PROPOSAL FOR THE ADDITION OF TISLELIZUMAB (TEVIMBRA®) TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE FIRST- AND SECOND-LINE TREATMENT OF ADULTS WITH UNRESECTABLE, LOCALLY ADVANCED, RECURRENT OR METASTATIC OESOPHAGEAL SQUAMOUS CELL CARCINOMA (OSCC)

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Section 1: Summary statement of the proposal

This submission advocates for the inclusion of tislelizumab (Tevimbra®) as an individual medicine in the complementary list of the EML for two lines of treatment of oesophageal squamous cell carcinoma (OSCC) as follows:

First-line therapy:

- in combination with chemotherapy for the treatment of adult patients with unresectable, locally advanced, recurrent or metastatic OSCC who are treatment naïve.

Second-line therapy:

- as monotherapy for the treatment of adult patients with unresectable or metastatic OSCC following prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

Oesophageal carcinoma is the 7th most common cancer globally with OSCC accounting for up to 90% of oesophageal carcinomas in some countries. *(1)* There were over half a million cases of OSCC in 2022.*(2)* However, there is huge global inequity in the rates and impact of OSCC with the highest rates in Eastern and South-Central Asia (particularly in China) and in East Africa.*(3)* Further, while the rates of some cancer types are decreasing, the incidence of OSCC is projected to increase; by 2040, it is estimated there will be over 800,000 global cases of OSCC per year.*(2)* Risk factors include smoking and chewing tobacco, alcohol consumption, and low fruit and vegetable intake. OSCC is approximately twice as prevalent in men compared to women.*(4)*

The prognosis of OSCC is particularly poor with 5-year survival of 10-30%. *(5)* Globally, it is the 6th leading cause of cancer-related death and ranks higher as a cause of cancer-related mortality in some low- and middle-income countries (LMIC).*(6)* This is primarily because many cases are identified when they are already at an advanced and non-curative stage and the disease is notably aggressive. The quality-of-life of people with unresectable, advanced or metastatic OSCC is very low, and this also has severe impacts on their families and carers, many of whom must take time off work to care for people with OSCC.*(7)*

Standard of care for the treatment of unresectable advanced OSCC differs according to the resources available. In some high-income countries, standard first-line therapy is now an immunotherapy (typically nivolumab or pembrolizumab as first-generation PD-1 inhibitors with regulatory approvals for OSCC) plus chemotherapy. Practice regarding treatment based on PD-L1 expression status appear to be quite variable globally with

some clinical guidelines requiring a particular PD-L1 expression status for treatment eligibility, whereas others are 'agnostic' to PD-L1 expression status.*(8-10)*

Second-line treatment in high-income settings is typically a taxane or irinotecan. However, in some countries with conditions around PD-L1 expression status for first-line usage of a PD-L1 inhibitor, then platinum-fluoropyrimidine followed by nivolumab may be recommended as a second-line treatment.*(10)*However, this is not mirrored globally and in some high-income countries and the majority of middle and low-income countries, nivolumab and pembrolizumab are not considered cost-effective treatment options. There are no PD-(L)1 inhibitors for the treatment of OSCC on the WHO EML. Therefore, in many countries around the world (and relevant to the WHO EML setting), standard first-line treatment is doublet chemotherapy (which may include a platinum-based chemotherapy if available). Second-line treatment is generally chemotherapy with taxanes or irinotecan.*(11)* Prognosis is poor with these treatment options. Patients can expect overall survival of 8-10 months with first-line chemotherapy treatment for unresectable OSCC (from treatment initiation).*(12)* Second-line chemotherapy treatment is associated with up to 6 months of overall survival after starting treatment.*(11)* In addition to the poor prognosis and quality-of-life associated with OSCC, patients receiving these chemotherapies also experience severe gastrointestinal, haematological and neurological toxicities. *(4)*

Results of the umbrella systematic literature reviews and pivotal randomised clinical trials indicate that adding tislelizumab to standard chemotherapy regimens leads to clinically important gains in overall survival, progression-free survival and improvements in quality-of-life when compared to chemotherapy alone for the first-line treatment of unresectable OSCC. The 3-year follow up data from the pivotal multi-centre, global randomised controlled trial of tislelizumab plus chemotherapy as a first line treatment (RATIONALE-306) demonstrated that participants receiving tislelizumab plus chemotherapy had a median overall survival of 17.2 months. This was in comparison to 10.6 months with placebo plus chemotherapy. This 6.6 month improvement in overall survival resulted in a hazard ratio of 0.70 (95% confidence interval 0.59, 0.83) and a 30% reduction in the risk of death.*(13)*

The number of all treatment-related adverse events with tislelizumab plus chemotherapy was marginally higher than with placebo plus chemotherapy (96.6% compared with 96.3% respectively).*(13)* The numbers of patients requiring dose reductions were similar between treatment arms (76.2% compared with 71.3% respectively). Further, those experiencing ≥grade 3 treatment-related adverse events in the pivotal trial were comparable between treatment arms at 67% in the tislelizumab plus chemotherapy arm versus 64.5% in the placebo plus chemotherapy arm.*(13)*

Based on an overall survival improvement of more than 6 months derived from 3-years of data from the pivotal multi-site randomised controlled trial, the self-estimated European Society for Medical Oncology (ESMO) magnitude of clinical benefit score of tislelizumab as a first-line treatment for unresectable OSCC is therefore 4.

At the time of writing, regulatory approvals for the first-line use of tislelizumab are pending, including the American Food and Drug Administration (FDA). The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending marketing authorisation for "Tevimbra in combination with platinum-based chemotherapy for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a tumour area positivity (TAP) score of ≥ 5%". However, given the global variation on usage relative to PD-L1 expression for other PD-(L)1 inhibitors, it is expected that this will vary globally for the first-line use of tislelizumab. It is anticipated that some countries will adopt an 'agnostic' approach (for example Australia and countries in Asia, such as Thailand, China and Macao), and some will apply conditions around PD-L1 expression status and treatment eligibility. Given the evidence from the pivotal trials (as described in section 8); based on both the intention-to-treat analysis and pre-defined subgroup analyses of baseline PD-L1 expression status, tislelizumab may be clinically effective in patients with high and low PD-L1 expression status. Therefore, an agnostic approach to treatment, irrespective of PD-L1 expression status, is proposed in this submission. While the survival benefits do appear higher with for people with higher PD-L1 expression, TAP ≥ 10% (overall survival = 16.6 months with tislelizumab plus chemotherapy versus 10,0 months with chemotherapy alone), an overall survival benefit is still observed for those with lower PD-L1 expression compared to chemotherapy as measured in the pivotal trial (overall survival = 16.0 months with tislelizumab plus chemotherapy versus 10.4 months with chemotherapy alone) at 3 years of follow-up.*(13)*

Adopting a PD-L1 agnostic approach also removes the need for PD-L1 testing; this is an advantage in the EML setting where testing brings possible additional infrastructure requirements, which could create some inequity in access. However, if PD-L1 conditions are applied by the committee, the increasing access to PD-L1 testing (as performed by immunohistochemistry) could provide a more targeted approach so tislelizumab is provided to those who may benefit the most from treatment.

Furthermore, subgroup analyses of the multi-country trials suggest that results are generally consistent with the intention-to-treat (ITT) or overall population based on regions and choice of combination chemotherapy regimen (which can differ according to resource setting).*(14)* This means that tislelizumab could provide a clinically effective first-line treatment option of OSCC in all countries in the WHO EML setting.

As a second-line treatment, the umbrella SLR also suggested that tislelizumab monotherapy improves overall survival and progression-free survival compared to chemotherapy alone. Adverse events with tislelizumab monotherapy were much lower than those experienced with chemotherapy. In the pivotal study of tislelizumab as a second-line treatment (RATIONALE-302), *(15)* tislelizumab monotherapy was compared with investigator-chosen chemotherapy (ICC: paclitaxel, docetaxel, or irinotecan) in patients with locally advanced or metastatic OSCC whose disease progressed after prior systemic therapy. There were 132 study sites across 11 countries and the RCT was deemed to be at a low risk of bias according to the GRADE framework. *(15)*

As of the data cut-off date 1st December 2020, the study met its primary endpoint with statistically significant and clinically meaningful improvement in OS compared with ICC (median OS: 8.6 versus 6.3 months; stratified HR: 0.70, 95%CI: 0.57, 0.85; one-sided P=0.0001). Survival benefit was consistently observed across all predefined subgroups, including those defined by baseline PD-L1 expression, region, and race.*(15)*

The primary endpoint of the clinical trial showed a statistically significant benefit in terms of overall survival and progression free survival compared to chemotherapy alone. Tislelizumab monotherapy for the second-line treatment of OSCC compared with chemotherapy alone has been given a magnitude of clinical benefit score of 4 (with a toxicity adjustment of +1) by ESMO as a second-line treatment for unresectable OSCC (ESMO-MCBS Scorecards | ESMO). *(15, 16)*

Finally, a systematic review for published cost-effectiveness analyses was conducted and the results are discussed. All studies were undertaken from the perspective of the Chinese health system and concluded that tislelizumab is likely to represent a cost-effective first- and second-line treatment option for unresectable advanced or metastatic OSCC. The availability of tislelizumab for patients with OSCC in the WHO EML setting is also discussed noting that BeiGene endeavours to price its medicines competitively in various countries and to provide affordable pricing to low- and middle-income countries (LMIC).

Section 2: Consultation with WHO technical departments

- WHO EML Secretariat (Lorenzo Moja and Bernadette Capello on Thursday 22nd August, follow up on 11th October)

Section 3: Other organizations(s) consulted and/or supporting the submission

A letter of support from the Union for International Cancer Control (UICC) is included with this submission. Key points from the letter of support include:

1. *Clinical Importance:* Tislelizumab is highlighted as essential for high-burden cancers such as OSCC with strong safety and efficacy profiles.
2. *Alignment with WHO and SDG Goals:* The letter of support aligns with WHO priorities and Sustainable Development Goal 3.4, emphasising the public health value.
3. *Commitment to Access:* Access to Oncology Medications (ATOM) commits to collaborating with BeiGene to establish affordable access pathways.

Additional stakeholders supporting this submission will provide comments as part of the public consultation process in 2025.

Section 4: Key information summary table for the proposed medicine(s)

INN	Tislelizumab
ATC Code	L01FF09
Indications	First-line: Tislelizumab in combination with chemotherapy for the treatment of adult patients with unresectable, locally advanced, recurrent or metastatic oesophageal squamous cell carcinoma who are treatment-naïve. Second-line: Tislelizumab monotherapy for the treatment of adult patients with unresectable or metastatic oesophageal squamous cell carcinoma following prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.
ICD-11 code	2B70.1 Squamous cell carcinoma of oesophagus
Dosage form	Concentrate for solution for infusion
Strength	100mg/10mL in vial
EML	Yes (Complementary)
EMLc	No

Section 5: Listing as an individual medicine or as representative of a pharmacological class or therapeutic group ('square box' listing)

Tislelizumab is being proposed for listing as an individual medicine.

Other medications within the same category in the ATC (L01FF PD/PD-L1 [Programmed cell death protein 1/ death ligand 1] inhibitors) that have regulatory approval for the treatment of OSCC include:

- **L01FF01 Nivolumab (plus ipilimumab)**
- **L01FF02 Pembrolizumab**
- **L01FF13 Toripalimab**

None of the above medications are currently on the WHO EML for the treatment of OSCC. No submissions have been made to date for nivolumab or pembrolizumab for this indication. Toripalimab was proposed for listing on the 2023 WHO EML for the treatment of nasopharyngeal cancer and OSCC but was not recommended.

- **Non-ATC alternatives**

Camrelizumab and sintilimab are two additional PD-1 inhibitors that have been trialled for the treatment of OSCC. However, at the time of submission, they have regulatory approval in China only and they do not appear on the ATC or WHO EML. Therefore, they are not considered as relevant therapeutic alternatives to tislelizumab at this time.

In addition, there are no studies that assess the therapeutic equivalence with any of these agents and tislelizumab that would support a square box listing.*(17)* Therefore, tislelizumab is proposed as an individual medicine for the treatment of OSCC.

Section 6: Information supporting the public health relevance

Oesophageal cancer is the seventh most commonly diagnosed cancer type and sixth most common leading cause of cancer-related death globally.*(2)* Oesophageal cancer is comprised of two main histological subtypes: squamous cell carcinoma and adenocarcinoma. Oesophageal squamous cell carcinoma (OSCC) is the most common subtype of oesophageal cancer; accounting for up to 85-90% of all oesophageal cancer cases. OSCC is considered one of the deadliest forms of malignancy of the digestive tract due to its complex aetiology and aggressive progression.*(18)* Unlike some cancers, where rates are decreasing, the incidence and prevalence of OSCC is expected to increase in the coming decades.*(2)* With the current poor prognosis and low quality-of-life associated with OSCC,*(17)* this will significantly increase the public health burden and burden and patients, their families and carers.

There is huge global inequity in the prevalence and disease burden associated with OSCC, with the greatest burden in low-and middle-income countries (LMIC), see Figure 1. Oesophageal cancer is the 3rd or 4th most common cause of cancer deaths in several LMICs, including China, Bangladesh, Pakistan, Sri Lanka, Tanzania, Kenya, Malawi, Uganda, Sudan and Botswana.*(5)* The incidence of OSCC is 2-3 times higher in men than women.*(19)* Other risk factors include age, alcohol consumption, smoking, chewing tobacco and betel leaves, and low fruit and vegetable intake.

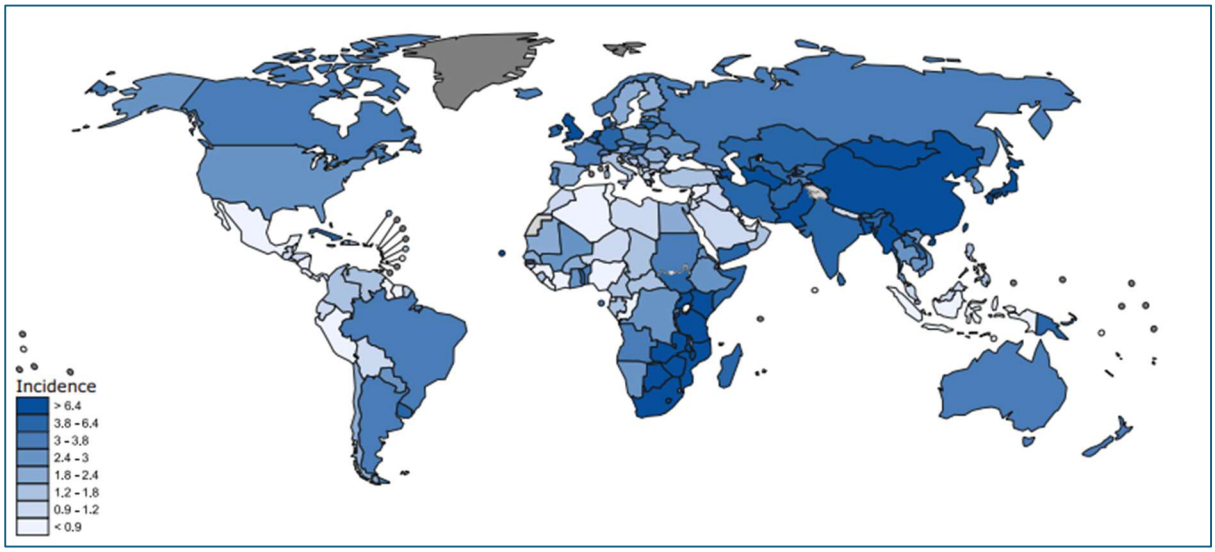


Figure 1 - Worldwide oesophageal cancer incidence rates (age-adjusted according to the world standard population, per 100,000), both sexes combined, in 2020. Source: Morgan et al, 2022 (2)

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organisation concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Based on the GLOBOCAN study, the burden of oesophageal cancer deaths is highest in East Asia (with more than half of these deaths in China), representing almost 60% of all

global oesophageal cancer deaths, see Figure 2. According to the Global Burden of Disease collaboration, *(5)* oesophageal cancer caused 9.78 million (9.53 – 10.03) disability-adjusted life years, with an age-standardised rate of 120 (117 – 123) per 100,000 population. At a national level, China had the highest number of incident cases, deaths and DALYs in 2017. The highest national age-standardised incidence rates were in Malawi and Mongolia. Countries with a high level of indoor air pollution had a higher proportion of OSCC than oesophageal adenocarcinoma.*(19)*

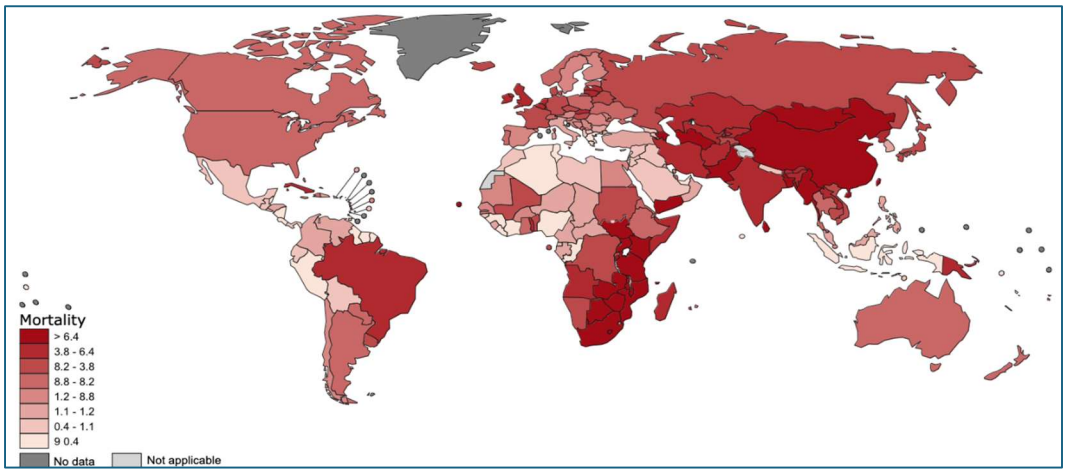


Figure 2 - Worldwide oesophageal cancer mortality rates (age-adjusted according to the world standard population, per 100,000), both sexes combined, in 2020. Source: Morgan et al, 2022 (2)

The boundaries and names shown, and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organisation concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

A retrospective cohort study by Davis et al.*(20)* analysed patient reported symptoms using the Edmonton Symptom Assessment System among Canadian oesophageal cancer patients (n=2,103) diagnosed between 2009 and 2016. Severe lack of appetite (53.1%), tiredness (51.1%), and impaired wellbeing (42.7%) were the most reported symptoms. In addition, symptoms associated with mental health, such as severe depression (19.6%), severe anxiety (27.5%), were frequently reported, see Figure 3.

