APPLICATION FOR SUBMISSION TO THE 24ND EXPERT COMMITTEE ON THE SELECTION AND USE OF ESSENTIAL MEDICINES

PROPOSAL TO INCLUDE TORIPALIMAB FOR NASOPHARYNGEAL CARCINOMA AND ESOPHAGEAL SQUAMOUS CELL CARCINOMA IN 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

Contents

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 multiple 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 (NPC) and recurrent or metastatic esophageal squamous cell carcinoma (ESCC) in combination with chemotherapy.

NPC is a rare and 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, including two randomized, double blind, placebo controlled, phase III studies (JUPITER-02 and JUPITER-06), indicate that adding toripalimab to chemotherapy regimens leads to clinically important gain of progression-free survival and overall survival both in first-line treatment for advanced 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
- Significant reduction in risk of death: mOS is not mature, but a 41% reduction in risk of death was observed with mDoR 18.0 vs. 6.0 months
- The improvements of PFS 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 first-line treatment of recurrent or metastatic NPC and ESCC.
- Evidence illustrated that toripalimab was more cost-effective than chemotherapy and camrelizumab in first-line treatment of recurrent or metastatic NPC.

Evidence further suggests that patients with advanced NPC and ESCC receiving toripalimab regimen may produce a clinically important gain in quality of life, than people no receiving toripalimab.

In addition, Junshi has solid experience in global supply chain and has supplied both API and finished products to more than 10 countries such as US, Singapore, Korea, Australia etc. with different supply temperature conditions (-65°C, 2-8°C and room temperature). Unopened toripalimab vial should be stored in a refrigerator and avoid freezing and shaking. 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.

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

Not Available

- **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**

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

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 2020, there were 133,354 new cases and 80,008 deaths worldwide. The incidence age-standardized rates (ASRs) for NPC is 1.5 per 100,000 and the mortality ASRs for NPC is 0.88 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 [2]. NPC has the highest prevalence in southeastern Asia, with ASRs ranging from 22.2 to 27.2 per 100,000 among males [3].

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% [4]. 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 [5].

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 [6][7]. The incidences of local recurrence and distant metastases in endemic NPC range from 10% to 20% [8]. The prognosis of NPC is not particularly satisfactory because it is detected mainly at the late stage of the disease due to its concealed location. 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 [9]. 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 [10].

NPC is highly chemosensitive and radiosensitive; thus, gemcitabine plus cisplatin is standard of care as a first-line treatment in these patients [11]. 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 [12]. Patients with stable disease may develop resistance to anticancer drugs, which is a major factor that leads to this pattern of failure [13]. 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

Esophageal cancer ranks seventh in terms of incidence (604,000 new cases) and sixth in mortality overall (544,000 deaths), corresponding to age-standardized incidence and mortality rates of 6.3 and 5.6 per 100,000, respectively. Survival from esophageal cancer remains low, in the range of 10%–30% at 5 years post diagnosis in most countries [14].

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 [15].

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 [15].

Moreover, SCC is more common in low-income countries than in high-income countries. 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 [16]. SCC new cases in developing countries represent 82% of all SCC new cases [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 [17].

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 (TP) appears to result in similar median progression-free survival (PFS) compared with 5-fluorouracil plus cisplatin (FP) (7.9 vs 6.5 months) in patients with advanced ESCC [18]. 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% [18], 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 [19].

➢ 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 [32].

➢ 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.

- **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 Version1.2022 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.

2) Guidelines of Chinese Society of Clinical Oncology (CSCO 2022 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.

8. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

- **Toripalimab for the first-line treatment of adult patients with Metastatic or recurrent，locally-advanced nasopharyngeal carcinoma.**

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

There are several researches consisting of individual trial, comparative effectiveness and meta-analyses review for toripalimab in NPC. Although the results come from a small number of trials, there's few immunotherapy choice for NPC, and toripalimab is the first approved anti-tumor PD-1 Antibody for NPC treatment, it's worth noting that toripalimab is a recommended therapeutic choice for people suffering from NPC around the world. The trials and studies are described below.

Mai et al reported a double-blind, multicenter randomized phase 3 trial (289 patients with recurrent or metastatic nasopharyngeal carcinoma, RM-NPC), locating at 35 centers in China, Taiwan and Singapore. (Jupiter-02, cutoff date: 30 May 2020) [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. At the prespecified interim PFS analysis, a significant improvement in PFS was detected in the toripalimab arm compared to the placebo arm: median PFS of 11.7 vs 8.0 months, hazard ratio (HR) = 0.52. As of 18 February 2021, a 40% reduction in risk of death was observed in the toripalimab arm compared to the placebo arm (HR = 0.603). The estimated proportion of patients who were alive at 2 years was 77.8% (95% CI: 68.0–85.0) for the toripalimab arm and 63.3% (95% CI: 49.8–74.1) for the placebo arm.

