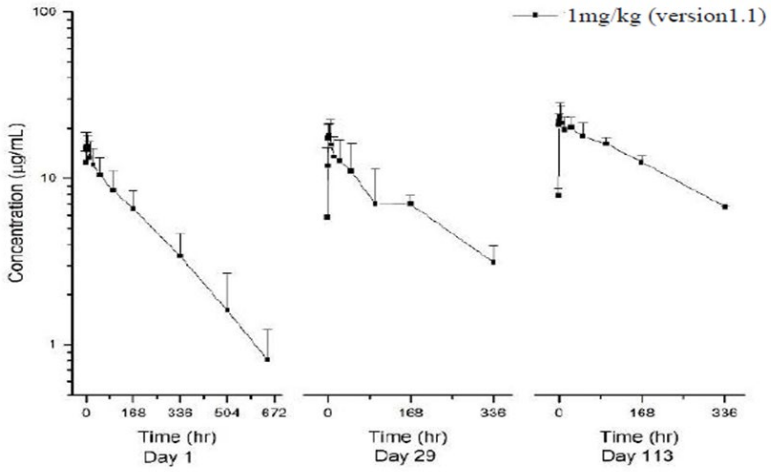
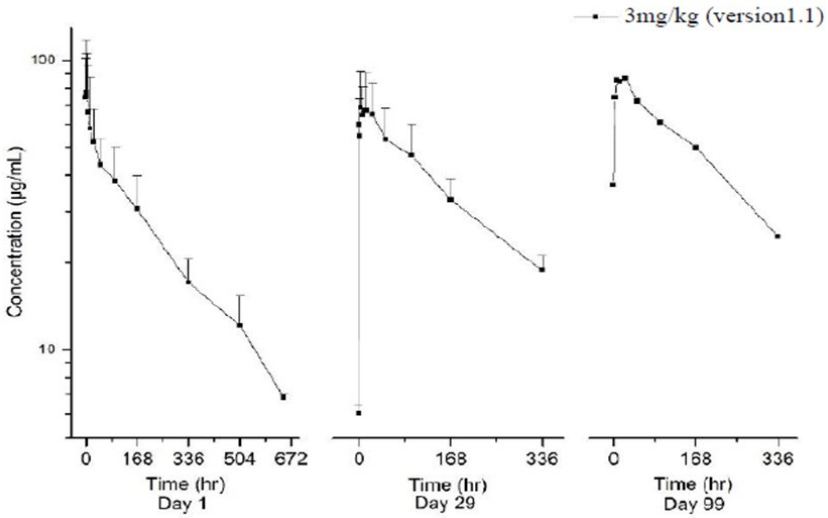
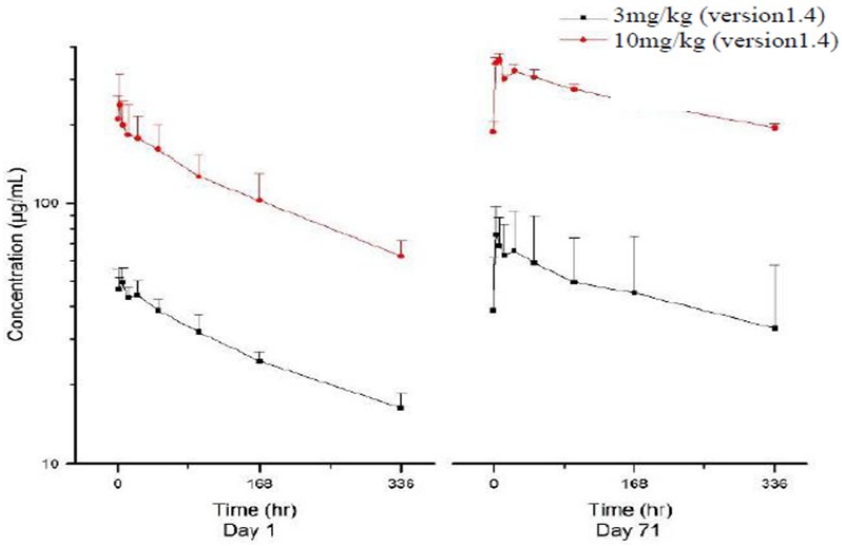


Figure 13. Serum Concentration-Time Profile Following 3 mg/kg Dose in Study CT9



Note: In version 1.1 of the protocol, pharmacokinetic sampling was conducted up to 4 weeks after a single dose. This single-dose period was deleted in version 1.4, the corresponding blood collection schedule were adjusted.

Figure 14. Serum Concentration-Time Profile Following 3 and 10 mg/kg Doses in Study CT9



Note: In version 1.1 of the protocol, pharmacokinetic sampling was conducted up to 28 days after the first dose. This single dose period was deleted in version 1.4, the corresponding blood collection schedule were adjusted.

PK parameters were estimated by non-compartmental analysis. The PK parameters following a single dose and following multiple doses of toripalimab are shown in the tables below.

Table 26. Mean (SD) PK Parameters of Toripalimab Following the First IV Infusion in Study CT9

PK Parameters	Units	1 mg/kg (n = 6)	3 mg/kg (n = 2)	10 mg/kg (n = 6)
T_{max}[1)]	h	2.01 (0.5, 11.98)	0.32 (0.12, 0.52)	1.89 (0.00, 2.02)
C_{max}	µg/mL	16.4 ± 3.36	80.3 ± 35.4	240 ± 77.8
$AUC_{(0-t)}$[2)]	h•µg/mL	3020 ± 948	14900 ± 4170	37700 ± 7970
AUC_{inf}	h•µg/mL	3190 ± 1060	17200 ± 3890	NR
$AUC_{(t-inf)\%}$	%	4.61 ± 3.05	13.9 ± 4.79	38.0 ± 13.6
$t_{½}$	h	144 ± 42.2	234 ± 34.7	258 ± 93.2
CL	mL/h/kg	0.35 ± 0.13	0.18 ± 0.04	NR

[1] Median (range) reported
[2] For the calculation of $AUC_{(0-t)}$, t is 648 h for 1 mg/kg dose group, 648 h (v1.1) and 336 h (v1.4) for 3 mg/kg dose group, and 336 h for 10 mg/kg dose group.
$AUC_{(0-t)}$: area under the curve from time 0 to t; AUC_{inf}: area under the curve from 0 to infinity; $AUC_{(t-inf)\%}$: % AUC extrapolated from time t to infinity; CL: clearance; C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; NR: not reportable; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half-life; T_{max}: time to reach maximum serum concentration
Note: T_{max} is reported to 2 decimal places. Other PK parameters are reported to 3 significant figures.

Table 27. Mean (SD) PK Parameters of Toripalimab Following the First IV Infusion in the Multiple Dosing Period in Study CT9

PK Parameters	Units	1 mg/kg (n = 4)	3 mg/kg (Protocol v1.1) (n = 2)	3 mg/kg (Protocol v1.4) (n = 6)	10 mg/kg (n = 6)[1)]
T_{max}[2]	h	2.05 (0.53, 6.03)	1.22 (0.50, 1.93)	3.97 (0.00, 24.10)	1.89 (0.00, 2.02)
C_{max}	µg/mL	19.4 ± 4.03	70.0 ± 21.4	53.2 ± 3.71	240 ± 77.8
$AUC_{(0-t)}$	h•µg/mL	2140 ± 1170	12600 ± 2980	9260 ± 552	37700 ± 7970
$t_{½}$	h	119 ± 66.1	188 ± 38.9	260 ± 63.4	258 ± 93.2

[1] For patients in 10 mg/kg group, PK parameters reported after the single dose in Table 16 are the same as those reported after the first dose in the multiple dosing period as PK samples in all patients in the 10 mg/kg group were collected under protocol v1.4 i.e., there was no single dose stage.
[2] Median (range) reported.
$AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half life; T_{max}: time to reach maximum serum concentration; v: version
Notes: T_{max} is reported to 2 decimal places. Other PK parameters are reported to 3 significant figures.
In v1.1 of the protocol, PK sampling was conducted up to 4 weeks after a single dose. This single-dose period was deleted in v1.4, and the corresponding blood collection schedules were adjusted.

Table 28. Mean (SD) PK Parameters of Toripalimab After the Multiple IV Infusions in Study CT9

PK Parameters	Units	1 mg/kg (n = 2)	3 mg/kg (Protocol v1.1) (n = 1)	3 mg/kg (Protocol v1.4) (n = 2)	10 mg/kg (n = 3)
T_{max}[1)]	h	1.02 (0.08, 1.95)	23.95	1.98 (1.95, 2.00)	2 (1.98, 6.00)
C_{max}	μg/mL	23.9 ± 4.11	86.7	75.6 ± 22.0	365 ± 15.4
$AUC_{(0-t)}$	h•μg/mL	4420 ± 478	17400	15700 ± 9050	85300 ± 712
$t_{½}$	h	194 ± 21.4	185	331 ± 152	453 ± 45.2
AR		1.43 ± 0.08	1.4	1.99 ± 0.63	2.49 ± 0.19

[1] Median (range) reported
AR: accumulation ratio calculated per the formula $\frac{1}{1-e^{-k\times Tau}}$; AUC: area under the serum curve; $AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; IV: intravenous; n: number of patients; PK: pharmacokinetic; SD: standard deviation; $t_{½}$: elimination half-life; T_{max}: time to reach maximum serum concentration; v: version
Note: T_{max} and AR are reported to 2 decimal places. Other PK parameters are reported to 3 significant figures.

CT12 study

CT12 was a single arm, open-label Phase 2 trial conducted in patients with unresectable locally advanced or metastatic urothelial cancer who had progressed on or who were intolerant of at least 1 prior therapy. Four mL of blood were collected from each patient prior to the first dose and within 30 min pre-dose every 4 weeks afterwards to assess ADA and characterize pharmacokinetic trough concentration.

Results

PK data analysis: the Phase I clinical PK study of Toripalimab, conducted by Beijing Cancer Hospital and Sun-Yat Sen University Cancer Hospital, showed that, the Cmax was reached at end of administration of the study drug, and the half-life was 5-12 d. The steady-state was reached after administration of 3 doses, Q2W. At the dose of 3 mg/kg, the Ctrough was approximately 25 μg/mL, which was an ideal peripheral blood concentration level with the dose frequency of Q2W. No significant change was seen in in-vivo pharmacokinetic characteristics after consecutive multiple doses Q2W. An ideal peripheral blood concentration level was reached at the dose of 3 mg/kg Q2W, supporting the administration interval of once every two weeks.

CT14 study

CT14 is a single arm, Phase 2 trial conducted in patients with locally advanced or metastatic non-functioning neuroendocrine tumours. Samples were collected before the first dose and within 30 minutes (0 hour) before dosing every 4 weeks thereafter to assess the potential of anti-JS001 antibody (ADA) formation and explain immunogenicity results; and characterize the pharmacokinetic trough plasma concentrations.

Pharmacokinetic (PK) data analysis: Phase I clinical PK parameter analysis of JS001 conducted in Beijing Cancer Hospital and the Cancer Hospital of Sun Yat-sen University showed that the drug

basically reached the maximum concentration at the end of the administration, with a half-life of about 5 - 12 days. At the frequency of dosing every 2 weeks, steady-state levels were basically reached for 3 doses. The lowest steady-state concentration was approximately 1.5 μg/ml at 0.3 mg/kg, 8 μg/ml at 1 mg/kg, 25 μg/ml at 3 mg/kg, and 85 μg/ml at 10 mg/kg. The optimal peripheral blood concentration was achieved with a dose of 3mg/kg at a once/2-week dosing frequency.

Results

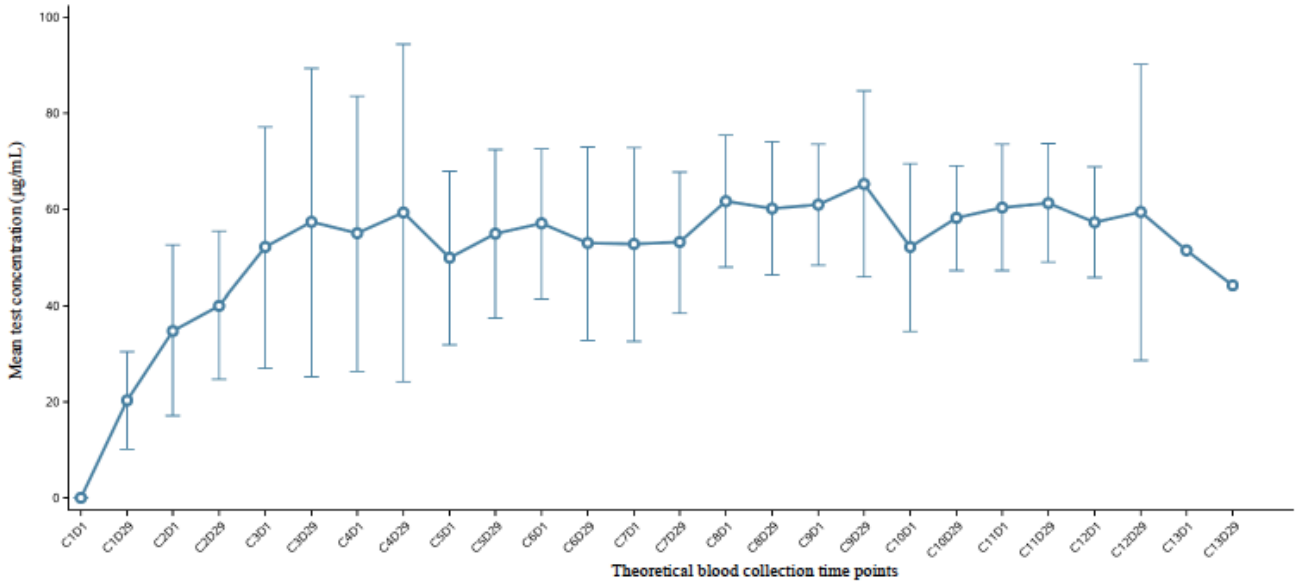
A total of 40 patients were enrolled in this study. A total of 221 serum samples were collected before the first dose and within 30 min before dosing every 4 weeks thereafter. JS001 concentrations were measured using a validated ECLA method (see method validation report for details). As can be seen from Table 33 and Figure 17, the plasma concentration of patients reached steady state before dosing on C3D1, at which time the plasma concentration was 52.074 +- 25.042 μg/mL.

Table 29. Statistical analysis of trough concentrations after intravenous infusion of JS001 (3 mg/kg, Q2W) to patients

Statistics	Concentration (μg/mL)																									
	C1D1	C1D29	C2D1	C2D29	C3D1	C3D29	C4D1	C4D29	C5D1	C5D29	C6D1	C6D29	C7D1	C7D29	C8D1	C8D29	C9D1	C9D29	C10D1	C10D29	C11D1	C11D29	C12D1	C12D29	C13D1	C1
Number of patients	40	35	18	17	10	10	9	8	7	7	5	5	5	5	4	4	4	4	4	4	4	4	4	2	1	1
Number of patients > BQL	0	35	18	17	10	10	9	8	7	7	5	5	5	5	4	4	4	4	4	4	4	4	4	2	1	1
Arithmetic mean	-	20.358	34.814	40.034	52.074	57.295	54.956	59.251	49.900	54.921	56.992	52.888	52.740	53.110	61.633	60.115	60.940	65.218	52.075	58.113	60.358	61.260	57.285	59.410	51.430	44.
Standard deviation	-	10.149	17.682	15.311	25.042	32.056	28.558	35.066	17.976	17.502	15.512	20.043	20.099	14.621	13.767	13.900	12.599	19.415	17.355	10.951	13.196	12.356	11.498	30.787	-	-
Arithmetic CV%	-	49.85	50.79	38.24	48.09	55.95	51.97	59.18	36.02	31.87	27.22	37.90	38.11	27.53	22.34	23.12	20.67	29.77	33.33	18.85	21.86	20.17	20.07	51.82	-	-
Geometric mean	-	17.638	29.740	37.540	47.553	50.777	48.340	49.322	47.551	52.870	55.153	49.497	49.338	51.203	60.462	58.894	59.942	63.051	49.805	57.332	59.271	60.318	56.499	55.278	51.430	44.
Geometric CV%	-	66.09	72.40	38.17	45.29	53.17	59.62	78.29	33.36	29.47	30.08	43.99	44.11	32.53	23.02	23.88	21.37	30.76	36.31	19.22	22.37	20.59	18.93	58.62	-	-
Median	-	19.750	33.855	37.740	38.520	42.900	41.990	47.575	44.820	45.260	55.150	60.370	58.500	56.770	62.105	59.690	61.530	62.975	51.595	58.030	59.760	61.230	53.125	59.410	51.430	44.
Minimum	BQL	2.6	5.39	16.56	30.68	30.17	18.32	13.67	32.75	39.36	35.28	29.14	28.78	30.56	47.77	44.13	47.11	48.31	31.43	46.67	45.69	50.03	48.84	37.64	51.43	44
Maximum	BQL	48.4	76.25	78.33	95.8	125.38	97.03	115.91	85.71	89.04	74.66	74.07	74.01	65.87	74.55	76.95	73.59	86.61	73.68	69.72	76.22	72.55	74.05	81.18	51.43	44

Source: Table 14.6.1.
Note: '-' indicates not applicable.

Figure 15. Mean trough concentration-time (theoretical time) curve after multiple intravenous infusions of JS001 (3 mg/kg, Q2W) in patients



Study S001-015-III-NPC (CT15)

This was a randomised, placebo-controlled, multi centre, double-blind, Phase 3 study designed to determine the efficacy and safety of toripalimab in combination with GC compared with placebo in combination with GC as first-line treatment in subjects with histologically or cytologically confirmed, recurrent or metastatic NPC. Eligible patients were randomised (1:1) to receive toripalimab (Arm A; N = 146) or placebo (Arm B; N = 143), in combination with GC. Randomisation was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) and disease stage (recurrent versus metastatic). The dosages for the individual drugs are summarised below:

Table 30. Dosages for individual drugs (Study CT15)

	Investigational Product	Placebo	Chemotherapy	Chemotherapy
Drug	toripalimab	toripalimab placebo	gemcitabine	cisplatin
Dose	240 mg	Not Applicable	1000 mg/m^2	80 mg/m^2
Dosage schedule	Q3W, Day 1 of each 3-week cycle	Q3W, Day 1 of each 3-week cycle	Days 1 and 8 in 3-week cycles for up to 6 cycles	Day 1 in 3-week cycles for up to 6 cycles
Mode of Administration	IV infusion	IV infusion	IV infusion	IV infusion

PK samples were to be collected pre-dose on Day 1 of every 4th cycle for the first year, pre-dose on Day 1 of every 8th cycle thereafter, and at the end of treatment visit. 716 PK samples from 146 patients were analysed using a validated MSD-ECL assay. The LLOQ was 2.56 ng/mL.

Results

As only sparse PK data were available from this study, no independent PK analyses were conducted. Data from Study CT15 were included in the popPK analysis TOPA PMX-TORIPALIMAB-3355 described below.

PopPK model

An initial popPK model for toripalimab monotherapy (TOPA-PMX-TORI-2412) was developed in which the dataset included 13 clinical studies that evaluated the efficacy, safety, and PK in patients with various advanced cancers as a single agent.

A second popPK model was developed that included both data from the initial 13 studies used to develop the toripalimab monotherapy and the data from the pivotal study, Study CT15, along with Cohorts 5 to 8 of Study CT5 (TOPA-PMX-TORI-2412 Combination Therapy). These additional studies evaluated the efficacy, safety, and PK of toripalimab in combination with platinum-based chemotherapy in patients receiving first-line therapy for metastatic solid tumours, primarily NPC. These two models are not further described in this assessment report.

The current popPK model (TOPA PMX-TORIPALIMAB-3355) for toripalimab as monotherapy or in combination with chemotherapy was developed using data from 15 clinical studies, including 14 clinical studies from the previous analysis (TOPA-PMX-TORI-2412 Combination Therapy) and 1 additional study, Study CT21.

Evaluation and Qualification of Models

PK and Exposure-Response Modelling and Simulation of Toripalimab in Patients with Nasopharyngeal Carcinoma (TOPA-PMX-TORI-2412 Monotherapy)

The PK analysis included 12 clinical studies (7 Phase I, 1 Phase Ib/II, and 4 Phase II) conducted predominantly in China in patients with various cancers. Study TAB001-01 was conducted in the United States [US]), also conducted in patients with various cancers. Toripalimab concentrations were determined using validated assays with an assay lower limit of quantitation (LLOQ) of 2.56 ng/mL for all studies except Study TAB001-01, which had an LLOQ of 15.6 ng/mL.

Methodology

Pop PK analysis was performed using NONMEM to understand the sources of variability in PK.

A formal covariate analysis was performed using a forward addition process followed by backward elimination. The final model was qualified using goodness-of-fit (GOF), bootstrap resampling, and visual predictive check (VPC). Empirical individual Bayesian estimates of PK parameters were generated using the final pop PK model to derive exposure metrics. For safety, the average concentration (C_{ave}; over 2 weeks if the dosing frequency is every 2 weeks [Q2W], or over 3 weeks if the dosing frequency is a single dose or every 3 weeks [Q3W]) was calculated after the last dose prior to the first safety event. For efficacy, the C_{ave} was derived from the last dose to achieve the "highest" exposure for all PK subjects in Study CT5 given that the response is best overall. The toripalimab serum concentration-time data from fixed (80 to 480 mg Q2W or Q3W) and weight-based (range: 0.3 to 10 mg/kg Q2W) dosing administered via infusion in subjects with various tumour types were described by a 2-compartment model with time-varying clearance (CL) characterized by a sigmoidal-maximum effect (Emax) function. The developed model included 862 evaluable subjects for a total of 9377 toripalimab serum concentration samples in the pop PK analysis. Incorporation of the time-varying CL in the pop PK model resulted in a statistically significant improvement in the GOF, Covariate analysis was explored to further explain PK parameter variability. In the final model, significant covariates on CL included ADA-positive status, weight, lactate dehydrogenase (LDH), and sex.

The evaluation of the impact of covariates on the pop PK and E-R models focused on the most clinically relevant covariates was conducted. Covariates tested included the following: body weight, age, sex, cancer type, immunogenicity (ADA) status, baseline tumour burden (TUBURBL; sum of the longest diameters of all target lesions), Eastern Cooperative Oncology Group (ECOG) performance status, baseline albumin (BALB), baseline lactate dehydrogenase (LDH), baseline alkaline phosphatase (BALP),

baseline aspartate aminotransferase (AST), baseline alanine aminotransferase (ALT), baseline total bilirubin (BILI), baseline renal function based on estimated renal function by Cockcroft-Gault formula from serum creatinine (CREAT), and baseline liver dysfunction based on grade per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.

Nonlinear Mixed Effects Modelling software (NONMEM® version 7.4.3; ICON, Hanover, MD, US), a software package for nonlinear mixed-effects analysis, was used for pop PK modelling. R was used for simulations to derive exposure metrics for the subsequent E-R analysis. Xpose and Perl-Speaks NONMEM (Department of Pharmacy, Uppsala University, Uppsala, Sweden) were also used for model diagnostics and facilitation of NONMEM tasks, such as covariate testing. R was used for graphical analysis, model diagnostics, and statistical summaries. E-R analyses were performed using R (versions 3.6.3 and 4.0.4). All analysis runs were performed using the FOCEI method in NONMEM.

Results

Population PK and Exposure-Response Modelling and Simulation of Toripalimab in Patients with Nasopharyngeal Carcinoma (TOPA-PMX-TORI-2412 Combination Therapy).

Table 31. Final PK Model Parameter Estimates

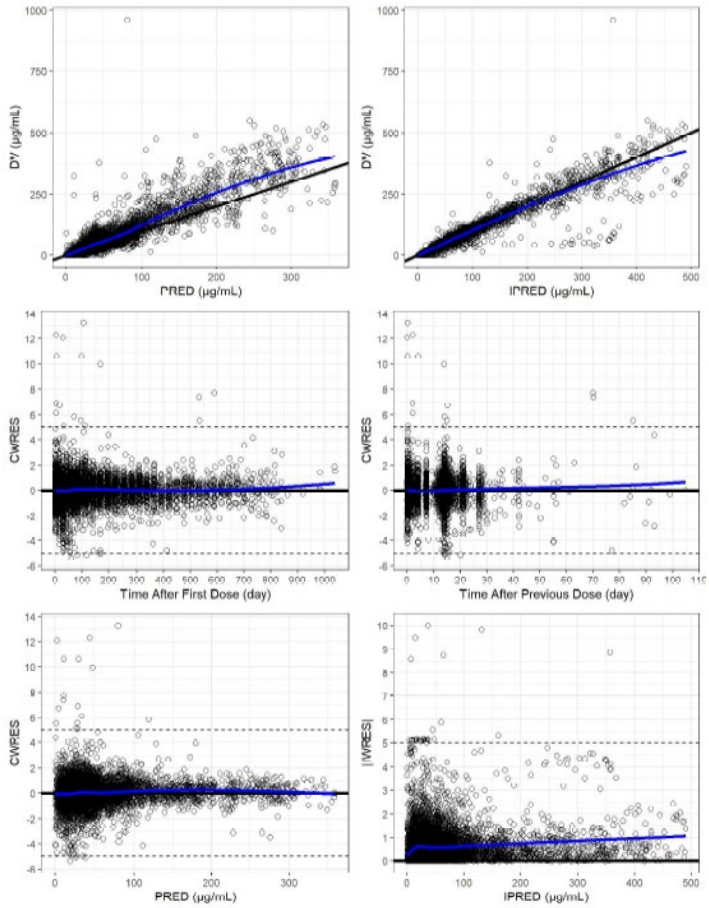
Parameters	Estimates	%RSE	95% CI	
E_{maxTV}	-0.372	13	(-0.512, -0.291)	
T_{50} (h)	1570	24	(1106, 4188)	
Gamma	1.325	18	(0.845, 1.902)	
CL_{TV} (mL/h)	14.58	3	(13.74, 15.53)	
CL_{ADA}	0.195	26	(0.104, 0.302)	
CL_{LDH}	0.18	14	(0.133, 0.226)	
CL_{Female}	-0.197	12	(-0.244, -0.154)	
$CL_{Albumin}$	-0.678	17	(-0.911, -0.457)	
CL_{Weight}	0.209	31	(0.087, 0.338)	
$V1_{TV}$ (mL)	3701	2	(3518, 3889)	
$V1_{White\ Race}$	-0.22	14	(-0.289, -0.161)	
$V1_{Other\ Race}$	-0.314	11	(-0.381, -0.243)	
$V1_{Weight}$	0.496	18	(0.318, 0.661)	

Parameters	Estimates	%RSE	95% CI	
Q_{TV} (mL/h)	19.33	56	(8.05, 66.87)	
$V2_{TV}$ (mL)	886	18	(583.5, 1202)	
Random Effects	**(%CV)**	**%RSE**	**95% CI**	**Shrinkage (%)**
IIV on E_{max}	43	31	(33, 78)	30
IIV on CL	34	11	(30, 37)	10
IIV on V1	27	20	(21, 34)	35
Correlation CL and V1	0.42	21	(0.23, 0.55)	
Residual Error	**(%CV)**	**%RSE**		
Proportional error	19	9	(18, 21)	7

Source: sen1.lst and Sensitivity Models. Rmd Notes: %CV was calculated using exact formula sqrt(exp(variance) 1)×100; 95% CI was derived from 941 successful minimization models of 1000 replicates bootstrap analysis; and continuous covariates were centred at median values 64 kg for weight, 43.7 g/L for albumin, and 199 U/L for LDH. References for categorical covariates were ADA-negative status, male, and Asian race.

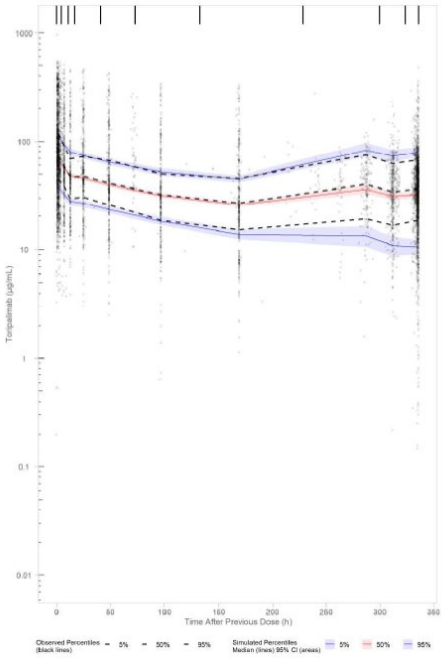
Abbreviations: %CV=percentage of coefficient of variation; %RSE=percentage of the relative standard error; ADA=antidrug antibody; CI=confidence interval; CL=clearance; Emax=maximum effect of time varying CL (in log form; exponentiated value of exp(-0.372) is 0.69); Gamma=sigmoidicity of the relationship with time (T) after first dose in sigmoidal Emax model for CL; IIV=inter-individual variability; LDH=lactate dehydrogenase; Q=intercompartmental clearance; T50=time (h) at which the change in CL is 50% of Emax; TV=typical value; V1=central volume of distribution; V2=peripheral volume of distribution

Figure 16. GOF Plots for the Final PK Model



Source: Sensitivity Models. Rmd Notes: black line=identity or zero horizontal line; blue line=locally weighted scatterplot smoothing; circles (individual value); dashed line=residuals at 5 or -5 value. Abbreviations: CWRES=conditional weighted residuals; DV=observed concentration; GOF=goodness-of-fit; IPRED=individual prediction; |IWRES|=absolute value of individual weighted residuals; PRED=population prediction

Figure 17. pcVPC for Final PK Model (Semi-log Scale, Time After Previous Dose)



Source: 30 VPC Plots for Final Model. Rmd Notes: Circles represent observed concentration. Top vertical bars represent binning optimized by partitioning around medoids methodology. Abbreviations: CI=confidence interval; pop PK=population pharmacokinetic; pcVPC=prediction-corrected VPC

Population PK and Exposure-Response Modelling and Simulation of Toripalimab in Patients with Nasopharyngeal Carcinoma (TOPA-PMX-TORI-2412 Combination Therapy)

The PK analysis included 14 clinical studies (8 Phase I, 1 Phase Ib, 1 Phase Ib/II, 3 Phase II, and 1 Phase III) investigated predominantly in China. The PK analysis dataset included 10694 measurable PK observations from 1076 patients. The analysis was conducted on a database containing 10430 PK observation records from 1014 patients, while 264 measurable PK observations were excluded from 62 patients.

Methodology

The structural PK model for toripalimab is a 2-compartment model with zero-order intravenous infusion and time-varying clearance (CL) characterized by a sigmoidal-maximum effect function. Methodology is similar to TOPA-PMX-TORI-2412 Monotherapy, unless state otherwise.

Results

Toripalimab CL decreases over time with a 50% maximal reduction after 65.8 days, increases with increasing body weight, lactate dehydrogenase (LDH), creatinine clearance derived using the Cockcroft-Gault Equation (CRCL), and antidrug antibody-positive status, Increases with decreasing albumin (ALB), and is higher in males than in females after adjustment for weight. None of these effects resulted in clinically relevant changes in CL.

Toripalimab volume of distribution of the central compartment increases with increasing body weight, which was not clinically relevant, is lower in White race compared to the Asian race and is not clinically relevant. Simulations for the first dose and steady state (SS) exposure metrics (AUC, Cavg, Cmax, and Ctrough) for 240 mg every 3 weeks (Q3W) are comparable to 3 mg/kg every 2 weeks (Q2W). The 3 mg/kg Q2W dose regimen would provide approximately 80% of the exposure as the 240 mg Q3W dose regiment after the first dose and at steady state.

Table 32. Final Model Parameter Estimates for Toripalimab PK

Parameters	Estimates	%RSE	95% CI	
E_{maxTV}	-0.444	11	(-0.54, -0.35)	
T_{50} (h)	1580	17	(1051, 2104)	
Gamma	1.32	14	(0.97, 1.68)	
CL_{TV} (mL/h)	14.9	2	(14.2, 15.6)	
CL_{ADA}	0.191	24	(0.102, 0.280)	
CL_{LDH}	0.161	13	(0.12, 0.20)	
CL_{Female}	-0.19	11	(-0.23, -0.15)	
$CL_{Albumin}$	-0.676	15	(-0.87, -0.49)	
CL_{Weight}	0.097	65	(-0.026, -0.22)	
CL_{CRCL}	0.226	17	(0.15, 0.30)	
V1 (mL)	3710	3	(3511, 3899)	
$V1_{White\ Race}$	-0.23	13	(-0.29, -0.17)	
$V1_{Other\ Race}$	-0.327	10	(-0.39, -0.26)	
$V1_{Weight}$	0.488	18	(0.31, 0.66)	
Q_{TV} (mL/h)	36.5	73	(-16.05, 89.01)	
$V2_{TV}$ (mL)	796	16	(549, 1042)	
Random Effects	**(%CV)**	**%RSE**	**95 % CI**	**Shrinkage (%)**
IIV on E_{max}	39	12	(0.080, 0.22)	29
IIV on CL	31	5	(0.075, 0.111)	12
IIV on V1	27	15	(0.031, 0.118)	38
Correlation CL and V1	39	11	(0.018, 0.047)	
Residual Error	**(%CV)**	**%RSE**	**95 % CI**	
Proportional error	19	4	(0.0308, 0.0423)	8

Source: final_forward5.lst, final_forward5.lst -ci

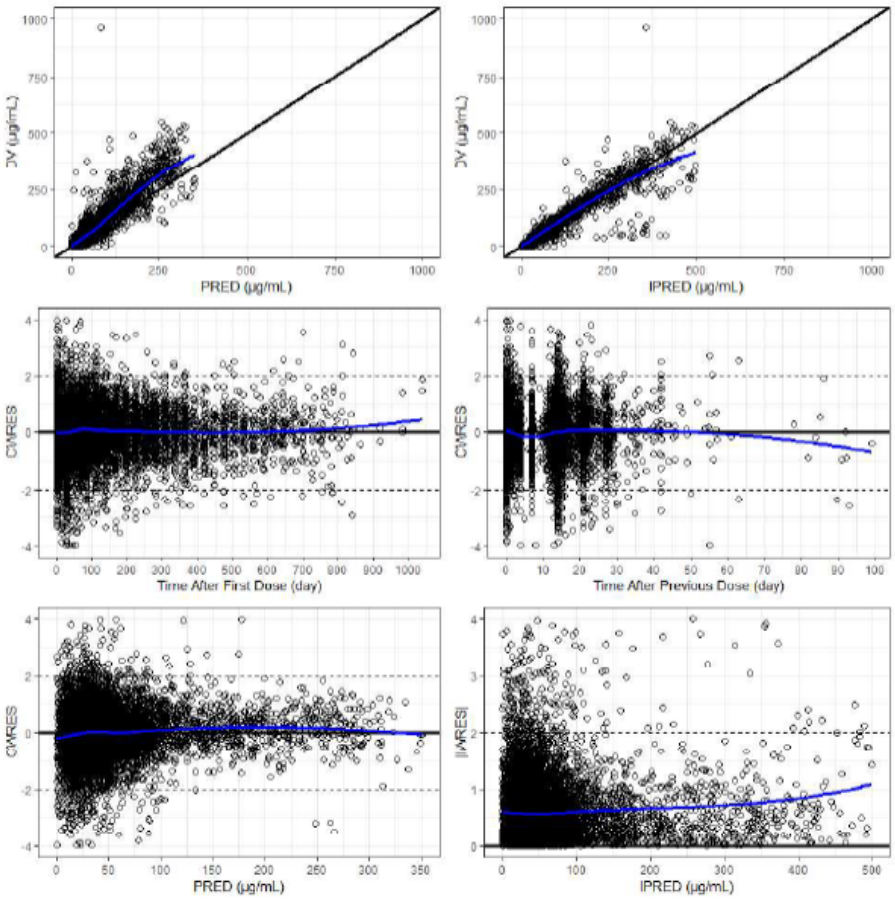
Notes: The mathematical expressions for the covariate-parameter relationships are:

$$CL = CL_{TV} * e^{\frac{E_{max} * Time^{Gamma}}{T_{50}^{Gamma} + Time^{Gamma}}} * CL_{ADA}\,(\text{if ADA-positive}) * \left(\frac{BLDH}{199}\right)^{CL_{LDH}} * CL_{Female}\,(\text{if Female}) * \left(\frac{BALB}{43{,}7}\right)^{CL_{Albumin}} * \left(\frac{BWT}{64}\right)^{CL_{Weight}} * \left(\frac{CRCL}{94{,}31}\right)^{CL_{CRCL}}$$

$$V1 = V1_{TV} * V1_{White\ Race}\,(\text{if White Race}) * V1_{Other\ Race}\,(\text{if Other Race}) * \left(\frac{BWT}{64}\right)^{V1_{Weight}}$$

Abbreviations: %CV=percentage of the coefficient of variation; %RSE=percentage of the relative standard error; ADA=antidrug antibody; CI=confidence interval; CL=clearance; CRCL=creatinine clearance; E_{max}=maximum effect (maximum effect of time-varying CL in log form; exponentiated value of exp[-0.444] is 0.64); Gamma=sigmoidicity of the relationship with time (T) after first dose in sigmoidal-E_{max} model for CL; IIV=interindividual variability; LDH=lactate dehydrogenase; PK=pharmacokinetic; Q=intercompartmental clearance; T_{50}=time (h) at which the change in CL is 50% of E_{max}; TV=typical value; V1=volume of distribution of the central compartment; V2=volume of distribution of the peripheral compartment

Figure 18. GOF Plots for the Final PK Model

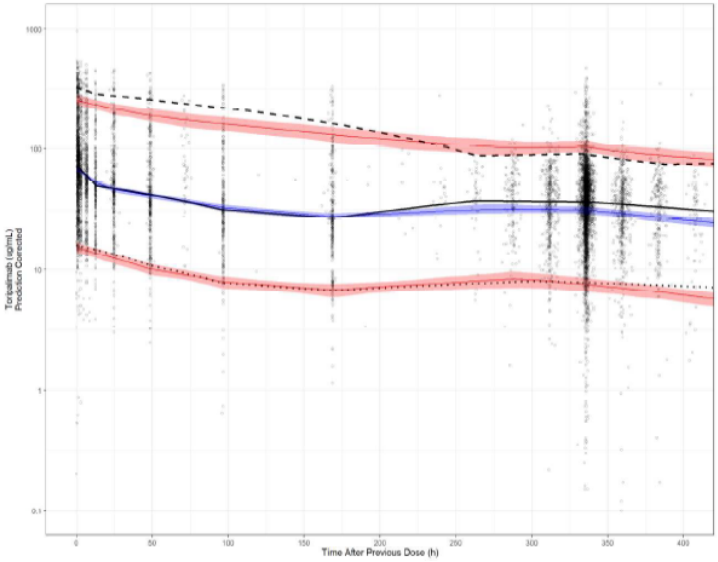


Source: Proposed_Final_PopPK_Model_2.Rmd

Notes: Dots are individual data points (red: concentrations following IV administration; blue: concentrations following SC administration), and solid lines are smoothed LOESS lines. In the 2 plots in the first row, dashed lines are lines of identity, while in the 2 plots in the second row, dashed lines show the boundaries of the CWRES±5 interval.

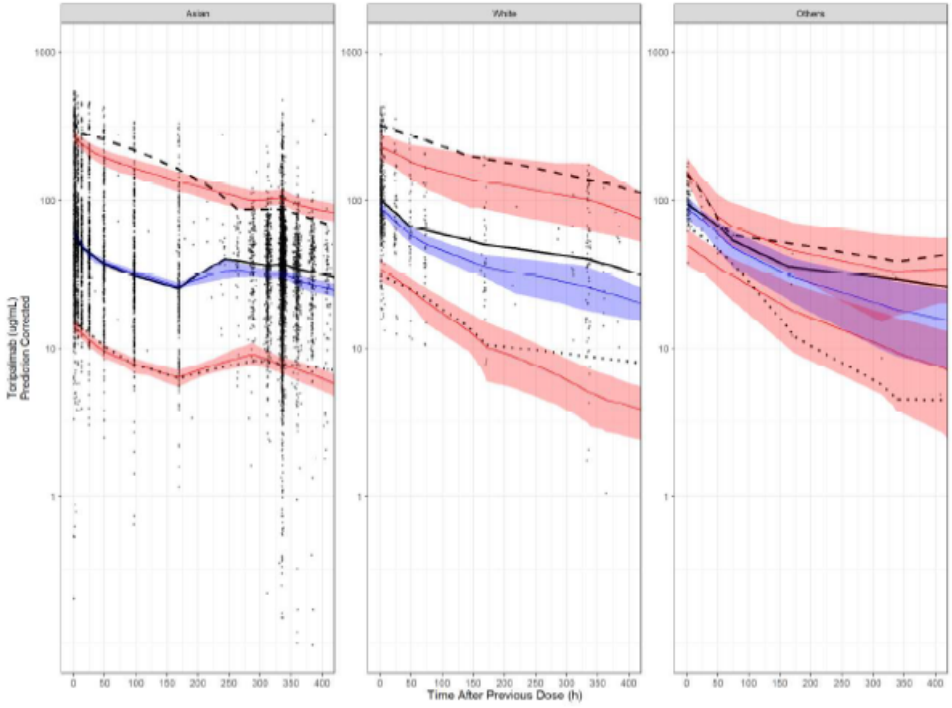
Abbreviations: |IWRES|=absolute value of individual weighted residuals; CWRES=conditional weighted residuals; DV=observed data value(s); GOF=goodness of fit; IPRED=individual predictions; IV=intravenous; LOESS=locally weighted scatterplot smoothing; PK=pharmacokinetic; PRED=population predictions; SC=subcutaneous

Figure 19. pcVPC for Final PK Model (Semi-log Scale, Time After Previous Dose)



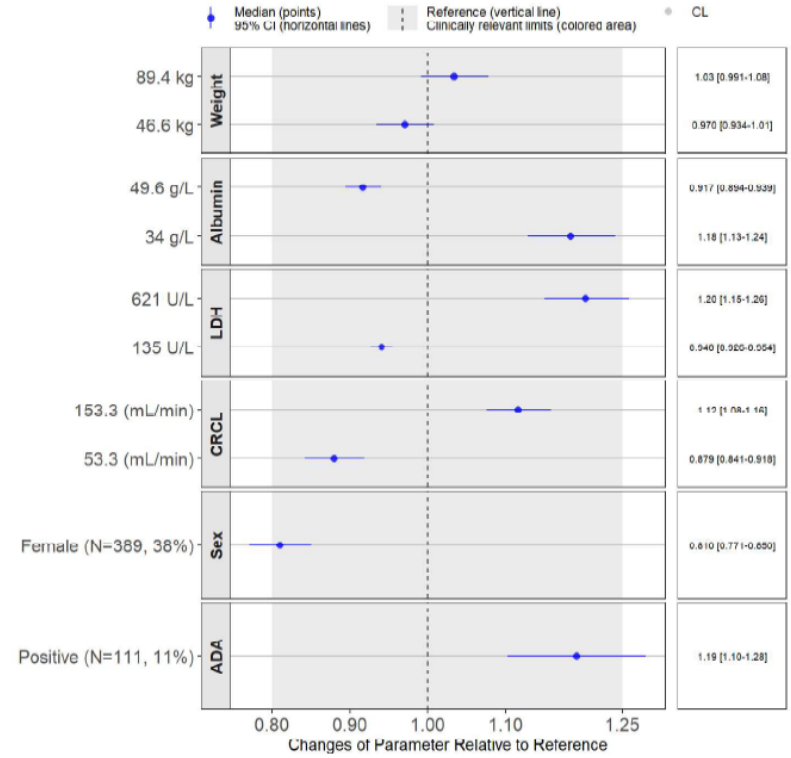
Source: Proposed_Final_PopPK_Model_2.Rmd
Notes: Black dots are observed data points, the black solid line is the observed median, the black dashed line is the observed p95, and the black dotted line is the observed p5. The blue solid line is the simulated median, and the red solid lines are simulated p5 and p95. The blue area is the 95% PI of the simulated median, and the pink areas are the 95% PI of the simulated p5 and p95.
Abbreviations: p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval; PK=pharmacokinetic

Figure 20. pcVPC for Final PK Model Stratify by Race (Semi-log Scale, Time After Previous Dose)



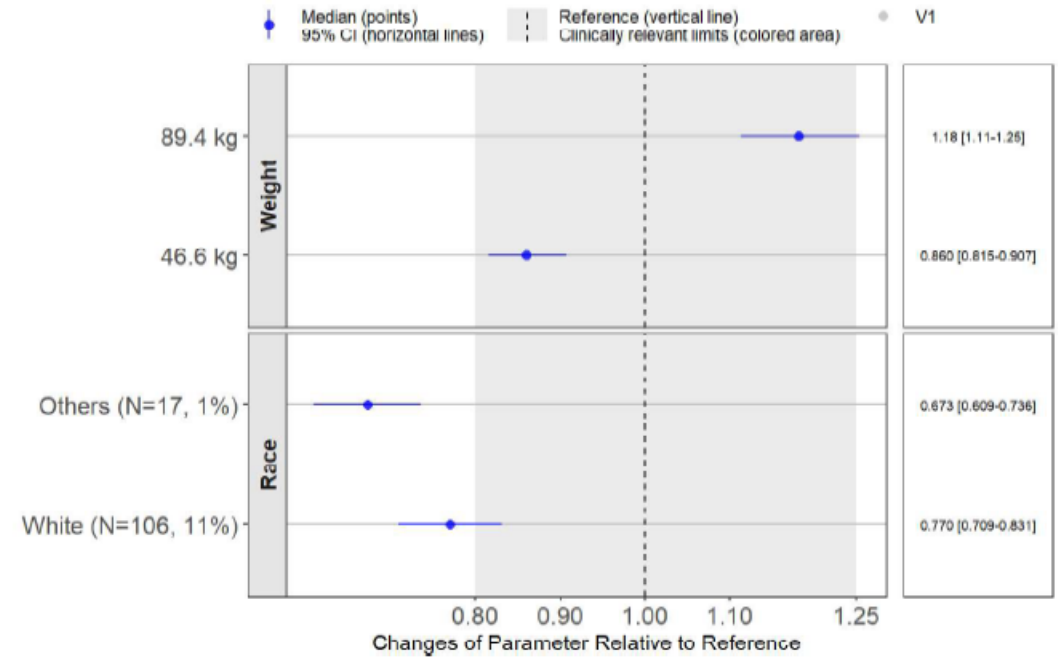
Source: Proposed_Final_PopPK_Model_2.Rmd
Notes: Black dots are observed data points, the black solid line is the observed median, the black dashed line is the observed p95, and the black dotted line is the observed p5. The blue solid line is the simulated median, and the red solid lines are simulated p5 and p95. The blue area is the 95% PI of the simulated median, and the pink areas are the 95% PI of the simulated p5 and p95.
Abbreviations: p5=5th percentile; p95=95th percentile; pcVPC=prediction-corrected visual predictive check; PI=prediction interval; PK=pharmacokinetic

Figure 21. Forest Plot: Covariate Effects on CL



Source: 31 Forest Plots Final Model-09092021.Rmd
Notes: Reference patient is a 63.5 kg Asian male with albumin 43.6 g/L, LDH 198 U/L, CRCL 94.3 mL/min, and ADA-negative status.
Abbreviations: ADA=antidrug antibody; CI=confidence interval; CL=clearance; CRCL=creatinine clearance; LDH=lactate dehydrogenase; N=number of patients

Figure 22. Forest Plot: Covariate Effects on V1



Source: 31 Forest Plots Final Model-09092021.Rmd
Notes: Reference patient is a 63.5 kg Asian male with albumin 43.6 g/L, LDH 198 U/L, and ADA-negative status.
Abbreviations: ADA=antidrug antibody; CI=confidence interval; LDH=lactate dehydrogenase; N=number of patients; V1=volume of distribution of the central compartment

Population PK and Exposure Response Modelling and Simulation of Toripalimab as Monotherapy or in Combination with Platinum-Based Chemotherapy in Patients with Advanced Cancer (TOPA PMX TORIPALIMAB-3355)

The overall objectives of the popPK modelling were as follows:

• To develop a popPK model of toripalimab in patients with various primary cancers

• To investigate selected covariate effects potentially impacting the PK of toripalimab in patients with cancer

• To inform dose selection, dose schedules, and dose optimization

The pharmacokinetic (PK) analysis included 15 clinical studies (eight Phase 1, one Phase 1b, one Phase 1b/2, three Phase 2, and two Phase 3) that investigated toripalimab predominantly in China. The popPK analysis was conducted on a database of 1250 patients and 11343 measurable PK observations. The median age and body weight of the patients across studies were 56 years (18.9 to 85 years) and 62.6 kg (31.6 to 164 kg), respectively.

Serum concentration-time data were analysed using a nonlinear mixed-effects modelling approach by first-order conditional estimation method with interaction with the nonlinear mixed effects modelling software (NONMEM; v7.4.3; ICON, Hanover, MD, US).

Toripalimab was administered as an IV infusion over 1 hour for the first dose and over 30 to 60 minutes for subsequent doses at 2- or 3-week intervals. The monotherapy weight-based doses of toripalimab in these studies ranged from 0.3 to 10 mg/kg Q2W (or single dose), whereas fixed doses ranged from 80 to 480 mg/kg Q2W or 240 mg Q3W. When administered with chemotherapy, toripalimab was given at doses of 240 or 360 mg Q3W. The median toripalimab infusion duration was 44 minutes (28% coefficient of variation). The dosing regimen of 3 mg/kg Q2W comprised 63.6% of all dose records, with the next most common dosing regimen of 240 mg Q3W (25.9%) in the popPK dataset.

Covariate analysis was performed using a forward addition process followed by backward elimination; significance levels of 0.01 and 0.001 were used. All continuous covariates were incorporated into the population model using a scaled structure based on either the median value of the covariate in the population or a standard value of the covariate. All categorical covariates were initially incorporated into the population model using a proportional structure, with either the most common level of the covariate being the reference or a level specific to the analysis.

The evaluation of the impact of covariates on the popPK focused on the most clinically relevant covariates. Covariates tested included the following: body weight, age, sex, race, primary cancer type, immunogenicity (ADA) status, baseline tumour burden (TUBURBL; sum of the longest diameters of all target lesions), ECOG performance status, combination treatment (COMBOTRT), baseline immunoglobulin G (IgG), baseline albumin (BALB), baseline lactate dehydrogenase (BLDH), baseline alkaline phosphatase (BALP), baseline aspartate aminotransferase (AST), baseline alanine aminotransferase (BALT), baseline total bilirubin (BILI), baseline renal function based on estimated renal function by the Cockcroft-Gault equation from serum creatinine, baseline creatinine clearance (BCRCL), and baseline liver dysfunction based on grade per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5).

The final model was qualified using goodness of fit (GOF), bootstrap resampling, and visual predictive check (VPC). Empirical individual Bayesian estimates of PK parameters were generated using the final popPK model to derive exposure metrics.

Results

The base structural model used for the TOPA-PMX-TORIPALIMAB-3355 analysis consisted of a 2-compartment model with zero order IV infusion and time-varying CL characterized by a sigmoidal Emax function. This was based on the final popPK model in the previous analysis, the TOPA-PMX-TORI-2412-Combination Therapy model.

Table 33. Final Model Parameter Estimates

Parameters	**Estimates**	**%RSE**	**95% CI**	**Shrinkage (%)**
E_{maxTV}	-0.445	9	(-0.52, -0.368)	--
T_{50} (h)	1508	11	(1177, 1839)	--
Gamma	1.57	13	(1.165, 1.974)	--
CL_{TV} (mL/h)	14.46	2	(13.89, 15.02)	--
CL_{ADA}	0.211	20	(0.13, 0.29)	--
CL_{LDH}	0.164	11	(0.13, 0.20)	--
CL_{Female}	-0.176	10	(-0.21, -0.14)	--
$CL_{Albumin}$	-0.607	14	(-0.769, -0.443)	--
CL_{Weight}	0.186	32	(0.070, 0.302)	--
CL_{CRCL}	0.212	17	(0.143, 0.282)	--
$V1_{TV}$ (mL)	3673	2	(3514, 3832)	--
$V1_{White\ race}$	-0.222	13	(-0.278, -0.165)	--
$V1_{Other\ race}$	-0.320	10	(-0.385, -0.256)	--
$V1_{Weight}$	0.501	18	(0.321, 0.682)	--
Q_{TV} (mL/h)	41.09	46	(4.096, 78.09)	--
$V2_{TV}$ (mL)	786	15	(559, 1014)	--
Random Effects	**%CV**	**%RSE**	**95% CI**	**Shrinkage (%)**
IIV on E_{max}	33	9	(0.069, 0.151)	30
IIV on CL	30	4	(0.075, 0.104)	31
IIV on V1	28	13	(0.040, 0.120)	83
Correlation CL and V1	41	4	(0.02, 0.050)	--
Residual Error	**%CV**	**%RSE**	**95% CI**	**Shrinkage (%)**
Proportional error	20	4	(0.33, 0.44)	16

%CV: percentage of the coefficient of variation; %RSE: percentage of the relative standard error; ADA: antidrug antibody; BALB: baseline albumin; BLDH: baseline lactate dehydrogenase; BWT: baseline body weight; CI: confidence interval; CL: clearance; CRCL: creatinine clearance; E_{max}: maximum effect (maximum effect of time varying CL in log form; exponentiated value of exp [-0.445] is 0.64); Gamma: sigmoidicity of the relationship with time (T) after first dose in sigmoidal E_{max} model for CL; IIV: interindividual variability; LDH: lactate dehydrogenase; PK: pharmacokinetic; Q: intercompartmental clearance; T50: time (h) at which the change in CL is 50% of E_{max}; TV: typical value; V1: volume of distribution of the central compartment; V2: volume of distribution of the peripheral compartment

Notes: The base PK model parameters included covariates on CL, which included ADA-positive status, weight, LDH, CRCL and sex; covariates on V1 included race and weight. The mathematical expressions for the covariate parameter relationships are as follows:

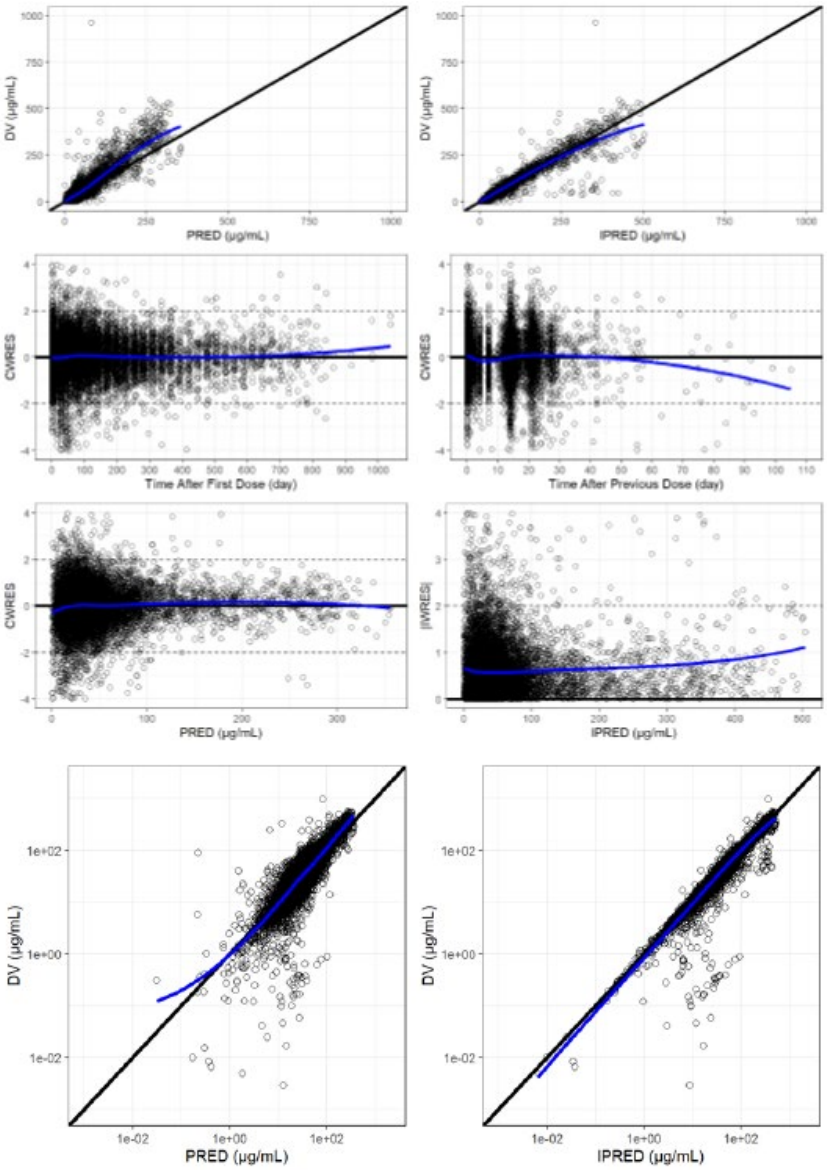
$$CL = CL_{TV} * e^{\frac{E_{max} * Time^{Gamma}}{T_{50}^{Gamma} + Time^{Gamma}}} * CL_{ADA}(\text{if ADA positive}) * \left(\frac{BLDH}{199}\right)^{CL_{LDH}} * CL_{Female}(\text{if Female})$$

$$* \left(\frac{BALB}{43.7}\right)^{CL_{Albumin}} * \left(\frac{BWT}{64}\right)^{CL_{Weight}} * \left(\frac{CRCL}{94.31}\right)^{CL_{CRCL}}$$

$$V1 = V1_{TV} * V1_{White\ Race}(\text{if White Race}) * V1_{Other\ Race}(\text{if Other Race}) * \left(\frac{BWT}{64}\right)^{V1_{Weight}}$$

The final model adequately described individual toripalimab serum concentration profiles.

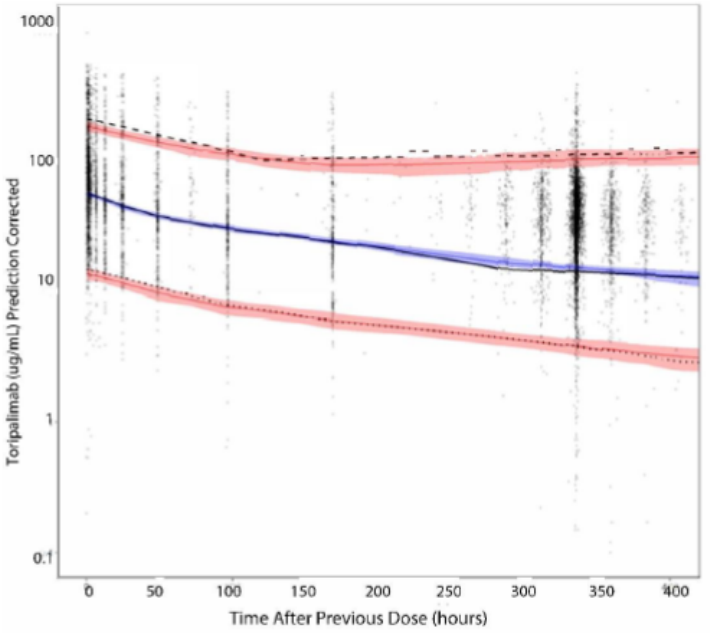
Figure 23. GOF Plots for the Final popPK Model



Source: Figure 4 and Appendix 2.1.4.1, TOPA-PMX-TORIPALIMAB-3355

CWRES: conditional weighted residuals; DV: dependent variable; GOF: goodness-of-fit; IPRED: individual predictions; IWRES: individual weighted residuals; LOWESS: locally weighted scatterplot smoothing; popPK: population pharmacokinetic; PRED: population predictions

Figure 24. pcVPC for the Final PK Model (Semilogarithmic Scale, Time After the Previous Dose)



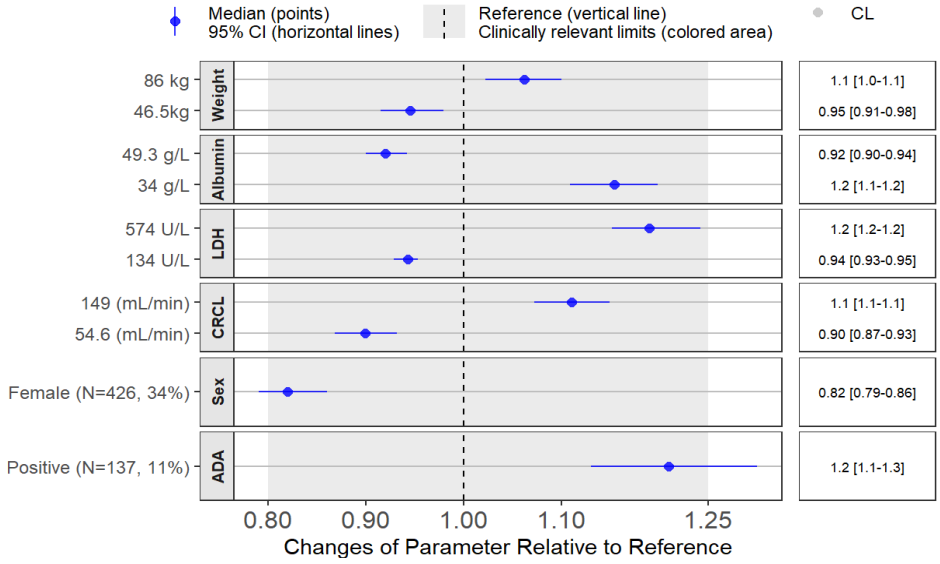
Source: Figure 8, TOPA-PMX-TORIPALIMAB-3355

CL: clearance; p5: 5th percentile; p95: 95th percentile; PI: prediction interval

Notes: Black dots are observed data points, the black solid line is the observed median, and black dashed lines are observed p5 and p95. The blue solid line is the simulated median, and the red solid lines are simulated p5 and p95. The purple area is the 95% PI of the simulated median, and pink areas are the 95% PI of the simulated p5 and p95.

