Tislelizumab (Tevimbra®) as monotherapy for the treatment of unresectable, locally advanced, or metastatic oesophageal squamous cell carcinoma (OSCC)

General information [1]

Drug description

The active substance of Tevimbra® is tislelizumab, an antineoplastic agent. Tislelizumab is a humanised IgG4 variant monoclonal antibody that potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Indication

Tislelizumab (Tevimbra®, BGB-A317) as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced, or metastatic OSCC after prior platinum-based chemotherapy.

Incidence [2]

In Austria, in 2020, a total of 480 persons were newly diagnosed with oesophageal cancer.
The age-standardised incidence rate[1] was 9.1 per 100,000 men and 2.0 per 100,000 women.

Current treatment [3]

For the second-line treatment of OSCC, Onkopedia recommends the following:

- Based on data from the ATTRACTION-3 trial, nivolumab is approved for the second-line treatment of advanced OSCC after prior platinum/fluoropyrimidine based combination therapy if no prior checkpoint-inhibitor was administered.
- In ATTRACTION-3 trial, patients with advanced or relapsed OSCC after prior therapy with platinum/fluoropyrimidine-based therapy were randomised either to receive chemotherapy (paclitaxel or docetaxel) vs. nivolumab (240 mg). Approximately 50% of patients had PD-L1-positive carcinomas.
- Regardless from the PD-L1 status, OS was significantly improved in patients receiving immunotherapy (median 10.9 months vs. 8.4 months; HR 0.77, 0.62-0.96, p=0.019). Additionally, there was a higher rate of overall AEs and of grade 3-4 AEs. Premature discontinuation of study treatment was observed in both treatment arms in 9% of patients. After 4 months, there was no disease progression in 30% of patients of both treatment arms. Although the trial was open for patients from Western countries, the majority (96%) of patients were Asian.
- Another phase 3 trial (KEYNOTE-181) was conducted, assessing the PD-1 inhibitor pembrolizumab. More than 60% of patients were not Asian. Patients with squamous cell carcinoma (64%) or adenocarcinoma of the oesophagus (including tumours of the gastro-oesophageal junction) with disease progression after first-line chemotherapy were randomised to receive either chemotherapy (paclitaxel, docetaxel or irinotecan) or pembrolizumab (200 mg fixed dose). Approximately 35% of patients had high levels of PD-L1 (CPS≥10%). ITT-analysis showed no significant difference between both treatment groups. Solely in patients with high levels of PD-L1, immunotherapy led to a significant improvement of OS (median 9.3 vs. 6.7 months, p=0.0074). Furthermore, patients with squamous cell carcinoma showed a trend towards prolongation of OS (median 8.2 vs. 7.1 months). Subgroup analysis showed benefits especially in Asian patients with PD-L1-positive squamous cell cancer. Due to multiple co-primary endpoints, there are difficulties to interpret the trial. In the U.S., pembrolizumab was approved in July 2019 (based on this data); in Europe, this indication is not approved.

Regulatory status

EMA [1]	FDA
Approval status for this indication: On 20 July 2023, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tevimbra®. UPDATE: Marketing authorisation issued on 15/09/2023 The full indication is: ❖ Tevimbra® as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced, or metastatic OSCC after prior platinum-based chemotherapy. Tevimbra is available as a 100 mg concentrate for solution for infusion. **Other indications**: none	**Approval status for this indication**: not approved According to BeiGene, tislelizumab is currently under review by the FDA [4]. UPDATE 01/2024: According to BeiGene, the FDA accepted for review a Biologics License Application (BLA) for tislelizumab as a first-line treatment for patients with unresectable, recurrent, locally advanced, or metastatic ESCC. The FDA also granted tislelizumab Orphan Drug Designation for the treatment of previously untreated advanced or metastatic ESCC [5]. **Other indications**: none

[1] European Standard Population 2013.

✓	**Medicine is under additional monitoring**

Manufacturer

Tevimbra® is manufactured by Novartis Europharm Limited.

For further information regarding the license agreement of Tevimbra®, please see press release [6].

Costs

Currently, there is no cost information available.

Posology

- Tevimbra® treatment must be initiated and supervised by physicians experienced in the treatment of cancer.
- The recommended dose of Tevimbra is 200 mg administered by intravenous infusion once every 3 weeks.
- Patients should be treated with Tevimbra until disease progression or unacceptable toxicity.
- **Method of administration**
  - Tevimbra® is for intravenous use only. It is to be administered as an infusion and must not be administered as an intravenous push or single bolus injection.
  - The first infusion should be administered over a period of 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes. The infusion should be given via an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron inline or add-on filter.

Special warnings and precautions for use [7]

