Toripalimab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.3. Immunomodulators

ATC codes: L01FF13

Indication	Squamous cell carcinoma of oesophagus ICD11 code: 2B70.1
INN	Toripalimab
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 240 mg per 6 mL in vial
EML status history	Application rejected in 2023 (TRS 1049) Application rejected in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Biological Cancer
Wikipedia	Toripalimab
DrugBank	Toripalimab

Expert Committee recommendation

The Expert Committee recognized the significant public health burden of oesophageal squamous cell carcinoma and nasopharyngeal carcinoma, particularly in Asia where the diseases are considered endemic with disproportionately high incidence, prevalence and mortality. The Asian region accounts for about 75% and 85% of the global burden of oesophageal squamous cell carcinoma and nasopharyngeal carcinoma, respectively. In nasopharyngeal carcinoma, the Committee considered evidence from toripalimab clinical trials that showed promising overall survival gains, surpassing the EML threshold of 4–6 months, for toripalimab in combination with chemotherapy over chemotherapy alone in the first-line setting. The magnitude of overall survival benefit in the second-line setting was more limited, However, the Committee also noted that trials of other immune checkpoint inhibitors in treatment of nasopharyngeal carcinoma (e.g. camrelizumab and tislelizumab) are ongoing. The Committee considered it would be of interest to evaluate the benefits of these medicines as a class in treatment of nasopharyngeal carcinoma, particularly in the first-line setting. The Expert Committee therefore did not recommend the inclusion of toripalimab on the EML for the treatment of nasopharyngeal carcinoma at this time. The Committee underscored that more mature additional data for all immune checkpoint inhibitors approved for nasopharyngeal carcinoma, especially on overall survival and quality of life, will be pivotal to inform judgements

on whether to include toripalimab on the EML in the future. In oesophageal squamous cell carcinoma, the Committee considered evidence from the JUPITER-06 trial that showed an overall survival benefit of around 6 months for toripalimab plus chemotherapy compared with chemotherapy alone in the first-line setting. As regards the comparative effectiveness of toripalimab and other immune checkpoint inhibitors for oesophageal squamous cell carcinoma in the first-line setting, the Committee found the magnitudes of effect on overall survival to be relatively consistent at about 6 months overall survival gain compared with chemotherapy, which the Committee judged to be moderate. In each case, treatment was in combination with chemotherapy. The Committee considered that this finding suggested a class effect and the potential for medicines within the class to be considered as therapeutic alternatives. Data for toripalimab in the second-line setting were not available. The Committee agreed with the EML cancer expert group that the role of PD-L1 expression as a predictive biomarker for benefit was unclear. The Committee also noted the lack of long-term survival data for the class of immune checkpoint inhibitors. The Committee noted the potential for increased harm in patients with a poor performance status and poorer prognosis at baseline, a population that is relatively unrepresented in trials. The Committee noted that toripalimab was likely to be the more cost-effective option compared with pembrolizumab, nivolumab, nivolumab plus ipilimumab, and tislelizumab. However, the Committee considered that the cost of treatment may still have a substantial budget impact, particularly in resource-constrained settings. Based on these considerations, the Expert Committee did not recommend the inclusion of toripalimab (or any other immune checkpoint inhibitor) on the EML for the treatment of oesophageal squamous cell carcinoma in the first- or later-line setting. In terms of the class, the Committee considered that ongoing trials and determination of the role of PD-L1 expression as a predictive biomarker would be informative for future consideration of these medicines for this indication.

Background

An application for the addition of toripalimab to the EML for treatment of nasopharyngeal carcinoma and oesophageal squamous cell carcinoma was considered by the Expert Committee in 2023. The 2023 Committee's recommendations are presented below. The 2023 Expert Committee acknowledged the global health burden of nasopharyngeal and oesophageal cancers and noted the endemic nature of nasopharyngeal cancer in low- and middle-income countries. The Committee agreed that better therapeutic options were needed for treatment of these cancers. The Committee noted that the evidence presented in the application focused on patients with metastatic or recurrent, locally advanced disease and that the patients included in the trials were not selected based on the level of tumour expression of PD-L1, although this aspect was explored in post hoc analyses based on aggregated data from multiple randomized controlled trials on oesophageal cancer. The Committee considered that more evidence analysing the effect of treatment based on PD-L1 expression or other biomarkers would be informative to understand whether a particular subgroup of patients might benefit more from treatment. The Committee considered that the benefits observed when toripalimab was added to chemotherapy in the first-line treatment for advanced nasopharyngeal cancer were modest, and that toripalimab was assigned a score of 3 on the European Society for Medical Oncology (ESMO) magnitude of clinical benefit scale, which is lower than the accepted threshold for EML consideration. For advanced oesophageal squamous cell cancer, the Committee acknowledged that the addition of toripalimab to chemotherapy might be associated with relevant improvements in survival compared with chemotherapy alone, although the evidence is still immature, with short follow-up. A score on the ESMO magnitude of clinical benefit scale is not available for toripalimab for this indication. The Committee acknowledged that the reported price of toripalimab was considerably lower than other immune checkpoint inhibitors However, the price estimates were only available from China, the only country where toripalimab is currently marketed. The Expert Committee therefore did not recommend the inclusion of toripalimab on the complementary list of the EML for the treatment of nasopharyngeal and oesophageal squamous cell carcinomas. The Committee acknowledged the promising role of chemoimmunotherapy in the treatment of these cancers and recommended that the evidence for these treatments continue to be monitored for potential future EML consideration (1).