The impact of individual covariates included in the final model on CL and V1 parameters for the final model is shown in the figures below.

Figure 25.Forest Plot of Covariate Effects on CL



ADA: antidrug antibody; CI: confidence interval; CL: clearance; CRCL: creatinine clearance; LDH: lactate dehydrogenase; N: number of patients

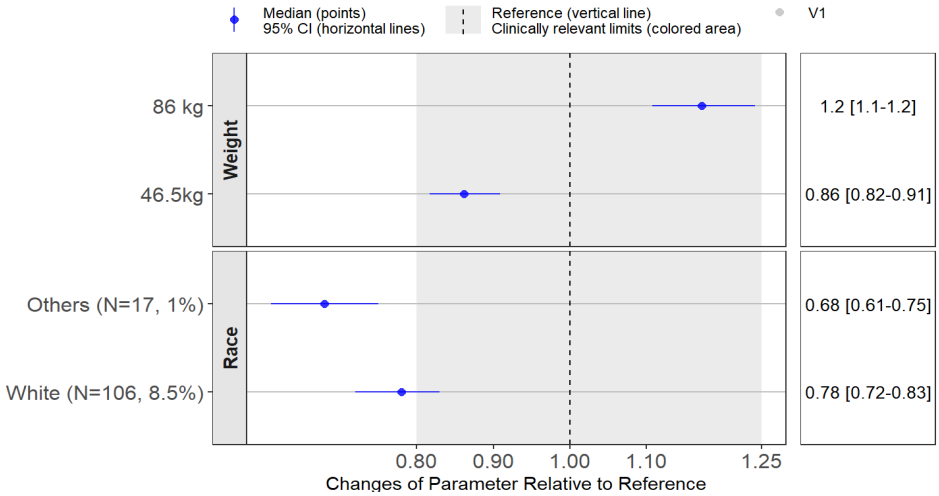
Notes: The reference subject was a 62.6-kg male with albumin of 43 g/L, LDH of 194 U/L, CRCL of 90.6 mL/min, and ADA-negative status.

Body weight was identified as a statistically significant covariate on CL and V1. However, the impact of body weight on toripalimab exposure is expected to be limited. Body weight is projected to result in a

≤20% change in any PK parameter at the p5 (46.5 kg) and p95 (86 kg) of weight in the popPK analysis population. Additionally, for the Study CT21 population as a representative example (body weight range in this study was 38.5 to 101 kg), at the 240 mg Q3W IV dosage, geometric mean steady-state toripalimab average serum concentration (C_{ave}) in patients with body weight <50 and >75 kg is expected to be 1.17- and 0.84-fold of that in patients with body weight of 50 to 75 kg.

Various tumour types did not show a clinical impact on toripalimab PK.

Figure 26. Forest Plot of Covariate Effects on V1



CI: confidence interval; N: number of patients; V1: volume of distribution of the central compartment
Notes: The reference subject was a 62.6-kg Asian male.

Table 34. Predicted Toripalimab Exposure Across Body Weight Subgroups in Study CT21

Dose	Weight Range	C_{ave} Dose 1 (μg/mL)	C_{max} Dose 1 (μg/mL)	C_{trough} Dose 1 (μg/mL)	Number of Patients
240 mg Q3W	<50 kg	32.5 [22, 77.9]	80 [67.4, 227.1]	13.8 [5, 40.5]	28
	50–75 kg	28.1 [15.8, 49.9]	69.2 [38, 103.7]	11.3 [1.5, 31.3]	190
	>75 kg	24.3 [15.1, 30.3]	61 [46, 117.6]	9.1 [1.9, 16.1]	18
	Weight Range	**C_{ave}, ss (μg/mL)**	**C_{max}, ss (μg/mL)**	**C_{trough}, ss (μg/mL)**	**Number of Patients**
	<50 kg	68 [34.2, 104.4]	121.9 [87.8, 277]	40.4 [12.3, 75.6]	28
	50–75 kg	58.2 [13.8, 112.4]	104.8 [54.4, 168.1]	33.1 [0.8, 85]	190
	>75 kg	48.7 [33.4, 73.2]	89.3 [65.3, 133.6]	27 [13.3, 53]	18

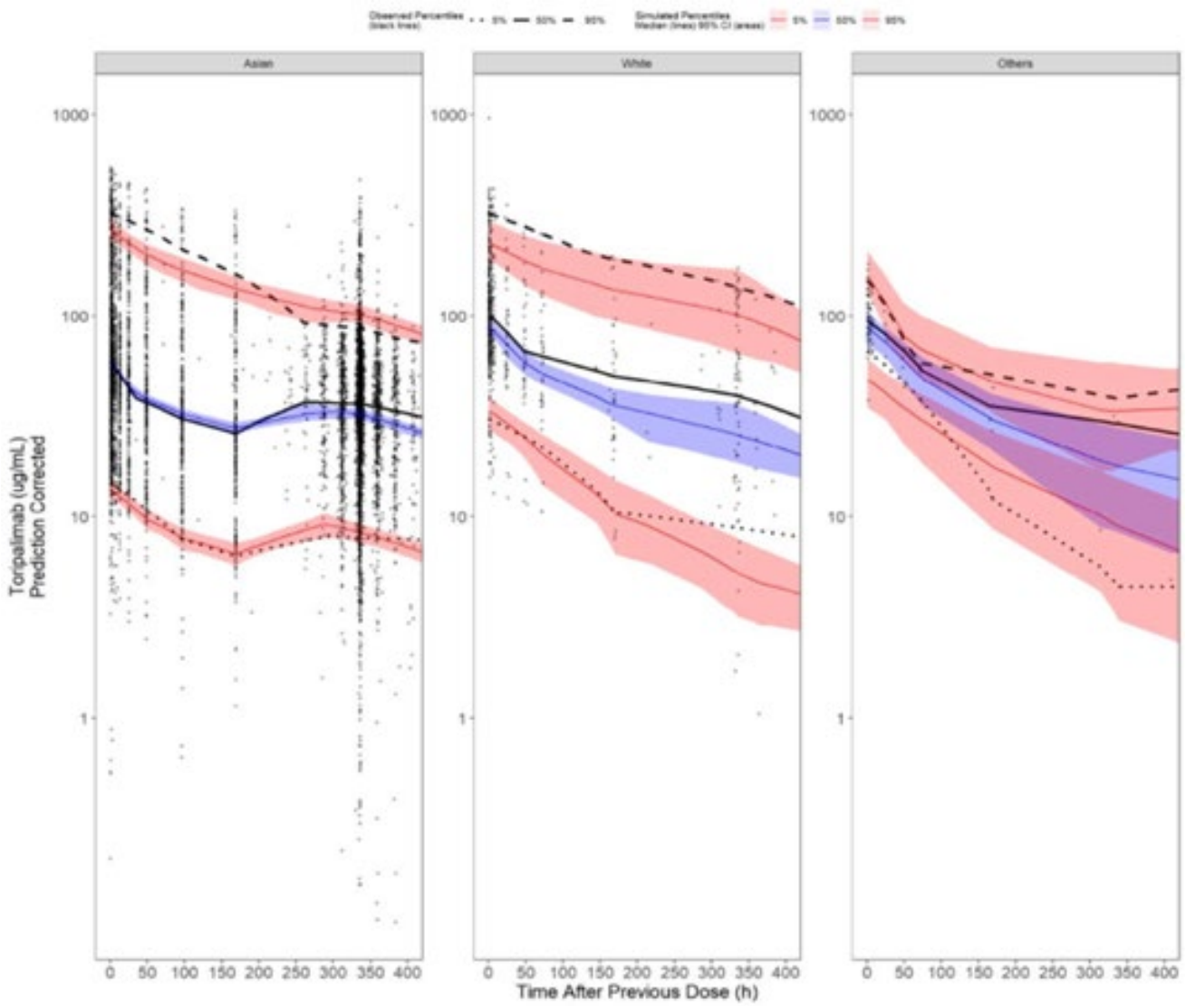
Source: Appendix 2.1.6. Table 6, TOPA-PMX-TORIPALIMAB-3355

C_{ave}: average serum concentration; C_{max}: maximum serum concentration; C_{trough}: pre-dose trough serum concentration; Q3W: every 3 weeks; ss: steady state; V1: volume of distribution of the central compartment

Notes: Overall range of body weight in Study CT21 was 38.5 to 101 kg. Values for the 240 mg Q3W dose level for Study CT21 patients are reported as geometric mean in μg/mL [minimum, maximum]. Dose 1 indicates the first dose, and "ss" indicates steady state.

Race was a statistically significant covariate on V1, with White patients having a 22% lower V1 compared to Asian patients. Similar findings apply to other races, with 32% lower V1 compared to Asians, although the sample size of this group is limited (n = 17). This difference does not lead to a meaningful impact on steady-state toripalimab Cave, Cmax, and pre-dose trough serum concentration (Ctrough; Cave and Ctrough) at the 240 mg Q3W IV dosage in White patients compared to Asian patients, i.e., exposures are comparable between Asian and White in the 240 mg Q3W dose regimen (see "Special populations – Race").

Figure 27. pcVPC for the Final PK Model Stratify by Race (Semilogarithmic Scale, Time After the Previous Dose)



Study JS001-021-III-ESCC (CT21)

Study CT21 was a Phase 3, randomized, double-blind, multi centre, placebo-controlled study. As only sparse PK data were available from this study, no independent PK analyses were conducted. Data from Study CT15 were included in the popPK analysis TOPA PMX-TORIPALIMAB-3355 described in **Study S001-015-III-NPC (CT15)** section.

Study TAB001-01

This was a Phase 1, multi-centre, open-label study to evaluate safety, tolerability, PK, immunogenicity, and antitumour activity of TAB001 (toripalimab) following IV infusions in 184 adult patients with advanced solid malignancies who were refractory to standard therapy or for whom no standard therapy existed. This was a 2-part study (Part A = dose escalation, Part B = disease-specific cohort expansion). Patients were dosed with 80 (Cohort 1), 240 (Cohort 2), or 480 (Cohort 3) mg Q2W in Part A of the study, and patients were dosed with 240 mg Q3W in Part B of the study. In Part A, the treatment cycle was 28 days (4 weeks) during which toripalimab was administered through IV infusions Q2W. In Part B, the treatment cycle was 42 days (6 weeks) during which toripalimab was administered through IV infusion Q3W. The PK study design is summarized in the table below.

Table 35. Pharmacokinetic Study Design of Study TAB001-01

Cohort		Drug Product	Dose	Maximum Number of Doses	Route	Number of Patients	Dense Blood Sampling
Part A	1	toripalimab	80 mg	4	IV Q2W	3	1st infusion
	2	toripalimab	240 mg	13	IV Q2W	8	1st and 5th or 6th infusions
	3	toripalimab	480 mg	13	IV Q2W	7	1st and 6th infusion
Part B		toripalimab	240 mg	13	IV Q3W	23	1st and 6th or 7th infusion in first 20 patients enrolled

IV: intravenous; n: number of patients; Q2W: every 2 weeks; Q3W: every 3 weeks

Blood Sampling Times in Part A (per protocol v7.0): On Day 1 of Cycle 1 (after the 1st dose) and on Cycle 3 Day 15: pre-dose; end of infusion; and 0.5, 2, 4, 6, 12, 24, 4, 72, and 168 hours after the end of infusion. On Days 1 and 15 of Cycles 2, 4, 5, and 6 and on Cycle 3 Day 1: pre dose and at the end of infusion. In Cycle 8 and every 4 cycles thereafter: pre-dose and at the end of infusion.

Blood Sampling Times in Part B (per protocol v7.0): On Day 1 of Cycle 1 (after the 1st dose) and on Cycle 3 Day 22 in the first 20 patients enrolled: pre-dose; end of infusion; and 0.5, 2, 4, 6, 12, 24, 48, 72, 168, and 336 hours after the end of infusion. On Day 1 of Cycle 1 for all subjects thereafter: pre-dose and at the end of infusion. On Days 1 and 22 of Cycles 2, 4, 5, and 6 and on Cycle 3 Day 1 in the first 20 patients enrolled: pre-dose and at the end of infusion. On Day 1 of Cycles 2, 4, and 6 for all subjects thereafter: pre-dose and at the end of infusion. In Cycle 8 and every 4 cycles thereafter: pre-dose and at the end of infusion.

Serum concentrations of toripalimab in patients were determined using a validated enzyme linked immunosorbent assay (ELISA) method. LLOQ was 15.6 ng/mL.

Results

Serum concentration-time profiles of toripalimab following a single dose and following multiple doses are presented in the tables below.

Figure 28. Toripalimab Concentration-Time Profile Following 80 mg Dose (First IV Infusion) in Study TAB001-01

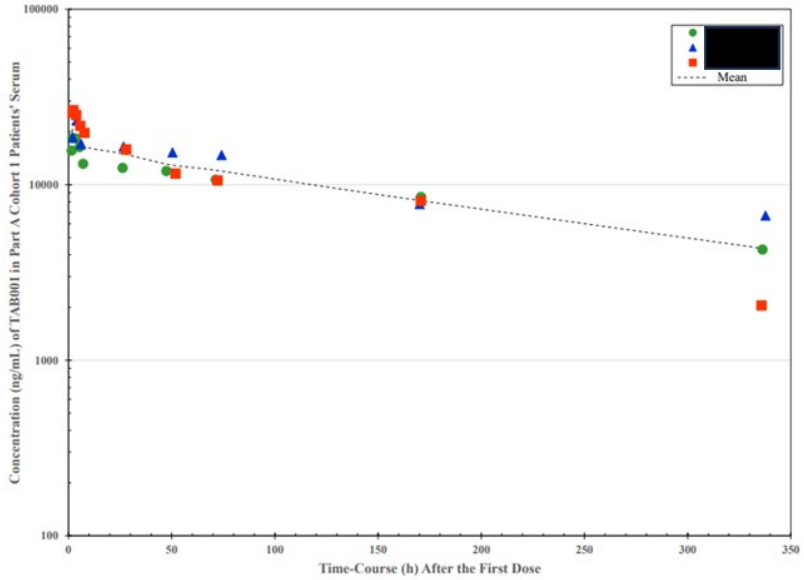


Figure 29. Toripalimab Concentration-Time Profile Following 240 mg Dose (First and Fifth/Sixth IV Infusions) in Study TAB001-01

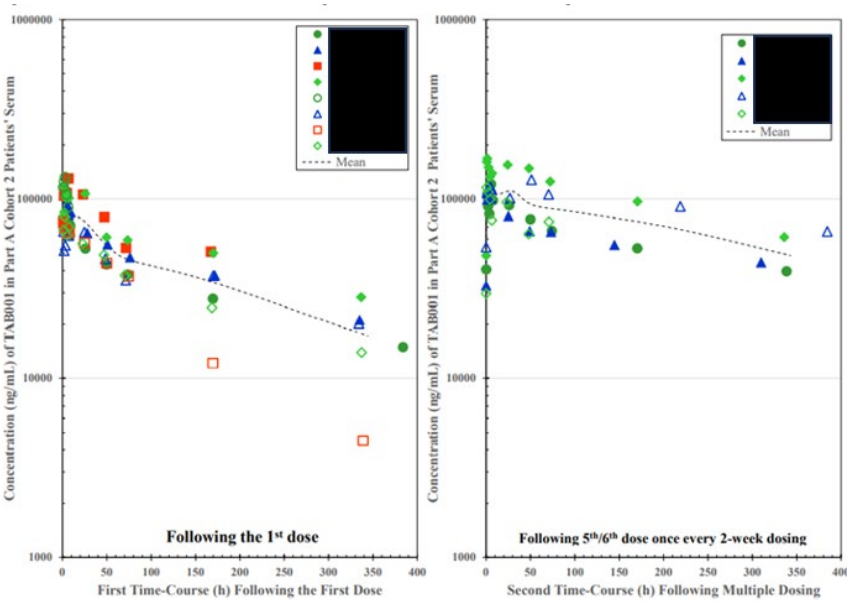


Figure 30. Toripalimab Concentration-Time Profile Following 480 mg Dose (First and Sixth IV Infusions) in Study TAB001-01

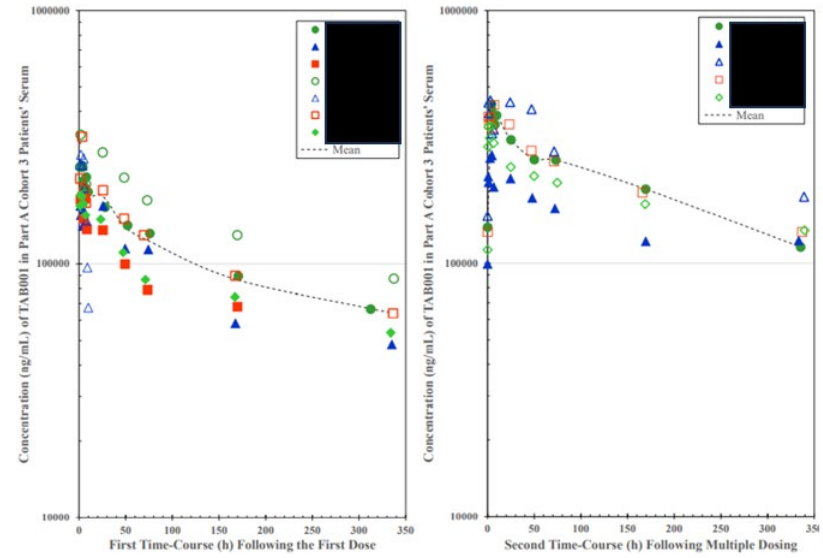
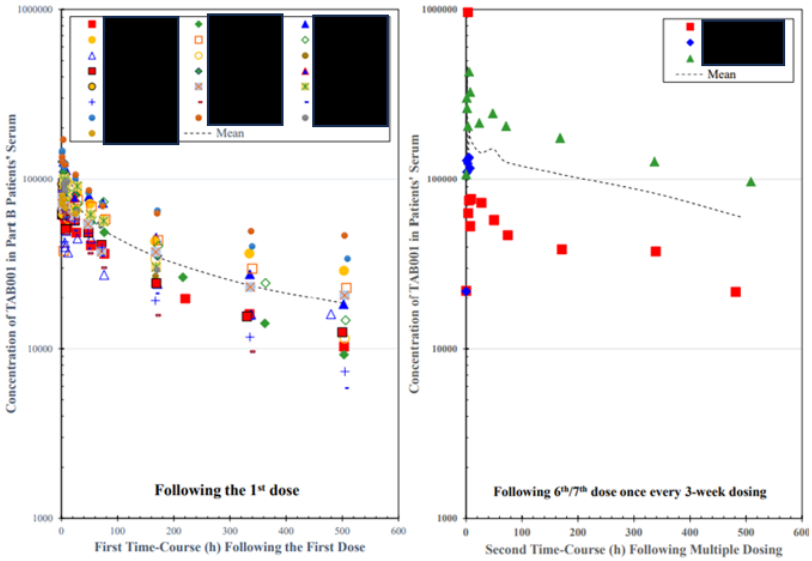


Figure 31. Toripalimab Concentration-Time Profile Following 240 mg Dose in Part B (First and Sixth/Seventh IV Infusions) in Study TAB001-01



PK parameters were estimated by non-compartmental analysis using WinNonlin (v8.3.2.116; Pharsight Corporation, St. Louis, MO) Model 202 (IV infusion administration). The PK parameters following single and multiple dosing of toripalimab are shown in the tables below.

Table 36. Mean (±SD) PK of TAB001 Following the First IV Infusion in Study TAB001-01

PK Parameters	Part A Cohort 1 (80 mg Q2W)	Part A Cohort 2 (240 mg Q2W)	Part B (240 mg Q3W)	Part A Cohort 2 and Part B (240 mg Q2W or Q3W)[1)]	Part A Cohort 3 (480 mg Q2W)
N	3	8	22	30	7
T_{max} (h)	2.21 ± 0.39	4.07 ± 2.33	4.03 ± 2.61	4.04 ± 2.50	2.46 ± 0.96
C_{max} (µg/mL)[2)]	23.9 ± 4.79	96.9 ± 26.8	95.1 ± 27.8	95.6 ± 27.1	242 ± 64.4
$AUC_{(0-t)}$ µg•h/mL[2]	3000 ± 387	13000 ± 6700	15500 ± 11200	14900 ± 10100	32400 ± 10700
$t_{½}$ (h)	177 ± 62.4	189 ± 68.9	293 ± 186	236 ± 167	237 ± 78.4

1 Pharmacokinetics of the subjects in Part A Cohort 2 and Part B following the 1st IV infusion were pooled for this table

2 Original calculations are in ng/mL or ng•h/mL, units converted for reporting purposes in this table

$AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; IV: intravenous; N: number of patients; PK: pharmacokinetic; Q2W: every 2 weeks; Q3W: every 3 weeks; SD: standard deviation; t½: elimination half-life; T_{max}: time to reach maximum serum concentration

Note: T_{max} is reported to 2 decimal places. All other PK parameters are reported to 3 significant figures where appropriate.

Table 37. PK of TAB001 Following Multiple (Fifth/Sixth/Seventh) IV Infusions in Study TAB001-01

PK Parameters	Part A Cohort 1 (80 mg Q2W)	Part A Cohort 2 (240 mg Q2W)	Part B (240 mg Q3W)	Part A Cohort 3 (480 mg Q2W)
N	0	5	3	4
T_{max} (h)	NA	12.8 ± 21.6	4.57 ± 1.23	4.91 ± 1.47
C_{max} (µg/mL) [1)]	NA	130 ± 21.6	509 ± 420	411 ± 41.7
$AUC_{(0-t)}$ (µg•h/mL)	NA	22600 ± 12300	33900 ± 41200	72600 ± 11200
$t_{½}$ (h)	NA	326 ± 141	352 ± ND	298 ± 77.7
AR (AUC)	NA	1.71 ± 0.87	1.98 ± 0.58	2.14 ± 0.10

1 Original calculations are in ng/mL or ng•h/mL, units converted for reporting purposes in this table

AR(AUC): accumulation ratio based on AUC; AUC: area under the curve; $AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; IV: intravenous; N: number of patients; ND: Not determined; PK: pharmacokinetic; Q2W: every 2 weeks; Q3W: every 3 weeks; SD: standard deviation; t½: elimination half life; T_{max}: time to reach maximum serum concentration

1 Original calculations are in ng/mL or ng•h/mL, units converted for reporting purposes in this table

Note: T_{max} is reported to 2 decimal places. All other PK parameters are reported to 3 significant figures where appropriate.

Inter-conversion

The Applicant did not perform dedicated inter-conversion studies.

Pharmacokinetics of metabolites

No definitive metabolism studies in humans have been performed.

Consequences of possible genetic polymorphism

No definitive metabolism studies in humans have been performed. Like other monoclonal antibodies, toripalimab is metabolized to peptides and amino acids by target cell interaction and circulating phagocytic cells. Toripalimab is not, therefore, affected by genetic polymorphisms in metabolizing

enzymes.

Dose proportionality and time dependencies

Dose proportionality

The single- and multiple-dose PK of toripalimab in Chinese patients with advanced tumours was investigated in 3 dose escalation studies (Studies CT1, CT2, and CT3) across which, 5 dose levels (0.3, 1, 3, 10, and 240 mg administered Q2W) were evaluated. A total of 93 patients were enrolled in these 3 studies, and PK parameters after single and multiple (6th or 7th dose) IV infusions of toripalimab are summarized in Table 42. Over the dosage range of 1 to 10 mg/kg Q2W, toripalimab maximum serum concentration (C_{max}) and area under the serum concentration-time curve increased approximately dose proportionally based on an analysis of dose normalized exposure parameters.

Table 38. Summary of Key Toripalimab PK Parameters Using Pooled Data from Studies CT1, CT2, and CT3

PK Parameters	Units	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	240 mg
Single dose						
		n = 3	n = 26	n = 35	n = 16	n = 3
C_{max}	µg/mL	5.77 ± 1.33	21.8 ± 6.24	67.9 ± 26.7	214 ± 32.1	71.7 ± 8.7
$AUC_{(0-t)}$	h•µg/mL	655 ± 199	2930 ± 699	10100 ± 3330	34500 ± 8000	11400 ± 5890
Multiple dose (Q2W)						
		n = 2	n = 17	n = 28	n = 11	n = 1
C_{max}	µg/mL	6.58 ± 2.19	30.4 ± 11.0	93.3 ± 30.6	319 ± 102	153
$AUC_{(0-t)}$	h•µg/mL	1100 ± 448	4820 ± 1040 (n = 16)	18200 ± 6100	68600 ± 30300	34200

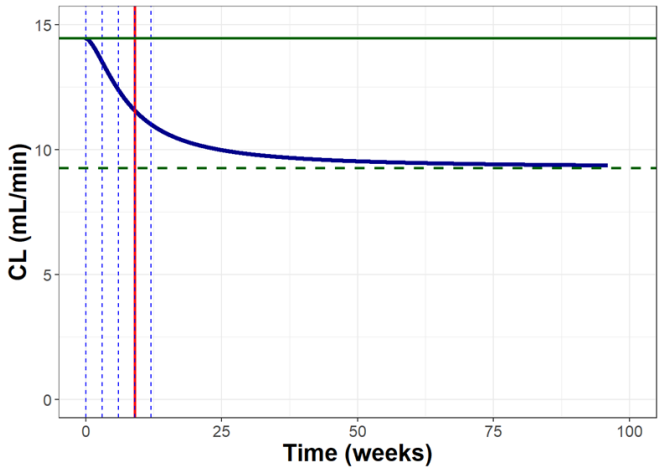
$AUC_{(0-t)}$: area under the curve from time 0 to t; C_{max}: maximum serum concentration; n:number of patients; PK: pharmacokinetic; Q2W: every 2 weeks

Notes: Parameters rounded to 3 significant figures.

Time dependency

As shown in the figure below, the time-varying CL results showed that, on average, CL decreases by approximately 31% over time compared to the baseline CL. The time at which the change in CL is at 50% of E_{max} was estimated to be approximately 65 days in a typical patient.

Figure 32. Typical Toripalimab CL Versus Time



CL: clearance; E_{max}: maximum effect; Q3W: every 3 weeks; T50: time at which the change in CL is 50% of E_{max}
Notes: The horizontal green solid line represents the typical value of CL (CL = 14.46 mL/min), the horizontal green dashed line represents the maximum decrease in CL (36%), and the vertical red line represents T50 (T50 = 1508 hours). The vertical blue dashed lines represent the first 5 toripalimab doses for the 240 mg Q3W regimen.CL: clearance; p5: 5th percentile; p95: 95th percentile; PI: prediction interval

The accumulation index is of approximately 2 fold in AUC3wk,ss for the 240 mg dose Q3 regimen.

Intra- and inter-individual variability

The variability in toripalimab exposure across NCA studies is moderate for Cmax, and AUC.

In the POP PK analysis, inter-individual variability (IIV) was evaluated on all parameters. However, due to the sparseness of the data, only IIV on CL and V1 was supported and retained in the model. The POP PK model showed a moderate inter-individual variability (%CV) for CL (30%) and volume of distribution at SS (28%).

Special populations

Impaired renal function

Renal function (renal impairment if baseline CRCL<89 mL/min) was not identified as statistically significant covariate in the popPK model. See current popPK analysis population (TOPA PMX TORIPALIMAB-3355). Renal impairment is not expected to alter the PK of monoclonal antibodies, including toripalimab. The lack of dedicated studies in subjects with renal impairment is sufficiently justified. Given that toripalimab is a monoclonal antibody with a molecular weight of 147 kDa without gycans, it is not expected to undergo significant renal elimination and its pharmacokinetics is therefore not expected to be impacted by renal impairment.

This expectation was confirmed by using popPK analyses to evaluate the impact of renal impairment on toripalimab PK.

For PK analyses, there were 653 and 597 patients with normal renal function and any degree of renal impairment, respectively, in the analysis. The renal impairment population included patients with CRCL ranging from 30.5 to 89 mL/min and therefore included patients with mild (CRCL = 60 to 89 mL/min; N = 483) and moderate (CRCL = 30 to 59 mL/min; N = 114) renal impairment as defined in the EMA guideline (EMA/CHMP/83874/2014, 2015).

The categorical variables baseline renal impairment were not significant covariates in the final popPK model, and although the continuous BCRCL variable was included in the final model, the change in toripalimab exposure with changes in BCRCL was minimal. Overall, popPK analyses support that mild or moderate renal impairment do not impact the PK of toripalimab. The recommended dosage of toripalimab is therefore appropriate for use in patients with mild or moderate renal impairment.

Renal impairment is not expected to alter the PK of monoclonal antibodies, including toripalimab. The lack of dedicated studies in subjects with renal impairment is sufficiently justified. Given that toripalimab is a monoclonal antibody with a molecular weight of 147 kDa without gycans, it is not expected to undergo significant renal elimination and its pharmacokinetics is therefore not expected to be impacted by renal impairment.

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The categorical variables baseline renal impairment were not significant covariates in the final popPK model, and although the continuous BCRCL variable was included in the final model, the change in toripalimab exposure with changes in BCRCL was minimal. Overall, popPK analyses support that mild or moderate renal impairment do not impact the PK of toripalimab. The recommended dosage of toripalimab is therefore appropriate for use in patients with mild or moderate renal impairment.

PK has not been evaluated in patients with severe renal impairment, or end-stage renal disease.

Impaired hepatic function

Liver dysfunction was not identified as statistically significant covariate in the popPK model. See current popPK analysis population (TOPA PMX TORIPALIMAB-3355).). No specific studies have been conducted in study participants to determine the effect of hepatic impairment on the PK of toripalimab. As a monoclonal antibody, toripalimab is not expected to undergo significant hepatic elimination and the lack of dedicated studies in subjects with hepatic impairment is justified.

In the updated popPK analyses, there were 1083, 166, and 1 patient with normal hepatic function or with CTCAE Grade 1 or 2 hepatic impairment, respectively, out of 1250 patients included in the analysis.

The categorical variables baseline hepatic impairment were not significant covariates in the final popPK model, and although the continuous BCRCL variable was included in the final model, the change in toripalimab exposure with changes in BCRCL was minimal.

Based on the POP PK results, this is not a significant covariate and it is agreed that a dose adjustment in patients with mild hepatic impairment is not warranted.

There is inadequate data in patients with moderate hepatic impairment, and toripalimab PK has not been evaluated in patients with severe hepatic impairment.

Gender

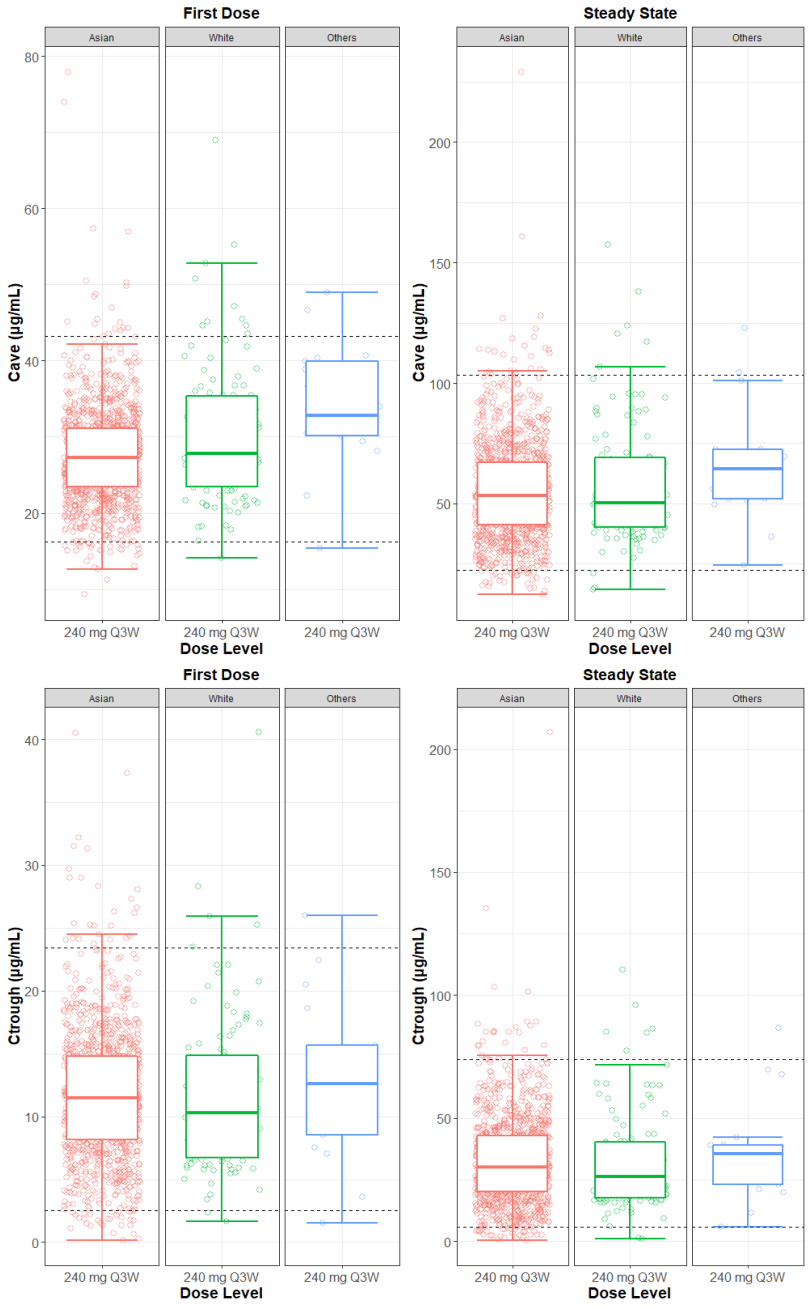
In the popPK analysis, sex was identified as a statistically significant covariate of toripalimab CL with females having 20% lower CL compared to males, independent of body weight. See current popPK analysis population (TOPA PMX TORIPALIMAB-3355). As exposure-safety analyses indicate that the probability of AEs does not increase with increasing toripalimab exposure, this minor difference in exposure is unlikely to be clinically meaningful. Overall, no toripalimab dose adjustment based on sex is recommended in the NPC or OSCC indications

Race

In the toripalimab popPK analysis, race was a statistically significant covariate on V1, with White patients having a 22% lower V1 compared to Asian patients in the popPK model. Similar findings apply to other races, with 32% lower V1 compared to Asians. This difference does not lead to a meaningful impact on steady-state toripalimab Cave, Cmax, and Ctrough at the 240 mg Q3W IV dosage in White patients compared to Asian patients. Patients of other races trended toward slightly higher toripalimab exposures (Cave) (TOPA-PMX-TORIPALIMAB-3355).

Race was a statistically significant covariate on V1, with White patients having a 22% lower V1 compared to Asian patients. Similar findings apply to other races, with 32% lower V1 compared to Asians, although the sample size of this group is limited (n = 17). This difference does not lead to a meaningful impact on steady-state toripalimab C_{ave}, C_{max}, and pre-dose trough serum concentration (C_{trough}; C_{ave} and C_{trough} shown in the figure below) at the 240 mg Q3W IV dosage in White patients compared to Asian patients, i.e., exposures are comparable between Asian and White in the 240 mg Q3W dose regimen.

Figure 33. Model-Predicted C_{ave} (Upper Panels) and C_{trough} (Lower Panels) Comparison at 240 mg Q3W Stratified by Asian, White, and Other Races



C_{ave}: average serum concentration; C_{trough}: pre-dose trough serum concentration; Q3W: every 3 weeks
Notes: Horizontal dashed lines represent the 2.5th and 97.5th percentiles of 240 mg Q3W exposures for all patients from Study CT21. Y-axis scales differ between first dose and steady state.

Weight. The body weight range included in the current popPK analysis population (TOPA PMX TORIPALIMAB-3355) was 31.6 to 164 kg (median: 62.6 kg), which is expected to encompass the typical body weight range of the general oncology patient population in the European Union (EU). In the popPK analysis, body weight was identified as a statistically significant covariate on CL and V1. The body weight is projected to result in a ≤20% change in any PK parameter at the p5 (46.5 kg) and p95 (86 kg) of weight in the popPK analysis population. Additionally, at the 240 mg Q3W IV dosage, geometric mean steady-state toripalimab Cave in patients with body weight <50 and >75 kg is expected to be 1.17- and 0.84-fold of that in patients with body weight of 50 to 75 kg.

Table 39. Predicted Toripalimab Exposure Across Body Weight Subgroups in Study CT21

Dose	Weight Range	C_{ave} Dose 1 (μg/mL)	C_{max} Dose 1 (μg/mL)	C_{trough} Dose 1 (μg/mL)	Number of Patients
240 mg Q3W	<50 kg	32.5 [22, 77.9]	80 [67.4, 227.1]	13.8 [5, 40.5]	28
	50–75 kg	28.1 [15.8, 49.9]	69.2 [38, 103.7]	11.3 [1.5, 31.3]	190
	>75 kg	24.3 [15.1, 30.3]	61 [46, 117.6]	9.1 [1.9, 16.1]	18
	Weight Range	**C_{ave}, ss (μg/mL)**	**C_{max}, ss (μg/mL)**	**C_{trough}, ss (μg/mL)**	**Number of Patients**
	<50 kg	68 [34.2, 104.4]	121.9 [87.8, 277]	40.4 [12.3, 75.6]	28
	50–75 kg	58.2 [13.8, 112.4]	104.8 [54.4, 168.1]	33.1 [0.8, 85]	190
	>75 kg	48.7 [33.4, 73.2]	89.3 [65.3, 133.6]	27 [13.3, 53]	18

C_{ave}: average serum concentration; C_{max}: maximum serum concentration; C_{trough}: pre-dose trough serum concentration; Q3W: every 3 weeks; ss: steady state; V1: volume of distribution of the central compartment
Notes: Overall range of body weight in Study CT21 was 38.5 to 101 kg. Values for the 240 mg Q3W dose level for Study CT21 patients are reported as geometric mean in μg/mL [minimum, maximum]. Dose 1 indicates the first dose, and "ss" indicates steady state.

Elderly. Age was not identified as a statistically significant covariate of toripalimab PK parameters in the popPK analysis. Although age was identified as an independent predictor of response in the efficacy-exposure analysis in the OSCC population, the 95% CI of the odds ratio at both the p5 and p95 of age included 1, suggesting that this finding is unlikely to be clinically meaningful. No toripalimab dose adjustment based on age is recommended in the NPC or OSCC indications.

Table 40. Age groups vs. PK

PK Trials	Age 65-74 (Older subjects number /total subjects number)	Age 75-84 (Older subjects number /total subjects number)	Age 85+ (Older subjects number /total subjects number)
TAB001-01	39/131	21/131	2/131
CT21	100/236	1/236	0/236
CT15	4/92	0/92	0/92
CT14	12/34	2/34	0/34
CT12	49/136	8/136	0/136
CT9	0/20	0/20	0/20
CT8	19/69	0/69	0/69
CT7	12/67	0/67	0/67
CT6	0/13	0/13	0/13
CT5	24/240	0/240	0/240
CT4	17/119	2/119	0/119
CT3	1/32	0/32	0/32
CT2	2/25	0/25	0/25
CT1	2/36	0/36	0/36

Children. No studies were conducted in children. The safety and efficacy of Loqtorzi in children and adolescents aged under 18 years have not been established. No data are available.

Anti-drug antibodies. Among the patients who received toripalimab in combination with chemotherapy, 39/402 (9.7%) were ADA-positive at any timepoint. Among the patients who received toripalimab monotherapy, 121/1109 (10.9%) were ADA-positive at any timepoint. In the final popPK model (N = 1250), the presence of ADA at any timepoint led to a 20% increase in CL but had no significant effect on exposure as measured by AUC.

Pharmacokinetic interaction studies. As monoclonal antibodies are primarily cleared via catabolism by proteolytic enzymes and in vitro studies have confirmed the absence of induction of cytokine release with toripalimab, drug drug interaction studies were not conducted and are not planned. This approach is consistent with the risk-based recommendations in the EMA guideline titled "Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins" (CHMP/EWP/89249/2004, 2007).

In vitro. No pharmacokinetic interaction can be expected; therefore, no pharmacokinetic drug interaction studies have been performed in vitro.

In in vitro experiments, toripalimab, pembrolizumab, and nivolumab did not induce cytokine release compared to the positive control (CD3 agonist antibody) (TAB001 In Vitro Cytokine Release Assay Report). There is therefore minimal risk for cytokine-induced drug interactions.

In vivo. No pharmacokinetic drug interaction studies have been performed in vivo. This is agreed. The concurrent treatment with chemotherapy (COMBOTRT) was tested in the POP PK analysis dataset to investigate the potential impact of chemotherapy on toripalimab PK behaviour. The final model showed that COMBOTRT was not clinically significant. This covariate resulted in a <20% change in any PK parameter and was removed from the model.

Pharmacokinetics using human biomaterials. No studies regarding pharmacokinetics using human biomaterials were conducted.

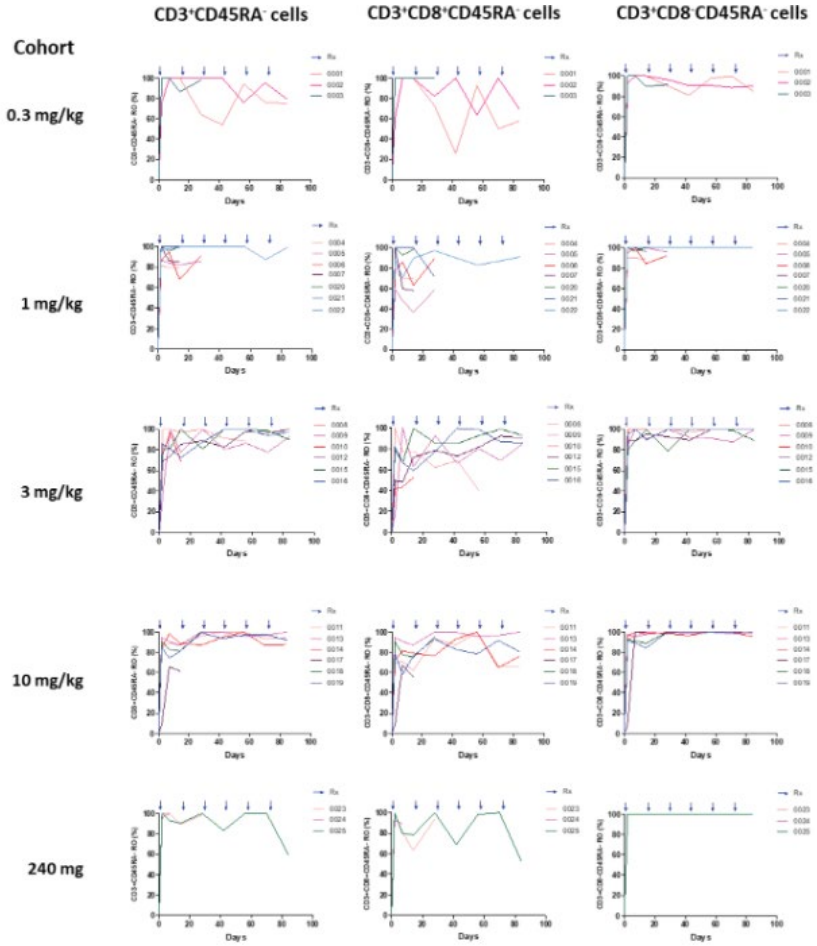
3.6.2.3. Pharmacodynamics

The primary pharmacodynamics of Toripalimab were explored in Studies CT1, CT2, and CT3 (PD-1 binding). Dose response data was also evaluated: the ORR was explored in studies CT3, CT4, CT5, CT6, CT12, while the CT8 study explored Relapse-free survival. The PK/PD relationship for PFS in CT15 and for both PFS and OS in CT21 were explored.

Mechanism of action

Toripalimab pharmacodynamics were evaluated using receptor occupancy measurements on peripheral white blood cells and analysis of lymphocyte subsets in Studies CT1, CT2, and CT3. In both Studies CT1 and CT2, analysis of whole blood samples by flow cytometry showed that toripalimab had no significant effect on the proportion of T-lymphocyte subsets. Flow cytometry was used to evaluate receptor occupancy in both Studies CT1 and CT2. At all dosage levels evaluated in these studies, i.e., 1 to 10 mg/kg Q2W IV, binding of toripalimab to the target molecule PD-1 on the surface of activated T lymphocytes was observed shortly after the first dose. Complete receptor occupancy (>80%) was achieved and maintained throughout the 2 week dose interval in most patients at doses ≥3 mg/kg.

Figure 34. Study CT2 - Receptor Occupancy (%) in T-Cell Subgroup



Notes: In Study CT2, whole blood samples were collected prior to the first dose (Day 0) and at 48 hours (Day 2), 168 hours (Day 7), and Day 14 after the first dose and thereafter prior to administration every 2 weeks.

In Study CT9, blood samples from 20 patients were collected after IV administration of toripalimab at doses of 1, 3, or 10 mg/kg IV Q2W. PD-1 receptor occupancy was measured on activated immune T cells in patient samples at different timepoints using flow cytometry. Toripalimab bound to the PD-1 receptor on activated T lymphocytes and maintained complete PD-1 receptor occupancy (>80%) on peripheral CD4+ T cells. This was observed in the majority of the patients in dose cohorts ≥1 mg/kg throughout the observation period after the first administration of toripalimab. However, high variability in PD-1 receptor occupancy was observed on CD8+ T cells.

Figure 35. Percentage of Mean PD-1 Receptor Occupancy (RO) of CD4 and CD8 Peripheral Blood T-Cell Populations Versus Time (days)

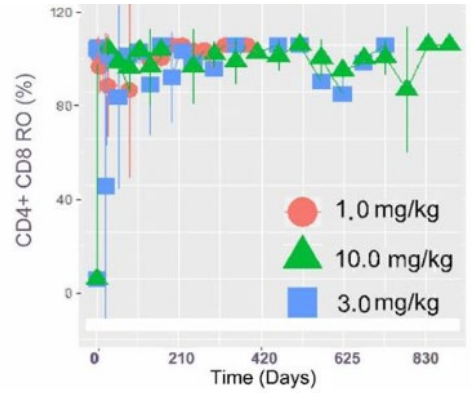


Figure 36. Percentage of Mean PD-1 Receptor Occupancy (RO) of CD8 Peripheral Blood T-Cell Populations Versus Time (days)

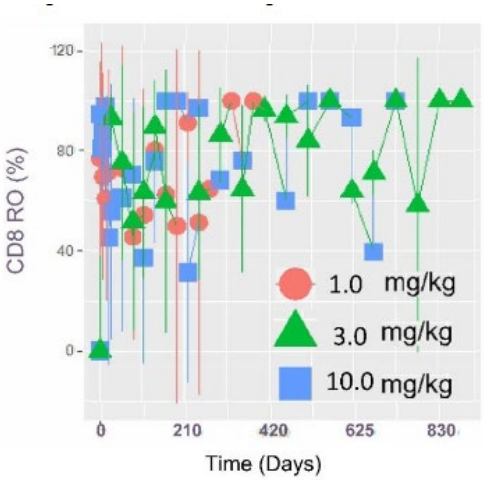
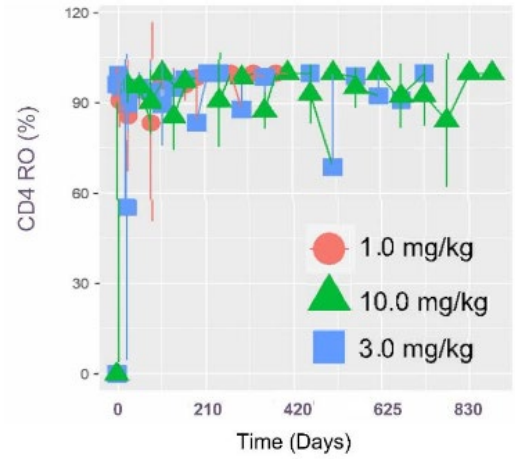


Figure 37. Percentage of Mean PD-1 Receptor Occupancy (RO) of CD4 Peripheral Blood T-Cell Populations Versus Time (days)



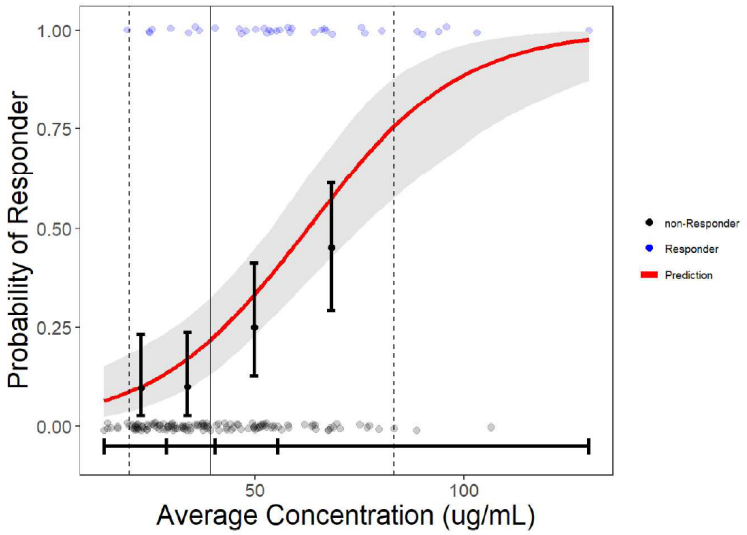
Primary and Secondary pharmacology

PK and Exposure-Response Modelling and Simulation of Toripalimab in Patients with Nasopharyngeal Carcinoma (TOPA-PMX-TORI-2412 Monotherapy)

Efficacy E-R

The final efficacy E-R model included toripalimab Cave, baseline body weight, baseline ALT, BALB, baseline BILI, baseline LDH, and renal impairment. The efficacy E-R response rate is 22% (36 responders out of 161 evaluable subjects), which included 11 subjects excluded due to having no PK information. Toripalimab Cave was the strongest predictor of being a responder: a subject with a median model predicted Cave (39 μg/mL) has a 21% chance of being a responder. Subjects at the Cave 5th percentile (p5) were 3 times more likely to be a responder than a reference subject, which is stronger than the Emax of all other predictors in the final model.

Figure 38. Predicted Probability of Responder for the Final Efficacy Exposure-Response Model



Notes: The black circles in the error bars represent the proportion of subjects who were responders at the median of the Cave quartiles. Solid vertical black lines in the error bars are the 95% CI around the probability of responder. The solid red line is the predicted probability of responder. The solid vertical black line is the median observed Cave. The dashed vertical black lines are the observed 5th and 95th Cave percentiles. The gray-shaded area is the 95% CI of the model prediction. The small blue and gray dots are the individual observations (jittered to more easily visualize individual subjects). Abbreviations: Cave=average concentration; CI=confidence interval.

Safety E-R

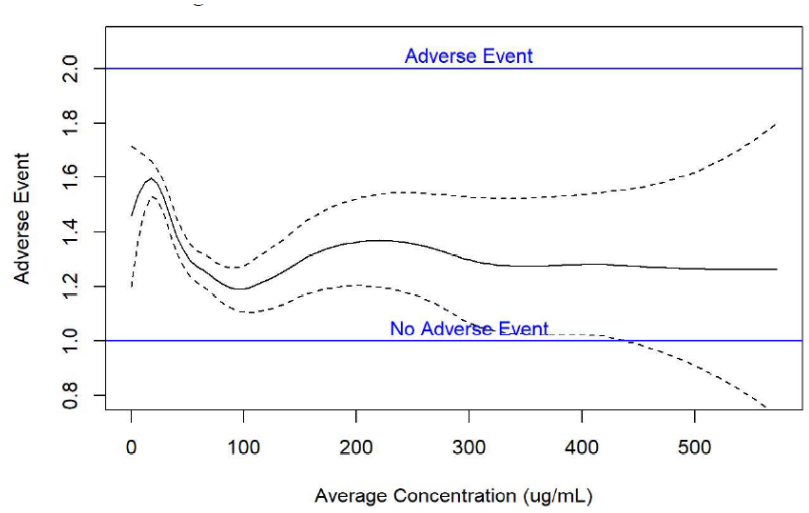
The final toxicity Grade ≥ 3 model included terms of C_{ave}, TUBURBL, BALB, BALP, and race.

The final toxicity Grade ≥ 3 drug related model included terms of C_{ave}, BALB, BALP, and race.

The final toxicity leading to drug discontinuation model included terms for Cave, BALB, baseline CRCL, liver impairment, sex, race, and ECOG.

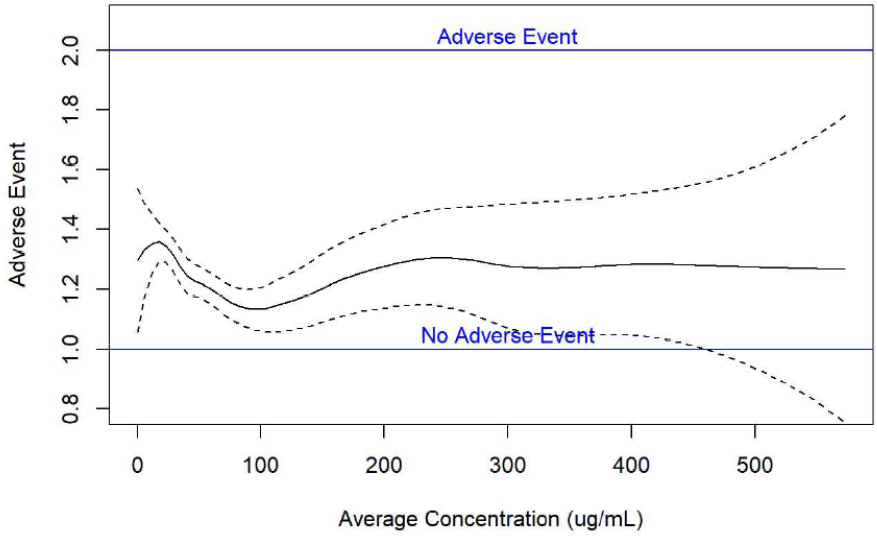
For each of these 3 safety endpoints, the probability of an AE occurring did not increase with increases in toripalimab exposure.

Figure 39. Localised Logistic Regression of Adverse Events, Grade ≥ 3 AEs versus Average Concentration



Source: TOPA-ER-safety-06052021-final.Rmd
Notes: The y axis values of 1 corresponds to no adverse event and a value of 2 corresponds to an adverse event. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.

Figure 40. Localised Logistic Regression of Adverse Events, Drug-related Grade ≥ 3 AEs versus Average Concentration



Source: TOPA-ER-safety-06052021-final.Rmd
Notes: The y axis values of 1 corresponds to no adverse event and a value of 2 corresponds to an adverse event. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.

Population PK and Exposure-Response Modelling and Simulation of Toripalimab in Patients with Nasopharyngeal Carcinoma (TOPA-PMX-TORI-2412 Combination Therapy)

Efficacy E-R: ORR

There were 174 responders out of 234 evaluable patients, among whom 5 patients were missing overall response data and were imputed as No Response. The final efficacy E-R ORR model included toripalimab treatment (240 mg toripalimab + chemotherapy vs placebo + chemotherapy), baseline body mass index (BMI), liver impairment, and Eastern Cooperative Oncology Group (ECOG).

The reference patient for the final efficacy E-R ORR model is a patient who received placebo + chemotherapy, whose BMI is 21.4 kg/m2, does not have liver impairment, and has ECOG Grade 0.

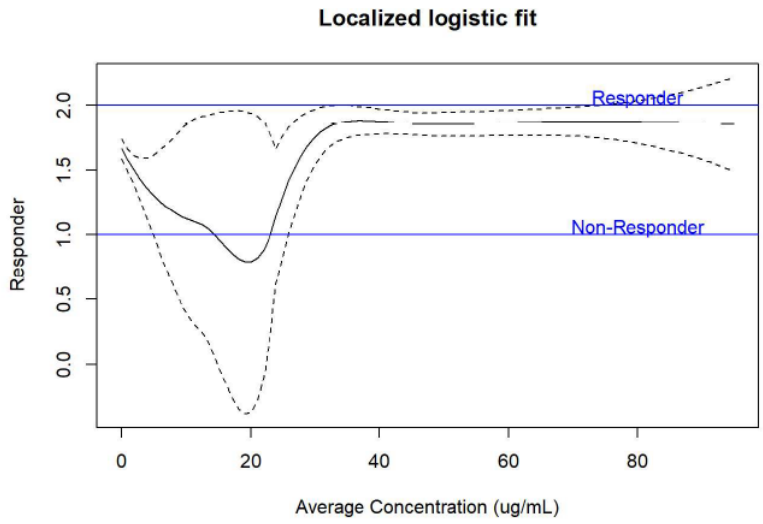
The probability of being a responder for a hypothetical reference patient who received placebo + chemotherapy is 76.3%.

The probability of being a responder for a hypothetical patient who received 240 mg toripalimab (Cave range: 25.2 94.9 g/mL) + chemotherapy is 92.0%. Toripalimab treatment was the strongest predictor of being a responder.

Patients receiving 240 mg toripalimab + chemotherapy were 3.58 times as likely to be a responder as a patient receiving placebo + chemotherapy. BMI: Patients with a higher BMI have a greater probability of being a responder.

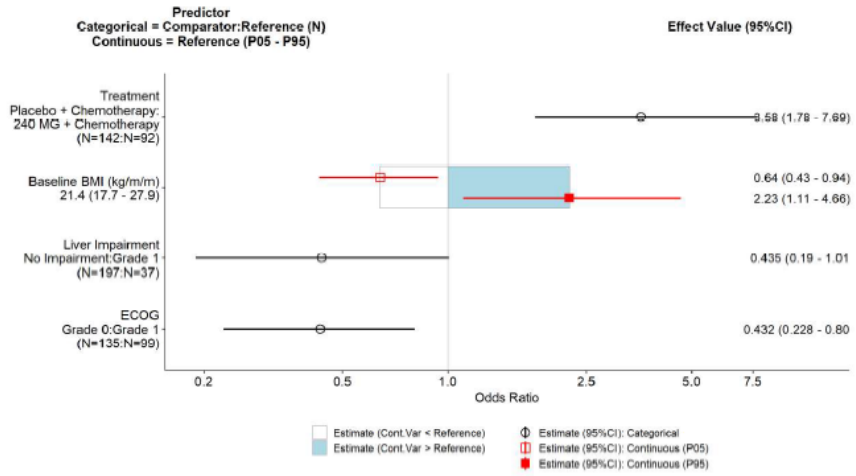
Patients at the 95th percentile baseline BMI (27.9 kg/m2) were 2.23 times as likely to be a responder as a patient at the median baseline BMI (21.4 kg/m2).

Figure 41. Localised Logistic Regression of Responder Versus Average Concentration for the Final Efficacy Exposure-Response Model



Source: TOPA-eff-ER-15Sep2021-final.Rmd
Notes: A y-axis value of 1 corresponds to non-responder status, and a value of 2 corresponds to responder status. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.

Figure 42. Odds Ratio for Responder for the Final Efficacy Exposure-Response Model for Best Overall Response With Treatment as the Predictor



Source: TOPA-eff-ER-15Sep2021-final.Rmd
Notes: The vertical gray line at odds ratio = 1 is the line of null effect. The reference patient is a patient receiving placebo + chemotherapy and with a baseline BMI of 21.4 kg/m^2, who does not have liver impairment, and who has ECOG Grade 0. The reference patient has a 76.3% probability of being a responder.
Abbreviations: BMI=body mass index; CI=confidence interval; ContVar=continuous variable; ECOG=Eastern Cooperative Oncology Group; N=number of patients; p5=5th percentile; p95=95th percentile

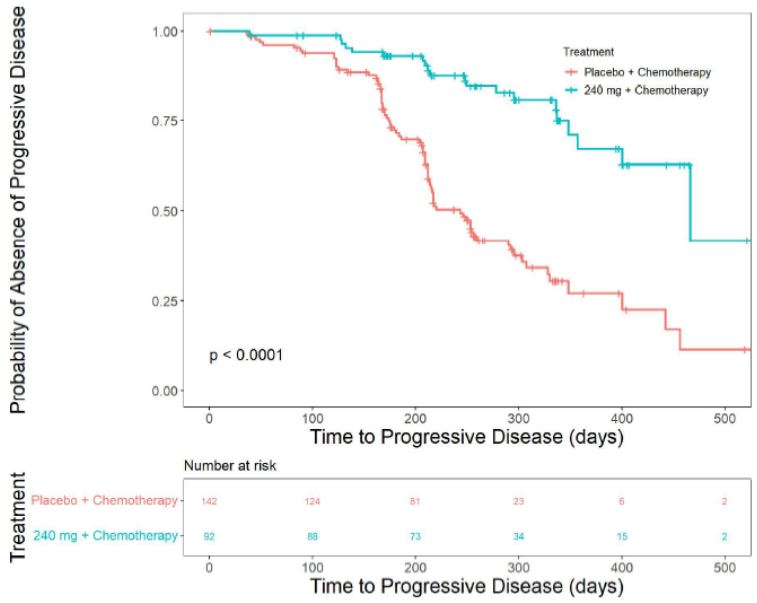
Liver impairment: Patients with liver impairment are 2.5 times less likely to be a responder than a reference patient.

