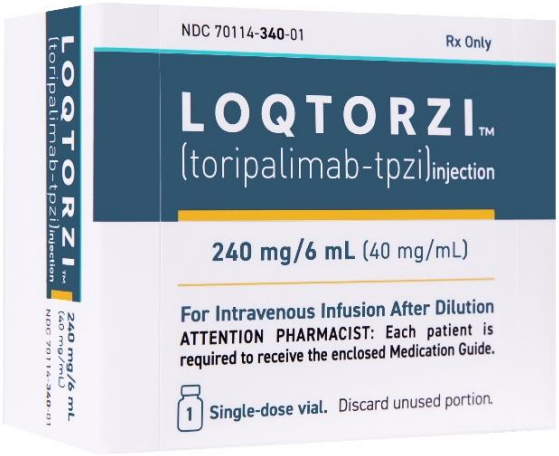
APPLICATION FOR SUBMISSION TO THE 25th EXPERT COMMITTEE ON THE SELECTION AND USE OF ESSENTIAL MEDICINES



PROPOSAL FOR THE ADDITION OF TORIPALIMAB FOR NASOPHARYNGEAL CARCINOMA AND ESOPHAGEAL SQUAMOUS CELL CARCINOMA TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES

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This application was prepared by Shanghai Junshi Biosciences Co., Ltd. (Junshi), a biotech company based in China, aiming to become an innovative and globally competitive biopharmaceutical company with a whole-industry-chain layout that encompasses R&D, manufacturing and commercialization. Founded in December 2012, Junshi stands at the forefront of R&D for large molecule drugs. Junshi is the first PRC company to commercialize anti-PD-1 monoclonal antibody, Toripalimab. Junshi has listed on main board of the Hong Kong Exchange (stock code:1877.HK) on 12/24/2018 and the Science and Technology Innovation Board of Shanghai Stock Exchange on 06/15/2020 (stock code: 688180.SHSE).

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Cover Photo: Toripalimab Injection Package

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1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION OF TORIPALIMAB FOR NASOPHARYNGEAL CARCINOMA AND ESOPHAGEAL SQUAMOUS CELL CARCINOMA ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES

This submission advocates the inclusion of toripalimab, an anti PD-1 antibody developed by Junshi for the treatment of two types of cancers, as an individual medicine in the complementary list of the EML for the treatment of adult patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma (RM-NPC) and recurrent or metastatic esophageal squamous cell carcinoma (ESCC) in combination with chemotherapy.

NPC is a rare malignant cancer, while esophageal cancer ranks sixth in mortality of all cancers. However, global data from Global Cancer illustrates low-income countries in Southeast Asia for NPC and in Eastern Asia for ESCC have an unbalanced global burden of 67% and 59% respectively. With the poor implement of early diagnosis and high rate of recurrence and metastasis of NPC and ESCC, countries in Asia carry heavier burden of disease than others and even more in the future. Considering that the clinical benefits of first-line chemotherapy for advanced NPC and ESCC remain limited, an efficient and accessible immunomodulator medicine is an urgent unmet clinical need especially for developing countries.

The evidence presented in this application suggests that adding toripalimab would provide a number of public health and normative benefits that would ultimately help bring down global mortality rates associated with the burden of nasopharyngeal carcinoma and esophageal squamous cell carcinoma, as well as improving access of developing countries to medicines.

Results of the clinical studies indicate that adding toripalimab to chemotherapy regimens leads to clinically important gain of progression-free survival and overall survival both in the treatment for NPC and ESCC. Regarding to harms and toxicity, toripalimab has manageable safety profile compared with chemotherapy.

Lifesaving properties, safety, and cost-effectiveness of toripalimab plus chemotherapy for the treatment of NPC and ESCC have been well-demonstrated with several improvements highlighted below:

1) Efficacy of the first-line treatment of recurrent or metastatic NPC

- Significant improvement in PFS: mPFS 21.4 vs. 8.2 months. The HR was 0.52
- Significant reduction in risk of death: A statistically significant OS improvement was observed with median OS not reached for the toripalimab-containing regimen and 33.7 months for the placebo-containing regimen. The HR was 0.63.
- The improvements of PFS and OS in the toripalimab arm were observed across key subgroups, including all PD-L1 expression subgroups

2) Efficacy of the first-line treatment of advanced or metastatic ESCC

- Significant improvement in OS: mOS 17.0 vs. 11.0 months, reduced the risk of deaths by 42%
- Statistically significant improvement in PFS: mPFS 5.7 vs. 5.5 months, reduced the risk of progression or deaths by 42%
- An outperformed ORR: 69.3% vs 52.1%, increased by 17.2%

3) No new safety signals were identified with toripalimab added to chemotherapy.

4) Cost and cost-effectiveness

- Toripalimab was more affordable among immunotherapies in the treatment of RM-NPC and ESCC.
- Wholesale acquisition cost of the one-cycle-usage of toripalimab is only 80% of the cost of pembrolizumab

Considering the excellent clinical benefits shown in the two clinical trial results, toripalimab was firstly approved to use in China for first-line and next-line treatment of adults with RM-NPC, and for the first-line treatment of adult patients with unresectable advanced ESCC.

On October 27th 2023, the U.S. Food and Drug Administration("FDA") approved toripalimab for the first-line treatment of adults with RM-NPC and for adults with RM-NPC with disease progression on or after a platinum-containing chemotherapy.

On September 14th 2024, the European Medicines Agency("EMA") approved that toripalimab is indicated for the first-line treatment of adult patients with RM-NPC and indicated for the first-line treatment of adult patients with ESCC.

Toripalimab has also been approved for marketing in India and China's Hong Kong Special Administrative Region for the first-line treatment of adult patients with RM-NPC, and for the treatment of adult patients with RM-NPC with disease progression on or after a platinum-containing chemotherapy.

As of now, toripalimab has been approved for marketing in over 30 countries and regions across 3 continents worldwide, and new drug applications are under review by regulatory authorities in the UK, Australia, Singapore, South Africa, Chile and Jordan and other countries.

At present, the WHO Essential Medicines List (EML) does not include any immunomodulator for NPC and there is no recommended medicine for ESCC. Inclusion of toripalimab for the proposed indication would widen access to innovative medications for the treatment and provide an effective alternative for many patients around world, especially in developing countries.

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

The relevant WHO technical department is the WHO Department of Non-communicable Diseases. Our contact in the preparation of this application have been:

- Dr. André Ilbawi, M.D., Technical lead, Cancer Control

On December 13, 2022, an online consultation meeting was held with Dr Ilbawi to have a general discussion of this application. The key outcomes of that meeting are summarized in Annex I.