Results show that the clinical benefits of the toripalimab–GP combination could be observed regardless of PD-L1 expression status. Patients with PD-L1-positive and -negative tumors had a similar median PFS (11.4 vs 11.0 months) when treated with the toripalimab-GP combination. Improvement in PFS was also observed across other relevant subgroups, including gender, ECOG performance score, EBV baseline copy number and disease stage (recurrent or primary metastatic).

All patients enrolled in the JUIPTER-02 study were Asian, the vast majority (99%) having nonkeratinizing NPC. It is believed the results in JUPITER-02 can be extrapolated to Western populations, because the majority of patients with NPC in the West and China/Southeast Asia have the nonkeratinizing histology. 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 GP chemotherapy as a first-line treatment for patients with RM-NPC provided superior PFS compared to GP alone, and with a manageable safety profile. ESMO-MCBS score for this trial is 3.

In the AACR annual meeting 2022, Mai also updated the final progression-free survival analysis of Jupiter-02 (cutoff date: 8 June 2021) [23]. At the final PFS analysis, the median follow-up time was 22.1 months for the toripalimab arm and 21.4 months for the placebo arm by the cutoff date. The toripalimab arm had a significantly longer PFS than the placebo arm as assessed by BIRC: median PFS 21.4 vs. 8.2 months, HR=0.52 (95% CI: 0.37-0.73), two-sided p<0.0001. The 1-year PFS rates were 59.0% vs. 32.9%. The ORR was 78.8% vs. 67.1% (P=0.022) and the median duration of response (DOR) was 18.0 vs. 6.0 months, HR= 0.49 (95% CI: 0.33-0.72). Consistently, PFS as assessed by investigator was also significantly longer in the toripalimab arm than the placebo arm: median PFS 17.3 vs. 8.1 months, HR=0.43 (95% CI: 0.31-0.58), P<0.0001. As of June 8, 2021, the median OS was not reached in either arm, with a trend favoring the toripalimab arm, HR=0.59 (95% CI: 0.37-0.94), P=0.024. The improvements of PFS and OS in the toripalimab arm were observed across key subgroups, including PD-L1 expression subgroups. Notably, dynamic decrease of plasma Epstein-Barr Virus DNA copy number from baseline was associated with favorable response.

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 [24]. 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. Patients with ≥50% decrease of plasma Epstein-Barr virus (EBV) DNA copy number on day 28 had significantly better ORR than those with ＜50% decrease, 48.3% vs 5.7%.

Hua et al conducted an open-label single-arm, phase II trial, to investigate the efficacy and safety of toripalimab in combination with intensity-modulated radiotherapy (IMRT) for recurrent nasopharyngeal carcinoma (rNPC) [25]. A total of 25 patients with rNPC were enrolled and received IMRT in combination with toripalimab administered via intravenous infusion of 240 mg once every 3 weeks for a maximum of seven cycles. It turned out 19 patients (79.2%) achieved an overall response, and disease control was achieved in 23 (95.8%) patients at 3 months post radiotherapy. The 12-month PFS was 91.8%. These results supported that toripalimab combined with IMRT was tolerable and showed promising antitumor activity in patients with rNPC.

Zhang et al introduced the approval of toripalimab as the first domestic anti-tumor PD-

1 antibody in China, and the efficacy of toripalimab in tumors including nasopharyngeal, Non-Small Cell Lung Cancer, Esophageal Cancer, Gastric and Gastroesophageal Junction Cancer, Colorectal Cancer, Hepatobiliary Cancers, Neuroendocrine Neoplasms, Nasopharyngeal Cancer, Urothelial Carcinoma, and other cancers [26]. For Nasopharyngeal Cancer treatment, toripalimab was shown to be effective when used alone or with radiotherapy in treating NPC patients. Toripalimab monotherapy led to an ORR of 20.5% (39/190) and a DCR of 41.6% (79/190), which led to its approval for treating patients with recurrent/metastatic NPC as a third-line therapy. The results were also compared with nivolumab, and pembrolizumab, of which the ORRs were 20.5% (9/44) and 26.3% (5/19), respectively. The author thus recommended toripalimab a superior clinical benefit.