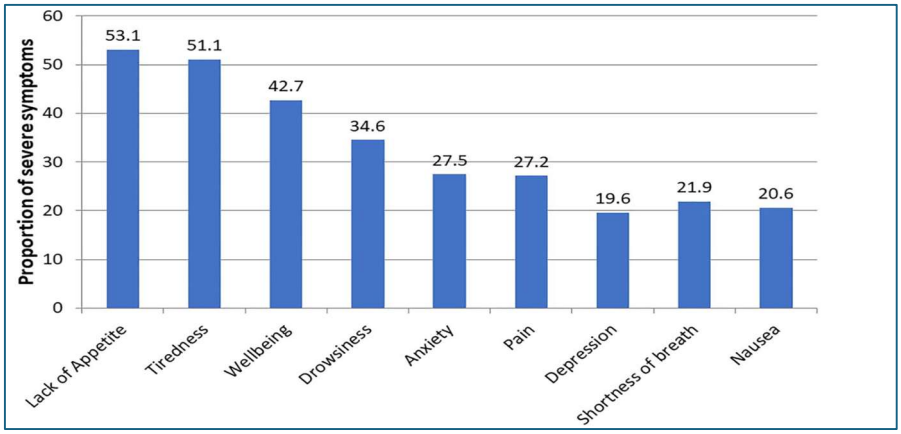


Figure 3 - Proportion of oesophageal cancer patients reporting at least one severe symptom in the 6 months following diagnosis. Source: Davis et al, 2020(12)

OSCC often remains unnoticed in the early stage due to lack of symptoms or presence of mild, non-specific symptoms (e.g., heartburn, dyspepsia) and is usually detected only in the advanced or metastatic stage. The most common presenting symptoms include dysphagia and weight loss.*(12)* The patient may also present with epigastric or retrosternal pain, regurgitation, persistent cough, hoarseness, and chronic gastrointestinal blood loss. Physical examination of the patient usually provides no evidence suggestive of OSCC unless the disease has metastasised. Therefore, more than half of OSCC patients are diagnosed by the time they have locally advanced or metastatic, unresectable OSCC. Accordingly, the 5-year survival of OSCC is poor, and ranges between 10% and 30% in most countries.*(5)*

OSCCs, which are usually located in the proximal to middle oesophagus, tend to be more aggressive tumour types and may lead to a fast deterioration of the patient's physical status due to insufficient nutrition intake.*(21)* Clinical symptoms of OSCC are debilitating and significantly impair patient's quality-of-life and that of their families.*(22)* In the advanced stages of OSCC, symptoms include: worsening cough and sore throat; laboured breathing; difficulty speaking above a whisper; nausea and vomiting; fatigue due to anaemia; difficulty and pain when swallowing; bleeding in the oesophagus leading to blood in the digestive tract and stool.*(19)*,*(23)* There is a huge associated burden of disease with locally advanced or metastatic OSCC, resulting from high risk of metastasis, poor prognosis, morbidity due to symptoms and complications, significant negative impact on patient's and caregiver's financial situations and reduced quality-of-life.*(24)*, *(25)*, *(26)*

The economic burden of patients with OSCC is also high relative to other cancer populations, owing to a protracted disease process, frequent chemotherapy-related complications and the high frequency of monitoring and diagnostic procedures.*(4)*, *(27)*

Standard of care for the treatment of unresectable advanced OSCC differs according to the in-country resources available. Recent research has demonstrated that PD-L1 is a relevant biomarker in OSCC. *(28)* Therefore, the emergence of PD-1 inhibitors has the potential to lead a 'paradigm shift' in the management of unresectable, locally advanced and metastatic cancers. In some high-income countries, standard first-line therapy is now a PD-1 inhibitor (typically nivolumab or pembrolizumab) plus chemotherapy. However, there are restrictions on the type of therapy used in some countries, with choice being based on PD-L1 expression (for example as per the ESMO guidelines *(10)*). However, some countries (such as Australia and others in South-East Asia) have adopted an 'agnostic' approach and do not have restrictions by PD-L1 expression status. Second-line treatment in higher-income countries is typically a taxane or irinotecan. For patients with low or negative PD-L1 expression status, platinum-fluoropyrimidine may be offered first followed by nivolumab as a second-line treatment with chemotherapy as a third-line option.

These treatment guidelines are not mirrored globally. Nivolumab and pembrolizumab are generally considered expensive and could significantly increase a patient's financial burden if they are not publicly reimbursed. In the majority of middle and low-income countries, nivolumab and pembrolizumab are not reimbursed as they have been associated with high incremental cost-effectiveness ratios.*(29, 30)*

There are no PD-(L)1 inhibitors for the treatment of OSCC on the WHO EML. In most of the world, and particularly countries in the WHO EML setting, the most common standard first-line treatment is doublet chemotherapy, which may include a platinum-based chemotherapy if resources permit, plus fluoropyrimidine or taxanes. Second-line treatment is typically chemotherapy. Prognosis is poor with chemotherapy treatment options. Patients can expect overall survival of 8-10 months with first-line chemotherapy treatment for unresectable OSCC (from treatment initiation). Second-line chemotherapy treatment is associated with up to 6 months of overall survival after starting treatment.*(11)*

The goals of treating locally advanced or metastatic OSCC are to prolong survival and improve or maintain patient's quality-of-life.*(31)* Patients thus require anti-cancer treatment to control tumour-associated symptoms even in a palliative therapeutic setting at the end of life. However, in addition to the poor quality-of-life associated with OSCC, patients receiving chemotherapies as first- and second-line treatments also experience severe gastrointestinal, haematological and neurological toxicities.

Therefore, there is an unmet need for an efficacious, tolerated, and cost-effective treatment that can bring meaningful improvements in survival outcomes and the quality-of-life of patients with advanced or metastatic OSCC at an acceptable cost to payers in the EML setting. In the 2023 review of toripalimab for OSCC, the reviewer

comments highlighted that the landscape of "*combination chemotherapy + immune checkpoint inhibitors in oesophageal cancer deserves attention for future WHO EML applications*". Further, in a recent systematic literature review of the current and projected future treatment innovations for OSCC, it was noted that the integration of immunotherapy represents a significant shift in the treatment paradigm of OSCC.*(32)* Additionally, research optimising combination therapies (with existing and novel molecules) and moving treatments to earlier in the pathway– for example as neoadjuvant to surgical resection – is underway and the importance of establishing PD-1 treatment availability now to allow future innovative treatment regimens should be noted.

Section 7: Treatment details

Programmed death-ligand 1 (PD-L1) is a protein that has been speculated to play a major role in suppressing the adaptive arm of immune systems during particular events such as pregnancy, tissue grafts and autoimmune disease. PD-L1 is shown to be highly expressed in a variety of malignancies and blocking the PD-1 or PD-L1 checkpoints, PD-L1 might be seen as a prognostic marker and target for anti-cancer therapies. *(33)* PD-L1 overexpression that is linked with poor clinical outcomes has been observed in various types of solid tumours including oesophageal, gastric, pancreatic, melanoma, lung, ovarian, bladder cancers, hepatocellular carcinoma and renal cell carcinoma.*(33)* Studies have shown that PD-L1 may be a prognostic biomarker in OSCC, meaning that patients with OSCC may benefit from PD-(L)1 inhibitor-based therapy.*(28, 34)*

This submission proposes that while the overall survival benefit of tislelizumab is higher for patients with higher PD-L1 expression status, patients with low PD-L1 expression status still benefit from tislelizumab therapy. Therefore an 'agnostic' approach to providing treatment is appropriate. Further details around measuring PD-L1 expression status are provided below for completeness.

Mechanism of Action

Tislelizumab is a humanised anti-PD-1 antibody, which is specifically engineered to minimise binding to Fc-gamma receptors (FcγRs) on macrophages. The molecular binding mechanism of tislelizumab shows a high target affinity to the PD-1 receptor. T-cell proliferation and cytokine production is inhibited by the binding of PD-1 ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), to the PD-1 receptor found on T-cells. Upregulation of PD-1 ligands occurs in some tumours, and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours.*(35)*

Tislelizumab does not bind to FcγRs or complement component 1q (C1q), and therefore does not induce antibody-dependent cellular cytotoxicity, antibody dependent cellular phagocytosis or complement-dependent cytotoxicity. In addition, tislelizumab has

demonstrated decreased tumour growth in several human cancer allogeneic xenograft models and a human PD-1 transgenic mouse model.

The molecular binding mechanism of tislelizumab shows a higher affinity to the PD-1 receptor than pembrolizumab and nivolumab, potentially due to its differential PD-1 binding orientation.*(36)* Unlike the other currently approved PD-1 inhibitors, tislelizumab binds to the CC' loop region of PD-1; unlike pembrolizumab, which binds to the C'D loop, and nivolumab, which binds to the N loop.*(37)* It is the first antibody to bind to this region of PD-1, which creates a high specificity and affinity when binding to the PD-1 protein.

Tislelizumab has a comparable or longer half-life than other PD-1 inhibitors.*(37)* See Table 1 for a comparison of half-lives and steady states of the PD-1 inhibitors that are approved or being trialled in OSCC.*(38)* This table has been modified to add in the steady-state of tislelizumab which was not available at the time of the original publication.

Generic Name	Half-life, days	Steady-state, weeks
Tislelizumab	23.8	12*
Camrelizumab	6	12
Nivolumab	25	12
Pembrolizumab	22	16
Sintilimab	21.2	15
Toripalimab	12.6	6-8

*Table 1- Half-life and steady states of PD-(L)1 inhibitors: source Yan et al. (38) *Note – the steady-state of tislelizumab was not presented in this publication but has been extracted from the EPAR for tislelizumab.(39)*

Measuring PD-L1 expression

PD-L1 protein expression in tumours can be quantified using various techniques, however immunohistochemistry (IHC) is the only widely available, practical and economical approach for studying PD-L1 expression in tumours.*(40)* Multiple commercial PD-L1 assays are available, but the Ventana SP263, DAKO 22C3 and DAKO 28-8 have been used specifically for testing OSCC tumours. Pre-packaged kits are available for use on the platforms, with specific reagents, protocols and thresholds for defining positive PD-L1 expression.

There are different scoring methods to assess PD-L1 expression status of a tumour are described in brief in Table 2.

Method	Numerator	Denominator
Tumour Proportion Score (TPS)	Number of PD-L1 positive tumour cells	Total number of tumour cells

Combined Positive Score (CPS)	Number of PD-L1 positive tumour cells, lymphocytes and macrophages	Total number of tumour cells
Tumour Area Positivity (TAP) score	Area occupied by PD-L1 staining tumour cells and immune cells	Tumour area

Table 2- Description of PD-L1 expression scoring methods

PD-L1 Testing Availability

As researchers' understanding of PD-L1 protein expression in tumour patients has deepened, the methods for detecting PD-L1 have also evolved. More specific and higher-affinity antibodies and improved immunohistochemistry (IHC) technology can better eliminate interfering factors and increase the stability of detection.*(41)*

The most extensive use of PD-L1 testing with IHC to date is in lung cancer patients. The International Association for the Study of Lung Cancer (IASLC) conducted a global survey on PD-L1 testing. This type of testing uses the same assays and methods as would be done with OSCC, it is the biopsy or cell samples that differ in origin. The results of the survey by Mino-Kenudson et al.*(42)* published in 2021 are reported below:

- A total of 344 pathologists from 64 countries participated in the voluntary survey. Of these, 41% were from Europe; 24% were from North America; 18% were from Asia; 7.3% were from Central & South America; 6.4% from Africa and the Middle East and 3.8% were from Oceania.
- Of the responses received, 38% of pathologists practiced multiple subspecialties or general pathology; the authors concluded that this provided a global vision in the real-life practice in pathology laboratories.
- An overall total of 90% of pathologists sent out samples to undertake IHC testing (as opposed to in-house testing). The highest send-out rate was 25% as reported in North America.
- The vast majority of participants (82%) reported their laboratories had external quality assessment in place. Almost all laboratories (96%) had guidelines in place for PD-L1 testing.
- Overall, the median turn-around time (TAT) from the acquisition of samples was 1–2 days, with a TAT of 2–3 days in South & Central America and Asia, and 3–4 days in Africa & Middle East. The vast majority (76%) reported results within 3 days, while it took more than 5 days in 21% - 23% of laboratories in Asia, Central & South America and Africa & Middle East.

- The type of assay was also surveyed; as noted, the assays used for testing PD-L1 expression in OSCC have been the Ventana SP263, DAKO 22C3 and DAKO 28-8; all of which are available in all regions as seen in Figure 4.

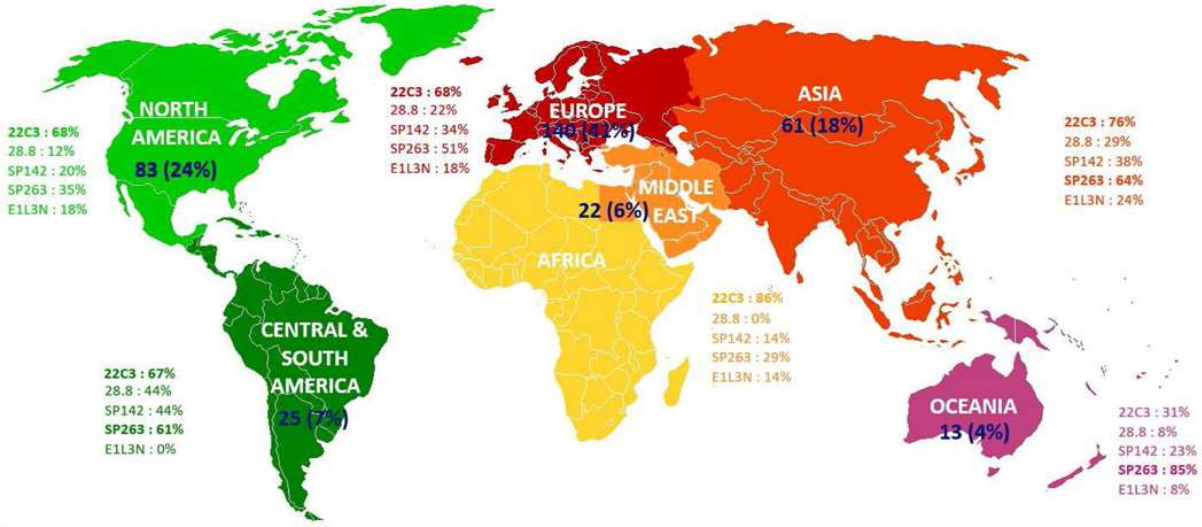


Figure 4 - Participation rate of pathologists and use of different PD-L1 clones by region. Source Mino-Kenudson et al. (42)

- The survey concluded that to provide more reproducible PD-L1 IHC scoring, it is important for pathologists to attend training session(s) or gain more experience. A total of 84% of participants reported attendance at some training on the assessment of PD-L1 IHC. The authors further noted that there are free training programs organized by vendors, pharmaceutical companies and pathology societies, either as formal hands-on sessions or via website, all increasing the accessibility for pathologists to receive future training wherever they are based.
- Costs of PD-L1 testing kits (including the reagents) are relatively low. In high-income countries, IHC testing is generally publicly reimbursed, with example fees of AUD $59.60 in Australia (Item 72846 | Medicare Benefits Schedule (health.gov.au)), and between 50 to 150 euro in European countries.*(43)* Additional upfront investment in the purchase of the assays and training is also required, however as noted these are increasingly available across the world.
- When considering the increasing role of biomarkers to guide treatment of various other cancer types, the ONCOLLEGE study considered the global landscape on the access to cancer medicines for breast cancer. In this study, the authors noted the valuable role trastuzumab and trastuzumab biosimilars based on HER2 status for breast cancer patients. In 2019, the WHO added both

trastuzumab and biosimilars for breast cancer to the EML and HER2 pathology assays to the in-vitro diagnostics list (EDL). *(44)*

Administration

Tislelizumab is available as 100 mg concentrate for solution for infusion. Each millilitre of concentrate for solution for infusion contains 10 mg tislelizumab. Each vial of 10 ml contains 100 mg tislelizumab. The recommended dose of tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks. The infusion of initial dose should be delivered over 60 minutes; if well-tolerated, the second and subsequent infusions may be administered over 30 minutes.