ECOG: Patients with ECOG Grade 1 are 2.5 times less likely to be a responder than a reference patient.

Efficacy E-R: PFS

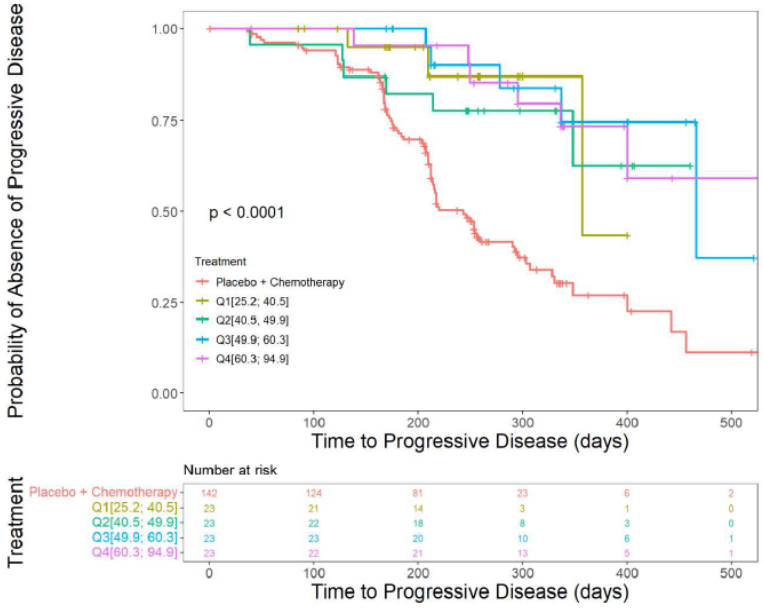
The final efficacy E-R PFS model included toripalimab treatment (240 mg toripalimab + chemotherapy). Toripalimab + chemotherapy provides a 76% reduction in risk of death or disease progression over placebo + chemotherapy.

Figure 43. Kaplan-Meier Survival Curve for Progression-Free Survival Stratified by Treatment



Source: TOPA-eff-ER-15Sep2021-final-amendment.Rmd
Note: The number of patients at selected time points for each treatment group are shown in the lower panel titled "Number at risk".

Figure 44. Kaplan-Meier Survival Curve for Progression-Free Survival Stratified by Average Concentration Quantiles



Source: TOPA-eff-ER-15Sep2021-final-amendment.Rmd
Abbreviations: AUC=area under the serum concentration-time curve; Q1=first C_{ave} quartile (25.2–40.5 µg/mL); Q2=second C_{ave} quartile (40.5–49.9 µg/mL); Q3=third C_{ave} quartile (49.9–60.3 µg/mL); Q4=forth C_{ave} quartile (60.3–94.9 µg/mL)
Note: The placebo group was considered separate from patients that received toripalimab. Therefore, the exposure quantiles are based only on the patients that received toripalimab. The number of patients at selected timepoints for each treatment group are shown in the lower panel titled "Number at risk".

Safety E-R

The safety E-R analysis included 152 patients who had both PK information and one or more adverse events (AE). 2 patients were excluded due to missing PK information.

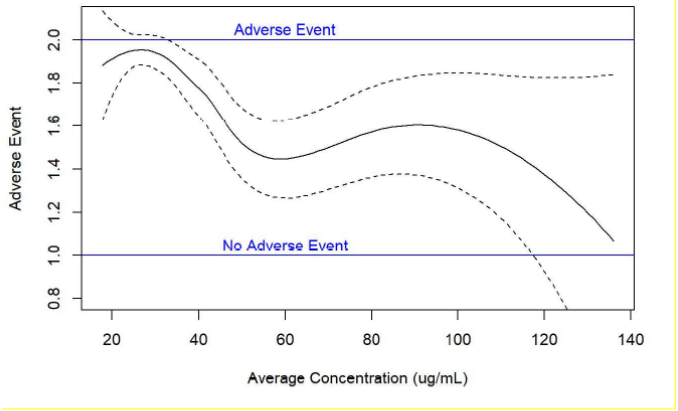
The final baseline Grade ≥ 3 AE model included terms for average concentration (C_{ave}), tumour burden (TUBURBL), baseline alkaline phosphatase (BALP), and baseline ECOG performance status.

The final treatment-related Grade ≥ 3 AE model included terms for Cave, TUBURBL, and baseline ECOG performance status.

The final AEs leading to drug discontinuation model included terms for Cave, BALP, baseline LDH, baseline CRCL, and sex.

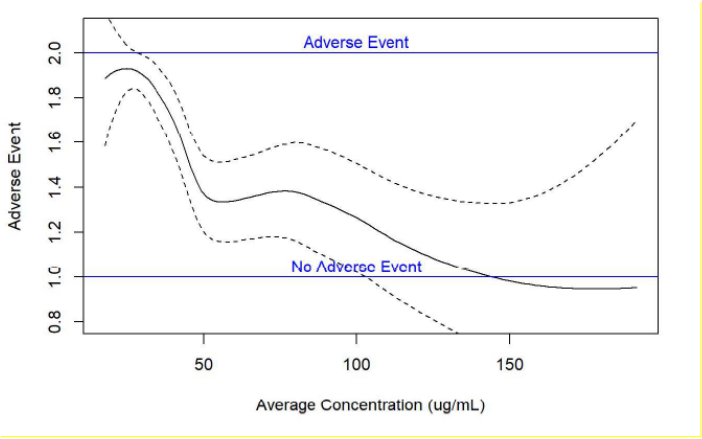
For each of these 3 adverse event categories (Grade ≥ 3 AE, treatment -related Grade≥ 3 AE, and AE leading to drug discontinuation), the probability of an AE occurring did not increase with increases in toripalimab exposure.

Figure 45. Localised Logistic Regression Analysis of Grade ≥ 3 Adverse Event Versus



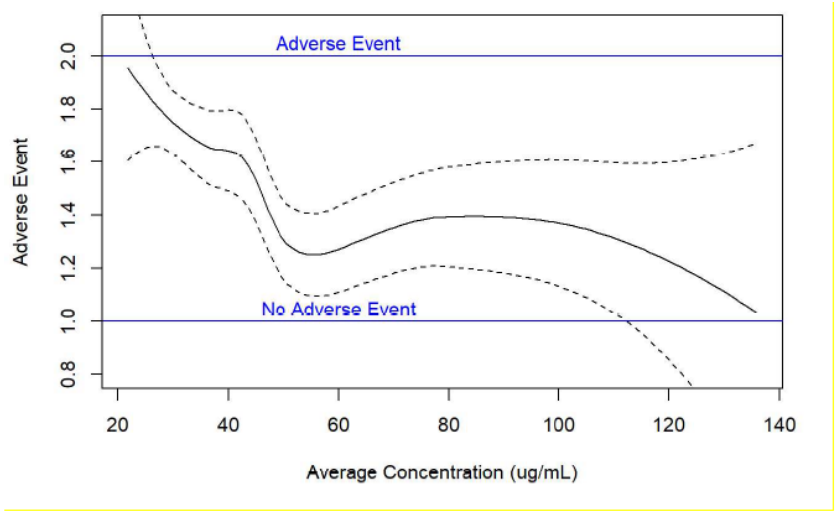
Source: TOPA-ER-safety-09072021.Rmd
Notes: A y-axis value of 1 corresponds to no adverse event, and a value of 2 corresponds to an adverse event. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.

Figure 46. Localised Logistic Regression of Treatment-related Grade ≥ 3 Adverse Event Versus Average Concentration



Source: TOPA-ER-safety-09072021.Rmd
Notes: A y-axis value of 1 corresponds to no adverse event, and a value of 2 corresponds to an adverse event. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.

Figure 47. Localised Logistic Regression of Adverse Event Leading to Drug Discontinuation Versus Average Concentration



Source: TOPA-ER-safety-09072021.Rmd
Notes: A y-axis value of 1 corresponds to no adverse event, and a value of 2 corresponds to an adverse event. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.

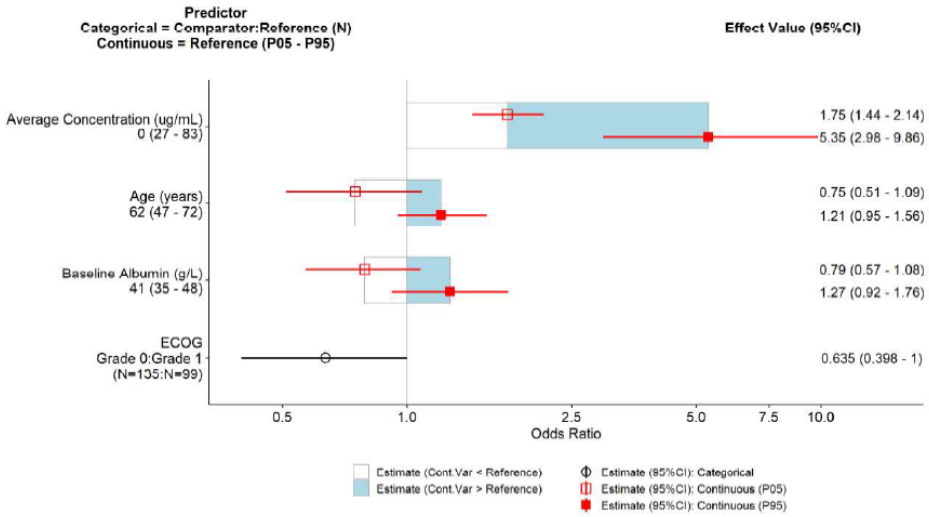
Population PK and Exposure Response Modelling and Simulation of Toripalimab as Monotherapy or in Combination with Platinum-Based Chemotherapy in Patients with Advanced Cancer (TOPA PMX TORIPALIMAB-3355)

Efficacy E-R: Overall response rate (ORR)

There were 307 responders out of 493 evaluable patients with OSCC with available PK data enrolled in JUPITER-06 (CT21), among whom 9 patients were in the placebo group, missing overall response data, and their response status was imputed as “no response” Of the 307 responders, there were 134 "placebo with chemotherapy" patients and 173 "toripalimab with chemotherapy" patients. The final efficacy E-R ORR model included toripalimab average concentration (Cave), age, baseline albumin (BALB), and Eastern Cooperative Oncology Group (ECOG) performance status.

The reference patient for the final efficacy E-R ORR model was a patient who received placebo with chemotherapy; whose Cave was 0 µg/ml, age was 62 years, and BALB was 41g/L; and who had an ECOG performance status of 0. The probability of being a responder for a hypothetical reference patient who received placebo with chemotherapy was 60.1%. Toripalimab C_{ave} was the strongest predictor of being a responder.

Figure 48. Odds Ratio for Responder for the Final Efficacy Exposure-Response Model for Best Overall Response With Cave as the Predictor

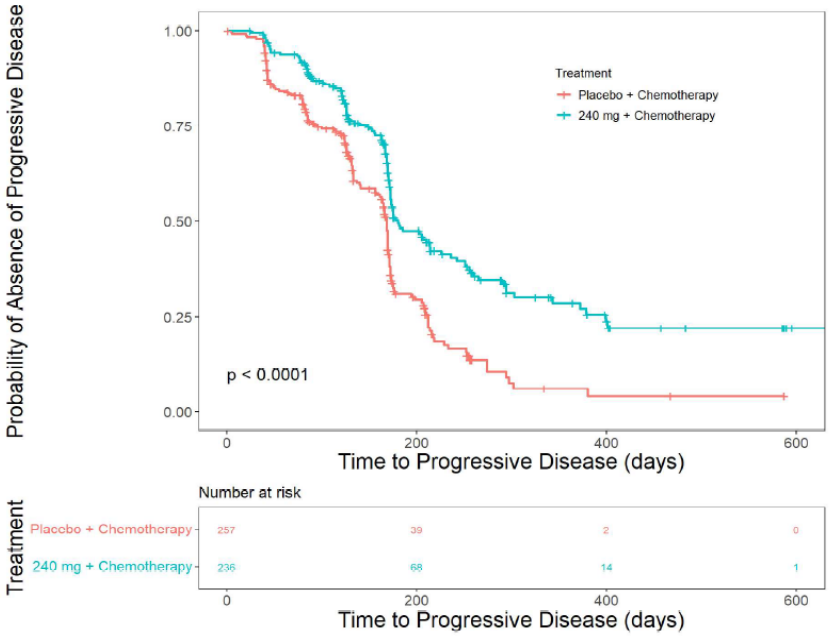


Source: TOPA-ER-efficacy-01022022.RMD
Notes: The vertical gray line at odds ratio=1 is the line of null effect. The reference subject was a patient receiving placebo with chemotherapy, with a median age of 62 years and a baseline ALB of 41.1 g/L,and had a baseline ECOG performance status of 0. The reference subject has a 60.1% probability of being a responder.
Abbreviations: ALB= albumin; C_{ave}=average concentration; CI=confidence interval; ContVar=continuous variable; ECOG=Eastern Cooperative Oncology Group; N=number of patients; p5=5th percentile; p95=95th percentile

The odds of being a responder are 5.35 times higher for patients with toripalimab Cave of 83 ug/mL (95th percentile) compared to a patient receiving placebo with chemotherapy. The odds of being a responder are 1.75 times higher (and the 95% confidence interval [CI] excludes 1) for patients with toripalimab Cave of 27 ug/mL (5th percentile) compared to a patient receiving placebo with chemotherapy.

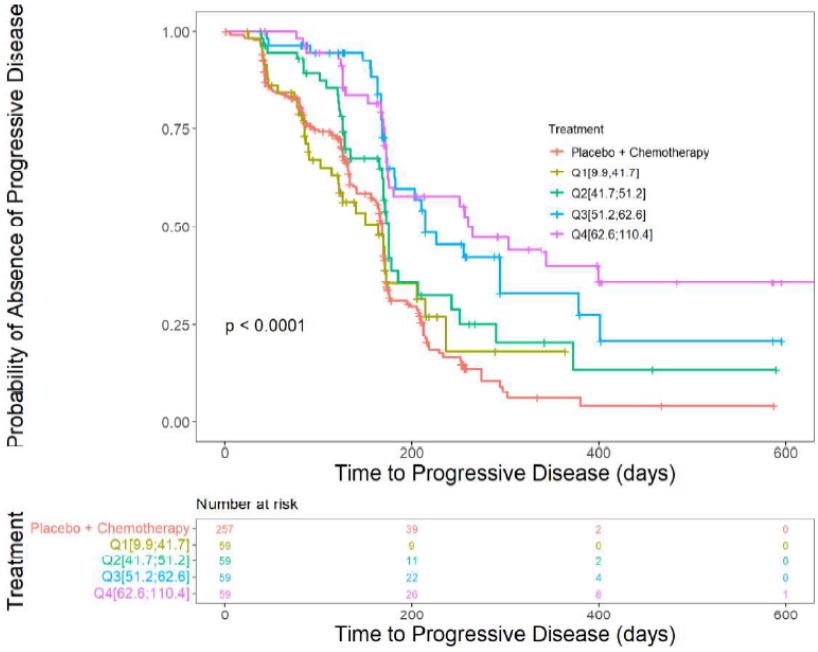
Efficacy E-R: Progression-free survival (PFS) for patients with OSCC enrolled in Study JUPITER-06 (CT21). The final efficacy E-R PFS model included toripalimab treatment (240 mg toripalimab with chemotherapy). Toripalimab with chemotherapy provides a 47% reduction in the immediate risk of death or disease progression over placebo with chemotherapy.

Figure 49. Kaplan-Meier Survival Curve for Progression-Free Survival, Stratified by Treatment



Source: TOPA-ER-efficacy-01022022.RMD
Notes: The numbers of patients at selected timepoints for each treatment group are shown in the lower panel titled "Number at risk." Of the 493 patients at the beginning, only 107 patients remained after 200 days.

Figure 50. Kaplan-Meier Survival Curve for Progression-Free Survival, Stratified by Average Concentration Quantiles



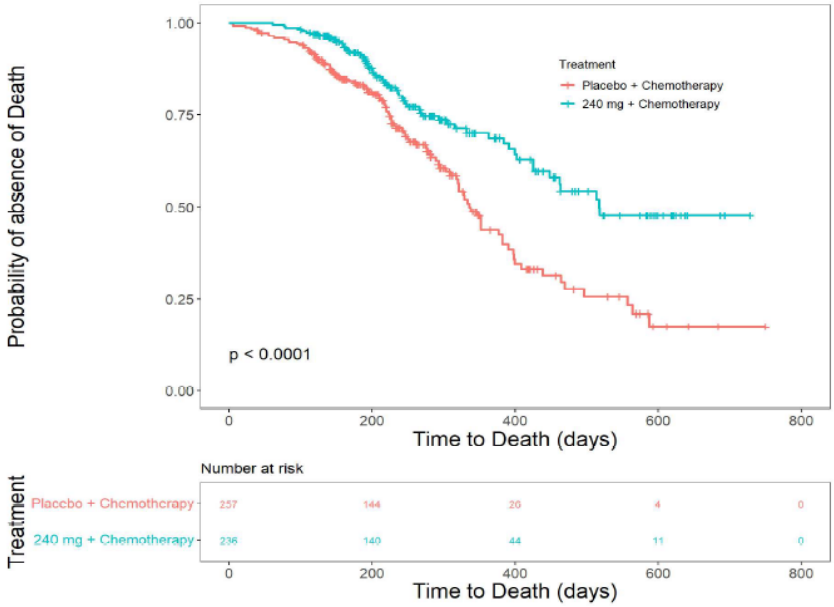
Source: TOPA-ER-efficacy-01022022.RMD

Notes: The placebo group was considered separate from patients who received toripalimab. Therefore, the exposure quantiles are based only on the patients who received toripalimab. The numbers of patients at selected timepoints for each treatment group are shown in the lower panel titled "Number at risk." Of the 493 patients at the beginning, only 107 patients remained after 200 days.

Abbreviations: C_{ave}=average concentration; Q1=first C_{ave} quartile (9.9 – 41.7 µg/mL); Q2=second C_{ave} quartile (41.7 – 51.2 µg/mL); Q3=third C_{ave} quartile (51.2 – 62.6 µg/mL); Q4=forth C_{ave} quartile (62.6 – 110.4 µg/mL)

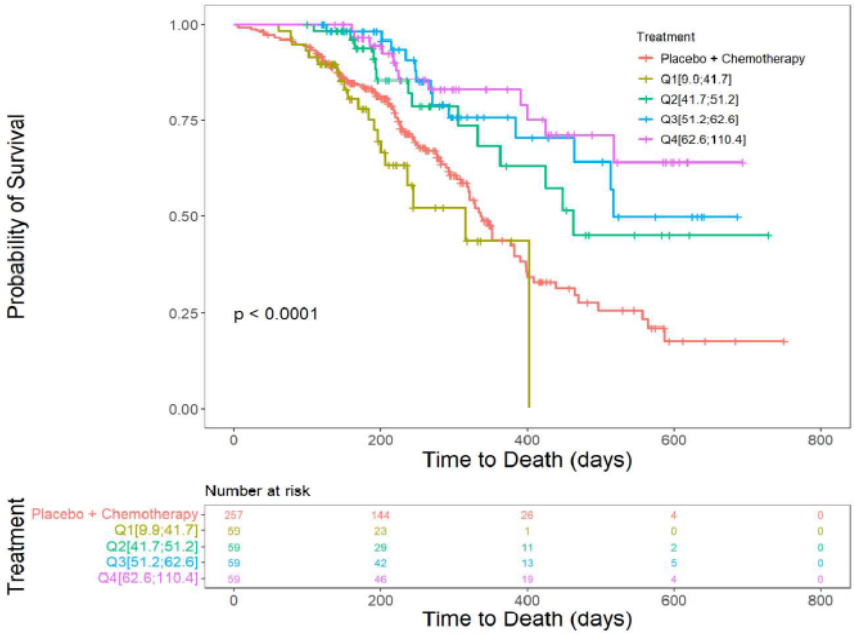
Efficacy E-R: Overall survival for patients with OSCC enrolled in Study JUPITER-06 (CT21). Toripalimab with chemotherapy provides a 49% reduction in risk of death over placebo with chemotherapy.

Figure 51. Kaplan-Meier Curves for OS, Stratified by Toripalimab Exposure Quantiles



Source: TOPA-ER-efficacy-01022022.RMD
Notes: The number of patients at selected timepoints for each treatment group are shown in the lower panel titled "Number at risk." Of the 493 patients at the beginning, only 280 patients remained after 200 days.
Abbreviations: OS=overall survival

Figure 52. Kaplan-Meier Curves for OS, Stratified by Average Concentration Quantiles

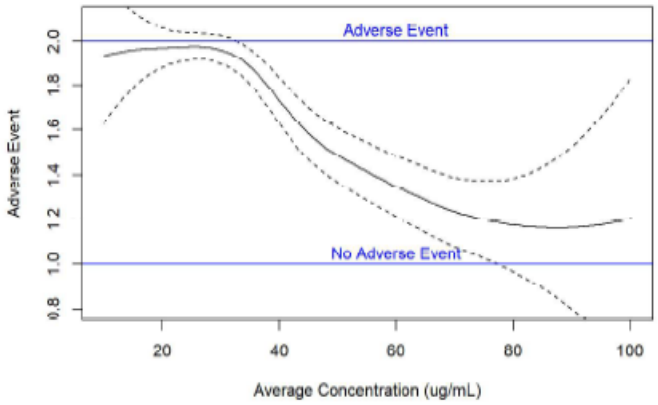


Source: TOPA-ER-efficacy-01022022.RMD
Notes: The placebo group was considered separate from patients who received toripalimab. Therefore, the exposure quantiles are based only on the patients who received toripalimab. The number of patients at selected timepoints for each treatment group are shown in the lower panel titled "Number at risk." Of the 493 patients at the beginning, only 284 patients remained after 200 days.
Abbreviations: C_{ave}=average concentration; OS=overall survival; Q1=first C_{ave} quartile (9.9 – 41.7 μg/mL); Q2=second C_{ave} quartile (41.7 – 51.2 μg/mL); Q3=third C_{ave} quartile (51.2 – 62.6 μg/mL); Q4=fourth C_{ave} quartile (62.6 – 110.4 μg/mL)

Safety E-R for patients with OSCC enrolled in Study JUPITER-06 (CT21) Grade ≥ 3. The safety E-R analysis included 236 patients who had both PK information and 1 or more adverse events (AEs) in the toripalimab arm of JUPITER-06. The final Grade ≥ 3 AE model included terms for Cave, baseline alkaline phosphatase, baseline bilirubin, and baseline CRCL. The final treatment-related Grade ≥ 3 AE

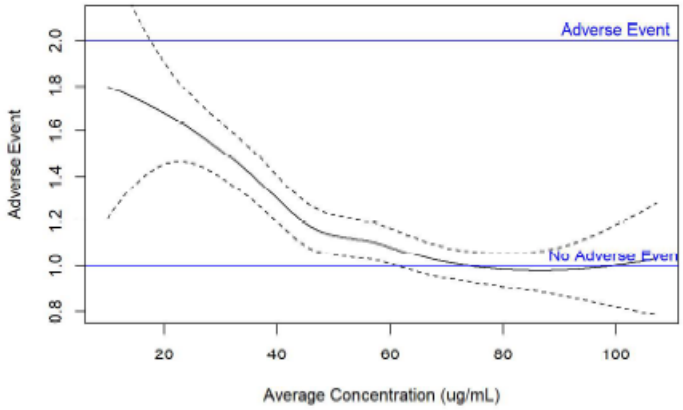
model included terms for C ave, BALB, and baseline CRCL. The final AEs leading to drug discontinuation model included terms for Cave, baseline body weight, and sex. For each of these 3 AE categories (Grade ≥3 AE, treatment-related Grade≥ 3 AE, and AE leading to drug discontinuation), the probability of an AE occurring did not increase with increases in toripalimab exposure.

Figure 53. Logistic Regression of Grade ≥ 3 Adverse Event Versus Exposure



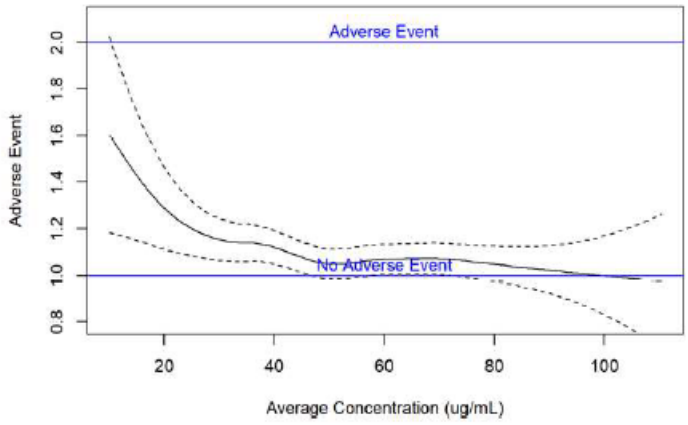
Source: TOPA-ER-safety-01032022v2.RMD
Notes: A y-axis value of 1 corresponds to no AE, and a value of 2 corresponds to an AE. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.
Abbreviations: AE=adverse event

Figure 54. Logistic Regression of Treatment-related Grade ≥ 3 Adverse Event Versus Exposure



Source: TOPA-ER-safety-01032022v2.RMD
Notes: A y-axis value of 1 corresponds to no AE, and a value of 2 corresponds to an AE. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.
Abbreviations: AE=adverse event

Figure 55. Logistic Regression Analysis of AE Leading to Study Drug Discontinuation Versus Exposure



Source: TOPA-ER-safety-01032022v2.RMD
Notes: A y-axis value of 1 corresponds to no AE, and a value of 2 corresponds to an AE. The black line is the localized logistic fit (similar to a moving average) of the relationship between average concentration and responder status. The dashed lines are the 95% confidence interval for the localized logistic fit.
Abbreviations: AE=adverse event

Effects on Electrocardiographic Physiology (QT Interval)

Per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E14/S7B, large, targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions. Per Schreiber et al 2014, available data suggest that monoclonal antibodies are unlikely to cause QT/QTc interval prolongation, therefore, no dedicated QT assessment is necessary. Consistent with the low risk of QTc interval prolongation for toripalimab per ICH E14/S7B and with Schreiber et al 2014, no dedicated QT assessment has been conducted for toripalimab. No safety signals for effects on cardiac electrophysiology were observed in the safety database.

3.6.3. Discussion on clinical pharmacology

The clinical pharmacology data in the current submission are derived from 15 clinical studies. None of the studies were conducted in healthy volunteers. All PK parameters were calculated using conventional non-compartmental methods using actual times of sampling, unless otherwise stated in the clinical study report. Pop PK and PK/PD studies were conducted to guide and justify the posology.

Toripalimab pharmacokinetics were characterised using population PK analyses that included data from 1,250 patients with various solid tumours who received fixed (80 to 480 mg Q2W or Q3W) or weight-based (range: 0.3 to 10 mg/kg Q2W) dosing, including 234 patients with NPC and 236 patients with OSCC who received toripalimab at doses of 240 mg every 3 weeks in JUPITER-02 and JUPITER-06, respectively.

Analytical methods

Overall, the bioanalytical methods applied for the determination of toripalimab in human serum is adequately validated. Methods for quantitative determination of TAB001/JS001 in human serum have been developed and validated, providing appropriate proof for methods' suitability. Similarly, the electrochemiluminescence assay for the detection of anti-T001 antibodies in human serum has been developed and validated.

Reference standard used in "Validation of Enzyme-Linked Immunosorbent Assay (ELISA) to Measure TAB001 in Human Serum" (2352-13514) is defined as TAB001, 40.0 mg/mL, Lot# 20161212 (supplied by sponsor) in method description. Also the certificate of analysis for TAB001, anti-human PD-1 mAb bulk reference standard form TopAlliance Biosciences, Inc Lot # BR121715 is provided in validation report. The principles applied for acceptance criteria definition (at least 67% of the samples, the diff% between different methods was within ± 30%) is adequately justified in bridge validation result of ELISA method and MSD method in S5445MVHuSe validation study.

The information on "Qualitative Detection of Anti-recombinant Human Anti-PD-1 Monoclonal Antibody Injection (JS001) Antibody in Human Serum Using a Bridging-ECLA Assay" and its validation has been provided confirming it's suitability to screen, confirm and titter for antibody response.

In general, the demonstrated analytical characteristics of validated methods confirm their suitability for purpose and reliability of the obtained results in TAB001/JS001 biopharmaceutical evaluation studies.

Immunogenicity assays

A standard multi-tiered approach was employed including screening, confirmatory and titer assays to evaluate anti-drug antibodies (ADAs) in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) in the phase I study TAB001-01, the phase Ib/II CT5 study (except titer) and the phase III clinical studies JUPITER-02 and JUPITER-06. The neutralizing capacity of ADAs has also been investigated for these studies..

Sensitivity, precision, selectivity, hook effect and drug tolerance were correctly discussed for the confirmatory assay in both ADA methods MTD081V and S5403ADAHuSeAP01. As requested, the recalculation of CCP using a 1% FPR was conducted and the immunogenicity data with this recalculated CCP were submitted by the applicant**.** The precision of the confirmatory assay was not assessed in the validation study of method MTD081V. The precision of the confirmatory assay was calculated using the assay control data from all of the accepted validation runs. The % CV for the negative control results (measured in RLU) in runs with toripalimab is 6.2%. The plate acceptance criteria of %CV ≤ 25.0 is for the average RLU values of the negative control (N=3).

In response to the Co-Rapp question on the screening cut point, the Applicant clarified that the screening cut point S/N of 1.05 was obtained using normal human serum in the assay validation study. In the assay validation study, 54 individual normal human serum samples were tested by 2 analysts through 6 analytical runs. All the valid S/N values were statistically analysed and the 95th percentile calculation of the dataset resulted in the S/N of 1.05 as the screening cut point.

The soluble level of PD1 in the plasma of patients with cancer is considered insufficient to cause interference with the ADA methods S5403ADAHuSeAP01 and MTD081V. According to the Applicant, the ADA results from both methods can be compared and allow a comparison of immunogenicity of toripalimab across geographical regions.

ADME

Toripalimab is administered via the intravenous route; therefore, it is completely bioavailable.

Due to the nature of the product, no in vitro dissolution studies, clinical bioavailability studies, or food effect studies were required. Near steady-state concentrations of toripalimab were generally reached after 3 to 4 doses based on observed toripalimab concentrations.

Dedicated metabolism studies were not performed. As a monoclonal antibody, toripalimab is expected to be metabolized into small peptides, amino acids, and small carbohydrates by catabolic pathways or by receptor-mediated endocytosis. The degradation products are eliminated by renal excretion or returned to the nutrient pool without biological effects.

POP PK

The PK characteristics of toripalimab in patients with solid tumours were first analysed as a function of the dose in the dose escalation cohorts (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W), for monotherapy and for combination therapy. The concentrations of toripalimab were then further investigated in the expansion cohorts in the broader population of patients with different solid tumour types receiving monotherapy or combination therapy. Sparse sampling was collected in the phase I study TAB001-01 and in phase III studies (JUPITER-02 and JUPITER-06) and used in the POP PK analysis.

Toripalimab pharmacokinetics followed a 2-compartment model with time-varying clearance (CL). The mean CL was 14.46 mL/h (CV = 9%) after the first dose and 9.25 mL/h (CV = 11%) at steady state. Given the time-varying clearance, elimination was measured using washout (approximating 5 half-lives). At steady state, the median washout time was 4.99 months with toripalimab administered at 240 mg Q3W.

Exposure to toripalimab, as expressed by peak concentrations (C_{max}), increased dose proportionally over the dose range of 80 to 480 mg Q2W (data not shown). The geometric mean trough concentrations (C_{min}) at steady-state were estimated in the population PK model to be 26.3 µg/mL in patients receiving 240 mg every 3 weeks. The mean accumulation of C_{min} at steady state is 2.7-fold compared to the C_{min} after the first dose.

In the overall patient population after repeated dosing, the total clearance decreased over time. This time-varying CL has previously been reported for a number of monoclonal antibodies.

PK studies in special populations

The effect of renal impairment based on the estimated creatinine clearance on the clearance and volume of distribution of toripalimab were evaluated using population pharmacokinetic analyses. No differences in clearance or volume of distribution were found between patients with mild (CLcr 60 to 89 mL/min; n=483) or moderate (CLcr 30 to 59 mL/min; n=114) renal impairment and patients with normal renal function. The effect of severe (CLcr 15 to 29 mL/min) renal impairment on the pharmacokinetics of toripalimab has not been studied. No dose adjustment is needed for patients with mild or moderate renal impairment. There are insufficient data in patients with severe renal impairment for dosing recommendations.

The effects of hepatic impairment using the US National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) grading system for hepatic dysfunction on the clearance and volume of distribution of toripalimab were evaluated using population pharmacokinetic analyses. No differences in clearance or volume of distribution were found between patients with mild (Grade 1, n=166) hepatic impairment (total bilirubin up to 1.5 times the upper limit of normal (ULN) or total bilirubin within normal limits and aspartate transaminase (AST) or alanine transaminase (ALT) >1 and ≤ 3 ULN compared to patients with normal liver function. There was a limited number of patients with moderate (Grade 2, n=1; total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment and no patients with severe (Grade 3; total bilirubin > 3 times ULN and any AST) hepatic impairment enrolled in clinical studies of toripalimab. No dose adjustment is recommended for patients with mild hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

No clinically significant differences in the pharmacokinetics of toripalimab were observed based on age (range: 19 to 85 years), body weight (range: 32 to 164 kg), sex, race (White and Asian), concomitant chemotherapy, mild or moderate renal impairment, mild hepatic impairment, tumour burden and primary cancer.

The safety and efficacy of toripalimab in children and adolescents aged under 18 years have not been established.

Based on the available data, no dose adjustment is recommended for patients who are aged 65 years or over.

Drug-drug interactions

The Applicant did not conduct any drug interaction studies. Since toripalimab is cleared from the circulation through catabolism, no metabolic drug drug interactions are expected. Toripalimab is not a substrate for cytochrome P450 or active substance transporters. Toripalimab is not a cytokine and is unlikely to be a cytokine modulator. Additionally, PK interaction of toripalimab with small molecule active substances is not expected. There is no evidence of interaction mediated by nonspecific clearance of lysosome degradation for antibodies.

The use of systemic corticosteroids or immunosuppressants before starting toripalimab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of toripalimab. However, systemic corticosteroids or other immunosuppressants can be used after starting toripalimab to treat immune related adverse reactions. Corticosteroids can also be used as premedication, when toripalimab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy related adverse reactions (see section 4.5 of the SmPC).

Posology justification

The proposed recommended dose of 240 mg Q3W administered as an intravenous infusion over 60 minutes (followed by infusion over 30 minutes if no significant infusion-related reactions occurred)was justified based on critical data from E-R (exposure-safety and exposure-efficacy) analyses, assessment of receptor occupancy (RO) and PopPK analysis of the effects of body weight and race on toripalimab PK.

Pharmacodynamics and PK/PD

The primary pharmacodynamics of Toripalimab were explored in Studies CT1, CT2, and CT3 (PD-1 binding). Dose response data was also evaluated: the ORR was explored in studies CT3, CT4, CT5, CT6, CT12, while the CT8 study explored Relapse-free survival. And the pivotal studies explored the PFS (CT 15) and (OS) based PK/PD data.

Toripalimab binds to the target molecule PD-1 on the surface of activated T lymphocytes as shown in PD studies. This is acceptable.

Anticipated full receptor occupancy of PD-1 in immune cells was achieved at exposures below mean trough concentrations after the first dose and steady state at dose of 240 mg Q3W.

Exposure-response relationship

Toripalimab exposure-response relationships for efficacy are essentially flat over the range of exposures achieved for nasopharyngeal carcinoma in JUPITER-02. There was a positive relationship for OSCC with apparent lesser treatment effects at exposures below the median in JUPITER-06. These analyses may be confounded by the complex pharmacokinetic profile of toripalimab, with time-varying clearance and toripalimab accumulation. The toripalimab exposure-response relationships for safety showed negative (inverse) relationships over the range of exposures achieved; however, this is likely an artifact reflecting toripalimab accumulation.

3.6.4. Conclusions on clinical pharmacology

The clinical pharmacology data in the current submission are derived from 15 clinical studies. None of the studies were conducted in healthy volunteers. All PK parameters were calculated using conventional non-compartmental methods using actual times of sampling. Pop PK and PK/PD studies were conducted to guide and justify the posology. The PK data provided support the use of toripalimab in the applied indications.

The proposed flat dosing regimen of toripalimab in the NPC and OSCC indications is justified based on E-R (exposure-safety and exposure-efficacy) analyses, assessment of receptor occupancy (RO) and PopPK analysis of the effects of body weight and race on toripalimab PK.

Toripalimab binds to the target molecule PD-1 on the surface of activated T lymphocytes as shown in PD studies. The probability of an AE occurrence did not increase with increase in toripalimab exposure.

3.6.5. Clinical efficacy

3.6.6. Clinical efficacy Nasopharyngeal Carcinoma (NPC)

3.6.6.1. Dose-response studies

According to *in vitro* experiments when the plasma concentration of toripalimab was > 3 μg/mL, PD-1 receptors on the surface of peripheral T-cells were saturated. This was supported by data from CT1 and CT2 studies where flow cytometry was used to evaluate receptor occupancy. At all dosage levels evaluated in these studies, i.e., 1 to 10 mg/kg Q2W IV, binding of toripalimab to the target molecule PD-1 on the surface of activated T lymphocytes was observed shortly after the first dose. Complete receptor occupancy (>80%) was achieved and maintained throughout the 2 week dose interval in most patients at doses ≥3 mg/kg. Given the uncertainties regarding penetration of immunoglobulins into the tumour microenvironment, the concentration of toripalimab in the peripheral blood was chosen to achieve Cmin of 20 μg/mL or higher to attempt to ensure PD-1 receptor full occupancy on T lymphocytes in the tumour microenvironment.

Maximum tolerated dose, a dose selection strategy that derives from cytotoxic agent development, has proven challenging for checkpoint inhibitors and molecularly targeted agents because there is no clear dose-response relationship, and the identification of an MTD may not be a realistic objective. In fact, in studies performed with pembrolizumab and nivolumab, the investigators did not identify an MTD. Since the maximum tolerated dose was not exceeded at the highest doses evaluated (10 mg/kg Q2W and 480 mg Q2W), the dosage regimen selected relied on the relationship between exposure after approximately 5 doses (approximating steady state in the Phase 1 studies using non-compartmental analysis) and assurance of sustained, complete receptor occupancy over the dosing interval. In simulations based on the original popPK model, the proposed clinical dose regimen of 240 mg Q3W gave a predicted geometric mean Ctrough value at steady state of 26.3 μg/mL, which exceeded the target of ≥ 20 μg/mL but yielded a wide coefficient of variation (85.5%). The Ctrough value of dose 3 mg/kg Q2W at steady state was higher, 38.1 μg/mL (

Table **45**).

Table 41. Population Pharmacokinetic Parameters for Toripalimab (Modelled)

	240 mg IV Q3W	3 mg/kg IV Q2W
First Dose		
Geometric Mean C_{max} (%CV), μg/mL	67.1 (21.0)	53.9 (23.7)
Geometric Mean C_{avg} (%CV), μg/mL	26.7 (25.2)	26.3 (25.1)
Geometric Mean C_{trough} (%CV), μg/mL	10.2 (61.8)	13.9 (43.5)
Geometric Mean $AUC_{0-\tau}$ (%CV), hr•μg/mL	13386 (27.0)	8894 (26.7)
Steady-State		
Geometric Mean C_{max} (%CV), μg/mL	97.6 (26.4)	93.7 (28.9)
Geometric Mean C_{avg} (%CV), μg/mL	50.7 (43.6)	58.5 (41.6)
Geometric Mean C_{trough} (%CV), μg/mL	26.3 (85.5)	38.1 (65.1)
Geometric Mean $AUC_{0-\tau}$ (%CV), hr•μg/mL	25555 (43.6)	19644 (41.6)

Source: Table 16 PopPK Report TOPA-PMX-TORI-2412-Combination Therapy – amendment 1 (11 Jan 2022)
AUC=area under the curve; C_{avg}=average concentration over the dosing interval; C_{max}=maximum concentration; C_{trough}=trough concentration; % CV=percentage of the coefficient of variation

The applicant chose the dose of 240 mg Q3W IV for both indications based on these data.

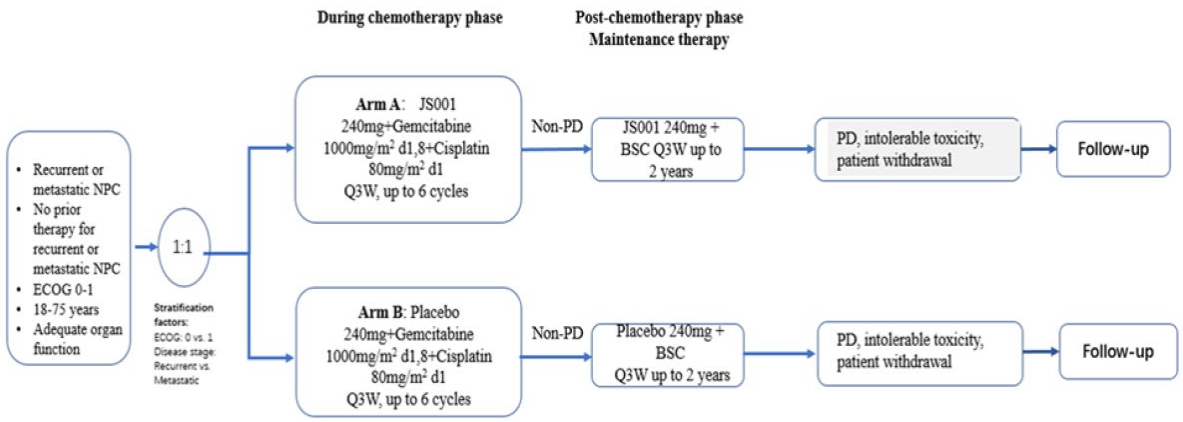
3.6.6.2. Main study(ies)

JS001-015-III-NPC (JUPITER-02), a randomized, placebo-controlled, multi-centre, double-blind study. And one clinical phase Ib/II basket trial: JS001-1b-CRP-1.0 CT5 (POLARIS-02), single-arm, multi-cohort, multi-centre, open label with NPC patients in Cohort 3 and 7.

Methods

JUPITER-02 study was designed to determine the efficacy and safety of toripalimab in combination with gemcitabine and cisplatin compared with placebo in combination with gemcitabine and cisplatin as first-line treatment in subjects with histologically or cytologically confirmed, recurrent, or metastatic NPC (see figure below.

Figure 56. JS001-015-III-NPC study schema



Abbreviations: BSC=best supportive care; PD=disease progression; Q3W=every 3 weeks

Eligible patients had a biopsy confirmed diagnosis of NPC, had metastatic disease or recurrent NPC after treatment with curative intent, at least 1 measurable lesion according to RECIST version 1.1., life expectancy ≥ 3 months, ECOG performance status 0 or 1, adequate organ function.

Study Participants

Main inclusion criteria:

1) Histological/cytological confirmation of NPC.

2) Primarily metastatic (stage IVB as defined by the International Union against Cancer and American Joint Committee on Cancer staging system for NPC, eighth edition) or recurrent NPC after curative treatment, which is not amenable for local regional treatment or curative treatment. No previous systemic chemotherapy was given for the recurrent or metastatic disease.

3) For the recurrent NPC after curative treatment (including radiotherapy and/or induction, concurrent or adjuvant chemotherapy), the interval between recurrence and the last dose of previous radiotherapy or chemotherapy must be more than 6 months.

Main exclusion criteria: Active or untreated CNS metastases, patients with necrotic lesions, malignancies other than NPC within 5 years prior to randomization, prior therapy targeting PD-1 receptor, or its ligand PD-L1, treatment with systemic immunostimulatory agents. Patients with autoimmune disease, other than stable hypothyroidism or Type I diabetes, were ineligible

Treatments

In induction phase patients received toripalimab/placebo in combination with gemcitabine and cisplatin. They received 240 mg toripalimab/placebo administered by IV infusion Q3W. Study drug/placebo were administered in 100-mL 0.9% NaCl IV infusion bags at the dose of 240 mg as an intravenous infusion (IV) over 60 (± 15) minutes followed by a 60-minute observation period (only required in the first 2 cycles). If no clinically significant infusion reactions were observed during or after the first 2 cycles, toripalimab/placebo were administrated as a 30-minute IV infusion (±10 minutes is permitted). Toripalimab/placebo was given first on Day 1 of each cycle.

The treatment with gemcitabine and cisplatin were given according to drug label and to local standards for premedication and prophylactic medications. Gemcitabine was given 1000 mg/m2 over 30 minutes IV on Days 1 and 8, and cisplatin was given 80 mg/m2 IV over 4 hours on Day 1, in 3-week cycles for up to 6 cycles.

Treatment continued until progressive disease, excessive toxicity, noncompliance, withdrawal of consent, or a maximum of 6 cycles, whichever occurred first in the 'during chemotherapy' phase.

In the maintenance phase, subjects randomized to Arm A or Arm B continued treatment with toripalimab or placebo Q3W until unacceptable toxicity or progressive disease, withdrawal of consent or Investigator's judgement or a maximum of 2 years (including induction phase with chemotherapy and maintenance phase). Patients could continue treatment with toripalimab or placebo beyond radiographic progression per RECIST v1.1, provided the subjects were experiencing clinical benefit, as assessed by the Investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the Investigator after an integrated assessment of radiographic data and clinical status.

The scans of tumour evaluation were performed at screening and then every 6 weeks for the first 12 months and every 9 weeks thereafter until the confirmation of disease progression.

Objectives

The primary objective of this study was to evaluate efficacy of toripalimab in combination with chemotherapy compared with placebo in combination with chemotherapy, as measured by IRC-assessed PFS according to RECIST v1.1 in patients with histological/cytological confirmation of recurrent or metastatic NPC.

The secondary objectives were to evaluate efficacy of toripalimab in combination with chemotherapy compared with placebo in combination with chemotherapy, as measured by OS, as measured by investigator- and IRC-assessed ORR, DoR, and DCR according to RECIST v1.1.

The aim is to demonstrate clinical superiority of toripalimab in combination with chemotherapy over the placebo in combination with chemotherapy in terms of PFS.

Outcomes/endpoints

The primary efficacy endpoint was PFS, defined as the time from randomization to the occurrence of disease progression, as determined by IRC from tumour assessments, per RECIST v1.1, or death from any cause, whichever occurs first.

Secondary efficacy endpoints were as follows:

1. Overall survival - the time from randomization to death from any cause
2. IRC-assessed ORR, DoR, and DCR according to RECIST v1.1
3. Investigator-assessed PFS, ORR, DoR, and DCR according to RECIST v1.1

Sample size

The sample size was determined based on the need to detect significant results of PFS, 1:1 randomization and the following assumptions:

- PFS was to be exponentially distributed.
- The median PFS was to be 7 months for the standard chemotherapy.
- The interim and final analyses of PFS would use the Lan DeMets alpha spending function to approximate the O'Brien Fleming boundary.
- The recruitment of 280 subjects would be completed in 14 months.
- The dropout rate was to be 5% over 12 months for PFS.

Calculations were made that total of 280 patients (140 per arm) were needed to observe 200 PFS events at approximately 25 months after the first subject was randomized to detect the PFS improvement of HR = 0.67 with 80% power at an overall 2-sided significance level of 0.05.

Randomisation and blinding (masking)

Patients were randomized in a 1:1 ratio using IWRS, based on a permuted-block randomization method to one of two treatment arms, toripalimab combined with gemcitabine and cisplatin or placebo combined with gemcitabine and cisplatin. The stratification was based on ECOG performance status (0 versus 1) and disease stage (recurrent versus metastatic).

This was double-blind, placebo-controlled study. Placebo and toripalimab were identical in physical appearance. All patients, investigators, and study centre staff, sponsor, CRO, IRC were blinded to treatment assignment except for a Clinical Supplies Department of the Sponsor, sponsor personnel who were responsible for performing ADA and trough concentration assays.

Unblinding was only allowed in the case of a serious adverse events, unexpected suspected adverse reactions that were considered by the investigator or Sponsor to be related to study drug. If needed unblinding was done through IWRS.

All the patients were unblinded if the pre-defined stopping boundary was crossed and the Sponsor accepted the recommendation to unblind the study by the iDMC. When all the subjects were unblinded, patients receiving toripalimab were continuing the study drug open label until the treatment

discontinuation criteria were met according to protocol. Placebo arm were not continuing the treatment with placebo.

Statistical methods

Intention to treat Set (ITT): This population includes all the randomized patients.

Safety Analysis Set (SS): This population includes all the patients who have received any dose of the investigational drugs (including toripalimab or chemotherapy).

Per-Protocol Analysis Set (PPS): This population includes all ITT subjects without any major protocol violations that had significant impact on interpretation of safety or efficacy.

The primary and secondary endpoint statistical methods are shown in Table 46.

Table 42. Statistical analysis strategy for efficacy endpoints

Endpoint	Statistical method	Analysis population
Primary		
Progression free survival	Stratified log-rank test Stratified Cox proportional hazards model and the 95% CI Kaplan-Meier method	ITT
Secondary		
Overall survival	Stratified log-rank test Stratified Cox proportional hazards model and the 95% CI Kaplan-Meier method	ITT
Objective response rate	Clopper-Pearson method	ITT
Disease control rate	Clopper-Pearson method	ITT

Overall missing data was not imputed, only if the day of date of death was missing, the missing day of date was imputed as 15.

Interim analyses of efficacy of PFS were to be assessed when approximately 130 PFS events in the ITT population were observed, which was projected to occur approximately 18 months after the first subject was randomized. The final analysis was to be assessed when approximately 200 PFS events in the ITT population were observed, which was projected to occur approximately 25 months after the first subject was randomized (see table below).

Table 43. Timing and Stopping Boundary of PFS Analyses

Type of Analysis	Timing Since FSI (month)	Planned Information Fraction (Event #)	Stopping Boundary (Two-Sided p-Value)
PFS interim analysis	18	65% (130)	0.011
PFS final analysis	25	100% (200)	0.047

FSI = First subject in; PFS = progression-free survival; HR = hazard ratio.

Two interim analyses of efficacy of OS were to be performed when the interim and final analyses of PFS occur, where it is expected to observe approximately 49 and 74 deaths respectively. OS will be summarized and tested when 130 deaths will be observed in the ITT population and both PFS and ORR reach their statistical significance.

Results

Participant flow

The study was conducted from 18 October 2018 to 8 May 2022, all the patients have completed the treatment period.

From 408 patients that were screened a total of 289 patients were randomized (

Figure **59**) with 146 patients in the toripalimab group combined with chemotherapy and 143 patients in placebo group combined with chemotherapy.

From 408 screened patients 108 patients were screen failures as they did not meet eligibility criteria and 9 patients withdraw the consent.

When the interim analysis crossed pre-specified boundary for efficacy, after the first interim analysis, the study was unblinded and patients in the treatment arm received open label toripalimab, whereas patients in the control arm discontinued placebo.

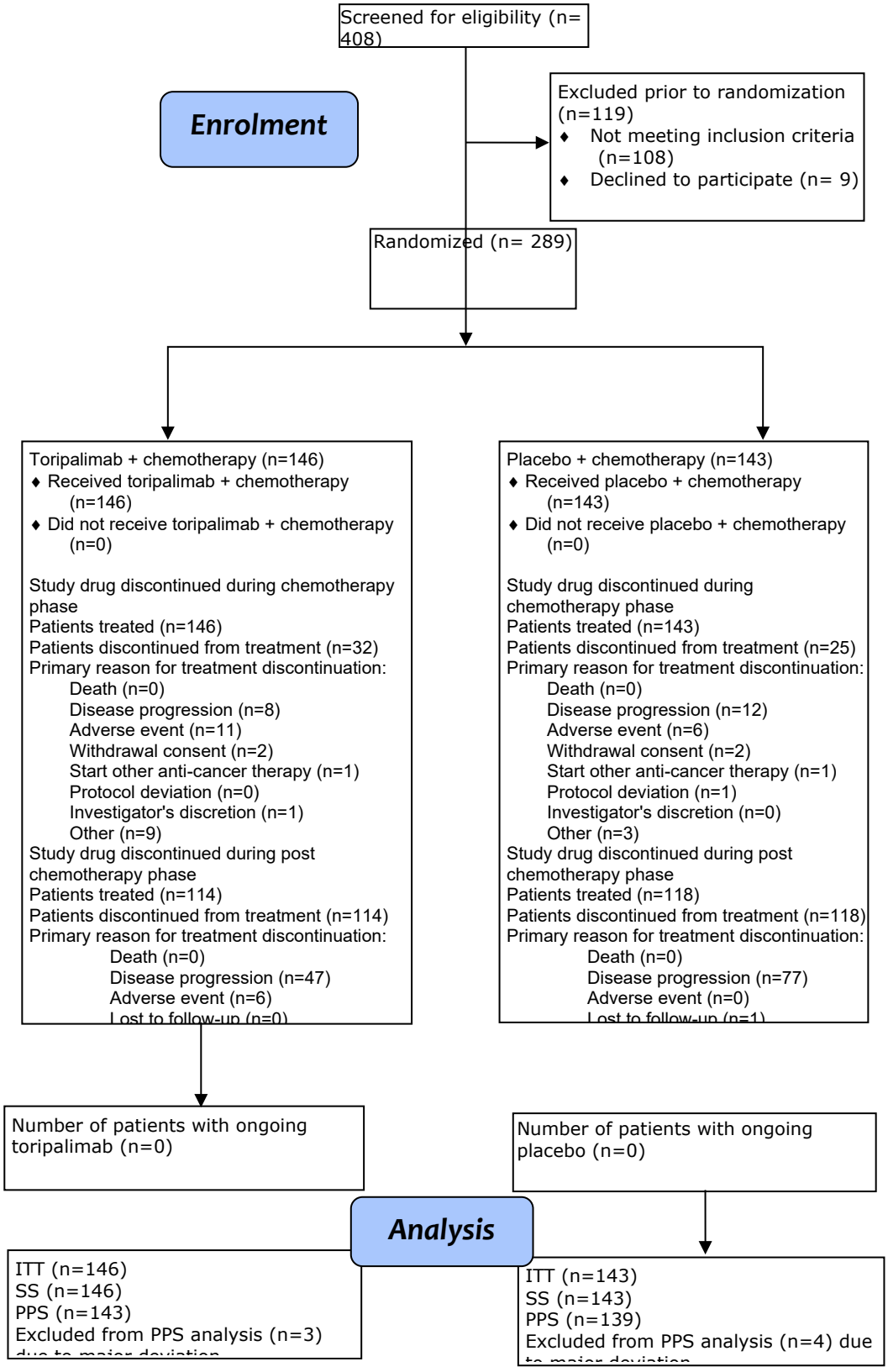
During the induction phase (with gemcitabine and cisplatin) all 289 patients received at least one dose of study drug (toripalimab/placebo). 57 patients discontinued treatment (32 in toripalimab and 25 in placebo group) due to disease progression for 20 patients (8 in the toripalimab arm and 12 in the placebo arm), adverse events for 17 patients (11 in the toripalimab arm and 6 in the placebo arm).

During the maintenance phase (post-chemotherapy) 232 patients were receiving study drug (114 in the toripalimab arm and 118 in the placebo arm). At the second interim analysis all the patients discontinued the treatment due to disease progression for 124 patients (47 in the toripalimab arm and 77 in the placebo arm).

Recruitment

Study JS001-015-III-NPC

Figure 57. Subjects Disposition in JS001-015-III-NPC study



Study Period: 2-year period of treatment

Initiation Date: 18 October 2018 (first written consent obtained)

Completion Date: 18 November 2022, all the patients have discontinued the treatment

Cut-off date for CSR: 30 May 2020

Cut-off date for CSR Addendum 1: 08 June 2021

Cut-off date for CSR Addendum 2: 8 May 2022

Cut-off date for CSR Addendum 3: 18 Nov 2022

Follow-up period: follow-up is foreseen until progression and/or survival until death, loss to follow-up, or withdrawal of consent.

The study was unblinded after the first interim analysis as prespecified O'Brien-Fleming boundary was reached of the IRC-assessed PFS. Patients who remained on study drug in the investigational arm continued to receive toripalimab, whereas patients in the control arm discontinued placebo.

Conduct of the study

Study JS001-015-III-NPC

The changes in the conduct of the study are presented in the table below.

Table 44. Changes in the Conduct of the Study

Protocol Version	Protocol Date	Majors change(s)
Original Protocol	02 March 2018	Original
Version 2.0	17 September 2018	The dose of toripalimab was changed from 360mg IV Q3W to 240mg IV Q3W due to new efficacy and safety data from completed and ongoing clinical studies. The timing of the conduct of the interim analysis for PFS was clarified. Exclusion criteria were modified to further specify subject eligibility.
Version 3.0	28 May 2019	Inclusion and exclusion criteria were modified to further specify subject eligibility. Changes were made to enhance operational efficiency.
Version 4.0	15 May 2020	This version was not submitted to any ethics committees and was not approved for implementation at any clinical study site.
Version 4.1	26 May 2020	Changed the primary endpoint from investigator-assessed PFS to IRC-assessed PFS and modified secondary endpoints and related sections of the protocol to reflect this change in the primary endpoint as needed. Removed the plan for interim analysis, re-calculated the sample size and adjusted other related sections of the protocol as needed based on removal of the planned interim analysis. Added toripalimab trough concentration test to keep consistent with secondary endpoint and meet the request of regulatory agency.

		Others: erratum or modified other details throughout the protocol for clarity, consistency and to enhance operational efficiency.
Version 5.0	18 August 2020	Re-inserted the plan for interim analysis of PFS and revised relevant sections of the protocol, as needed, based on this modification. Incorporated plans for assessment of exploratory biomarkers based on information from other studies of toripalimab and information in recent peer-reviewed literature. Others: modifications to address regulatory agency's request or feedback, erratum, as well as corrected the grammar and punctuation error to meet the requirements of good writing.
Version 6.0	14 October 2020	Modified to clarify that if the stopping boundary was crossed at the interim analysis of PFS, leading to unblinding of treatment assignment, subjects in Arm A remaining on therapy would be provided with open label toripalimab and subjects in Arm B remaining on therapy would have placebo infusions discontinued. Deleted references to "no crossover" based on ethical considerations and potential approval of toripalimab for this indication.

Changes in the Planned Analyses are presented in the table below.

Table 45. SAP changes

Version/Date	Summary of Major Changes and Rationale	Included in the BLA
1.0 (SAP submitted to IND 147826 on June 30-2021 to address comments from US FDA and to support US regulatory submission)	Original SAP submission to the FDA	To be provided upon request
1.0 (Revised SAP submitted to IND 147826 on August 21, 2020 to address comments from US FDA and to support US regulatory submission)	1. The analysis plan was revised to provide control of Type I error for the key secondary efficacy endpoints of ORR and OS, through a hierarchical testing procedure 2. Provided additional censoring rules for handling of missing data due to COVID-19 3. Provided the stopping boundaries for the interim analysis of PFS and a plan for alpha spending 4. Added sensitivity analyses including analyses to evaluate the impact of COVID-19 5. Added the plan to conduct two interim analyses of OS for descriptive purposes only at the time of the interim and final analyses of PFS, respectively 6. Provided detailed information concerning the safety analyses 7. Added a list of preferred terms that will be used to capture irAEs	Yes
2.0/October 30, 2020 (For the planned interim analysis of PFS supporting the BLA submission in China)	1. Included plan for an interim analysis of PFS 2. Added a definition of the study follow up time 3. Clarified definition of the per protocol analysis set 4. Stated data will be coded per MedDRA v 23.0, WHO Drug Global Dictionary Mar 2020 B3 5. Included definitions for the duration of exposure to toripalimab/placebo, cisplatin, and gemcitabine	To be provided upon request
3.0/July 21, 2021 (For the final analysis of PFS supporting the BLA submission in China)	1. Added the analysis plan for the key secondary endpoints including ORR and OS from revised version v1.0 (submitted to IND 147826 on August 21, 2020) 2. Modified the timing of the final PFS analysis for the descriptive purposes only given that the boundary of the interim PFS analysis had been crossed	To be provided upon request
3.1/August 2, 2021 (To address comments received at preBLA meeting with US FDA and to support US regulatory submission)	1. Adjusted the alpha level for the final analysis of OS by specifying that a nominal alpha of 10^{-6} should be spent for each unplanned ad hoc interim look 2. Added the detailed OS analysis plan from revised version v1.0 (submitted to IND 147826 on August 21, 2020) used for US IND application that was not included in version 3.0	Yes

Major protocol deviations

There were 147 patients that had at least one major protocol deviation, 75 patients in the toripalimab and 72 in the placebo arm.

83 patients (50 in toripalimab and 33 in placebo arm) had procedural deviations such as tumour assessments that were not read prior to infusion, change in their method of tumour assessment, incomplete or not done baseline imaging within 28 days of C1D1, missing laboratories or their laboratories were not done prior to dosing, missing tumour assessments due to COVID-19, missing tumour assessments for other reasons (due to patient refusal, site errors).