Public health relevance

Nasopharyngeal carcinoma According to Globocan, in 2022 there were 120 434 incident cases and 73 482 deaths worldwide from nasopharyngeal carcinoma. The incidence, mortality and 5-year prevalence vary substantially by geographical region, with Asia accounting for almost 85% (2). Oesophageal squamous cell carcinoma According to Globocan, in 2022 there were 511 054 incident cases of oesophageal cancer and 445 391 deaths worldwide (3). Oesophageal cancer can be categorized into two main histological subtypes with different etiologies: adenocarcinoma and squamous cell carcinoma. Globally, squamous cell carcinoma is the most common subtype in both male and female patients, contributing to 85% of all oesophageal cancer cases (4). Oesophageal cancer shows substantial geographical variance, with Asia accounting for around 75% of the global incidence, mortality and 5-year prevalence (3).

Benefits

Nasopharyngeal carcinoma JUPITER-02 was an international, multicentre, randomized, double-blind phase III study conducted in Asian regions endemic for nasopharyngeal carcinoma. The study compared toripalimab in combination with gemcitabine and cisplatin with gemcitabine and cisplatin in 289 patients with previously untreated recurrent or metastatic nasopharyngeal cancer (5). Most patients in the Asian regions endemic for nasopharyngeal carcinoma have non-keratinizing histology, closely associated with the Epstein–Barr virus. Participants were randomized 1:1 to receive toripalimab 240 mg or placebo in combination with gemcitabine 1000 mg/m2 and cisplatin 80 mg/m2 every 3 weeks for up to six cycles, followed by toripalimab or placebo monotherapy. The primary endpoint was progression-free survival as assessed by a blinded independent review committee. Overall survival was assessed as a secondary endpoint. At the final progression-free survival analysis (8 June 2021), median follow-up was 22.1 months for the toripalimab arm and 21.4 months for the placebo arm. Median progression-free survival was 21.4 months and 8.2 months in the toripalimab and placebo arms, respectively (hazard ratio (HR) 0.52, 95% confidence interval (CI) 0.37 to 0.73). As of the cut-off date of 18 November 2022, following 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 and was 33.7 months in the placebo group. Toripalimab was associated with a significant improvement in overall survival compared with placebo (HR 0.63, 95% CI 0.45 to 0.89). Overall survival rates for toripalimab versus placebo groups at 1, 2 and 3 years were 90.9% versus 87.1%, 78.0% versus 65.1% and 64.5% versus 49.2%, respectively. 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 (HR 1.23, 95% CI 0.70 to 2.18). Treatment effects on overall survival favoured toripalimab in PD-L1 expression subgroups of $< 1\%$ (HR 0.36, 95% CI 0.4 to 0.93) and $\geq 1\%$ (HR 0.71, 95% CI 0.48 to 1.04). Additionally, a subgroup analysis showed benefit favouring toripalimab in patients with both low ($<$ 2000 baseline Epstein–Barr virus DNA copy number; HR 0.76, 95% CI 0.40 to 1.46) and high ($\geq$ 2000 baseline Epstein–Barr virus DNA copy number; HR 0.59, 95% CI 0.40 to 0.89), suggesting that toripalimab will benefit patients with keratinizing nasopharyngeal cancer in non-endemic settings for nasopharyngeal carcinoma. POLARIS-02 was a single-arm, multicentre phase II study that evaluated the antitumour activity, safety and biomarkers of toripalimab 3 mg/kg once every 2 weeks in 190 patients in China with previously treated recurrent or metastatic nasopharyngeal carcinoma (6). Participants received toripalimab until disease progression, unacceptable toxicity or withdrawal of informed consent. The primary endpoint was objective response rate as determined by an independent review committee. Almost half of the participants had received at least two prior lines of systemic chemotherapy. Most participants (95.8%) had non-keratinizing nasopharyngeal carcinoma histology. One year after the last enrolment, 18 (9.5%) participants remained on treatment. Median treatment duration was 3.7 months. The objective response rate for the 190 patients was 20.5%. Median duration of response was 12.8 months, median progression-free survival was 1.9 months and median overall survival was 17.4 months. In the subgroup of participants who had received at least two prior lines of treatment ($n = 92$), the objective response rate was 23.9%, median duration of response was 21.5 months, median progression-free survival was 2.0 months and median overall survival was 15.1 months. Objective response rates in participants with PD-L1 expression $> 1\%$ and participants with negative PD-L1 expression were 27.1% and 19.4%, respectively, however, the difference was not statistically significant. Oesophageal squamous