Tislelizumab must be administered under the guidance of a clinician who is experienced in cancer treatment. Tislelizumab should be administered using an intravenous infusion line with a sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron in-line filter. Tislelizumab must not be administered as an intravenous push or single bolus injection. Tislelizumab should be diluted to a concentration between 1 mg/mL to 5 mg/mL in sterile sodium chloride 9 mg/mL (0.9%) before infusion (depending on the recommendations of national marketing authorisations). When administering tislelizumab in combination with chemotherapy, administer tislelizumab before chemotherapy when given on the same day. Other medicinal products must not be mixed or co-administered through the same infusion line.*(39)*

Treatment duration and dose adjustments

The treatment should last until disease progression or intolerable toxicity.

No dose reductions of tislelizumab as monotherapy are recommended. Tislelizumab should be withheld or discontinued in certain cases of immune-related adverse reactions or infusion-related reactions.

No dose adjustments are needed for:

- patients aged 65 years and above
- patients with mild or moderate renal impairment
- patients with mild or moderate hepatic impairment

The safety and efficacy of tislelizumab in the following patients are too limited to make recommendations:

- patients aged below 18 years
- patients with severe renal impairment
- patients with severe hepatic impairment

Immune-related adverse reactions have been reported during treatment with tislelizumab. The majority of these events improved with interruption of tislelizumab, administration of corticosteroids and/or supportive care. Based on data from clinical studies, administration of other systemic immunosuppressants can be considered in patients whose immune-related adverse reactions are not controlled with corticosteroid use. Upon improvement to grade ≤1, corticosteroid tapering should be initiated and continued for at least 1 month.

To date, there have been over 1 million people treated with tislelizumab (over all approved or pending indications) globally.

Section 8: Review of evidence for benefits and harms

An 'umbrella' systematic literature review was conducted to identify any existing systematic literature reviews (SLRs) that included tislelizumab as either a first- or second-line treatment for adults with unresectable advanced and/or metastatic OSCC.

Table 3 shows the 'Population, Intervention, Comparator, Outcome' (PICO) sets that were used to guide study selection:

	PICO 1 (first-line)	**PICO 2 (second-line)**
Population	Adult patients with unresectable, locally advanced, recurrent or metastatic OSCC who are treatment-naïve	Adult patients with unresectable, or metastatic OSCC who have received prior systemic chemotherapy that did not include a PD-(L)1 inhibitor
Intervention	Tislelizumab plus chemotherapy	Tislelizumab monotherapy
Comparator	Chemotherapy	Chemotherapy
Outcomes	Overall survival, progression-free survival, objective response rate, adverse events, quality-of-life	Overall survival, progression-free survival, objective response rate, adverse events, quality-of-life

Table 3 - PICO sets for the umbrella reviews.

The search strategy was deliberately broad at this stage, with no restrictions placed on comparators, year of publication or language to ensure all relevant SLRs would be identified.

Databases searched included:

- OVID, which included Embase and MEDLINE;
- PubMed Database;
- Cochrane Library
- INAHTA Database
- CRD Database (including Prospero for registered systematic reviews)
- ResearchGate

The search terms applied are described in brief in Table 4.

Category	Description	Search terms
Study design	Systematic reviews Meta-analyses Network meta-analyses (NMA)	Relevant filters applied in each search
Population	Patients aged ≥18 years with unresectable locally advanced, recurrent, or metastatic oesophageal squamous cell carcinoma	((esophageal squamous cell carcinoma) or (oesophageal squamous cell carcinoma)) and (unresectable or advanced or recurrent or metastatic)
Intervention	Tislelizumab	Tislelizumab or BGB A317 or BGB-A317 or Tevimbra

Table 4 - Search terms for the systematic literature review

Umbrella SLR Results

Studies Identified

A total of 9 published systematic literature reviews (SLRs) including tislelizumab for the treatment of unresectable, locally advanced, recurrent or metastatic OSCC were identified with the search strategy.

Five of the SLRs focused on the of immunotherapies (plus chemotherapy) as first-line treatments *(45-49)* and four focused on immunotherapies compared with chemotherapy as second-line treatments.*(50-53)*

SLRs that did not explicitly include or report studies of tislelizumab either individually or within pooled analyses were excluded (for example, Yap et al.*(54)*).

In all of the SLRs identified, the only randomised controlled trials (RCTs) that included a tislelizumab treatment arm were the pivotal RCTs, RATIONALE-306 (first-line treatment) and RATIONALE-302 (second-line treatment) conducted by the applicant, BeiGene.*(14, 15)*

The PRISMA flowchart describing the steps of study selection is described in Figure 5.

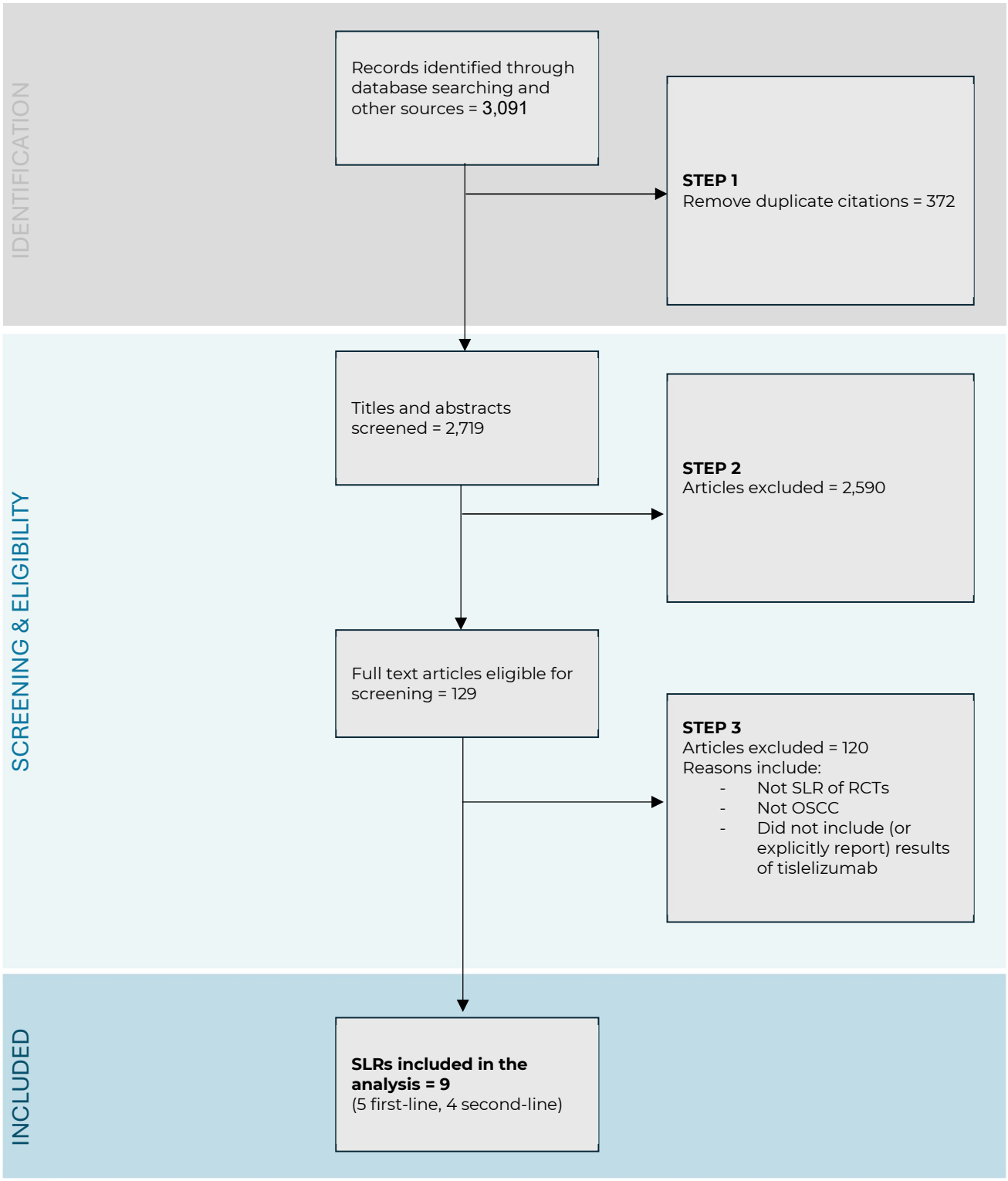


Figure 5 - PRISMA Flowchart for umbrella SLR

A brief summary table detailing the studies identified (title name, year, technologies included and line of treatment) with the primary outcomes for the comparison of tislelizumab (+/- chemotherapy) versus chemotherapy are presented in Appendix 1.

The ROBIS tool to assess the risk of bias in systematic reviews was applied to each of the included SLRs.*(55)* The overall level of bias is also included in the summary table; with possible ratings ranging from low, unclear, to a high risk of bias. Most of the SLRs were considered to be at a low or unclear risk of bias. Appropriate search strategies and methods were generally employed. However, the evidence synthesis and investigation and reporting of results presented did vary so there was some potential for introduction of bias in some SLRs. The results from this umbrella review are synthesised and discussed narratively below.

Outcomes of first-line treatment of unresectable metastatic and/or advanced OSCC

Overall and Progression Free Survival

Tislelizumab plus chemotherapy compared to chemotherapy as a first-line treatment, demonstrated statistically and clinically meaningful improvements in overall survival (OS) in all of the SLRs identified. The OS hazard ratios (HR) for tislelizumab plus chemotherapy compared with chemotherapy in all of the meta-analyses that were conducted were around 0.70 or below, all with 95% confidence intervals that were below 1.

In terms of progression-free survival (PFS), tislelizumab plus chemotherapy also demonstrated statistically and clinically significant improvements compared to chemotherapy alone. The HRs for PFS for tislelizumab plus chemotherapy in all SLRs were even lower than those for OS and ranged from 0.50 to 0.62, again with 95% confidence intervals all below 1. Where reported, the overall response rate (ORR) was statistically and clinically improved compared to chemotherapy alone.

Where tislelizumab plus chemotherapy was compared to other PD-1 inhibitors, the SLRs generally concluded that it was at least comparable, or better than other PD-1 inhibitors in terms of improving OS compared to chemotherapy alone:

In the Bayesian NMA conducted by Chen et al. *(46)*, tislelizumab as a first-line treatment for OSCC ranked 3rd in terms of PFS, 4th in terms of OS and 5th in terms of grade 3 adverse events or higher. Looking more closely at the comparison of tislelizumab plus chemotherapy against the currently recommended PD-1 inhibitors outside of the WHO EML setting (pembrolizumab and nivolumab), tislelizumab had favourable HRs for both PFS and OS, although this did not quite reach statistical significance as the 95% confidence intervals crossed 1. See Figure 6 for further details from the published SLR.

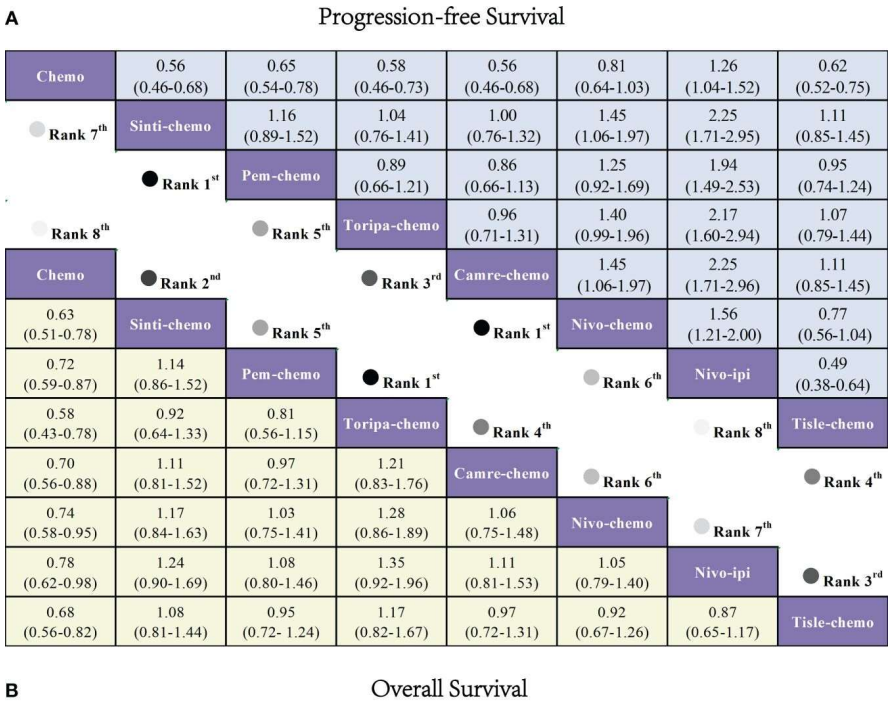


Figure 6-Results of Bayesian NMA from Chen et al.(46)

Nian et al.*(45)* conducted an SLR and NMA of first-line treatments of unresectable OSCC. In terms of the ranking, tislelizumab plus chemotherapy ranked fourth in terms of OS and PFS and second for ORR. However, as can be seen from Figure 7, the hazard ratios for all outcomes were relatively close to 1, indicating that there were no significant differences between treatment options. The authors conclude that sintilimab, toripalimab and tislelizumab (all plus chemotherapy) reached the balance to be considered superior first-line treatments for advanced unresectable OSCC.

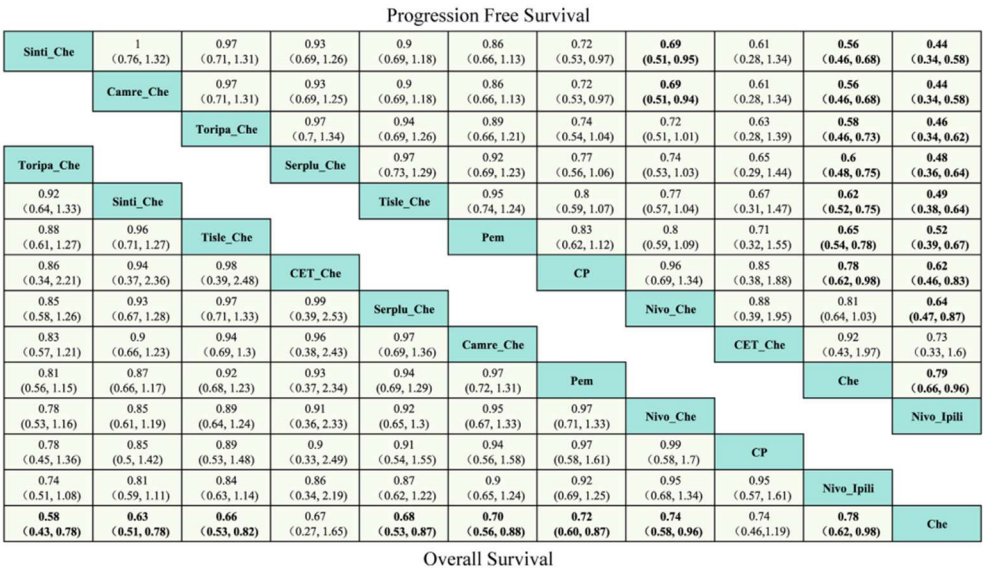


Figure 7 - Efficacy and safety estimates of the network meta-analysis from Nian et al.(45) The lower part represents hazard ratios and 95% confidence intervals of overall survival and the upper part represents progression-free survival. A hazard ratio <1.00 represents better benefits.

Yan et al. *(47)* conducted an SLR and then analysed the effects of PD-1 inhibitors using reconstructed individual patient-level data (IPD). The survival analyses were conducted two by two based on the reconstructed IPD. As shown in Figure 8, the toripalimab, tislelizumab, and sintilimab group had the best OS performance among the seven PD-1 inhibitors included in the analysis (median OS: 17.0 months, 17.2 months, and 16.7 months, respectively). The authors also noted that the pembrolizumab and nivolumab group showed unsatisfied OS benefit (median OS: 12.6 months and 13.2 months, respectively). The authors also concluded that sintilimab and tislelizumab were superior to other regimens regarding PFS, with a median PFS of 7.2 and 7.3 months, respectively.