38 patients (14 in toripalimab and 24 in placebo arm) were non-compliant with treatment such as receiving incorrect dose or had omitted the dose for any component of treatment, continuing treatment despite disease progression.

50 patients (24 in toripalimab and 26 in placebo arm) had other protocol deviations such as late reporting of SAEs, incorrect randomization. (

Table **50**).

Table 46. Major protocol deviations (ITT)

	JS001+chemotherapy (N=146) n (%)	Placebo+chemotherapy (N=143) n (%)	Total (N=289) n (%)
Any major protocol deviation	58 (39.7)	62 (43.4)	120 (41.5)
Type of deviation			
Procedural deviation*	39 (26.7)	31 (21.7)	70 (24.2)
Treatment compliance deviation	12 (8.2)	21 (14.7)	33 (11.4)
Other protocol deviation	13 (8.9)	16 (11.2)	29 (10.0)
Inclusion/exclusion criteria deviation	5 (3.4)	11 (7.7)	16 (5.5)
Prohibited therapy	0	2 (1.4)	2 (0.7)
Withdrawal criteria deviation	0	2 (1.4)	2 (0.7)
COVID-19 related major protocol deviation	13 (8.9)	11 (7.7)	24 (8.3)
Type of deviation			
Procedural deviation	13 (8.9)	11 (7.7)	24 (8.3)
Treatment compliance deviation	0	1 (0.7)	1 (0.3)

Note: Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the patient's rights, safety, well-being, and/or on the validity of the data for analysis.

Note: * Examples of procedural deviation including tumor assessment in Screening visit didn't include CT scans (with oral/IV contrast unless contraindicated) or MRIs of the neck, nasopharynx, chest and abdomen or laboratory test chemistry results were not available when commencing an infusion at the same visit, et al.
Program Location: /projects/shenb237456/stats/primary/prog/tables/t pd.sas/04DEC2020/7:32
Database Cutoff Date: 30MAY2020 Extract Date: 02NOV2020
Final

Baseline data

Study JS001-015-III-NPC

Patient's mean age at screening was 48 years. All patients were Asian (100%), and approximately three quarters were male (83%). 163 patients (56.4 %) had the baseline ECOG PS per IWRS 0 and 126 patients (43.6%) had the baseline ECOG PS per IWRS 1. 165 patients (57.1%) had recurrent NPC per IWRS and 124 (42.9%) had primary metastatic NPC per IWRS. The demographic and baseline characteristics were well balanced between the toripalimab and placebo groups (see table below).

Table 47. Demographic Data and Baseline Characteristics

	JS001+chemotherapy (N=146)	Placebo+chemotherapy (N=143)	Total (N=289)
Age (years)			
N	146	143	289
Mean	45.84	49.68	47.74
Sd	11.260	10.355	10.973
Minimum	18.9	21.3	18.9
Median	45.55	50.70	48.40
Maximum	72.2	71.8	72.2
Sex, n (%)			
Male	124 (84.9)	116 (81.1)	240 (83.0)
Female	22 (15.1)	27 (18.9)	49 (17.0)
Race, n (%)			
White	0	0	0
American Indian or Alaska Native	0	0	0
Asian	146 (100)	143 (100)	289 (100)
Black or African American	0	0	0
Native Hawaiian or the Pacific Islander	0	0	0
Other	0	0	0
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Chinese	146 (100)	143 (100)	289 (100)
Indian (Indian subcontinent)	0	0	0
Japanese	0	0	0
Mixed Ethnicity	0	0	0
Other	0	0	0
Baseline height (cm)			
N	146	143	289
Mean	165.87	164.98	165.43
Sd	7.183	7.272	7.228
Minimum	145.5	145.5	145.5
Median	166.00	166.00	166.00
Maximum	188.5	182.5	188.5
Baseline weight (kg)			
N	146	143	289
Mean	60.08	59.48	59.79
Sd	10.103	9.928	10.004
Minimum	42	36.5	36.5
Median	58.80	58.00	58.00
Maximum	85.4	88.4	88.4
Baseline ECOG performance status per IWRS, n (%)			
0	83 (56.8)	80 (55.9)	163 (56.4)
1	63 (43.2)	63 (44.1)	126 (43.6)
Baseline ECOG performance status per CRF, n (%)			
0	83 (56.8)	81 (56.6)	164 (56.7)
1	63 (43.2)	62 (43.4)	125 (43.3)
Baseline disease stage per IWRS, n (%)			
Recurrent	83 (56.8)	82 (57.3)	165 (57.1)
Primary metastatic	63 (43.2)	61 (42.7)	124 (42.9)
Baseline disease stage per CRF, n (%)			
Recurrent	85 (58.2)	87 (60.8)	172 (59.5)
Type of recurrence [1]			
Local recurrence only	19 (13.0)	20 (14.0)	39 (13.5)
Distant recurrence	66 (45.2)	65 (45.5)	131 (45.3)
Unknown*	0	2 (1.4)	2 (0.7)
Primary metastatic	61 (41.8)	56 (39.2)	117 (40.5)
Metastatic organs at baseline[2]			
Liver	61 (41.8)	57 (39.9)	118 (40.8)
Lung	59 (40.4)	56 (39.2)	115 (39.8)
Bone	60 (41.1)	55 (38.5)	115 (39.8)
Others	123 (84.2)	124 (86.7)	247 (85.5)
Cigarette used, n (%)			
Yes	76 (52.1)	59 (41.3)	135 (46.7)
No	70 (47.9)	84 (58.7)	154 (53.3)
Alcohol used, n (%)			
Yes	30 (20.5)	18 (12.6)	48 (16.6)
No	116 (79.5)	125 (87.4)	241 (83.4)

IWRS = interactive web response system, Sd = standard deviation.
[1] Local recurrence only is defined from stage I to stage IVA and distant recurrence is defined as IVb based on the stage of disease at the time of ICF signed.
[2] Metastatic organ is based on any occurrence of lesion location of the target lesion or non-target lesion measurement at screening.
Note: * The 2 subjects were not diagnosed with NPC. One of them was diagnosed with colorectal cancer and the other was rhabdomyosarcoma.

NPC disease's baseline characteristics: 206 patients (71.3%) had undifferentiated non-keratinizing squamous cell carcinoma, 8 patients (2.8%) – differentiated non-keratinizing squamous cell carcinoma, 3 patients (1%) - keratinizing squamous cell carcinoma, 59 patients (20.4%) - unclassified

nasopharyngeal carcinoma. At the time of initial diagnosis, 113 (39.1%) subjects had metastatic disease. There were 4 subjects without metastatic disease at initial diagnosis who didn't receive treatment for NPC until after development of metastatic disease (see table below).

Table 48. Baseline NPC Disease Characteristics

	JS001+chemotherapy (N=146) n (%)	Placebo+chemotherapy (N=143) n (%)	Total (N=289) n (%)
Primary tumor site			
Superior Wall of Nasopharynx	5 (3.4)	5 (3.5)	10 (3.5)
Posterior Wall of Nasopharynx	19 (13.0)	17 (11.9)	36 (12.5)
Lateral Wall of Nasopharynx	13 (8.9)	17 (11.9)	30 (10.4)
Anterior Wall of Nasopharynx	2 (1.4)	0	2 (0.7)
Other*	107 (73.3)	104 (72.7)	211 (73.0)
Histology type			
Non-keratinizing squamous cell carcinoma, undifferentiated	104 (71.2)	102 (71.3)	206 (71.3)
Non-keratinizing squamous cell carcinoma, differentiated	2 (1.4)	6 (4.2)	8 (2.8)
Keratinizing squamous cell carcinoma	1 (0.7)	2 (1.4)	3 (1.0)
Nasopharyngeal carcinoma, unclassified	30 (20.5)	29 (20.3)	59 (20.4)
Non-keratinizing carcinoma, unclassified	9 (6.2)	3 (2.1)	12 (4.2)
Other	0	1 (0.7)	1 (0.3)
Metastasis observed at the time of initial diagnosis			
Yes**	59 (40.4)	54 (37.8)	113 (39.1)
No	87 (59.6)	89 (62.2)	176 (60.9)

Note: * "Other" included other sites of nasopharynx (96[65.8%] subjects in the JS001 arm and 94[65.7%] subjects in the placebo arm) and unknown (11[7.5%] subjects in the JS001 arm and 10[7.0%] subjects in the placebo arm).
Note: ** Four subjects had non- metastatic NPC at initial diagnosis, but didn't receive any treatment until enrollment into this study. They were classified as having metastatic disease at randomization.

Table 49. PD-L1 Staining (JUPITER-02)

	Toripalimab + GC N = 146 (%)	Placebo + GC N = 143 (%)
Tumour Cell Staining		
< 1%	31 (21.2)	42 (29.4)
≥ 1%	99 (67.8)	91 (63.6)
< 5%	37 (25.3)	49 (34.3)
≥ 5%	93 (63.7)	84 (58.7)
< 10%	**42 (28.8)**	**51 (35.7)**
≥ 10%	88 (60.3)	82 (57.3)
Missing	16 (11.0)	10 (7.0)
Immune Cell Staining		
< 1%	30 (20.5)	37 (25.9)
≥ 1%	100 (68.5)	96 (67.1)
< 5%	76 (52.1)	83 (58.0)
≥ 5%	54 (37.0)	50 (35.0)
< 10%	**98 (67.1)**	**106 (74.1)**
≥ 10%	32 (21.9)	27 (18.9)
Missing	16 (11.0)	10 (7.0)

Treatment compliance

38 patients (14 in toripalimab group and 24 in placebo group) had treatment compliance deviations. These deviations included overdose or incorrect dose administration of chemotherapy, patient didn't discontinue study drug after second progression, dose of chemotherapy was not modified per haematological toxicities, etc. A total of 2 patients had overdose as a protocol deviation: 1 patient needed a second dose reduction of chemotherapy due to adverse events and at Cycle 5 Day 1, the dose of gemcitabine should be 521.3 mg instead of 635 mg and cisplatin dose should be 41.7 mg

instead of 55.6 mg. The other patient's dose of chemotherapy was incorrectly calculated due to incorrect patient height record.

Numbers analysed

Study JS001-015-III-NPC

289 of 289 patients were included in ITT and SS Analysis Set (146 patients in the toripalimab arm and 143 patients in the placebo arm).

282 of 289 patients were included in PPS analysis, 143 patients in the toripalimab arm and 139 in the placebo arm. 7 patients were excluded from the PPS analysis due to receiving study drug with the wrong kit number, being diagnosed with other malignant tumour, not having measurable lesions at baseline, not having CT or MRIs scans of the neck, nasopharynx, chest, and abdomen at baseline.

Outcomes and estimation

Study JS001-015-III-NPC

Primary endpoint results

For the final primary efficacy endpoint analysis 289 patients were analysed, 146 patients in toripalimab treatment arm and 143 in placebo arm. The primary efficacy endpoint was IRC-assessed PFS, defined as the time from randomization to the occurrence of disease progression per RECIST v1.1 or death from any cause, whichever occurred first. The PFS final analysis cut-off date was 08 June 2021.

The final PFS analysis was triggered by 180 investigator-determined PFS events, based on SAP V3.0. The median duration of treatment were 65.7 weeks in toripalimab arm and 37.3 weeks in placebo arm (Table 54).

By the time of the analysis 150 (51.9) patients had disease progression or died, 63 patients (43.2%) in toripalimab treatment arm and 87 patients (60.8%) in placebo treatment arm by the IRC assessment.

The median PFS was 21.4 (95% CI: 11.73, NE) months in the toripalimab treatment arm and 8.2 (95% CI: 7.03, 9.79) months in the placebo treatment arm, the stratified HR was 0.52 (95% CI: 0.374, 0.726; nominal $p<0.0001$). Also unstratified analysis of the IRC-assessed PFS was performed, and the results were consistent with stratified analysis (HR=0.52; 95% CI: 0.377, 0.727; nominal $p<0.0001$) (Table 55).

Kaplan-Meier survival plot of PFS based on the IRC assessment per RECIST 1.1 in the ITT population showed that PFS curves separate early at approximately 5 months, with continuous separation between the 2 curves over the course of follow-up (see figure below).

Table 50. Extent of exposure (SS Population)

	JS001 (N=146)	Placebo (N=143)
The number of JS001/Placebo cycles		
Nx	146	143
Mean	19.1	12.7
Sd	11.41	6.75
Median	20.0	12.0
Minimum, Maximum	1, 35	1, 31
Actual duration of JS001/Placebo (weeks)[1]		
Nx	146	143
Mean	61.79	41.54
Sd	35.998	21.748
Median	65.70	37.30
Minimum, Maximum	3.1, 107.3	3.0, 101.1

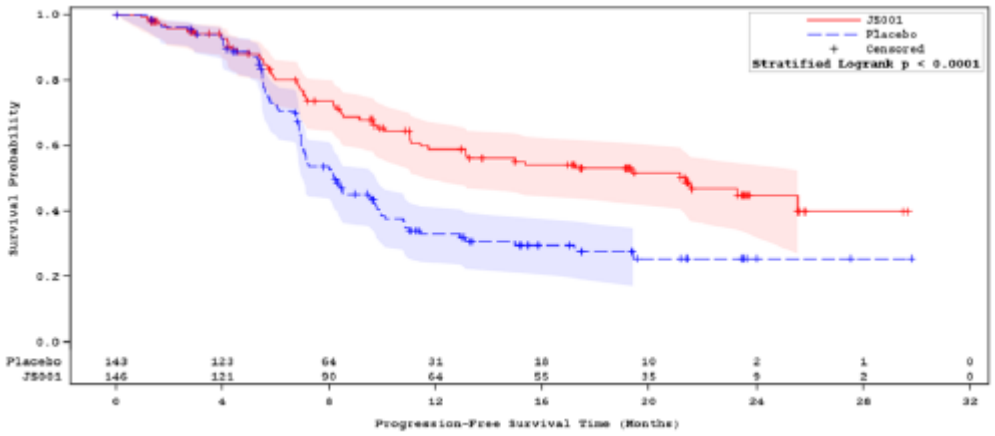
Nx = number of patients with non-missing values, Sd = standard deviation.
[1] Actual duration of exposure (in weeks) is calculated as: (the last dosing date at the end of treatment - the first dosing date + 21)/7.
[2] The actual cumulative total dose received (mg) is defined as the summation of all actual total dose administered from the first dosing date to the last dosing date at the end of treatment.
[3] Dose intensity is calculated as: actual cumulative total dose received/actual duration of exposure.
[4] Relative dose intensity will be calculated as: (actual cumulative total dose received / planned cumulative total dose received) * 100%.
[5] Weeks of chemotherapy is calculated as (the last dosing date - the first dosing date + 21)/7.

Table 51. IRC-Assessed PFS Per RECIST v1.1 (ITT Population)

	Toripalimab + chemotherapy (N=146)	Placebo + chemotherapy (N=143)	Total (N=289)
Status, n (%)			
Events observed	63 (43.2)	87 (60.8)	150 (51.9)
Progressive disease	60 (41.1)	86 (60.1)	146 (50.5)
Death	3 (2.1)	1 (0.7)	4 (1.4)
Censored	83 (56.8)	56 (39.2)	139 (48.1)
No post-baseline tumor assessment	2 (1.4)	5 (3.5)	7 (2.4)
No disease progression or death at the time of analysis	47 (32.2)	14 (9.8)	61 (21.1)
Missing two or more consecutive tumor assessments[1]	14 (9.6)	7 (4.9)	21 (7.3)
Started new anti-cancer therapy prior to IRC-determined progression	20 (13.7)	30 (21.0)	50 (17.3)
Estimate of median PFS (months) (95% CI)[2]	21.4 (11.73, NE)	8.2 (7.03, 9.79)	10.8 (9.53, 13.17)
Stratified analysis[3]			
Estimate of hazard ratio (Toripalimab vs Placebo)[4]	0.52		
(95% CI)	(0.374, 0.726)		
Nominal log-rank p-value (two-sided)	<0.0001		
Unstratified analysis			
Estimate of hazard ratio (Toripalimab vs Placebo) [4]	0.52		
(95% CI)	(0.377, 0.727)		
Nominal log-rank p-value (two-sided)	0.0002		
1-Year PFS Rate (95% CI)[5]	59.0% (49.72, 67.16)	32.9% (24.55, 41.53)	46.2% (39.72, 52.34)
Difference of 1-Year PFS Rates (95% CI)[6]	26.1% (13.8, 38.3)		
2-Year PFS Rate (95% CI)[5]	44.8% (34.39, 54.71)	25.4% (16.95, 34.81)	35.1% (28.14, 42.10)
Difference of 2-Year PFS Rates (95% CI)[6]	19.4% (5.7, 33.1)		

CI = confidence interval, IRC = independent review committee, IWRS = interactive web response system, NE = not estimable, PFS = progression- free survival, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1,
Note: IRC-Assessed PFS is defined as the time from randomization until the earliest occurrence of disease progression, as determined by independent review committee from tumor assessments, per RECIST v1.1, or death from any cause, whichever occurs first.
Note: PFS (in month) = (event date or censoring date - randomization date + 1)/30.4375.
[1] For patients who had two or more consecutive missing tumor assessments due to COVID-19, but had subsequent tumor assessments with no immediate disease progression, the subsequent tumor assessments were used in the PFS analysis and those patients were not counted in this category.
[2] The Brookmeyer Crowley methodology was used to construct the 95% CI for the median PFS.
[3] The stratified analyses used ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic) as recorded in the IWRS.
[4] The hazard ratio was estimated with the use of the Cox proportional hazards model. Efron's method was used to handle ties.
[5] The 95% CI was estimated with use of the standard error derived from Greenwood's formula.
[6] The 95% CI was estimated with use of the normal approximation method.

Figure 58. Kaplan-Meier Survival Plot of IRC-Assessed PFS (ITT Population)



Key secondary endpoint results

Overall Survival

In the CSR Addendum 2 overall survival was assessed at the data cut off 8 May 2022, OS events did not reach the pre-specified final analysis requirement (130 events) as of the cut-off date. In the latest CSR Addendum 3 (10 March 2023), final OS analysis was provided with the data maturity of 46%, which was formally tested according to the final statistical analysis plan. Median OS was not estimable (95% CI:38.70, NE) in the toripalimab arm and 33.7 months (95% CI:27.01, 44.19) in the placebo arm, stratified HR for OS was 0.63 (95% CI: 0.446, 0.891).

Results of 1-year OS rate was 90.9% (95% CI: 84.87%, 94.62%) in the toripalimab arm and 87.1% (95% CI: 80.36%, 91.69%) in the placebo arm with a difference of 3.8% (95% CI: -3.5%, 11.1%). Results of 2-year OS rate was 78.0% (95% CI: 70.18%, 83.97%) in the toripalimab and 65.1% (95% CI: 56.5%, 72.44%) in the placebo arm with difference of 12.9% (95% CI: 2.3%, 23.4%) Results of 3-year OS rate was 64.5% (95% CI: 55.86%, 71.87%) in the toripalimab and 49.2% (95% CI: 40.53%, 57.32%) in the placebo arm with difference of 15.3% (95% CI: 3.6%, 26.9%) (Table 56).

Kaplan-Meier survival plot of final OS analysis in the ITT population in the toripalimab arm was clear (See Figure 59 and consistent with previous analyses (final CSR dated 15 January 2021, CSR Addendum 1 dated 22 November 2021 and CSR Addendum 2 dated 13 October 2022) (Figure 62, Figure 63 and Figure 64).

Table 52. Overall Survival (ITT Population)

	Toripalimab + chemotherapy (N=146)	Placebo + chemotherapy (N=143)	Total (N=289)
Status, n (%)			
Death	57 (39.0)	76 (53.1)	133 (46.0)
Censored	89 (61.0)	67 (46.9)	156 (54.0)
Alive	82 (56.2)	60 (42.0)	142 (49.1)
Lost to Follow-up	7 (4.8)	7 (4.9)	14 (4.8)
Unknown	0	0	0
Estimate of median OS (months) (95% CI)[1]	NE (38.70, NE)	33.7 (27.01, 44.19)	41.8 (36.57, NE)
Stratified analysis[2]			
Estimate of hazard ratio (Toripalimab vs Placebo)[3]	0.63		
(95% CI)	(0.446, 0.891)		
Log-rank p-value (two-sided)	0.0083		

Unstratified analysis				
Estimate of hazard ratio (Toripalimab vs Placebo)[3]		0.66		
(95% CI)		(0.465, 0.925)		
Log-rank p-value (two-sided)		0.0154		
1-Year OS Rate	90.9%		87.1%	89.1%
(95% CI)[4]	(84.87, 94.62)		(80.36, 91.69)	(84.80, 92.17)
Difference of 1-Year OS Rates		3.8%		
(95% CI)[5]		(-3.5, 11.1)		
2-Year OS Rate	78.0%		65.1%	71.6%
(95% CI)[4]	(70.18, 83.97)		(56.50, 72.44)	(65.93, 76.55)
Difference of 2-Year OS Rates		12.9%		
(95% CI)[5]		(2.3, 23.4)		
3-Year OS Rate	64.5%		49.2%	56.9%
(95% CI)[4]	(55.86, 71.87)		(40.53, 57.32)	(50.83, 62.58)
Difference of 3-Year OS Rates		15.3%		
(95% CI)[5]		(3.6, 26.9)		

CI = confidence interval, IWRS = interactive web response system, NE = not estimable, OS = overall survival
Note: OS is defined as the time from randomization to death from any cause and is calculated as (death date or censoring date - randomization date + 1)/30.4375 in month.
[1] The Brookmeyer Crowley methodology was used to construct the 95% CI for the median overall survival.
[2] The stratified analyses used ECOG performance status (0 vs. 1), and disease stage (recurrent vs. metastatic) as recorded in the IWRS.
[3] The hazard ratio was estimated with the use of the Cox proportional hazards model. Efron's method was used to handle ties.
[4] The 95% CI was estimated with use of the standard error derived from Greenwood's formula.
[5] The 95% CI was estimated with use of the normal approximation method.

Figure 60. Kaplan-Meier Survival Plot of Overall Survival (ITT Population) CSR Addendum 3

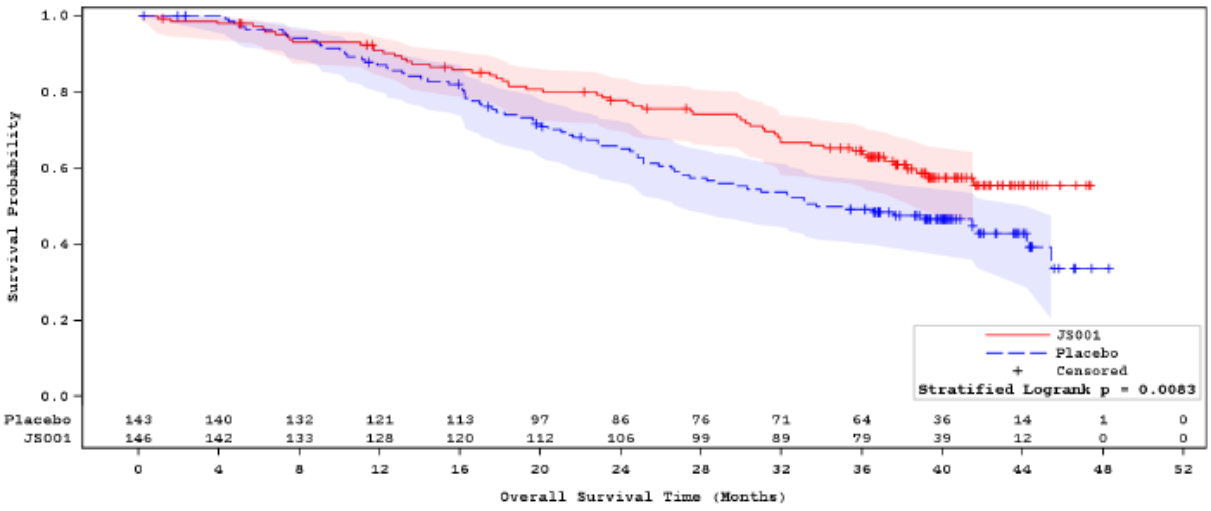


Figure 61. Kaplan-Meier Survival Plot of Overall Survival (ITT Population) CSR 15 January 2021

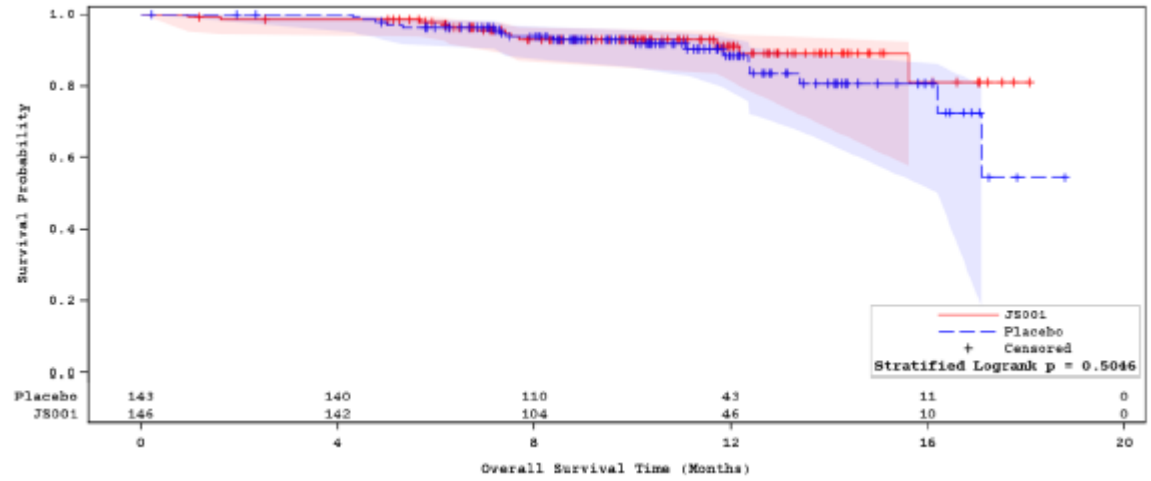


Figure 62. Kaplan-Meier Survival Plot of Overall Survival (ITT Population) CSR Addendum 1

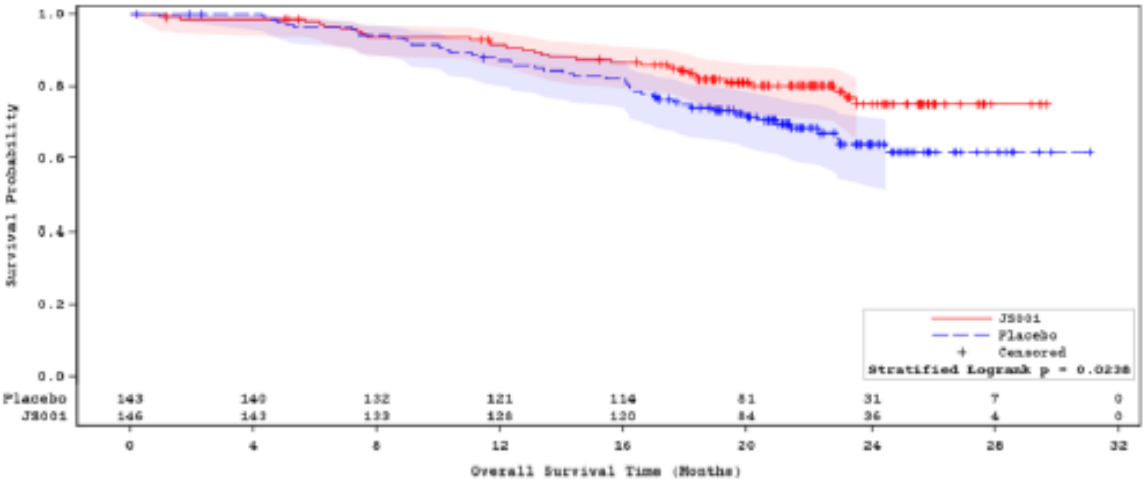
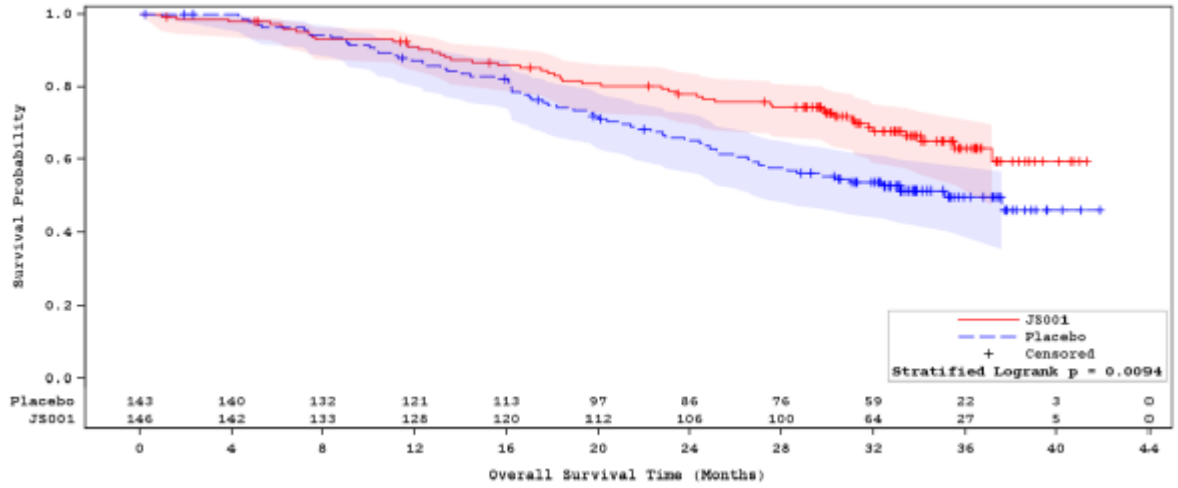


Figure 63. Kaplan-Meier Survival Plot of Overall Survival (ITT Population) CSR Addendum 2



Secondary endpoint results

Objective Response Rate and Disease Control Rate

Objective response was defined as either a confirmed complete response (CR) or partial response (PR) per RECIST v1.1. Overall response rate (ORR) was defined as the proportion of patients with a confirmed objective response per RECIST v1.1. Objective response was assessed at the data cut off 08 June 2021.

IRC assessed confirmed CR was the BOR in 39 (26.7%) patients in the toripalimab arm and 19 (13.3%) patients in the placebo arm. Confirmed PR was the BOR in 76 (52.1%) patients in the toripalimab and 77 (53.8%) patients in the placebo arm. Confirmed stable disease was the BOR in 14 (9.6%) patients in toripalimab treatment arm and 19 (13.3%) patients in the placebo treatment arm.

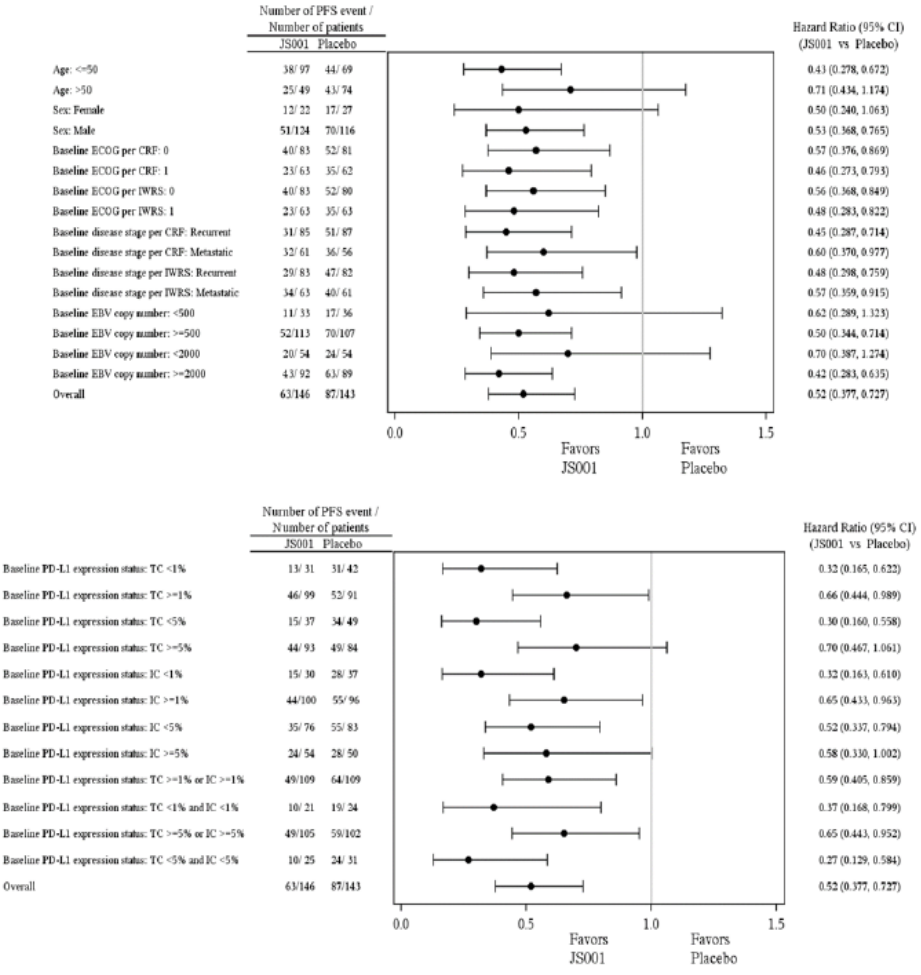
ORR was 78.8% (95% CI: 71.24%, 85.09%) in the toripalimab arm and 67.1% (95% CI: 58.79%, 74.75%) in the placebo arm. The difference of ORR was 11.4% (95% CI: 1.65%, 21.23%, nominal p value 0.0221).

Ancillary analyses

Study JS001-015-III-NPC

The results of the subgroup analyses didn't show any major differences between subgroups (See Figure 65).

Figure 64. Forest Plot of Subgroup Analyses of IRC-Assessments PFS (ITT Population)



3.6.6.3. Summary of main efficacy results

Table 53. Summary of efficacy for trial JS001-015-III-NPC

Title: A Phase 3, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined with Chemotherapy Versus Placebo Combined with Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer			
Study identifier	JS001-015-III-NPC (CT15) NCT03581786		
Design	The efficacy of toripalimab was investigated in JUPITER-02, a randomised, placebo-controlled, multi-centre, double-blind trial that enrolled 289 patients with recurrent locally advanced or metastatic nasopharyngeal cancer (NPC) who had not previously received systemic therapy for recurrent or metastatic disease. Patients were randomised (1:1) to toripalimab in combination with gemcitabine and cisplatin (GC) or placebo plus GC. Randomization was stratified by Eastern Cooperative Oncology Group performance status (0 vs. 1) and disease stage (recurrent vs. metastatic). The treatment phase included an induction period and a maintenance period. In the induction period, patients received toripalimab or placebo combined with GC on Day 1 of each cycle (3 weeks per cycle) for up to 6 cycles. After completion of GC, patients entering the maintenance period received toripalimab or placebo monotherapy on day 1 of each subsequent cycle (3 weeks per cycle). Tumour imaging was obtained every 6 weeks for the first year and then every 9 weeks. Treatment was continued until disease progression, intolerable toxicity, withdrawal of consent, or Investigator decision. In the absence of unacceptable toxicity or symptomatic deterioration, patients could continue treatment with study drug (toripalimab or placebo) beyond radiographic progression provided they were experiencing clinical benefit as assessed by the Investigator. The primary endpoint was Blinded Independent Review Committee (BIRC)-determined PFS per RECIST v1.1. Overall survival (OS) and objective response rate (ORR) were key secondary endpoints.		
	Duration of main phase:		Up to 2 years of study drug (toripalimab or placebo)
	Duration of Run-in phase:		Not applicable.
	Duration of Extension phase:		Not applicable.
Hypothesis	This study was designed to test for superiority. The null hypothesis was that there was no difference between the two arms in the primary efficacy endpoint, BIRC-assessed PFS. The alternative hypothesis was that there was a difference between the two arms in this endpoint.		
Treatments groups	Toripalimab Arm		Induction period: Toripalimab 240 mg Day 1, gemcitabine 1000 mg/m^2 on Days1 and 8, and Cisplatin 80 mg/m^2 on Day 1 intravenously (IV) every 3 weeks (Q3W) for up to 6 cycles Maintenance period: Toripalimab 240 mg IV Q3W
	Placebo Arm		Induction period: Placebo on Day 1, gemcitabine 1000 mg/m^2 on Days 1 and 8, and Cisplatin 80 mg/m^2 on Day 1 IV Q3W for up to 6 cycles Maintenance period: Placebo IV Q3W
Endpoints and definitions	Primary endpoint	BIRC-determined PFS	Time from randomization to disease progression, as determined by the BIRC per RECIST v1.1, or death due to any cause, whichever occurred first.

		BIRC- and Investigator (INV)-determined ORR	Proportion of patients who achieved a confirmed complete or partial response, as determined by the BIRC and Investigator, per RECIST v1.1
		OS	Time from randomization to death due to any cause.
		INV-determined PFS	Time from randomization to disease progression, as determined by the Investigator per RECIST v1.1, or death due to any cause, whichever occurred first
		BIRC- and INV-determined duration of response (DOR)	Time from the first recorded complete or partial response until the date of disease progression or death, whichever occurs first
		BIRC- and INV-determined disease control rate	Proportion of patients with a complete response, partial response or stable disease per RECIST v1.1
		BIRC- and INV-determined PFS at 1 and 2 years	Proportion of patients without documented disease progression, as evaluated by the BIRC or INV per RECIST v1.1, at 1 or 2 years after randomisation
		OS at 1 and 2 years	Proportion of patients alive at 1 or 2 years after randomisation
Database lock	Interim (definitive) Analysis of PFS: 02 Nov 2020 Final Analysis of PFS: 20 Jul 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All efficacy analyses were conducted in the intent-to-treat population defined as all randomized patients. One interim efficacy analysis of BIRC-determined PFS was planned at approximately 130 PFS events. The actual analysis was performed at 128 BIRC-determined PFS events with a database lock of November 2, 2020. This analysis crossed the pre-specified efficacy boundary and is considered the definitive analysis. The first interim analysis of OS was performed at this time. The final analysis of PFS was to be conducted at approximately 200 PFS events or approximately 18 months after the last patient was randomized. The actual analysis was performed at 150 BIRC-assessed PFS events with a database lock of July 20, 2021. The second interim analysis of OS was performed at this time. An ad hoc analysis of OS is included in the submission with a data cutoff of 8 May 2022. The final analysis of OS at 133 events was submitted on 10 March 2023. The study was completed on 18 November 2022.		
Descriptive statistics and estimate variability	Treatment group	Toripalimab Arm	Placebo Arm
	Number of subjects	146	143
	BIRC-determined PFS (month)	21.4	8.2

	Database lock: 20 Jul 2021 Median		
	95% confidence interval (CI)	11.73, not estimable (NE)	7.03, 9.79
	OS (month) Data cutoff: 18 Nov 2022 Median	NE	33.7
	95% confidence interval	38.7, NE	27.0, 44.2
	BIRC-determined ORR (%) Database lock: 02 Nov 2020	77.4%	66.4%
	95% confidence interval	69.7, 83.9	58.1, 74.1
	BIRC-determined DOR Median (months) Database lock: 02 Nov 2020	10.0	5.7
	95% confidence interval	8.8, NE	5.4, 6.8
Effect estimates per comparison	Primary endpoint BIRC-determined PFS Database lock: 02 Nov 2020	Comparison groups	Toripalimab Arm and Placebo Arm
		Hazard ratio	0.52
		95% confidence interval	0.37, 0.73
		p-value (stratified log-rank test)	<0.0001
	Secondary endpoint BIRC-determined ORR Database lock: 02 Nov 2020	Comparison groups	Toripalimab Arm and Placebo Arm
		Difference in ORR	10.8%
		95% confidence interval	0.8, 20.7
		p-value (stratified log-rank test)	0.0335
	Secondary endpoint OS Data cutoff: 18 Nov 2022	Comparison groups	Toripalimab Arm and Placebo Arm
		Hazard ratio	0.63
		95%CI	0.45, 0.89
		p-value	0.0083
Notes	When the interim analysis crossed the pre-specified boundary for efficacy, the Independent Data Monitoring Committee recommended unblinding. The Sponsor chose to unblind the study. Patients in the treatment arm were transitioned to open-label toripalimab, whereas all patients in the control arm discontinued placebo. Tumour imaging continued in the toripalimab arm but not in the placebo arm. Survival follow-up and the collection of subsequent anticancer		

	therapy was continued in both arms. Safety information was collected, as per protocol, up to 60 days after the last dose of toripalimab or placebo.
Analysis description	**Primary Analysis and Key Secondary analysis**
BIRC-PFS	The null hypothesis for the primary analysis was that there was no difference in BIRC-determined PFS between arms while the alternative hypothesis was that a difference existed between arms. The null hypothesis was tested using a stratified (stratification factors at randomization, performance status and disease stage) log rank test. The null hypothesis was rejected at the time of the interim analysis. A pre-specified group sequential design with O'Brien-Fleming boundaries approximated by the Lan-DeMets spending function was used to control the overall alpha for the interim and final analyses of BIRC-determined PFS at a two-sided level of 0.05. The HR and the corresponding confidence interval were estimated using the stratified (stratification factors at randomization) Cox proportional hazards model. The Kaplan-Meier method was used to estimate the median for each arm, and the corresponding confidence interval was estimated using the Brookmeyer-Crowley method with log-log transformation.
ORR and OS	Once the null hypothesis for BIRC-determined PFS was rejected, the key secondary endpoints, BIRC-determined ORR and OS, were tested hierarchically at a two-sided alpha level of 0.05. The difference in ORR between arms was formally tested at the time of the interim (definitive) analysis of PFS. This testing crossed the boundary for statistical significance. OS was to be summarized descriptively at the time of the interim and final analyses of PFS and formally tested only at the final analysis after observing 130 OS events. The statistical analysis plan was modified, at the request of US FDA, so that an alpha of 10^{-6} was spent each time OS was analysed for descriptive purpose. An alpha of 0.05 minus the alpha spent for the descriptive analyses will be available at the time of the final OS analysis. There was no plan for alpha spending for additional secondary endpoints.

3.6.6.4. Clinical studies in special populations

Data by Age groups

Table 54. Age at Enrolment in JUPITER-02 and JUPITER-06

Study	Age< 65 years (n/N)	Age 65-74 years (n/N)	Age 75-84 years (n/N)	Age ≥85 years (n/N)
JUPITER-02	139/146	7/146	0/146	0/146
JUPITER-06	156/257	100/257	1/257	0/257

Data by renal and hepatic impairment

Table 55. Renal and Hepatic Impairment at Enrolment in JUPITER-02 and JUPITER-06

Study	Renal Impairment[1] (n/N)	Hepatic Impairment (n/N)
JUPITER-02	67/146	22/146
JUPITER-06	176/257	12/257

[1]Creatinine clearance is calculated from the Cockcroft-Gault equation using ideal body weight for patients with obesity.

3.6.6.5. In vitro biomarker test for patient selection for efficacy

None.

3.6.6.6. Analysis performed across trials (pooled analyses and meta-analysis)

No meta-analysis or pooled analysis was conducted.

3.6.6.7. Supportive study(ies)

Studies to support the efficacy of toripalimab in nasopharyngeal cancer:

POLARIS-02 JS001-1b-CRP-1.0 CT5

Cohorts 3 and 7 of POLARIS-02

Study design

POLARIS-02, was a Phase 2 basket trial with 8 cohorts (based on extent of prior therapy and tumour type) that included the following 4 tumour types.

1. Gastric and gastroesophageal junction carcinoma (Cohorts 1 and 5)
2. Oesophageal squamous cell carcinoma (Cohorts 2 and 6)
3. Nasopharyngeal carcinoma (Cohorts 3 and 7)
4. Squamous cell carcinoma of the head and neck (Cohorts 4 and 8)

Cohort 3

Eligible patients in Cohort 3 had a diagnosis of advanced and/or metastatic NPC and received at least 2 prior lines of therapy for advanced NPC (including but not limited to chemotherapy or chemoradiotherapy) and had confirmed tumour progression or intolerance to existing treatment regimens.

In Cohort 3 patients received toripalimab 3mg/kg IV infusion Q2W of each 28-day (4 weeks) cycle, until disease progression, intolerable toxicity, the investigator's decision to terminate treatment, the patient's withdrawal of consent or death.

The primary objective of this study was to evaluate the anti-tumour activity of toripalimab for the treatment of advanced NPC. The primary efficacy endpoint was objective response rate based on RECIST v1.1.

Table 56. Statistical analysis strategy for efficacy endpoints

Endpoint	Statistical method	Analysis population
Primary		
ORR	Clopper-Pearson method	BTDAS PTAS FAS
Secondary		
Duration of response	Kaplan-Meier method Brookmeyer-Crowley method	BTDAS PTAS FAS
Disease control rate	Clopper-Pearson method	BTDAS PTAS FAS

Cohort 7

Eligible patients in Cohort 7 had a diagnosis of advanced and/or metastatic NPC who have not received any systemic treatment for metastatic disease.

In Cohort 7 patients received toripalimab Q3W IV in combination with gemcitabine and cisplatin, until disease progression, intolerable toxicity, investigator's decision to discontinue treatment, withdrawal of consent by the patients or death.

The scans of tumour evaluation were performed every 6 weeks for the first year and every 12 weeks thereafter.

Patients received toripalimab in combination with gemcitabine and cisplatin. They received 240 mg or 360 mg of toripalimab administered by IV infusion Q3W.

Gemcitabine was given 1000 mg/m2 over 30 minutes IV on Days 1 and 8, and cisplatin was given 80 mg/m2 IV over 3 hours on Day 1, in 3-week cycles.

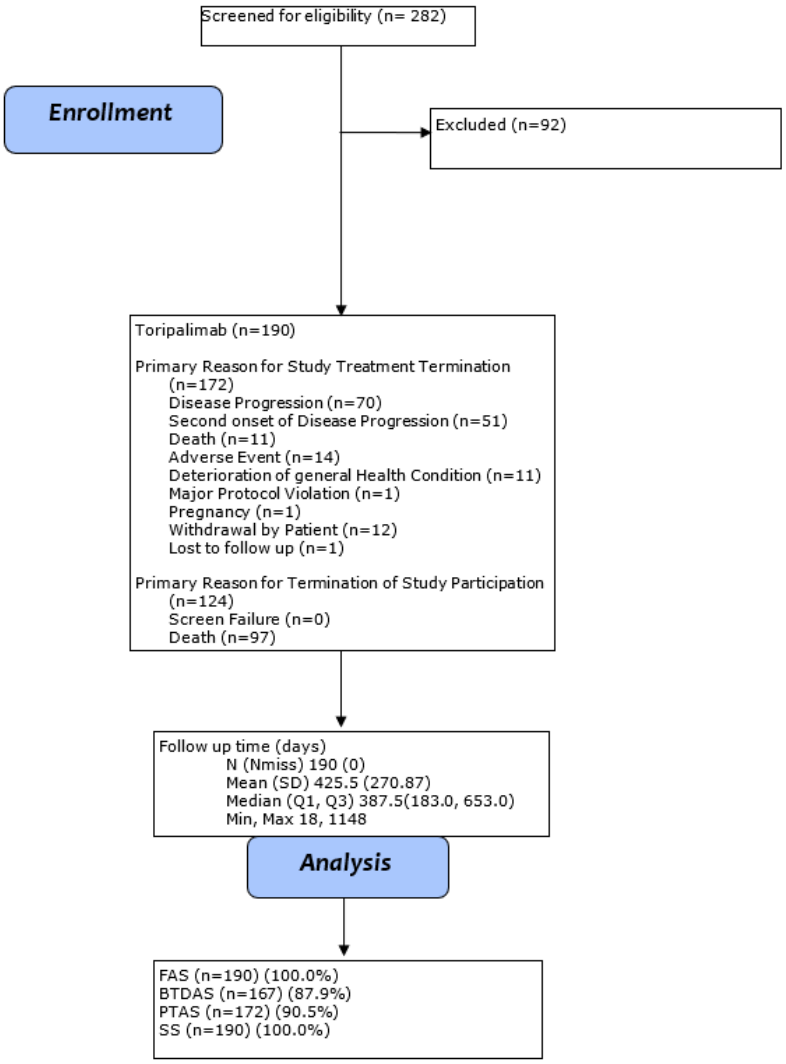
The treatment was given until absence of further benefits judged by the investigator, disease progression, occurrence of intolerable toxicity, investigator's decision to discontinue treatment, withdrawal of informed consent by the patient, or death.

The primary objective of this study was to evaluate the anti-tumour activity of toripalimab combined with standard first-line chemotherapy for the treatment of NPC. The primary efficacy endpoint was objective response rate based on RECIST v1.1.

Study results

Cohort 3

Figure 65. Subjects Disposition in JS001-1b-CRP-1.0 study Cohort 3



Cohort 7

Figure 66. Subjects Disposition in JS001-1b-CRP-1.0 study Cohort 7

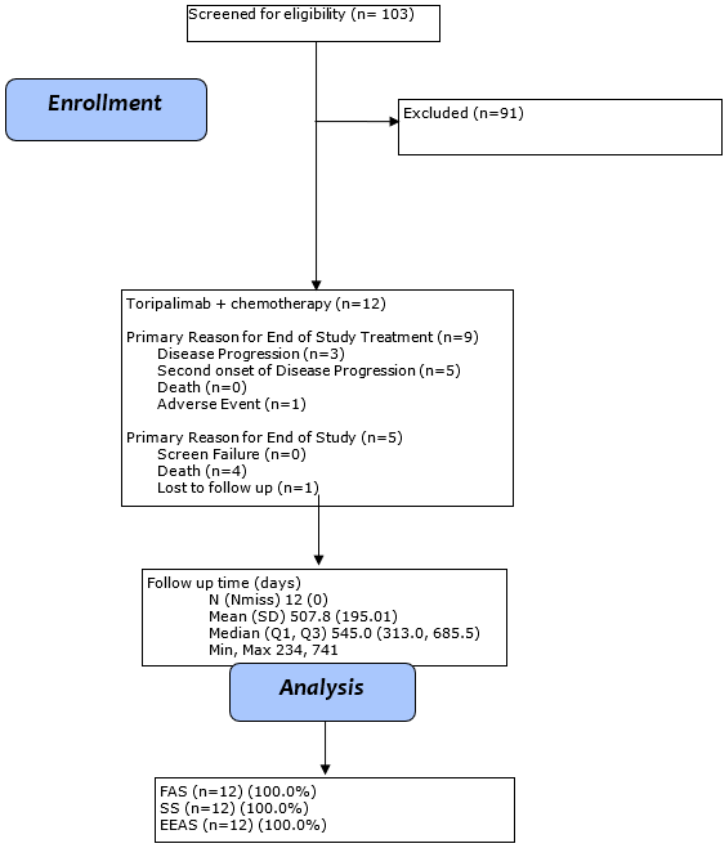


Table 57. Demographics and Baseline Characteristics (Cohorts 3 and 7/POLARIS-02)

Demographic and Baseline Characteristics	Cohort 3 Toripalimab Monotherapy		Cohort 7 Toripalimab + GC N=12
	PTAS N=172	Safety Set N=190	
Median Age (range)	45 years (22-68)	46 years (22-71)	46 years (30-55)
Gender, N (%)			
Male	143 (83.1)	158 (83.2)	10 (83.3)
Female	29 (16.9)	32 (16.8)	2 (16.7)
Race, N (%)			
Asian	172 (100)	190 (100)	12 (100)
ECOG Performance Status, N (%)			
0	63 (36.6)	66 (34.7)	6 (50.0)
1	109 (63.4)	124 (65.3)	6 (50.0)
Nasopharyngeal Cancer	172 (100)	190 (100)	12 (100)
Keratinising	5 (2.9)	7 (3.7)	UK
Non-keratinising	164 (95.3)	180 (94.7)	UK
Missing	3 (1.7)	3 (1.6)	UK
PD-L1 Status[1], N (%)			
Tumour Proportion Score ≥ 1%	47 (27.3)	52 (27.4)	9 (75.0)
Tumour Proportion Score < 1%	118 (68.6)	130 (68.4)	3 (25.0)
Unknown	7 (4.1)	8 (4.2)	0
Systemic Therapies for Advanced/Metastatic Disease			
Median (range)	4 (1-15)	4 (1-15)	0
Prior Therapies, N (%)			
Radiation Therapy	155 (90.1)	169 (88.9)	10 (83.3)
Cisplatin	157 (91.3)	172 (90.5)	5 (41.7)

Source: Cohort 3/CT5 Tables 14.1.3.1.3, 14.1.3.1.11, 14.1.5.1.3, 14.1.5.1.11 DCO: 19-Feb-2020
Cohort 7/CT5 Tables 14.1.3.1, 14.1.4.1, Listing 16.2.10
[1]Clinical trial assay using immunohistochemistry with SP142 antibody.
GC=gemcitabine/cisplatin; PD-L1=programmed death ligand-1; PTAS=platinum-treated analysis set; UK=unknown

In cohort 3 primary efficacy endpoint was ORR based on RECIST v1. 1.. In the PTAS analysis 20.9% (95% CI: 15.1%, 27.8%) of the patients achieved a CR or PR after toripalimab monotherapy per IRC assessment. Investigators ORR assessed the same as IRC (see table below).

In cohort 7 primary efficacy endpoint was ORR based on RECIST v1. 1.. In the FAS analysis confirmed ORR was 75.0% (95% CI: 42.8%, 94.5%) after toripalimab in combination with chemotherapy per investigator assessment (see table below).

Table 58. Response Rate and Duration of Response (Cohorts 3 and 7/POLARIS-02)

	BIRC-determined PTAS N=172	Investigator-determined Cohort 7 N=12
Response Rate, N (%) (95% CI)	36 (20.9) (15.1, 27.8)	9 (75.0) (42.8, 94.5)
Median Duration of Response, months (95% CI)	14.9 (10.3, NE)	7.1 (4.2, 15.3)
Source: Cohort 3/CT5 14.2.1.1.4.3, 14.2.2.4.3; Cohort 7/CT5 14.2.1.1.1, 14.2.2.1 DCO: 19-Feb-2020 CI=confidence interval; BIRC=blinded independent review committee; NE=not estimable		

Immunogenicity

In JUPITER-02, ADA was detected in 10/146 (6.8%) patients; none of these patients had evidence of neutralizing antibodies. This includes 5 patients who were ADA positive at baseline and 5 who became ADA positive on-study. All 5 patients who were positive at baseline had no evidence of ADA in post-baseline samples. The ORR was 80.0% in those with ADA (N = 10) and 77.2% (N = 136) in those without. Similarly, a Kaplan-Meier plot of PFS showed no significant difference when stratified by ADA status (p=0.94).

In Cohort 3 of POLARIS-02, ADA was detected in 7/190 (3.7%) patients. Three of the 7 patients in whom ADA was detected were also neutralising antibody (NAb)-positive on Day 15 (2 patients) or Day 43 (1 patient). However, all were ADA-negative or NAb-negative at the end of treatment. All seven of these patients were in the 172 patients in the PTAS population. The ORR was 28.6% in those with ADA (N = 7) and 20.6% (N = 165) in those without.

In Cohort 7 of POLARIS-02, ADA was detected in none of the 12 patients with NPC. The presence of ADA did not appear to affect efficacy in either JUPITER-02 or Cohort 3 of POLARIS-02. However, the number of patients with ADA is too small to draw firm conclusions.

3.6.7. Discussion on clinical efficacy

Design and conduct of clinical studies

JUPITER-02 (JS001-015-III-NPC), a randomized, placebo-controlled, multi-centre, double-blind, phase 3 study was conducted to support the use of toripalimab for the treatment of nasopharyngeal carcinoma. It was designed to determine the efficacy and safety of toripalimab in combination with gemcitabine and cisplatin compared with placebo in combination with gemcitabine and cisplatin as first-line treatment in subjects with histologically or cytologically confirmed, recurrent or metastatic NPC not amenable to curative therapy who had not received previous systemic chemotherapy for recurrent or metastatic disease.

The key inclusion for the JUPITER-02 study included patients with metastatic or recurrent NPC (histologically or cytologically confirmed), who did not receive systemic chemotherapy for recurrent or metastatic disease.

Patients received toripalimab/placebo in combination with gemcitabine and cisplatin and the dose of toripalimab was 240 mg IV Q3W.

The choice of the combination therapy with gemcitabine and cisplatin is acceptable as a first line treatment for recurrent or metastatic NPC, as it is in line with 2021 ESMO-EURACAN clinical guidelines on NPC. However, the choice of gemcitabine and cisplatin for locally advanced NPC is uncertain, as according to 2021 ESMO-EURACAN the standard and most used treatment is cisplatin 100 mg/m^2 every 3 weeks, other possible and used treatments are cisplatin with gemcitabine or cisplatin with 5-fluoruracil.

The objectives of the JUPITER-02 study are focused on the assessment of efficacy and safety of toripalimab in combination with chemotherapy compared with placebo in combination with chemotherapy.

The primary endpoint was PFS as determined by IRC from tumour assessments, per RECIST v1.1, or death from any cause, whichever occurred first. The PFS assessment by independent review committee reduced possible bias. Secondary endpoints were OS, IRC-assessed ORR, DoR, and DCR according to RECIST v1.1. The primary and secondary endpoints are in line with EMA/CHMP/205/95 Rev.6 and EMA/CHMP/27994/2008/Rev.1 (Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials), and are therefore considered acceptable.

The assumptions of the sample size calculations appear reasonable. Simeon's two-stage design is common and appropriate in oncology (Simon 1989). The calculations are acceptable.

Randomized subjects were stratified according to their ECOG performance status (0 vs 1) and disease stage (recurrent vs metastatic). According to the applicant, PD-L1 tumour status was not selected as a stratification factor because the relationship between clinical efficacy and PD-L1 tumour status was still uncertain based on the limited literature available at the time the JUPITER-02 trial was designed. However, the total numbers of patients by TC/IC PD-L1 expression (< 10%, ≥ 10% and missing) was provided**.**

Patient's mean age, sex, race, status were symmetrical between treatments group. The number of patients that had ECOG performance 0 and 1 were similar in numbers and between treatment groups. Recurrent and metastatic NPC were similar in numbers and between treatment groups.

Protocol deviations were mainly due to overdose or incorrect dose administration of chemotherapy but not due to toripalimab.

NPC-related risk factors include genetic factors, EBV infection, and environmental factors such as smoking, drinking, eating salted fish and exposure to carcinogens (Hao Yu et al, 2022). According to WHO 2023 tobacco use in China, Taiwan and Singapore are quite similar comparing to Europe and alcohol consumption is higher in European countries than in these Asian countries.

The proportion of the NPC patients with keratinising histology is higher in EU population than in the Asian population, and these patients were underrepresented in the JUPITER-02 trial. Some pre-clinical studies showed that regulating both the tumour microenvironment and immune responsiveness of HNSCC using a syngeneic mouse HNSCC model, keratinizing disease presence may contribute to immune evasion and resistance to ICI treatment by broadly altering immune landscapes of tumours. However, there is currently no available clinical evidence to demonstrate the difference in OS benefit from ICIs to nonkeratinizing or keratinizing mNPC (Wang et al., 2022; PMID: 35621713).

The investigators remained blinded unless a serious adverse event occurred that was considered to be related to the study drug. Unblinded personnel were only Clinical Supplies Department of the sponsor and sponsor personnel who were responsible for performing ADA and trough concentration assays. The blinding was done appropriately.

After the initiation of recruitments minor amendments were performed on inclusion and exclusion criteria and this is acceptable.

Minor change to the primary endpoint was done before the first cut-off date. No major changes were done in SAP. The changes to the planned analyses do not impair the overall validity of the clinical trial.

The population (ITT), placebo control, and endpoint measurement are considered appropriately chosen in the JUPITER-02 study. One interim analysis was planned for PFS and two interim analyses for OS. Overall missing data was not imputed. The statistical approach for study JUPITER-02 is acceptable for showing clinical efficacy.

Efficacy data and additional analyses

In the JUPITER-02 study a total of 289 patients enrolled in the study, of which 146 were randomised toripalimab + chemotherapy group and 143 to placebo + chemotherapy group. In the toripalimab group 32 out of 146 patients discontinued treatment during chemotherapy phase, while in the placebo 25 out of 143, mainly due to disease progression. At the cut-off date 19 February 2020, 124 patients have discontinued the treatment. Relative risk of AE in toripalimab group leading to discontinuation = (11/146)/(6/143)= 1,8, when compared to placebo. All the enrolled patients were included in the ITT analysis. The analysed populations seem acceptable.

The study population characteristics were: median age of 48 years (range: 19 to 72), 4.8% age 65 or older, 83% male, 100% Asian, and ECOG PS of 0 (57%) or 1 (43%). Approximately 86% of the study population had metastatic disease at randomisation, with histological subtypes of NPC including 98% non-keratinizing, 1% keratinizing squamous cell carcinoma, and 1% unclassified NPC/other. The majority (75%) of patients had PD-L1 tumour expression in ≥ 1% of tumour or immune cells and 63% had serum Epstein-Barr virus (EBV) titres ≥ 2000 U/mL.