3. ORGANIZATIONS CONSULTED AND/OR SUPPORTING THE APPLICATION

The following organization was consulted in relation to this application. A letter of support is also provided, included in Annex II:

- The Center for Drug Safety and Policy Research, Xi'an Jiaotong University, Xi'an, China
  Contacts: Professor Yu Fang, yufang@mail.xjtu.edu.cn

4. KEY INFORMATION FOR THE PROPOSED MEDICINE

- **International non-proprietary name (INN) of the proposed medicine**

TORIPALIMAB

- **Anatomical therapeutic chemical (ATC) code of the proposed medicine**

L01FF13

- **Dosage form(s) and strength(s) of the proposed medicine**

A 6 mL vial of concentrate for solution contains 240 mg of toripalimab. Each mL of concentrate for solution contains 40 mg of toripalimab.

Toripalimab is an anti-programmed cell death protein-1 (PD-1) immunoglobulin G4 (IgG4) humanised monoclonal antibody, produced in Chinese hamster ovary cells by recombinant DNA technology.

- **Therapeutic indications**

Nasopharyngeal Carcinoma:

1) Toripalimab, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with recurrent or metastatic, locally advanced nasopharyngeal carcinoma.
2) Toripalimab as a single agent is indicated the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy

Esophageal Squamous Cell Carcinoma:

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

- **International Classification of Diseases (ICD-11) classification**

Nasopharyngeal carcinoma: 2B6B Malignant neoplasms of nasopharynx

Esophageal squamous cell carcinoma: 2B70.1 Squamous cell carcinoma of oesophagus

- **Listing Proposed For the EML only**

5. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP

This proposal requests the inclusion of toripalimab as an individual medicine under 8.2.3 Immunomodulators.

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

- **Epidemiological information on disease burden**

Nasopharyngeal carcinoma

NPC is considered as a special type of head and neck cancer due to its unique epidemiology, skewed pathology and specific response to treatment. NPC is a rare and malignant cancer with the highest incidences in South-Eastern Asia, Eastern Asia, Eastern Africa, and Middle Africa.[1] In 2022, there were 120,434 new cases and 73,482 deaths worldwide. The incidence age-standardized rates (ASRs) for NPC is 1.3 per 100,000 and the mortality ASRs for NPC is 0.77 per 100,000. There is a substantial geographical variance within the country. Asia accounts for above 85% of the incidence, mortality and 5-year prevalence and more than 70% occurred in Southeast and East Asia.[2]

Tragically, global data from the WHO illustrate poorer outcomes of NPC in endemic areas in Southeast Asia, which has an unbalanced global burden of 67% [3]. In the absence of a wide coverage of an effective screening programme in place on global scale, NPC diagnoses occur in advanced stages. In early detection, 80% of the patients are already at an advanced stage of the disease. For instance in Indonesia, lack of knowledge among the general practitioners working in health centers regarding the various aspects of nasopharynx cancer, may lead to a delay in diagnosis [4].

Moreover, NPC has a high rate of recurrence and metastasis. Nearly 80% of patients develop locally advanced disease and are at high risk of recurrence because patients at an early stage present anonymous symptoms in most cases [5, 6]. The incidences of local recurrence and distant metastases in endemic NPC range from 10% to 20% [7]. Until now, although there has been significant improvement in the early diagnosis and treatment strategy for NPC, the social and economic burden is still increasing. There was a consistent yearly increase in the NPC incidence from 2009 to 2019 worldwide (from 121.65×10^3 cases in 2009 to 176.50×10^3 cases in 2019, increasing by 45%). Globally, the Disability-Adjusted Life Years (DALYs) were increasing from 2046.98×10^3 in 2009 to 2335.10×10^3 in 2019 [8]. The globally projected age-standardized incidence rate may increase by 14.3% from 2019 to 2035. The total number of new cases may increase by 54.7% from 2019 to 2035 [9].

NPC is highly chemosensitive and radiosensitive; thus, gemcitabine plus cisplatin is currently the standard of care as a first-line treatment in these patients [10]. Although most patients with advanced NPC respond to chemotherapy, recurrence of distant metastases is the major cause of treatment failure and has a poor prognosis [11]. Gemcitabine plus cisplatin as the preferred treatment proved a PFS of 7 months.[10] Patients with stable disease may develop resistance to anticancer drugs, which is a major factor that leads to this pattern of failure [12]. The approval of immune checkpoint inhibitors in NPC addresses an unmet need for patients considered to have a poor prognosis in advanced stage, in the absence of an indication of new therapies.

Esophageal squamous cell carcinoma

In 2022, there were 511,054 new cases and 445,391 deaths worldwide. The incidence age-standardized rates (ASRs) for NPC is 5.0 per 100,000 and the mortality ASRs for NPC is 4.3 per 100,000. There is a substantial geographical variance within the country. Survival from esophageal cancer remains low, in the range of 10%–30% at 5 years post diagnosis in most countries [13].

Its burden varies greatly across countries and populations, which been linked to differences in the prevalence of underlying risk factors and the distribution of subtypes. Eastern Asia exhibits the highest regional incidence rates, in part because of the large burden in China, followed by Southern Africa, Eastern Africa, Northern Europe, and South Central Asia. Of all cases, 59.2% occurred in Eastern Asia, 53.7% in China alone. Of all esophageal cancer-related deaths, 58.7% occurred in Eastern Asia; 55.3% of all deaths were in China alone [14].

Esophageal cancer can be categorized by two main histologic subtypes; adenocarcinoma (AC) and squamous cell carcinoma (SCC), which have quite different etiologies. Globally, SCC was the most common subtype in both male and female patients, contributing to 85% of all esophageal cancer cases. There were an estimated 85,700 AC new cases and 512,500 SCC new cases (ASRs of 0.9 and 5.4 per 100,000, respectively) and 6000 remaining cases of other histologic subtypes diagnosed worldwide in 2020 [14].

Moreover, SCC is more common in low-income countries than in high-income countries. SCC new cases in developing countries represent 82% of all SCC new cases [14]. About 90% of all esophageal cancers in developing countries (HDI=low/medium/high) are ESCCs, with the highest incidence rates in populations within South-Eastern and Central Asia. By contrast, only 66% of all esophageal cancers in developed countries (HDI=very high) are SCC with an declining burden seen in Northern and Western Europe, Northern America, and Oceania [15]. Thus, countries with low and medium income carry heavier burden of disease than others and even more in the future.

Worldwide, an estimated 957,000 new esophageal cancer cases (141,300 AC and 806,000 SCC) are projected to occur in 2040, an increase of 58.4% compared with the 604,000 cases diagnosed in 2020 [14].