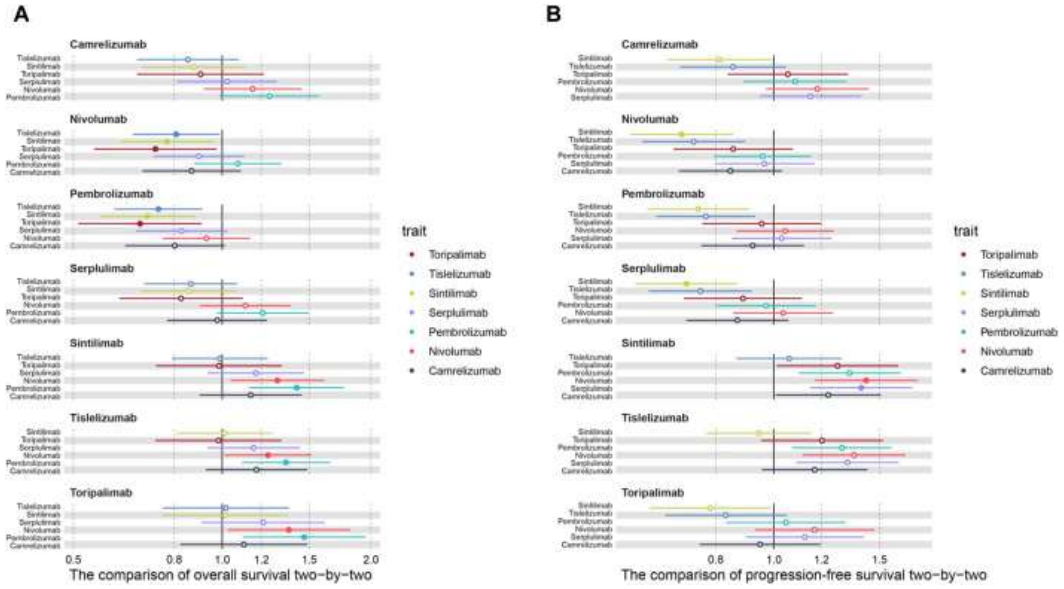
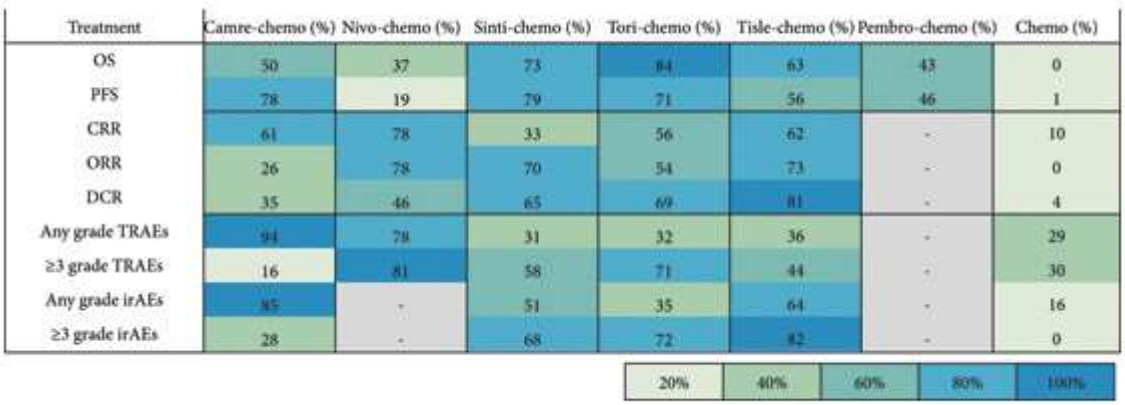


Figure 8 - Hazard ratios of the reconstructed (A) overall survival and (B) progression-free survival comparisons two by two from Yan et al.(47)

Gao et al. *(48)* conducted a SLR of oesophageal cancer and considered metastatic OSCC as a subgroup analysis. According to the authors, the Bayesian ranking profiles (SUCRA value) aligned with the direct/indirect results obtained by HRs and ORs. In the ranking, tislelizumab ranked third for OS (after toripalimab and sintilimab), however the authors considered that the OS and PFS benefits were comparable, with efficacy and safety being satisfactory and balanced and all were superior to the conventional chemotherapy group.

Ma et al. *(49)* conducted a NMA and looked at OS and PFS, where tislelizumab ranked 3rd and 4th however this was ahead of both nivolumab and pembrolizumab. To assess treatment optimality with respect to various outcomes, the ranking probabilities for all interventions were estimated using the surface under the cumulative ranking area (SUCRA). The treatment hierarchies were visualized by rankogram and the SUCRA values for all outcomes were summarized in a heat plot (see Figure 9). The authors

noted that tislelizumab plus chemotherapy attained the highest likelihood of achieving a disease control rate (DCR).



Treatment	Camre-chemo (%)	Nivo-chemo (%)	Sinti-chemo (%)	Tori-chemo (%)	Tisle-chemo (%)	Pembro-chemo (%)	Chemo (%)
OS	50	37	73	84	63	43	0
PFS	78	19	79	71	56	46	1
CRR	61	78	33	56	62	-	10
ORR	26	78	70	54	73	-	0
DCR	35	46	65	69	81	-	4
Any grade TRAEs	94	78	31	32	36	-	29
≥3 grade TRAEs	16	81	58	71	44	-	30
Any grade irAEs	85	-	51	35	64	-	16
≥3 grade irAEs	28	-	68	72	82	-	0

Figure 9- Heat plot for the analysis of different IO combinations from Ma et al. (49)

Abbreviations - IO: immunotherapy; OS: overall survival; PFS: progression-free survival; CRR: complete response rate; ORR: objective response rate; DCR: disease control rate; TRAEs: treatment-related adverse events; irAEs: immune-related adverse events. camre: camrelizumab; nivo: nivolumab; sinti: sintilimab; tori: toripalimab; tisle: tislelizumab; pembro: pembrolizumab; chemo: chemotherapy.

SLR subgroup analysis by PD-L1 expression status

As previously noted, there is global variability according to regulatory conditions around levels of PD-L1 expression in the marketing authorisations for the currently available PD-1 inhibitors for OSCC. Evidence suggests that tislelizumab is effective in the majority of patients. Although the clinical benefit is greatest in patients with high PD-L1 expression, there is still clinical benefit for patients with low PD-L1 expression, therefore an agnostic approach that requires no PD-L1 testing is proposed. Evidence supporting this statement is provided below from both the subgroup analyses in the umbrella SLR and RATIONALE-306 (the pivotal trial of tislelizumab as a first-line treatment of unresectable OSCC). Three of the included SLRs considered clinical efficacy according to PD-L1 expression status. The SLRs that conducted subgroup analyses by PD-L1 expression status presented pooled PD-1 inhibitors compared with chemotherapy only (i.e. the results for tislelizumab were not presented separately in these SLRs by PD-L1 subgroup).

In the pooled analyses that included tislelizumab, a CPS (or TAP) cut-off of ≥10% was considered to represent positive PD-L1 expression in the subgroup analyses. Two SLRs exploring the first-line treatment and one SLR of the second-line treatment of OSCC conducted such subgroup analyses.

- Nian et al. *(45)* (first-line treatment) reported a HR for OS for those with CPS ≥10% of 0.62 (95% 0.44, 0.87). The HR for OS for those with CPS < 10% was 0.77

(95% CI: 0.59, 1.01). This study reported PFS results but they did not include tislelizumab.

- Chen et al.*(46)* (first-line treatment) reported a HR for OS for those with a CPS ≥10% of 0.61 (95% CI: 0.53, 0.70). The HR for PFS for those with CPS ≥10% was 0.53 (95% CI: 0.47, 0.60). The OS or PFS for those with CPS <10% was not reported.
- Leone et al. *(51)* (second-line treatment) reported a HR for OS for those with CPS ≥10% of 0.60 (95% CI: 0.51, 0.70). The HR for OS for those with CPS < 10% was 0.83 (95% CI: 0.69, 1.00).

The authors of the above SLRs highlighted that the hazard ratios for overall survival were statistically and clinically significant with all participants (i.e. all levels of PD-L1 expression). However, as can be seen in the above table and from the results of the SLR subgroup analysis, for patients with low PD-L1 expression, the 95% confidence intervals for OS tended to favour PD-L1 treatments, but were not always statistically significant. The authors of these SLRs noted this could be impacted by the lower number of participants in the low PD-L1 expression subgroups; these results are likely underpowered to demonstrate statistical significance.

The authors of one SLR (Leone et al.) concluded that the efficacy of PD-(L)1 inhibitors is better for those with low PD-L1 expression in earlier treatment than in later lines. *(51)* Challenges with regards to conducting subgroup analysis according to PD-L1 expression were noted in the SLRs. The majority of authors concluded that given the relative immaturity of measuring PD-L1 expression in OSCC, the potential for fluctuation and heterogeneity of PD-L1 expression, method of assessment, type of specimen and other potential confounding factors, that further research is warranted.*(54)*

Since conducting the umbrella SLR, the FDA released a briefing note for consideration by the Oncologic Drugs Advisory Committee (ODAC).*(56)* In this briefing note, trials of nivolumab, pembrolizumab and tislelizumab as either first- or second-line treatments were included. A total of 17 RCTs were identified that included patients with gastric, oesophageal adenocarcinomas and OSCC and a post-hoc analysis based on published trial data was conducted to evaluate the OS benefit based on high versus absent versus low PD-L1 expression status. The results of the pooled analysis conducted by the FDA suggested that patients with higher PD-L1 expression derived the most benefit, and that patients who are PD-L1 negative appear not to benefit.

The FDA acknowledged that the pooled analysis had limitations; it was not pre-specified, and the subgroups were identified by different testing assays across trials. The FDA noted that as most patients with OSCC (90%) would have some PD-L1 expression then the majority of patients with OSCC would be expected to benefit from

PD-1 treatment (with effect consistent with the potential for benefit with even low levels of PD-L1 expression, i.e., >1%). However, in the context of the American healthcare system, the ODAC voted for inclusion of conditions round PD-L1 expression status in the regulatory approvals for nivolumab and pembrolizumab (the approval for tislelizumab is still pending at the time of writing).

The role of the treating clinician in determining additional factors, such as a patient's ability to tolerate therapy, level of frailty and other extraneous factors present in treatment decision-making were not discussed in the briefing note. Further, the briefing note and ODAC discussions were in the context of the American health system where PD-L1 testing is readily available, and there are multiple treatment options for both first-and second-line treatment of OSCC. This context would impact the interpretation of the risk-benefit conclusions around PD-L1 expression conditions for treatment.

Adverse events and quality-of-life

When tislelizumab was given as a first-line treatment in combination with chemotherapy, the SLRs generally concluded that the adverse event profile of tislelizumab was similar to that of chemotherapy alone.

As can be seen from the heat plot developed by Ma et al.*(49)* shown in Figure 9 above, tislelizumab had the best profile of all of the PD-1 inhibitors in terms of grade 3 or higher immune-related adverse events.

When compared with the other PD-1 inhibitors, Nian et al.*(45)* concluded that tislelizumab ranked fourth for grade 3 and above adverse events, see Figure 10.While there was no statistically significant different between tislelizumab and the other PD-1 inhibitors, it should be noted that the adverse events odds ratios for tislelizumab were most favourable when compared to chemotherapy and nivolumab.

Grade ≥3 Adeverse Events

Camre_Che	1 (0.62, 1.6)	0.84 (0.59, 1.18)	0.76 (0.47, 1.21)	0.72 (0.43, 1.19)	0.7 (0.43, 1.16)	0.67 (0.42, 1.06)	0.65 (0.39, 1.09)	**0.51 (0.32, 0.82)**	**0.25 (0.07, 0.76)**
	Nivo_Ipili	0.84 (0.6, 1.17)	0.76 (0.48, 1.21)	0.72 (0.43, 1.2)	0.7 (0.43, 1.16)	0.67 (0.43, 1.06)	0.66 (0.39, 1.1)	**0.51 (0.32, 0.82)**	**0.25 (0.07, 0.77)**
		Che	0.91 (0.66, 1.26)	0.86 (0.58, 1.25)	0.84 (0.58, 1.21)	0.8 (0.59, 1.09)	0.78 (0.53, 1.14)	**0.61 (0.44, 0.84)**	**0.29 (0.09, 0.87)**
Nivo_Che			**Tisle_Che**	0.95 (0.57, 1.55)	0.92 (0.57, 1.51)	0.88 (0.56, 1.37)	0.86 (0.52, 1.42)	0.67 (0.42, 1.06)	**0.32 (0.1, 1)**
1.04 (0.66, 1.64)	**Tisle_Che**			**Toripa_Che**	0.98 (0.58, 1.66)	0.93 (0.57, 1.53)	0.91 (0.53, 1.57)	0.71 (0.43, 1.18)	0.34 (0.1, 1.07)
1.05 (0.66, 1.65)	1.02 (0.65, 1.58)	**Sinti_Che**			**Serplu_Che**	0.96 (0.59, 1.55)	0.93 (0.54, 1.58)	0.73 (0.45, 1.19)	0.35 (0.1, 1.09)
1.18 (0.73, 1.93)	1.14 (0.71, 1.85)	1.13 (0.7, 1.83)	**Toripa_Che**			**Sinti_Che**	0.98 (0.59, 1.6)	0.76 (0.48, 1.19)	0.37 (0.11, 1.13)
1.31 (0.8, 2.13)	1.26 (0.78, 2.03)	1.24 (0.78, 2)	1.11 (0.66, 1.83)	**Serplu_Che**			**Pem**	0.78 (0.47, 1.29)	0.37 (0.11, 1.18)
1.55 (0.96, 2.51)	1.49 (0.94, 2.37)	1.48 (0.93, 2.36)	1.31 (0.79, 2.16)	1.18 (0.72, 1.94)	**Camre_Che**			**Nivo_Che**	0.48 (0.14, 1.49)
1.85 (0.76, 4.54)	1.78 (0.73, 4.42)	1.77 (0.72, 4.3)	1.56 (0.63, 3.95)	1.41 (0.57, 3.48)	1.19 (0.48, 2.91)	**CP**			**CET_Che**
2 (0.63, 6.24)	1.92 (0.61, 5.9)	1.9 (0.6, 5.89)	1.69 (0.53, 5.3)	1.52 (0.48, 4.75)	1.29 (0.41, 4.02)	1.08 (0.27, 4.19)	**CET_Che**		
2.35 (1.46, 3.8)	**2.27 (1.42, 3.62)**	**2.24 (1.4, 3.55)**	**1.98 (1.2, 3.27)**	**1.8 (1.1, 2.98)**	1.52 (0.93, 2.49)	1.28 (0.52, 3.11)	1.18 (0.38, 3.77)	**Nivo_Ipili**	
2.45 (1.78, 3.42)	**2.37 (1.73, 3.23)**	**2.34 (1.71, 3.22)**	**2.07 (1.44, 2.98)**	**1.87 (1.32, 2.69)**	**1.58 (1.12, 2.25)**	1.32 (0.57, 3.08)	1.23 (0.42, 3.73)	1.04 (0.74, 1.47)	**Che**

Objective Response Rate

Figure 10 - Efficacy and safety estimates of the network meta-analysis from Nian et al.(45) (B) The lower part represents odds ratios and 95% confidence intervals of objective response rate. An odds ratio >1.00 represents better benefits. The upper one represents odds ratios and 95% confidence intervals of grade ≥3 adverse events. An odds ratio of <1.00 indicates better safety.

These results were discordant with those presented by Chen et al. *(46)* ranked tislelizumab as fifth when compared to other PD-1 inhibitors in terms for grade 3 or higher adverse events, see Figure 11. The authors concluded that almost all PD-1 inhibitors reviewed showed no safety benefits compared to chemotherapy. This is not in line with the conclusions drawn by the other SLRs identified in this umbrella review.

Rank 3rd	Rank 8th	Rank 7th	Rank 4th	Rank 1st	Rank 9th	Rank 2nd	Rank 6th	Rank 5th
Chemo								
1.25 (0.92- 1.70)	**Sinti-chemo**							
1.23 (0.83- 1.84)	0.99 (0.59- 1.63)	**Pem-chemo**						
1.06 (0.72- 1.56)	0.85 (0.52- 1.39)	0.86 (0.49- 1.51)	**Toripa-chemo**					
0.83 (0.59- 1.16)	0.66 (0.42- 1.05)	0.67 (0.4- 1.13)	0.78 (0.47- 1.31)	**Camre-chemo**				
1.64 (1.19, 2.26)	1.31 (0.84, 2.05)	1.33 (0.8, 2.22)	1.54 (0.93, 2.56)	1.98 (1.24, 3.15)	**Nivo-chemo**			
0.84 (0.6- 1.17)	0.67 (0.43- 1.06)	0.68 (0.41- 1.15)	0.79 (0.48- 1.32)	1.02 (0.63- 1.63)	0.52 (0.05- 5.27)	**Nivo-ipi**		
1.22 (0.84- 1.77)	0.97 (0.60- 1.58)	0.99 (0.57- 1.71)	1.15 (0.67- 1.97)	1.47 (0.89- 2.43)	0.75 (0.07- 7.73)	1.45 (0.88- 2.38)	**Serplu-chemo**	
1.10 (0.8- 1.52)	0.88 (0.56- 1.38)	0.89 (0.53- 1.49)	1.04 (0.63- 1.73)	1.33 (0.83- 2.13)	0.68 (0.07- 6.95)	1.31 (0.82- 2.08)	0.91 (0.55- 1.48)	**Tisle-chemo**

Grade ⩾3 Adverse Events

Figure 11 - ORs and 95% CIs for ≥grade 3 AEs from Chen et al.(46) OR < 1.00 indicates better safety.

