Tislelizumab

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: L01FF09

Indication	Squamous cell carcinoma of oesophagus ICD11 code: 2B70.1
INN	Tislelizumab
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 100 mg per 10 mL concentrate for solution for infusion
EML status history	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.
Wikipedia	Tislelizumab
DrugBank	Tislelizumab

Expert Committee recommendation

The Expert Committee recognized the significant public health burden of oesophageal squamous cell carcinoma, particularly in Asia where the disease is considered endemic and its incidence and prevalence and the mortality it causes are disproportionately high, accounting for about 75% of the global burden. The Committee noted the availability of tislelizumab in regions most affected by this disease. The Committee considered evidence from tislelizumab clinical trials that showed an overall survival benefit of about 6 months for tislelizumab plus chemotherapy compared with chemotherapy alone in the first-line setting. In the later-line setting, tislelizumab monotherapy was associated with an overall survival benefit of only 2 months compared with chemotherapy, which is below the established 4–6 month threshold for the EML. The Committee considered the comparative effectiveness of tislelizumab and other immune checkpoint inhibitors for oesophageal squamous cell carcinoma in the first-line setting and found that the magnitudes of effect on overall survival were 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 there was potential for medicines within the class to be considered as therapeutic alternatives. 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 across the class of immune checkpoint inhibitors. As regards harms, the Committee noted the potential for increased

harm associated with a poorer prognosis at baseline and the concomitant use of chemotherapy. The Committee noted that tislelizumab was likely to be a more cost-effective option compared with pembrolizumab, nivolumab and nivolumab plus ipilimumab, but not toripalimab. 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 tislelizumab (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 medicine class, the Committee considered that ongoing trials and determination of the role of PD-L1 expression as a predictive biomarker will be informative for future consideration of these medicines for this indication.

Background

Tislelizumab has not previously been considered for inclusion on the Model List for the treatment of oesophageal squamous cell carcinoma. An application for the addition of toripalimab to the EML for treatment of oesophageal squamous cell carcinoma was considered by the Expert Committee in 2023. The Committee acknowledged that the addition of toripalimab to chemotherapy might be associated with relevant improvements in survival compared with chemotherapy alone, however, the evidence was immature with short follow-up. Although the Committee acknowledged the promising role of chemoimmunotherapy in the treatment of this cancer, listing was not recommended. The Committee recommended that the evidence for these treatments continue to be monitored for potential future EML consideration (1). There are currently no medicines included on the Model List for the treatment of oesophageal squamous cell carcinoma.

Public health relevance

According to Globocan, in 2022 there were 511 054 incident oesophageal cancer cases and 445 391 deaths worldwide (2). Oesophageal cancer can be categorized into two main histological subtypes with different etiologies: adenocarcinoma and squamous cell carcinoma. Globally, squamous cell carcinoma was the most common subtype in both male and female patients, contributing to 85% of all oesophageal cancer cases (3). Oesophageal cancer shows substantial geographical variance, with Asia accounting for around 75% of the global incidence, mortality and 5-year prevalence (2). According to the Global Burden of Disease study, in 2021, oesophageal cancer was responsible for almost 540 000 deaths globally, and almost 13 million disability-adjusted life years (4).

Benefits

The application identified nine published systematic literature reviews including tislelizumab for treatment of unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma. In all these reviews, the only randomized controlled trials that included a tislelizumab treatment arm were the pivotal trials conducted by the applicant: RATIONALE-306 in first-line treatment (5) and RATIONALE-302 in second-line treatment (6). First-line treatment A 2024 systematic review and network meta-analysis of seven randomized controlled trials (4688 participants) evaluated the efficacy and safety of first-line immunotherapy for advanced oesophageal squamous cell carcinoma (7). Pooled analysis showed that immunotherapy agents were associated with significantly prolonged overall survival compared with chemotherapy alone, irrespective of programmed death-ligand 1 (PD-L1) expression (hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.62 to 0.74), including tislelizumab (HR 0.68, 95% CI 0.56 to 0.82) which ranked third in prolonging overall survival after toripalimab and sintilimab. Similarly, all immunotherapy agents evaluated were associated with significantly prolonged progression-free survival, irrespective of PD-L1 expression (HR 0.62, 95% CI 0.57 to 0.67), including tislelizumab (HR 0.62, 95% CI 0.52 to 0.74), which ranked fourth after camrelizumab, sintilimab and toripalimab. No significant differences were seen between tislelizumab and pembrolizumab, nivolumab, nivolumab plus ipilimumab or toripalimab for overall survival or progression-free survival. A second systematic review and network meta-analysis in 2024 of nine randomized controlled trials (4499 participants) also evaluated the efficacy and safety of first-line immunotherapy for advanced oesophageal squamous cell carcinoma (8). This review included the same randomized controlled trials involving immunotherapies as the above-mentioned review, plus one randomized