Wei et al conducted a phase I study of toripalimab, in patients with refractory malignant solid tumors [27], 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 [28]. 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.

Meng et al reported a 55-year-old patient with nasopharyngeal inflammatory myofibroblastic tumors (IMT) and the recurrence in the skull base, slope and pterygoid sinus who underwent cranial base and slope tumor resection [29]. The patient achieved partial remission after receiving 7 cycles of immunotherapy (Toripalimab 240 mg for 1 cycle followed by 6 cycles of sintilimab 200 mg), and MRI examination indicated an almost complete remission of intracranial IMT after 16 cycles of immunotherapy. In summary, the novel class of immune-targeted agents may be effective in clinical management of rare intracranial IMT.

Comparative effectiveness (Review and meta-analysis)

Lv et al performed a comparison of safety and antitumor activities of pembrolizumab, nivolumab, camrelizumab and JS001 (toripalimab) with/without chemotherapy in recurrent/metastatic nasopharyngeal carcinoma (RM-NPC), based on different regimens of these anti-PD-1 drugs [30]. Results presented that the ORR of anti-PD-1 monotherapy used as >1st line therapy ranged 19.0–34.1%, relatively higher in

camrelizumab (34.1%), followed by pembrolizumab (26.3%), JS001 (23.3%), and nivolumab (19.0%).

Zhu et al [31] performed a meta-analysis of the two newly approved treatment strategies, toripalimab or camrelizumab combined with gemcitabine and cisplatin for RM-NPC treatment (TGP or CGP), to assess which treatments provide the greatest clinical benefits at a reasonable cost. An indirect comparison of the data revealed that TGP (HR, 0.60; 95% CI, 0.364–0.998 and HR, 0.52; 95% CI, 0.363–0.746) led to meaningful statistical enhancements in OS and PFS in comparison to gemcitabine and cisplatin (GP). No statistically meaningful discrepancies in OS and PFS were detected across the two chemo-immunotherapy (TGP or CGP) regimens.

- **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 [32], 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 [HR] = 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 [33]. In addition, the current treatment guidelines regarding the management of advanced ESCC are similar in the West and East [34][35][36].

A single-center phase I study was conducted in Sun Yat-sen University Cancer Center [37]. 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 [38]. 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 [39]. 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 [40]. 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.

Thuss-Patience and Stein reported that immunotherapy in addition to chemotherapy achieved significant survival benefits over chemotherapy alone, but this study did not conduct direct comparison between the selective PD-1 (programmed cell death ligand-1)-inhibitors [41]. 5 clinical trials in first-line treatment for esophageal carcinoma were identified and described. It was reported that toripalimab may also show survival benefit as demonstrated in the randomized phase III (JUPITER 06) as first-line treatment in 659 Chinese ESCC patients.

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) [42]. 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.

Wu et al conducted a post hoc analysis of the Chinese JUPITER-06 study focusing on efficacy stratified by PD-L1 tumor proportion score (TPS; using JS311 antibody) [43]. The results showed more prominent clinical benefit with PD-1 antibody plus chemotherapy than with chemotherapy alone in both the high and low PD-L1–expressing subgroups. Moreover, a meta-analysis was conducted to further explore the superiority of programmed death-1 (PD-1) antibody plus chemotherapy over chemotherapy alone in patients with low PD-L1–expressing ESCC. Five randomized controlled trials were included in the meta-analysis, and two PD-L1 expression scoring criteria, TPS (≥1%/,1%) and combined positive score (CPS, ≥10/,10), were analyzed. Significant overall survival benefit by adding PD-1 antibody to chemotherapy was observed in both the TPS,1% (HR, 0.74; 95% CI, 0.56 to 0.97) and CPS , 10 (HR, 0.77;

95% CI, 0.66 to 0.89) subgroups. Similarly, significantly prolonged progression-free survival was observed in both the TPS,1% (HR, 0.66; 95% CI, 0.50 to 0.86) and CPS,10 (HR, 0.63; 95% CI, 0.47 to 0.84) subgroups. In addition, the objective response rate of the TPS, 1% subgroup was significantly improved (odds ratio, 1.71; 95% CI, 1.27 to 2.29). In all high PD-L1–expressing subgroups, the pooled benefit of PD-1 antibody plus chemotherapy was significantly better than that of chemotherapy. It was concluded that this study provides further evidence supporting the superiority of adding PD-1 antibody to chemotherapy as a first-line treatment for patients with advanced ESCC with low PD-L1 expression. On the basis of the post hoc analysis of JUPITER-06 and a meta-analysis, this study presented novel evidence in response to this highly disputed issue. Furthermore, the findings also indicate the necessity of multiomics research to uncover more effective biomarkers that could be used to identify patients with ESCC who might benefit from immunotherapy-chemotherapy combination.