cell carcinoma JUPITER-06 was a randomized, double-blind, multicentre, phase III trial that compared toripalimab in combination with paclitaxel and cisplatin with paclitaxel and cisplatin in 514 Chinese patients with previously untreated advanced oesophageal squamous cell carcinoma (7). Patients were randomized 1:1 to receive toripalimab 240 mg or placebo in combination with paclitaxel 175 mg/kg and cisplatin 75 mg/m2 every 3 weeks for up to six cycles followed by toripalimab or placebo monotherapy. Coprimary endpoints were progression-free survival as assessed by a blinded independent central review committee and overall survival in the intention-to-treat population. At the prespecified final analysis, median progression-free survival was 5.7 months in the toripalimab arm versus 5.5 months in the placebo arm (stratified HR for progression or death 0.58, 95% CI 0.46 to 0.74). The 1-year progression-free survival rates were 27.8% in the toripalimab arm and 6.1% in the placebo arm. Median overall survival was 17 months versus 11 months in the toripalimab and placebo arms, respectively (stratified HR for death 0.58, 95% CI 0.43 to 0.78). In the intention-to-treat population, the objective response rate and disease control rate as assessed by the blinded independent central review committee was higher in the toripalimab arm (objective response rate 69.3% versus 52.1%; disease control rate 89.1% versus 82.1%). Treatment effects on overall survival favoured toripalimab in subgroups of patients with low and high PD-L1 expression. A 2022 systematic review and network meta-analysis of five randomized controlled trials (3163 participants) evaluated the efficacy and safety of different PD-1 inhibitors (camrelizumab, nivolumab, pembrolizumab, sintilimab and toripalimab) in combination with chemotherapy as first-line treatment for advanced oesophageal cancer (8). Significant improvements in overall survival (HR 0.69, 95% CI 0.62 to 0.76), progression-free survival (HR 0.62, 95% CI 0.55 to 0.70) and objective response rate (risk ratio 1.41, 95% CI 1.23 to 1.62) were observed when a PD-1 inhibitor was added to chemotherapy. Toripalimab plus chemotherapy achieved greater overall survival benefit relative to chemotherapy alone than the other PD-1 inhibitors plus chemotherapy. Pooled subgroup analyses suggested a significant overall survival benefit associated with PD-1 inhibitor therapy in patients with PD-L1 tumour-positive score ≥ 10% (HR 0.57, 95% CI 0.46 to 0.70). Similar findings have been reported in another systematic review and meta-analysis of immune-checkpoint inhibitors for first- and later-line treatment of advanced or metastatic oesophageal squamous cell carcinoma (9).

Harms

Treatment-related adverse events occurring in ≥ 5% of patients from the toripalimab monotherapy safety database, or the JUPITER-02 and JUPITER-06 trials of toripalimab in combination with chemotherapy were reported in the application and were unchanged from those reported in the 2023 application. Treatment-related adverse events (all grades) that occurred more frequently in the toripalimab monotherapy population than the toripalimab plus chemotherapy population include hyperbilirubinaemia, abnormal thyroid function test, abnormal creatine phosphokinase, abnormal lipids, increased amylase and proteinuria. Grade ≥ 3 hyperbilirubinaemia was reported slightly more frequently in the monotherapy group.