controlled trial comparing capecitabine plus paclitaxel versus capecitabine plus cisplatin, and one randomized controlled trial comparing cetuximab plus chemotherapy with cisplatin plus 5-fluoropurimidine. In this review, tislelizumab ranked fourth for overall survival and progression-free survival. Another 2024 systematic review performed a survival analysis of immunotherapy-based therapies in first-line treatment of oesophageal squamous cell carcinoma using reconstructed patient-level data (9). The same seven randomized controlled trials involving immunotherapies as the previous reviews were included. The study reported that tislelizumab, toripalimab and sintilimab had the best overall survival performance of the seven immunotherapies evaluated, with median overall survival of 17.2 months, 17.0 months and 16.7 months, respectively. Median overall survival for nivolumab and pembrolizumab was 13.2 months and 12.6 months , respectively. For progression-free survival, sintilimab (median progression-free survival 7.2 months) and tislelizumab (median progression-free survival 7.3 months) were superior to other regimens. A 2023 systematic review and network meta-analysis of 17 randomized controlled trials (9128 participants) evaluated the efficacy and safety of 19 treatment regimens involving immunochemotherapy, immunotherapy, chemotherapy and targeted therapy as first-line treatment for advanced and metastatic oesophageal cancer (10). Consistent with previous reviews, chemoimmunotherapy was associated with improvements in overall survival and progression-free survival compared with chemotherapy alone. For overall survival, toripalimab, sintilimab and tislelizumab ranked first, second and third, respectively. Another 2023 systematic review and network meta-analysis of six randomized controlled trials (3611 participants) also evaluated the efficacy and safety of first-line chemoimmunotherapy for advanced oesophageal squamous cell carcinoma (11). This review did not include the ASTRUM-007 trial of serplulimab included in the previous reviews. Findings were generally consistent with the findings of the previous reviews. RATIONALE-306 is a phase III randomized, double-blind, placebo-controlled, multicentre study comparing the safety and efficacy of tislelizumab plus chemotherapy versus chemotherapy alone (5, 12). Participants were randomized 1:1 to receive tislelizumab plus chemotherapy (n = 326) or placebo plus chemotherapy (n = 323). A total of 146 participants in the tislelizumab plus chemotherapy arm and 144 participants in the placebo plus chemotherapy arm received the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with fluoropyrimidine (5-fluorouracil/capecitabine). The remaining participants received platinum (cisplatin/oxaliplatin) with paclitaxel. At the interim analysis from the 28 February 2022 cut-off, tislelizumab plus chemotherapy was associated with significantly superior overall survival compared with chemotherapy alone (median overall survival 17.2 months versus 10.6 months; HR 0.66, 95% CI 0.54 to 0.80) (5). At an extended 3-year follow-up from the 24 November 2023 data cut-off, median overall survival was 22.1 months versus 14.1 months; HR 0.70, 95% CI 0.59 to 0.83) (12). Overall survival benefits were observed in all prespecified subgroups (choice of chemotherapy, baseline PD-L1 expression, geographic region, performance status, age, sex and smoking status). Second-line treatment The application identified four systematic reviews and network meta-analyses that assessed immunotherapies versus chemotherapy as second-line treatment of advanced oesophageal squamous cell carcinoma (13–16). Details of the reviews and their findings were not presented in the application. The application stated that consensus existed across all the reviews identified that there were statistically significant and clinically meaningful improvements in overall survival with tislelizumab monotherapy compared with chemotherapy. In addition, the application stated that where tislelizumab was compared with other PD-1 inhibitors in the second-line setting, it showed comparable progression-free survival and was “particularly efficacious”. RATIONALE-302 is a phase III randomized, open label study of tislelizumab monotherapy versus chemotherapy as second-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (6). Participants were randomized 1:1 to receive tislelizumab (n = 256) or chemotherapy (paclitaxel, docetaxel or irinotecan) (n = 256). At the 1 December 2020 data cut-off, tislelizumab was associated with significantly superior overall survival compared with chemotherapy (median overall survival 8.3 months versus 6.3 months; stratified HR 0.70, 95% CI 0.57 to 0.85). Median progression-free survival as assessed by the study investigator was 1.6 months and 2.1 months in the tislelizumab and chemotherapy arms, respectively (stratified HR 0.83, 95% CI 0.67 to 1.01). Overall survival benefits were observed across all predefined subgroups (choice of chemotherapy, baseline PD-L1 expression, geographic region, performance status, age, sex and smoking status).