Although surgery is the best curative treatment option for non-metastatic ESCC, postoperative relapse is common. Since the clinical symptoms of early ESCC are not distinctive, a majority of newly diagnosed ESCC patients present with advanced disease. Currently, standard first-line treatments for advanced or metastatic ESCC are combination chemotherapeutic regimens such as 5-fluorouracil or taxane plus platinum. In a retrospective, real-world evaluation, first-line chemotherapy with

paclitaxel plus cisplatin appears to result in similar median progression-free survival (PFS) compared with 5-fluorouracil plus cisplatin (7.9 vs 6.5 months) in patients with advanced ESCC [16]. Nevertheless, the clinical benefits of such platinum-containing doublets remain limited, with a median OS of 7 to 13 months and a 5-year overall survival (OS) rate of less than 20% [16], highlighting the urgent, unmet medical need for novel drugs and strategies for advanced ESCC.

- **Target populations**

All adult patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma and with recurrent or metastatic esophageal squamous cell carcinoma.

- **Alternative medicines currently included on the Model Lists for the proposed indication(s)**

Malignant neoplasms of nasopharynx: Carboplatin(L01XA02), Cisplatin(L01XA01), Fluorouracil(L01BC02), Paclitaxel(L01CD01)

Esophageal squamous cell carcinoma: Not Available

7. TREATMENT DETAILS

- **Dosage regimen and duration of treatment**

Nasopharyngeal carcinoma

➢ Clinical Trial: JUPITER-02

In the international, double-blind, randomized, placebo-controlled phase III study (JUPITER-02), Gemcitabine-cisplatin in combination with either toripalimab or placebo was compared in patients with recurrent or metastatic NPC as a first-line treatment.

Patients were randomized to receive either toripalimab or placebo in combination with gemcitabine and cisplatin once every 3 weeks (Q3W) for up to six cycles, followed by either toripalimab or placebo monotherapy. All medicines were given through intravenous infusion. In the chemotherapy phase, patients received toripalimab (240 mg) or placebo on Day 1, gemcitabine (1,000 mg/m^2 body surface area) on Day 1 and 8 and cisplatin (80 mg/m^2 body surface) on Day 1 of each 3-week cycle. Chemotherapy was continued until progressive disease, intolerable toxicity, withdrawal of consent or a maximum of six cycles, whichever occurred first. In the maintenance phase, patients received either toripalimab (240 mg) or placebo Q3W until progressive disease, intolerable toxicity, withdrawal of consent or a maximum of 2 years of treatment. Crossover was not permitted as part of the study [17].

➢ Regulatory Label

The recommended dosing regimen of toripalimab is 240 mg every 3 weeks (Q3W) as an intravenous (IV) infusion over 60 minutes for the first infusion and over 30 minutes for subsequent infusions. Treatment should continue until disease progression, unacceptable toxicity or up to a maximum duration of 24 months.

Esophageal squamous cell carcinoma

➢ Clinical Trial: JUPITER-06

In the randomized, double-blind, placebo-controlled, phase III study (JUPITER-06), toripalimab plus paclitaxel/cisplatin (TP) was compared versus placebo plus TP as the first-line treatment for patients with advanced ESCC. Patients were randomized to receive either toripalimab or placebo in combination with TP once every 3 weeks (Q3W) for up to six cycles, follows by toripalimab or placebo maintenance. All medicines were given through intravenous infusion. In the chemotherapy phase, patients would receive toripalimab (240 mg) or placebo on Day 1, paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2) on Day 1 of each 3-week cycle. Chemotherapy was to continue until progressive disease, intolerable toxicity, withdrawal of consent, or a maximum of 6 cycles, whichever occurred first. In the maintenance phase, patients would receive toripalimab (240 mg) or placebo every 3 weeks until progressive disease, intolerable toxicity, withdrawal of consent, start of new anti-cancer therapy or a maximum of 2-year treatment. Crossover was not permitted as part of the study [18].

➢ Regulatory Label

The recommended dosing regimen of toripalimab is 240 mg every 3 weeks (Q3W) as an intravenous (IV) infusion over 60 minutes for the first infusion and over 30 minutes for subsequent infusions. Treatment should continue until disease progression, unacceptable toxicity or up to a maximum duration of 24 months.

- **Requirements to ensure appropriate use of the medicine**

Biomaker testing is not needed before the treatment decision with toripalimab in patients with NPC and ESCC.

Toripalimab is for intravenous use only and must be administered by infusion. The first infusion should be administered over 60 minutes via an infusion pump through an in-line filter (0.2 micron or 0.22 micron pore size). If no infusion-related reactions occurred during the first infusion, subsequent infusions may be administered over 30 minutes.

When administered on the same day as chemotherapy, toripalimab should be administered prior to chemotherapy through a different intravenous line. Unopened vial should be stored in a refrigerator (2°C to 8°C) and avoid freezing and shaking. Store in the original carton in order to protect from light.

8. REVIEW OF EVIDENCE FOR BENEFITS AND HARMS

8.1 Review of benefits: summary of evidence of comparative effectiveness

- **Toripalimab for adult patients with recurrent or metastatic , locally-advanced nasopharyngeal carcinoma.**

Search strategy: PubMed search of ((Toripalimab[Title/Abstract]) OR (JS001[Title/Abstract])) AND (Nasopharyngeal Neoplasms[MeSH Terms])

There are several clinical trials for toripalimab in NPC. Since toripalimab is the first approved anti-tumor PD-1 Antibody for NPC treatment by the FDA and EMA, it's worth noting that toripalimab is a recommended therapeutic choice for people suffering from NPC around the world. Toripalimab plus chemotherapy may replace chemotherapy and become the global standard of care for the first-line treatment of recurrent or metastatic NPC. The trials and studies are described below.

Mai et al reported an international, multicenter, randomized, double-blind phase 3 study conducted in NPC-endemic regions, including mainland China, Taiwan, and Singapore. From November 10, 2018, to October 20, 2019, 289 patients with recurrent/metastatic nasopharyngeal carcinoma (RM-NPC) with no prior systemic chemotherapy in the RM setting were enrolled from 35 participating centers (Jupiter-02, cutoff date: November 18, 2022) [19]. In the study, patients were randomized (1/1) to receive either toripalimab, or placebo in combination with Gemcitabine-cisplatin (GP) every 3 weeks for up to six cycles, followed by monotherapy with toripalimab or placebo. The primary endpoint was progression-free survival (PFS) as assessed by a blinded independent review committee according to RECIST v.1.1. Secondary end points included objective response rate, overall survival, progression-free survival assessed by investigator, duration of response, and safety.