Gao et al.*(52)* noted that the type of adverse event and overall safety profile likely differs according to each PD-1 inhibitor. The authors concluded that the addition of nivolumab (+/- ipilimumab) and pembrolizumab resulted in increased toxicity profiles compared to chemotherapy alone. Further, the authors highlighted that the types and frequencies of

treatment-related and immune-related adverse events varied across the PD-1 inhibitors evaluated. This could be important for clinical decision-making when choosing which PD-1 inhibitor is preferred.

Health-related quality-of-life was not reported in any of the identified SLRs.

Second-line treatment of unresectable metastatic and/or advanced OSCC

Tislelizumab monotherapy was compared to chemotherapy as a second-line treatment for unresectable advanced or metastatic OSCC. There was consensus across all SLRs identified that there was a statistically significant and clinically meaningful improvement in OS compared to chemotherapy.

Where tislelizumab was compared to other PD-1 inhibitors as a second-line treatment for OSCC, it ranked well, and was comparable in regards to PFS (when reported – some of the SLRs did not include this outcome for tislelizumab as the data were not available at the time the reviews were conducted). In terms of OS and ORR, tislelizumab was noted as being particularly efficacious compared to other PD-1 inhibitors.

Other key points noted, included that the dosing regimen of tislelizumab is less frequent and so this can be more favourable for patients and health systems compared with some of the other PD-(L)1 inhibitors which need to be administered more frequently. For example, tislelizumab is given once every 3 weeks and nivolumab is given once every 2 weeks. Additionally, it was noted that other PD-1 inhibitors with approval for the second-line treatment of OSCC are approved only after platinum-based chemotherapy, whereas tislelizumab can be given as a second-line treatment as long as the first-line treatment did not include a PD-(L)1 therapy (ie., in line with the FDA marketing authorisation).

When tislelizumab monotherapy was given as a second-line treatment, then the rates of adverse events were lower than with chemotherapy alone. Tislelizumab given as monotherapy for the second-line treatment of OSCC was comparable to the other PD-1 inhibitors (e.g., pembrolizumab and nivolumab) included in the SLRs.

Health-related quality-of-life was not reported in any of the identified SLRs.

Systematic Literature Review of Primary Randomised Controlled Trials

In the umbrella SLR conducted, the SLRs only identified the pivotal trials of each PD-1 inhibitor as conducted by the respective manufacturers. To ensure that no additional randomised controlled trials of tislelizumab were missed by any of the identified SLRs, a ‘de novo’ SLR was conducted.

This SLR was conducted in August 2024 to identify relevant studies evaluating the efficacy and safety of tislelizumab as either a first- or second-line treatment for adults

with unresectable, advanced and/or metastatic OSCC, regardless of PD-L1 expression status.

A comprehensive search of the published literature was conducted, which included searches of:

- OVID, which included Embase and MEDLINE
- Cochrane Library
- PubMed Database
- Search of clinical trial registries (i.e. www.clinicaltrials.gov)

The search was restricted to randomised studies only and excluded editorials, letters, comments, errata, notes and non-human studies. There was no restriction on language or comparators at this stage.

The PRISMA flowchart below describes the search, screening and identification of studies. Only the pivotal studies (with associated publications) for tislelizumab as a first- and second-line treatment were identified. No other head-to-head RCTs were found. The study design and results of these pivotal studies are described in Figure 12.

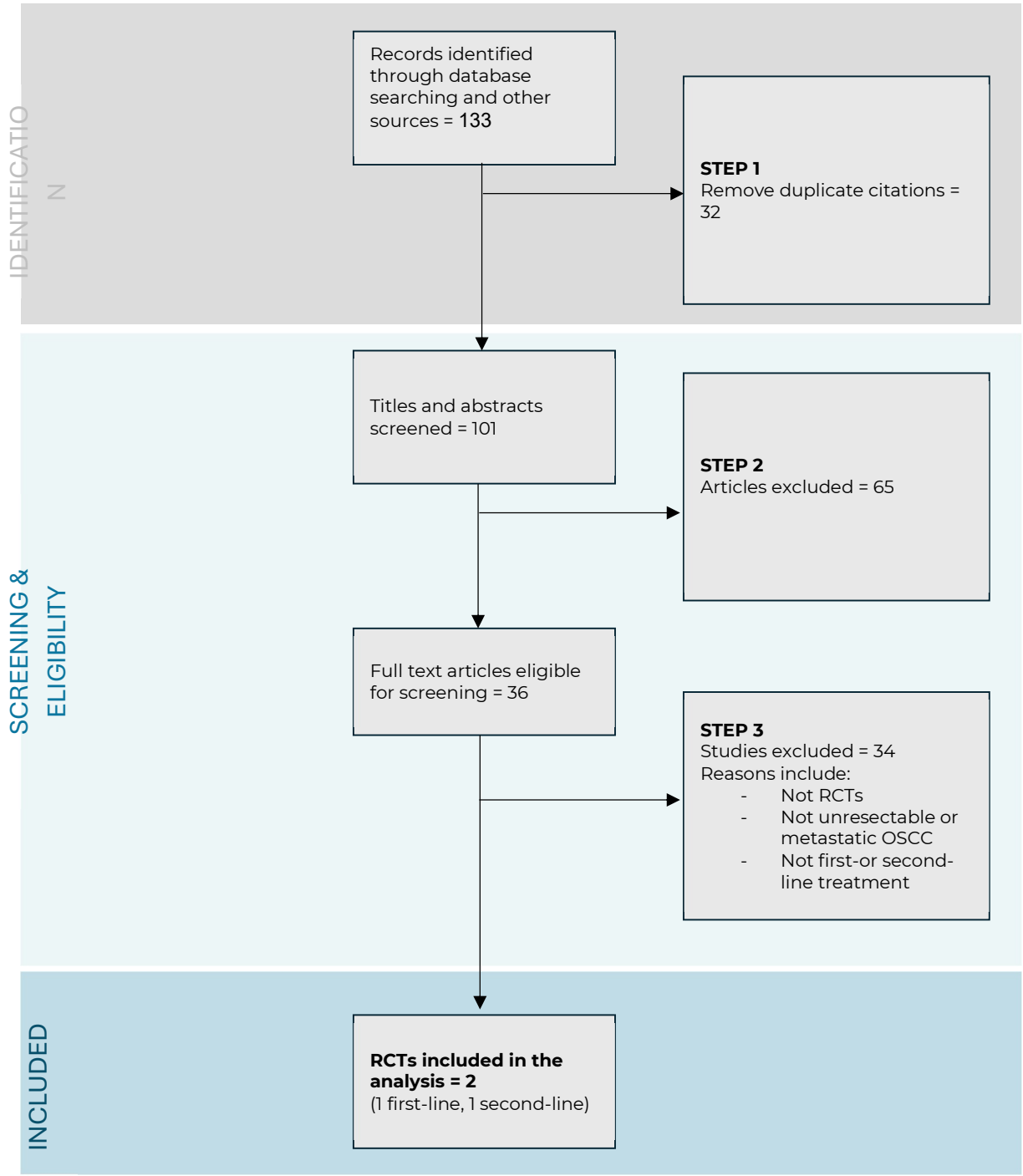


Figure 12 - PRISMA flowchart for SLR of RCTs

RATIONALE-306 (tislelizumab plus chemotherapy versus chemotherapy as a first-line treatment)

RATIONALE-306 *(14),(13)* is a phase III, randomised, double-blind, placebo-controlled, multicentre international study comparing the safety and efficacy of tislelizumab plus chemotherapy versus placebo plus chemotherapy. The risk of bias of the RATIONALE-306 study was deemed to be low in accordance with the GRADE checklist.*(57)*

Study design

In RATIONALE-306, 649 patients were randomly assigned to tislelizumab plus chemotherapy (n=326) or placebo plus chemotherapy (n=323). Within the study treatment arms, 146 patients (45.1%) in the tislelizumab plus chemotherapy arm and 144 patients (44.9%) in the placebo plus chemotherapy arm received the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with fluoropyrimidine (5-FU/capecitabine). The remaining 178 patients (54.9%) in the tislelizumab plus chemotherapy arm and 177 patients (55.1%) in the placebo plus chemotherapy arm received the chemotherapy regimen of platinum (cisplatin/oxaliplatin) with paclitaxel. Just over half of the patients in RATIONALE-306 received chemotherapy regimen containing paclitaxel, which is relevant to the EML setting.

The study design and numbers of participants recruited is summarised in Figure 13. Baseline characteristics between treatment arms were considered to be well-balanced by trial investigators.

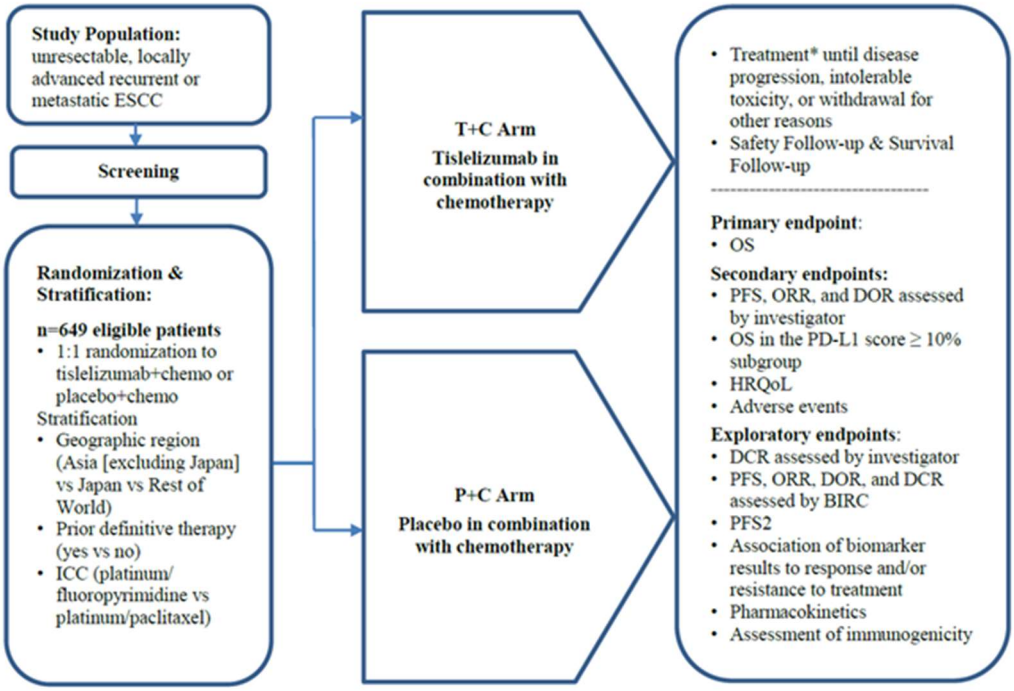


Figure 13 - RATIONALE-306 Study design, Source: Xu, et al. 2023 (14)

Abbreviations: BIRC: blinded independent review committee; Chemo: chemotherapy; DCR: disease control rate; DOR: duration of response; ESCC: (o)esophageal squamous cell carcinoma; HRQoL: health-related quality-of-life; ICC: investigator choice of chemotherapy; ORR: objective response rate; OS: overall survival; PD-L1: programmed cell death protein ligand-1; PFS: progression-free survival; PFS2: PFS after next line of treatment; vCPS: visually estimated combined positive score.

Overall and progression free survival

The interim analysis from 28 February 2022 data cutoff *(14)* demonstrated that tislelizumab plus chemotherapy provided superior overall survival with a 34% reduction in the risk of a death event and improvement in median OS by 6.6 months in the tislelizumab plus chemotherapy arm over the placebo plus chemotherapy arm (HR 0.66; 95% CI 0.54 to 0.80; p-value of < 0.0001; median OS 17.2 months vs 10.6 months). Treatment with tislelizumab plus chemotherapy also resulted in a statistically significant improvement in the secondary endpoints of PFS and objective response rate.

In an extended 3-year follow-up with 24 November 2023 data cutoff,*(13)* tislelizumab plus chemotherapy continues to demonstrate clinically meaningful survival benefit (HR 0.70; 95% CI 0.59 to 0.83), see Figure 14.

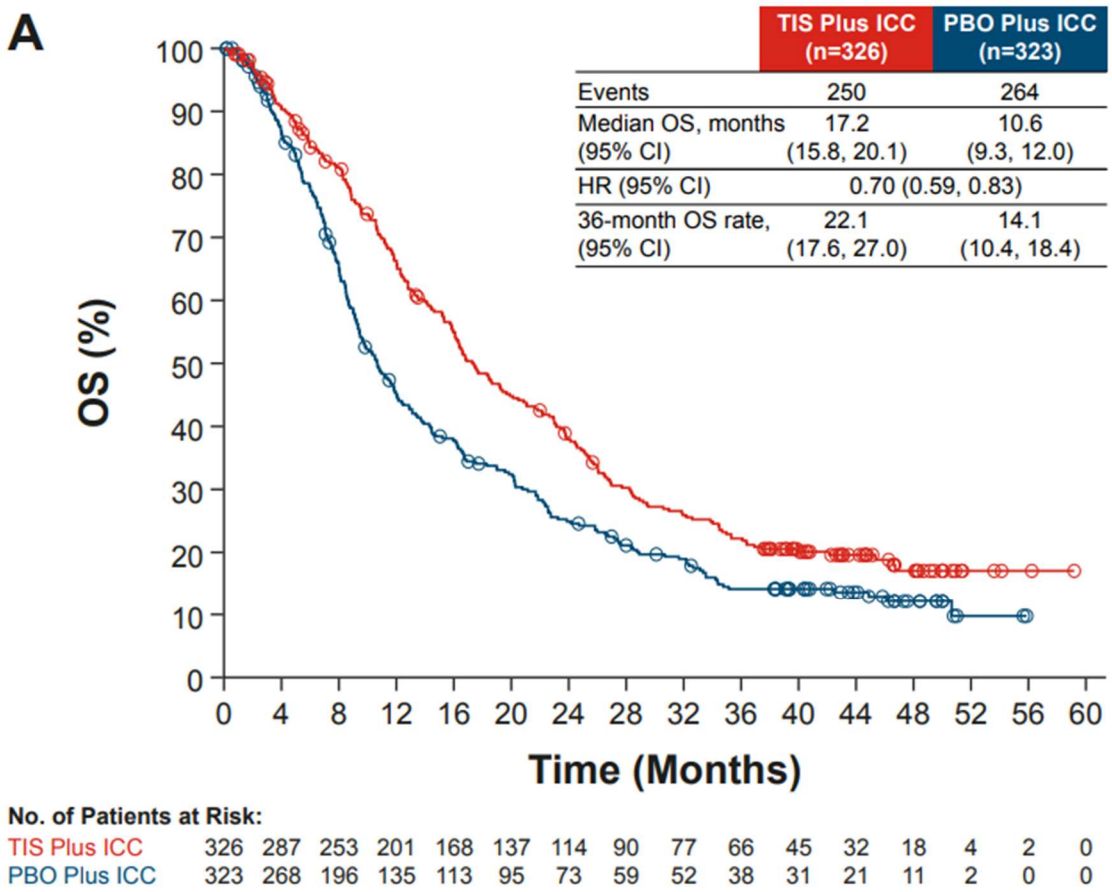


Figure 14 - Overall survival in RATONALE-306 study. *Source: (Harry H. Yoon 2024)*
Abbreviations: TIS: tislelizumab; ICC: investigator-chosen chemotherapy; PBO: placebo; N: number; HR: hazard ratio; OS: overall survival; CI: confidence interval

At the same later data cut, durable PFS (HR 0.60; 95% CI 0.50 to 0.72; p-value of < 0.0001) and response difference compared to chemotherapy alone was also observed, with no new safety signals identified, see Table 5.