Harms

Pooled analysis in the first 2024 systematic review and network meta-analysis previously described showed that the use of immunotherapy with chemotherapy was associated with a greater incidence of grade 3 or higher adverse events compared with chemotherapy alone (risk ratio (RR) 1.04, 95% CI 1.00 to 1.09). Individually, only camrelizumab and nivolumab plus ipilimumab were associated with a reduced risk of grade 3 or higher adverse events. Tislelizumab ranked fifth for this outcome (RR 1.10, 95% CI 0.80 to 1.52). Commonly reported treatment-related adverse events included anaemia, decreased white-cell count, nausea, vomiting, decreased neutrophil count, alopecia, asthenia, decreased appetite, decrease platelet count and diarrhoea. Frequently reported immune-mediated adverse events included rash, hypothyroidism, hyperthyroidism, immune-mediated lung disease, pruritus and pneumonitis (7). Where reported, the other systematic reviews presented consistent findings. At the 3-year follow-up of RATIONALE-306, the incidence of any grade, and grade ≥ 3 treatment-related adverse events were comparable between treatment groups. Serious treatment-related adverse events and treatment-emergent adverse events leading to treatment discontinuation occurred more frequently in the tislelizumab arm. The most common treatment-related adverse events of grade ≥ 3 were decreased neutrophil count (30.9% versus 32.7%), anaemia (14.8% versus 12.8%) and decreased white blood cell count (10.8% versus 15.6%). Health-related quality of life was comparable between treatment groups (12). In RATIONALE-302, treatment-related adverse events were reported in 73.3% and 93.8% of participants in the tislelizumab and chemotherapy arms, respectively. Grade ≥ 3 treatment-related adverse events were reported in 18.8% and 55.8% of participants in the tislelizumab and chemotherapy arms, respectively. The incidence of serious treatment-emergent adverse events was similar between treatment groups (41.2% versus 43.8%). Participants receiving tislelizumab showed more favourable quality of life outcomes compared with participants receiving chemotherapy (6).

Cost / cost effectiveness

The application identified nine cost–effectiveness analyses for tislelizumab in first- (17–23) and second-line (13, 24) therapy of advanced or metastatic oesophageal squamous cell carcinoma. All included data from RATIONALE-306 or study populations consistent with RATIONALE-306, had a 10- or 12-year time horizon and were conducted from the Chinese health-system perspective. Among the economic analyses for tislelizumab plus chemotherapy versus chemotherapy alone in the first-line setting, incremental cost–effectiveness ratios ranged from 18 846 United States dollars (US$) to US$ 34 699 per quality-adjusted life year (QALY) gained. One study considered multiple programmed cell death protein 1 (PD-1) inhibitors in first-line treatment (23). The resultant base-case incremental cost–effectiveness ratios per QALY gained were US$ 21 771 for sintilimab, US$ 22 694 for toripalimab, US$ 24 853 for camrelizumab, US$ 25 973 for tislelizumab, US$ 107 042 for serplulimab, US$ 183 825 for nivolumab and US$ 256 937 for pembrolizumab. One study conducted an economic evaluation of tislelizumab versus chemotherapy as second-line therapy using data from RATIONALE-302 (24). The resultant incremental cost–effectiveness ratio was US$ 11 073 per QALY gained. Another study considered the cost–effectiveness of five PD-1 inhibitors versus chemotherapy in the second-line setting (13). The resultant base-case incremental cost–effectiveness ratios per QALY gained were US$ 4724 for sintilimab, US$ 8913 for tislelizumab, US$ 13 549 for camrelizumab, US$ 170 710 for nivolumab and US$ 269 654 for pembrolizumab. In sensitivity analyses, medicine prices had the greatest impact on the outcomes.

WHO guidelines

WHO guidelines for the treatment of oesophageal squamous cell carcinoma are not currently available.