At the final analysis, among the 289 patients enrolled, toripalimab treatment had a significantly longer progression-free survival than placebo (median, 21.4 vs 8.2 months; HR, 0.52 [95% CI, 0.37-0.73]). As of the cut-off date, with a median survival follow-up of 36.0 months, 133 overall survival events were recorded, triggering the prespecified final overall survival analysis. The median overall survival was not reached in the toripalimab group, while it was 33.7 months in the placebo group. A significant improvement in overall survival was detected for toripalimab over placebo (HR, 0.63 [95% CI, 0.45-0.89]; 2-sided P = .008, crossing the prespecified efficacy boundary). At 1 year, the overall survival rates were 90.9% in the toripalimab group vs 87.1% in the placebo group; at 2 years, 78.0% vs 65.1%; and at 3 years, 64.5% vs 49.2%. The incidence of all adverse events, grade 3 or greater adverse events, and fatal adverse events were similar between the 2 groups. Consistent progression-free survival treatment effects were observed across all major subgroups. The overall survival treatment effects were generally consistent across major subgroups, with the

exception of patients with primary metastatic disease at baseline. Notably, the treatment effects on overall survival favored toripalimab in all PD-L1 expression subgroups and EBV DNA copy number subgroups.

The current study exclusively enrolled patients in NPC-endemic Asian regions, where the majority of patients have nonkeratinizing histology, closely associated with EBV infection. In contrast, keratinizing NPC, which accounts for 25% of NPC in the West, is not caused by EBV infection. The subgroup analysis demonstrated that the treatment effects of overall survival favored toripalimab in both the subgroup with high EBV copy number and the subgroup with low EBV copy number, indicating that toripalimab will benefit patients with low EBV copy numbers, who are representative of patients with NPC in the West. It is believed the results in JUPITER-02 can be extrapolated to Western populations. The outcome with NPC was very similar among Asian and non-Asian patients with NPC who were treated in Australia [20]. Furthermore, in a matched control trial there was no difference in disease-specific survival by ethnicity [21]. In addition, the current treatment guidelines for NPC are very similar in both the West and East [22].

In conclusion, the addition of toripalimab to chemotherapy as first-line treatment for RM-NPC provided statistically significant and clinically meaningful progression-free survival and overall survival benefits compared with chemotherapy alone, with a manageable safety profile. ESMO-MCBS score for this trial is 3, while the reference of Agent Score only includes the prespecified interim PFS analysis(cutoff date: May 30 2020) instead of this final analysis of the trial.

Wang et al described a single-arm, multicenter phase II clinical study (POLARIS-02), involved 190 patients with RM-NPC. Patient received toripalimab via intravenous infusion until confirmed disease progression or unacceptable toxicity [23]. Based on the results from this study, toripalimab provided durable responses to patients with NPC in the second-line-plus setting, with ORR of 20.5%, a median DoR of 12.8months and a median OS of 17.4months in the ITT population. An outstanding findings comes from 92 patients who failed at least two lines of systemic chemotherapy, the ORR was 23.9%. The ORRs were 27.1% and 19.4% in PD-L1+ and PD-L1- patients respectively, which led to the approval of toripalimab monotherapy for treating patients with recurrent/metastatic NPC as next-line therapy in China and US.

Wei et al conducted a phase I study of toripalimab, in patients with refractory malignant solid tumors [24], and six patients suffered from nasopharyngeal. The efficacy result turned out 1 nasopharyngeal carcinoma patient from the 0.3 mg/kg group experienced partial remission (PR).

You et al described a research enrolled 41 patients with RM-NPC, to explore the role of a triple combination of gemcitabine (chemotherapy) plus apatinib (anti-vascular endothelial growth factor [VEGFR]) and toripalimab (anti-PD-1) (GAT) in

recurrent/metastatic nasopharyngeal carcinoma [25]. Several endpoints were evaluated and the ORR was 90.2%. The median PFS was 25.8 months, and the 24-month PFS rate was 50.7%.The research indicated that GAT therapy exhibits a promising antitumor activity and manageable toxicities in patients with RM-NPC. Patients with repeated radiotherapy and an interval of less than 12 months from the last radiotherapy should be carefully selected for antiangiogenic therapies. MRGPRF expression and serial ctDNA monitoring could identify patients that derive benefits from the combination therapy.

- **Toripalimab for the first-line treatment of adult patients with recurrent or metastatic esophageal squamous cell carcinoma**

Search strategy: PubMed search of ((Toripalimab[Title/Abstract]) OR (JS001[Title/Abstract])) AND (Esophageal Neoplasms[MeSH Terms])

Individual trials:
Platinum-based chemotherapy is the standard first-line treatment for advanced esophageal squamous cell carcinoma. In the phase 3 study (Jupiter-06, cutoff date: 22 March 2021) conducted by Wang et al [18], 514 patients with treatment-naive advanced ESCC were randomized (1:1) to receive toripalimab or placebo in combination with paclitaxel plus cisplatin (TP) every 3 weeks for up to 6 cycles, followed by toripalimab or placebo maintenance. At the prespecified final analysis, an improvement in PFS is observed for the toripalimab arm over the placebo arm (5.7 vs 5.5months, hazard ratio = 0.58). The prespecified interim analysis also reveals a significant OS improvement for patients treated with toripalimab plus TP over placebo plus TP (17 vs 11months, HR = 0.58). In the ITT population, the BICR ORR per RECIST v.1.1 was higher in the toripalimab arm than in the placebo arm: 69.3% vs 52.1%. The DCR was 89.1% vs 82.1%. As assessed by the BICR, the median DoR was 5.6 vs 4.2 months. This study also showed that the PFS and OS benefits of the the toripalimab-TP combination were independent of the PD-L1 expression level.
All patients enrolled in the JUIPTER-06 were Chinese with 100% squamous histology, which is the predominant subtype in Asia. It could be speculated that the findings from JUPITER-06 might be extrapolated to western ESCC patients, as the efficacy and survival of the immuno-chemotherapy combination did not differ by race in the CheckMate 648 study, which enrolled both white and Asian ESCC patients [26]. In addition, the current treatment guidelines regarding the management of advanced ESCC are similar in the West and East [27-29].

A single-center phase I study was conducted in Sun Yat-sen University Cancer Center [24]. Eligible patients were adults with histologically confirmed, treatment-refractory, advanced, solitary malignant tumors. Toripalimab was intravenously infused every 2 weeks in dose-escalating cohorts at 0.3mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 240 mg. The study followed standard 3 +3 design. Between 15th March 2016 and 27th September 2016, 25 patients were enrolled, of whom 3 (12.0%), 7 (28.0%), 6 (24.0%),

6 (24.0%), 3 (12.0%) received 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 240 mg toripalimab, respectively. After a median follow-up time of 5.0 months (range: 1.5-19.8 months), this study observed that the commonest treatment-related adverse events (TRAEs) were fatigue (64.0%) and rash (24.0%). No grade 3 or higher TRAEs were observed. No dose-limiting toxicity, treatment-related serious adverse events (SAEs), or treatment-related death occurred. Objective response rate was 12.5%. The half-life of toripalimab was 150-222 h after a single dose infusion. Most patients, including those from the 0.3 mg/kg group, maintained complete PD-1 receptor occupancy (> 80%) on activated T cells since receiving the first dose of toripalimab.