At the pre-specified interim analysis of PFS, the study demonstrated statistically and clinically significant improvements in BIRC-assessed PFS (HR 0.52, 95% CI: 0.37, 0.73; p=0.0003) and overall response rate (ORR) for patients randomised to toripalimab in combination with cisplatin/gemcitabine compared to cisplatin and gemcitabine with placebo. At the pre-specified final analysis of OS (DCO 18 November 2022), the study further demonstrated statistically significant improvement in OS (HR 0.63, 95% CI: 0.45, 0.89 ; p=0.0083).

The sensitivity analysis for PFS to account for patients with missing TAs regardless of cause resulted in a similar outcome with HR 0.52 (95% CI: 0.38, 0.71). Other performed sensitivity analyses also resulted in a similar outcome as primary analysis.

A sensitivity analysis was also conducted in the per protocol population. This was defined as patients who did not have a major protocol deviation that would impact efficacy, with similar results to the primary analysis.

In addition, the study completed on 18 November 2022 and the applicant submitted the final OS analysis on 10 March 2023. At study completion, 133 (46.0%) patients had completed the study and 156 (54.0%) patients discontinued prematurely the study. Nine additional patients with at least 1 major protocol deviation were reported and currently a total of 156 (54.0%) patients (80 in the toripalimab and 76 in the placebo arm) had at least 1 major protocol deviation in JUPITER-02 trial. The applicant provided the sensitivity analyses on BIRC-Determined PFS and OS, which exclude all patients with a major protocol deviation (OS sensitivity analysis 1) and patients with certain major protocol deviations likely to affect survival (OS sensitivity analysis 2), per request.

In 147 patients at least one major protocol deviation was reported with similar number of participants in both arms. A sensitivity analysis was performed to evaluate the potential impact of delayed (>21 days) and missing tumour assessments on BIRC-determined PFS. As compared to the primary analysis, patients whose first progression, determined by BIRC, was at a delayed tumour assessment (>21 days), were considered to have had a PFS event at the planned date of that tumour assessment.

Further, patients who had a missing tumour assessment before their first progression, determined by BIRC, were considered to have had a PFS event at the planned date of the missing tumour assessment. Since this had been addressed by a pre-specified censoring rule, there was no special handling for patients with two or more consecutive missing tumour assessments in this new sensitivity analysis. The primary analysis censoring rules provided are considered acceptable. Of note, patients with 2 or more missing consecutive tumour assessment due to COVID-19 who had no evidence of disease progression were not automatically censored and were included in the primary analysis.

PD-L1 expression

PD-L1 expression was detected by immunohistochemical staining of tumour and immune cells in a clinical trial assay using JS311. JS311 is a PD-L1 IHC antibody developed by Shanghai Junshi Biosciences used to test the baseline PD-L1 expression in both phase 3 clinical trials (NPC and OSCC).

Exploratory subgroup analyses based on the chosen PD-L1 status (with variable cut-off values) were included and updated in the different versions of SAPs.

A meta-analysis including 1836 NPC patients from 15 studies with PD-L1 expression did not show a significant correlation between PD-L1 expression and OS among the NPC patients treated by PD-1 and PD-L1 blockades) (Huang ZL, Liu S, Wang GN, et al. Cancer Cell Int 2019; 19: 141.)

Correlation between baseline PD-L1 expression level in NPC trial and the main clinical efficacy endpoints (PFS and OS) in JUPITER-02 trial as well consistency with other trials in the similar clinical setting with other ICIs was discussed. In general, the clinical benefit from ICI treatment (monotherapy or in combination with SOC) regardless of PD-L1 expression was observed from most trials, except KEYNOTE-122 trial. Of note, the efficacy improvement due to the add-on treatment in JUPITER-02 trial was consistent with the primary analysis.

Wording of the indication

The inclusion criteria for this study was not in line with the originally proposed indication "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", as toripalimab in combination with cisplatin and gemcitabine was used only in patients with metastatic or recurrent NPC and not locally advanced NPC.

The indication was amended to reflect the eligible and effectively enrolled patient population as follows:

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

3.6.8. Conclusions on the clinical efficacy

The clinical efficacy data submitted in support of toripalimab in combination with cisplatin and gemcitabine for the first line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy or metastatic NPC is considered acceptable. The efficacy analyses of JUPITER-02 showed statistically significant improvements in PFS and OS.

3.6.9. Clinical efficacy Oesophageal Squamous Cell Carcinoma (ESCC/OSCC)

3.6.9.1. Dose-response studies

According to *in vitro* experiments when the plasma concentration of toripalimab was > 3 μg/mL, PD-1 receptors on the surface of peripheral T-cells were saturated. This was supported by data from CT1 and CT2 studies where flow cytometry was used to evaluate receptor occupancy. At all dosage levels evaluated in these studies, i.e., 1 to 10 mg/kg Q2W IV, binding of toripalimab to the target molecule PD-1 on the surface of activated T lymphocytes was observed shortly after the first dose. Complete receptor occupancy (>80%) was achieved and maintained throughout the 2 week dose interval in most patients at doses ≥3 mg/kg. Given the uncertainties regarding penetration of immunoglobulins into the tumour microenvironment, the concentration of toripalimab in the peripheral blood was chosen to achieve Cmin of 20 μg/mL or higher to attempt to ensure PD-1 receptor full occupancy on T lymphocytes in the tumour microenvironment.

Maximum tolerated dose, a dose selection strategy that derives from cytotoxic agent development, has proven challenging for checkpoint inhibitors and molecularly targeted agents because there is no clear dose-response relationship, and the identification of an MTD may not be a realistic objective. In fact, in studies performed with pembrolizumab and nivolumab, the investigators did not identify an MTD. Since the maximum tolerated dose was not exceeded at the highest doses evaluated (10 mg/kg Q2W and 480 mg Q2W), the dosage regimen selected relied on the relationship between exposure after approximately 5 doses (approximating steady state in the Phase 1 studies using non-compartmental analysis) and assurance of sustained, complete receptor occupancy over the dosing interval. In simulations based on the original popPK model, the proposed clinical dose regimen of 240 mg Q3W gave a predicted geometric mean Ctrough value at steady state of 26.3 μg/mL, which exceeded the target of ≥ 20 μg/mL but yielded a wide coefficient of variation (85.5%). The Ctrough value of dose 3 mg/kg Q2W at steady state was higher, 38.1 μg/mL (see table below).

Table 59. Population Pharmacokinetic Parameters for Toripalimab (Modelled)

	240 mg IV Q3W	3 mg/kg IV Q2W
First Dose		
Geometric Mean C_{max} (%CV), μg/mL	67.1 (21.0)	53.9 (23.7)
Geometric Mean C_{avg} (%CV), μg/mL	26.7 (25.2)	26.3 (25.1)
Geometric Mean C_{trough} (%CV), μg/mL	10.2 (61.8)	13.9 (43.5)
Geometric Mean $AUC_{0-\tau}$ (%CV), hr•μg/mL	13386 (27.0)	8894 (26.7)
Steady-State		
Geometric Mean C_{max} (%CV), μg/mL	97.6 (26.4)	93.7 (28.9)
Geometric Mean C_{avg} (%CV), μg/mL	50.7 (43.6)	58.5 (41.6)
Geometric Mean C_{trough} (%CV), μg/mL	26.3](85.5)	38.1 (65.1)
Geometric Mean $AUC_{0-\tau}$ (%CV), hr•μg/mL	25555 (43.6)	19644 (41.6)
Source: Table 16 PopPK Report TOPA-PMX-TORI-2412-Combination Therapy – amendment 1 (11 Jan 2022) AUC=area under the curve; C_{avg}=average concentration over the dosing interval; C_{max}=maximum concentration; C_{trough}=trough concentration; % CV=percentage of the coefficient of variation		

The applicant chose the dose of 240 mg Q3W IV for both indications based on these data.

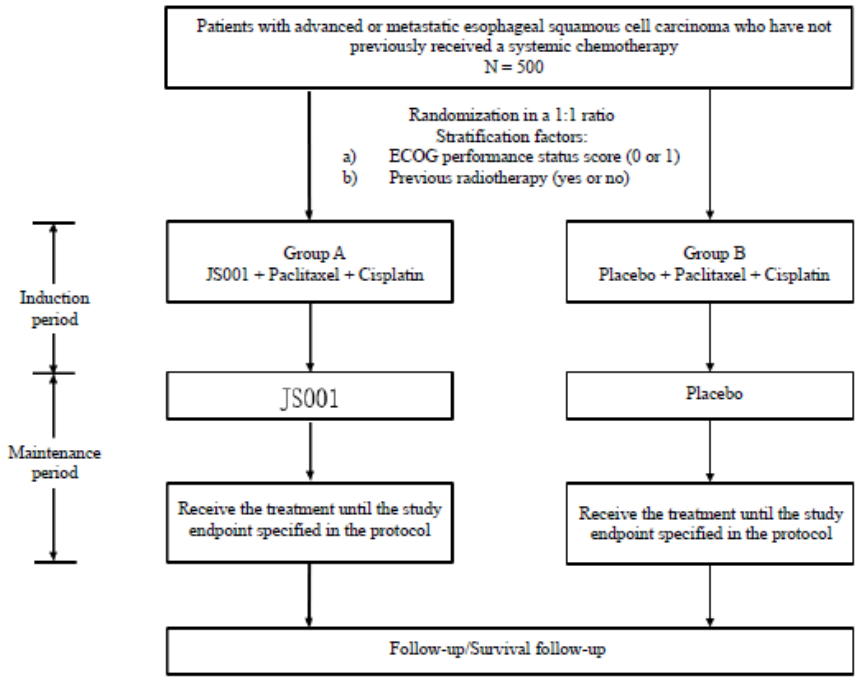
3.6.9.2. Main study(ies)

JS001-021-III-ESCC (JUPITER-06): A randomized, placebo-controlled, multi-centre, double-blind study. And one clinical phase Ib/II basket trial: JS001-1b-CRP-1.0 CT5 (POLARIS-02), single-arm, multi-cohort, multi-centre, open label with ESCC patients in Cohort 2 and 6.

Methods

This study is a randomised, placebo-controlled, multi-centre, double-blind, phase 3 study. It was designed to determine the efficacy and safety of toripalimab in combination with paclitaxel and cisplatin compared with placebo in combination with paclitaxel and cisplatin in patients with advanced or metastatic OSCC who have not received systemic chemotherapy previously (See Figure 68).

Figure 67. JS001-021-III-ESCC study schema



Eligible patients were randomised in a 1:1 ratio to receive toripalimab or placebo in combination with paclitaxel and cisplatin given every 3 weeks (Q3W) for up to 6 cycles followed by toripalimab or placebo as a single agent on Day 1 of each 3-week cycle. Study treatment was continued until intolerable toxicity, progression of disease, judgment by investigator that the patient needs to be withdrawn from the treatment, or up to two years of treatment, whichever occurs first. During the induction period, if one or both chemotherapeutic agents were discontinued due to toxicity, the study drug was continued until criteria for discontinuation of treatment were met. For patients with progression of disease in accordance with the RECIST version 1.1; the patient may continue to receive the study drug in blinded state after the investigator determines, and the Sponsor agrees, that the patient may benefit from continuation of study drug and after the patient signs the corresponding informed consent form for continuation of treatment after disease progression.

Study Participants

Main inclusion criteria:

1) Histologically or cytologically confirmed, locally advanced/relapsed, or metastatic OSCC that cannot be eradicated.
2) No prior systemic chemotherapy for relapsed or metastatic tumour.
3) Patients who have previously received neoadjuvant chemotherapy, concurrent chemoradiotherapy or adjuvant chemotherapy for non-metastatic disease must be free of disease recurrence for at least 6 months from the end of the last chemotherapy to the time of randomization.
4) No risk of major haemorrhage or oesophageal fistula

Patients with recurrent OSCC after treatment with curative intent were required to have an interval of at least 12 months between the last dose of adjuvant chemotherapy/chemoradiotherapy with paclitaxel and cisplatin.

Main exclusion criteria: active or untreated CNS metastases, history of autoimmune disease, history of malignant tumours, within 5 years prior to randomization, radiotherapy within 28 days prior to enrolment or radiopharmaceutical therapy within 8 weeks, except for localized palliative radiotherapy for metastatic bone lesions, previous immune checkpoint blocking therapy, for example, therapeutic antibodies of anti-PD-1 and anti-PD-L1 antibody. Patients with autoimmune disease, other than stable hypothyroidism or Type I diabetes, and patients who required systemic immunosuppression were ineligible.

Treatments

In induction phase patients received toripalimab/placebo in combination with paclitaxel and cisplatin. They received 240 mg toripalimab/placebo administered by IV infusion Q3W. Study drug/placebo were administered in 100-mL 0.9% NaCl IV infusion bags at the dose of 240 mg as an intravenous infusion (IV) over ≥ 60 minutes, followed by an observation period of 60 min (required in the first 2 cycles only). If no clinically significant, infusion related adverse reactions occur in the first 2 cycles, then the study drug may be infused over 30 (±10) minutes in subsequent cycles. Toripalimab/placebo was given first on Day 1 of each cycle.

The treatment with paclitaxel and cisplatin were given 1 h after the end of infusion of the study drug in the first 2 cycles, if and vital signs are normal and stable. Paclitaxel was given first than cisplatin. Paclitaxel was given 175 mg/m2 3 h iv infusion (or per local clinical practices) on Day 1 of each cycle, and cisplatin was given 75 mg/m2 IV at a rate of approximately 1 mg/min or per local clinical practices on Day 1 of each cycle, in 3-week cycles for up to 6 cycles.

After completion of induction phase, patients entered the maintenance period to receive toripalimab or placebo monotherapy on day 1 of each subsequent cycle Q3W.

Treatment continued until progression of disease, no potential for clinical benefit per investigator, intolerable toxicity, patient death, patient refusal, withdrawal of informed consent, loss of follow-up, termination of the study by the Sponsor, start of new anti-cancer therapy or completion of 2 years of treatment, whichever came first.

Administration of toripalimab was permitted beyond radiographic progression if the patient was deriving benefit as assessed by the investigator.

Tumour assessments were performed every 6 weeks for the first 12 months and every 9 weeks thereafter.

Objectives

The primary objective of this study was to evaluate PFS, in all randomized population, of toripalimab in combination with chemotherapy compared to placebo in combination with chemotherapy, as measured by BICR as per RECIST 1.1 in patients who had not received systemic chemotherapy for treatment of incurable recurrent, locally advanced, or metastatic OSCC. Also, to evaluate OS, in all randomized population, of toripalimab in combination with chemotherapy compared to placebo in combination with chemotherapy, as measured by BICR as per RECIST 1.1 in patients who had not received systemic chemotherapy for treatment of incurable recurrent, locally advanced, or metastatic OSCC.

Outcomes/endpoints

Co-primary efficacy endpoints were consisting of:

- PFS evaluated by BICR, defined as the time from randomisation to the occurrence of disease progression per RECIST v1.1 or the time from randomization to death for any reason, whichever came first.

- OS.

Secondary efficacy endpoints were as follows:

- Objective response rate (ORR) was defined as the proportion of patients with the best overall response of complete response or partial response as per RECIST v1.1.
- Disease control rate (DCR) was defined as the proportion of patients with a best overall response of CR or PR or SD.
- DOR and
- TTR evaluated by BICR and investigators in accordance with RECIST 1.1.

Sample size

The sample size was determined based on the need to detect significant results of PFS, OS and the following assumptions:

- PFS and was to be exponentially distributed.
- The median PFS of group B was to be 5 months and median OS was to be 10 months.
- α-spending function of O'Brien-Fleming type (approximation using Lan-DeMets method) would be used for interim analysis as to control the overall type I error rate.
- The recruitment of 500 subjects would be completed in 22 months.
- The dropout rate was to be 5% over 1 year for PFS and OS.

Calculations were made that total of 500 patients were needed to observe 283 PFS events at approximately 24 months after randomization of the first patient to detect the PFS improvement of HR = 0.7 with 85% power at an overall 2-sided significance level of 0.05. For OS calculations were made that total of 500 patients were needed to observe 366 OS events at approximately 39 months after randomization of the first patient to detect the OS improvement of HR = 0.73 with 85% power at an overall 2-sided significance level of 0.05.

Randomisation and blinding (masking)

Patients were randomized in a 1:1 ratio using IWRS, based on a permuted-block randomization method to one of two treatment arms, toripalimab combined with paclitaxel and cisplatin or placebo combined with paclitaxel and cisplatin. The stratification was based on ECOG performance status (0 versus 1) and previous radiotherapy (yes or no). Patients received the first dose of study drug on the day of randomization whenever possible, if not fist dose was given within 3 calendar days after randomization.

This was double-blind, placebo-controlled study. Unblinding was only allowed in the case of a serious adverse events, unexpected suspected adverse reactions that were considered by the investigator or Sponsor to be related to study drug. If needed unblinding was done through IWRS.

All the patients were unblinded at the end of the study. Only the patients randomized into the toripalimab arm could continue the treatment with toripalimab. The patients in the placebo arm were not allowed to be crossed over to toripalimab arm.

Statistical methods

Intention to treat Set (ITT): This population includes all the randomized patients.

Safety Analysis Set (SS): This population includes all the patients who have received any dose of the investigational drugs (including toripalimab or chemotherapy) in the ITT set.

The primary and secondary endpoint statistical methods are shown in the table below.

Table 60. Statistical analysis strategy for efficacy endpoints

Endpoint	Statistical method	Analysis population
Co-primary		
Progression free survival	Stratified log-rank test Stratified Cox proportional hazards model and the 95% CI Kaplan-Meier method	ITT
Overall survival	Stratified log-rank test Stratified Cox proportional hazards model and the 95% CI Kaplan-Meier method	ITT
Secondary		
Objective response rate	Clopper-Pearson method NEWCOMBE method	ITT
Disease control rate	Clopper-Pearson method NEWCOMBE method	ITT

For the co-primary efficacy endpoint including BICR-PFS and OS hierarchical testing method was performed. To test the hypothesis of PFS firstly the alpha level (2-sided 0.05) was used. When the null hypothesis of PFS was rejected, the hypothesis test for OS was conducted at the 2-sided significance level of 0.05. For PFS and OS the null and alternative hypotheses were represented by corresponding survival functions SA(t) for Group A and SB(t) for Group B:H0: SA(t) = SB(t) vs H1: SA(t) ≠ SB(t).

Missing data was imputed on years of age, date for concomitant medication, the day of the death - the day of the death was missing only then the date of death would be imputed with the first day of the month of the year, which was an OS event. If tumour evaluation data was missing after the first dose of study drug in ORR analysis, it was considered as "no response" and was included into the analysis. If the day of the death was missing only then the date of death would be imputed with the first day of the month of the year, which was an OS event.

Interim analysis of efficacy of OS was to be assessed when the analysis of final PFS was performed, about 212 OS events were expected to be observed. The interim analysis was performed by an independent statistical analysis service provider (see Table 65).

Table 61. The efficacy boundary for the interim and final analyses of OS calculated by O'Brien-Fleming α-spending function (approximation using Lan-DeMets method)

OS Analysis	Information Fraction[a]	No. of OS Events	Efficacy boundary (two-sided p-value)
Interim analysis	58%	212	0.0066
Primary Analysis	100%	366	0.0480

[a] The information fraction refers to the proportion of the number of OS events required for analysis to the total number of OS events required for scheduled primary analysis.

Results

Participant flow

The study was conducted from 28 January 2019 to 15 February 2022. Among all randomized patients, a total of 31 patients remained on toripalimab treatment as of data cut-off date.

From 809 patients that were screened a total of 514 patients were randomized (see figure below) with 257 patients in the toripalimab group combined with chemotherapy and 257 patients in placebo group combined with chemotherapy.

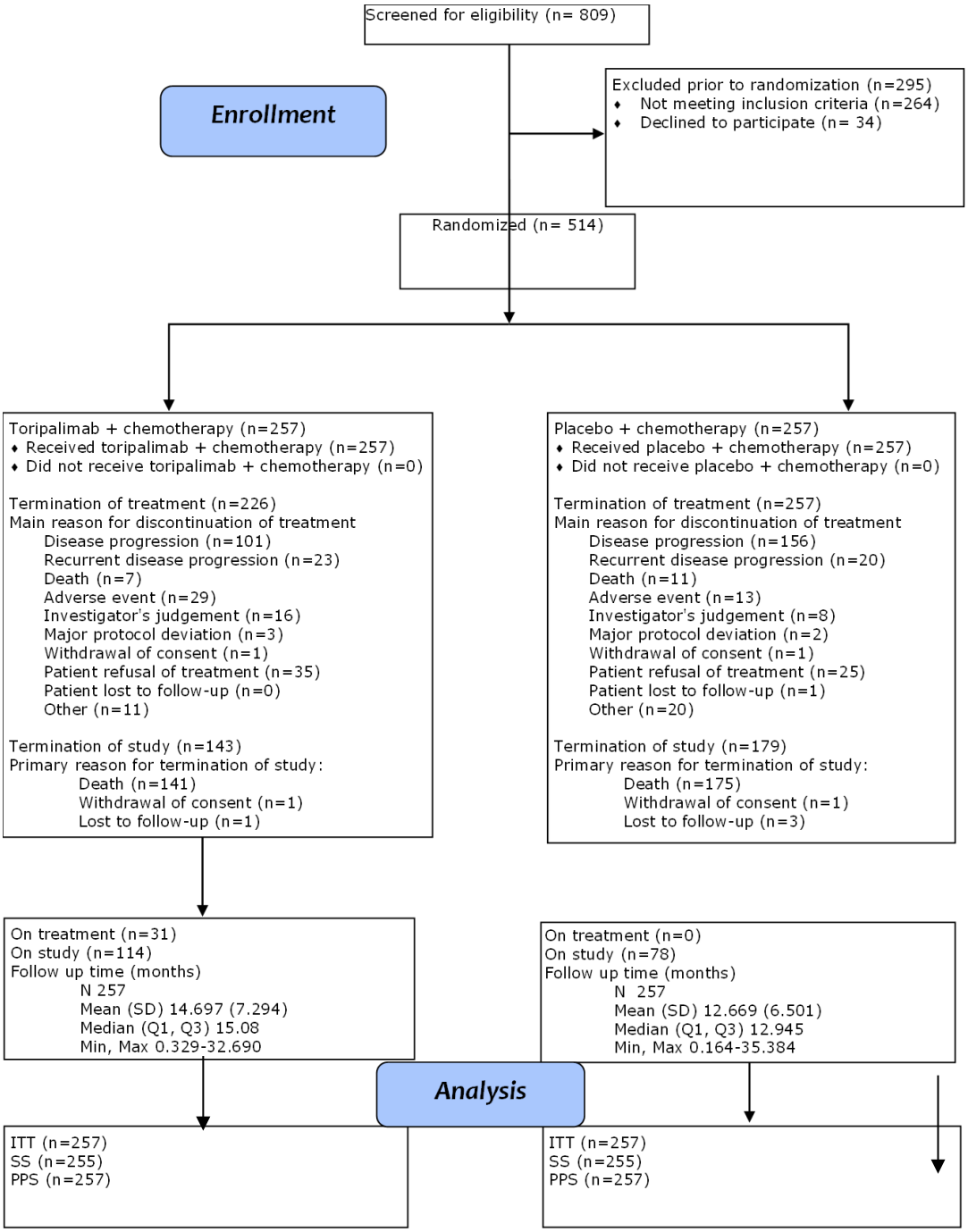
From 809 screened patients 295 patients were screen failures as they did not meet eligibility criteria and 34 patients withdraw the consent.

When the interim analysis crossed pre-specified boundary for efficacy, after the first interim analysis, the study was unblinded and patients in the treatment arm received open label toripalimab, whereas patients in the control arm discontinued placebo. Patients continuing toripalimab with unconfirmed disease progression continued to have tumour assessments, survival follow-up, and safety information collected as per the protocol. Patients who were no longer on active treatment were followed for survival only.

483 patients discontinued treatment (226 in toripalimab and 257 in placebo group) due to disease progression for 257 patients (101 in the toripalimab arm and 156 in the placebo arm), recurrent disease progression for 43 patients (23 in the toripalimab arm and 20 in the placebo arm), adverse events for 42 patients (29 in the toripalimab arm and 13 in the placebo arm), patients refusal of the treatment for 60 patients (35 in the toripalimab arm and 25 in the placebo arm)

322 patients discontinued the participation in study (143 in toripalimab and 179 in placebo group) mainly due to death for 316 patients (141 in the toripalimab arm and 175 in the placebo arm).

Figure 68. Subjects Disposition in JS001-021-III-ESCC study



Recruitment

Study Period: 2-year period of treatment

Initiation Date: 28 January 2019 (first written consent obtained)

Completion Date: 23 February 2023

Cut-off date for CSR: 22 March 2021

Cut-off date for CSR Addendum: 15 February 2022

Follow-up period: after the end-of-treatment visit, patients will be followed for survival every month (±7 days) until death, withdrawal of consent to continue on study, loss to follow-up, or termination of the study by the sponsor.

The study was unblinded when the interim analysis crossed the pre-specified boundary for efficacy. Patients who remained on study drug in the investigational arm continued to receive toripalimab, whereas patients in the control arm discontinued placebo.

Conduct of the study

The changes in the conduct of the study are presented in the table below.

Table 62. Changes in the Conduct of the Study

Protocol Version	Protocol Date	Majors change(s)
Original Protocol Version 1.0	25 October 2018	Original
Version 2.0	30 April 2019	The analysis of the subgroup of patients without 11q13 amplification was added to the primary endpoint, secondary endpoints, and safety endpoints, with the statistical analysis methods modified accordingly and the rationale for exploring 11q13 provided. EBV was deleted as an exploratory biomarker analysis since EBV was not significantly associated with prognosis in oesophageal carcinoma. 11q13 testing was added to the exploratory biomarker analyses as toripalimab was initially shown to demonstrate better efficacy in the OSCC patients without amplification of 11q13 in the phase II study. Planned enrolment was adjusted from 430 to 500 patients because of altered study endpoints, with approximately 55% (i.e., 275 patients) of all enrolled patients expected not to carry 11q13 region amplification, and the end of study time and duration were modified accordingly. Eligibility criteria were clarified, including clarified upper limit values for systemic therapy, previously treated non-metastatic disease, creatinine and creatinine clearance, hepatitis B DNA testing, so as to avoid ambiguity.
Version 3.0	19 August 2019	Inclusion and exclusion criteria were adjusted to further account for the patient's eligibility requirements. Changes made to improve run efficiency.
Version 4.0	30 June 2020	The analysis of the subgroup of patients without 11q13 region amplification was deleted from the primary study endpoint, secondary study endpoints, and safety endpoints, with relevant content deleted from the statistical analysis methods 11q13 relevant content was deleted from the planned enrolment of patients. Inclusion and exclusion criteria were adjusted to further account for the patient's eligibility requirements. Two planned interim analyses were changed to be one planned interim analysis. Adjusted based on study endpoints and interim analysis, with corresponding adjustments for end of study date and duration. The administration dose was clarified in the trial medication and the administration method, and the duration of induction treatment was clarified, to avoid ambiguity. Imaging of the neck was classified as a mandatory test to protect patients' interests and for data integrity.
Version 5.0	18 August 2021	The interim analysis was planned for this study.

Original SAP was issued on 12 April 2021. No changes in SAP have been made.

Major protocol deviations:

There were 209 patients that had at least one major protocol deviation, 108 patients in the toripalimab and 101 in the placebo arm. 71 patients (41 in the toripalimab arm and 30 in the placebo arm) had major protocol deviations due to the impact of the COVID-19 epidemic.

158 patients had major protocol deviations not related to COVID-19 (82 in toripalimab and 76 in placebo arm), most common were due to delayed or missing tumour imaging, delayed reporting of SAEs.

Table 63. Major Protocol Deviations (Toripalimab Arm or Placebo Arm >3 Patients) - ITT

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	Total (N=514) n (%)
Number of patients with major protocol deviations	108 (42.0)	101 (39.3)	209 (40.7)
Impacted by COVID-19	41 (16.0)	30 (11.7)	71 (13.8)
Non-epidemic impact	82 (31.9)	76 (29.6)	158 (30.7)
Reasons of major protocol deviations			
The patient has a visit exceeding the time window by > 7 days due to non-AE reasons, or a treatment cycle is missed	45 (41.7)	28 (27.7)	73 (34.9)
Impacted by COVID-19	35 (85.4)	25 (83.3)	60 (84.5)
Non-epidemic impact	12 (14.6)	3 (3.9)	15 (9.5)
The EOT visit is not conducted due to the refusal of the patient	26 (24.1)	27 (26.7)	53 (25.4)
Impacted by COVID-19	1 (2.4)	3 (10.0)	4 (5.6)
Non-epidemic impact	25 (30.5)	24 (31.6)	49 (31.0)
Tumor imaging is performed > 21 days after scheduled date or the patient has one missing assessment	21 (19.4)	15 (14.9)	36 (17.2)
Impacted by COVID-19	10 (24.4)	5 (16.7)	15 (21.1)
Non-epidemic impact	12 (14.6)	10 (13.2)	22 (13.9)
SAEs are not reported within 24 hours	19 (17.6)	11 (10.9)	30 (14.4)
Impacted by COVID-19	0	0	0
Non-epidemic impact	19 (23.2)	11 (14.5)	30 (19.0)
The patient has missing scheduled tumor imaging for two consecutive occasions	17 (15.7)	13 (12.9)	30 (14.4)
Impacted by COVID-19	1 (2.4)	1 (3.3)	2 (2.8)
Non-epidemic impact	16 (19.5)	12 (15.8)	28 (17.7)
The patient used other drugs with anti-tumor indications during the study drug treatment, or other anti-tumor treatments that were prohibited in the protocol	2 (1.9)	7 (6.9)	9 (4.3)
Impacted by COVID-19	0	0	0
Non-epidemic impact	2 (2.4)	7 (9.2)	9 (5.7)
Other PDs related with compliance to the investigational product[1]	3 (2.8)	5 (5.0)	8 (3.8)
Impacted by COVID-19	0	0	0
Non-epidemic impact	3 (3.7)	5 (6.6)	8 (5.1)
The patient fails to meet one or more of the inclusion criteria	5 (4.6)	2 (2.0)	7 (3.3)
Impacted by COVID-19	0	0	0
Non-epidemic impact	5 (6.1)	2 (2.6)	7 (4.4)
Other PDs related with efficacy criteria[2]	3 (2.8)	4 (4.0)	7 (3.3)
Impacted by COVID-19	0	0	0
Non-epidemic impact	3 (3.7)	4 (5.3)	7 (4.4)
Two or more consecutive treatment cycles are missed due to non-AE reasons	5 (4.6)	1 (1.0)	6 (2.9)
Impacted by COVID-19	5 (12.2)	1 (3.3)	6 (8.5)
Non-epidemic impact	0	0	0
Met the suspension/ permanent discontinuation criteria specified in the protocol, but drug was not withheld/permanently discontinued[3]	4 (3.7)	1 (1.0)	5 (2.4)
Impacted by COVID-19	0	0	0
Non-epidemic impact	4 (4.9)	1 (1.3)	5 (3.2)
Met the criteria for discontinuation of the investigational products, but the investigational product was not discontinued promptly[4]	4 (3.7)	1 (1.0)	5 (2.4)
Impacted by COVID-19	0	0	0
Non-epidemic impact	4 (4.9)	1 (1.3)	5 (3.2)
Data related with stratification of randomization is incorrectly recorded or incorrectly entered into EDC, resulting in stratification error	1 (0.9)	3 (3.0)	4 (1.9)
Impacted by COVID-19	0	0	0
Non-epidemic impact	1 (1.2)	3 (3.9)	4 (2.5)
During treatment with study drug, used contraindicated medications other than those with an antineoplastic indication	1 (0.9)	3 (3.0)	4 (1.9)
Impacted by COVID-19	0	0	0
Non-epidemic impact	1 (1.2)	3 (3.9)	4 (2.5)
SAEs not reported to all supervising institutes as required by regulations	0	4 (4.0)	4 (1.9)
Impacted by COVID-19	0	0	0
Non-epidemic impact	0	4 (5.3)	4 (2.5)
Other PDs related with scheduled visits[5]	3 (2.8)	0	3 (1.4)
Impacted by COVID-19	0	0	0
Non-epidemic impact	3 (3.7)	0	3 (1.9)

Baseline data

Patient's mean age at screening was 61 years. 488 (94.9%) patients were Han, 26 (5.1%) had another ethnicity, and most of them were male (85%). 134 patients (26.1 %) had the baseline ECOG PS per IWRS 0 and 380 patients (73.9%) had the baseline ECOG PS per IWRS 1. 70 patients (13.6%) have received prior radiotherapy and 444 patients (86.4%) have not. 87 patients (16.9%) had PD-L1 CPS<1, 401 patients (78.0%) had PD-L1 CPS≥1, 276 patients (53.7%) had PD-L1 CPS<10, 212 patients (41.2%) had PD-L1 CPS≥10 and in 26 patients (5.1%) the information about PD-L1 expression was missing. The demographic and baseline characteristics were well balanced between the toripalimab and placebo groups (see table below).

Table 64. Demographic Data and Baseline Characteristics

	Toripalimab + TP (N=257) n (%)	Placebo + TP (N=257) n (%)	Total (N=514) n (%)
Age (year)			
N	257	257	514
Mean (SD)	61.3 (8.04)	60.9 (7.30)	61.1 (7.67)
Median	63.0	62.0	62.5
(Min – Max)	20 - 75	40 - 74	20 - 75
Age group			
<65 years	156 (60.7)	163 (63.4)	319 (62.1)
≥65 years	101 (39.3)	94 (36.6)	195 (37.9)
Gender			
Male	217 (84.4)	220 (85.6)	437 (85.0)
Female	40 (15.6)	37 (14.4)	77 (15.0)
Ethnicity			
Han	245 (95.3)	243 (94.6)	488 (94.9)
Others	12 (4.7)	14 (5.4)	26 (5.1)
Height (cm)			
N (missing)	257	254 (3)	511 (3)
Mean (SD)	165.53 (7.363)	166.28 (7.698)	165.90 (7.534)
Median	167.00	167.00	167.00
(Min – Max)	140.0 - 183.0	145.0 - 186.0	140.0 - 186.0
Weight (kg)			
N (missing)	257	254 (3)	511 (3)
Mean (SD)	59.58 (9.736)	59.41 (9.777)	59.50 (9.747)
Median	58.00	58.00	58.00
(Min – Max)	38.5 - 101.0	37.0 - 95.0	37.0 - 101.0
BMI (kg/m^2)			
N (missing)	257	254 (3)	511 (3)
Mean (SD)	21.701 (2.939)	21.453 (2.979)	21.578 (2.959)
Median	21.359	21.337	21.340
(Min – Max)	14.314 - 33.360	14.453 - 33.659	14.314 - 33.659
ECOG PS score - randomization			
0	66 (25.7)	68 (26.5)	134 (26.1)
1	191 (74.3)	189 (73.5)	380 (73.9)
Previous radiotherapy - randomization			
Yes	35 (13.6)	35 (13.6)	70 (13.6)
No	222 (86.4)	222 (86.4)	444 (86.4)
Disease stage at enrollment			
Distant metastasis	206 (80.2)	198 (77.0)	404 (78.6)
Local recurrence/unresectable	50 (19.5)	59 (23.0)	109 (21.2)
Not available or not done	1 (0.4)	0	1 (0.2)
PD-L1 expression			
CPS<1	43 (16.7)	44 (17.1)	87 (16.9)
CPS≥1	201 (78.2)	200 (77.8)	401 (78.0)
CPS<10	129 (50.2)	147 (57.2)	276 (53.7)
CPS≥10	115 (44.7)	97 (37.7)	212 (41.2)
Missing	13 (5.1)	13 (5.1)	26 (5.1)
ECOG PS score - CRF			
0	66 (25.7)	65 (25.3)	131 (25.5)
1	191 (74.3)	192 (74.7)	383 (74.5)
Previous radiotherapy - CRF			
Yes	35 (13.6)	34 (13.2)	69 (13.4)
No	222 (86.4)	223 (86.8)	445 (86.6)

OSCC disease's baseline characteristics: at the time of enrolment 404 patients (78.6) had distant metastasis, 109 patients (21.2%) had local recurrence/unresectable locally advanced disease and for 1 patient (0.2%) the information on disease state was not available. At the time of enrolment 5 patients (1.0%) had stage I/IA/IB disease, 2 patients (0.4%) had stage II/IIA/IIB disease, 47 patients (9.1%)

had stage III/IIIA/IIIB disease, 459 patients (89.3%) had stage IV/IVA/IVB disease, and 1 patient (0.2%) had no information on clinical stage. The OSCC disease characteristics were well balanced between the toripalimab and placebo groups.

Table 65. History of oesophageal squamous cell carcinoma - ITT

	Toripalimab + TP (N=257) n (%)	Placebo + TP (N=257) n (%)	Total (N=514) n (%)
Initial diagnosis of esophageal squamous cell carcinoma			
Site of tumor			
Cervical esophagus	6 (2.3)	7 (2.7)	13 (2.5)
Upper thoracic esophagus	27 (10.5)	25 (9.7)	52 (10.1)
Middle thoracic esophagus	80 (31.1)	82 (31.9)	162 (31.5)
Lower thoracic esophagus	83 (32.3)	81 (31.5)	164 (31.9)
Esophagogastric junction	10 (3.9)	5 (1.9)	15 (2.9)
Others	51 (19.8)	57 (22.2)	108 (21.0)
Clinical stage			
0	1 (0.4)	2 (0.8)	3 (0.6)
I/IA/IB	5 (1.9)	7 (2.7)	12 (2.3)
II/IIA/IIB	19 (7.4)	22 (8.6)	41 (8.0)
III/IIIA/IIIB	40 (15.6)	41 (16.0)	81 (15.8)
IV/IVA/IVB	153 (59.5)	156 (60.7)	309 (60.1)
Not available or not done	39 (15.2)	29 (11.3)	68 (13.2)
Diagnosis of esophageal squamous cell carcinoma at enrollment			
Disease stage			
Distance metastasis	206 (80.2)	198 (77.0)	404 (78.6)
Local recurrence/unresectable locally advanced	50 (19.5)	59 (23.0)	109 (21.2)
Not available or not done	1 (0.4)	0	1 (0.2)
Clinical stage			
0	0	0	0
I/IA/IB	2 (0.8)	3 (1.2)	5 (1.0)
II/IIA/IIB	1 (0.4)	1 (0.4)	2 (0.4)
III/IIIA/IIIB	22 (8.6)	25 (9.7)	47 (9.1)
IV/IVA/IVB	231 (89.9)	228 (88.7)	459 (89.3)
Not available or not done	1 (0.4)	0	1 (0.2)

Treatment compliance

More than 99% of the patients in the two arms had good compliance (>=80% and <=120%), 256 (99.6%) patients in toripalimab arm and 257 (100%) patients in placebo arm. Only one patient in toripalimab arm had a poor compliance to the treatment.

Numbers analysed

514 patients were included in ITT and SS Analysis Set (257 patients in the toripalimab arm and 257 patients in the placebo arm).

510 of 514 patients were included in PPS analysis, 255 patients in the toripalimab arm and 255 in the placebo arm. 4 patients were excluded from the PPS analysis due to not meeting eligibility criteria: receiving previous systemic anti-tumour therapy (containing docetaxel and nedaplatin), with a second primary gastric adenocarcinoma, with the hypopharyngeal carcinoma in situ, with the occurrence of uncontrolled tumour-related pain before the enrolment.

Outcomes and estimation

Co-primary endpoint results

Progression free survival

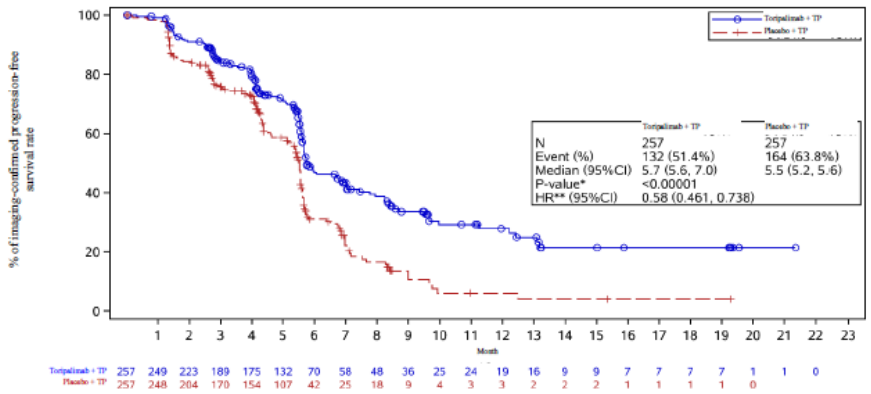
The PFS analysis cut-off date was 22 March 2021.

Table 66. Progress-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) - ITT

	Toripalimab + TP (N=257) n (%)	Placebo + TP (N=257) n (%)
Number of PFS events	132 (51.4)	164 (63.8)
Disease progression	117 (45.5)	152 (59.1)
Death before the first tumor evaluation	0	0
Death between two tumor evaluations	15 (5.8)	12 (4.7)
Number of censored patients	125 (48.6)	93 (36.2)
Without death and no tumor assessment after randomization	4 (1.6)	3 (1.2)
Incomplete or without any baseline tumor evaluation	0	1 (0.4)
PD or death after missing ≥2 consecutive tumor evaluations	6 (2.3)	16 (6.2)
PD or death after subsequent anti-tumor treatment	2 (0.8)	4 (1.6)
No PD, no death, and starting subsequent anti-tumor treatment	19 (7.4)	10 (3.9)
No PD, no death, and no subsequent anti-tumor treatment	94 (36.6)	59 (23.0)
Progression-free survival (months)		
25% quantile (95% CI)	4.2 (4.0, 5.4)	3.1 (2.7, 4.1)
Median (95% CI)	5.7 (5.6, 7.0)	5.5 (5.2, 5.6)
75% quantile (95% CI)	12.4 (9.7, NE)	7.0 (5.8, 7.5)
Minimum, maximum	0.033+, 21.355+	0.033+, 19.285+
12-month PFS rate (95% CI)	27.8 (20.4, 35.8)	6.1 (2.2, 12.6)
24-month PFS rate (95% CI)	NE (NE, NE)	NE (NE, NE)
Toripalimab + TP vs. placebo + TP		
Stratified analysis		
Hazard ratio (95% CI)	0.58 (0.461, 0.738)	
p-value	<0.00001	
Non-stratified analysis		
Hazard ratio (95% CI)	0.57 (0.451, 0.719)	
p-value	<0.00001	

Kaplan-Meier survival plot of PFS based on the BIRC assessment per RECIST 1.1 in the ITT population showed that PFS curves separate clearly at approximately 6 months, with continuous separation between the 2 curves over the course of follow-up (see figure below).

Figure 69. Kaplan-Meier plot of progression-free survival evaluated by BICR (BICR-PFS) in accordance with RECIST 1.1 - ITT



Data source: Figure 14.4.1.1
Note: HR was estimated by the COX proportional hazard model, and the stratified analysis adopted the stratified COX proportional hazard model. The stratification factors during the randomization process were: ECOG PS score (0 vs. 1), prior radiotherapy (yes vs. no); P-value (two-sided) was calculated using log-rank test, and the stratified log-rank test was used for stratified analysis. The stratification factors were the same as HR.

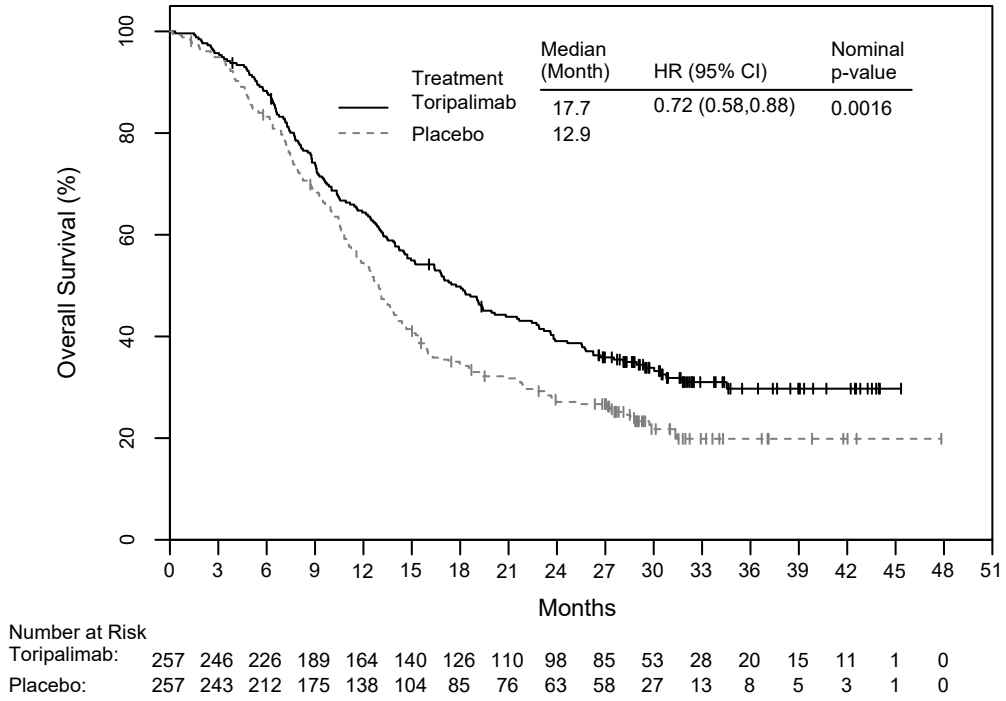
Overall survival

The final OS analysis was conducted at the data cut off of 23 February 2023.

Table 67. Final OS analysis at DCO of 23 Feb 2023

	Toripalimab Arm (N=257) n (%)	Placebo Arm (N=257) n (%)
Number of deaths	172 (66.9)	195 (75.9)
Number of censored patients	85 (33.1)*	62 (24.1)*
Overall survival (month)		
25% quantile (95% CI)	8.8 (7.5, 9.9)	7.5 (6.9, 8.7)
Median (95% CI)	17.7 (14.6, 20.8)	12.9 (11.6, 14.1)
75% quantile (95% CI)	NE (34.5, NE)	28.4 (21.8, NE)
Minimum, Maximum	0.3, 45.3+	0.2, 47.8+
12-month survival rate (95% CI)	64.4 (58.2, 69.9)	54.5 (48.1, 60.4)
24-month survival rate (95% CI)	39.1 (33.1, 45.0)	27.1 (21.7, 32.7)
Stratified analysis		
Hazard ratio (95% CI)	0.72 (0.584, 0.882)	
p-value	0.00156	
Unstratified analysis		
Hazard ratio (95% CI)	0.73 (0.591, 0.893)	
p-value	0.00227	

Figure 70: Kaplan-Meier curves for overall survival in JUPITER-06



Data cutoff date: 23 Feb 2023

Secondary efficacy endpoints

Objective response rate and Disease control rate

BIRC assessed confirmed CR was the BOR in 30 (11.7%) patients in the toripalimab arm and 18 (7.0%) patients in the placebo arm. Confirmed PR was the BOR in 148 (57.6%) patients in the toripalimab and 116 (45.1%) patients in the placebo arm. Confirmed stable disease was the BOR in 51 (19.8%) patients in toripalimab treatment arm and 77 (30.0%) patients in the placebo treatment arm.

ORR was 69.3% (95% CI: 63.2%, 74.8%) in the toripalimab arm and 52.1% (95% CI: 45.8%, 58.4%) in the placebo arm. The difference of ORR was 17.2% (95% CI: 9.0%, 25.4%, nominal p value <0.0001).

Ancillary analyses

Progression free survival

The results of the sensitivity analyses of BIRC-assessed PFS based on sensitivity censoring rule 1 of the ITT analysis set showed similar results to primary analysis. Stratified HR was 0.60 (95% CI: 0.482, 0.739; nominal p-value <0.00001) (see table below).

Table 68. Progression-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) – sensitivity analysis 1- Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Number of PFS events	160 (62.3)	194 (75.5)	
Progressive Disease	119 (46.3)	153 (59.5)	
Death before first tumor evaluation	0	0	
Death between two tumor evaluations	18 (7.0)	17 (6.6)	
PD/Death after the start date of a new anti-tumor treatment	3 (1.2)	14 (5.4)	
No PD, no death, but starting a new anti-tumor treatment	20 (7.8)	10 (3.9)	
Number of censored subjects	97 (37.7)	63 (24.5)	
No death, no evaluation after randomization	3 (1.2)	3 (1.2)	
Missing baseline tumor evaluation	0	1 (0.4)	
No PD, no death, and no new anti-tumor treatment	94 (36.6)	59 (23.0)	
Progression-free survival (month)			
25% quantile (95% CI)	4.1 (3.6, 4.8)	2.8 (2.6, 3.7)	
Median (95% CI)	5.7 (5.6, 6.0)	5.4 (4.4, 5.5)	
75% quantile (95% CI)	10.6 (8.4, 13.2)	6.9 (5.7, 7.2)	
Minimum, Maximum	0.033+, 21.355+	0.033+, 19.285+	
12-month PFS rate (95% CI)	22.6 (16.2, 29.6)	6.1 (2.7, 11.3)	
24-month PFS rate (95% CI)	NE (NE, NE)	NE (NE, NE)	
Stratified analysis			
Hazard ratio (95% CI)			0.60 (0.482, 0.739)
p-value			<0.00001
Unstratified analysis			
Hazard ratio (95% CI)			0.58 (0.473, 0.723)
p-value			<0.00001

The results of the sensitivity analyses of BIRC-assessed PFS based on sensitivity censoring rule 2 of the ITT analysis set showed similar results to primary analysis. Stratified HR was 0.58 (95% CI: 0.460, 0.736; nominal p-value <0.00001).

Table 69. Progression-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) – sensitivity analysis 2- Intent-to-Treat analysis set (ITT)

	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Number of PFS events	132 (51.4)	164 (63.8)	
Progressive Disease	117 (45.5)	152 (59.1)	
Death before first tumor evaluation	0	0	
Death between two tumor evaluations	15 (5.8)	12 (4.7)	
Number of censored subjects	125 (48.6)	93 (36.2)	
No death, no evaluation after randomization	4 (1.6)	3 (1.2)	
Missing baseline tumor evaluation	0	1 (0.4)	
PD/Death after missing >=2 consecutive tumor evaluations	6 (2.3)	16 (6.2)	
PD/Death after the start date of a new anti-tumor treatment	2 (0.8)	4 (1.6)	
No PD, no death, but starting a new anti-tumor treatment	19 (7.4)	10 (3.9)	
No PD, no death, and no new anti-tumor treatment	94 (36.6)	59 (23.0)	
Progression-free survival (month)			
25% quantile (95% CI)	4.2 (4.0, 5.4)	3.1 (2.7, 4.1)	
Median (95% CI)	5.7 (5.6, 7.0)	5.5 (5.2, 5.6)	
75% quantile (95% CI)	12.4 (9.7, NE)	7.0 (5.8, 7.5)	
Minimum, Maximum	0.033+, 21.355+	0.033+, 19.285+	
12-month PFS rate (95% CI)	27.8 (20.4, 35.8)	6.1 (2.2, 12.6)	
24-month PFS rate (95% CI)	NE (NE, NE)	NE (NE, NE)	
Stratified analysis			
Hazard ratio (95% CI)			0.58 (0.460, 0.736)
p-value			<0.00001
Unstratified analysis			
Hazard ratio (95% CI)			0.57 (0.450, 0.718)
p-value			<0.00001

The results of the sensitivity analyses of BIRC-assessed PFS based on the CRF stratification factors of ECOG PS score (0 vs. 1) and prior radiotherapy (yes vs. no) of the ITT analysis set showed similar results to primary analysis. Stratified HR was 0.58 (95% CI: 0.460, 0.736; nominal p-value <0.00001) (Table 74).

Table 70. Progression-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) – sensitivity analysis 3 - Based on the stratification factors collected from CRF - Intent-to-Treat analysis set (ITT)

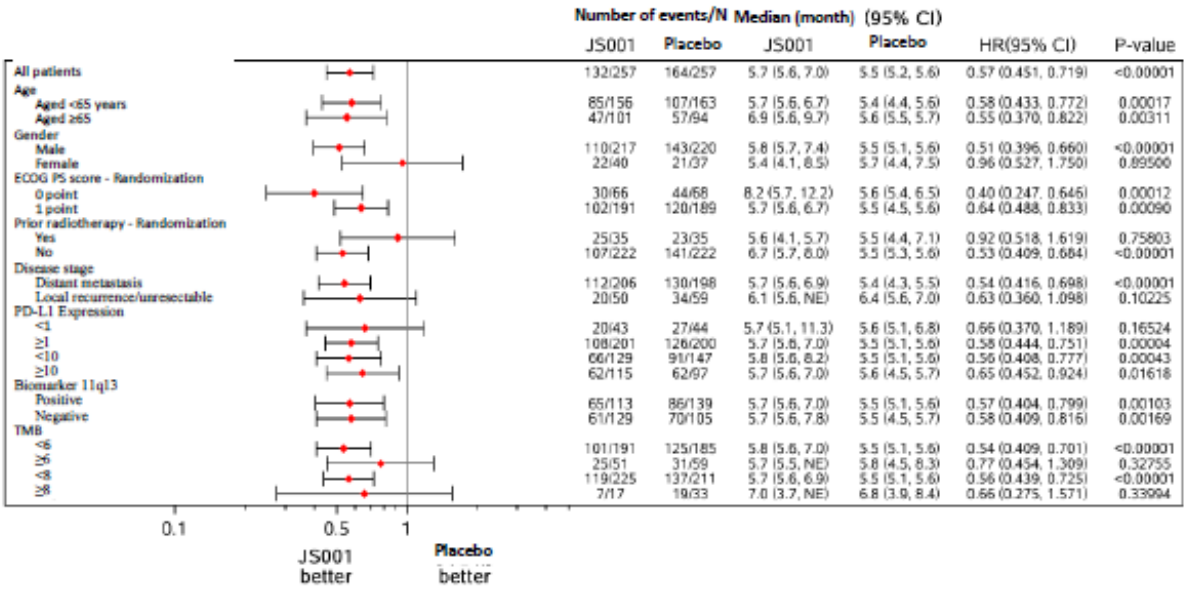
	JS001+TP Regimen (N=257) n (%)	Placebo+TP Regimen (N=257) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Number of PFS events	132 (51.4)	164 (63.8)	
Progressive Disease	117 (45.5)	152 (59.1)	
Death before first tumor evaluation	0	0	
Death between two tumor evaluations	15 (5.8)	12 (4.7)	
Number of censored subjects	125 (48.6)	93 (36.2)	
No death, no evaluation after randomization	4 (1.6)	3 (1.2)	
Missing baseline tumor evaluation	0	1 (0.4)	
PD/Death after missing >=2 consecutive tumor evaluations	6 (2.3)	16 (6.2)	
PD/Death after the start date of a new anti-tumor treatment	2 (0.8)	4 (1.6)	
No PD, no death, but starting a new anti-tumor treatment	19 (7.4)	10 (3.9)	
No PD, no death, and no new anti-tumor treatment	94 (36.6)	59 (23.0)	
Progression-free survival (month)			
25% quantile (95% CI)	4.2 (4.0, 5.4)	3.1 (2.7, 4.1)	
Median (95% CI)	5.7 (5.6, 7.0)	5.5 (5.2, 5.6)	
75% quantile (95% CI)	12.4 (9.7, NE)	7.0 (5.8, 7.5)	
Minimum, Maximum	0.033+, 21.355+	0.033+, 19.285+	
12-month PFS rate (95% CI)	27.8 (20.4, 35.8)	6.1 (2.2, 12.6)	
24-month PFS rate (95% CI)	NE (NE, NE)	NE (NE, NE)	
Stratified analysis			
Hazard ratio (95% CI)			0.58 (0.460, 0.736)
p-value			<0.00001
Unstratified analysis			
Hazard ratio (95% CI)			0.57 (0.451, 0.719)
p-value			<0.00001

The results of the sensitivity analyses of BIRC-assessed PFS in the PPS analysis set showed similar results to primary analysis. Stratified HR was 0.59 (95% CI: 0.463, 0.744; nominal p-value <0.00001) (see table below).

Table 71. Progression-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) - per protocol set (PPS)

	JS001+TP Regimen (N=255) n (%)	Placebo+TP Regimen (N=255) n (%)	JS001+TP Regimen vs Placebo+TP Regimen
Number of PFS events	130 (51.0)	162 (63.5)	
Progressive Disease	116 (45.5)	151 (59.2)	
Death before first tumor evaluation	0	0	
Death between two tumor evaluations	14 (5.5)	11 (4.3)	
Number of censored subjects	125 (49.0)	93 (36.5)	
No death, no evaluation after randomization	4 (1.6)	3 (1.2)	
Missing baseline tumor evaluation	0	1 (0.4)	
PD/Death after missing >=2 consecutive tumor evaluations	6 (2.4)	16 (6.3)	
PD/Death after the start date of a new anti-tumor treatment	2 (0.8)	4 (1.6)	
No PD, no death, but starting a new anti-tumor treatment	19 (7.5)	10 (3.9)	
No PD, no death, and no new anti-tumor treatment	94 (36.9)	59 (23.1)	
Progression-free survival (month)			
25% quantile (95% CI)	4.2 (4.0, 5.4)	3.7 (2.7, 4.1)	
Median (95% CI)	5.7 (5.6, 7.0)	5.5 (5.3, 5.6)	
75% quantile (95% CI)	13.1 (9.7, NE)	7.0 (5.8, 7.5)	
Minimum, Maximum	0.033+, 21.355+	0.033+, 19.285+	
12-month PFS rate (95% CI)	28.3 (20.8, 36.3)	6.1 (2.3, 12.7)	
24-month PFS rate (95% CI)	NE (NE, NE)	NE (NE, NE)	
Stratified analysis			
Hazard ratio (95% CI)			0.59 (0.463, 0.744)
p-value			<0.00001
Unstratified analysis			
Hazard ratio (95% CI)			0.57 (0.453, 0.724)
p-value			<0.00001

Figure 71. Subgroup analysis forest plot of progression-free survival evaluated by BICR in accordance with RECIST 1.1 (BICR-PFS) - ITT

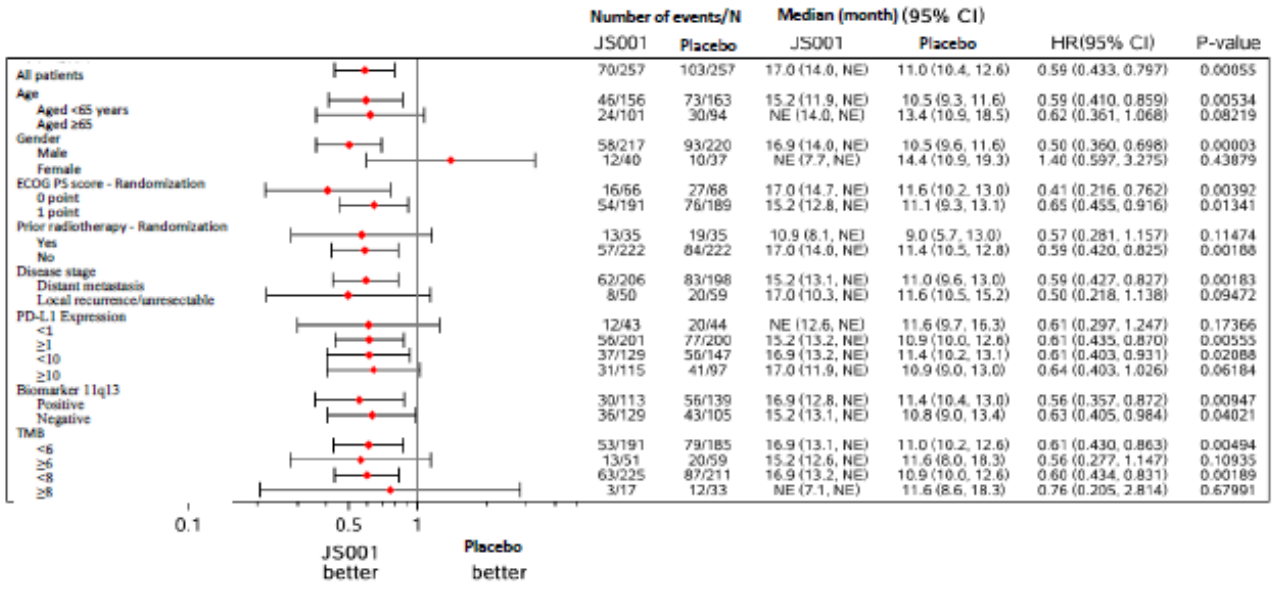


Data source: Figure 14.4.1.3

Note: CI = confidence interval, NE = not estimable; HR was estimated by the non-stratified COX proportional hazard model; P-value (two-sided) was calculated using the non-stratified log-rank test.

