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	Malignant neoplasms of nasopharynx ICD11 code: 2C3B.Z
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)
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 acknowledged the global health burden of nasopharyngeal and oesophageal cancer 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 first-line treatment for advanced nasopharyngeal cancer were modest, and that toripalimab was assigned a score of 3 on the 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 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.

Background

Toripalimab has not previously been considered for inclusion on the EML for the proposed indications, or any other indications. Medicines currently included on the EML for the treatment of nasopharyngeal carcinoma are carboplatin, cisplatin, fluorouracil and paclitaxel. Medicines for the treatment of oesophageal carcinoma have not previously been evaluated. The PD-1 immune checkpoint inhibitor nivolumab (with a square box indicating pembrolizumab as a therapeutic alternative) was added to the EML in 2019 for first-line monotherapy in patients with unresectable and metastatic melanoma (1).

Public health relevance

Nasopharyngeal carcinoma Nasopharyngeal carcinoma is a rare and malignant cancer. Substantial geographical variation in incidence exists with the highest incidence in south-eastern Asia, eastern Asia, eastern Africa, and middle Africa (2). Overall, Asia accounts for more than 85% of the global incidence, mortality and 5-year prevalence. The geographic pattern is associated with differences in genetic susceptibility and the prevalence of Epstein–Barr virus infection in different regions. In 2020, more than 130 000 new cases and 80 000 deaths were recorded worldwide. The incidence age-standardized rate was 1.5 per 100 000 and the mortality age-standardized rate was 0.88 per 100 000 (3). Oesophageal squamous cell carcinoma Globally, oesophageal cancer ranks eighth in incidence and sixth in mortality among all cancers. In 2020, more than 600 000 new cases and 544 000 deaths occurred worldwide, corresponding to age-standardized rates for incidence and mortality of 6.3 and 5.3 per 100 000, respectively (4). The burden of oesophageal cancer varies greatly across countries and populations. Eastern Asia has 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, with 53.7% in China alone. As regards deaths related to oesophageal cancer, 58.7% occurred in eastern Asia with 55.3% in China alone (5). Oesophageal cancer can be categorized into two main histological subtypes, 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 (5). The burden of disease of oesophageal squamous cell carcinoma is greater in low-income countries than in high-income countries. About 90% of all oesophageal cancers in developing countries are squamous cell carcinoma s, compared with 66% in high-income countries, with developing countries representing 82% of all new squamous cell carcinoma cases worldwide (6).

Benefits

Nasopharyngeal carcinoma JUPITER-02 is a randomized, double-blind, multicentre, phase III trial (289 participants) that compared toripalimab with placebo, in combination with gemcitabine plus cisplatin as first-line treatment of recurrent or metastatic nasopharyngeal carcinoma (7). All enrolled patients in the JUPITER-02 study were Asian and 99% had non-keratinizing nasopharyngeal carcinoma. Patients were randomized (1:1) to receive either toripalimab or placebo in combination with chemotherapy every 3 weeks for up to six cycles, followed by monotherapy with toripalimab or placebo. The primary endpoint was progression-free survival as assessed by a blinded independent review committee. At the prespecified interim progression-free survival analysis, median progression-free survival was 11.7 months in the toripalimab arm compared with 8.0 months in the placebo arm (hazard ratio (HR) 0.52, 95% confidence interval (CI) 0.36 to 0.74). As of 18 February 2021, median survival had not been reached (stratified HR 0.60, 95% CI 0.36 to 1.00). The estimated proportion of patients who were alive at 2 years was 77.8% (95% CI 68.0% to 85.0%) for the toripalimab arm and 63.3% (95% CI 49.8% to 74.1%) for the placebo arm. Patients with PD-L1-positive and -negative tumours had a similar median progression-free survival (11.4 versus 11.0 months) when treated with the toripalimab in combination with gemcitabine plus cisplatin. Improvement in progression-free survival was also observed in other relevant subgroups, stratified by sex, Eastern Cooperative Oncology Group (ECOG) performance score, Epstein–Barr virus baseline copy number and disease stage (recurrent or primary metastatic). 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, assessed by a blinded independent review committee, was 21.4 months in the toripalimab arm versus 8.2 months in the placebo arm (HR 0.52, 95% CI 0.37 to 0.73). The 1-year progression-free survival rates were 59.0% versus 32.9%. The overall response rate was 78.8% in the toripalimab arm versus 67.1% in the placebo arm and the median duration of response was 18.0 versus 6.0 months (HR 0.49, 95% CI 0.33 to 0.72). Investigator-assessed progression-free survival was 17.3 months in the toripalimab arm versus 8.1 months in the placebo arm (HR 0.43, 95% CI 0.31 to 0.58). Median overall survival was not reached in