An open-label, single-arm, phase II trial included patients with unresectable stage IV esophageal squamous cell carcinoma who have not received prior systemic therapy [30]. The patients will be treated with two cycles of toripalimab (240 mg, 1 day before chemotherapy, Q3W) combined with induction chemotherapy (paclitaxel, 135–175 mg/m2 + carboplatin, area under the curve = 4–6, day 1, intravenous, Q3W). Thereafter, they will undergo two cycles of the aforementioned treatment with concurrent radiotherapy (30–50 Gy in 15–25 fractions), followed by toripalimab (240 mg, day 1, Q3W) for 1 year. The primary outcome measure will be progression-free survival; the secondary outcome measures will include the objective response rate, disease control rate, duration of remission, 1- and 2-year overall survival rates, safety and tolerability, and changes in health-related quality of life. The Ethics Committee of Sichuan Cancer Hospital (SCCHEC-02-2021-021) approved the study protocol. The trial is underway in accordance with the Declaration of Helsinki.

Comparative effectiveness (Review and meta-analysis)

Li et al used PubMed, Embase, and Cochrane Library databases for systematic retrieval [31]. Five phase-III randomized controlled trials involving 3,163 patients met the inclusion criteria. Significantly improved OS (HR: 0.69), PFS (HR: 0.62) and ORR (RR: 1.41) were observed when programmed death 1 (PD-1) inhibitor was added to chemotherapy. Toripalimab plus chemotherapy achieved the best OS benefit than any other treatment examined (HR: 0.58, 95% CI: 0.43–0.78). Subgroup analyses suggested significant OS advantage in programmed death-ligand 1(PD-L1) tumor-positive score (TPS) ≥ 10% groups and obviously longer PFS in PD-L1 combined positive score (CPS) ≥ 10 groups. As concluded, in advanced esophageal cancer, PD-1 inhibitors combined with chemotherapy as first-line therapy have better survival outcomes than chemotherapy with greater but manageable toxicity. Toripalimab chemotherapy showed the best OS benefit over chemotherapy, while sintilimab-chemotherapy and camrelizumab-chemotherapy generated the best PFS. The highest ORR improvement was founded in patients receiving nivolumab plus chemotherapy.

A recently published review depicted the current scenario in the field of immunotherapy for esophageal squamous cell carcinoma (ESCC) according to the stage of disease [32]. In the metastatic setting, this review identified 5 landmark phase III trials and 4 main phase II/III ongoing trials and explored the effectiveness of current

immunotherapy including nivolumab, pembrolizumab, camrelizumab, sintilimab and toripalimab for ESCC. This review did not select a single best choice of anti-PD-1 inhibitor as the first-line treatment due to the lack of direct comparison as well as the heterogeneity of the study population and methods (e.g., PD-L1 score and assessment). However, this study concluded that immunotherapy improved survival outcomes as a first-line treatment in addition to chemotherapy and in an Asian population, the addition of toripalimab to chemotherapy could be good therapeutic option.

Gao et al conducted a systematic review and Bayesian network meta-analysis to compare efficacy and safety of various immune checkpoint inhibitors for patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) [33]. Ten eligible trials with 5250 patients were included. In the network meta-analysis, it was found that immune checkpoint inhibitors showed significant OS and PFS benefits over chemotherapy except nivolumab plus chemotherapy on PFS (hazard ratio, HR, 0.82; 95% credible interval, CI, 0.64–1.04). Toripalimab in combination with chemotherapy was most likely to be ranked first for OS (HR, 0.58; 95% CI, 0.43-0.78; probability, 61%). For PD-L1 low expression group, toripalimab plus chemotherapy ranked the highest probability to be the best treatment in terms of both OS and PFS. Each study's risk of bias was assessed using the Cochrane Risk of Bias Tool, but the results were not reported.

8.2 Review of harms and toxicity: summary of evidence of comparative safety

To our knowledge, there is no published estimates of total patient exposure to toripalimab, and there are only some individual cases and few trials reported safety in the Pubmed database.

Meanwhile, safety warning, black box warning or withdrawal information of this product has not been issued by any applicable regulatory authorities around the world. Clinical trials related to toripalimab have not been requested to suspend or discontinue due to any safety concerns. The adverse events collected in clinical overview are as following:

The toripalimab safety database includes:
1. Nasopharyngeal carcinoma
a) JUPITER-02, N = 146 toripalimab, N = 143 placebo
b) POLARIS-02/Cohort 3, N = 190 toripalimab
c) POLARIS-02/Cohort 7, N = 12 toripalimab
2. Squamous cell cancer of the oesophagus
a) JUPITER-06, N = 257 toripalimab, N = 257 placebo
b) POLARIS-02/Cohort 2, N = 59 toripalimab
c) POLARIS-02/Cohort 6, N = 12 toripalimab
3. Toripalimab monotherapy safety database

a) Data from 13 trials, N = 1111 toripalimab
b) Treated in China and East Asia, N = 927
c) Treated in the United States (US), N = 184

Safety analyses included the examination of treatment-related adverse events (TRAEs), deaths, treatment-related serious adverse events, TRAEs leading to permanent discontinuation, infusion-related reactions, and laboratory abnormalities.

Treatment-related adverse events (≥ 5%) in either the toripalimab monotherapy safety database or in patients who received toripalimab in combination with chemotherapy on JUPITER-02 or JUPITER-06 are shown in the table below. The incidence of most individual or aggregate preferred terms was higher when toripalimab was used in combination with chemotherapy than when toripalimab was administered as monotherapy. Many of these differences may be related to the use of concurrent chemotherapy.

A small number of TRAEs were more common (≥ 5% all grades) in the monotherapy population that in patients receiving toripalimab in combination with chemotherapy. These included increased hyperbilirubinaemia, thyroid function test abnormal, creatine phosphokinase, lipids abnormal, amylase increased, and proteinuria. While there was an increase in all grades hyperbilirubinaemia, ≥ Grade 3 events were minimally increased in the monotherapy population when compared to those receiving toripalimab in combination with chemotherapy. The differences seen in the incidence of thyroid function test abnormal, hypothyroidism, and hyperthyroidism among patients receiving toripalimab alone and toripalimab in combination with chemotherapy may be related to differences in the way these terms were reported as well as differences in the frequency of assessment of thyroid function tests. Lipids and amylase/lipase were routinely assessed in most of the early trials of toripalimab monotherapy but not in the later trials of toripalimab in combination with chemotherapy. This may account for the differences with which these laboratories were reported as adverse events.