	Tislelizumab + Chemotherapy N=326 (% [95% CI])	**Placebo + Chemotherapy N=323 (% [95% CI])**
Median PFS (95% CI), months	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)
HR (95% CI)	0.60 (0.50, 0.72)	
36-month PFS rate (95% CI), %	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)
ORR (95% CI), %	63.5 (58.0, 68.7)	42.4 (37.0, 48.0)
Median DOR (95% CI), months	7.1 (6.1, 8.1)	5.7 (4.4, 7.1)
36-month DOR rate (95% CI), %	17.7 (12.3, 24.0)	5.0 (1.5, 11.8)

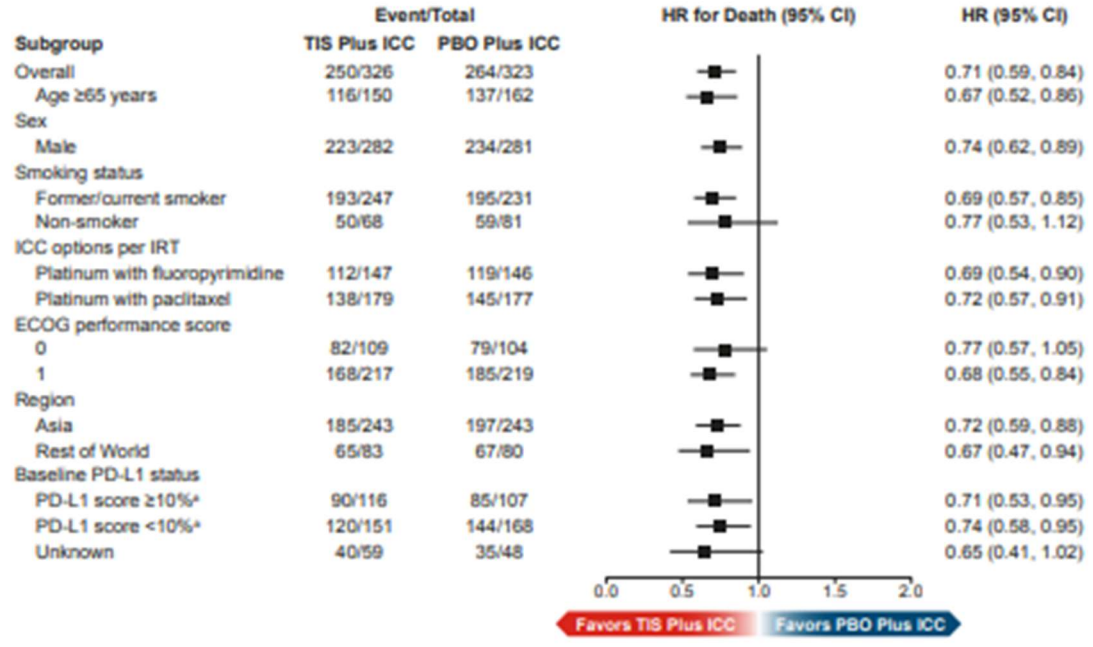
Table 5 - Secondary efficacy endpoints (ITT Analysis Set) - RATIONALE-306 (24/11/23 data cutoff). (13) Abbreviations: CI: confidence interval; DOR: duration of response; n/N: number; ORR: objective response rate

Subgroup analyses

Subgroup analyses were conducted to assess the impact of the following factors:

- ICC option (platinum with fluoropyrimidine or platinum with paclitaxel)
- Baseline PD-L1 expression status (low, high, unknown)
- Geographic region (Asia +/- Japan versus rest of the world)
- Performance status (ECOG 0 or 1)
- Age (under or over 65 years)
- Sex
- Smoking status

Overall, the benefit of treatment with tislelizumab plus chemotherapy in improving OS, when compared to placebo plus chemotherapy was observed across all the prespecified subgroups, see Figure 15.



The ITT Analysis Set includes all randomized patients. HR was based on unstratified Cox regression model including treatment as covariate.
* PD-L1 score based on TAP score. **Abbreviations:** CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICC, investigator-chosen chemotherapy; IRT, interactive response technology; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, tumor area positivity; TIS, tislelizumab.

Figure 15 - Overall Survival by Subgroup (ITT Analysis Set), 24/11/2023 data cutoff. Source: Yoon et al.(13)

More detail on the effect of tislelizumab by baseline PD-L1 expression status is provided below.

RATIONALE-306 results by PD-L1 expression status

Table 6, Figure 16 and Figure 17 below provide more detail regarding the subgroup analysis by baseline PD-L1 expression status in the RATIONALE-306 study (first-line use of tislelizumab plus chemotherapy).

The RATIONALE studies both used the TAP scoring method as this is considered to be the most straightforward method, significantly less time-consuming and demonstrated a high concordance rate with CPS. Note that studies of other PD-1 inhibitors have used tumour proportion score (TPS), others used combined positive score (CPS) or tumour area positivity (TAP). The CPS and TAP scores include PD-L1 expression on both tumour and surrounding immune cells and may be preferential for gastric cancers and there is a high concordance rate between TAP score and CPS.*(58)*

	Events/Total		**Median OS (95% CI), months**		**Stratified HR (95% CI)**	**Interaction P-value**
PD-L1 status subgroup	Tislelizumab plus chemo	Placebo plus chemo	Tislelizumab plus chemo	Placebo plus chemo		
PD-L1 status on CPS						
CPS ≥ 10	68/115	82/113	17.2 (15.3, 25.0)	9.4 (8.5, 12.3)	0.57 (0.41, 0.80)	0.22
CPS < 10	96/149	111/160	15.8 (12.5, 19.2)	10.6 (9.1, 13.8)	0.82 (0.62, 1.08)	
Unknown	32/62	33/50	22.9 (16.6, 27.7)	11.7 (7.4, 21.7)	0.59 (0.36, 0.98)	
PD-L1 status on TC						
TC ≥ 1%	95/152	103/147	16.8 (15.3, 21.8)	9.3 (8.4, 12.4)	0.65 (0.49, 0.87)	0.36
TC < 1%	69/112	90/126	15.8 (12.3, 19.6)	11.2 (9.4, 14.4)	0.79 (0.57, 1.09)	
Unknown	32/62	33/50	22.9 (16.6, 27.7)	11.7 (7.4, 21.7)	0.59 (0.36, 0.98)	
PD-L1 status on TAP score						
TAP ≥ 10%	69/116	74/107	16.6 (15.3, 24.4)	10.0 (8.6, 13.3)	0.62 (0.44, 0.87)	0.30
TAP < 10%	98/151	120/168	15.8 (12.3, 19.6)	10.4 (9.0, 13.6)	0.77 (0.59, 1.01)	
Unknown	29/59	32/48	23.7 (16.6, 28.4)	11.7 (7.4, 21.7)	0.54 (0.32, 0.91)	

Table 6 - Details of subgroup analysis by PD-L1 expression status in RATIONALE-306 (tislelizumab as a first-line treatment)

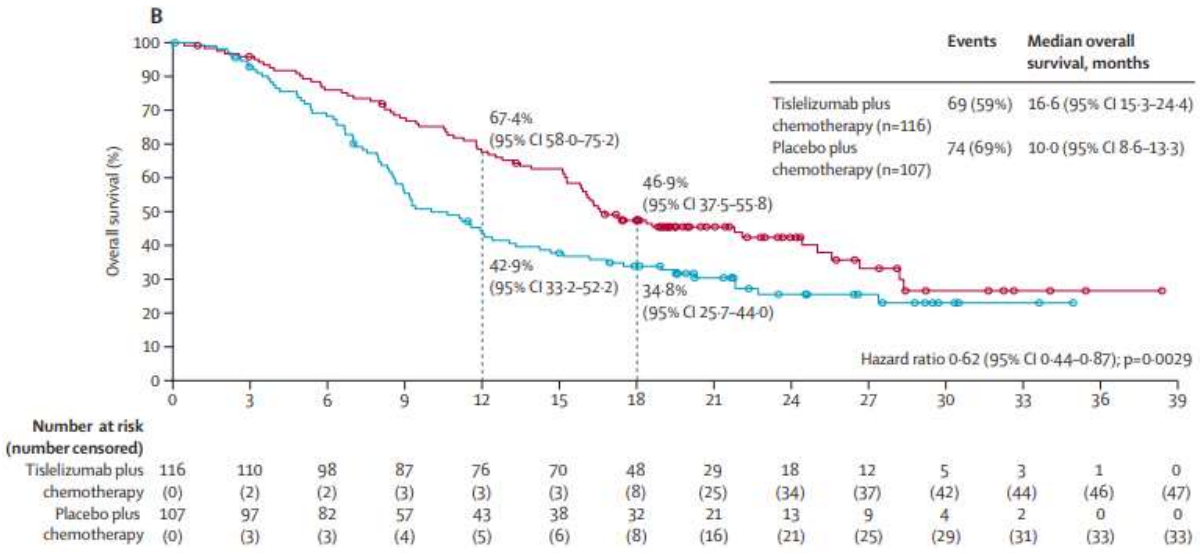


Figure 16 - Kaplan Meier Plot of Overall Survival by Baseline PD-L1 Status - PD-L1 TAP Score ≥ 10% (ITT Analysis Set), 28/02/2022 data cutoff. Source Xu et al. (14)

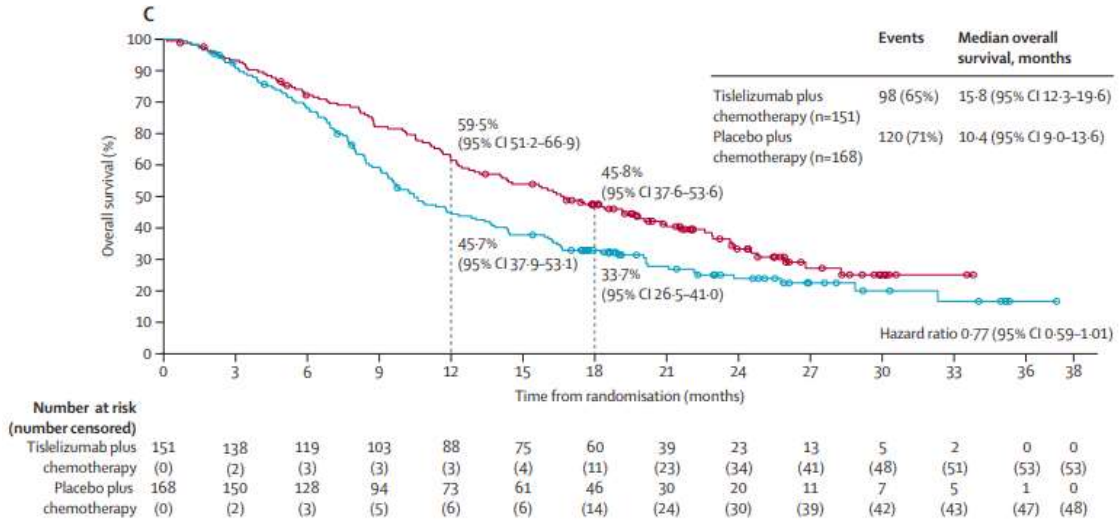


Figure 17 - Kaplan Meier Plot of Overall Survival by Baseline PD-L1 Status - PD-L1 TAP Score < 10% (ITT Analysis Set), 28/02/2022 data cutoff. Source Xu et al.(14)

Subgroup analysis by baseline PD-L1 expression was also conducted for PFS, ORR and duration of response. This was assessed at the 28/02/2022 data analysis. Results are summarised in brief below:

<u>Progression-Free Survival (PFS)</u>

- In patients with PD-L1 ≥10%, PFS = 8.3 months with tislelizumab and 5.6 months with chemotherapy, HR = 0.50 (95% CI 0.37, 0.69)
- In patients with PD-L1 <10%, PFS = 6.9 months with tislelizumab and 5.5 months with chemotherapy, HR = 0.68 (95% CI 0.53, 0.88)

<u>Objective response rate (ORR)</u>

- In patients with PD-L1 ≥10%, ORR = 73% with tislelizumab and 40% with chemotherapy
- In patients with PD-L1 <10%, ORR = 58% with tislelizumab and 46% with chemotherapy

Adverse events and quality-of-life

Overall, the safety profile of tislelizumab plus chemotherapy was considered manageable.*(13, 14)* Almost all patients in both arms experienced ≥ 1 treatment related adverse event (TRAE): 99.7% in the tislelizumab plus chemotherapy arm versus 99.4% in the placebo plus chemotherapy arm. At the 3-year follow-up, incidences of any-Grade and Grade ≥3 TRAEs were comparable between patients receiving tislelizumab plus chemotherapy and placebo plus chemotherapy. Serious TRAEs and TEAEs leading to treatment discontinuation occurred more frequently with tislelizumab plus chemotherapy compared to placebo plus chemotherapy while treatment discontinuations were comparable between the two arms. The most common grade ≥3 TRAEs were decreased neutrophil count (30.9% vs 32.7%), anaemia (14.8% vs 12.8%), and decreased white blood cell count (10.8% vs 15.6%). The incidence of adverse events leading to death was low and comparable between the two treatment arms: 1.9% in the tislelizumab plus chemotherapy arm versus 1.2% in the placebo plus chemotherapy arm.

A summary of overall adverse events at the latest data cut are presented in Table 7.

TEAE category, n (%)	**Tislelizumab plus Chemotherapy N=324**	**Placebo plus Chemotherapy N=321**
Any treatment-related AE	313 (96.6%)	309 (96.3%)
Serious	97 (29.9%)	63 (19.6%)
Grade 3+	217 (67.0%)	207 (64.5%)
Leading to death	6 (1.9%)	4 (1.2%)
TEAEs leading to treatment discontinuation	104 (32.1%)	71 (22.1%)
TEAE leading to dose modification	247 (76.2%)	229 (71.3%)

Table 7 - Summary of adverse events (SAS) - RATIONALE-306 (24/11/23 data cutoff). (13)

Abbreviations: TEAE: Treatment emergency adverse event; N: number

Adding tislelizumab to chemotherapy did not increase patients' symptoms related to OSCC. Health-related quality-of-life of those receiving tislelizumab was comparable to that of participants receiving placebo plus chemotherapy as measured by HRQoL-EORTX QLQ-C30; HRQoL-EORTX QLQ-C18 and EuroQol 5D EQ-5D-5L. Completion rates of the HRQoL questionnaires were over 90% at cycle 8. Overall changes of scores from baseline to cycle 8 indicated that there was no significant difference between treatment arms. Physical function did decrease in both treatment arms, but there were no differences between treatment arms in terms of fatigue, pain, dysphagia and reflux.

RATIONALE-302 (tislelizumab as a second-line treatment)

Study design

In RATIONALE-302, *(15)* tislelizumab monotherapy was compared with investigator-chosen chemotherapy (ICC: paclitaxel, docetaxel, or irinotecan) in patients with locally advanced or metastatic OSCC whose disease progressed after prior systemic therapy. There were 132 study sites across 11 countries and the RCT was deemed to be at a low risk of bias according to the GRADE framework.

A summary of the study design and participants recruited to each arm is displayed in Figure 18.

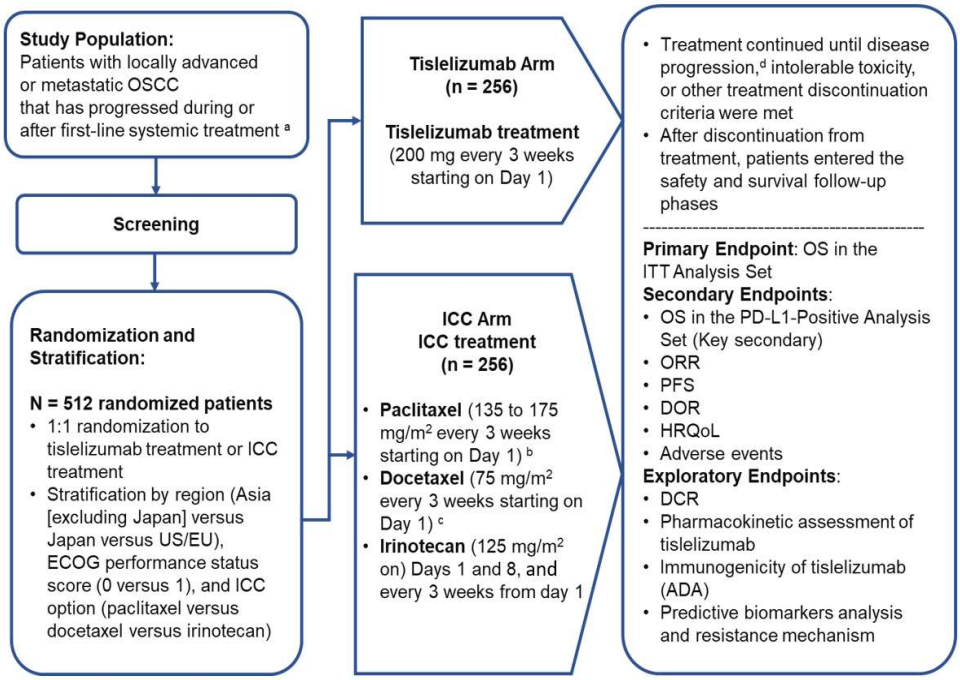


Figure 18 - RATIONALE-302 study design, source Shen et al. (15)

Overall and progression free survival

As of the data cut-off date 1st December 2020, the study met its primary endpoint with statistically significant and clinically meaningful improvement in OS compared with ICC (median OS: 8.6 versus 6.3 months; stratified HR: 0.70, 95%CI: 0.57, 0.85; one-sided P=0.0001).*(15)*

Median PFS as assessed by the investigator was 1.6 months (95% CI: 1.4, 2.7) and 2.1 months (95% CI: 1.5, 2.7) in the tislelizumab and ICC arms, respectively(stratified HR: 0.83 [95% CI: 0.67, 1.01]). Additionally, treatment with tislelizumab was associated with a higher objective response rate (20.3% versus 9.8%) and longer median duration of response (7.1 months versus 4.0 months) than with ICC.