either arm, with interim results favouring toripalimab (HR 0.59, 95% CI 0.37 to 0.94) (8). Based on the JUPITER-02 trial, toripalimab has a score of 3 on the European Society for Medical Oncology (ESMO) magnitude of clinical benefit scale V1.1. Oesophageal squamous cell carcinoma JUPITER-06 is a randomized, double-blind, multicentre, phase III trial (514 participants) that compared toripalimab versus placebo, in combination with paclitaxel plus cisplatin, as first-line treatment of advanced oesophageal squamous cell carcinoma (9). Patients were randomized (1:1) to receive toripalimab or placebo in combination with chemotherapy every 3 weeks for up to six cycles, followed by toripalimab or placebo maintenance. Coprimary endpoints were progression-free survival 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. At the prespecified interim analysis median overall survival was 17 months in the toripalimab arm versus 11 months in the placebo arm (stratified HR for death 0.58, 95% CI 0.43 to 0.78). The 1-year overall survival rates were 66.0% versus 43.7% in the toripalimab and placebo arms, respectively. A post-hoc analysis of the JUPITER-06 study evaluated efficacy stratified by PD-L1 tumour proportion score < 1% and ≥ 1% (10). The results showed significantly greater clinical benefit with PD-1 antibody plus chemotherapy versus chemotherapy alone in both the high and low PD-L1-expressing subgroups. All enrolled patients in the JUPITER-06 study were Chinese with 100% squamous histology. An ESMO magnitude of clinical benefit scale score for toripalimab in oesophageal squamous cell carcinoma is not available. A systematic review and network meta-analysis (five randomized controlled trials, 2163 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 (11). 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 (RR) 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. Subgroup analyses suggested a significant overall survival advantage in groups with PD-L1 tumour-positive scores ≥ 10% and longer progression-free survival in groups with PD-L1 combined positive scores ≥ 10.

Harms

Treatment-related adverse events occurring in ≥ 5% of patients from the toripalimab monotherapy safety database or the JUPITER-02 and JUPITER-06 trials were reported in the application. Such treatment-related adverse events that were more common in the toripalimab monotherapy population included increased hyperbilirubinaemia, abnormal thyroid function test, abnormal creatine phosphokinase, abnormal lipids, increased amylase and proteinuria. Nasopharyngeal carcinoma In the JUPITER-02 study, the incidence of grade ≥3 adverse events was similar between the toripalimab and placebo arms (89.7% versus 90.2%), as was the incidence of fatal adverse events (2.7% versus 2.8%). Immune-related adverse events were more frequent with toripalimab (53.4% versus 21.7%), including those of grade ≥ 3 (8.9% versus 1.4%) (7). Oesophageal squamous cell carcinoma In the JUPITER-06 study, treatment-emergent adverse events of grade ≥ 3 occurred in 73.2% of patients in the toripalimab arm and 70.0% of patients in the placebo arm. Fatal treatment-emergent adverse events occurred in 8.2% of patients in each treatment arm, of which 0.4% in the toripalimab arm and 1.2% in the placebo arm were related to the study treatment. The incidence of serious adverse events (36.2% versus 28.8%) and infusion-related reactions (3.5% versus 3.1%) were similar between treatment arms. Treatment emergent adverse events that led to treatment discontinuation occurred in 11.7% and 16.2% of patients in the toripalimab and placebo arms, respectively (9).

Cost / cost effectiveness

Nasopharyngeal carcinoma Two cost–effectiveness analyses evaluated toripalimab or camrelizumab combined with chemotherapy and chemotherapy alone for patients with recurrent or metastatic nasopharyngeal carcinoma from the Chinese payers' perspective (12,13). Compared with chemotherapy alone, toripalimab plus chemotherapy was associated with incremental cost–effectiveness ratios of US$ 6696 (12) and US$ 19 726 (13) per quality-adjusted life year. The medicine cost for one cycle of treatment with toripalimab (240 mg) reported in the analyses were US$ 426.02 (12) and US$ 659.40 (13). Oesophageal squamous cell carcinoma Published cost–effectiveness evaluations for toripalimab in treatment-naive advanced oesophageal squamous cell cancer are not available.

WHO guidelines

WHO guidelines for treatment of nasopharyngeal and oesophageal carcinomas are not currently available.

Availability

Toripalimab has regulatory approval from the National Medical Product Administration in China for six indications, including those requested in the application. Regulatory applications have been submitted to the United States Food and Drug Administration, the European Medicines Agency and the United Kingdom Medicines and Healthcare products Regulatory Agency and are currently under review.

Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases reviewed and provided comments on the application. It was the view of the technical department that there were currently insufficient mature data on the efficacy and safety of toripalimab. However, the technical team noted with interest the relevant early findings in nasopharyngeal and oesophageal cancers, and advised that further consideration could be made as additional studies are reported and a greater understanding of feasibility of use was gained. The EML Cancer Medicines Working Group did not support the inclusion of toripalimab on the EML for the treatment of nasopharyngeal or oesophageal squamous cell cancer at this time because the absolute benefits are still unclear and data from trials have a short follow-up (22 months). The Working Group considered that toripalimab could have potentially high therapeutic value for the treatment of patients with nasopharyngeal cancer, a cancer which is endemic in some low- and middle-income countries with limited therapeutic options. The Working Group noted that multiple immune checkpoint inhibitors suggesting similar benefits are under development or have been granted approval for the management of advanced oesophageal carcinoma. A comprehensive evaluation of the treatment landscape is appropriate to identify those immune checkpoint inhibitors that provide the best value for health care systems. The Working Group noted that the lower price of toripalimab compared with other immune-checkpoint inhibitors and improvement of the overall survival may result in better cost–effectiveness, although the cost for treatment may still have a large impact on health budgets.

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