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

	Toripalimab Monotherapy Safety Database N = 1111 (%)		Toripalimab in Combination with Chemotherapy N = 403 (%)	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
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)
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

	Toripalimab Monotherapy Safety Database N = 1111 (%)		Toripalimab in Combination with Chemotherapy N = 403 (%)	
	All Grades	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
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)

9. SUMMARY OF RECOMMENDATIONS IN CURRENT CLINICAL GUIDELINES

- **Recommendations in existing WHO guidelines**

Not Available

- **Recommendations in other current clinical guidelines**

1) National Comprehensive Cancer Network Clinical Guideline in Oncology of Head and Neck Cancers (NCCN Guideline)

Cisplatin/gemcitabine plus PD-1 Inhibitor is the recommended choice of systemic therapy of recurrent, unresectable, oligometastatic, or metastatic disease (with no surgery or RT option) in NCCN Guidelines Version4.2024 Cancer of the Nasopharynx. If not previously used, these regimens may be considered in subsequent-line therapy as other recommended regimens.

Toripalimab plus chemotherapy as first-line treatment is referred in above systemic therapy for nasopharyngeal carcinoma. Toripalimab as next-line treatment is preferred for nasopharyngeal carcinoma.

2) Guidelines of Chinese Society of Clinical Oncology (CSCO 2024 Guideline)

Guidelines of Chinese Society of Clinical Oncology of Nasopharyngeal Carcinoma

Toripalimab plus cisplatin/gemcitabine is the 1A recommended choice of recurrent or metastatic nasopharyngeal carcinoma for frontline and treatment-experienced patients are recommended toripalimab monotherapy.

Guidelines of Chinese Society of Clinical Oncology of Esophageal Carcinoma

Toripalimab plus paclitaxel/cisplatin is the 1A recommended choice of recurrent or metastatic esophageal squamous cell carcinoma for first-line patients.

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

Since toripalimab was approved in China in 2018, it has been the cheapest Anti-PD-1 antibody nationally, significantly reducing the disease burden on patients and national social medical insurance fund expenditures. After toripalimab was approved in US, the wholesale acquisition cost of 240-mg single-use vial was established at 20% lower than the triweekly price of pembrolizumab. There are some researches focusing on cost-effectiveness analysis and budget impact analysis for toripalimab in treatment of NPC and ESCC.

Lian et al evaluated the cost-effectiveness of toripalimab for RM-NPC patients in the American context.[34] A 3-state partitioned survival model was constructed when assessing the cost-effectiveness of toripalimab plus chemotherapy versus chemotherapy alone. The study involved participants with characteristics matching those in the JUPITER-02 trial. Main outcomes measured were quality-adjusted life year (QALY), and incremental cost-effectiveness ratio (ICER). The study found that the toripalimab regimen resulted in 4.390 QALYs at a cost of $361,813, while the chemotherapy-only regimen yielded 1.685 QALYs at a cost of $161,632. This translates to an ICER of $74,004/QALY, below the willingness-to-pay threshold of $150,000/QALY. With an 87.10% probability of being cost-effective at threshold, the probabilistic sensitivity analysis supports toripalimab plus chemotherapy as a viable option. Toripalimab in combination with chemotherapy is likely to be a cost-effective alternative to standard chemotherapy for American patients with RM-NPC.

MacDonald et al conducted economic evaluations of the costs of this toripalimab regimen versus the costs of a similar regimen with the PD-1 inhibitor pembrolizumab in the US.[35] The study found that, if 90% of new cases of recurrent or metastatic nasopharyngeal cancer were treated with toripalimab over 1 year, these savings are enough to purchase up to 4,717 additional doses on a budget-neutral basis, which could provide up to an additional 252 newly diagnosed patients with 1 year of treatment with toripalimab. In combination with gemcitabine and cisplatin, toripalimab can markedly improve access to care for patients with recurrent or metastatic nasopharyngeal cancer in a cost-responsible way.

Abraham et al estimated the budget impact of adding a toripalimab regimen as a treatment option to the existing pembrolizumab regimen, both including gemcitabine and cisplatin, in untreated RM-NPC in the US.[36] Budget impact analysis comparing a treatment mix “without” versus “with” the toripalimab regimen in the US eligible annual incident RM-NPC population, a 3-year time horizon, toripalimab/pembrolizumab market splits of 60/40 (Y1) and 80/20 (Y2/3). The study shows that savings between $174 million and $184 million can be achieved from treating 60% of R/M NPC patients in year 1 and 80% in years 2 and 3 with the toripalimab regimen over a similar pembrolizumab regimen.

Han et al conducted the cost-effectiveness analysis of four immunotherapies for RM-NPC among Chinese patients. The cost and efficacy of four first-line therapies were evaluated using the Markov model. The main outcome in the cost-effectiveness analysis was incremental cost-utility ratios. Compared to the placebo plus chemotherapy group, toripalimab, camrelizumab, and tislelizumab plus chemotherapy groups resulted in additional costs of $48 339, $22 900, and $23 162, with additional 1.89, 0.73, and 0.960 QALYs respectively, leading to the ICURs of $25 576/QALY, $31 370/QALY, and $31 729/QALY. From the Chinese payers' perspective, first-line immunotherapy combination therapies provided significant survival and cost-effectiveness superiority over chemotherapy alone for patients with RM-NPC at the WTP of $38 029/QALY. Among the three chemo-immunotherapy groups, toripalimab plus chemotherapy group was the most cost-effective option.

In the current market for the treatment of ESCC in China, toripalimab provides a more affordable immunotherapy for patients, compared with other approved immunotherapies. There is no published economic evaluations for toripalimab in treatment-naive advanced ESCC out of China, since it is a short time after the indication was approved by EMA.

Liu et al investigate the cost-effectiveness of all available PD-1 inhibitors combined with chemotherapy in the first-line treatment of advanced ESCC from the Chinese healthcare system perspective.[37] Compared with mono-chemotherapy, toripalimab, sintilimab and camrelizumab plus chemotherapy were cost-effective treatment regimens, while serplulimab, pembrolizumab and nivolumab plus chemotherapy were not cost-effective options. Toripalimab plus chemotherapy provided the highest QALYs of 0.95 with the lower cost of $8,110.53 compared to other competing alternatives. At a willingness-to-pay threshold of three times per capita gross domestic product ($38,351.20) in 2021, the probability of toripalimab plus chemotherapy being the optimal option was 74.25% compared with other six competing alternatives. Toripalimab plus chemotherapy represented the most cost-effective option as the first-line therapy for advanced ESCC patients in China.