Adverse events and quality-of-life

The safety profile of tislelizumab demonstrated in RATIONALE-302 was in line with the known safety profiles of PD-1 inhibitors used as monotherapy. Overall, the majority of patients in both treatment arms experienced at least one TRAE (tislelizumab: 95.7%; ICC: 98.3%). Despite the longer median duration of drug exposure (84.0 days versus 45.5 days), a smaller proportion of patients in the tislelizumab arm experienced TRAEs (73.3% versus 93.8%) and ≥grade 3 TRAEs (18.8% versus 55.8%) compared to the ICC arm. The incidence of serious treatment emergent adverse events (TEAEs) was comparable between arms (41.2% versus 43.8%).*(15)*

RATIONALE-302 evaluated pre-specified secondary quality-of-life endpoints, assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) 30-item Quality-of-Life Core Questionnaire (QLQ-C30), EORTC Quality-of-Life Questionnaire Oesophageal Cancer 18-item module (QLQ-OES18) and EuroQoL-5 dimensions-5 levels (EQ-5D-5L). Patients treated with tislelizumab showed more favourable quality-of-life outcomes compared to those treated with ICC.*(16)*

Subgroup analyses

The survival benefit of tislelizumab was also consistently observed across all predefined subgroups:*(15)*

- Baseline PD-L1 (as measured by TAP and visually compared to CPS). In patients with PD-L1 TAP score ≥10%, median OS was 10.3 versus 6.8 months for tislelizumab and ICC arms, respectively (stratified HR: 0.54 [95% CI: 0.36, 0.79]; P=0.0006); among patients with PD-L1 TAP <10%, median OS was 6.9 versus 5.8 months, P=0.0859; in patients missing PD-L1 status, median OS was 9.8 months versus 7.0 months, P=0.0630.
- In the Asia subgroup, the median OS was 8.5 months (95% CI: 7.1, 10.3) for the tislelizumab arm and 6.3 months (95% CI: 5.3, 7.4) for the ICC arm (HR: 0.73 [95% CI: 0.59, 0.90]) (45). In the Europe/North America subgroup, the median OS was 11.2 months (95% CI: 5.9, 14.8) for the tislelizumab arm and 6.3 months (95% CI: 4.6, 7.7) for the ICC arm (HR: 0.55 [95% CI: 0.35, 0.87])

Section 9: Summary of recommendations in current clinical guidelines

There are no WHO guidelines for the treatment of unresectable advanced or metastatic OSCC.

ASCO 2023 Guidelines *(59)*

First-line:

- For patients with PD-L1 CPS ≥ 10%, pembrolizumab plus fluoropyrimidine- and platinum-based chemotherapy is recommended
- For patients with PD-L1 TPS ≥ 1%, nivolumab plus fluoropyrimidine- and platinum-based chemotherapy or nivolumab plus ipilimumab are recommended
- For patients with low or negative PD-L1 expression status, platinum-fluoropyrimidine is offered first followed by nivolumab.

Second-line:

- A taxane or irinotecan (after nivolumab or pembrolizumab)

NCCN 2023 Guidelines *(8)*

First-line, if not MSI-H/dMMR tumors:

- Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin and nivolumab (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin and pembrolizumab (category 2A for PD-L1 CPS ≥10%; category 2B for PD-L1 CPS < 10%)
- Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin
- Fluoropyrimidine (fluorouracil or capecitabine), cisplatin and nivolumab (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine), cisplatin and pembrolizumab (category 1 for PD-L1 CPS ≥10%; category 2B for PD-L1 CPS < 10%)
- Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin
- Nivolumab and ipilimumab

Second-line treatment:

- Nivolumab if no prior tumour progression while on therapy with a checkpoint inhibitor
- Pembrolizumab, if PD-L1 expression level of CPS of ≥10 if no prior tumour progression while on therapy with a checkpoint inhibitor
- Tislelizumab if no prior tumour progression while on therapy with a checkpoint inhibitor
- Additional second-line treatments include docetaxel, paclitaxel, irinotecan, fluorouracil and irinotecan.

ESMO 2022 Guidelines *(10, 12)*

First-line:

- PD-L1 CPS ≥10: pembrolizumab-chemotherapy
- PD-L1 TPS ≥1: nivolumab – chemotherapy or nivolumab – ipilimumab
- PD-L1 negative/low: chemotherapy

Second-line:

- Taxanes or irinotecan is still the treatment of choice after progression on immunochemotherapy
- If PD-L1 is negative or low then chemotherapy is followed by nivolumab, followed by taxanes and/or irinotecan

Japanese 2023 Guidelines *(60)*

First-line:

- Pembrolizumab + cisplatin + 5-FU therapy
- Nivolumab + cisplatin + 5-FU or nivolumab + ipilimumab or chemotherapy alone; however the patient's general condition, PD-L1 expression (TPS) and treatment tolerability should be taken into account.

Second-line:

- In patients without a history of anti-PD-1 antibody therapy, nivolumab therapy is recommended
- In patients without a history of anti-PD-1 antibody therapy, pembrolizumab therapy may be recommended with a CPS of ≥ 10
- In patients without a history of anti-PD-1 antibody therapy or taxane therapy, paclitaxel therapy may be recommended
- In patients with a history of anti-PD-1 antibody therapy, but no history of taxane therapy, paclitaxel therapy may be recommended

Chinese 2022 Guidelines *(9)*

First-line:

- Pembrolizumab and cisplatin+5-fluoropyrimidine
- Camrelizumab and paclitaxel+cisplatin.
- If immune checkpoint inhibitors are not suitable, chemotherapy only should be considered, including cisplatin+fluorouracil or paclitaxel+platinum.

Second-line:

- For patients who have failed first-line chemotherapy, camrelizumab or tislelizumab may be selected as second-line treatment. Tislelizumab could be the second-line treatment strategy of recommendation for patients with late-stage esophageal cancer after it is approved by CFDA.
- For patients with esophageal squamous cell carcinoma and PD-L1 CPS≥10 who have failed first-line chemotherapy, pembrolizumab monotherapy may be the option of second-line therapy.

Section 10: Summary of available data on comparative cost and cost-effectiveness

A systematic literature review has been conducted to identify published studies that conducted a cost-effectiveness analysis (CEA) or budget impact analysis including tislelizumab. Similar search terms and databases were searched as described earlier. Study types include CEAs, cost-utility analyses and budget impact analyses.

A total of 9 published CEAs were identified. Seven CEAs considered the first-line use of tislelizumab plus chemotherapy versus chemotherapy. Six of these only assessed tislelizumab *(61-66)* and one included multiple PD-1 inhibitors in the analysis.*(67)* Two CEAs looked at the second-line use of tislelizumab monotherapy compared to chemotherapy. One assessed tislelizumab only *(68)* and one considered multiple PD-1 inhibitors, using results of a network meta-analysis as reported in the umbrella SLR.*(50)*

All of the published CEAs were from the perspective of the Chinese health system. Brief details of the studies identified (title name, year, technologies included and line of treatment and results) are presented in Appendix 2.

There was a reasonable level of discrepancy in the CEAs when considering tislelizumab plus chemotherapy as a first-line treatment for unresectable OSCC. In the studies that assessed only tislelizumab, the QALYs gained ranged from 0.328 to 0.48 and the incremental costs ranged from $7,117 to $16,587. The resulting ICERs ranged from $18,846 to $34,699 per QALY gained. *(61-66)*

The CEA by Zhao et al. *(67)* that considered multiple PD-1 inhibitors included all treatment-related costs, including drug costs, drug administration costs, disease management costs and costs for treatment of adverse events, best supportive care and terminal care costs were taken from the Chinese healthcare system perspective. Drug costs were sourced from the Yaozhi database and adjusted to 2023, based on the Chinese consumer price index for healthcare as follows:

- Tislelizumab = $1.95 per mg (range $1.56 – $2.34)
- Camrelizumab = $1.82 per mg (range $1.46 – $2.19)
- Nivolumab = $13.61 per mg (range $10.89 - $16.33)

- Pembrolizumab = $25.35 per mg (range $20.28 - $30.42)
- Serplulimab = $7.91 per mg (range $6.33 – $9.49)
- Sintilimab = $1.53 per mg (range $1.22 – $1.83)
- Toripalimab = $1.46 per mg (range $1.17 - $1.75)

The resultant total costs, life years and QALYs gained for each of the PD-1 inhibitors assessed compared with chemotherapy are summarised in Table 8.

Strategies	Cost	Incr Cost	LYs	Incr LYs	ICER/LYs	QALYs	Incr QALYs	ICER/QALYs
Chemotherapy	13956.26		1.32			0.88		
Camrelizumab plus Chemotherapy	27625.84	13669.58	2.01	0.70	19527.97	1.44	0.55	24853.78
Nivolumab plus Chemotherapy	98516.13	84559.87	2.01	0.69	122550.54	1.34	0.46	183825.80
Pembrolizumab plus Chemotherapy	124439.46	110483.2	1.90	0.58	190488.28	1.31	0.43	256937.67
Serplulimab plus Chemotherapy	77111.41	63155.15	2.14	0.24	263146.46	1.47	0.59	107042.63
Sintilimab plus Chemotherapy	27019.43	13063.17	2.14	0.83	15738.76	1.48	0.60	21771.95
Tislelizumab plus Chemotherapy	27722.32	13766.06	2.04	0.72	19119.53	1.41	0.53	25973.70
Toripalimab plus Chemotherapy	30522.89	16566.63	2.35	1.03	16084.11	1.62	0.73	22694.01

Table 8 - Basic analysis results from Zhao et al.(67)

The authors concluded that "*basic analysis revealed that the incremental cost-effectiveness ratios (ICERs) for camrelizumab, sintilimab, tislelizumab and toripalimab plus chemotherapy versus chemotherapy alone were $24,853.78, $21,771.95, $25,973.70, and $22,694.01/QALY, respectively, all of which were less than 3 times the per capita GDP in China. Sensitivity analysis indicated that the base-case results were robust*."

Generally, in all of the cost-effectiveness analyses identified, the ICERs were most sensitive to the utility values given to the PFS health state and the costs used for tislelizumab and chemotherapies. All authors concluded that tislelizumab plus chemotherapy presented a cost-effective first-line treatment option compared to chemotherapy in the Chinese health system.

When considering tislelizumab versus chemotherapy as a second-line treatment, the incremental QALYs and costs differed, with QALY gains of 0.27 and 0.77 and

incremental costs of $2,917 and $7,371. However, the resulting ICERs of $11,073 and $8,913 per QALY gained were similar, with the latter coming from the network meta-analysis of multiple PD-1 inhibitors. *(50)*

In this analysis, costs were of implementing each treatment was calculated from the perspective of the Chinese healthcare system, including drug acquisition costs, hospitalization expenses, laboratory testing costs, costs of managing adverse events, follow-up costs, best supportive care and end-of-life costs. Drug costs were derived from the average bid-winning price announced by YAOZH (www.yaozh.com) in 2023. All costs were adjusted to US dollars (2022 annual average exchange rate: $1 = ¥6.7261), with average drug costs for the PD-1 inhibitors as follows:

- Tislelizumab (100mg) = $215.58 (range $172.46 - $258.69)
- Camrelizumab (200mg) = $383.08 (range $306.46 - $459.70)
- Nivolumab (100mg) = $1,375.24 (range $1,100.19 - $1,650.29)
- Pembrolizumab (100mg) = $2,663.95 (range $2,131.16 - $3,196.74)
- Sintilimab (100mg) = $160.57 (range $128.45 - $192.68)

The resulting base-case results are summarised in Figure 19.

Strategy	Costs	QALYs	ICER ($/QALY, pairwise comparison)*				
Chemotherapy	5433.86	0.5504	Chemotherapy				
Sintilimab	5939.33	0.6574	4724.46	Sintilimab			
Tislelizumab	7371.44	0.7678	8913.28	12,972.94	Tislelizumab		
Camrelizumab	9050.74	0.8173	13,549.69	19,452.96	33,889.03	Camrelizumab	
Pembrolizumab	40,686.44	0.6811	269,654.18	1,463,422.39	Dominated	Dominated	Pembrolizumab
Nivolumab	50,617.95	0.8151	170,710.46	283,325.20	914,278.66	Dominated	74,143.38

*Other treatment regimes compared with treatment options in the first row.

ICER, incremental cost-effectiveness ratios; QALY, quality-adjusted life years.

Figure 19 - Base-case cost-effectiveness results from Liu et al.(50)

The authors of both reviews of the second-line treatment of OSCC concluded that the ICERs were robust. They suggested that tislelizumab represents a cost-effective option for the second-line treatment of unresectable, advanced or metastatic OSCC in China.

Section 11: Regulatory status, market availability and pharmacopeial standards

First-line regulatory status

- The FDA is reviewing tislelizumab as a first-line treatment of unresectable, locally advanced, or metastatic OSCC. Decision is expected late 2024/early 2025.
- The EMA is reviewing tislelizumab as a first-line treatment of unresectable, locally advanced, or metastatic OSCC. The CHMP adopted a positive opinion, recommending marketing authorisation for "Tevimbra in combination with platinum-based chemotherapy for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a tumour area positivity (TAP) score of ≥ 5%"
- Approval in Thailand received in September 2024: "TEVIMBRA in combination with chemotherapy is indicated for the first-line treatment of patients with unresectable, locally advanced or metastatic esophageal squamous cell carcinoma (ESCC)"
- Approval in China received in May 2023 for "Tislelizumab in combination with platinum-based doublet chemotherapy is indicated for the first-line treatment of patients with unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma".
- Submissions are also under review in Australia, Indonesia, Japan, S Korea, Singapore, Switzerland

Second-line regulatory approvals

- EMA (20 July 2023) authorised tislelizumab (Tevimbra®) as monotherapy for the treatment of adult patients with unresectable, locally advanced or metastatic OSCC after prior platinum-based chemotherapy.
- FDA (14 March 2024): authorised tislelizumab (Tevimbra®) as monotherapy for adults with unresectable or metastatic OSCC after prior systematic chemotherapy that did not include a PD-1 inhibitor.
- Tislelizumab has also been approved in Korea, Switzerland, Australia, UK, Israel, Brazil, Singapore, Thailand, Hong Kong and China for the indication of second-line treatment of OSCC.
- Regulatory submissions for tislelizumab are also under review by authorities in Japan, Malaysia, India and New Zealand for the second-line treatment of OSCC

Market availability

BeiGene's vision is to transform the biotechnology industry by creating impactful medicines that are affordable and accessible to far more cancer patients around the world. Our mission is to build the first next-generation oncology company—one that expands the highest quality therapies to more people globally through courage, persistent innovation, and challenging the status quo. With a geographically diverse, state-of-the-art supply chain and manufacturing facilities operating under GMP standards from the U.S. FDA, China's NMPA, and Europe's EMA, BeiGene is positioned to achieve these ambitious goals.

Our global clinical trials span diverse geographies and patient populations, employing advanced technologies and strategic operations to increase access in previously underserved regions.

BeiGene's commitment to affordability means our medicines are competitively priced, with considerations for middle- and low-income countries, ensuring that more patients worldwide benefit from our high-quality, life-changing treatments.

The company is aware that in addition to testing costs and infrastructure that pathologists may also require training to undertake PD-L1 expression testing. BeiGene is currently partnering with partners in multiple countries in the Asia Pacific region (with a focus on South-East Asia) to increase access to PD-L1 testing.

Patent information

World Intellectual Property Organization (WIPO)：Valid

United States Patent: Valid

European Patent：Valid

Japanese Patent：Valid

Chinese Patent：Valid

Pharmacopeial standards

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

Appendix 1

Summary of SLRs including Tislelizumab for the first- and second-line treatment of unresectable advanced and/or metastatic OSCC