Overall survival

Figure 72. Subgroup analysis forest plot of overall survival (OS)—ITT

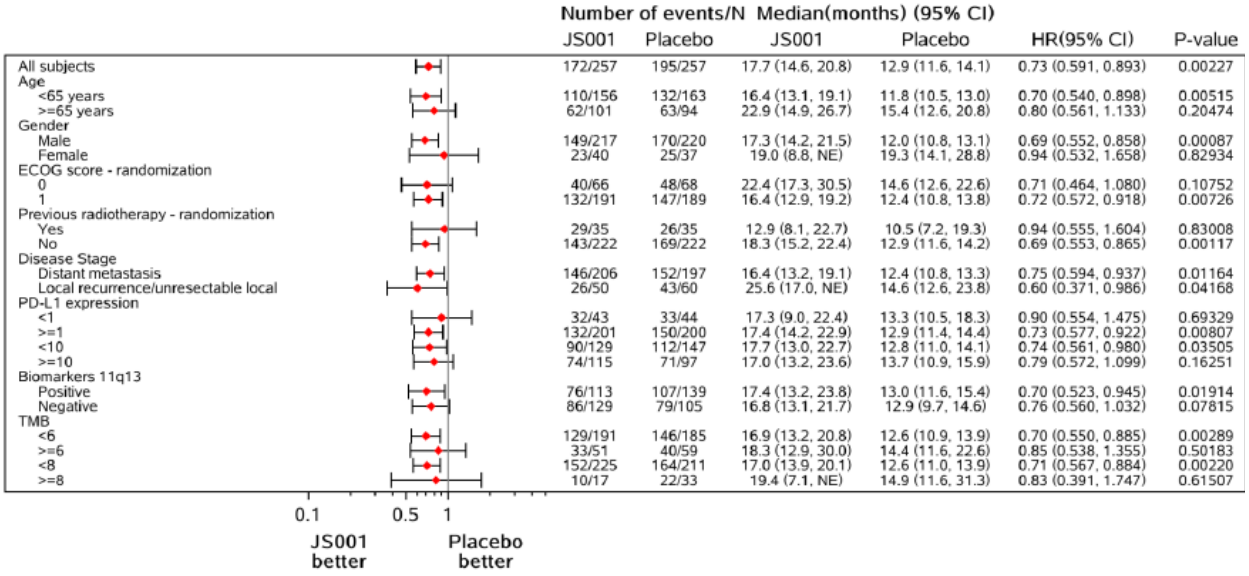


Data source: Figure 14.4.2.3

Note: CI = confidence interval, NE = not estimable; HR was estimated by the non-stratified COX proportional hazard model; P-value (two-sided) was calculated using the non-stratified log-rank test.

Subgroup analysis forest plot of overall survival (OS)—ITT at final OS analysis (23 Feb 2023)

Figure 73. Forest plot of subgroup analyses of overall survival (OS) - Intent-to-Treat analysis set (ITT)



Note: CI = confidence interval, NE = not evaluable, The hazard ratio was estimated through unstratified Cox proportional hazard model, Unstratified Log-rank test was used for calculation of p-value (two-sided).

Subgroup analysis by PD-L1 status

Table 72: Subgroup Analyses of BIRC-Determined PFS by PD-L1 Status

	# Patients	# Events	HR (95% CI)
Final PFS Analysis			
Overall	514	296	0.57 (0.45, 0.72)
CPS < 1	87	47	0.66 (0.37, 1.19)
CPS ≥ 1	401	234	0.58 (0.44, 0.75)
CPS < 10	276	157	0.56 (0.41, 0.78)
CPS ≥ 10	212	124	0.65 (0.45, 0.92)
TPS < 1%[1]	193	103	0.59 (0.40, 0.88)
TPS ≥ 1%[1]	295	178	0.59 (0.44, 0.79)
TPS < 5%[1]	318	189	0.60 (0.45, 0.81)
TPS ≥ 5%[1]	170	92	0.59 (0.39, 0.89)
TPS < 10%[1]	371	219	0.62 (0.47, 0.81)
TPS ≥ 10%[1]	117	62	0.59 (0.44, 0.79)
Missing	26	-	-

DCO: 22Mar2021

#=number; CI=confidence interval; CPS=combined positive score; HR=hazard ratio; TPS=tumour proportion score

Table 73: Subgroup Analyses of Overall Survival by PD-L1 Status

	# Patients	# Events	HR (95% CI)
Final OS Analysis			
Overall	514	367	0.73 (0.59, 0.89)
CPS < 1	87	65	0.90 (0.55, 1.48)
CPS ≥ 1	401	282	0.73 (0.58, 0.92)
CPS < 10	276	202	0.74 (0.56, 0.98)
CPS ≥ 10	212	145	0.79 (0.57, 1.10)
Missing	26	-	-
Interim (definitive) Analysis			
Overall	514	173	0.59 (0.43, 0.80)
CPS < 1	87	32	0.61 (0.30, 1.25)
CPS ≥ 1	401	133	0.61 (0.44, 0.87)
CPS < 10	276	93	0.61 (0.40, 0.93)
CPS ≥ 10	212	72	0.64 (0.40, 1.03)
TPS < 1%[1]	193	58	0.63 (0.37, 1.08)
TPS ≥ 1%[1]	295	107	0.61 (0.42, 0.90)
TPS < 5%[1]	318	108	0.66 (0.45, 0.97)
TPS ≥ 5%[1]	170	57	0.57 (0.33, 0.97)
TPS < 10%[1]	371	128	0.66 (0.46, 0.93)
TPS ≥ 10%[1]	117	37	0.51 (0.26, 1.02)
Missing	26	-	-

CT21 DCO: Final analysis 23Feb2023;

CT21 DCO: Interim analysis 22Mar2021

#=number; CI=confidence interval; CPS=combined positive score; HR=hazard ratio; TPS=tumour proportion score

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Subgroup analysis by disease status

Table 74: Subgroup Analyses by Disease Status (JUPITER-06)

	Overall Survival		BIRC-Determined PFS	
	Events/Total	HR (95% CI)	Events/Total	HR (95% CI)
ITT Population	367/514[1]	0.72 (0.58, 0.88)	296/514[1]	0.58 (0.46, 0.74)
Locally Advanced/Relapsed	69/110	0.60 (0.37, 0.99)	55/110	0.61 (0.35, 1.07)
Distant Metastases	298/403	0.75 (0.59, 0.94)	241/403	0.54 (0.42, 0.70)

OS Tables 14.4.2.3, 14.4.2.1 DCO: 23Feb2023

PFS Tables 14.4.1.3 (revised), 14.4.1.1 DCO: 22Mar2021

[1]Disease status was missing in 1 patient.

BIRC=Blinded Independent Review Committee; CI=confidence interval; ITT=intent-to-treat; HR=hazard ratio; PFS=progression-free survival

3.6.9.3. Summary of main efficacy results

Table 75. Summary of efficacy for trial JS001-021-III-ESCC

Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Compare Toripalimab (JS001, TAB001) Combined with Standard Chemotherapy with Placebo Combined with Standard Chemotherapy in the Treatment of Advanced or Metastatic Oesophageal Squamous Cell Cancer without Previous Systemic Chemotherapy	
Study identifier	JUPITER-06 JS001-021-III-ESCC (CT21)

	NCT03829969		
Design	The efficacy of toripalimab was investigated in JUPITER-06, a randomized, multi-centre, double-blind trial conducted in 514 patients with recurrent locally advanced or metastatic squamous cell cancer of the oesophagus (OSCC) who had not previously received systemic therapy for recurrent or metastatic disease. Patients were randomized (1:1) to toripalimab combined with paclitaxel and cisplatin (TP) or placebo plus TP. Randomization was stratified by Eastern Cooperative Oncology Group performance status score (0 vs. 1) and previous radiotherapy (yes vs. no). The treatment phase included an induction period and a maintenance period. In the induction period, patients received toripalimab or placebo combined with TP on Day 1 of each cycle (3 weeks per cycle) for up to 6 cycles. After completion of TP, patients entering the maintenance period received toripalimab or placebo monotherapy on day 1 of each subsequent cycle (3 weeks per cycle). Tumour imaging was obtained every 6 weeks for the first year and then every 9 weeks. Treatment was continued until disease progression, no potential for clinical benefit per Investigator, intolerable toxicity, death, patient refusal, withdrawal of consent, lost to follow up, start of a new anticancer therapy, or completion of 2 years of treatment. The co-primary endpoints were blinded independent review committee (BIRC)-determined progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and overall survival (OS).		
	Duration of main phase:		Up to 2 years of treatment with toripalimab or placebo
	Duration of Run-in phase:		Not applicable.
	Duration of Extension phase:		Not applicable.
Hypothesis	This study was designed to test for superiority. The null hypothesis was that there was no difference between the two arms in both the co-primary efficacy endpoints, BIRC-assessed PFS and OS. The alternative hypothesis was that there was a difference between the two arms in at least one of the co-primary endpoints.		
Treatments groups	Toripalimab Arm		Induction period: Toripalimab 240 mg, Paclitaxel 175 mg/m^2 and Cisplatin 75 mg/m^2 intravenously (IV) every 3 weeks (Q3W) for up to 6 cycles Maintenance period: Toripalimab 240 mg IV Q3W
	Placebo Arm		Induction period: Placebo, Paclitaxel 175 mg/m^2 and Cisplatin 75 mg/m^2 IV Q3W for up to 6 cycles Maintenance period: Placebo IV Q3W
Endpoints and definitions	Co-Primary endpoint	BIRC-determined PFS	Time from randomisation to first recorded date of progressive disease, as evaluated by the BIRC per RECIST v1.1, or death due to any cause (whichever comes first)
	Co-Primary endpoint	OS	Time from randomisation to death due to any cause
	Secondary endpoints	Investigator (INV)-determined PFS	Time from randomization to first recorded date of progressive disease, as evaluated by the Investigator per RECIST v1.1, or death due to any cause

		1- and 2-year BIRC- and INV-determined PFS	Proportion of patients without documented disease progression, as evaluated by the BIRC or INV per RECIST v1.1, at 1 or 2 years after randomisation
		1- and 2-year OS	Proportion of patients alive at 1 or 2 years after randomisation
		BIRC- and INV-determined objective response rate (ORR)	Proportion of patients who achieved a complete or partial response per RECIST v1.1
		BIRC- and INV-determined disease control rate (DCR)	Proportion of patients with a complete response, partial response or stable disease per RECIST v1.1
		BIRC- and INV-determined duration of response	Time from the first recorded response (complete or partial response) per RECIST v1.1 to the first recorded date of progressive disease or death due any cause (whichever comes first)
		BIRC- and INV-determined PFS, ORR, disease control rate, duration of response, and time to response per immune-related RECIST (irRECIST)	Each of these endpoints, as defined above, will be assessed per irRECIST
Database lock	Final PFS and Interim (definitive) OS Analyses: 20 May 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All efficacy analyses were conducted in the intent-to-treat population, defined as all the randomized patients. The analysis of BIRC-determined PFS was to be conducted after 283 events. The PFS analysis was conducted at 296 events with a database lock of May 20, 2021 An interim analysis of OS was planned at the time of the PFS analysis. The interim OS analysis was conducted at the time of the PFS analysis, database lock May 20, 2021, with 173 OS events. An ad hoc analysis was conducted, data cutoff February 15, 2022, with 312 OS events and is also included in the submission. For the final OS analysis data cutoff was 23 February 2023.		
Descriptive statistics and estimate variability	Treatment group	Toripalimab Arm	Placebo Arm
	Number of subjects	257	257
	Co-primary endpoint OS (months) Median	17.7	12.9
	95% confidence interval	14.6, 20.8	11.6, 14.1
	Co-primary endpoint BIRC-PFS (months)	5.7	5.5

	Median		
	95% confidence interval	5.6, 7.0	5.2, 5.6
Effect estimate per comparison	Co-primary endpoint OS	Comparison groups	Toripalimab Arm and Placebo Arm
		Hazard ratio	0.72
		95% confidence interval	0.58, 0.88
		p-value (stratified log-rank test)	0.0016
	Co-primary endpoint BIRC-PFS	Comparison groups	Toripalimab Arm and Placebo Arm
		Hazard ratio	0.58
		95% confidence interval	0.46, 0.74
		p-value (stratified log-rank test)	<0.00001
Notes	When the interim analysis crossed the pre-specified boundary for efficacy, the Independent Data Monitoring Committee recommended unblinding. The Sponsor chose to unblind the study. Patients in the treatment arm were transitioned to open-label toripalimab, whereas all patients in the control arm discontinued placebo. Tumour imaging continued in the toripalimab arm but not in the placebo arm. Survival follow-up and the collection of subsequent anticancer therapy was continued in both arms. Safety information was collected, as per protocol, up to 60 days after the last dose of toripalimab or placebo.		
Analysis description	**Co-primary Analysis**		
OS and PFS	The co-primary efficacy endpoints were BIRC-determined PFS per RECIST 1.1 and OS. A pre-specified hierarchical testing procedure was used for the analyses of the co-primary efficacy endpoints and there was no plan of alpha spending for the analyses of secondary efficacy endpoints. BIRC-determined PFS was tested first using a stratified (stratification factors at randomization, performance status and prior radiation) log rank test with a two-sided alpha of 0.05. If the null hypothesis for BIRC-determined PFS was rejected, OS was tested using a stratified log rank test. The overall alpha for the interim and final analyses of OS was controlled at a two-sided level of 0.05 using the pre-specified group sequential design with O'Brien-Fleming boundaries approximated by the Lan-DeMets spending function. The HRs and the corresponding confidence intervals for BIRC-determined PFS and OS were estimated using a stratified (stratification factors at randomization) Cox proportional hazards model. The Kaplan-Meier method was used to estimate the medians for each arm, and the corresponding confidence intervals were estimated using the Brookmeyer-Crowley method with log-log transformation. The analysis of BIRC-determined PFS was to be conducted after 283 events. The PFS analysis was conducted at 296 events with a database lock of May 20, 2021. An interim analysis of OS was planned at the time of the final PFS analysis. The interim OS analysis was conducted at the time of the PFS analysis, database lock May 20, 2021, with 173 events. An ad hoc analysis was conducted, data cutoff February 15, 2022, with 312 events and is included in the submission. The final OS analysis at study completion with data cutoff February 23 2023 included 375 events.		

3.6.9.4. Clinical studies in special populations

See section 3.6.6.4, Table 58, Table 59.

3.6.9.5. In vitro biomarker test for patient selection for efficacy

None.

3.6.9.6. Analysis performed across trials (pooled analyses and meta-analysis)

No meta-analysis or pooled analysis was conducted.

3.6.9.7. Supportive study(ies)

Studies to Support the Efficacy of Toripalimab in Oesophageal Squamous Cell Carcinoma

Cohorts 2 and 6 of POLARIS-02

Cohort 2

Eligible patients in Cohort 2 had a diagnosis of advanced and/or metastatic OSCC (histologically or cytologically confirmed), who received at least one line of treatment for advanced OSCC and have documented tumour progression or be intolerant of these chemotherapy regimens.

In Cohort 2 patients received toripalimab 3mg/kg IV once every 2 weeks of each 28-day (4 weeks) cycle, until disease progression, intolerable toxicity, the investigator's decision to terminate treatment, the patient's withdrawal of consent or death.

The scans of tumour evaluation were performed every 6 weeks for the first year and every 12 weeks thereafter.

The primary objective of this study was to evaluate the anti-tumour activity of toripalimab for the treatment of advanced OSCC. The primary efficacy endpoint was objective response rate based on RECIST v1.1.

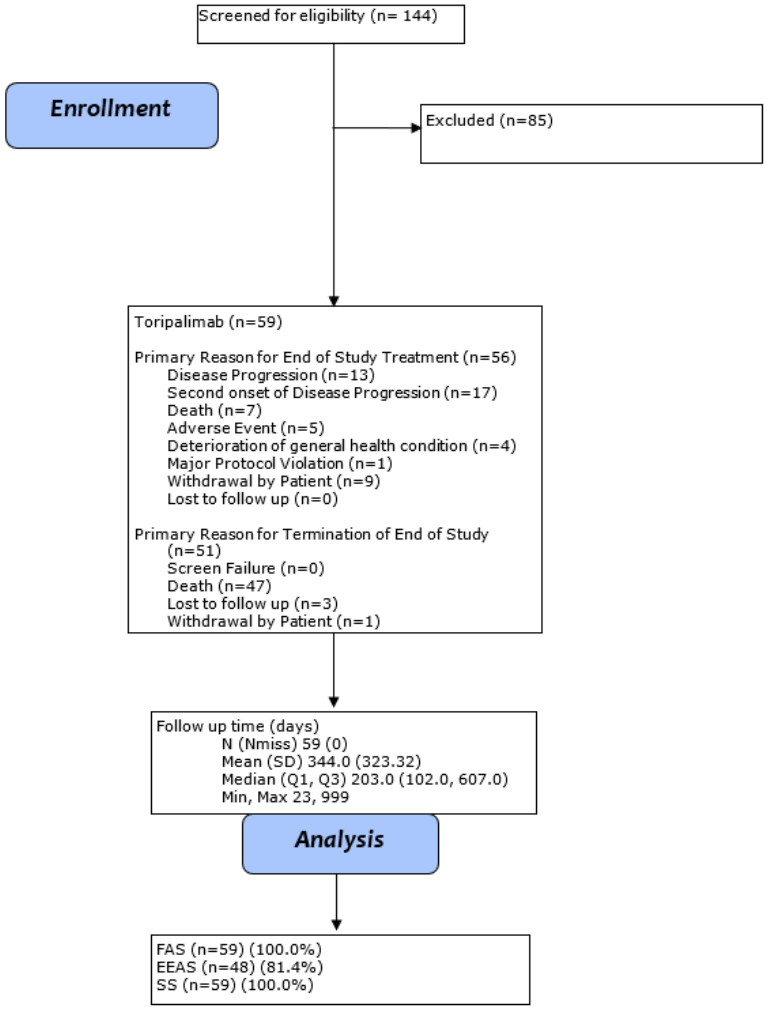
The primary and secondary endpoint statistical methods are shown in Table 80.

Table 76. Statistical analysis strategy for efficacy endpoints

Endpoint	Statistical method	Analysis population
Primary		
ORR	Clopper-Pearson method	FAS EEAS
Secondary		
Disease control rate	Clopper-Pearson method	FAS EEAS
Duration of response	Kaplan-Meier method	EEAS

	Brookmeyer-Crowley method	

Figure 74. Subjects Disposition in JS001-1b-CRP-1.0 study Cohort 2



Cohort 6

Eligible patients in Cohort 6 had a diagnosis of advanced and/or metastatic NPC, who have not received any systemic treatment.

In Cohort 6 patients received toripalimab Q3W IV in combination with paclitaxel and cisplatin, until absence of further benefits judged by the investigator, disease progression, occurrence of intolerable toxicity, investigator's decision to discontinue treatment, withdrawal of informed consent by the patient, or death. They received 240 mg or 360 mg of toripalimab administered by IV infusion Q3W. Paclitaxel was given 175 mg/m2 3 h iv infusion on Day 1 of each cycle, and cisplatin was given 75 mg/m2 IV at a rate of approximately 1 mg/min or per local clinical practices on Day 1 of each cycle, in 3-week cycles.

The scans of tumour evaluation were performed every 6 weeks for the first year and every 12 weeks thereafter.

The primary objective of this study was to evaluate the anti-tumour activity of toripalimab combined with standard first-line chemotherapy for the treatment of OSCC. The primary efficacy endpoint was objective response rate based on RECIST v1.1.

The primary and secondary endpoint statistical methods are shown in the table below.

Table 77. Statistical analysis strategy for efficacy endpoints

Endpoint	Statistical method	Analysis population
Primary		
ORR	Clopper-Pearson method	FAS EEAS
Secondary		
Disease control rate	Clopper-Pearson method	FAS EEAS

Figure 75. Subjects Disposition in JS001-1b-CRP-1.0 study Cohort 6

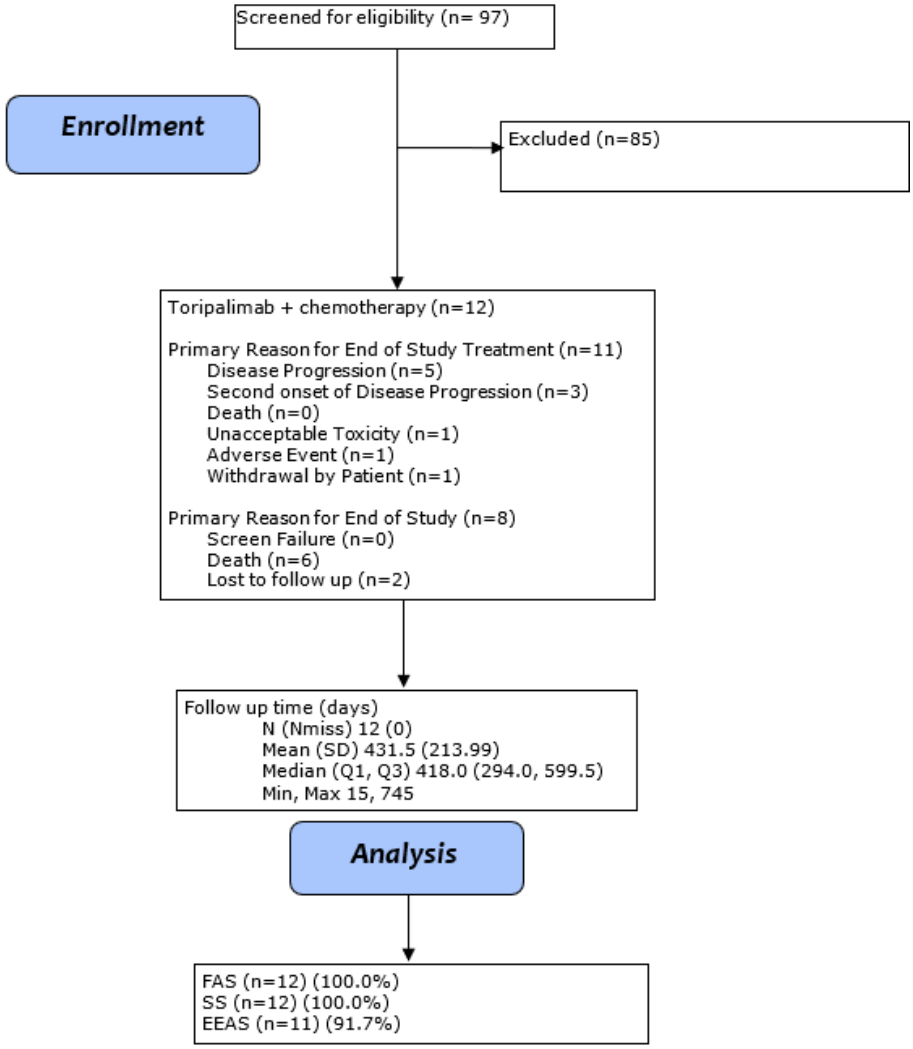


Table 78. Demographics and Baseline Characteristics (Cohorts 2 and 6 of POLARIS-02)

	Cohort 2 Toripalimab Monotherapy N=59	Cohort 6 Toripalimab + TP N=12
Median Age (range)	60.0 years (42.0-73.0)	56.5 years (42-72)
Age > 65 years, N (%)	14 (23.7)	3 (25.0)
Gender, N (%)		
Male	52 (88.1)	9 (75.0)
Female	7 (11.9)	3 (25.0)
Race, N (%)		
Asian	59 (100)	12 (100)
ECOG Performance Status, N (%)		
0	6 (10.2)	5 (41.7)
1	53 (89.8)	7 (58.3)
Stage at Entry (AJCC 8th Edition)		
III	2 (3.4)	0
IV	55 (93.2)	11 (91.7)
Missing	2 (3.4)	1 (8.3)
Liver Metastases	15 (25.4)	4 (33.3)
Prior Radiotherapy	41 (69.5)	2 (16.7)
Prior Cytotoxic Therapy	59 (100)	0
Source: CT5 Cohorts 2 and 6/Tables 14.1.3.1, 14.1.4.1.1 DCO: 19-Feb-2020 AJCC=American Joint Commission on Cancer; TP=paclitaxel/cisplatin		

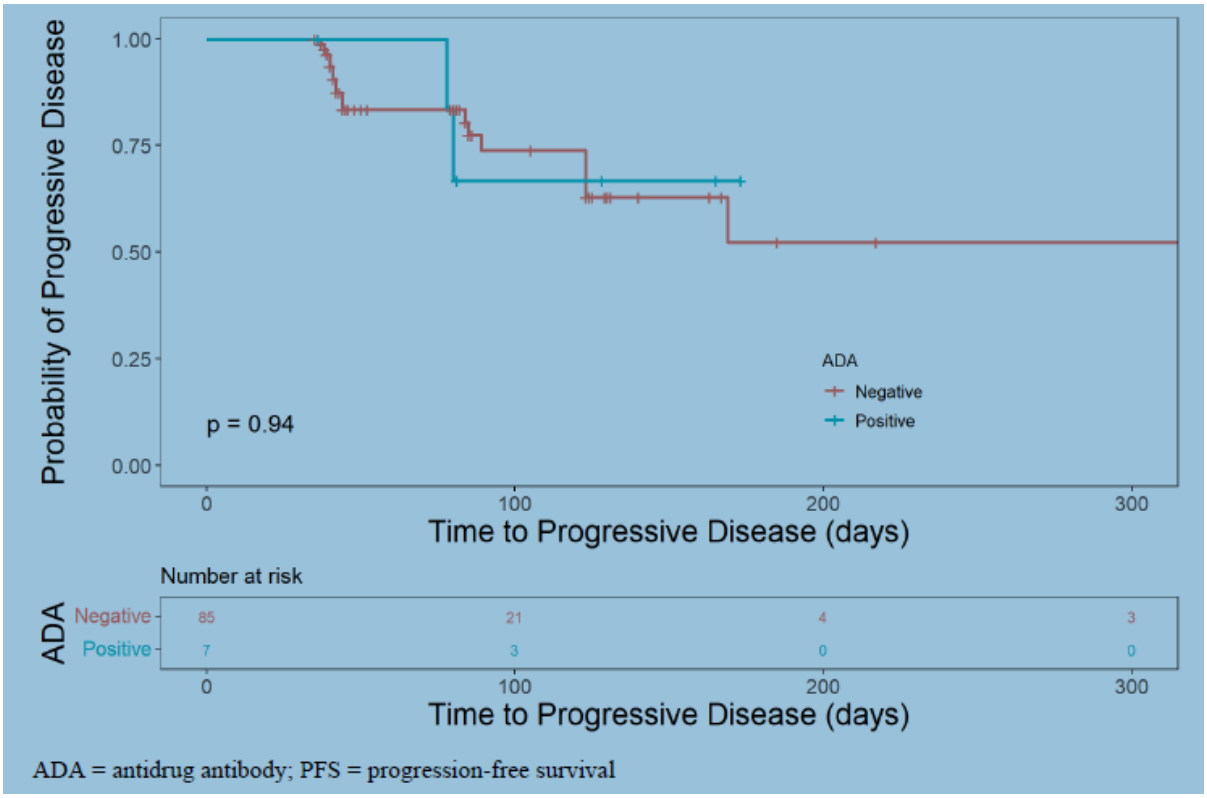
In cohort 2 primary efficacy endpoint was ORR based on RECIST v1.1. In the FAS analysis 15.3% (95% CI: 7.2%, 27.0%) of the patients achieved a CR or PR after toripalimab monotherapy per IRC assessment. Investigators ORR assessed the same as IRC (see table below).

In cohort 6 primary efficacy endpoint was ORR based on RECIST v1.1. In the FAS analysis confirmed ORR was 66.7% (95% CI: 34.9%, 90.1%) after toripalimab in combination with chemotherapy per investigator assessment (see table below).

Table 79. Response Rate and Duration of Response (Cohorts 2 and 6 of POLARIS-02)

	BIRC-determined Cohort 2 N=59	Investigator-determined Cohort 6 N=12
Overall Response Rate, N (%) (95% CI)	9 (15.3) (7.2, 27.0)	8 (66.7) (34.9, 90.1)
Median Duration of Response, months (95% CI)	12.2 (4.6, NE)	6.8 (4.2, 18.2)
Source: Cohorts 2 and 6/CT5 Tables 14.2.1.1.1, 14.2.2.1 DCO: 19-Feb-2020 Responses assessed using RECIST v1.1. CI=confidence interval; NE=not estimable		

Figure 76. Kaplan-Meier Plot for PFS Stratified by ADA Status (CT15)



ADA = antidrug antibody; PFS = progression-free survival

Table 80. CT15 PopPK Responder and Non responder Data Categorised by ADA Status (Toripalimab Arm Only)

ADA Status	Nonresponder (N = 12)	Responder (N = 80)
Negative	11 (91.7%)	74 (92.5%)
Positive at baseline	0 (0%)	3 (3.8%)
Treatment emergent positive	1 (8.3%)	3 (3.8%)
Missing	0 (0.0%)	0 (0.0%)

ADA = antidrug antibody; N = number of patients; popPK = population pharmacokinetic

ADA was detected in 11.3% (29/256) of patients enrolled on JUPITER-06. This included 7 (2.7%) patients who were positive at baseline and (8.8%) who became ADA positive on-study. Among the 7 patients who were positive at baseline, 5 were ADA negative on-study and 2 remained ADA positive but did not have 4-fold increase in titre following exposure to toripalimab (i.e., no evidence of treatment-boost) The ORR was 62.1% (95% CI: 42.3, 79.3) in patients with ADA (N = 29) and 70.0% (95% CI: 63.6, 75.9) in those without (N = 227). The confidence intervals for these response rates overlap and these findings should be considered in that context. A univariate analysis was performed for JUPITER-06 with ADA status as a predictor of ORR; in this analysis ADA status was found to not be a significant covariate (p=0.937). Similarly, Kaplan-Meier plots of PFS and OS showed no significant difference when stratified by ADA status (p=0.67 and p=0.87, respectively). ADA was detected in 5/59 (8.5%) patients in Cohort 2 and 1/12 (8.3%) patients in Cohort 6. There were no responses (95% CI: 0, 52.3) in the 5 patients with ADA as compared with an ORR of 16.7% (95% CI: 7.9, 29.3) among those who were ADA-negative in Cohort 2. In Cohort 6, the 1 patient who developed ADA had a partial response while the ORR was 63.6% (95% CI: 30.8, 89.1) among those who were ADA-negative.

In the popPK model (TOPA-PMX-TORIPALIMAB-3355), which includes data from 15 clinical studies, 9% of patients (113 of 1250 patients with available data) developed ADA post treatment; an additional 1.9% of patients (24 of 1250 patients) had pre-existing ADA at baseline.

3.6.10. Discussion on clinical efficacy

Design and conduct of clinical studies

One placebo controlled pivotal study, JUPITER-06 (JS001-021-III-ESCC) was conducted to support the use of toripalimab for the treatment of oesophageal squamous cell carcinoma.

Study JUPITER-06 is a randomized, placebo-controlled, multi-centre, double-blind, phase 3 study. It was designed to determine the efficacy and safety of toripalimab in combination with paclitaxel and cisplatin compared with placebo in combination with paclitaxel and cisplatin in patients with advanced or metastatic OSCC who have not received systemic chemotherapy previously.

The key inclusion for the JUPITER-06 study included patients with locally advanced/relapsed or metastatic OSCC that cannot be eradicated (histologically or cytologically confirmed), with no prior systemic chemotherapy for relapsed or metastatic tumour.

In study JUPITER-06, patients received toripalimab/placebo in combination with paclitaxel and cisplatin, the dose of toripalimab was 240 mg IV Q3W.

The Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6), recommends that if an experimental agent is used in combination, it should be compared with the best available, evidence-based therapeutic options.

According to 2022 ESMO guidelines on Oesophageal cancer the treatment of advanced and metastatic OSCC, the recommended first line standard treatment is a platinum-based chemotherapy. The ESMO guideline favours a combination of platinum and fluoropyrimidine, however the NCCN guidelines (2024) lists the combination of paclitaxel and cisplatin as an acceptable first line therapy and available data indicate similar effect with different chemotherapy options used in clinical practice. Even though the combination used in JUPITER-06 study is not the best available, it is considered acceptable. The dose of cisplatin and paclitaxel was modified in accordance with local treatment practices at the discretion of the investigator.

In JUPITER-06 study, the co-primary efficacy endpoints were PFS evaluated by BICR in accordance with RECIST 1.1 and OS. The PFS assessment by blinded independent review committee reduce possible bias. Secondary endpoints included ORR, DOR, DCR and TTR evaluated by BICR and investigators in accordance with RECIST 1.1. The primary and secondary endpoints are in line with EMA/CHMP/205/95 Rev.6 and EMA/CHMP/27994/2008/Rev.1 (Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials), and are therefore considered acceptable.

The assumptions of the sample size calculations appear reasonable. Simeon's two-stage design is common and appropriate in oncology (Simon 1989).

Randomized subjects were stratified by their ECOG performance status (0 vs 1) and previous radiotherapy (yes or no) which is considered acceptable. Prior radiotherapy has been described in the literature as a prognostic factor of OSCC. Multiple factors have been investigated and reported as prognostic factors for OSCC, including tumour volume, node disease and gender among others.

PD-L1 expression has been associated with unfavourable prognosis in OSCC (Wang et al 2018); stratification by PD-L1 expression has been used previously in studies with ICIs. A meta-analysis (Guo et al., 2018) has shown that high PD-L1 expression was significantly associated with poor OS (HR 1.38, 95% CI =1.11-1.19, p =0.008) particularly in Asian population.

According to the applicant, PD-L1 tumour status was not selected as a stratification factors because of the relatively high prevalence of overexpressed PD-L1 in OSCC and expectation that it would be

balanced by randomization alone. However, based on the results from other studies and from JUPITER-06, PD-L1 is overexpressed in less than (or nearly) half of OSCC patients.

The distribution of patients by PD-L1 expression (either CPS and TPS) in JUPITER-06 does not appear to be imbalanced between active arm and placebo.

Patient's mean age, sex, race, status were balanced between treatments group. The number of patients that had ECOG performance 0 and 1 were similar in numbers and between treatment groups. Baseline disease characteristics were balanced between treatment arms. The study population reflects the intended indication part "for the first-line treatment of adult patients with recurrent or metastatic oesophageal squamous cell carcinoma". Compliance to the study protocol was good. All patients recruited were Asian.

The representativity of the study population to the EU population was therefore questioned in line with the EMA guidance on multi-regional clinical trials and the extrapolation of foreign (CPMP/ICH/289/95; EMEA/CHMP/EWP/692702/2008; EMA/CHMP/ICH/453276/2016 Rev.1). The acceptability of foreign clinical data depends on whether it can be extrapolated to the EU population as there are intrinsic and extrinsic factors that may be different between populations.

No clear difference in the treatment effect of PD-1 blocking antibodies was seen by region and the risk factors for OSCC as well as genetic mutations and PD-L1 expression status are all comparable between Asian and non-Asian populations allowing extrapolation of data from JUPITER-06 to patients with OSCC in the European Union.

There are differences in the applied first-line combination treatment (as well as comparator) in the JUPITER-06 study compared to the clinical practice in the EU countries. In EU countries the choice of treatment takes into consideration PD-L1 expression and HER-2 overexpression. In China the standard first line treatment for late-stage OSCC currently is combination of pembrolizumab and cisplatin+5-fluoropyrimidine or combination of camrelizumab and paclitaxel + cisplatin. If immune checkpoint inhibitors are not suitable, then only chemotherapy is considered. Common chemotherapy regimens for late-stage oesophageal squamous cell carcinoma include cisplatin + fluorouracil, paclitaxel + platinum (Health Commission Of The People's Republic Of China N, 2022). As mentioned above, the NCCN guidelines (2024) lists the combination of paclitaxel and cisplatin as an acceptable first line therapy and available data indicate similar effect with different chemotherapy options used in clinical practice (Honing et al, 2014; Liu et al, 2016, Hu et al, 2016; Blom et al, 2014). Even though the combination used in JUPITER-06 study is not the best available, it is considered acceptable.

In study JUPITER-6, the population, placebo control, and endpoint measurement are considered appropriate. One interim analysis was planned for OS. The imputation of missing data is acceptable. The statistical approach is acceptable to establish clinical efficacy.

Overall, 209 patients had at least one major protocol deviation, similar number of participants in both arms. The number of major protocol deviations is high, most common were due to delayed or missing tumour imaging, which is the main tool of evaluation for PFS, however these patients were censored.

A number of potential GCP issues were identified and requested to be addressed within the procedure for JUPITER-06 which was only inspected by the National Medical Products Administration (NMPA). The CHMP triggered a GCP inspection, which was performed at two investigator sites and the sponsor site, all located in China, between 11 March 2024 – 18 April 2024. The inspectors concluded that the findings identified during this inspection do not affect the quality and reliability of the data supporting this application. Overall, it was considered that the trial was conducted in accordance to GCP. The instances where deviations from GCP were observed did not have a relevant impact on the rights, safety or dignity of the trial participants, the quality and robustness of the data or the overall assessment of the GCP compliance of the clinical trial.

Efficacy data and additional analyses

A total of 514 patients enrolled in the JUPITER-06 study, of which 257 were randomised to toripalimab + chemotherapy group and 257 to placebo + chemotherapy group. In the toripalimab group 226 out of 257 patients discontinued treatment, while in the placebo group all subjects discontinued treatment, mainly due to disease progression.

In the clinical trial protocol Version 2.0, planned enrolment was adjusted from 430 to 500 patients because of altered study endpoints. In version 4.0 the time of an induction period was clarified to be a maximum of 6 cycles.

All the enrolled patients were included in the ITT analysis. The analysed populations seem acceptable.

The study population characteristics were: median age of 63 years (range: 20 to 75), 38% age 65 or older, 85% male, 100% Asian, and ECOG PS of 0 (26%) or 1 (74%). Seventy-nine percent of patients had metastatic disease at study entry. Using a clinical study assay (JS311 immunohistochemistry) in a central laboratory, 78% of patients had PD-L1 combined positive score (CPS) ≥ 1 and 41% had a CPS of ≥10.

At a pre-specified interim analyses of OS, conducted at 47.3% of the planned OS events and at the time of the final PFS analysis, the study demonstrated a statistically significant improvement in OS (HR 0.58; 95% CI: 0.42, 0.78; p=0.0004) which is clinically significant.

The results of the final analysis of BIRC-determined PFS also demonstrated a statistically significant improvement in PFS. The HR for the final analysis of PFS was 0.58 (95% CI: 0.46, 0.74; p< 0.0001).

However, the difference of 0.2 month in median PFS is not considered clinically significant. Although the PFS curves separate before the median, and the magnitude of the effect appears to be consistent throughout the survival curves, after the 6th month, the number of events decreases, therefore the curves should be interpreted with caution after the median.

The primary analysis censoring rules were provided by the applicant and are considered acceptable. Of note, patients with 2 or more missing consecutive tumour assessment due to COVID-19 who had no evidence of disease progression were not automatically censored and were included in the analysis.

The sensitivity analysis to account for patients with missing TA due to COVID-19 resulted in similar outcome i.e. 0.58 (95% CI: 0.46, 0.74).

Other sensitivity analyses were performed to account for patients who started a new anticancer therapy without disease progression and for patients who had incorrect recording of stratification factors performance status and/or prior radiotherapy resulted in a similar outcome as primary analysis.

A sensitivity analysis was also conducted in the per protocol population. This was defined as patients who did not have a major protocol deviation that would impact efficacy, with results similar as the primary analysis.

The censoring rules used in the primary analysis and the results of pre-specified sensitivity analyses of BIRC-determined PFS were re-iterated.

Due to the substantial amount of missing data in JUPITER-06 study, the applicant conducted sensitivity analyses to evaluate the potential impact on the results. The major protocol deviations and missing data mainly occurred in the context of COVID-19 pandemic (frequent missing TA visits). The incidence of major protocol deviations including missing TA visits appears higher in the toripalimab arm than in the placebo. Although the delay in TA readings could theoretically have a potential impact on the PFS endpoint results, the various sensitivity analyses did not confirm this hypothesis since the PFS had similar HR and 95%CI across these analyses.

Sensitivity analyses for OS, which exclude all patients with a major protocol deviation (OS sensitivity analysis 1) and patients with major protocol deviations likely to affect survival (OS sensitivity analysis 2) were submitted. The HR point estimate for OS in sensitivity analyses 1 and 2 are below 1.0 and numerically higher than the HR point estimate for OS in the primary analysis. Unlike the primary analyses, the 95% confidence interval included 1 in both sensitivity analysis 1 and 2. As noted above, these post-hoc analyses excluded a significant number of patients who had major protocol deviations or major protocol deviations that impacted safety respectively. It is therefore reasonable to believe that exclusion of patients from these analyses led to a wider 95%CI.

Based on the results of sensitivity analyses, no major impact on the efficacy results was observed.

Based on the popPK analysis, the presence of ADA (at baseline or post treatment) resulted in increased (20% higher) CL relative to patients without ADA at any timepoint. While ADA leads to a modest increase in toripalimab CL, it was not identified as a statistically significant predictor of efficacy in the E-R analyses in either indication, suggesting that ADA have no independent impact on efficacy or safety.

PD-L1 expression

Efficacy results by PD-L1 expression in several large phase 3 studies including KEYNOTE-590, CheckMate 648, and ESCORT-1st all suggest a positive correlation between PD-L1 expression level (either on tumour cells or both tumour and immune cells) and the efficacy of PD-1 blockade in combination with chemotherapy. In Europe, pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma, in adults whose tumours express PD-L1 with a CPS ≥ 10. Nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%. Nivolumab in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

In contrast to other Phase 3 trials with other checkpoint inhibitors, no prominent effect of PD-L1 expression on either PFS or OS is apparent in toripalimab-treated patients in JUPITER-06. In order to rule out potential deficiencies in the study design that could have explained this outcome, the applicant provided additional analyses and justifications further discussed below.

One of the uncertainties was related to the biomarker assay. PD-L1 expression was detected by immunohistochemical staining of tumour and immune cells using the JS311 assay. JS311 is a PD-L1 IHC antibody developed by Shanghai Junshi Biosciences. The JS311 assay has been analytically validated in a variety of tumour types, including NPC and OSCC, and is CE marked in the EU (RPS/1750/2021) for other intended use, triple negative breast cancer and gastric cancer. The analytic validation supporting the CE mark included concordance studies between JS311 and 22C3 (used for detection of PD-L1 in tumour specimens in trials of pembrolizumab) and JS311 and 28-8 (used for detection of PD-L1 in tumour specimens in trials of nivolumab). The JS311 assay showed high level of concordance for specificity and negative predictive value, thus indicating consistency between PD-L1-negative (<1%) tumour testing as determined by JS311 and either 22C3 or 28-8. JS311 is therefore considered reliable to determine the PD-L1 expression of patients included in JUPITER-06.

The review of baseline characteristics from JUPITER-06 did not suggest a difference between PD-L1 expression subgroups that could question the interpretation of the data, acknowledging the lack of stratification by PD-L1 expression. The subgroup analyses by CPS and TPS (using different thresholds)

as well as comparisons with other trials with ICIs (nivolumab and pembrolizumab) were submitted and did not identify major differences in term of efficacy; the HR point estimates for OS and PFS in all PD-L1 subgroups evaluated in JUPITER-06 were consistently below 1.

In some of the PD-L1 subgroups, the 95% CI included "1", i.e. at the interim and final OS analysis in subgroup TPS<1% and at the interim and final OS and PFS analysis in subgroup CPS<1. However, for some of these subgroups (particularly CPS<1) the number of patients is relatively low. Absence of stratification by PD-L1 expression may have confounded the results in subgroups as well, baseline/disease characteristics do not appear to explain the findings. Overall, the available data do not indicate significant differences of efficacy depending on PD-L1 expression that could justify a restriction of the indication to a specific patient population.

In addition, the lack of apparent correlation between efficacy and different PD-L1 expression levels for toripalimab in contrast to what has been observed with pembrolizumab and nivolumab might potentially be explained by the improved binding affinity of toripalimab.

The primary objective of the study has been met. In study JUPITER-06 sensitivity analyses showed results, consistent to primary effect. There weren't any major differences between subgroups, except for female group as it appears to favour placebo, but possibly due to the smaller number of events in this group. According to subgroup analyses toripalimab appears to be equally effective in patients with high or low PD-L1 tumour status.

Wording of the indication:

The originally proposed wording of the indication was revised in order to better reflect the study population in JUPITER-06 study which also enrolled patients with unresectable advanced OSCC and to also take into consideration the 2022 ESMO guidelines on Oesophageal cancer recommending the same treatment for unresectable advanced and metastatic OSCC. In addition, data for these patients were provided as well as subgroup analyses for the 21.2% of patients with local recurrent/unresectable disease to adequately assess the benefit in these patients with different baseline disease characteristics.

3.6.11. Conclusions on clinical efficacy

For OSCC, the intended patient population with unresectable advanced, recurrent, or metastatic cancer is considered aligned to the patient populations in which efficacy has been investigated in the pivotal trial. Detailed demographics and baseline characteristics of patients with locally advanced/recurrent or metastatic disease of OSCC in the JUPITER-06 study have been provided and the efficacy comparing advanced/recurrent and metastatic disease have been discussed.

Further, the chosen chemotherapy combination with paclitaxel and cisplatin is not standard first-line treatment in Europe for OSCC, but following justification it has been accepted as a backbone therapy. Overall, the extrapolation ground for efficacy data provided with toripalimab in Asian patients (e.g. with regards to differences in histology, aetiology, clinical care etc.) to the EU population could be supported.

3.6.12. Clinical safety

- ***Nasopharyngeal Carcinoma (NPC)***
    - *CT15/JUPITER-02:* phase III randomized, placebo-controlled double-blind study, comparing toripalimab injection (JS001 or TAB001) combined with chemotherapy versus placebo combined

with chemotherapy for recurrent or metastatic nasopharyngeal cancer. Chemotherapy consisted of gemcitabine/cisplatin.

- *POLARIS-02, Cohort 3:* phase 1b/2 open-label study evaluating toripalimab (JS001 or TAB001) in subjects with NPC, who had progressed on or were intolerant of at least 1 prior line of therapy for locally advanced/metastatic disease.
- *POLARIS-02, Cohort 7:* phase 1b/2 open-label study evaluating toripalimab (JS001 or TAB001) in combination with standard first-line chemotherapy to patients who had received no prior therapy for recurrent or metastatic in subjects with NPC.

- ***Squamous Cell Carcinoma of the Oesophagus (OSCC)***
  - *CT21/JUPITER-06:* phase III randomized, placebo-controlled double blind study, comparing toripalimab injection (JS001 or TAB001) plus chemotherapy versus placebo plus chemotherapy for locally advance or metastatic OSCC without previous systemic chemotherapy. Chemotherapy consisted of paclitaxel/cisplatin.
  - *POLARIS-02, Cohort 2*: phase 1b/2 open-label study evaluating toripalimab (JS001 or TAB001) in subjects with OSCC, who had progressed on or were intolerant of at least 1 prior line of therapy for locally advanced/metastatic disease.
  - *POLARIS-02, Cohort 6:* phase 1b/2 open-label study evaluating toripalimab (JS001 or TAB001) in combination with standard first-line chemotherapy to patients who had received no prior therapy for recurrent or metastatic in subjects with OSCC.

- ***Toripalimab monotherapy safety database***
  - 13 clinical trials (list of these trials is provided below).

The safety of toripalimab was examined in all patients receiving protocol-specified treatment in the following populations**:**

Table 81. Populations receiving toripalimab protocol-specified treatment

Population	Trial name	Trial phase	Number of patients exposed to toripalimab	Number of patients exposed to placebo	Cut-off date
Nasopharyngeal carcinoma (NPC)	CT15 / JUPITER-02	III	146	143	18-Nov-2022
	CT5 / POLARIS-02, Cohort 3	Ib/II	190	0	19-Feb-2020
	CT5 / POLARIS-02, Cohort 7	Ib/II	12[#]	0	19-Feb-2020
Total for NPC:			**348**	**143**	
Squamous cell cancer of the oesophagus (OSCC)	CT21 / JUPITER-06	III	257	257	23-Feb-2023
	CT5 / POLARIS-02, Cohort 2	Ib/II	59	0	19-Feb-2020
	CT5 / POLARIS-02, Cohort 6	Ib/II	12[#]	0	19-Feb-2020
Total for OSCC:			**328**	**257**	
Toripalimab monotherapy	CT1	I	36	0	31-Aug-2017
	CT2	Ia	25	0	24-Jan-2018
	CT3	I	33	0	4-Jun-2019
	CT4	II	128	0	15-Mar-2018

	CT5 / POLARIS-02, Cohorts 1-4	Ib/II	92*	0	19-Feb-2020
	CT6	I	13	0	2-Dec-2018
	CT7-1	I	41	0	12-Jan-2019
	CT7-2	I	26	0	8-Nov-2018
	CT8	II	73	0	31-Mar-2021
	CT9	I	20	0	25-Oct-2018
	CT12	II	151	0	8-Sep-2020
	CT14	Ib	40	0	14-Jul-2020
	TAB001-01	I	184	0	7-Jun-2022
Total for monotherapy:			**862**	**0**	
TOTAL:			**1,538**	**400**	

* CT5 / POLARIS-02, Cohorts 1-4 – patients' numbers for cohorts 3 (N190) and 2 (N59) were added already above in NPC and OSCC sections, so here only numbers from cohorts 1 and 4 were provided.

CT5 / POLARIS-02, Cohorts 5-8 administered toripalimab 240 mg or 360 mg IV every 3 weeks (Q3W) in combination with standard first-line chemotherapy to patients who had received no prior therapy for recurrent or metastatic disease. Given the small number of patients in these trials (N = 12 in the NPC, N = 12 in the OSCC cohorts), patients in these cohorts are not included in the analyses of the safety of toripalimab in combination with chemotherapy.

NOTE: CT5 / POLARIS-02, subjects of Cohorts 1-4 were treated with toripalimab monotherapy, subjects of Cohorts 5-8 were treated with toripalimab in combination with chemotherapy.

Safety analyses were conducted in these groups:

- Toripalimab monotherapy safety database.
- Two clinical trials where patients received toripalimab in combination with chemotherapy (JUPITER-02 and JUPITER-06).
- Individually in CT15/JUPITER-02.
- Individually in CT21/JUPITER-06.

Additional/supportive information was also received from post-marketing experience, as toripalimab was first approved in China on December 27, 2018. The most recent 4th DSUR (17-Dec-2020 to 16-Dec-2021) provided data from 25,972 patient-years experience with toripalimab.

3.6.12.1. Patient exposure

Table 82. Patient exposure

Type of study	List of studies	Patients enrolled	Patients exposed to toripalimab	Patients exposed to the proposed dose range (240 mg IV Q3W)	Patients with long term* safety data
Placebo-controlled	CT15 (JUPITER-02), CT21 (JUPITER-06)	803	403	403	Not provided
Active-controlled (open)	CT8	73	73	N/A	Monotherapy: 185
Open studies	CT1, CT2, CT3, CT4, CT5, CT6, CT7-1, CT7-2, CT9, CT12, CT14, TAB001-01	1098	1098	60[1] + 166	
Post marketing	N/A	N/A	25972patient-years	N/A	No data provided

Type of study	List of studies	Patients enrolled	Patients exposed to toripalimab	Patients exposed to the proposed dose range (240 mg IV Q3W)	Patients with long term* safety data
			(toripalimab 3 mg/kg)[#]		
Compassionate use	N/A	N/A	N/A	N/A	N/A
*12 or more months continuous exposure data, or intermittent exposure. [1] Patients in Cohorts 5-8 (CT5) were exposed to 240/360 mg Q3W of toripalimab. [#] DLP 16-Dec-2021. Q3W - every 3 weeks					

Nasopharyngeal Carcinoma

The median duration of exposure to study drug (toripalimab/placebo) was substantially longer in the toripalimab than the placebo arm, 15.1 and 8.6 months, respectively. This was, in part, due to the unblinding of the trial following the interim PFS analysis and to the continuation of toripalimab in the experimental arm.

Table 83. Extent of Exposure (JUPITER-02) (DCO: 08-May-2022)

	Toripalimab + GC N = 146	Placebo + GC N = 143
Toripalimab/Placebo		
Median Duration of Exposure (range)	14.5 months (0.07- 24.1)	7.9 months (0.03- 22.6)
Median Dose Intensity[1] (range)	75.5 mg/week (11.6-82.8)	NA
Cisplatin		
Median Duration of Exposure (range)	4.2 months (0.7- 7.6)	4.2 months (0.7- 6.7)
Median Dose Intensity[1] (range)	38.2 mg/week (21-53)	37.7 mg/week (22-55)
Gemcitabine		
Median Duration of Exposure (range)	4.4 months (0.7- 7.8)	4.5 months (0.7- 6.7)
Median Dose Intensity[1] (range)	836.8 mg/week (331-1209)	845.4 mg/week (316, 1298)
GC=gemcitabine/cisplatin [1]Dose intensity = actual cumulative dose/actual duration of exposure; NA=not applicable		

The median duration of exposure to toripalimab in the 12 patients in Cohort 7 of POLARIS-02 (toripalimab and cisplatin/gemcitabine in the 1st-line treatment of NPC) was 8.6 months (range; 4.7-14.1).

Table 84. JUPITER-02: Demographics and Baseline Characteristics

	Toripalimab + GC N=146 (%)	Placebo + GC N=143 (%)
Median Age (range)	46 years (19-72)	51 years (21-72)
≥ Age 65	7 (4.8%)	7 (4.9%)
Gender		
Male	124 (84.9)	116 (81.1)
Female	22 (15.1)	27 (18.9)
Race		
Asian	146 (100)	143 (100)
ECOG Performance Status, N (%) per IWRS		
0	83 (56.8)	80 (55.9)
1	63 (43.2)	63 (44.1)
Stage at Consent (AJCC 8th Edition)		
Stage II-IVA	19 (13.0)	20 (14.0)
Stage IVB	127 (87.0)	121 (84.6)
CT15 AJCC=American Joint Commission on Cancer; IWRS= Interactive Web Response System		

Table 85. Cohorts 3 and 7 in POLARIS-02: Demographics and Baseline Characteristics (DCO: 19-Feb-2020)

Demographic and Baseline Characteristics	Cohort 3 Toripalimab Monotherapy		Cohort 7 Toripalimab + GC N=12
	PTAS N=172	Safety Set N=190	
Median Age (range)	45 years (22-68)	46 years (22-71)	46 years (30-55)
Gender, N (%)			
Male	143 (83.1)	158 (83.2)	10 (83.3)
Female	29 (16.9)	32 (16.8)	2 (16.7)
Race, N (%)			
Asian	172 (100)	190 (100)	12 (100)
ECOG Performance Status, N (%)			
0	63 (36.6)	66 (34.7)	6 (50.0)
1	109 (63.4)	124 (65.3)	6 (50.0)
Cohort 7/CT5 Tables 14.1.3.1, 14.1.4.1, GC=gemcitabine/cisplatin; PD-L1=programmed death ligand-1; PTAS=platinum-treated analysis set; UK=unknown			

Squamous Cell Carcinoma of the Oesophagus

Table 86. Extent of Exposure (JUPITER-06) (DCO: 15-Feb-2022)

	Toripalimab + TP N = 257	Placebo + TP N = 257
Toripalimab/Placebo		
Median Duration of Exposure (range)	5.1 months (0.03-25.3)	4.9 months (0.03-24.1)
Median Dose Intensity[1] (range)	76.3 mg/week (29.2-81.5)	NA
Cisplatin		
Median Duration of Exposure (range)	3.5 months (0.03-6.4)	3.5 months (0.03-5.9)
Median Dose Intensity[1] (range)	36.8 mg/week (12.0-49.5)	37.5 mg/week (17.8-51.7)
Paclitaxel		
Median Duration of Exposure (range)	3.5 months (0-6.4)	3.5 months (0.03-5.9)
Median Dose Intensity[1] (range)	87.4 mg/week (28.0-115.3)	88.7 mg/week (8.8-120.7)
[1]Dose intensity = average actual cumulative dose received per week; NA=not applicable; TP= cisplatin/paclitaxel		

The median duration of exposure in the 12 patients in Cohort 6 of POLARIS-02 (toripalimab with cisplatin/paclitaxel in the 1st-line treatment of OSCC) was 13.6 months (range; 2.2-24.5).

Table 87. JUPITER-06: Demographics and Baseline Characteristics (DCO: 22-March-2021)

Demographics and Baseline Characteristics	Toripalimab + TP N=257	Placebo + TP N=257
Median Age (range)	63 years (20-75)	62 years (40-74)
Age ≥ 65 years, N (%)	101 (39.3)	94 (36.6)
Gender, N (%)		
Male	217 (84.4)	220 (85.6)
Female	40 (15.6)	37 (14.4)
Race, N (%)		
Asian	257 (100)	257 (100)
ECOG Performance Status per IWRS, N (%)		
0	66 (25.7)	68 (26.5)
1	191 (74.3)	189 (73.5)
Baseline Disease Stage, N (%)		

Demographics and Baseline Characteristics	Toripalimab + TP N=257	Placebo + TP N=257
Recurrent	50 (19.5)	59 (23.0)
Metastatic	206 (80.2)	198 (77.0)
Unknown	1 (0.4)	0
IWRS=Interactive Web Response System; PD-L1=programmed death ligand-1; TP=paclitaxel/cisplatin		

Table 88. Cohorts 2 and 6 in POLARIS-02: Demographics and Baseline Characteristics (DCO: 19-Feb-2020)

	Cohort 2 Toripalimab Monotherapy N=59	Cohort 6 Toripalimab + TP N=12
Median Age (range)	60.0 years (42.0-73.0)	56.5 years (42-72)
Age > 65 years, N (%)	14 (23.7)	3 (25.0)
Gender, N (%)		
Male	52 (88.1)	9 (75.0)
Female	7 (11.9)	3 (25.0)
Race, N (%)		
Asian	59 (100)	12 (100)
ECOG Performance Status, N (%)		
0	6 (10.2)	5 (41.7)
1	53 (89.8)	7 (58.3)
Stage at Entry (AJCC 8th Edition)		
III	2 (3.4)	0
IV	55 (93.2)	11 (91.7)
Missing	2 (3.4)	1 (8.3)
AJCC=American Joint Commission on Cancer; TP=paclitaxel/cisplatin		

Toripalimab Monotherapy

Table 89. Extent of Exposure (Toripalimab Monotherapy Safety Database):

	Toripalimab Monotherapy Safety Database N = 1111
Median Duration of Exposure (range)	3.3 months (0.03-35.9)
≥ 6 months of Exposure	352 (31.7%)
≥ 12 months of Exposure	185 (16.7%)

The toripalimab monotherapy safety database included 184 patients treated in the US on TAB001-01 and 927 patients treated in China. TAB001-01 was a dose escalation/dose expansion trial in which 184 patients with a variety of tumour types received varying doses of toripalimab; 166 patients received toripalimab 240 mg IV Q3W. The number of patients on TAB001-01, other than those who identified as White, was small. Therefore, rather than compare TRAEs by race within TAB001-01, TAB001-01 was compared with data from 927 patients from 12 clinical trials treated in China. These patients had a variety of tumour types and received varying doses of toripalimab - 851 patients received toripalimab 3 mg/kg IV Q2W. The pharmacokinetics of toripalimab 240 mg IV Q3W and toripalimab 3 mg/kg IV Q2W are similar.

Table 90. Toripalimab Monotherapy: Demographics and Baseline Characteristics

	Western Region N = 184 (%)	Non-Western Region N = 927 (%)
Median Age (range)	62 years (21-85)	55 years (21-82)
Sex		

	Western Region N = 184 (%)	Non-Western Region N = 927 (%)
Male	104 (56.5)	595 (64.2)
Female	80 (43.5)	332 (35.8)
Race		
Asian	0	927 (100)
White	151 (82.1)	0
Black or African-American	14 (7.6)	0
Asian-American	9 (4.9)	0
American Indian/Alaskan Native	1 (0.5)	0
Native Hawaiian/Other Pacific Islander	1 (0.5)	0
Missing	8 (4.3)	0
Ethnicity		
Hispanic or Latino	14 (8.0)	0
Tumour Types		
Sarcoma	64 (34.8)	12 (1.3)
Biliary tract cancer	44 (23.9)	1 (0.1)
Gastric cancer	30 (16.3)	63 (6.8)
Neuroendocrine cancer	23 (12.5)	40 (4.3)
Oesophageal cancer	12 (6.5)	65 (7.0)
Melanoma	0	252 (27.2)
Nasopharyngeal	2 (1.1)	197 (21.3)
Urothelial cancer	0	160 (17.3)
Non-small cell lung cancer	0	48 (5.2)
Head and neck cancer	0	37 (4.0)
Hodgkin and Non-Hodgkin Lymphoma	0	24 (2.6)
Breast cancer	2 (1.1)	20 (2.2)
Other	9 (4.9)[1]	8 (0.9)2
Median Duration of Exposure (range)	1.7 months (0.03-35.9)	3.3 months (0.03-35.4)
[1]Includes ovarian cancer (N = 3), pancreatic cancer (2), adrenal cancer (1), colorectal cancer (1), endometrial cancer (1) and renal cell cancer (1).; 2Includes renal cell cancer (N = 6) and pancreatic cancer (2)		

No paediatric safety data is available for toripalimab.

1. Adverse events

In most trials, AEs were collected from the time of dosing until 60 days after the last dose of toripalimab. This ranged from 14 days (1 trial) to 90 days (5 trials).

All AEs were treatment-emergent adverse events (TEAEs), which was defined as any AE occurring from the first dose to 60 days after the last dose of study treatment or prior to start of a new systemic antitumour therapy, whichever came first (definition in CT21 CSR).

In JUPITER-02 and JUPITER-06 (toripalimab in Combination with Chemotherapy), 99.5% patients experienced TEAEs and 83.1% patients experienced TRAEs. In Toripalimab Monotherapy 97.5% patients experienced TEAEs and 77.9% patients experienced TRAEs.