9. 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 the Chinese drug regulatory authorities (including the National Center for Drug Evaluation and the National and Shanghai Adverse Reaction Monitoring Centers) and applicable regulatory authorities around the world (such as the US FDA). 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
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				

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

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

There is no published economic evaluations or reviews/mata-analysis for toripalimab in treatment-naive advanced ESCC since it is a short time after the indication was approved. An economic evaluation may be premature. However, in the current market for the treatment of ESCC in China, toripalimab provides a more affordable immunotherapy for ESCC, compared with other approved immunotherapies. In addition, MacDonald et al estimated the potential cost-savings achieved by treating patients in NSCLC with toripalimab regimen over pembrolizumab regimen from the US payer perspective, on the basis of assumption in the costs of toripalimab [44]. This study concluded that potential savings afforded by use of toripalimab in NSCLC may be substantial. Such results are consistent with the results revealed by Calamia et al, which is a budget impact analysis of adding the toripalimab regimen to the pembrolizumab regimen in squamous NSCLC [45]. The results illustrated that prescribing toripalimab instead of pembrolizumab in squamous NSCLC would be associated with cost savings in excess of $971 million. Such two studies revealed the forward ability in affordability of toripalimab in oncotherapy.

As for the indication NPC, the publications are as following:

Tian et al evaluated the cost-effectiveness of toripalimab combined with GP compared with GP alone and camrelizumab plus GP for patients with RM-NPC, respectively [46]. A markov model was established to estimate the cost and effectiveness for different first-line therapies. Data of safety and efficacy were derived from the JUPITER-02 trial [19] for toripalimab regimen and GP and CAPTAIN-1st trial for camrelizumab regimen [47]. The analysis was conducted from the perspective of a Chinese health care payer (updated to US$, year 2016 values). Compared with the GP chemotherapy, toripalimab regimen would be expected to result in an incremental cost of $6,026 with additional 0.90 quality-adjusted life-years (QALYs), resulting in an incremental cost-effectiveness ratio (ICER) of $6,696/QALY, which is cost-effective in China using a threshold of three times GDP per capita. In the pairwise comparison between the two immunotherapy-related groups, toripalimab plus GP was the dominant strategy with lower costs and higher QALYs than the camrelizumab plus GP group.

Zhu et al conducted a cost-effectiveness analysis and network meta-analysis based on the JUPITER-02 trial [19] and CAPTAIN-1st trial [47] to assess the cost-effectiveness of toripalimab plus GP versus camrelizumab plus GP and GP alone, respectively [48]. A Markov model was expanded for the evaluation of the effectiveness and cost of toripalimab regimen, camrelizumab regimen and GP chemotherapy with a 10-years horizon and measured the health achievements in QALYs and life-years (LYs). A network meta-approach was used to reconstruct the OS and PFS data at the individual patient level based on the JUPITER-02 and CAPTAIN-1st trials to conduct the indirect comparison between the therapies. The results revealed that toripalimab

regimen was associated with a total cost of $48,525 and 2.778 QALYs (4.991 LYs), leading to an ICER of $15,103 per QALY ($10,321 per LY) compared to camrelizumab regimen. On comparing the GP chemotherapy, this study found toripalimab regimen incurred substantial health costs, resulting in an ICER of $19,726 per QALY. The authors concluded that considering the usually accepted thresholds in China, toripalimab regimen would be more cost-effective compared with camrelizumab regimen and GP for first-line treatment of patients with RM-NPC.

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.

Junshi has submitted BLA for toripalimab to the U.S. FDA and MAA to the EMA and the MHRA of the UK. These applications are currently under reviewed. Toripalimab is granted Breakthrough Therapy for both first line and 2nd line NPC by U.S. FDA. Toripalimab has also bee granted multiple Orphan Drug Designations for various cancers by U.S. FDA.

- **Pharmacopoieal standards**

Not Available

12. REFERENCE

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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

RECOMMENDATION 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

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 characteristic 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.

Yu Fang

Authorized Signature of Professor Yu Fang

Director of the Center for Drug Safety and Policy Research, Xi'an Jiaotong University

Vice-Dean of the School of Pharmacy, Xi'an Jiaotong University

For and on behalf of

THE CENTER FOR DRUG SAFETY AND POLICY RESEARCH

西安交通大学药品安全与政策研究中心