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

- **Regulatory status of the proposed medicine**

Toripalimab is the first commercialized anti-PD-1 monoclonal antibody in China and was approved by the National Medical Product Administration in China for 6 indications: 1) the second-line treatment of metastatic melanoma; 2) the second-line treatment of urothelial carcinoma; 3) recurrent or metastatic nasopharyngeal carcinoma NPC after failure of at least two lines of prior systemic therapy; 4) the first-line treatment of nasopharyngeal carcinoma; 5) the first-line treatment of recurrent or metastatic esophageal squamous cell carcinoma; 6) the first-line treatment of non-squamous NSCLC without EGFR/ALK mutations; 7) the perioperative treatment, and with continuation of this product monotherapy as the adjuvant treatment, for adult patients with resectable Stage IIIA-IIIB NSCLC; 8) the first-line treatment of patients with intermediate or poor risk, unresectable or metastatic renal cell carcinoma; 9) the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC); 10) the first-line treatment of patients with recurrent or metastatic triple-negative breast cancer (TNBC) that is PD-L1 positive (CPS≥1) as assessed by a well-validated assay.

On October 27, 2023, the US Food and Drug Administration approved toripalimab with cisplatin and gemcitabine for the first-line treatment of adults with metastatic or recurrent, locally advanced nasopharyngeal carcinoma. FDA also approved toripalimab as a single agent for adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

On September 19, 2024, the European Medicines Agency authorized toripalimab for use in two following therapeutic indication in the European Union. Toripalimab, 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. Toripalimab, 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.

In October 2024, toripalimab has been approved for marketing in India and China's Hong Kong Special Administrative Region in combination with cisplatin and gemcitabine for the first-line treatment of adult patients with metastatic or recurrent, locally advanced nasopharyngeal carcinoma, and as a single agent for the treatment of adult patients with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

- **Market availability of the proposed medicine**

Shanghai Junshi Biosciences Co. Ltd has solid experience in global supply chain and has supplied both API and finished products to countries around the world with different supply temperature conditions (-65°C, 2-8°C and room temperature). Together with its

partners, Junshi Biosciences has built a commercialization network in more than 50 countries and regions, and has started the registration process. Currently, Toripalimab has been approved in China, US, European Union and India, and under reviewed by the authorities of other countries such as UK, Australia, Singapore, India, South Africa, Chile and Jordan. As the marketing authorization holder of the exported products, Junshi has a profound quality control team and system to ensure product safety during global transportation of toripalimab.

- **Pharmacopoieal standards**

Not Available

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Annex I. Consultation meeting with WHO Technical Department

WHO Essential Medicine List (EML) Consultation about Application of Toripalimab Meeting Minutes

Meeting Name:	WHO Consultation Meeting about Toripalimab		
Technical Department consulted:	WHO cancer team, Department of Noncommunicable Diseases		
Focal point consulted:	Dr Andre Ilbawi, M.D., Technical lead, Cancer Control		
Date of Meeting:	December 13, 2022	**Time:**	8:00 - 8:30 AM CET
Minutes Issued By:	Jiayu Huang	**Location:**	Online meeting through Teams

Meeting Objective:

To consult about the application for inclusion of the PD-1 product, Toripalimab, for nasopharyngeal carcinoma and esophageal squamous cell carcinoma on the 23rd WHO Model Lists of Essential Medicines.

Attendees:

WHO cancer team, focal point: Dr Andre Ilbawi
Junshi Biosciences staffs: Fang Zhang, Maya Zhu, Siyuan Wang, Dr Lingyan Tao, Jiang Niu, Jia Liu, Jiayu Huang

Meeting Agenda:

1. Introduction about Shanghai Junshi Biosciences Co., Ltd. and the proposed medicine toripalimab from Junshi side (around 10 minutes);
2. Consultation with Dr Andre Ilbawi regarding issues in applying for the inclusion of Toripalimab on the 23rd EML as well as other related questions (around 20 minutes).

Discussion Items:

Q: Evidence quality and price are two major concerns about PD-1 medicine in last two Committee Meeting. Since the Committee considered that PD-1's precise place in the treatment/ immunotherapy of many indications is still evolving and Dr. Moja has mentioned that PD-1 was prioritized in the last meeting, we are wondering the prospect of a more affordable PD-1 medicine as well as relevant combination therapy.

A: The primary variable that determines inclusion in the essential medicines list is effect/efficacy, not price or affordability. Moreover, access in a broader sense and value pertaining to efficacy or effectiveness and cost are parameters that have merit. Accessibility on the technical side: dimensions such as supply chain considerations, ease of diagnostics, delivery of that product and issues related to market affordability or price and cost effectiveness.

Q: As we learned, for cancer medicines, a threshold for benefit of 4-6 months overall survival gain, and ESMO-MCBS score of 4 or 5 are important criteria for consideration. In term of clinical studies, the outcomes of nasopharyngeal carcinoma (NPC) and esophageal squamous cell carcinoma (ESCC) is encouraging and meet the benefit criteria. However, there is no ESMO-MCBS score of toripalimab for ESCC. Are there any minimum requirements or prerequisites for inclusion of the medicine?

A: The WHO working group discussions agreed that an endpoint of interest is overall survival and the WHO EML would require more mature data on overall survival. For some indications there are provisional results and for those results that have overall survival even if they have not been reviewed by MCBS, please do consider submitting those indications specifically.

Q: The cost/cost-effectiveness section has the issue that there is no published economic evaluations for ESCC up to now. Also, toripolimab has been approved for 1st line treatment of NPC and ESCC for less than three years. We are wondering whether these will be a key weakness when experts assessing the inclusion of toripalimab in the EML.

A: Yes, it will be considered an area or a small gap that formal economic analysis has not been completed. But at the same point we understand that it's a short time between the product now having completed an initial phase three clinical trials. So an economic evaluation may be premature. However, if there is any data on market entry or forward ability or price data that you feel willing to share and that could be included even if it were done as a provisional estimation and not as a formal economic evaluation.

It is difficult to say whether this will be a key weakness but the expert committee will be very pleased to know that there are products that may be more affordable.

Q: Although tumor diseases have high incidence rates and mortality rates, there are no corresponding therapies for some of them in current EML. In our case, while low-and-middle-income countries carry unbalance burdens of ESCC and chemotherapy is a consensual choice for frontline treatment, no medicine is recommended for ESCC. What is the Committes's attitude on these indications?

A: For the purposes of the EML, you are right that we often look at disease burden and we acknowledge that the disease burden for esophageal cancer squamous cell in particular low and middle-income countries is very high. Now that is only one parameter, one of the challenges that we can also acknowledge with the efficacy and effectiveness of systemic therapy. For cancers like liver cancer, there are limited data to regarding systemic therapy providing significant overall survival benefit. The point is that it's not just the disease burden, while the disease burden is very important, the expert committee will also want to look at evidence related to the impact of the therapeutic intervention, that is the overall survival gain for some cancers that are highly prevalent but not explicitly listed on the EML and as I shared, an example of pancreas cancer, liver cancer and even gastric cancer. It is important to refer the disease burden because it helps justify that there is a population impact, but I would just add to be sure you highlight what regimen you are proposing and why that regimen has a high therapeutic potential or high overall survival gain in the metastatic setting. That is the merits that the application will be reviewed, in addition to a consideration on the disease burden.