Nasopharyngeal Carcinoma (JUPITER-02)

Hypothyroidism, pyrexia, diarrhoea, rash, and pruritus occurred more commonly in patients receiving toripalimab. The incidence of hypothyroidism seen in the toripalimab arm of JUPITER-02 is greater than that seen in the toripalimab arm of JUPITER-06 or in the toripalimab monotherapy safety database.

Treatment-emergent adverse events (TEAES) occurred in all patients; Grade ≥ 3 events occurred in 89.7% and 90.2% of patients in the toripalimab and placebo arms, respectively.

Table 91. Treatment-Related Adverse Events in ≥ 5% of Patients (JUPITER-02) (DCO: 08-May-2020)

	Toripalimab + GC N=146		Placebo + GC (N=143)	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Any TRAE	141 (96.6)	119 (81.5)	139 (97.2)	120 (83.9)
Blood Disorders				
Leukopenia	123 (84.2)	**83 (56.8)**	130 (90.9)	**78 (54.5)**
Neutropenia	115 (78.8)	79 (54.1)	124 (86.7)	81 (56.6)
Anaemia	**117 (80.1)**	**62 (42.5)**	**120 (83.9)**	**50 (35.0)**
Thrombocytopenia	**87 (59.6)**	**43 (29.5)**	**81 (56.6)**	**39 (27.3)**
Lymphopenia	13 (8.9)	11 (7.5)	15 (10.5)	9 (6.3)
Endocrine Disorders				
Hypothyroidism	**48 (32.9)**	1 (0.7)	**25 (17.5)**	0
Gastrointestinal Disorders				
Nausea	89 (61.0)	1 (0.7)	108 (75.5)	3 (2.1)
Vomiting	85 (58.2)	1 (0.7)	86 (60.1)	3 (2.1)
Constipation	50 (34.2)	0	51 (35.7)	0
Diarrhoea	37 (25.3)	2 (1.4)	33 (23.1)	0
Stomatitis	27 (18.5)	0	22 (15.4)	1 (0.7)
Abdominal pain	21 (14.4)	0	14 (9.8)	0
Abdominal distension	12 (8.2)	0	8 (5.6)	0
Dry mouth	10 (6.8)	0	7 (4.9)	0
Toothache	8 (5.5)	0	3 (2.1)	0
General Disorders				
Fatigue	47 (32.2)	2 (1.4)	41 (28.7)	0
Pyrexia	**42 (28.8)**	2 (1.4)	**30 (21.0)**	1 (0.7)
Oedema	9 (6.2)	0	14 (9.8)	0
Chest discomfort	8 (5.5)	0	9 (6.3)	0
Hepatobiliary Disorders				
Hepatic function abnormal	12 (8.2)	**3 (2.1)**	10 (7.0)	**4 (2.8)**
Infections				
Upper respiratory tract infection	**27 (18.5)**	4 (2.7)	**12 (8.4)**	1 (0.7)
Pneumonia	**20 (13.7)**	14 (9.6)	**7 (4.9)**	4 (2.8)
Investigations				
Alanine aminotransferase increased	53 (36.3)	1 (0.7)	53 (37.1)	0
Aspartate aminotransferase increased	**53 (36.3)**	1 (0.7)	**44 (30.8)**	2 (1.4)
Blood creatinine increased	25 (17.1)	1 (0.7)	27 (18.9)	0
Weight decreased	12 (8.2)	0	10 (7.0)	0
Thyroid function test abnormal	9 (6.2)	0	9 (6.3)	0
Metabolism and Nutrition				
Decreased appetite	70 (47.9)	1 (0.7)	77 (53.8)	0
Hyponatraemia	31 (21.2)	8 (5.5)	49 (34.3)	6 (4.2)
Hypokalaemia	31 (21.2)	11 (7.5)	34 (23.8)	11 (7.7)
Hypochloraemia	21 (14.4)	2 (1.4)	36 (25.2)	0
Hyperuricaemia	15 (10.3)	0	15 (10.5)	0
Hypoproteinaemia	17 (11.6)	1 (0.7)	13 (9.1)	0
Hypomagnesaemia	9 (6.2)	3 (2.1)	17 (11.9)	6 (4.2)
Musculoskeletal Disorders				
Musculoskeletal pain	25 (17.1)	0	29 (20.3)	0
Nervous System Disorders				
Peripheral neuropathy	42 (28.8)	0	41 (28.7)	1 (0.7)
Dizziness	29 (19.9)	0	24 (16.8)	0
Headache	18 (12.3)	0	24 (16.8)	0
Psychiatric Disorders				
Insomnia	25 (17.1)	0	21 (14.7)	0
Renal Disorders				
Haematuria	8 (5.5)	0	3 (2.1)	0
Respiratory Disorders				
Cough	36 (24.7)	0	31 (21.7)	0
Epistaxis	12 (8.2)	3 (2.1)	16 (11.2)	4 (2.8)
Rhinorrhea	12 (8.2)	0	10 (7.0)	0

	Toripalimab + GC N=146		Placebo + GC (N=143)	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Skin Disorders				
Rash	**47 (32.2)**	5 (3.4)	**30 (21.0)**	2 (1.4)
Pruritus	**23 (15.8)**	0	**10 (7.0)**	0
Vascular Disorders				
Hypertension	8 (5.6)	5 (3.4)	7 (4.9)	6 (4.2)

TRAEs that occurred more commonly in the toripalimab arm (between arm difference of ≥ 5% for all Grades or ≥ 2% for Grade ≥3) are shown in bold.

In Cohort 7 of POLARIS-02, TRAEs occurred in 91.7% and Grade ≥ 3 TRAEs in 58.3% of patients. TRAEs of any grade that occurred in > 2 patients included leukopenia, neutropenia, thrombocytopenia, anaemia, hypothyroidism, nausea, upper respiratory infection, vomiting, asthenia, chills, dizziness, hiccups, and pruritus.

Squamous Cell Cancer of the Oesophagus (JUPITER-06)

The most common TRAEs occurring at a higher incidence in the toripalimab arm, were cytopenias, fatigue, rash, decreased appetite, hypothyroidism, and nausea. TRAEs such as thyroid function test abnormal, rash, and pruritus have also been reported with other PD-1 blocking antibodies. Increased AST, but not ALT, also occurred at a higher incidence in the toripalimab arm. However, the incidence of Grade ≥ 3 TRAEs were generally similar between arms.

Table 92. Treatment-Related Adverse Events in ≥ 5% of Patients (JUPITER-06) (DCO: 15-Feb-2022)

	Toripalimab + TP N=257 (%)		Placebo + TP N=257 (%)	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Any	194 (75.5)	64 (24.9)	163 (63.4)	35 (13.6)
Blood Disorders				
Anaemia	**64 (24.9)**	**11 (4.3)**	**46 (17.9)**	**10 (3.9)**
Leukopenia	**45 (17.5)**	**8 (3.1)**	**28 (10.9)**	**8 (3.1)**
Neutropenia	**42 (16.3)**	**19 (7.4)**	**23 (8.9)**	**12 (4.7)**
Thrombocytopenia	**35 (13.6)**	**2 (0.8)**	**12 (4.7)**	**1 (0.4)**
Cardiac Disorders				
Arrhythmia	16 (6.2)	0	7 (2.7)	0
Endocrine Disorders				
Hypothyroidism	26 (10.1)	0	14 (5.4)	0
Gastrointestinal Disorders				
Nausea	26 (10.1)	0	18 (7.0)	1 (0.4)
Vomiting	24 (9.3)	2 (0.8)	17 (6.6)	2
Diarrhoea	18 (7.0)	1 (0.4)	9 (3.5)	0
Constipation	17 (6.6)	0	10 (3.9)	0
General Disorders				
Fatigue	48 (18.7)	4 (1.6)	42 (16.3)	0
Pyrexia	13 (5.1)	0	10 (3.9)	0
Investigations				
AST increased	**23 (8.9)**	1 (0.4)	**10 (3.9)**	0
Thyroid function test abnormal	**23 (8.9)**	0	**10 (3.9)**	0
ALT increased	22 (8.6)	1 (0.4)	11 (4.3)	0
Weight decreased	13 (5.1)	1 (0.4)	10 (3.9)	1
Metabolism and Nutrition				
Decreased appetite	26 (10.1)	1 (0.4)	26 (10.1)	2 (0.8)
Hyperglycaemia	17 (6.6)	0	13 (5.1)	0
Nervous System Disorders				

	Toripalimab + TP N=257 (%)		Placebo + TP N=257 (%)	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Peripheral neuropathy	16 (6.2)	1	9 (3.5)	1
Skin Disorders				
Rash	**49 (19.1)**	**7 (2.7%)**	**19 (7.4)**	**0**
Pruritus	**23 (8.9)**	1 (0.4)	**7 (2.7)**	0
AST=aspartate aminotransferase				

In Cohort 6 of POLARIS-02, TRAEs occurred in 83.3% and Grade ≥ 3 events in 50.0% of patients. All grade TRAEs in > 2 patients included anaemia, cough, decreased appetite, hypoaesthesia, rash, alopecia, proteinuria, and pruritus.

Comparison of Treatment-Emergent and Treatment-Related Events in JUPITER-02 and JUPITER-06.

Table 93. TEAEs and TRAEs in ≥ 5% of Patients (Toripalimab in combination with chemotherapy in JUPITER-02 and JUPITER-06), (DCO for JUPITER-02: 08-May-2022 and DCO for JUPITER-06: 15-Feb-2022)

	Toripalimab in Combination with Chemotherapy[1] N = 403 (%)	
	Treatment-Related	**Treatment-Emergent**
Any	335 (83.1)	401 (99.5)
Blood Disorders		
Anaemia	181 (44.9)	335 (83.1)
Leukopenia	168 (41.7)	308 (76.4)
Neutropenia	157 (39.0)	299 (74.2)
Thrombocytopenia	122 (30.3)	170 (42.2)
Cardiac Disorders		
Arrhythmia	22 (5.5)	38 (9.4)
Endocrine Disorders		
Hypothyroidism	74 (18.4)	82 (20.3)
Gastrointestinal Disorders		
Nausea	120 (29.8)	222 (55.1)
Vomiting	110 (27.3)	207 (51.4)
Constipation	67 (16.6)	128 (31.8)
Colitis	57 (14.1)	107 (26.6)
Stomatitis	33 (8.2)	50 (12.4)
Abdominal pain	29 (7.2)	61 (15.1)
Abdominal distension	18 (4.5)	33 (8.2)
Dry mouth	15 (3.7)	29 (7.2)
Dysphagia	1 (0.2)	25 (6.2)
General Disorders		
Fatigue	95 (23.6)	164 (40.7)
Pyrexia	55 (13.6)	89 (22.1)
Pain	20 (5.0)	56 (13.9)
Hepatobiliary Disorder		
Hepatitis	23 (5.7)	28 (6.9)
Hyperbilirubinaemia	14 (3.5)	21 (5.2)
Infections		
Upper respiratory infection	29 (7.2)	61 (15.1)
Pneumonia	25 (6.2)	53 (13.2)
Investigations		
Liver function tests abnormal	90 (22.3)	116 (28.8)
Creatinine clearance decreased	45 (11.2)	85 (21.1)
Thyroid function tests abnormal	32 (7.9)	36 (8.9)

	Toripalimab in Combination with Chemotherapy[1] N = 403 (%)	
	Treatment-Related	**Treatment-Emergent**
Lymphocytes decreased	20 (5.0)	45 (11.2)
Blood urea increased	11 (2.7)	26 (6.5)
Lipids abnormal	11 (2.7)	33 (8.2)
Metabolism and Nutrition		
Decreased appetite	96 (23.8)	184 (45.7)
Hyponatraemia	41 (10.2)	82 (20.3)
Hypokalaemia	40 (9.9)	80 (19.9)
Hypoproteinaemia	29 (7.2)	85 (21.1)
Hypochloraemia	25 (6.2)	50 (12.4)
Weight decreased	25 (6.2)	91 (22.6)
Hyperglycaemia	23 (5.7)	39 (9.7)
Hyperuricaemia	23 (5.7)	44 (10.9)
Hypomagnesaemia	16 (4.0)	44 (10.9)
Hypocalcaemia	6 (1.6)	23 (5.7)
Musculoskeletal Disorders		
Musculoskeletal pain	40 (9.9)	115 (28.5)
Nervous System Disorders		
Neuropathy	61 (15.1)	120 (29.8)
Dizziness	30 (7.4)	45 (11.2)
Headache	20 (5.0)	34 (8.4)
Neurotoxicity	1 (0.2)	32 (7.9)
Psychiatric Disorders		
Sleep disorders	31 (7.7)	65 (16.1)
Renal Disorders		
Haematuria	11 (2.7)	21 (5.2)
Proteinuria	11 (2.7)	23 (5.7)
Respiratory Disorders		
Cough	46 (11.4)	100 (24.8)
Upper respiratory tract disorders	16 (4.0)	23 (5.7)
Pneumonitis	15 (3.7)	26 (6.5)
Skin Disorders		
Rash	96 (23.8)	113 (28.0)
Pruritus	46 (11.4)	57 (14.1)
Alopecia	10 (2.5)	98 (24.3)
Vascular Disorders		
Hypertension	11 (2.7)	34 (8.4)

Comparison of Treatment-Emergent and Treatment-Related Events in Toripalimab Monotherapy Safety Database

Table 94. TEAEs and TRAEs in ≥ 5% of Patients (Toripalimab Monotherapy Safety Database)

	Toripalimab Monotherapy Safety Database N = 1111 (%)	
	Treatment-Related	**Treatment-Emergent**
Any	865 (77.9)	1083 (97.5)
Blood Disorders		
Leukopenia	138 (12.4)	191 (17.2)
Anaemia	106 (9.5)	381 (34.3)
Neutropenia	92 (8.3)	121 (10.9)
Thrombocytopenia	34 (3.1)	60 (5.4)
Leucocytosis	10 (0.9)	81 (7.3)
Cardiac Disorders		
Arrhythmia	45 (4.1)	185 (16.7)
Endocrine Disorders		

	Toripalimab Monotherapy Safety Database N = 1111 (%)	
	Treatment-Related	**Treatment-Emergent**
Hypothyroidism	155 (14.0)	173 (15.6)
Hyperthyroidism	76 (6.8)	77 (6.9)
Gastrointestinal Disorders		
Colitis	52 (4.7)	115 (10.4)
Nausea	52 (4.7)	160 (14.4)
Stomatitis	26 (2.3)	89 (8.0)
Vomiting	26 (2.3)	102 (9.2)
Abdominal pain	21 (1.9)	157 (14.1)
Constipation	20 (1.8)	165 (14.9)
Abdominal distension	8 (0.7)	60 (5.4)
General Disorders		
Fatigue	173 (15.6)	283 (25.5)
Pyrexia	76 (6.8)	194 (17.5)
Pain	26 (2.3)	110 (9.9)
Oedema	14 (1.3)	92 (8.3)
Hepatobiliary Disorders		
Hyperbilirubinaemia	106 (9.5)	168 (15.1)
Infections		
Pneumonia	20 (1.8)	62 (5.6)
Upper respiratory tract infection	15 (1.4)	185 (16.7)
Urinary tract infection	9 (0.8)	80 (7.2)
Investigations		
Thyroid function test abnormal	234 (21.1)	262 (23.6)
Liver function test abnormal	207 (18.6)	332 (29.9)
Creatine phosphokinase abnormal	90 (8.1)	98 (8.8)
Lipids abnormal	86 (7.7)	211 (19.0)
Amylase increased	78 (7.0)	91 (8.2)
Urinalysis abnormal	26 (2.3)	212 (19.1)
Creatinine clearance decreased	25 (2.3)	66 (5.9)
Alkaline phosphatase increased	23 (2.1)	66 (5.9)
Lactate dehydrogenase increased	22 (2.0)	93 (8.4)
Metabolism and Nutrition		
Hyperglycaemia	104 (9.4)	185 (16.7)
Decreased appetite	77 (6.9)	188 (16.9)
Weight decreased	35 (3.2)	158 (14.2)
Hyponatremia	27 (2.4)	170 (15.3)
Hypoproteinaemia	20 (1.8)	145 (13.1)
Hyperuricaemia	16 (1.4)	114 (10.3)
Hypokalaemia	15 (1.4)	108 (9.7)
Hypochloraemia	11 (1.0)	90 (8.1)
Musculoskeletal Disorders		
Musculoskeletal pain	41 (3.7)	274 (24.7)
Nervous System Disorders		
Dizziness	21 (1.9)	68 (6.1)
Neuropathy	21 (1.9)	61 (5.5)
Psychiatric Disorders		
Sleep disorders	7 (0.6)	80 (7.2)
Renal Disorders		
Proteinuria	100 (9.0)	264 (23.8)
Haematuria	21 (1.9)	162 (14.6)
Respiratory Disorders		
Cough	34 (3.1)	222 (20.0)
Dyspnoea	16 (1.4)	80 (7.2)
Skin Disorders		
Rash	161 (14.5)	188 (16.9)
Pruritus	116 (10.4)	138 (12.4)

	Toripalimab Monotherapy Safety Database N = 1111 (%)	
	Treatment-Related	Treatment-Emergent
Vascular Disorders		
Hypertension	14 (1.3)	71 (6.4)

TRAEs in ≥ 5% of Patients

Table 95. Treatment-Related Adverse Events in ≥ 5% of Patients (Toripalimab Monotherapy Safety Database and Toripalimab in Combination with Chemotherapy)

	Toripalimab Monotherapy Safety Database N = 1111 (%)		Toripalimab in Combination with Chemotherapy N = 403 (%)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any	865 (77.9)	162 (14.6)	355 (83.1)	183 (45.4)
Blood Disorders				
Leukopenia	138 (12.4)	3 (0.3)	168 (41.7)	91 (22.6)
Anaemia	106 (9.5)	7 (0.6)	181 (44.9)	73 (18.1)
Neutropenia	92 (8.3)	8 (0.7)	157 (39.0)	98 (24.3)
Thrombocytopenia	34 (3.1)	6 (0.5)	122 (30.3)	45 (11.2)
Cardiac Disorders				
Arrhythmia	45 (4.1)	0	22 (5.5)	0
Endocrine Disorders				
Hypothyroidism	155 (14.0)	0	74 (18.4)	1 (0.2)
Hyperthyroidism	76 (6.8)	1 (0.1)	13 (3.2)	0
Gastrointestinal Disorders				
Colitis	52 (4.7)	1 (0.1)	57 (14.1)	4 (1.0)
Nausea	52 (4.7)	1 (0.1)	120 (29.8)	1 (0.2)
Stomatitis	26 (2.3)	1 (0.1)	33 (8.2)	0
Vomiting	26 (2.3)	3 (0.3)	110 (27.3)	3 (0.7)
Abdominal pain	21 (1.9)	1 (0.1)	29 (7.2)	1 (0.2)
Constipation	20 (1.8)	0	67 (16.6)	0
General Disorders				
Fatigue	173 (15.6)	6 (0.5)	95 (23.6)	6 (1.5)
Pyrexia	76 (6.8)	0	55 (13.6)	2 (0.5)
Pain	26 (2.3)	0	20 (5.0)	0
Hepatobiliary Disorders				
Hyperbilirubinaemia	106 (9.5)	3 (0.3)	14 (3.5)	0
Hepatitis	28 (2.5)	8 (0.7)	23 (5.7)	7 (1.7)
Infections				
Pneumonia	20 (1.8)	10 (0.9)	25 (6.2)	18 (4.5)
Upper respiratory tract infection	15 (1.4)	1 (0.1)	29 (7.2)	4 (1.0)
Investigations				
Thyroid function test abnormal	234 (21.1)	0	32 (7.9)	0
Liver function test abnormal	207 (18.6)	13 (1.2)	90 (22.3)	4 (1.0)
Creatine phosphokinase abnormal	90 (8.1)	9 (0.8)	9 (3.9)	0
Lipids abnormal	86 (7.7)	8 (0.7)	11 (2.7)	1 (0.2)
Amylase increased	78 (7.0)	9 (0.8)	0	
Urinalysis abnormal	26 (2.3)	1 (0.1)	10 (6.9)	0
Creatinine clearance decreased	25 (2.3)	1 (0.1)	45 (11.2)	2 (0.5)
Alkaline phosphatase increased	23 (2.1)	1 (0.1)	5 (4.1)	0
Lactate dehydrogenase increased	22 (2.0)	1 (0.1)	4 (2.5)	0
Lymphocytes abnormal	30 (2.7)	4 (0.4)	20 (5.0)	15 (3.7)
Metabolism and Nutrition				
Hyperglycaemia	104 (9.4)	5 (0.5)	23 (5.7)	0
Decreased appetite	77 (6.9)	1 (0.1)	96 (23.8)	2 (0.5)

	Toripalimab Monotherapy Safety Database N = 1111 (%)		Toripalimab in Combination with Chemotherapy N = 403 (%)	
Weight decreased	35 (3.2)	1 (0.1)	25 (6.2)	1 (0.2)
Hyponatremia	27 (2.4)	11 (1.0)	41 (10.2)	10 (2.5)
Hypoproteinaemia	20 (1.8)	0	29 (7.2)	1 (0.2)
Hyperuricaemia	16 (1.4)	1 (0.1)	23 (5.7)	0
Hypokalaemia	15 (1.4)	3 (0.3)	40 (9.9)	12 (3.0)
Hypochloraemia	11 (1.0)	4 (0.4)	25 (6.2)	2 (0.5)
Musculoskeletal Disorders				
Musculoskeletal pain	41 (3.7)	1 (0.1)	40 (9.9)	1 (0.2)
Nervous System Disorders				
Dizziness	21 (1.9)	0	30 (7.4)	0
Neuropathy	21 (1.9)	1 (0.1)	61 (15.1)	2 (0.5)
Headache	12 (1.1)	0	20 (5.0)	0
Psychiatric Disorders				
Sleep disorders	7 (0.6)	1 (0.1)	31 (7.7)	0
Renal Disorders				
Proteinuria	100 (9.0)	1 (0.1)	11 (2.7)	0
Haematuria	21 (1.9)	0	11 (2.7)	1 (0.2)
Respiratory Disorders				
Cough	34 (3.1)	0	46 (11.4)	0
Skin Disorders				
Rash	161 (14.5)	3 (0.3)	96 (23.8)	12 (3.0)
Pruritus	116 (10.4)	1 (0.1)	46 (11.4)	1 (0.2)

Table 96. TRAEs by Region in ≥ 5% of patients (Toripalimab Monotherapy

	Western Region N = 184 (%)	Non-Western Region N = 927 (%)
	All Grades	**All Grades**
Any	110 (59.8)	755 (81.4)
Blood Disorders		
Leukopenia	**2 (1.1)**	**136 (14.7)**
Anaemia	**7 (3.8)**	**99 (10.7)**
Neutropenia	**1 (0.5)**	**91 (9.8)**
Endocrine Disorders		
Hypothyroidism	**10 (5.4)**	**145 (15.6)**
Hyperthyroidism	9 (4.9)	67 (7.2)
General Disorders		
Fatigue	25 (13.6)	148 (16.0)
Pyrexia	6 (3.3)	70 (7.6)
Hepatobiliary Disorders		
Hyperbilirubinaemia	**4 (2.2)**	**102 (11.0)**
Investigations		
Thyroid function test abnormal	**0**	**234 (25.2)**
Liver function test abnormal	**21 (11.4)**	**186 (20.1)**
Creatine phosphokinase abnormal	**0**	**90 (9.7)**
Lipids abnormal	**0**	**86 (9.3)**
Amylase increased	**4 (2.2)**	**74 (8.0)**
Metabolism and Nutrition		
Hyperglycaemia	**2 (1.1)**	**102 (11.0)**
Decreased appetite	10 (5.4)	67 (7.2)
Renal Disorders		
Proteinuria	**3 (1.6)**	**97 (10.5)**
Skin Disorders		
Rash	**17 (9.2)**	**144 (15.5)**
Pruritus	**10 (5.4)**	**106 (11.4)**

The incidence of TRAEs is higher in patients treated in non-Western regions.

Table 97. Comparison of Laboratory Abnormalities in US and Non-Western Regions (Toripalimab Monotherapy)

	Western Regions		Non-Western Regions	
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Leukopenia	**17 (9.3)**	**0**	**181 (19.9)**	**2 (0.2)**
Anaemia	64 (35.2)	12 (6.6)	344 (37.8)	67 (7.4)
Neutropenia	**10 (5.5)**	**2 (1.1)**	**125 (14.4)**	**10 (1.2)**
Increased bilirubin	**36 (19.7)**	**9 (4.9)**	**141 (15.5)**	**17 (1.9)**
AST Increased	**61 (33.3)**	**9 (4.9)**	**223 (24.5)**	**25 (2.8)**
ALT Increased	48 (26.2)	3 (1.6)	224 (24.6)	15 (1.7)
Proteinuria	**47 (29.6)**	**1 (0.6)**	**381 (42.5)**	**5 (0.6)**
MedDRA v21 NCI CTCAE v4.03				

Immune-related AEs

Immune-related adverse events are the most clinically significant ones in patients treated with PD-1 blocking antibodies. They occur due to the underlying mechanism of action of the drug, i.e., activation of the immune system. To screen for irAEs, TEAEs were matched to a pre-defined set of MedDRA preferred terms. All Grade 1-2 AEs treated with topical or systemic corticosteroids or other immunosuppressants and all Grade ≥ 3 AEs were then reviewed. In addition, all SAEs, events designated as irAEs by the investigator, Grade 1-2 endocrine events, and Grade 1-2 reports of interstitial lung disease were reviewed. The review was conducted by two physicians employed by the sponsor. If the two physicians differed as to whether an event was an irAE, a second assessment was conducted by a senior physician to determine if the event should be considered an irAE.

The overall incidence of irAEs was higher in JUPITER-02, compared with JUPITER-06.

Table 98. Sponsor-Adjudicated Immune-Related Adverse Events (JUPITER-02 and JUPITER-06)

	JUPITER-02[1] N = 146 (%)		**JUPITER-06[1] N = 257 (%)**	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Any irAE	60 (41.1)	10 (6.8)	75 (29.2)	21 (8.2)
Immune-related Pneumonitis	3 (2.1)	0	10 (3.9)	2 (0.8)
Immune-related Colitis	0	0	3 (1.2)	2 (0.8)
Immune-related Hepatitis	2 (1.4)	2 (1.4)	6 (2.3)	5 (2.0)
Immune-related Endocrinopathies				
Hypothyroidism[2]	44 (30.1)	0	25 (9.7)	0
Hyperthyroidism	2 (1.4)	0	6 (2.3)	0
Diabetes mellitus/Hyperglycaemia	0	0	1 (0.4)	1 (0.4)
Adrenal insufficiency	0	0	1 (0.4)	1 (0.4)
Thyroiditis	3 (2.1)	0	5 (1.9)	0
Hypophysitis	1 (0.7)	0	0	0
Immune-related Nephritis	1 (0.7)	1 (0.7)	0	0
Immune-related Skin Reactions	13 (8.9)	5 (3.4)	25 (9.7)	7 (2.7)
Immune-related Myocarditis	1 (0.7)	1 (0.7)	2 (0.8)	2 (0.8)
Immune-related Myositis	1 (0.7)	1 (0.7)	1 (0.4)	1 (0.4)
Other irAEs				
Platelet Count Decreased	4 (2.7)	4 (2.7)	3 (1.2)	0
Arthralgia	0	0	1 (0.4)	1 (0.4)
Cystitis	1 (0.7)	0	1 (0.4)	1 (0.4)
Thyroid disorder[2]	0	0	1 (0.4)	0
[1]Data cut-off was May 8, 2022 for JUPITER-02 and February 15, 2022 for JUPITER-06.				

	JUPITER-02[1] N = 146 (%)	JUPITER-06[1] N = 257 (%)
[2]Two patients (1071013, 1010017) were reported to have thyroid disorder. One (1010017) was diagnosed with hypothyroidism later had a low total T4 (reported as thyroid disorder). This patient is counted once as hypothyroidism. The other (1071013) had a minimally elevated total T4 and normal free T4 that was not treated. Hyper or hypothyroidism were never reported. This is included as thyroid disorder among the other irAEs.		

The most clinically significant irAEs were:

- Immune-related Pneumonitis
    - Toripalimab in Combination with Chemotherapy

Immune-related pneumonitis occurred in 13 (3.2%) patients with no Grade 4-5, 2 (0.5%) Grade 3, and 7 (1.7%) Grade 2 events. Among the 10 patients with oesophageal cancer on JUPITER-06 who developed pneumonitis, only 1 had received prior radiation therapy. Median time to onset was 5.4 months (range; 1.3-16.6). Corticosteroids were administered to 9/13 (69.2%) patients. Permanent discontinuation of toripalimab occurred in 3 (0.7%) patients and 5 (1.2%) patients interrupted dosing.

- Immune-related Colitis
    - Toripalimab in Combination with Chemotherapy

Immune-related colitis occurred in 3 (0.7%) patients with no Grade 4-5, 2 (0.5%) Grade 3 and 1 (0.2%) Grade 2 events. Median time to onset was 3.7 months (range; 1.5-5.1). Corticosteroids were administered to 2/3 (66.7%) patients. Permanent discontinuation of toripalimab occurred in 2 (0.5%) patients and dose interruption in 1 (0.2%) patient.

- Immune-related Hepatitis
    - Toripalimab in Combination with Chemotherapy

Immune-related hepatitis occurred in 8 (2.0%) patients with no Grade 5, 2 (0.5%) Grade 4, 5 (1.2%) Grade 3, and 1 (0.2%) Grade 2 events. The median time to onset was 4.0 months (range; 21 days-22.7 months). Corticosteroids were administered to 7/8 (87.5%) patients. Permanent discontinuation of toripalimab occurred in 5 (1.2%) patients and 2 (0.5%) patients interrupted dosing.

One patient (1007012) on JUPITER-06 developed concomitant increases in bilirubin, ALT and AST. The results of this patient's viral panel were unclear (HBsAg negative but HBcAb, HBeAg, and HBeAb positive). The patient received corticosteroids with normalization of bilirubin, AST and ALT, strongly suggesting immune-mediated hepatitis. The patient permanently discontinued toripalimab due to this adverse event.

- Immune-related Endocrine Disorders

Adrenal Insufficiency

    - Toripalimab in Combination with Chemotherapy

Immune-related adrenal insufficiency occurred in 1 (0.2%) patient with no Grade 4-5, 1 (0.2%) Grade 3, and no Grade 2 event. Time to onset was 2.0 months. Corticosteroids were administered and the patient permanently discontinued toripalimab.

Hypophysitis

    - Toripalimab in Combination with Chemotherapy

Immune-related hypophysitis occurred in 1 (0.2%) patient with no Grade 3-5 and 1 (0.2%) Grade 2 event. Time to onset was 23.7 months. Corticosteroids were administered and the patient did not permanently discontinue toripalimab or interrupt dosing.

Thyroid Disease

- Toripalimab in Combination with Chemotherapy

Immune-related hypothyroidism occurred in 69 (17.1%) patients with no Grade 3-5 and 46 (11.4%) Grade 2 events. Median time to onset was 5.9 months (range; 1.2-20.7). No patient received corticosteroids and no patient permanently discontinued toripalimab. Five (1.2%) patients interrupted toripalimab.

Immune-related hyperthyroidism occurred in 8 (2.0%) patients with no Grade 2-5 events. Median time to onset was 6.5 months (range; 1.5-12.5). No patient received corticosteroids and no patient discontinued or interrupted toripalimab.

Immune-related thyroiditis occurred in 8 (2.0%) patients with no Grade 3-5, 4 Grade 2 (1.0%) and 4 Grade 1 (1.0%) events. Median time to onset was 5.9 months (range; 21 days-13.5 months). Corticosteroids were administered to 1/8 (12.5%) patients. Permanent discontinuation of toripalimab occurred in 1 (0.2%) patient and 1 (0.2%) patient interrupted dosing.

Diabetes Mellitus

- Toripalimab in Combination with Chemotherapy

Immune-related diabetes mellitus or hyperglycaemia occurred in 1 (0.2%) patient with no Grade 4-5, 1 (0.2%) Grade 3, and no Grade 2 events. The time to onset was 20 days. No patient received corticosteroids and no patient permanently discontinued or interrupted toripalimab for immune-related diabetes mellitus or hyperglycaemia.

- Immune-related Nephritis
  - Toripalimab in Combination with Chemotherapy

Immune-related nephritis occurred in 1 (0.2%) patient with no Grade 5, 1 (0.2%) Grade 4, and no Grade 2-3 events. Time to onset was 18.2 months. Corticosteroids were administered to this patient. The patient permanently discontinued toripalimab and did not interrupt dosing prior to discontinuation.

- Immune-related Skin Disorders
  - Toripalimab in Combination with Chemotherapy

Immune-related skin disorders occurred in 38 (9.4%) patients with no Grade 4-5, 12 (3.0%) Grade 3, and 8 (2.0%) Grade 2 events. Median time to onset was 1.0 month (range; 3 days-23.1 months). Systemic corticosteroids were administered to 7 (18.4%) patients and topical corticosteroids to 8 (21.1%) patients. Permanent discontinuation of toripalimab occurred in 6 (1.5%) patients and interruption in 6 (1.5%) patients.

- Immune-related Myocarditis
  - Toripalimab in Combination with Chemotherapy

Immune-related myocarditis occurred in 3 (0.7%) patients with no Grade 5, 2 (0.5%) Grade 4, and 1 (0.2%) Grade 3 event. Median time to onset was 1.7 months (range; 1.4-4.1). All 3 patients received corticosteroids. One patient received infliximab and mycophenolate mofetil while another received only mycophenolate mofetil in additional to corticosteroids. One patient died due to thrombocytopenia with intracranial haemorrhage (see description below under thrombocytopenia) and the other 2 patients permanently discontinued toripalimab. No patient interrupted dosing.

- Immune-related Myositis
  - Toripalimab in Combination with Chemotherapy

Immune-related myositis occurred in 2 (0.5%) patients with no Grade 4-5, 2 (0.5%) Grade 3, and no Grade 2 events. Median time to onset 2.5 months (range; 1.2-3.9). Corticosteroids were administered

to both patients. One patient with myositis, myocarditis, and thrombocytopenia received infliximab and mycophenolate mofetil in additional to corticosteroids. This patient died due to thrombocytopenia with intracranial haemorrhage (description under thrombocytopenia). The other patient permanently discontinued toripalimab. No patient interrupted dosing prior to discontinuation.

There was a higher incidence of irAEs leading to permanent discontinuation or dose interruption with toripalimab in combination with chemotherapy as compared to toripalimab monotherapy. Immune-related adverse events leading to permanent discontinuation occurred in 38 (3.4%) patients and dose interruption occurred in 36 (3.2%) patients in the toripalimab monotherapy safety database. In patients receiving toripalimab in combination with chemotherapy, 24 (6.0%) patients permanently discontinued due to an irAE while 19 (4.7%) interrupted dosing. Based on these differences, a decision was made to not pool data from toripalimab in combination with chemotherapy and the toripalimab monotherapy database in the evaluation of irAEs.

Table 99. Sponsor-Adjudicated Immune-Related Adverse Events (All Treated Patients)

	Toripalimab in Combination with Chemotherapy N=403 (%)		**Toripalimab Monotherapy N = 1111 (%)**	
	All Grades	**Grade > 3**	**All Grades**	**Grade > 3**
Any irAE	135 (33.5)	31 (7.7)	292 (26.3)	67 (6.1)
Immune-related pneumonitis	13 (3.2)	2 (0.5)	26 (2.3)	10 (0.9)
Immune-related colitis	3 (0.7)	2 (0.5)	4 (0.4)	2 (0.2)
Immune-related hepatitis	8 (2.0)	7 (1.7)	36 (3.2)	31 (2.8)
Immune-related endocrinopathies				
Hypothyroidism[1]	69 (17.1)	0	154 (13.9)	1 (0.1)
Hyperthyroidism	8 (2.0)	0	70 (6.3)	1 (0.1)
Thyroiditis	8 (2.0)	0	5 (0.5)	0
Diabetes mellitus/Hyperglycaemia	1 (0.2)	1 (0.2)	8 (0.7)	7 (0.6)
Adrenal insufficiency	1 (0.2)	1 (0.2)	7 (0.6)	0
Hypophysitis	1 (0.2)	0	5 (0.5)	2 (0.2)
Immune-related nephritis	1 (0.2)	1 (0.2)	6 (0.5)	5 (0.5)
Immune-related skin reactions	38 (9.4)	12 (3.0)	43 (3.9)	5 (0.5)
Immune-related myocarditis	3 (0.7)	3 (0.7)	4 (0.4)	2 (0.2)
Immune-related myositis	2 (0.5)	2 (0.5)	5 (0.5)	3 (0.3)
Immune-related pancreatitis[2]	0	0	7 (0.6)	1 (0.1)
Other irAEs				
Platelet count decreased	7 (1.7)	4 (1.0)	2 (0.2)	2 (0.2)
Arthralgia	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Uveitis	0	0	1 (0.1)	1 (0.1)
Iritis	0	0	1 (0.1)	1 (0.1)
Cystitis	2 (0.5)	1 (0.2)	0	0
Serum sickness/IRR	0	0	1 (0.1)	1 (0.1)
Pancytopenia	0	0	1 (0.1)	1 (0.1)
Thyroid disorder[1]	1 (0.2)1	0	0	0

[1]Two patients (1071013, 1010017) were reported to have thyroid disorder. One (1010017) diagnosed with hypothyroidism later had a low total T4 (reported as thyroid disorder). This patient is counted once as hypothyroidism. The other (1071013) had a minimally elevated total T4 and normal free T4 and was not treated. Hyper/hypothyroidism were never reported. This patient is included as thyroid disorder among the Other irAEs.
[2]One patient included in Other irAEs as lipase increased was grouped with immune-related pancreatitis.
IRR=infusion-related reaction

TEAE of Special Interest (AESI)

AESIs were limited to suspected cases of immune-related myocarditis and cases of abnormal liver function tests that met the criteria of Hy's Law. Per investigator assessment, 1 patient in the

toripalimab group was identified as having immune-related myocarditis and 1 patient in placebo group was identified with an event of hepatic function abnormal that met the criteria of Hy's Law.

Infusion-related reactions (IRRs)

Toripalimab plus Chemotherapy

IRRs occurred in 4.0% of toripalimab and in 3.8% of placebo patients. The majority of the events were Grade 1-2. Grade 3 and 4 events recorded in 2 patients, one per each. They both occurred with the 2nd dose of toripalimab and resolved with treatment. These patients permanently discontinued toripalimab.

Long-term exposure

Patients who remain on toripalimab for a long period are less likely to have TRAEs than the study population in general. TRAEs that occurred in patients who had received at least 1 year of treatment in the toripalimab monotherapy safety database are listed in the table below. The most common events (≥ 10%) were abnormal thyroid function tests, abnormal lipid levels, and leukopenia. Thyroid disease may occur at any time during treatment with a PD-1 blocking antibody.

Table 100. TRAEs After 1 Year of Exposure to Toripalimab in ≥ 5% of Patients (Toripalimab Monotherapy Safety Database)

	Toripalimab Monotherapy Safety Database After 1 Year N = 185 (%)	
	All Grades	**Grade ≥ 3**
Any	142 (76.8)	17 (9.2)
Blood Disorders		
Leukopenia	24 (13.0)	0
Neutropenia	18 (9.7)	0
Anaemia	15 (8.1)	0
Endocrine Disorders		
Hypothyroidism	15 (8.1)	0
Hepatobiliary Disorders		
Hyperbilirubinaemia	16 (8.6)	0
Investigations		
Thyroid function test abnormal	47 (25.4)	0
Lipids abnormal	26 (14.1)	2 (1.1)
Liver function test abnormal	18 (9.7)	2 (1.1)
Lymphocyte count abnormal	10 (5.4)	0
Metabolism and Nutrition		
Hyperglycaemia	17 (9.2)	1 (0.5)
Renal Disorders		
Proteinuria	14 (7.6)	0
Skin Disorders		
Rash	10 (5.4)	0

2. Serious adverse events, deaths, and other significant events

Deaths

Nasopharyngeal carcinoma

In JUPITER-02, there were 5 (3.4%) deaths in the toripalimab arm and 3 deaths (2.1%) in the placebo arm within 60 days of the last dose of study drug.

Table 101. TEAEs Leading to Death Within 60 Days of the Last Dose of Study Drug (JUPITER-02) (DCO: 08-May-2022)

	Toripalimab + GC N = 146 (%)	Placebo + GC N = 143 (%)
Deaths	5 (3.4)	3 (2.1)
Disease progression	2 (1.4)	2 (1.4)
Death	1 (0.7)	0
Intracranial haemorrhage	1 (0.7)	0
Epistaxis	1 (0.7)	0
Cerebral infarction	0	1 (0.7)

Four (4) of 5 deaths in the toripalimab arm were considered by the investigator to be related to toripalimab:

- Patient 1: This death was due to disease progression and was recorded, by the investigator, as related to toripalimab, chemotherapy, and the patient's underlying disease. The patient's last tumour assessment showed disease progression. The sponsor determined that the death was not related to toripalimab.
- Patient 2: This death was due to epistaxis and was recorded, by the investigator, as related to toripalimab, chemotherapy, and the patient's underlying disease. The patient had no post-baseline tumour imaging. The patient's most recent coagulation parameters were normal or elevated (platelets 716,000/μL). The sponsor assessed that the death was not related to toripalimab but to the patient's underlying disease.
- Patients 3: This death was due to intracranial haemorrhage and was recorded, by the investigator, as related to toripalimab. This was a complex autoimmune disorder that included myositis, hepatitis, myocarditis, and thrombocytopenia. The sponsor considered the death to be related to toripalimab. To be noted that this death occurred 61 days after the last dose of toripalimab.
- Patient 4: This death was reported as "death" and was recorded, by the investigator, as related to toripalimab and chemotherapy. The patient experienced fever on the day of death and had previously been hospitalized for intestinal obstruction. The patient had no post-baseline tumour imaging. The sponsor assessed that the death was not related to toripalimab but was related to disease progression.

One (1) of 5 deaths in the toripalimab arm were considered by the investigator to be not related to toripalimab:

- Patient 5: patient died due to disease progression and was recorded, by the investigator, as not related to toripalimab or chemotherapy but related to the patient's underlying disease. The patient's last on-study tumour imaging showed stable disease.

There were no deaths due to an adverse event within 60 days of the last dose of study drug patients in Cohort 7 of POLARIS-02.

Squamous cell carcinoma of the oesophagus

In JUPITER-06, deaths within 60 days of the last dose of study drug occurred in 22 (8.6%) and 21 (8.2%) patients in the toripalimab and placebo arms, respectively.

Table 102. TEAEs Leading to Death Within 60 Days of the Last Dose of Study Drug (JUPITER-06) (DCO 15-Feb-2022)

	Toripalimab + TP N = 257 (%)	Placebo + TP N = 257 (%)
Deaths	22 (8.6)	21 (8.2)
Disease progression	10 (3.9)	8 (3.1)
Gastrointestinal haemorrhage	2 (0.8)	2 (0.8)
Asphyxia	1 (0.4)	1 (0.4)
Carbon monoxide poisoning	1 (0.4)	0
Death	1 (0.4)	2 (0.8)
Gastric fistula	1 (0.4)	0
Haemorrhage	1 (0.4)	1 (0.4)
Multiple organ dysfunction syndrome	1 (0.4)	1 (0.4)
Oesophageal fistula	1 (0.4)	1 (0.4)
Pneumonia	1 (0.4)	0
Pulmonary embolism	1 (0.4)	0
Respiratory failure	1 (0.4)	0
Cardiac failure	0	1 (0.4)
Cerebral infarction	0	1 (0.4)
Haemorrhagic shock	0	1 (0.4)
Intestinal obstruction	0	1 (0.4)
Pneumonitis	0	1 (0.4)

According to the investigators' assessment, no deaths were reported as related to toripalimab. Causality was not reported for 1 death in the toripalimab arm. The AE leading to death in one patient was reported as "death". This patient had radiographic progression prior to his death. The sponsor determined that the death was not related to toripalimab.

Among the 12 patients in Cohort 6 of POLARIS-02, there was 1 death within 60 days of the last dose of study drug.

Toripalimab monotherapy

There were 69 (6.2%) deaths due to TEAE within 60 days of the last dose of toripalimab in the toripalimab monotherapy population. The most common AEs leading to death were disease progression, death, pneumonia, and respiratory failure. Pneumonia and respiratory failure are frequent causes of death in patients with advanced cancer.

Table 103. TEAEs Leading to Death Within 60 Days of the Last Dose of Toripalimab (Toripalimab Monotherapy)

Events	Toripalimab Monotherapy Safety Database N = 1111 (%)
Deaths	69 (6.2)
Disease progression	13 (1.2)
Death	12 (1.1)
Pneumonia	8 (0.7)
Respiratory failure	8 (0.7)
Cardiac failure	3 (0.3)
Cerebrovascular accident	3 (0.3)
Circulatory collapse	3 (0.3)
Multiple organ dysfunction syndrome	3 (0.3)
Neoplasm progression	3 (0.3)
Hyperbilirubinemia	2 (0.2)
Intestinal obstruction	2 (0.2)
Myocardial infarction	2 (0.2)
Renal injury	2 (0.2)
Accidental death	1 (0.1)
Ascites	1 (0.1)
Biliary tract infection	1 (0.1)
Brain stem haemorrhage	1 (0.1)

Events	Toripalimab Monotherapy Safety Database N = 1111 (%)
Cachexia	1 (0.1)
Decreased appetite	1 (0.1)
Haemorrhage	1 (0.1)
Hyponatraemia	1 (0.1)
Pleural effusion	1 (0.1)
Pneumonitis	1 (0.1)
Pulmonary embolism	1 (0.1)
Sudden death	1 (0.1)
Thrombocytopenia	1 (0.1)
Tumour haemorrhage	1 (0.1)

Four deaths were considered possibly related to toripalimab by the investigator.

- Patient 1's death (reported as "death") and patient 2's death (interstitial pneumonia) were considered, by the investigator and sponsor, to be irAEs and to, therefore, be related to toripalimab. Both patients died due to immune-related pneumonitis.

- Patient 3 (hyperbilirubinemia) had an underlying NPC with cirrhosis due to hepatitis B and liver metastases. He developed a lung infection with concurrent liver failure and thrombocytopenia (10,000/μL). The patient had no post-baseline tumour imaging. He was discharged to palliative care and died. The sponsor determined that hyperbilirubinaemia was not related to toripalimab.

- Patient 4 (death due to thrombocytopenia) had an underlying gastric cancer and cirrhosis due to hepatitis B with a baseline platelet count of 119,000/μL. The patient developed disease progression with upper gastrointestinal haemorrhage and a gradually decreasing platelet count (11,000/μL). The patient had no post-baseline tumour imaging. He was discharged and died at home. Both the investigator and sponsor determined that the patient's death was related to toripalimab.

The AEs leading to death in 6 patients in whom the investigator did not report causality were:

- Patient 1: The AE leading to death was pneumonia. The patient was noted to have cough and sputum production but did not seek medical attention and died at home. The patient's most recent tumour imaging showed a partial response. No additional information is available. The sponsor determined that the death was related to toripalimab.

- Patient 2: The AE leading to death was sudden death. The patient was a 48 year-old male with non-cardiac chest pain, widely metastatic disease to the bones and vertebrae, bilateral pleural effusions, silicosis, and worsening anaemia (haemoglobin 7.2 g/dL 13 days prior to death) who was receiving opioids for pain control. The patient died in his sleep. The patient's most recent tumour imaging showed stable disease. The sponsor did not provide a determination concerning the relationship between the patient's death and the use of toripalimab.

- Patient 3: The AE leading to death was reported as "death". The cause of death in this patient was unclear. The patient had no post-baseline tumour imaging. The sponsor determined that the death was not related to toripalimab.

- Patient 4: The AE leading to death was reported as "death". The cause of death in this patient was unclear. The patient had no post-baseline tumour imaging. The sponsor did not consider the death to be related to toripalimab.

- Patient 5: The AE leading to death was reported as "death". The patient previously required paracentesis and died at home with abdominal distension and worsening oedema. The patient had no post-baseline tumour imaging. The sponsor determined that the death as possibly related to toripalimab, but likely related to the advanced cancer.

- Patient 6: The AE leading to death was reported as "death". The patient died in the evening after undergoing chest tube drainage earlier that day. The patient had no post-baseline tumour imaging. The sponsor did not provide a determination concerning the relationship between the patient's death and the use of toripalimab.

Other serious adverse events

Nasopharyngeal carcinoma

Treatment-related SAEs occurred in 3 patients in Cohort 7 of POLARIS-02. They were anaemia, autoimmune myocarditis, diarrhoea, infection, and upper respiratory tract infection.

On JUPITER-02, treatment-emergent SAEs occurred in 43.8% of patients in the toripalimab and 43.4% in the placebo arm. The incidences of treatment-related SAEs were 38.4% and 36.4% in the toripalimab and placebo arms, respectively. The most common both TEAEs and TRAEs were thrombocytopenia, neutropenia, pneumonia, anaemia, leukopenia, epistaxis, hepatic function abnormal, rash, and upper respiratory infection.

Two patients on the toripalimab arm developed pulmonary tuberculosis. One had a history of tuberculosis and developed disease reactivation. The other patient had no history of tuberculosis and received the BCG vaccine shortly before the report of tuberculosis. Neither received corticosteroids and both permanently discontinued toripalimab. One patient on the placebo arm developed tuberculosis (AE, not a SAE). The patient had no prior history of tuberculosis and permanently discontinued study drug. Patients with active tuberculosis were not permitted on JUPITER-02. A past medical history of tuberculosis was permitted and was reported in 4 patients in the toripalimab and 1 in the placebo arm. Reactivation of pulmonary tuberculosis is a known complication of treatment with a PD-1 blocking antibody.

Table 104. Treatment-Related SAEs (JUPITER-02) (DCO: 8 May 2022)

	Toripalimab + GC N=146 (%)	**Placebo + GC N=143 (%)**
Any	56 (38.4)	52 (36.4)
Blood Disorders		
Thrombocytopenia	19 (13.0)	21 (14.7)
Anaemia	11 (7.5)	14 (9.8)
Leukopenia	11 (7.5)	13 (9.1)
Neutropenia	15 (10.3)	9 (6.3)
Bone marrow failure	2 (1.4)	4 (2.8)
Lymphopenia	1 (0.7)	0
Cardiac Disorders		
Cardiac failure	1 (0.7)	1 (0.7)
Myocarditis	1 (0.7)	0
Ear Disorders		0
Vertigo	1 (0.7)	0
Endocrine Disorders		
Hypophysitis	1 (0.7)	0
Hypothyroidism	1 (0.7)	0
Gastrointestinal Disorders		
Diarrhoea	1 (0.7)	0
Gastroenteritis	1 (0.7)	0
Intestinal obstruction	1 (0.7)	0
Ileus	0	1 (0.7)
General Disorders		
Disease progression	1 (0.7)	2 (1.4)
Death	1 (0.7)	0
Fatigue	1 (0.7)	0
Pyrexia	0	1 (0.7)

	Toripalimab + GC N=146 (%)	Placebo + GC N=143 (%)
Hepatobiliary Disorders		
Hepatic function abnormal	5 (3.4)	4 (2.8)
Infections		
Pneumonia	11 (7.5)	3 (2.1)
Upper respiratory tract infection	3 (2.1)	0
Pulmonary tuberculosis	2 (1.4)	0
Bacteraemia	1 (0.7)	0
Infection	0	1 (0.7)
Localised infection	1 (0.7)	0
Septic shock	0	1 (0.7)
Soft tissue infection	0	1 (0.7)
Investigations		
Alanine aminotransferase increased	1 (0.7)	0
Aspartate aminotransferase increased	0	2 (1.4)
Musculoskeletal Disorders		
Arthritis	1 (0.7)	0
Myositis	1 (0.7)	0
Periarthritis	1 (0.7)	0
Metabolism and Nutrition		
Electrolyte imbalance	2 (1.4)	1 (0.7)
Hypoproteinaemia	2 (1.4)	0
Decreased appetite	1 (0.7)	1 (0.7)
Hypoglycaemia	1 (0.7)	0
Hypokalaemia	1 (0.7)	3 (2.1)
Hyponatraemia	1 (0.7)	1 (0.7)
Metabolic acidosis	1 (0.7)	0
Nervous System Disorders		
Epilepsy	2 (1.4)	0
Encephalopathy	1 (0.7)	0
Haemorrhage intracranial	1 (0.7)	0
Cerebral infarction	0	1 (0.7)
Seizure	0	1 (0.7)
Renal Disorders		
Immune-mediated renal disorder	1 (0.7)	0
Renal injury	1 (0.7)	0
Respiratory Disorders		
Epistaxis	3 (2.1)	2 (1.4)
Dysphonia	1 (0.7)	0
Skin Disorders		
Rash	3 (2.1)	1 (0.7)
Psoriasis	1 (0.7)	0

Squamous cell carcinoma of the oesophagus

Treatment-related SAEs, oesophageal-bronchial fistula, sepsis, and syncope, occurred in 2 patients (3 events) in Cohort 6 of POLARIS-02.

In JUPITER-06, treatment-emergent SAEs occurred in 41.2% of patients on the toripalimab arm and 30.7% on the placebo arm. Treatment-related SAEs occurred in 15.6% of patients in the toripalimab and 5.8% in the placebo arm.

The most common TEAEs were disease progression, neutropenia, leukopenia, and vomiting, TRAEs - SAEs were immune-mediated lung disease and hepatic function abnormal, both TEAEs and TRAEs – pneumonia. According to the applicant, any of the events (e.g., haematological or gastrointestinal toxicity) may be related to the patient's underlying disease or to concurrent chemotherapy.

Table 105. Treatment-Related SAEs (JUPITER-06) (DCO: 15 Feb 2022)

	Toripalimab + TP N=257 (%)	Placebo + TP N=257 (%)
Any	40 (15.6)	15 (5.8)
Blood Disorders		
Myelosuppression	2 (0.8)	0
Neutropenia	2 (0.8)	2 (0.8)
Anaemia	1 (0.4)	0
Leukopenia	1 (0.4)	2 (0.8)
Thrombocytopenia	1 (0.4)	1 (0.4)
Cardiac Disorders		
Immune-mediated myocarditis	1 (0.4)	0
Myocardial injury	1 (0.4)	0
Endocrine Disorders		
Adrenal insufficiency	1 (0.4)	0
Hypothyroidism	1 (0.4)	0
Thyroiditis	1 (0.4)	0
Gastrointestinal Disorders		
Colitis	1 (0.4)	0
Diarrhoea	1 (0.4)	0
Enteritis	1 (0.4)	0
Gastric fistula	1 (0.4)	0
Gastrointestinal disorder	1 (0.4)	0
Oesophageal obstruction	1 (0.4)	0
Vomiting	1 (0.4)	1 (0.4)
Gastrointestinal haemorrhage	0	2 (0.8)
Dysphagia	0	1 (0.4)
General Disorders		
Fatigue	2 (0.8)	0
Chest discomfort	1 (0.4)	0
Death	1 (0.4)	1 (0.4)
Pyrexia	1 (0.4)	0
Hepatobiliary Disorders		
Hepatic function abnormal	3 (1.2)	1 (0.4)
Hepatitis	1 (0.4)	2 (0.8)
Injury, Poisoning, and Procedural Complications		
Infusion-related reaction	1 (0.4)	0
Investigations		
Alanine aminotransferase increased	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.4)	0
Immune System Disorders		
Hypersensitivity	1 (0.4)	0
Infections		
Pneumonia	4 (1.6)	2 (0.8)
Gastroenteritis	1 (0.4)	0
Muscle abscess	1 (0.4)	0
Metabolism and Nutrition		
Decreased appetite	1 (0.4)	1 (0.4)
Hyponatraemia	1 (0.4)	0
Hypokalaemia	0	1 (0.4)
Musculoskeletal Disorders		
Arthritis	1 (0.4)	0
Myositis	1 (0.4)	0
Nervous System Disorders		
Neuropathy peripheral	1 (0.4)	0
Renal Disorders		
Cystitis haemorrhagic	1 (0.4)	0
Respiratory Disorders		
Immune-mediated lung disease	4 (1.6)	0
Pneumonitis	2 (0.8)	1 (0.4)

	Toripalimab + TP N=257 (%)	Placebo + TP N=257 (%)
Dyspnoea	1 (0.4)	0
Tracheo-oesophageal fistula	1 (0.4)	0
Skin Disorders		
Rash	2 (0.8)	0
Psoriasis	1 (0.4)	0
Vascular Disorders		
Hypertension	1 (0.4)	0

3. Laboratory findings

Laboratory values, which worsened by at least 1 grade when compared to baseline, are provided bellow. In the randomised trials, laboratory values which occurred at a higher incidence in the treatment arm (≥ 5% all grades, ≥ 2% Grade 3-4) are shown in bold.

Nasopharyngeal carcinoma

All patients had completed chemotherapy prior to unblinding. Treatment duration was longer in the toripalimab arm in JUPITER-02. Differences were noticed in haematological toxicity between arms. To be mentioned, that small differences in haematological toxicity have been inconsistently seen with other PD-1 blocking antibodies in combination with chemotherapy. This and longer time on treatment applicant stated to be the explanation for the differences in haematological toxicity.

Table 106. Worsening Laboratory Abnormalities (JUPITER-02) (DCO: 8 May 2022)

	Toripalimab + GC[1] N (%)		Placebo + GC[1] N (%)	
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Haematology				
Leukopenia	139 (95.2)	88 (60.3)	139 (97.2)	87 (60.8)
Anaemia	137 (93.8)	**73 (50.0)**	139 (97.2)	**56 (39.2)**
Neutropenia	127 (91.4)	81 (58.7)	129 (94.9)	86 (63.2)
Lymphopenia	124 (89.2)	**79 (56.8)**	120 (88.2)	**67 (49.3)**
Thrombocytopenia	104 (71.2)	**49 (33.8)**	96 (67.1)	**44 (30.8)**
Chemistries				
Hypomagnesaemia	113 (78.5)	6 (4.2)	109 (76.8)	12 (8.5)
Hypocalcaemia	**100 (69.4)**	5 (3.5)	**84 (58.7)**	6 (4.2)
Hyponatraemia	91 (63.2)	**13 (9.0)**	90 (62.9)	**8 (5.6)**
Alanine aminotransferase increased	**87 (59.6)**	**10 (6.9)**	**72 (50.3)**	**5 (3.5)**
Aspartate aminotransferase increased	86 (58.9)	5 (3.4)	78 (54.5)	7 (4.9)
Hypoalbuminaemia	71 (49.3)	1 (0.7)	68 (47.6)	0
Hypercalcaemia	**70 (48.6)**	1 (0.7)	**62 (43.4)**	1 (0.7)
Lactate dehydrogenase increased	**62 (43.4)**	0	**50 (35.0)**	0
Hypokalaemia	**59 (41.0)**	**17 (11.8)**	**57 (39.9)**	**12 (8.4)**
Creatinine increased	58 (39.7)	3 (2.1)	58 (40.6)	03 (2.1)
Alkaline phosphatase increased	40 (27.8)	0	38 (26.6)	0
Hypoglycaemia	**34 (23.8)**	2 (1.4)	**23 (16.1)**	0
Increased bilirubin	23 (16.0)	3 (2.1)	18 (12.6)	3 (2.1)
Hypermagnesaemia	**19 (13.2)**	**6 (4.2)**	**9 (6.3)**	**1 (0.7)**
Hyperkalaemia	13 (9.0)	2 (1.4)	10 (7.0)	0
Hypernatraemia	3 (2.1)	0	2 (1.4)	0

[1]Based on the number of patients with a baseline and on-study value for that laboratory.
GC=gemcitabine, cisplatin

Squamous cell carcinoma of the oesophagus

The haematological toxicity was more common in toripalimab arm comparing to placebo in JUPITER-06, and that difference between arms was greater than in JUPITER-02. The same as in JUPITER-02, chemotherapy had been completed prior to unblinding and this cannot be explained by differences in the dose intensity or duration of exposure to cisplatin/paclitaxel between arms.

AST/ALT/creatine phosphokinase increase and hyperglycaemia were more common in the toripalimab population. Number of Grade 3-4 events was relatively small though.