Article Title (author, year)	Technologies included (n = intervention /comparator)	RoB	Outcomes (T+C vs C)
First-line			
Efficacy and Safety of First-line Therapies for Advanced Unresectable Oesophageal Squamous Cell Cancer: a Systematic Review and Network Meta-analysis (Nian, 2023), *(45)* **Total studies identified = 9 RCTs including 4,499 patients**	-Tislelizumab (n=326/323); -Camrelizumab (n= 298/298); -Nivolumab and nivolumab + ipilimumab (n = 321/325/324); -Pembrolizumab (n= 274/274); -Serplulimab (n= 368/183); -Sintilimab (n = 327/332); -Toripalimab (n=257/257); -Capecitabine + paclitaxel or cisplatin (n = 46/48); -Cetuximab or cisplatin (n= 32/30)	Low	All results are pairwise (i.e. Tislelizumab + chemotherapy vs chemotherapy): PFS = 0.62 (95% CI: 0.52, 0.75); ranked 4th OS = 0.66 (95% CI: 0.53, 0.82); ranked 4th Grade 3-5 AEs = 0.91 (95% CI: 0.66, 1.26); ranked 4th ORR = 2.37 (95% CI: 1.73, 3.23); ranked 2nd Subgroup analysis of OS by CPS score (PFS not reported): CPS <10%, HR = 0.77 (95% CI: 0.59, 1.01) CPS ≥10%, HR = 0.62 (95% CI: 0.44, 0.87)
Efficacy and safety evaluation of frontline	-Tislelizumab (n=326/323);	Low	Tislelizumab + chemotherapy vs chemotherapy: PFS = 0.62 (95% CI: 0.52, 0.75); ranked 4th

immunotherapy combinations in advanced esophageal squamous cell carcinoma: a network meta-analysis highlighting the value of PD-L1 expression positivity scores (Chen, 2024), *(46)* **Total studies identified = 7 RCTs, including 4,688 patients**	-Camrelizumab (n= 298/298); -Nivolumab and Nivolumab + Ipilimumab (n= 321/325/324); -Pembrolizumab (n=373/376); -Serplulimab (n= 368/183); -Sintilimab (n=327/332); -Toripalimab (n=257/257)		OS = 0.68 (95% CI: 0.56, 0.82); ranked 3rd AEs = 1.1 (95% CI: 0.8, 1.52); ranked 5th Subgroup analysis by PD-L1 expression ≥10% Pairwise (tisle + chemo vs chemo): PFS HR = 0.50 (95% CI: 0.37, 0.68); ranked 2nd OS HR = 0.62 (95% CI: 0.44, 0.87); ranked 4th Pooled PD-L1 expression ≥10 % (using TAP or CPS method): PFS HR = 0.53 (95% CI: 0.47, 0.60) OS HR = 0.61 (95% CI: 0.53, 0.70) No significant heterogeneity detected.
PD-1 inhibitors in advanced esophageal squamous cell carcinoma: a survival analysis of reconstructed patient-level data (Yan, 2024), *(47)* **Total studies identified = 7 RCTs, including 4,162 patients**	-Tislelizumab (n=326/323); -Camrelizumab (n=298/298); -Nivolumab (n=321/324); -Pembrolizumab (n=274/274); -Serplulimab (n=368/163); -Sintilimab (n=327/332); -Toripalimab (n=257/257)	Low	Tisle + chemo vs chemo: PFS HR = 0.56 (95% CI: 0.48, 0.65) OS HR = 0.62 (95% CI: 0.53, 0.73) “Patients on tislelizumab had a relatively low risk of recurrence and metastasis”
Efficacy and safety of immunochemotherapy, immunotherapy, chemotherapy, and targeted therapy as first-	19 regimens including (mixture of Immunotherapy + chemotherapy and various chemotherapy	Uncle ar	Subgroup analysis for OSCC only: Tisle + FbCT vs FbCT: OS HR = 0.66 (95% CI: 0.54, 0.8) PFS HR = 1.61 (95% CI: 1.34, 1.94)

line treatment for advanced and metastatic esophageal cancer: a systematic review and network meta-analysis (Zhen Gao, 2023), *(48)* **Total studies identified = 17 trials that involved 9,128 patients.**	regimens). Immunotherapies included: -Tislelizumab (n=326/323); -Camrelizumab (n= 298/298); -Nivolumab and Nivolumab + Ipilimumab (n= 321/325/324); -Pembrolizumab (n=373/376); -Sintilimab (n=327/332); -Toripalimab (n=257/257)		Tisle + FbCT vs FfCT: OS HR = 0.67 (95% CI: 0.48, 0.93) PFS HR = 1.65 (95% CI: 1.12, 2.43)
Comparison of Efficacy and Safety of First-Line Chemoimmunotherapy in Advanced Esophageal Squamous Cell Carcinoma: A Systematic Review and Network Meta-Analysis (Xiaolu Ma, 2023), *(49)* **Total studies identified = 6 RCTs, that included 3,611 patients**	-Tislelizumab (n=326/323); -Camrelizumab (n=298/298); -Nivolumab (n=321/324); -Pembrolizumab (n=274/274); -Sintilimab (n=327/323); -Toripalimab (n=257/257)	Unclear	Tislelizumab vs chemo: OS HR = 0.66 (95% CI: 0.54, 0.80); rank 3rd PFS HR = 0.62 (95% CI: 0.52, 0.75); rank 4th Complete response = 62%; rank 2nd Objective tumour response = 73%; rank 2nd Disease control rates = 81%; rank 1st Any TRAEs = 36%; rank 4th ≥grade 3 TRAEs = 44%; rank 3rd IrAEs = 64%; rank 4th ≥ grade 3 irAEs = 82%; rank 5th (note nivolumab and pembrolizumab not included in any AE analyses)
Second-line			
Immune checkpoint inhibitors *versus*	-Tislelizumab (n=256/256);	Low	Tisle vs chemo: PFS HR = 0.83 (95% CI: 0.68, 1.02)

chemotherapy as second-line therapy for advanced oesophageal squamous cell carcinoma: a systematic review and economic evaluation (Liu, 2024), *(50)* **Total studies identified = 5 RCTs involving 2,837 patients**	-Camrelizumab (n=228/220); -Nivolumab (n=210/209); -Pembrolizumab (n=314/314); -Sintilimab (n=95/95)		OS HR = 0.72 (95% CI: 0.58, 0.89) All TRAEs = 0.18 (95% CI: 0.09, 0.32) Grade 3-5 TRAEs = 0.18 (95% CI: 0.12, 0.27)
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 (Leone, 2022), *(51)* **Total of 10 studies identified (5 first-line, n=3,488 and 5 second-line, n=2,197).** Note tislelizumab only included as a second-line treatment and so only these results are reported	-Tislelizumab (n=256/256); -Camrelizumab (n=228/220); -Nivolumab (n=210/209); -Pembrolizumab (n=314/314); -Sintilimab (n=95/95)	Unclear	Pooled results for OS only available (i.e. PD-1 inhibitors vs chemo): All 2nd-line ICI vs chemo, OS = 0.71 (95% CI: 0.65, 0.79) CPS ≥10%, HR = 0.60 (95% CI: 0.51, 0.70) - Note this analysis based on pembrolizumab and tislelizumab only (n = 174 for intervention and n = 150 for comparator arms) CPS < 10%, HR = 0.83 (95% CI: 0.69, 1.00) PFS not reported studies by CPS %
Comparative efficacy and safety of immunotherapy	-Tislelizumab (n=256/256);	Low	Tisle vs chemo: PFS = not reported

for patients with advanced or metastatic esophageal squamous cell carcinoma: a systematic review and network Meta-analysis (Gao, 2022), *(52)* **10 clinical trials (five studies for the first-line treatment and five studies for the second-line treatment) with a total of 5250 patients**	-Cambrelizumab (n=228/220); -Nivolumab (n=210/209); -Pembrolizumab (n=314/314); -Sintilimab (n=95/95) Note tislelizumab only included as a second-line treatment and so only these results are reported		OS = 0.7 (95% CI: 0.57, 0.86) ORR = 2.38 (95% CI: 1.43, 4.02) Grade 3-5 AEs = 0.19 (95% CI: 0.12, 0.28)
PD-1 inhibitors versus chemotherapy as second-line treatment for advanced esophageal squamous cell carcinoma: a meta-analysis (Zhu, 2021), *(53)* **Total studies identified = 5 RCTs, including 1,970 patients**	-Tislelizumab (n=256/256); -Camrelizumab (n=228/20); -Nivolumab (n=210/209); -Pembrolizumab (n=198/203); -Sintilimab (n=95/95)	Low	Tisle vs chemo: OS HR = 0.70 (95% CI: 0.50, 0.97) PFS HR = n/a ORR = 2.00 (95% CI: 0.78, 5.11) TRAEs = 0.60 (95% CI: 0.50, 0.73) Grade 3-5 TRAEs = 0.51 (95% CI: 0.32, 0.83)

Abbreviations: SLR = Systematic Literature Review; RCT = Randomised Controlled Trial; HR = Hazard Ratio; CI = confidence interval; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; TRAE = treatment-related adverse events; irAE = immune-response adverse events; FbCT = 5-FU-based chemotherapy; FfCT = 5-FU-free chemotherapy

Appendix 2

CEAs of tislelizumab for the first- and second-line treatment of unresectable advanced and/or metastatic OSCC

Title (author, year)	Interventions	Results (tislelizumab versus chemotherapy)
First-line		
Cost-effectiveness analysis of immune checkpoint inhibitors for first-line treatment of advanced esophageal squamous cell carcinoma based on fractional polynomial network meta-analysis (Zhao, 2024),*(67)*	Tislelizumab Camrelizumab, Sintilimab, Toripalimab versus chemotherapy alone	A partitioned survival model was established for comparing the cost-effectiveness of immunotherapies plus chemotherapy versus chemotherapy alone. The perspective of the Chinese health system was taken, and a 10-year time horizon with 1-month cycles was used. Clinical data from a network meta-analysis were used as well as data from databases and the published literature. ICERS: Tislelizumab plus chemo vs chemo = $25,973.70 per QALY gained Camrelizumab plus chemo vs chemo = $24,853.78 per QALY gained Sintilimab plus chemo vs chemo alone = $21, 771.95 per QALY gained Toripalimab plus chemo vs chemo = $22,694 per QALY gained. The authors conclude that all ICERs were under the WTP in China and that sensitivity analyses indicated that the base-case results were robust.
Cost-effectiveness analysis of tislelizumab plus chemotherapy as the first-line treatment for advanced or metastatic esophageal squamous cell carcinoma in China (Liu, 2024), *(61)*	Tislelizumab + chemotherapy versus chemotherapy	Partitioned survival model using data from RATIONALE-306, Chinese health system perspective taken: Tislelizumab plus chemotherapy = 0.48 QALYs gained at incremental cost of $16,587.20 versus chemotherapy alone ICER = $34,699.72 per QALY gained Results were sensitive to utilities of PFS and progression of disease. Most cost-effective in people with higher PD-L1 expression status.

First-Line Tislelizumab for Advanced or Metastatic Esophageal Squamous Cell Carcinoma:A Cost-Effectiveness Analysis (Zheng, 2023)*(62)*	Tislelizumab + chemotherapy versus chemotherapy	Partitioned survival model with a time horizon of 10 years from a Chinese perspective. The direct medical costs were collected from the local setting in China. Tislelizumab plus chemotherapy = 0.328 QALYs gained at an incremental cost of $9,833.69 vs chemotherapy alone ICER = $29,980.77 per QALY gained One-way sensitivity analyses did not alter the conclusion that tislelizumab plus chemotherapy is a cost-effective first-line treatment option for OSCC in China.
Cost-Effectiveness Analysis of Tislelizumab Plus Chemotherapy as First-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma in China (Zhou, 2023)*(63)*	Tislelizumab + chemotherapy versus chemotherapy	A partitioned survival model with three states was constructed based on the RATIONALE-306 trial. The time horizon was ten years, with three-week cycles. Direct medical costs were considered from the Chinese health system perspective. Tislelizumab plus chemotherapy = 0.46 QALYs gained at an incremental cost of $9,763.62 vs chemotherapy alone. ICER = $21,062.09/QALY. The utility values of the PFS heath state had the greatest impact on the ICER in one-way sensitivity analyses.
Tislelizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy as First-Line Treatment for Chinese Patients with Advanced Esophageal	Tislelizumab + chemotherapy versus chemotherapy	A Markov model with a 10-year time horizon, using data from the RATIONALE-306 trial was constructed. Tislelizumab + chemo = 0.40 QALY gained at an incremental cost of $7,604 vs chemotherapy alone. ICER = $18,846 per QALY gained.

Squamous Cell Carcinoma: A Cost-Effectiveness Analysis (Lu, 2023)*(64)*		The authors stated that the results were robust to one-way and probabilistic sensitivity analyses, suggesting that tislelizumab is a cost-effective first-line treatment for OSCC in the Chinese healthcare system.
Cost effectiveness analysis of tislelizumab plus chemotherapy in Chinese patients with advanced or metastatic oesophageal squamous cell carcinoma (Zhang, 2024)*(65)*	Tislelizumab + chemotherapy versus chemotherapy	A partitioned survival model was developed using data from the RATIONALE-306 RCT. Costs and utilities were obtained from local databases and published studies. Tislelizumab plus chemo = 0.414 QALYs at an incremental cost of $11,560 versus chemotherapy alone. ICER = $27,896 per QALY gained. The author stated that tislelizumab was a cost-effective option for the health care system in China and that the results of sensitivity analyses were stable.
Cost-effectiveness analysis of tislelizumab plus chemotherapy as the first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma in China (He, 2024)*(66)*	Tislelizumab + chemotherapy versus chemotherapy	A partitioned survival model was developed over a 10-year time horizon from the perspective of the Chinese healthcare system. Costs and utilities were derived from the drug procurement platform and published literature. Tislelizumab + chemotherapy = 0.337 QALYs gained at an incremental cost of $7,117 vs chemotherapy alone. ICER = $21,116.75 per QALY gained. In one-way sensitivity analyses, the ICER was most affected by the cost of oxaliplatin, paclitaxel and tislelizumab and the utility values in the PFS health state. The authors concluded that tislelizumab plus chemotherapy was probably cost-effective compared

		with chemotherapy alone for the first-line treatment of advanced or metastatic OSCC in China.
Second-line		
Immune checkpoint inhibitors *versus* chemotherapy as second-line therapy for advanced oesophageal squamous cell carcinoma: a systematic review and economic evaluation (Liu, 2024)*(50)*	Tislelizumab Camrelizumab Nivolumab Pembrolizumab Sintilimab	A partitioned survival model with 3-week cycles was developed. Direct medical costs and utility values were obtained from public drug bidding databases, clinical trials or published literature. Tislelizumab = 0.7678 QALYs at an incremental cost of $7,371.44 versus chemotherapy alone. ICERs : Tislelizumab vs chemotherapy = $8,913.28 per QALY gained. Camrelizumab vs chemotherapy = $13,549.69 per QALY gained Nivolumab vs chemotherapy = $170,710.46 per QALY gained Pembrolizumab vs chemotherapy = $269,654.18 per QALY gained Sintilimab vs chemotherapy = $4,724.46 per QALY gained
Economic evaluation of tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma in China (Shi, 2022)*(68)*	Tislelizumab versus chemotherapy	A partitioned survival model using the RATIONALE-302 clinical and safety data was developed to assess the cost-effectiveness of tislelizumab versus chemotherapy for the second-line treatment of advanced metastatic OSCC in China. Cost and resource use data were taken from online databases and published studies. Tislelizumab = 0.27 QALYs at an incremental cost of $2,917.06 versus chemotherapy alone. ICER = $11,073.85 per QALY gained.

		The authors concluded that tislelizumab could be a promising cost-effective strategy for the second-line treatment of patients with OSCC compared with chemotherapy in the Chinese setting.

Abbreviations: ICER = Incremental Cost-Effectiveness Ratio; QALY = Quality-Adjusted Life Year

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29 October 2024

The Secretary

Expert Committee on the Selection and Use of Essential Medicines

Medicines Selection, IP and Affordability (MIA)

Department of Health Products Policy and Standards (HPS)

20 Avenue Appia

CH-1211 Geneva 27

Dear Secretary and Expert Committee Members,

RE: Application to add tislelizumab to the WHO Model List of Essential Medicines

The Access to Oncology Medicines Coalition (ATOM) of the Union for International Cancer Control (UICC) submits this letter to support the application for the addition of tislelizumab to the 24th WHO Model List of Essential Medicines (WHO EML).

The Access to Oncology Medicines Coalition (ATOM Coalition) is a global initiative, led by the Union for International Cancer Control (UICC), in collaboration with over 40 partners across the private and civil society sectors. It aims to address the barriers to availability, affordability and appropriate use of oncology medicines in low- and lower-middle income countries (LLMICs). The Coalition was launched on 22 May, 2022 at the side-lines of the World Health Assembly in Geneva and brings together partners from civil society as well as the public and private sectors with expertise in implementing cancer-focused access programmes. The Coalition will focus on increasing access to medicines which are already included on the WHO EML and medicines which are likely candidates to be included in future revisions. One of the objectives of the Coalition is to support the inclusion of essential medicines on to the WHO EML and EMLc, as a crucial first step to increase access and availability.

Esophageal cancer ranks as the seventh most diagnosed and sixth deadliest cancer globally, with esophageal squamous cell carcinoma (OSCC) being its predominant subtype, making up 85-90% of cases. As also mentioned in the application, unlike some cancers where incidence is declining, OSCC rates are projected to rise. Currently, there is no medicine included in the EML for the treatment of OSCC. In this regard, this submission is for adding tislelizumab to the Essential Medicines List (EML) for OSCC in two specific treatment stages: first-line, in combination with chemotherapy for the treatment of adult patients with unresectable, locally advanced, recurrent or metastatic OSCC who are

treatment naïve and as second line, as monotherapy for the treatment of adult patients with unresectable or metastatic OSCC following prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

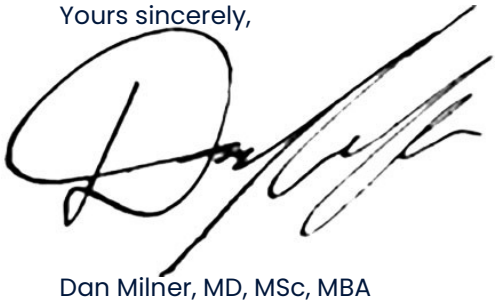
Tislelizumab is also prioritized as a key medicine for the ATOM coalition. Furthermore, immune checkpoint inhibitors are promising for cancer treatments, and we hope they will be included as a class.

Expanding access to essential cancer treatments in underserved regions and creating a sustainable pathway for affordable care is a priority for the ATOM coalition and its partners, including BeiGene. In this regard, the Coalition will be happy to explore the establishment of a robust and comprehensive access pathway with BeiGene to ensure broad, affordable access to tislelizumab in low- and middle-income countries (LMICs).

As the WHO EML serves to help countries prioritise their medicines procurement and is an important tool to ensure access, inclusion of tislelizumab on the list will help towards its increased availability (through inclusion on National Essential Medicines Lists and procurement lists). The addition of tislelizumab to the WHO EML will play a role in the much-needed progress towards achieving sustainable development goal (SDG) 3.4, addressing premature mortality from non-communicable diseases through prevention and treatment. Tislelizumab is available in high-income countries and should be available in resource-constrained settings also, where the burden of cancer is the highest.

We respectfully submit that the addition of tislelizumab to the WHO EML will support the objective of the WHO EML to identify priority medicines that meet the most important and urgent health needs for populations globally.

Yours sincerely,



Dan Milner, MD, MSc, MBA

Executive Director,

The ATOM Coalition