Availability

The application reported that tislelizumab has regulatory approval in China and Thailand for use in combination with chemotherapy as first-line treatment of patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma. Regulatory approval submissions in Australia, Europe, Indonesia, Japan, Republic of Korea, Singapore, Switzerland and United States were under review at the time of submission. The application reported that tislelizumab has regulatory approval in Australia, Brazil, China, Europe, Hong Kong,

Israel, Republic of Korea, Singapore, Switzerland, Thailand, United Kingdom of Great Britain and Northern Ireland and United States as monotherapy for second-line treatment of unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma. Regulatory approval submissions in India, Japan, Malaysia and New Zealand were under review at the time of submission. Tislelizumab is currently under patent protection and no generic versions are available.

Other considerations

Tislelizumab was one of five immune checkpoint inhibitors evaluated for the treatment of oesophageal squamous cell carcinoma during the Expert Committee meeting. Other immune checkpoint inhibitors evaluated were ipilimumab plus nivolumab, nivolumab (plus chemotherapy) and pembrolizumab (plus chemotherapy) (application A.22), and toripalimab (plus chemotherapy) (application A.28). The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of tislelizumab (or any other immune checkpoint inhibitor) on the EML for the treatment of oesophageal squamous cell carcinoma. The group considered 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 across the class of immune checkpoint inhibitors are lacking.

1. The selection and use of essential medicines. Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2023 (including the 23rd WHO Model List of Essential Medicines and the 9th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2024 (WHO Technical Report Series, No. 1049; https://iris.who.int/handle/10665/376570). Licence: CC BY-NC-SA 3.0 IGO.
2. The Global Cancer Observatory. Oesophagus fact sheet. Lyon: International Agency for Research on Cancer; 2020 (https://gco.iarc.who.int/media/globocan/factsheets/cancers/6-oesophagus-fact-sheet.pdf).
3. Morgan E, Soerjomataram I, Rumgay H, Coleman HG, Thrift AP, Vignat J et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from GLOBOCAN 2020. Gastroenterology. 2022;163(3):649–58.e2 (https://doi.org/10.1053/j.gastro.2022.05.054).
4. Global Burden of Disease database [online database]. Seattle, WA: Institute for Health Metrics and Evaluation; 2021 (https://vizhub.healthdata.org/gbd-results/).
5. Xu J, Kato K, Raymond E, Hubner RA, Shu Y, Pan Y et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2023;24(5):483–95 (https://doi.org/10.1016/s1470-2045(23)00108-0).
6. Shen L, Kato K, Kim S-B, Ajani JA, Zhao K, He Z et al. Tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma (RATIONALE-302): a randomized phase III study. J Clin Oncol. 2022;40(26):3065–76 (https://doi.org/10.1200/jco.21.01926).
7. Chen W, Cao K, Zhang L, Zhao X, Chen B, Li W et al. Efficacy and safety evaluation of frontline immunotherapy combinations in advanced esophageal squamous cell carcinoma: a network meta-analysis highlighting the value of PD-L1 expression positivity scores. Front Immunol. 2024;15:1414753 (https://doi.org/10.3389/fimmu.2024.1414753).
8. Nian Z, Zhao Q, He Y, Xie R, Liu W, Chen T et al. Efficacy and safety of first-line therapies for advanced unresectable oesophageal squamous cell cancer: a systematic review and network meta-analysis. Clin Oncol (R Coll Radiol). 2024;36(1):30–8 (https://doi.org/10.1016/j.clon.2023.09.011).
9. Yan C, Cao W, Li J, Zhang L, Diao R. PD-1 inhibitors in advanced esophageal squamous cell carcinoma: a survival analysis of reconstructed patient-level data. Front Pharmacol. 2024;15:1408458 (https://doi.org/10.3389/fphar.2024.1408458).
10. Gao Z, Huang S, Wang S, Tang D, Xu W, Zeng R et al. Efficacy and safety of immunochemotherapy, immunotherapy, chemotherapy, and targeted therapy as first-line treatment for advanced and metastatic esophageal cancer: a systematic review and network meta-analysis. Lancet Reg Health West Pac. 2023;38:100841 (https://doi.org/10.1016/j.lanwpc.2023.100841).
11. Ma X, Ding Y, Qian J, Wan M, Chen X, Xu N. Comparison of efficacy and safety of first-line chemoimmunotherapy in advanced esophageal squamous cell carcinoma: a systematic review and network meta-analysis. J Clin Pharm Ther. 2023;2023(1):3836855 (https://doi.org/https://doi.org/10.1155/2023/3836855).
12. Yoon HH, Kato K, Raymond E, Hubner R, Shu Y, Pan Y et al. Global, randomized, phase III study of tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced/metastatic esophageal squamous cell carcinoma (RATIONALE-306 update): minimum 3-year survival follow-up. J Clin Oncol. 2024;42(16 Suppl):4032 (https://doi.org/10.1200/JCO.2024.42.16_suppl.4032).
13. Liu S, Dou L, Li S. Immune checkpoint inhibitors versus chemotherapy as second-line therapy for advanced oesophageal squamous cell carcinoma: a systematic review and economic evaluation. Therap Adv Gastroenterol. 2024;17:17562848241233134 (https://doi.org/10.1177/17562848241233134).
14. Leone AG, Petrelli F, Ghidini A, Raimondi A, Smyth EC, Pietrantonio F. Efficacy and activity of PD-1 blockade in patients with advanced esophageal squamous cell carcinoma: a systematic review and meta-analysis with focus on the value of PD-L1 combined positive score. ESMO Open. 2022;7(1):100380 (https://doi.org/10.1016/j.esmoop.2021.100380).
15. Gao TT, Shan JH, Yang YX, Zhang ZW, Liu SL, Xi M et al. Comparative efficacy and safety of immunotherapy for patients with advanced or metastatic esophageal squamous cell carcinoma: a systematic review and network meta-