Table 107. Worsening Laboratory Abnormalities (JUPITER-06) (DCO: 15 Feb 2022)

	Toripalimab + TP[1] N (%)		**Placebo + TP[1] N (%)**	
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Haematology				
Anaemia	225 (88.9)	31 (12.3)	223 (88.1)	42 (16.6)
Leukopenia	**179 (71.0)**	**53 (21.0)**	**148 (58.5)**	**34 (13.4)**
Neutropenia	**179 (71.0)**	**114 (45.2)**	**158 (62.5)**	**92 (36.4)**
Lymphopenia	**159 (63.1)**	**44 (17.5)**	**142 (56.1)**	**31 (12.3)**
Thrombocytopenia	**85 (33.7)**	5 (2.0)	**48 (19.0)**	3 (1.2)
Chemistries				
Hypomagnesaemia	144 (57.8)	3 (1.2)	149 (59.1)	10 (4.0)
Hypoalbuminaemia	111 (44.0)	0	100 (39.5)	1 (0.4)
Hyponatraemia	111 (44.0)	26 (10.3)	105 (41.5)	22 (8.7)
Hyperglycaemia	**109 (43.8)**	7 (2.8)	**98 (39.0)**	9 (3.6)
Creatinine increased	104 (41.4)	4 (1.6)	99 (39.1)	2 (0.8)
Aspartate aminotransferase increased	**95 (37.8)**	8 (3.2)	**74 (29.2)**	6 (2.4)
Alanine aminotransferase increased	**83 (32.9)**	**15 (6.0)**	**61 (24.1)**	**5 (2.0)**
Increased lactate dehydrogenase	**76 (30.3)**	0	**57 (22.5)**	0
Hypokalaemia	70 (27.9)	15 (6.0)	73 (28.9)	31 (12.3)
Hypocalcaemia	70 (27.8)	5 (2.0)	69 (27.3)	6 (2.4)
Increased alkaline phosphatase	48 (19.1)	0	48 (19.0)	0
Creatine phosphokinase increased	**39 (15.6)**	5 (2.0)	**24 (9.6)**	1 (0.4)
Increased bilirubin	44 (17.5)	1 (0.4)	42 (16.6)	3 (1.2)
Hypercalcaemia	28 (11.1)	2 (0.8)	37 (14.6)	6 (2.4)
Hyperkalaemia	23 (9.2)	2 (0.8)	19 (7.5)	2 (0.8)
Hypermagnesaemia	23 (9.2)	8 (3.2)	17 (6.7)	4 (1.6)
Hypoglycaemia	21 (8.4)	0	17 (6.8)	1 (0.4)

NCI CTCAE v5.0; Hyperglycaemia based on NCI CTCAE v4.03
[1]Each calculation is based on the number of patients with a baseline and on-study value for that laboratory.
TP=paclitaxel, cisplatin

Toripalimab in combination with chemotherapy and as monotherapy

Table 108. Worsening Laboratory Abnormalities (Toripalimab in Combination with Chemotherapy, Toripalimab Monotherapy)

	Toripalimab in Combination with Chemotherapy N (%)		**Toripalimab Monotherapy Safety Database N (%)**	
	Grades 1-4	**Grade 3-4**	**Grades 1-4**	**Grade 3-4**
Haematology				
Anaemia	362 (90.7)	104 (26.1)	408 (37.4)	79 (7.2)
Leukopenia	318 (79.9)	141 (35.4)	198 (18.1)	2 (0.2)
Neutropenia	306 (78.3)	195 (49.9)	135 (12.9)	12 (1.1)
Lymphocytopenia	283 (72.4)	123 (31.5)	444 (42.3)	93 (8.9)

	Toripalimab in Combination with Chemotherapy N (%)		Toripalimab Monotherapy Safety Database N (%)	
	Grades 1-4	**Grade 3-4**	**Grades 1-4**	**Grade 3-4**
Thrombocytopenia	189 (47.5)	54 (13.6)	88 (8.1)	11 (1.0)
Chemistries				
Hypomagnesemia	257 (65.4)	9 (2.3)	75 (14.7)	2 (0.4)
Hyponatraemia	202 (51.0)	39 (9.8)	337 (30.9)	101 (9.2)
Hypoalbuminaemia	182 (46.0)	1 (0.3)	307 (28.1)	2 (0.2)
Aspartate aminotransferase increased	181 (45.5)	13 (3.3)	284 (26.0)	34 (3.1)
Hyperglycaemia	169 (43.1)	7 (1.8)	368 (33.7)	30 (2.7)
Hypocalcaemia	170 (42.9)	10 (2.5)	202 (18.5)	2 (0.2)
Alanine aminotransferase increased	170 (42.7)	25 (6.3)	272 (24.9)	18 (1.6)
Creatinine increased	162 (40.8)	7 (1.8)	122 (11.2)	12 (1.1)
Hypokalaemia	129 (32.7)	32 (8.1)	138 (12.6)	21 (1.9)
Hypercalcemia	98 (24.7)	3 (0.8)	85 (7.8)	11 (1.0)
Increased alkaline phosphatase	88 (22.3)	0	268 (24.5)	31 (2.8)
Increased bilirubin	67 (17.0)	4 (1.0)	177 (16.2)	26 (2.4)
Hypoglycaemia	55 (14.0)	2 (0.5)	43 (3.9)	3 (0.3)
Hypermagnesemia	42 (10.7)	14 (3.6)	49 (9.6)	8 (1.6)
Hyperkalaemia	36 (9.1)	4 (1.0)	74 (6.8)	6 (0.5)
Hypertriglyceridemia	ND	ND	282 (33.4)	21 (2.5)
Hypercholesterolemia	ND	ND	203 (24.1)	3 (0.4)
Lipase increased	ND	ND	70 (20.6)	18 (5.3)
Amylase increased	ND	ND	136 (13.5)	25 (2.5)
Creatine phosphokinase increased	39 (15.6)	5 (2.0)	ND	ND

Toripalimab in combination with chemotherapy: NCI CTCAE v5.0 (except hyperglycaemia which used v4.03)
Toripalimab monotherapy safety database: NCI CTCAE v4.03
[1]Each calculation is based on the number of patients with a baseline and on-study value for that laboratory.
ND=not done

The incidence of all haematologic toxicity in JUPITER-06 and the incidence of thrombocytopaenia in JUPITER-02 was increased in the toripalimab arm when compared to placebo. The absolute differences in Grade 3-4 haematological toxicities ranged from 0 to 12% higher in the toripalimab arms. According to applicant, this cannot be explained by differences in exposure to chemotherapy. Small increases in haematological toxicity have been seen when first-generation PD-1 blocking antibodies are combined with chemotherapy.

In regard to chemistries, increase of Grade 3-4 events in patients was less than 10%. The highest Grade 3-4 incidence was hyponatremia (9.8% and 9.2% in the toripalimab plus chemotherapy vs toripalimab monotherapy populations). However, hyponatraemia was not increased (with the addition of toripalimab) in JUPITER-06 and was only minimally increased in JUPITER-02.

4. In vitro biomarker test for patient selection for safety

N/A

5. Safety in special populations

Use in pregnant and lactating women

No reproductive and developmental toxicity studies have been conducted with toripalimab and none are planned. The PD-1 pathway is linked to the induction of immune tolerance to the foetus and there is substantial literature to support the negative effect of a PD-1 inhibitor on the foetus (Poulet et al.,

2016; Guleria et al., 2005). Embryofoetal toxicity is expected with toripalimab. The risk of foetal harm will be incorporated into product labelling; patients will be advised to use effective contraception while receiving toripalimab and for at least 4 months after the last dose of toripalimab (this is reflected in section 4.6 of the SmPC).

No studies have been conducted to determine whether toripalimab is excreted in breast milk. Monoclonal antibodies (small amounts relative to the administered dose) have been found in the breast milk of lactating women (Østensen et al., 2006). Section 4.6 of the SmPC states that patients should not breastfeed while taking toripalimab and for 4 months after the last dose of toripalimab.

The recommendation that patients should use effective contraception and should not breastfeed for at least 4 months after the last dose of toripalimab is based on the serum half-life of toripalimab obtained in early studies that included intensive pharmacokinetic sampling. In trials that conducted intensive PK sampling, sampling was typically obtained with the first dose and with the 6th or 7th dose. After multiple doses, the half-life ranged up to 20.1 days in non-compartmental analyses. The 4-month recommendation is based on 5 half-lives, 3.3 months, with several additional days to ensure complete clearance. This is similar to the washout period, approximating 5 half-lives, obtained with the popPK analyses calculated for the 3 mg/kg Q2W dosing regimen and close to the 4.9-month washout period calculated for the 240 mg Q3W dosing regimen.

Sex

Toripalimab + chemotherapy

The number of females is small (62) and it makes any interpretations to be examined with caution. Females appeared to be more likely to develop haematological and gastrointestinal toxicity than males while pneumonia was more common in males. Thyroid disease, both hypothyroidism and thyroid function test abnormal, were also more common in females.

Table 109. TRAEs by Sex, occurring in ≥ 5% of population (Toripalimab + Chemotherapy) (DCO: 08-May-2020 for JUPITER-02 and 15-Feb-2022 for JUPITER-06)

	Toripalimab in Combination with Chemotherapy	
	Male N = 341 (%)	**Female N = 62 (%)**
Blood Disorders		
Anaemia	151 (44.3)	30 (48.4)
Leukopenia	**135 (39.6)**	**33 (53.2)**
Neutropenia	**125 (36.7)**	**32 (51.6)**
Thrombocytopenia	**106 (31.1)**	**16 (25.8)**
Cardiac Disorders		
Arrhythmia	**16 (4.7)**	**6 (9.7)**
Endocrine Disorders		
Hypothyroidism	**59 (17.3)**	**15 (24.2)**
Gastrointestinal Disorders		
Nausea	**96 (28.2)**	**24 (38.7)**
Vomiting	**86 (25.2)**	**24 (38.7)**
Constipation	**52 (15.2)**	**15 (24.2)**
Colitis	48 (14.1)	9 (14.5)
Stomatitis	**24 (7.0)**	**9 (14.5)**
Abdominal pain	22 (6.5)	7 (11.3)
General Disorders		
Fatigue	81 (23.8)	14 (22.6)
Pyrexia	46 (13.5)	9 (14.5)
Pain	16 (4.7)	4 (6.5)
Hepatobiliary Disorder		
Hepatitis	20 (5.9)	3 (4.8)
Infections		

	Toripalimab in Combination with Chemotherapy	
	Male N = 341 (%)	**Female N = 62 (%)**
Upper respiratory infection	24 (7.0)	5 (8.1)
Pneumonia	**24 (7.0)**	**1 (1.6)**
Investigations		
Liver function tests abnormal	74 (21.7)	16 (25.8)
Creatinine clearance decreased	38 (11.1)	7 (11.3)
Thyroid function tests abnormal	**23 (6.7)**	**9 (14.5)**
Lymphocytes abnormal	18 (5.3)	2 (3.2)
Metabolism and Nutrition		
Decreased appetite	82 (24.0)	14 (22.6)
Hyponatraemia	**39 (11.4)**	**2 (3.2)**
Hypokalaemia	34 (10.0)	6 (9.7)
Hypoproteinaemia	26 (7.6)	3 (4.8)
Hypochloraemia	23 (6.7)	2 (3.2)
Weight decreased	21 (6.2)	4 (6.5)
Hyperglycaemia	18 (5.3)	5 (8.1)
Hyperuricaemia	19 (5.6)	4 (6.5)
Musculoskeletal Disorders		
Musculoskeletal pain	**30 (8.8)**	**10 (16.1)**
Nervous System Disorders		
Neuropathy	**47 (13.8)**	**14 (22.6)**
Dizziness	26 (7.6)	4 (6.5)
Headache	18 (5.3)	2 (3.2)
Psychiatric Disorders		
Sleep disorders	26 (7.6)	5 (8.1)
Respiratory Disorders		
Cough	37 (10.9)	9 (14.5)
Skin Disorders		
Rash	78 (22.9)	18 (29.0)
Pruritus	42 (12.3)	4 (6.5)

Hepatic/renal impairment

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.

Elderly

Table 110. TRAEs by Age, occurring in ≥ 5% of population (Toripalimab Monotherapy)

	Toripalimab Monotherapy Safety Database	
	< 65 years N = 856 (%)	**> 65 years N = 255 (%)**
Blood Disorders		
Leukopenia	115 (13.4)	23 (9.0)
Anaemia	84 (9.8)	22 (8.6)
Neutropenia	**81 (9.5)**	**11 (4.3)**
Endocrine Disorders		
Hypothyroidism	123 (14.4)	32 (12.5)
Hyperthyroidism	59 (6.9)	17 (6.7)
General Disorders		
Fatigue	129 (15.1)	44 (17.3)
Pyrexia	**69 (8.1)**	**7 (2.7)**
Hepatobiliary Disorders		
Hyperbilirubinaemia	84 (9.8)	22 (8.6)

	Toripalimab Monotherapy Safety Database	
	< 65 years N = 856 (%)	**> 65 years N = 255 (%)**
Investigations		
Thyroid function test abnormal	189 (22.1)	45 (17.6)
Liver function test abnormal	156 (18.2)	51 (20.0)
Creatine phosphokinase abnormal	65 (7.6)	25 (9.8)
Lipids abnormal	60 (7.0)	26 (10.2)
Amylase increased	58 (6.8)	20 (7.8)
Metabolism and Nutrition		
Hyperglycaemia	88 (10.3)	16 (6.3)
Decreased appetite	57 (6.7)	20 (7.8)
Renal Disorders		
Proteinuria	76 (8.9)	24 (9.4)
Skin Disorders		
Rash	120 (14.0)	41 (16.1)
Pruritus	85 (9.9)	31 (12.2)

Table 111. TRAEs by Age, occurring in ≥ 5% of population (Toripalimab + Chemotherapy)

	Toripalimab in Combination with Chemotherapy	
	< 65 years N = 295	**> 65 years N = 108**
Blood Disorders		
Anaemia	**150 (50.8)**	**31 (28.7)**
Leukopenia	**145 (49.2)**	**23 (21.3)**
Neutropenia	**137 (46.4)**	**20 (18.5)**
Thrombocytopenia	**105 (35.6)**	**17 (15.7)**
Cardiac Disorders		
Arrhythmia	15 (5.1)	7 (6.5)
Endocrine Disorders		
Hypothyroidism	58 (19.7)	16 (14.8)
Gastrointestinal Disorders		
Nausea	**99 (33.6)**	**21 (19.4)**
Vomiting	**98 (33.2)**	**12 (11.1)**
Constipation	**57 (19.3)**	**10 (9.3)**
Colitis	**49 (16.6)**	**8 (7.4)**
Stomatitis	28 (9.5)	5 (4.6)
Abdominal pain	23 (7.8)	6 (5.6)
General Disorders		
Fatigue	**74 (25.1)**	**21 (19.4)**
Pyrexia	**49 (16.6)**	**6 (5.6)**
Pain	18 (6.1)	2 (1.9)
Hepatobiliary Disorder		
Hepatitis	16 (5.4)	7 (6.5)
Infections		
Upper respiratory infection	28 (9.5)	1 (0.9)
Pneumonia	20 (6.8)	5 (4.6)
Investigations		
Liver function tests abnormal	**75 (25.4)**	**15 (13.9)**
Creatinine clearance decreased	36 (12.2)	9 (8.3)
Thyroid function tests abnormal	21 (7.1)	11 (10.2)
Lymphocytes abnormal	18 (6.1)	2 (1.9)
Metabolism and Nutrition		
Decreased appetite	**81 (27.5)**	**15 (13.9)**
Hyponatraemia	**34 (11.5)**	**7 (6.5)**
Hypokalaemia	30 (10.2)	10 (9.3)
Hypoproteinaemia	21 (7.1)	8 (7.4)
Hypochloraemia	**23 (7.8)**	**2 (1.9)**
Weight decreased	17 (5.8)	8 (7.4)

	Toripalimab in Combination with Chemotherapy	
	< 65 years N = 295	**> 65 years N = 108**
Hyperglycaemia	18 (6.1)	5 (4.6)
Hyperuricaemia	**21 (7.1)**	**2 (1.9)**
Musculoskeletal Disorders		
Musculoskeletal pain	31 (10.5)	9 (8.3)
Nervous System Disorders		
Neuropathy	**53 (18.0)**	**8 (7.4)**
Dizziness	**29 (9.8)**	**1 (0.9)**
Headache	18 (6.1)	2 (1.9)
Psychiatric Disorders		
Sleep disorders	**29 (9.8)**	**2 (1.9)**
Respiratory Disorders		
Cough	**42 (14.2)**	**4 (3.7)**
Skin Disorders		
Rash	**78 (26.4)**	**18 (16.7)**
Pruritus	**38 (12.9)**	**8 (7.4)**

The applicant provided a safety analysis performed in different elderly groups (i.e. people over 65 years old). To be noted, that 96.4% of patients are up to 74 years old. There were no patients of 85 or older included in toripalimab studies.

Table 112. Treatment-Emergent Adverse Event (TEAE) Summary by Age in Patients Treated with Toripalimab (JUPITER-02 and JUPITER-06 pool)

TEAE	Toripalimab				Placebo			
	N=403				N=400			
Adverse Event Category	**Age <65 n=295 (73.2%)**	**Age 65-74 n=107 (26.6%)**	**Age 75-84 n=1 (0.2%)**	**Age 85+ n=0 (0)**	**Age <65 n=299 (74.8%)**	**Age 65-74 n=101 (25.3%)**	**Age 75-84 n=0 (%)**	**Age ≥ 85 n=0 (0)**
Total AEs	293 (99.3)	107 (100.0)	1 (100.0)	0	297 (99.3)	101 (100.0)	0	0
Serious AEs - Total	118 (40.0)	51 (47.7)	1 (100.0)	0	106 (35.5)	35 (34.7)	0	0
Fatal	22 (7.5)	6 (5.6)	1 (100.0)	0	20 (6.7)	8 (7.9)	0	0
Hospitalization/prolongation of existing hospitalization	105 (35.6)	46 (43.0)	0	0	92 (30.8)	32 (31.7)	0	0
Life-threatening	9 (3.1)	6 (5.6)	0	0	9 (3.0)	1 (1.0)	0	0
Disability/incapacity	0	0	0	0	0	0	0	0
Other (medically significant)	7 (2.4)	2 (1.9)	0	0	7 (2.3)	0	0	0
AE leading to drop-out	37 (12.5)	16 (15.0)	0	0	21 (7.0)	7 (6.9)	0	0
Psychiatric disorders SOC	59 (20.0)	13 (12.2)	0	0	48 (16.1)	14 (13.9)	0	0
Nervous system disorders SOC	154 (52.2)	50 (46.7)	0	0	149 (49.8)	53 (52.5)	0	0
Accidents and injuries SMQ	10 (3.4)	4 (3.7)	0	0	4 (1.3)	2 (2.0)	0	0
Cardiac disorders SOC	31 (10.5)	17 (15.9)	0	0	18 (6.0)	12 (11.9)	0	0
Vascular disorders SOC	50 (17.0)	15 (14.0)	0	0	43 (14.4)	14 (13.9)	0	0
Cerebrovascular disorders[1]	3 (1.0)	1 (0.9)	0	0	3 (1.0)	2 (2.0)	0	0
Infections and infestations SOC	112 (38.0)	32 (29.9)	0	0	79 (26.4)	22 (21.8)	0	0
Anticholinergic syndrome (PT)	0	0	0	0	0	0	0	0
Quality of life decreased (PT)	1 (0.3)	0	0	0	0	0	0	0
AE of postural hypotension, falls, black outs, syncope, dizziness, ataxia, or fractures	42 (14.2)	8 (7.5)	0	0	33 (11.0)	6 (5.9)	0	0

[1] Central nervous system vascular disorders SMQ MedDRA version 25.1

6. Immunological events

In JUPITER-02, 10 of 146 patients on toripalimab in combination with chemotherapy were ADA-positive at any time. This included 5 patients who were ADA positive at baseline but negative after initiation of treatment.

In JUPITER-06, among the 256 patients on toripalimab in combination with chemotherapy who were evaluable for the presence of ADA, 29 tested positive for ADA at any time. This included 7 patients who

were positive at baseline and 22 who were positive only after treatment. Of those who were positive at baseline, they were either negative after treatment (N=5) or did not have a 4-fold rise in titre (N=2).

Among the 402 patients on toripalimab in combination with chemotherapy who were evaluable for the presence of ADA, 39/402 (9.7%) were ADA-positive at any time and 27/390 (6.9%) were ADA positive following initiation of treatment, i.e., treatment-emergent ADA.

In the toripalimab monotherapy safety database, 10.9% (121/1109) patients were ADA positive, including those who were positive at baseline. The incidence of treatment-emergent ADA was 9.3% (101/1089).

The incidence of ADA in patients receiving toripalimab monotherapy was essentially the same as that of patients receiving toripalimab in combination with chemotherapy (10.9% vs 9.7%). The incidence of TRAEs was higher (89.7% vs. 82.6% and 81.0% vs 77.6%) in patients who were ADA positive versus ADA negative for toripalimab plus chemotherapy or monotherapy, respectively. However, in patients receiving toripalimab in combination with chemotherapy, the number of ADA positive patients was too small to draw firm conclusions.

Table 113. Anti-drug antibodies

	Toripalimab in Combination with Chemotherapy		**Toripalimab Monotherapy Safety Database**	
Incidence of ADA	39/402 (9.7%)		121/1109 (10.9%)	
TRAEs by ADA Status	**ADA Positive N = 39 (%)**	**ADA Negative N = 363 (%)**	**ADA Positive N = 121**	**ADA Negative N = 988**
Any TRAE	35 (89.7)	300 (82.6)	98 (81.0)	767 (77.6)
Grade ≥ 3 TRAE	18 (46.2)	165 (45.5)	17 (14.0)	145 (14.7)
Infusion-related reactions	4 (10.3)	12 (3.3)	1 (0.8)	21 (2.1)

The relationships between 3 categories of clinically important AEs (Grade ≥3 treatment-emergent adverse event [TEAE], Grade ≥3 AE, and AEs leading to drug discontinuation) and ADA status were explored in the CT21 dataset, in which there were 26 patients who were ADA positive (defined as having either pre-existing or treatment-emergent ADAs).

Table 114. CT21 PopPK AE Data (Grade ≥3 TEAE, Grade ≥3 TRAE, and AEs Leading to Drug Discontinuation) Categorised by ADA Status

ADA Status	**Grade ≥3 TEAE**		**Grade ≥3 TRAE**		**AE Leading to Drug Discontinuation**	
	No AE (N = 68)	**AE (N = 168)**	**No AE (N = 184)**	**AE (N = 52)**	**No AE (N = 215)**	**AE (N = 21)**
Negative	57 (83.8%)	152 (90.5%)	163 (88.6%)	46 (88.5%)	189 (87.9%)	20 (95.2%)
Pre-existing	4 (5.9%)	3 (1.8%)	6 (3.3%)	1 (1.9%)	7 (3.3%)	0 (0.0%)
Treatment emergent	7 (10.3%)	12 (7.1%)	14 (7.6%)	5 (9.6%)	18 (8.4%)	1 (4.8%)
Missing	0 (0.0%)	1 (0.6%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)

AE = adverse event; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; N = number of patients; popPK = population pharmacokinetic

A univariate analysis was performed with ADA status as a predictor of each of the 3 categories of AEs. The ADA status was not a predictor of the incidence of Grade ≥3 TEAE (p = 0.112), Grade ≥3 TRAE (p = 0.892), or AEs leading to drug discontinuation (p = 0.355). Taken together, the safety endpoints suggest no relationship between ADA status and any of these 3 categories of AEs.

It should however be noted that the vast majority of ADA data, and all of the available Nab data, have been generated in patients of Chinese ethnicity, treated in Chinese centres. Immunogenic data for non-Asian patients is only available in 182 US subjects whom where part of the TAB001-01 monotherapy study. As noted prior, this imbalance (of a factor ~ 9,5) in ethnic makeup makes it

difficult to interpret transposability of overall immunogenicity findings to a non-Chinese population, even if the lopsided comparison (note the lack of confidence interval information) as shown in the below table does weakly indicate similar rates of treatment emergent ADAs.

Table 115. ADA-positive rates

Description	TAB001-01 [1] (N = 182)	All Other Studies [2] (N =1389)	p-Value [3] (Chi-Square)
ADA-positive rate (including baseline)	28 (15.4%)	135 (9.7%)	0.0814
ADA-positive rate (excluding baseline)	18 (9.9%)	113 (8.1%)	0.4207

[1] Analysed at Smithers, US.
[2] Analysed at UP Pharma, China.
[3] Comparisons by geographical region.

ADA = antidrug antibody; N = number of patients

7. Safety related to drug-drug interactions and other interactions

Drug Interactions

Since genetic polymorphisms have a limited, if any, role in the metabolism of monoclonal antibodies, drug interaction studies were not conducted and are not planned. While immunosuppressants may affect the clearance of some therapeutic proteins, corticosteroids and other immunosuppressants were not routinely administered with toripalimab but were limited to the treatment of irAEs. Drug interaction studies were not, therefore, conducted with toripalimab.

Food Effects

Toripalimab is administered intravenously, thus examination of the food effect was not necessary.

8. Discontinuation due to adverse events

Nasopharyngeal carcinoma

One patient in Cohort 7 of POLARIS-02 experienced a TRAE autoimmune myocarditis, leading to permanent discontinuation.

In JUPITER-02, TEAEs leading to discontinuation occurred in 11.6% and 4.9% of patients in the toripalimab and placebo arms, respectively. The only TRAE leading to discontinuation in the toripalimab arm in ≥ 2% of patients was pneumonia. Electrolyte imbalance, pulmonary tuberculosis, thrombocytopenia, rash, and vomiting occurred in ≥ 1% of patients.

TRAEs leading to permanent discontinuation occurred in 10.3% of patients in the toripalimab arm and 4.9% in the placebo arm. In the toripalimab arm, the most common TRAEs (≥ 1%) leading to permanent discontinuation were electrolyte imbalance, pneumonia, pulmonary tuberculosis, rash, and thrombocytopenia.

Table 116. TRAEs Leading to Permanent Discontinuation (JUPITER-02) (DCO: 8 May 2022)

Events	Toripalimab + GC N=146 (%)	Placebo + GC N=143 (%)
Any	15 (10.3)	6 (4.2)
Blood Disorders		
Thrombocytopenia	2 (1.4)	0
Anaemia	1 (0.7)	1 (0.7)

Events	Toripalimab + GC N=146 (%)	Placebo + GC N=143 (%)
Cardiac Disorders		
Cardiac failure	0	1 (0.7)
Endocrine Disorders		
Hypothyroidism	0	1 (0.7)
Eye Disorders		
Vision blurred	1 (0.7)	0
Gastrointestinal Disorders		
Abdominal pain	1 (0.7)	0
Nausea	1 (0.7)	0
Vomiting	1 (0.7)	0
General Disorders		
Fatigue	1 (0.7)	0
Disease progression	0	1 (0.7)
Hepatobiliary Disorders		
Hepatic function abnormal	1 (0.7)	0
Infections		
Pneumonia	2 (1.4)	0
Pulmonary tuberculosis	2 (1.4)	1 (0.7)
Metabolism and Nutrition		
Electrolyte imbalance	2 (1.4)	0
Hypoglycaemia	1 (0.7)	0
Musculoskeletal Disorders		
Myositis	1 (0.7)	0
Nervous System Disorders		
Headache	1 (0.7)	0
Cerebral infarction	0	1 (0.7)
Renal Disorders		
Immune-mediated renal disorder	1 (0.7)	0
Respiratory Disorders		
Epistaxis	1 (0.7)	0
Skin Disorders		
Rash	2 (1.4)	0
Psoriasis	1 (0.7)	0

Squamous cell carcinoma of the oesophagus

No patients in Cohort 6 of POLARIS-02 permanently discontinued toripalimab due to a TRAE.

TEAEs leading to permanent discontinuation occurred in 14.0% and 8.2% of patients in the toripalimab and placebo arms, respectively. Only pneumonitis resulted in discontinuation in ≥ 1% of patients.

TRAEs led to permanent discontinuation in 8.6% of patients on the toripalimab and 1.2% on the placebo arm of JUPITER-06. In the toripalimab arm, the only TRAE leading to permanent discontinuation in ≥ 1% of patients was pneumonitis.

Table 117. TRAEs Leading to Permanent Discontinuation (JUPITER-06) (DCO: 15 Feb 2022)

	Toripalimab + TP N=257 (%)	Placebo + TP N=257 (%)
Any	22 (8.6)	3 (1.2)
Cardiac Disorders		
Immune-mediated myocarditis	1 (0.4)	0
Myocardial injury	1 (0.4)	1 (0.4)
Arrhythmia	0	1 (0.4)

	Toripalimab + TP N=257 (%)	Placebo + TP N=257 (%)
Endocrine Disorders		
Adrenal insufficiency	1 (0.4)	0
Immune-mediated thyroiditis	1 (0.4)	0
Gastrointestinal Disorders		
Enteritis	1 (0.4)	0
General Disorders		
Death	1 (0.4)	0
Hepatobiliary Disorders		
Hepatic function abnormal	2 (0.8)	0
Hepatitis	1 (0.4)	0
Immune System Disorders		
Hypersensitivity	1 (0.4)	0
Injuries		
Infusion-related reaction	1 (0.4)	0
Investigations		
Alanine aminotransferase increased	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.4)	0
Blood urea increased	1 (0.4)	0
Creatinine renal clearance decreased	1 (0.4)	0
Musculoskeletal Disorders		
Arthritis	1 (0.4)	0
Myositis	1 (0.4)	0
Renal Disorders		
Cystitis haemorrhagic	1 (0.4)	0
Renal injury	0	1 (0.4)
Respiratory Disorders		
Pneumonitis	4 (1.6)	0
Tracheoesophageal fistula	1 (0.4)	0
Skin Disorders		
Rash	2 (0.8)	0
Psoriasis	1 (0.4)	0

9. Post marketing experience

Toripalimab was first approved in China on December 27, 2018. Four DSURs are available that altogether cover the period from December 23, 2017 to December 16, 2021. During the most recent reporting period, no unique safety risks that have not been reported with other PD-1 blocking antibodies were identified. Post-marketing reports have included solid organ transplant rejection and toxic epidermal necrolysis.

Toripalimab is not expected to cause cytokine release syndrome. This expectation is based on in vitro experiments demonstrating that toripalimab does not cause cytokine release. Four reports of cytokine release syndrome with toripalimab were received. Three have occurred when toripalimab was used in combination with the investigational drug RMX1002. Cytokine release syndrome is an expected adverse event for RMX1002. The 3 events occurred in a clinical trial of toripalimab (Day 1 Q3W) in combination with RMX1002 (Days 1-14 Q3W). The first patient developed fever, rash, and increased cytokine levels 9 days after administration of toripalimab. The patient responded to tocilizumab and corticosteroids and resumed both toripalimab and RMX1002. The second patient developed fever then rash 12 days after administration of toripalimab. The event worsened with multi-organ dysfunction and despite the use of tocilizumab, the patient had a seizure associated with a temperature of 39.20C. The patient ultimately responded to continued administration of corticosteroids and to discontinuation of RMX1002. The third patient developed fever, hypotension, coagulopathy, and increased cytokines 10 days after administration of toripalimab. The patient responded to corticosteroids and tocilizumab.

Rechallenge resulted in an increase in IL-6 levels (15 days after tocilizumab) but other cytokines improved.

Besides mentioned 3 patients, 1 patient developed increased liver enzymes and coagulopathy 1 day after administration of toripalimab, carboplatin, and paclitaxel. These resolved but were followed by fever, chest tightness, dyspnoea, and increased cytokine levels. The patient responded to corticosteroids.

3.6.13. Discussion on clinical safety

Phase III trials JUPITER-02 and JUPITER-06 are the main ones to provide safety information on patients with NPC and OSCC respectively, comparing toripalimab plus standard chemotherapy versus placebo plus standard chemotherapy. Study POLARIS-02 also provided an input on safety for NPC (cohort 7) and OSCC (cohort 6) together with 13 monotherapy trials on different cancer types. Additionally, safety information from post-marketing experience is available as well since toripalimab approval in China on December 27, 2018.

The applicant provided summary tables that only listed comparisons of the medians, not the means. As medians by themselves are less valuable in effect-finding comparisons between groups, this is highly unfortunate, especially given the large corpus of data provided. Comparison of the raw tables in the various CSRs does not seem to indicate that the comparisons based on means deviate significantly from those based on medians.

Median treatment duration in patients receiving monotherapy varied from 1.7 in US to 3.3 months in non-Western region. Median treatment duration in toripalimab plus chemotherapy population varied from 8.6 to 14.5 months in NPC patients and from 5.1 to 13.6 months in OSCC patients. To be noted, that median duration in JUPITER-02 was substantially longer in the toripalimab versus placebo arm - 14.5 vs. 7.9 month.

There were differences between the patients treated in the US and those outside the US, including differences in the laboratory assessments. In the majority of the patients treated in China, laboratories were obtained every 2 weeks while the majority of the patients on TAB001-01 had laboratories (after the first cycle) every 3 weeks. Further, there were differences in the laboratories collected. TAB001-01 did not routinely collect lipids, creatine phosphokinase, or amylase/lipase levels while these laboratories were collected on many of the trials conducted in China. While these groups are not directly comparable, to ensure the applicability of data from patients treated outside a Western region with the ADRs seen in a Western region, a comparison on TRAEs reported in the two groups was conducted to determine if there were any key differences. It is presented in section "Adverse events".

Overall, the strong imbalance in race representativity is noticeable, given the exclusively Asian participants in the CT15 and CT21 pivotal trials. The Applicant has 'bridged' the TRAE outcomes between both Asian and non-Asian monotherapy subgroups, by way of an inter-subgroup comparison to see if any differences could be noted. This approach is reasonable in theory, but as is discussed later, the large imbalance between Asian and non-Asian subjects, and the differences in certain testing/result acquisition, makes this comparison very difficult to interpret.

A similar bridging exercise cannot be done for the pivotal trial population owing to the lack of Non-Asian exposed patients, but given that the concomitant chemotherapies used are well known it should be entirely feasible to transpose findings of the monotherapy inter-subgroup comparison to the pivotal safety outcomes, though as noted in the previous paragraph the value and interpretability of this comparison exercise is questioned

ADR methodology

The applicant analysis for ADR selection focused on AEs identified as related to toripalimab by the Investigator or Applicant (TRAEs). The trials included in this submission collected Investigator-assessed relationship in the following ways:

- Related or unrelated (JUPITER-02, JUPITER-06)
- Definitely related, probably related, possibly related, possibly unrelated, unlikely related and unrelated (toripalimab monotherapy safety database)
- Definitely, probably, or possibly related AEs will be considered TRAEs.

Any AE identified as related, definitely related, probably related, or possibly related were considered TRAEs. In addition, the small number of adverse events in which the relationship to toripalimab was not recorded were considered related. In addition, as requested, the Applicant conducted a secondary review of investigator-assessed, treatment-related, out-of-bound investigations according to the process outlined in the response to D180.

As recommended in Guidance, closely related MedDRA preferred terms (PT) were aggregated to present a more accurate assessment of the incidence of AE.

The incidence of the TRAEs presented in the ADR table in section 4.8 of the SmPC is based on all AEs, regardless of relationship to toripalimab, in accordance with EMA guidelines.

The incidence of hypothyroidism seen in the toripalimab arm of JUPITER-02 is greater than that seen in the toripalimab arm of JUPITER-06 or in the toripalimab monotherapy safety database. This could be explained by the use of prior radiation to the neck in many of these patients. More common anaemia in toripalimab patients may be explained by the longer time on treatment in this arm. TRAEs such as thyroid function test abnormal, pyrexia, rash, and pruritus are known to be common for other PD-1 blocking antibodies as well.

In general, the incidences of thyroid disease (both hyper and hypothyroidism) and skin reactions were higher in with toripalimab in combination with chemotherapy, while pancreatitis and hepatitis were higher in the monotherapy population. Neither JUPITER-02 nor JUPITER-06 routinely collected amylase and lipase levels while 10 of the 13 trials included in the toripalimab monotherapy safety database routinely collected these laboratories. This may have resulted in a difference in the detection of pancreatitis.

Arrhythmias have not been associated with PD-1 blocking antibodies and the difference in incidence for arrhythmias identified as TEAEs or as TRAEs was less than 5% (9.4% [38 patients] vs. 5.5% [22 patients]). Of 38 toripalimab-treated patients with a TEAE of arrythmia, all 5 patients enrolled on JUPITER-02 experienced Grade 1-2 events and all were considered related to toripalimab. None of the patients required a modification of toripalimab dosing, and the outcome of all 5 events was recovered or recovering. One of these 5 patients had a history of arrhythmia. In JUPITER-06, 32/33 (97.0%) of patients had a Grade 1-2 adverse event, and one Grade 3 event, which was considered unrelated to toripalimab. Cardiac risk factors or a history of arrhythmia were present in 24/33 patients. In 13 patients (39%), the event was unresolved).

Immune-related adverse events are the most clinically significant ones in patients treated with PD-1 blocking antibodies. In JUPITER-02, irAEs occurred in 41.1% of patients. Grade ≥ 3 events occurred in 6.8% of patients. In JUPITER-06, irAEs occurred in 29.2% of patients. Grade ≥ 3 events occurred in 8.2% of patients.

In pooled analysis of JUPITER-02 and JUPITER-06, the most common events were Hypothyroidism (17.1%), Immune-related skin reactions (9.4%), Immune-related pneumonitis (3.2%). The most common Grade 3-4 events were Immune-related skin reactions (3%), Immune-related hepatitis

(1.7%). In toripalimab monotherapy, irAEs occurred in 26.3% of patients. Grade ≥ 3 events occurred in 6.1% of patients. The most common events were Hypothyroidism (13.9%), Immune-related skin reactions (3.9%), Hyperthyroidism (6.3%), Immune-related hepatitis (3.2%). The most common Grade 3-4 events were Immune-related hepatitis (2.8%) and Immune-related pneumonitis (0.9%). In section 4.2 of toripalimab SmPC, recommended treatment modifications due to immune-related adverse reactions are listed, based on their grade. TRAEs leading to discontinuation in toripalimab patients occurred in 10.3% of patients of JUPITER-02, 8.6% of patients of JUPITER-06 and 5.5% of patients in the toripalimab monotherapy safety database. To be noted, that in toripalimab plus chemotherapy group, 6.0% patients permanently discontinued and 4.7% interrupted dosing due to an irAE.

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 may occur in any organ or tissue and may affect more than one body system simultaneously.

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.

Toripalimab should be withheld or permanently discontinued depending on the type and severity of the adverse reaction. If treatment with toripalimab should be withheld or permanently discontinued, systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) should be administered until improvement to Grade 1 or less. If myocarditis is suspected, high-dose steroids (e.g., methylprednisolone 1 g/day intravenously for 3–5 days) should be initiated. Upon improvement to Grade 1 or less, corticosteroid taper should be initiated. Administration of other systemic immunosuppressants in patients whose immune-related adverse reactions are not controlled with corticosteroid therapy should be considered. Hormone replacement therapy for endocrinopathies should be instituted as warranted.

Treatment with toripalimab may be restarted within 12 weeks after last dose of toripalimab if the adverse reaction recovers to Grade ≤1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Treatment with toripalimab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones. Further information is included in section 4.4 of the SmPC on the specific immune-related adverse reactions of immune-related pneumonitis, immune-related colitis, immune-related hepatitis and hepatotoxicity, immune-related endocrinopathies including adrenal insufficiency, hypophysitis, thyroid disorders and type 1 diabetes mellitus which can present with diabetic ketoacidosis, immune-related nephritis, immune-related skin adverse reactions, immune-related myocarditis, immune-related myositis and other immune-related adverse reactions including potentially serious events (e.g., encephalitis, demyelinating neuropathy [including Guillain Barré syndrome] myasthenic syndrome, sarcoidosis, vasculitis, rhabdomyolysis).

Immune related adverse reactions are included as an important identified risk in the RMP. A patient alert card has been added as an additional risk minimisation measure for this risk.

Infusion-related reactions (IRRs) occurred in 4.0% of toripalimab plus Chemotherapy patients. There were two Grade 3 and 4 reactions, leading to permanent discontinuation. In toripalimab monotherapy,

IRRs occurred in 2.0% of patients. There was only one Grade 3 event. In case of IRRs, recommendations are listed in section 4.2 of toripalimab SmPC, based on grade of the reaction. A warning is also reflected in section 4.4 of the SmPC informing that toripalimab can cause severe and potentially life-threatening IRRs, advising that patients should be monitored for signs and symptoms of IRRs and informing that for patients with IRRs, pre-medications with antipyretics and antihistamines to mitigate the risk of subsequent infusion reactions may be considered.

With regards to long-term, TRAEs occurred in 76.8% of patients on toripalimab monotherapy. Of those, Grade ≥ 3 events occurred in 9.2% of patients. The most common TRAEs after 1 year were Thyroid function test abnormal (25.4%), Lipids abnormal (14.1%) and Leukopenia (13%). The incidence of TRAEs in general is similar after one year of treatment, comparing with monotherapy overall, with the lower incidence of Grade ≥ 3 events.

In total, there were 97 deaths in both monotherapy and combined treatment populations in toripalimab arm. 28 deaths occurred in combined treatment populations in toripalimab arm versus 24 deaths in placebo arm. Of mentioned 97 deaths, 8 were considered as treatment-related by the investigator. Of those 8, five (5) were considered as treatment-related by the applicant (to be noted that one of those 5 deaths occurred 61 days after the last dose of toripalimab).

The percentage of death in JUPITER-02 (toripalimab arm), JUPITER-06 (toripalimab arm) and toripalimab monotherapy is as follows: 3.4%, 8.6%, 6.2%, respectively. The larger percentage of deaths in JUPITER-06 may be explained by the more aggressive nature of the underlying disease OSCC, as compared to NPC in JUPITER-02.

On JUPITER-02, the most common TRAEs were thrombocytopenia, neutropenia, pneumonia, anaemia, leukopenia, epistaxis, hepatic function abnormal, rash, and upper respiratory infection. These are all listed in section 4.8 of SmPC. The largest difference in incidence of TRAEs in toripalimab and placebo arms were Pneumonia (7.5% vs. 2.1%) and Neutropenia (10.3% vs. 6.3%). In JUPITER-06, the most common TRAEs - SAEs were immune-mediated lung disease, hepatic function abnormal and pneumonia. The largest difference in incidence of TRAEs in toripalimab and placebo arms were Immune-mediated lung disease (1.6% vs. 0%) and Hepatic function abnormal (1.2% vs. 0.4%)..

A substantial number of the SAEs in JUPITER-02 and JUPITER-06 were due to irAEs.

According to the Applicant, the similar incidence of SAEs on the toripalimab and placebo arms of JUPITER-02 suggests that toripalimab did not increase the risks of SAEs when added to the underlying chemotherapeutic regimen.

With regards to worsening haematology parameters in JUPITER-02, the percentages of grade 1-4 cases were similar in both arms. Grade 3-4 events were more common in toripalimab arm, comparing with placebo: Anaemia (50% vs. 39.2%), Lymphopenia (56.8% vs. 49.3%), Thrombocytopenia (33.8% vs. 30.8%). In regard to worsening biochemistry values, higher incidence of worsening parameters (both all grades and grade 3-4) were recorded in toripalimab arm. The biggest difference between arms was in regard to grade 3-4 Hyponatraemia (9% vs. 5.6%), ALT increased (6.9% vs. 3.5%), Hypokalaemia (11.8% vs. 8.4%), Hypermagnesaemia (4.2% 0.7%). These results may be partially explained by longer time on treatment in toripalimab arm. Also, haematological toxicity has been noticed with other PD-1 blocking antibodies in combination with chemotherapy. The incidence of worsening haematology parameters in JUPITER-06 was greater in toripalimab arm for all grades in general and for grade 3-4 events. Grade 3-4 events in toripalimab arm versus placebo occurred as follows: Leukopenia (21% vs. 13.4%), Neutropenia (45.2% vs. 36.4%), Lymphopenia (17.5% vs. 12.3%). In regard to other parameters, grade 3-4 increase in ALT more commonly occurred in toripalimab arm (6% vs. 2%).

No studies have been conducted with toripalimab with pregnant and breast-feeding women. 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 (see section 4.6 of the SmPC).

In general, no differences in safety were observed between patients ≥ 65 years and < 65 years of age receiving toripalimab in combination with chemotherapy. Number of total AEs are comparable in three ages groups, with largest number of SAEs in the group of Age 75-84. However, due to the low number of patients in mentioned group, no meaningful conclusions can be drawn. In general, no dose modifications or special requirements are warranted with regards to race, sex, mild or moderate renal impairment or hepatic impairment.

The incidence of ADA in patients treated with toripalimab was approximately 10-11%. Number of TRAEs was slightly higher in ADA positive versus ADA negative patients for toripalimab plus chemotherapy (89.7% vs. 82.6%). However, it is difficult to draw conclusions due to the small number of ADA positive patients.

No paediatric safety data is available for toripalimab.

Post-marketing reports have included solid organ transplant rejection (reflected in section 4.4 of the SmPC) and toxic epidermal necrolysis (reflected in section 4.8 of the SmPC).

A warning in section 4.4 of the SmPC informs that the treatment with toripalimab may increase the risk of rejection in solid organ transplant recipients and that the benefit of treatment with toripalimab versus the risk of possible organ rejection should be considered in these patients.

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.

Solid organ transplant rejection is included as an important identified risk in the RMP, while GVHD with toripalimab after allogeneic HSCT is included as an important potential risk in the RMP. Both in the overall safety database and in the JUPITER-02/JUPITER-6 pooled dataset, most of the patients (≥82.6%) with laboratory abnormalities reported as either TEAEs or TRAEs required no change in toripalimab dosing. Permanent discontinuation for out-of-bounds investigations reported either as TEAEs or TRAEs was low, ranging from 0.8% to 2.4% of patients. A very large imbalance exists within the full safety data set regarding the race/ethnicity representativity and potential local differences in clinical practice. Asian, more specifically Chinese patients, treated in clinical centres in China outnumber the non-Asian population (consisting of mainly Caucasian subjects treated in the US) by a factor of approximately 9.5. However, based on new POPPK model and the flat E-R provided by the applicant, extrapolation of the safety results obtained with the flat dose in the Asian population to the non-Asian population is considered to be reasonable.

3.6.14. Conclusions on the clinical safety

In general, the safety data presented for toripalimab are acceptable and sufficient to support the evaluation of its safety profile. The main safety concerns are immune-related adverse reactions, as expected based on the mechanism of action. A substantial number of the SAEs in JUPITER-02,

JUPITER-06 was recognised as irAEs. Fatal cases due to irADRs were reported. Immune-related adverse reactions are listed in section 4.8 of SmPC and appropriate warnings and recommendations regarding, the identification, the management (including treatment modifications) and the monitoring of irADRs have been included in sections 4.2 and 4.4 of the SmPC. Immune-related adverse reactions are also included as an important identified risk in the RMP, for which additional risk minimisation measures (patient alert card) have been added.

3.7. Risk Management Plan

3.7.1. Safety concerns

Table 118 Summary of safety concerns

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

3.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities are planned.

3.7.3. 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:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

	SmPC section 4.4 PL section 2 and 4. Additional risk minimisation measures: 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

3.7.4. Conclusion

The CHMP considers that the risk management plan version 1.5 dated 12-07-2024 is acceptable.

3.8. Pharmacovigilance

3.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17.12.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

3.9. Product information

3.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Loqtorzi (toripalimab) is included in the additional monitoring list as it contains a new active substance not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

The approved indications are:

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

Loqtorzi, in combination with cisplatin and paclitaxel, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.

Nasopharyngeal Cancer (NPC)

NPC is a serious and life-threatening head and neck cancer that is associated with EBV infection, tobacco and alcohol. It is rare in EU. Diagnosis is based on inspection and biopsy, with CT, MRI, or PET to evaluate extent. Treatment is with radiation, chemotherapy, and, rarely, surgery(NCCN Guidelines, 2022).

Oesophageal Squamous Cell Carcinoma (OSCC)

OSCC is both adenocarcinoma and squamous cell carcinoma of the oesophagus. It is rare in EU. The most common malignant tumour in the proximal two thirds of the oesophagus is squamous cell carcinoma; adenocarcinoma is the most common in the distal one third (Globocan, 2020). Symptoms are progressive dysphagia and weight loss. Diagnosis is by endoscopy, followed by CT and endoscopic ultrasound for staging. Treatment varies with stage and generally includes surgery with or without chemotherapy and radiation. Long-term survival is poor except for patients with local disease.

4.1.2. Available therapies and unmet medical need

Nasopharyngeal cancer (NPC)

The European Society of Medical Oncology (ESMO) guidelines for the treatment of patients with recurrent or metastatic NPC recommend first-line treatment with cisplatin and gemcitabine.

Oesophageal squamous cell carcinoma (OSCC)

The recently updated ESMO guidelines (Obermannova et al, 2022) recommend a platinum-fluoropyrimidine doublet with a PD-1 blocking antibody for treatment of locally advanced or metastatic OSCC but note that a recent trial of a PD-1 inhibitor in combination with carboplatin/paclitaxel has been conducted. The ESMO guidelines also discuss the use of carboplatin and paclitaxel in patients with early-stage disease (van Hagen et al, 2012). Patients with oesophageal cancer that is metastatic or unresectable and cannot be treated with curative-intent CRT have a poor prognosis; survival in clinical trials has historically been <1 year; however, the use of ICIs with ChT has recently improved survival for this patient group.

NPC and OSCC are severe and life-threatening conditions that constitute an unmet medical need.

4.1.3. Main clinical studies

The main study in NPC patients was a randomised, placebo-controlled, multi-centre, double-blind trial that enrolled 289 patients with recurrent locally advanced or metastatic nasopharyngeal cancer (NPC) who had not previously received systemic therapy for recurrent or metastatic disease (JUPITER-02).

The main study in OSCC patients was a randomised, multi-centre, double-blind trial conducted in 514 patients with recurrent locally advanced or metastatic squamous cell cancer of the oesophagus (OSCC) who had not previously received systemic therapy for recurrent or metastatic disease (JUPITER-06).

4.2. Favourable effects

In the NPC population in the pivotal trial JUPITER-02, the median PFS was 21.4 months (95% CI: 11.73, NE) in the toripalimab treatment arm and 8.2 months (95% CI: 7.03, 9.79) in the placebo treatment arm, the stratified HR was 0.52 (95% CI: 0.374, 0.726; nominal p<0.0001) at the time of the pre-specified interim analysis. The final PFS results were also reported. At the pre-specified final analysis of OS, the study showed a statistically significant improvement in OS (HR 0.63; p=0.0083) with median OS NE (38.7, NE) and 33.7 months (27.0, 44.2) in active and control group, with 39% and 53% of maturity, respectively.

In OSCC population the pivotal trial JUPITER-06 showed for the co-primary efficacy endpoint BIRC-assessed PFS, that the stratified HR was 0.58 (95% CI: 0.461, 0.738; nominal p<0.00001), median PFS was 5.7 months (95% CI: 5.6, 7.0) in the toripalimab treatment arm and 5.5 months (95% CI: 5.2, 5.6) in the placebo treatment arm. Median OS was 17.0 months (95% CI:14.0, NE) in the toripalimab arm and 11.0 months (95% CI:10.4, 12.6) in the placebo arm, stratified HR for OS was 0.58 (95% CI: 0.425, 0.783, p value 0.00036) at the DCO of February 2022. Final OS analysis was conducted with DCO 23 February 2023 and the results were consistent.

4.3. Uncertainties and limitations about favourable effects

In OSCC population, efficacy results by PD-L1 expression in several large phase 3 studies including KEYNOTE-590, CheckMate 648, and ESCORT-1st all suggest a positive correlation between PD-L1

expression level (either on tumour cells or both tumour and immune cells) and the efficacy of PD-1 blockade in combination with chemotherapy. No such correlation has been observed with toripalimab in the different PD-L1 expression subgroups defined with different cut-offs and not used as stratification factors. Data supporting the reliability of the JS311 assay, an analysis of the baseline demographics and disease characteristics by PD-L1 expression status together with arguments regarding the potential higher binding affinity compared to previously approved PD-1 blocking antibodies were submitted providing further reassurance on the robustness of the data in the PD-L1-low/negative OSCC patients.

4.4. Unfavourable effects

In JUPITER-02 and JUPITER-06 (toripalimab plus chemotherapy), 99.5%/83.1% patients experienced TEAEs/TRAEs

The most important unfavourable effects were immune-related AEs – 3 deaths occurred due to irAEs and permanent discontinuation occurred in 6.0% of patients receiving toripalimab in combination with chemotherapy.

In the patient population treated with toripalimab in combination with chemotherapy, the most frequent adverse reactions were anaemia (44.9%), leukopenia (41.7%), neutropenia (39.0%), thrombocytopenia (30.3%), nausea (29.8%), vomiting (27.3%), decreased appetite (23.8%), rash (23.8%), fatigue (23.6%), liver function test abnormal (22.3%), hypothyroidism (18.4%), constipation (16.6%), neuropathy (15.1%), colitis (14.1), pyrexia (13.6%), cough (11.4%), pruritus (11.4%), creatinine renal clearance decreased (11.2%), and hyponatraemia (10.2%). Incidences of grades 3-5 adverse reactions in patients with NPC were 81.5% for toripalimab combination therapy and 83.9% for chemotherapy alone and in patients with OSCC were 24.9% for toripalimab combination therapy and 13.6% for chemotherapy alone.

4.5. Uncertainties and limitations about unfavourable effects

Not applicable.

4.6. Effects Table

Table 119: Effects Table for toripalimab in nasopharyngeal carcinoma (data cut-off: 08 June 2021 for PFS and 18 November 2022 for OS)

Effect	Short Description	Unit	Toripalimab + cisplatin+ gemcitabine N=146	Placebo +cisplatin + gemcitabine N=143	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median PFS	Progression-free survival	Months (95% CI)	21.4 (11.7, NE)	8.2 (7.0, 9.8)	**SoE:** Consistent among sensitivity analyses and soubgroup analyses	(1)
		HR (95% CI) p-value	0.52 (0.37, 0.73) <0.0001			
Median OS	Overall survival (OS)	Months (95% CI)	NE (38.7, NE)	33.7 (27.0, 44.2)	**SoE:** Consistent among sensitivity analyses and subgroup analyses	
		HR (95% CI) p-value	0.63 (0.45, 0.89) 0.0083			

Effect	Short Description	Unit	Toripalimab + cisplatin+ gemcitabine N=146	Placebo +cisplatin + gemcitabine N=143	Uncertainties/ Strength of evidence	References
Any TRAE	Grade ⩾ 3	%	81.5	83.9	N/A	(1)
Hypothyroidism	All Grades	%	32.9	17.5	N/A	(1)
Pneumonia	All Grades	%	13.7	4.9	N/A	(1)
Immune-Related TEAE	Any Investigator-assessed immune-Related TEAE	%	54.1	21.7	N/A	(1)
Immune-related Endocrine disorders	Investigator-assessed Immune-related TEAE Endocrine disorders	%	24.0	9.1	N/A	(1)
Immune-related Skin disorders	Investigator-assessed Immune-related TEAE Skin disorders	%	18.5	7.7	N/A	(1)
Immune-related Investigations	Investigator-assessed Immune-related TEAE Investigations	%	17.8	4.2	N/A	(1)
Immune-related Pneumonia	Investigator-assessed Immune-related TEAE Pneumonia	%	2.1	0	N/A	(1)

Abbreviations: T – toripalimab (+ chemotherapy), P – placebo (+ chemotherapy), NE: Not estimable
Notes: (1) JS001-015-III-NPC (JUPITER-02) study report, (2) JS001-021-III-ESCC (JUPITER-06) study report.

Table 120: Effects Table for toripalimab in oesophageal squamous cell carcinoma (data cut-off: 22 March 2021 for PFS and 23 February 2023 for OS)

Effect	Short Description	Unit	Toripalimab + paclitaxel/ cisplatin N=257	Placebo +paclitaxel/ cisplatin N=257	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median OS	Overall survival (OS)	Months (95% CI)	17.7 (14.6, 20.8)	12.9 (11.6, 14.1)	**SoE:** Consistent among sensitivity analyses and soubgroup analyses	(2)
		HR (95% CI) p-value	0.72 (0.58, 0.88) 0.0016			
median PFS	Progression free survival (PFS)	Months (95% CI)	5.7 (5.6, 7.0)	5.5 (5.2, 5.6)	**Unc:** PFS difference not clinically significant. **SoE:** Consistent among sensitivity analyses and subgroup analyses	(2)
		HR (95% CI) p-value	0.58 (0.46, 0.74) < 0.0001			

Effect	Short Description	Unit	Toripalimab + paclitaxel/ cisplatin N=257	Placebo +paclitaxel/ cisplatin N=257	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
Any TRAE	Grade ≥ 3	%	24.9	35 (13.6)	N/A	(2)
Hypothyroidism	All Grades	%	10.1	14 (5.4)	N/A	(2)
Thyroid function test abnormal	All Grades	%	8.9	10 (3.9)	N/A	(2)
Immune-Related TEAE	Any Investigator-assessed immune-Related TEAE	%	43.6	26.5	N/A	(2)
Immune-related Rash	Investigator-assessed Immune-related TEAE Rash	%	12.1	3.5	N/A	(2)
Immune-related Pneumonitis	Investigator-assessed Immune-related TEAE Pneumonitis	%	1.6	0.4	N/A	(2)
Immune-related Hypothyroidism	Investigator-assessed Immune-related TEAE Hypothyroidism	%	6.6	3.9	N/A	(2)

Abbreviations: T – toripalimab (+ chemotherapy), P – placebo (+ chemotherapy), NE: Not estimable
Notes: (2) JS001-021-III-ESCC (JUPITER-06) study report.

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

JUPITER-02, investigating toripalimab in adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma showed a statistical improvement of the median PFS when compared to placebo, with chemotherapy backbone in both arms. In the final OS results at DCO 18 November 2022, a statistically significant improvement was observed (median OS: not estimable in the toripalimab arm vs 33.7 months in the placebo arm) for patients in the add-on toripalimab treatment group.

In JUPITER-06, toripalimab in combination with standard chemotherapy prolonged OS compared to placebo in combination with standard chemotherapy in patients with recurrent locally advanced or metastatic squamous cell cancer of the oesophagus who had not previously received systemic therapy for recurrent or metastatic disease. The results of OS are clinically and statistically significant. However, for the co-primary efficacy endpoint of PFS, even if statistically significant, only 0.2 month difference in median PFS was observed for toripalimab compared to placebo. Nevertheless, the primary objective of the study was met.

In general, the safety profile of toripalimab is acceptable in the proposed indications. Consistent with other anti PD-1/PD-L1, one of the main safety concerns is immune-related adverse reactions. A significant number of the SAEs reported in JUPITER-02, JUPITER-06 and in studies conducted in monotherapy, was recognized as irADRs. Fatal irADRs were reported. Early identification and management of irADRs 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. The SmPC has been updated to reflect the available data and recommendations regarding the management of irADRs in sections 4.2, 4.4 and 4.8 of the SmPC.

4.7.2. Balance of benefits and risks

The benefit/risk balance of toripalimab is positive for:

- the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma (in combination with cisplatin and gemcitabine) and
- the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (in combination with cisplatin and paclitaxel).

In general, the safety data presented from toripalimab are acceptable to support the assessment of its safety profile and benefit-risk conclusions for the respective indications.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4.8. Conclusions

The overall benefit/risk balance of Loqtorzi is positive for both NPC and OSCC indications, subject to the conditions stated in section 'Recommendations'.

5. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by a majority of 28 out of 29 votes that the benefit-risk balance of Loqtorzi is favourable in the following indications:

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

Loqtorzi, in combination with cisplatin and paclitaxel, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Loqtorzi is marketed, all healthcare professionals who are expected to prescribe and use Loqtorzi have access to/are provided with the patient alert card.

The Patient Alert Card shall contain the following key messages:

- That Loqtorzi treatment may increase the risk of:
    - Immune-related pneumonitis
    - Immune-related colitis
    - Immune-related hepatitis
    - Immune-related nephritis
    - Immune-related endocrinopathies
    - Immune-related skin adverse reactions
    - Other immune-related adverse reactions
- Signs or symptoms of the safety concern and when to seek attention from a healthcare provider (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).

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Toripalimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Divergent position

Divergent position to the majority recommendation is appended to this report.

6. Appendix

6.1. Divergent position dated 25 July 2024

APPENDIX

DIVERGENT POSITION DATED 25 July 2024

DIVERGENT POSITION DATED 25 July 2024

Loqtorzi EMEA/H/C/006120/0000

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Loqtorzi indicated for the following indication:

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.

The reason for divergent opinion was the following:

Loqtorzi in combination with cisplatin and paclitaxel showed progression free survival (PFS) and overall survival (OS) benefits vs. cisplatin and paclitaxel in the intention-to-treat population of pivotal trial JUPITER-06. In this trial, PD-L1 expression was evaluated with assay JS311, and the exploratory analysis of efficacy by PD-L1 status suggests that no prominent effect on either PFS or OS is apparent in the experimental arm. The results of large international trials in similar clinical settings (KEYNOTE-590 and CheckMate 648, in which PD-L1 status was evaluated by assays 22C3 and 28-8, respectively) are considerably divergent and resulted in PD-L1 restricted oesophageal cancer indications for the related medicinal products. Based on an *ad hoc* analysis on 50 samples from patients with non-small cell lung cancer (NSCLC) and 50 with oesophageal squamous cell cancer, the Applicant for Loqtorzi concluded that PD-L1 expression assays JS311, 22C3 and 28-8 are concordant among themselves. Concordance was also apparently shown between JS311 and 22C3 in 88 gastric cancer and 70 triple negative breast cancer samples. Concordance among 22C3, 28-8, SP263, and JS311 among 280 samples from patients with NSCLC is also described in a published article (Wang et al, JAMA Netw Open 2020 Oct).

Given biological plausibility and the fact that results from the pivotal trial considerably differ from what has been previously evidenced in this setting, the results of the *ad hoc* concordance analyses in a limited number of patients with oesophageal cancer are not considered reliable and a PD-L1 unrestricted indication for toripalimab + cisplatin + paclitaxel in oesophageal squamous cell carcinoma is not considered justified.

CHMP Members expressing a divergent opinion:

Thalia Marie Estrup Blicher

Hrefna Gudmundsdottir