Cost / cost effectiveness

Nasopharyngeal carcinoma A 2024 analysis evaluated the cost–effectiveness of toripalimab plus chemotherapy versus chemotherapy alone in American patients with recurrent or metastatic nasopharyngeal carcinoma from the United States payer perspective (11). Compared with chemotherapy, toripalimab plus chemotherapy was associated with an incremental cost–effectiveness ratio of 74 004 United States dollars (US$) per quality-adjusted life year (QALY), which is lower than the willingness-to-pay threshold of US$ 150 000 per QALY. A 2024 economic simulation study estimated the cost–efficiency of toripalimab plus chemotherapy versus pembrolizumab plus chemotherapy for the treatment of recurrent or metastatic nasopharyngeal carcinoma for an assumed 1207 incident cases in the United States in 2024 (12). The simulation used wholesale acquisition costs and an assumed price for toripalimab of 80% of the average sales price of pembrolizumab. The study found that assuming 90% of new cases of recurrent or metastatic nasopharyngeal cancer were treated with toripalimab instead of pembrolizumab, savings realized over 1 year would be US$ 43.5 million, which would be sufficient to purchase an additional 4717 doses on a budget-neutral basis. A 2024 modelling study estimated the budget impact of toripalimab versus pembrolizumab in the first-line treatment of recurrent or metastatic nasopharyngeal carcinoma in the United States (13). The model used a 3-year time horizon and assumed a market share split

(toripalimab/pembrolizumab) of 60/40 in year 1 and increasing to 80/20 in years 2 and 3. The study used published wholesale acquisition costs and average sales prices and considered a treatment mix without versus with toripalimab in the eligible incident US population. It was estimated that savings of about US$ 180 million over 3 years could be achieved by using a toripalimab-containing regimen over a pembrolizumab-containing regimen. A 2023 network meta-analysis and cost–effectiveness analysis evaluated the cost–effectiveness of toripalimab, camrelizumab and tislelizumab, all plus chemotherapy, and chemotherapy alone as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma from a Chinese payer perspective (14). Compared with chemotherapy alone, toripalimab, camrelizumab and tislelizumab added to chemotherapy were associated with incremental cost–utility ratios of US$ 25 576, US$ 31 370 and US$ 31 729 per QALY, respectively. All were found to be cost-effective at a willingness-to-pay threshold of US$ 38 029 per QALY. In pairwise comparisons between the PD-1 inhibitors, toripalimab with chemotherapy was the most cost-effective option. Oesophageal squamous cell carcinoma A 2023 analysis evaluated the cost–effectiveness of PD-1 inhibitors in combination with chemotherapy as first-line therapy for advanced oesophageal squamous cell carcinoma from the Chinese health-care system perspective (15). In the base-case analysis over a 10-year time horizon, compared with chemotherapy alone, toripalimab, sintilimab and camrelizumab added to chemotherapy were associated with incremental cost–effectiveness ratios of US$ 14 047, US$ 18 622 and US$ 29 771 per QALY, respectively, which are lower than a willingness-to-pay threshold of US$ 38 351 per QALY. In contrast, other PD-1 inhibitors were not cost-effective, with incremental cost–effectiveness ratios versus chemotherapy alone of US$ 170 911, US$ 211 350 and US$ 400 769 per QALY for serplulimab, pembrolizumab and nivolumab plus chemotherapy, respectively.

WHO guidelines

WHO guidelines for treatment of nasopharyngeal and oesophageal squamous cell carcinoma are not currently available. Toripalimab in combination with gemcitabine and cisplatin is recommended in the 2025 guidelines of the United States National Comprehensive Cancer Network guidelines for first-line treatment of recurrent, unresectable, oligometastatic or metastatic nasopharyngeal cancer (10). The application reported that the 2024 guidelines of the Chinese Society of Clinical Oncology include the following recommendations for toripalimab use: • in combination with gemcitabine and cisplatin as first-line treatment of recurrent or metastatic nasopharyngeal carcinoma, and as monotherapy for treatment-experienced patients; • in combination with paclitaxel and cisplatin as first-line treatment of recurrent or metastatic oesophageal squamous cell carcinoma.

Availability

Toripalimab has regulatory approval for use in the treatment of metastatic or recurrent locally advanced nasopharyngeal carcinoma in China, Europe, India and the United States. Regulatory approval for toripalimab in the treatment of oesophageal squamous cell carcinoma has, to date, only been granted in China. Regulatory applications have been submitted in Australia, Chile, Jordan, Singapore, South Africa and the United Kingdom of Great Britain and Northern Ireland.

Other considerations

The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical team highlighted that overall survival data for toripalimab were still insufficiently mature and advised that further consideration could be made as additional studies are reported. The EML cancer experts group reviewed the application but were unable to reach consensus on whether to support the inclusion of toripalimab on the EML for nasopharyngeal cancer. The group did not support the inclusion of toripalimab (or any other immune checkpoint inhibitor) on the EML for the treatment of oesophageal squamous cell carcinoma. The group judged that the reported gains in overall survival were moderate in size and offset by the unclear role of PD-L1 expression as a predictive biomarker. Long-term data on the class of immune checkpoint inhibitors were lacking.

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