analysis. BMC Cancer. 2022;22(1):992 (https://doi.org/10.1186/s12885-022-10086-5).
16. Zhu X, Shanzhou Q, Li D, Pang X, Ma D. PD-1 inhibitors versus chemotherapy as second-line treatment for advanced esophageal squamous cell carcinoma: a meta-analysis. BMC Cancer. 2021;21(1):1195 (https://doi.org/10.1186/s12885-021-08958-3).
17. Liu Y, Shao R. Cost–effectiveness analysis of tislelizumab plus chemotherapy as the first-line treatment for advanced or metastatic esophageal squamous cell carcinoma in China. Front Pharmacol. 2024:15:1225076 (https://doi.org/10.3389/fphar.2024.1225076).
18. Zheng Z, Chen H, Cai H, Zhu H. First-line tislelizumab for advanced or metastatic esophageal squamous cell carcinoma: a cost–effectiveness analysis. Expert Rev Pharmacoecon Outcomes Res. 2024;24(3):397–404 (https://doi.org/10.1080/14737167.2023.2290609).
19. Zhou C, Wei J, Xu K, Lin Y, Zhang L, Li X. Cost–effectiveness analysis of tislelizumab plus chemotherapy as first-line treatment for advanced or metastatic esophageal squamous cell carcinoma in China. Risk Manag Healthc Policy. 2023;16:2447–58 (https://doi.org/10.2147/rmhp.S436750).
20. Lu S, Lou Y, Rong Y, Huang Z, Lin X, Chen J et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for Chinese patients with advanced esophageal squamous cell carcinoma: a cost–effectiveness analysis. Clin Drug Investig. 2023;43(8):643–52 (https://doi.org/10.1007/s40261-023-01295-2).
21. Zhang L, Su H, Liang X, Chen X, Li Y. Cost–effectiveness analysis of tislelizumab plus chemotherapy in Chinese patients with advanced or metastatic oesophageal squamous cell carcinoma. Sci Rep. 2024;14(1):17734 (https://doi.org/10.1038/s41598-024-68399-3).
22. He C, Mi X, Xu G, Xu X, Xin W, Zhong L et al. Cost–effectiveness analysis of tislelizumab plus chemotherapy as the first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma in China. PLoS One. 2024;19(5):e0302961 (https://doi.org/10.1371/journal.pone.0302961).
23. Zhao YL, Zhu R, Fenghao J, Song S, Huang W, Junyan M et al. Cost–effectiveness analysis of immune checkpoint inhibitors for first-line treatment of advanced esophageal squamous cell carcinoma based on fractional polynomial network meta-analysis [preprint]. London: Research Square; 2024 (https://doi.org/10.21203/rs.3.rs-3896491/v1).
24. Shi F, He Z, Su H, Wang L, Han S. Economic evaluation of tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma in China. Front Pharmacol. 2022;13:961347 (https://doi.org/10.3389/fphar.2022.961347).