Q: We are wondering whether the sites of the clinical trials will influence the inclusion?

A: The number of countries that a clinical trial is performed is informative. It may not directly influence the application and the review by the EML expert committee.

I was very happy to hear of the clinical trials that are inclusive of multiple countries in the region and your collaboration across different settings. It is quite helpful for us as we look at the broader landscape with the cancer market and improving access to care for people living in countries with weaker health systems.

Annex II. Letter of support

RECOOMENDATION FOR INCLUSION OF TORIPALIMAB FOR NASOPHARYNGEAL CARCINOMA AND ESOPHAGEAL SQUAMOUS CELL CARCINOMA ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES

The current list of essential medicines in China is the National Essential Medicine list (2018), with a total of 685 medicines included. The selection of essential medicine is rationally determined with reference to international experience in accordance with the its function of "highlighting the essence, supporting prevention and treatment, ensuring supply, using preferentially, assuring quality and reducing burden".

In addition to the changes in the demand and security level of basic medical and health services, the most important indicators include the burden of disease, safety (including adverse events), efficacy, economics, suitability (rational usage and monitor), innovation and accessibility (including temporal and spatial accessibility). Evaluation methods include evidence-based medicine (including real world study) and pharmacoeconomics, etc.

According to the WHO Essential Medicines List (2021), the PD-1 immune checkpoint inhibitor, nivolumab and pembrolizumab, have been included for the same indication (melanoma) in the list in 2019, while toripalimab has not yet included in the list. It is worth noting that, given the high affordability requirements for essential medicines, toripalimab has a significant advantage in this regard.

Value of information of toripalimab is listed as following:

1. Efficacy

A total of 3 clinical trials (all single-arm trials) have been published on toripalimab in the treatment of melanoma, with no head-to-head RCT to pembrolizumab. A side-by-side comparison was made between Polaris-01 of toripalimab and Keynote-151 of pembrolizumab, both in treatment for advanced melanoma in Chinese population. Results shown that ORR, DCR, PFS and OS of toripalimab were all better than that of pembrolizumab, though the sample size of the comparison was relatively small. In addition, by comparing the literature of pembrolizumab in Chinese and foreign populations, it can be seen that the efficacy of pembrolizumab varies significantly between different ethnic groups.

Clinical benefits of toripalimab for patients with recurrent or metastatic nasopharyngeal carcinoma or esophageal squamous cell carcinoma have been confirmed. Researches have revealed that toripalimab in combination with chemotherapy as first-line treatment for advanced nasopharyngeal carcinoma and esophageal squamous cell carcinoma both provided superior survival benefit than chemotherapy alone. Representative studies are as following:

For nasopharyngeal carcinoma treatment, significant improvements of progression-free survival were observed in a randomized, double blind, phase 3 study (Jupiter-02), which indicated the primary endpoint mPFS was 21.4 and 8.2 months (HR=0.52) of toripalimab plus chemotherapy arm and the chemotherapy arm, respectively. It is also the longest mPFS in the treatment for NPC registry study up to now.

For esophageal squamous cell carcinoma treatment, a random multi-center phase 3 trial (Jupiter-06) also demonstrated the prominent clinical benefit of combination therapy of toripalimab plus chemotherapy. The primary endpoint, mOS, was 17.0 vs 11.0 months (HR=0.58) of toripalimab plus chemotherapy set and the chemotherapy set.

Meanwhile, toripalimab plus chemotherapy extends progression-free survival and overall survival of the patients irrespective of PD-L1 expression in these studies. This provided a promising alternative to oncology patients.

2. Safety

A meta-analysis of the safety of toripalimab was derived from 10 literature meta-analyses of adverse effects that did not distinguish indications: 8 single-arm clinical trials and 2 retrospective cohort studies. There were also 19 case reports of adverse effects. The results showed that the adverse events related to toripalimab were generally mild, and the incidence of serious adverse events was not high. However, combination therapy may increase the incidence of grade 3-5 adverse events than using toripalimab

alone (0.17% vs 0.37%). The incidences of adverse events, immune-related adverse events, and serious adverse events of grade 3-4 in the regulatory labels of toripalimab are generally similar to those of pembrolizumab. Research information on children, patients with moderate to severe liver and kidney function impairment and other special populations is lacking. Considering the short time to market, the relatively small sample size of cluster data, and long-term post-marketing monitoring of some specific adverse events, it is urgent to conduct real-world studies on safety to provide an important evidence for the inclusion of toripalimab in the essential medicine list.

3. Cost-effectiveness

According to the results of economic evaluation in China, toripalimab has absolute economic advantage compared with the referenced medicine (pembrolizumab). The probability of having a cost effect of toripalimab compared with pembrolizumab is 99.7% when the willing payment threshold is equal to GDP per capita of China. When the willingness to pay threshold is equal to three times GDP per capita of China, the probability of having a cost effect is 100%. The model results are robust based on univariate sensitivity and probability sensitivity analysis.

4. Innovation

Toripalimab is a novel recombinant humanized (97%) PD-1 inhibitor, human lgG4/Kappa subtype, with a novel CDR sequence and independent FG ring binding site. Toripalimab has characteristics such as stable biological structure, high affinity and low immunogenicity. Toripalimab is developed by the local innovative enterprises in China independently, with completely independent intellectual property rights of class I biological innovative drugs, owing patent number ZL201310258289.2. Toripalimab is also the first approved domestic PD-1 monoclonal antibody in China. It was supported by the "National Science and Technology Major Project" to fill the gap of clinical immunotherapy demand in 2015 and 2017 respectively. In 2021, toripalimab was granted for FDA's Breakthrough Therapy and Orphan-drug designation for treatment of nasopharygeal carcinoma, Orphan Drug Designation for the treatment of esophageal cancer. Toripalimab was also awarded the China Patent Gold Award by China National Intellectual Property Administration and World Intellectual Property Organization in 2021.

5. Suitability

By collecting information such as the packaging, dosage form, duration of treatment and storage conditions of toripalimab and pembrolizumab for comparison, there was little difference in the suitability of the technical characteristics of the two medicines.

6. Accessibility

Toripalimab has been officially included in the China's National Reimbursement Drug List by national drug price negotiation channel, and the affordability has been greatly improved in terms of the out-of-pocket part of patient's reimbursement.

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