- Traceability
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- Patient Card
  - Patients treated with Tevimbra must be given the Patient Card to be informed about the risks of immune-related adverse reactions during Tevimbra therapy. The prescriber must discuss the risks of immune-related adverse reactions during Tevimbra therapy with the patient.
- Immune-related adverse reactions
  - Immune-related adverse reactions have been reported, including fatal cases, during treatment with tislelizumab. The majority of these events improved with interruption of tislelizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also been reported after the last dose of tislelizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.
  - For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude alternative aetiologies, including infection, should be ensured. Based on the severity of the adverse reaction, tislelizumab should be withheld and corticosteroids administered. Based on limited 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 taper should be initiated and continued over at least 1 month.
  - Immune-related pneumonitis
    - Immune-related pneumonitis, including fatal cases, has been reported in patients receiving tislelizumab. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and infectious or disease-related aetiologies should be ruled out.
    - Patients with immune-related pneumonitis should be managed according to the treatment modifications as recommended in Table 1.
  - Immune-related hepatitis
    - Immune-related hepatitis, including fatal cases, has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of hepatitis and changes in liver function. Liver function tests should be performed at baseline and periodically during treatment. Patients with immune-related hepatitis should be managed according to the treatment modifications as recommended in Product Information.
  - Immune-related skin reactions
    - Immune-related skin rash or dermatitis have been reported in patients receiving tislelizumab. Patients should be monitored for suspected skin reactions and other causes should be excluded. Based on the severity of the skin adverse reactions, tislelizumab should be withheld or permanently discontinued as recommended in Product Information.
    - Cases of severe cutaneous adverse reactions (SCARs) have been reported in patients receiving tislelizumab. Patients should be monitored for signs or symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash) and other causes should be excluded. For suspected SCARs (including severe erythema multiforme [EM], SJS or TEN), tislelizumab should be withheld and the patient should be referred to specialised care for assessment and treatment. If SCARs, including SJS or TEN, is confirmed, tislelizumab should be permanently discontinued.

- Immune-related colitis
  - Immune-related colitis, frequently associated with diarrhoea, has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of colitis. Infectious and disease-related aetiologies should be ruled out. Patients with immune-related colitis should be managed according to the treatment modifications as recommended in Product Information.
- Immune-related endocrinopathies
  - Immune-related endocrinopathies, including thyroid disorders, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, have been reported in patients treated with tislelizumab. These may require supportive treatment depending on the specific endocrine disorder. Long-term hormone replacement therapy (HRT) may be necessary in cases of immune-related endocrinopathies.Patients with immune-related endocrinopathies should be managed according to the treatment modifications as recommended in Product Information.
- Thyroid disorders
  - Thyroid disorders, including thyroiditis, hypothyroidism and hyperthyroidism, have been reported in patients treated with tislelizumab. Patients should be monitored (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) for changes in thyroid function and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with HRT without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically.
- Adrenal insufficiency
  - Adrenal insufficiency has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of adrenal insufficiency. Monitoring of adrenal function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated.
- Hypophysitis
  - Hypophysitis has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of pituitary function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated.
- Type 1 diabetes mellitus
  - Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients treated with tislelizumab. Patients should be monitored for hyperglycaemia and other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes. In patients with severe hyperglycaemia or ketoacidosis (grade ≥3), tislelizumab should be withheld and anti-hyperglycaemic treatment should be administered. Treatment with tislelizumab may be resumed when metabolic control is achieved.
- Immune-related nephritis with renal dysfunction
  - Immune-related nephritis with renal dysfunction has been reported in patients treated with tislelizumab. Patients should be monitored for changes in renal function (elevated serum creatinine), and other causes of renal dysfunction should be excluded.
  - Patients with immune-related nephritis with renal dysfunction should be managed according to the treatment modifications as recommended in Product Information.
- Other immune-related adverse reactions
  - Other clinically important immune-related adverse reactions were reported with tislelizumab: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis and Guillain-Barré syndrome. Patients with other immune-related adverse reactions should be managed according to the treatment modifications as recommended in Product Information.

❖ Solid organ transplant rejection
- Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with tislelizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with tislelizumab versus the risk of possible organ rejection should be considered in these patients.

❖ Infusion-related reactions
- Severe infusion-related reactions (grade 3 or higher) have been reported in patients receiving tislelizumab as a single agent. Patients should be monitored for signs and symptoms of infusion-related reactions. Infusion-related reactions should be managed as recommended in Product Information.

❖ Patients excluded from clinical studies
- Patients with any of the following conditions were excluded from clinical studies: baseline ECOG PS greater than or equal to 2; active brain or leptomeningeal metastases; active autoimmune disease or history of autoimmune disease that may relapse; any condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressants within the 14 days prior to study treatment; active or untreated HIV; untreated hepatitis B or hepatitis C carriers; history of interstitial lung disease; administration of live vaccine within the 14 days prior to study treatment; infection requiring systemic therapy within the 14 daysprior to study treatment; history of severe hypersensitivity to another monoclonal antibody. In the absence of data, tislelizumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

❖ Patients on controlled sodium diet
- Each ml of this medicinal product contains 0.069 mmol (or 1.6 mg) sodium. This medicinal product contains 16 mg sodium per 10 ml vial, equivalent to 0.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Study characteristics [8, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up (I vs. C)	Characteristics	Biomarker	Funding	Publication(s)
RATIONALE-302, BGB-A317-302 NCT03430843	512 (1:1)	tislelizumab IV 200 mg once every 3 weeks	investigator's choice of single-agent chemotherapies: paclitaxel, docetaxel, or irinotecan[2]	OS in the ITT population	8.5 months (0.2-31.7) vs. 5.8 months (0.0 to 30.8)	open-label, randomised, active-controlled, multicentre, phase 3 study	PD-1	BeiGene	RATIONALE-302 [8]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (I vs. C)
❖ Patients aged ≥ 18 years with histologically confirmed diagnosis of OSCC ❖ Tumour progression during or after first-line systemic treatment for advanced unresectable/metastatic OSCC ❖ At least one measurable/evaluable lesion by RECIST v1.1 as determined by local site investigator/radiology assessment within 28 days prior to randomisation ❖ ECOG PS of 0 or 1 prior to randomisation ❖ ANC ≥1500 cells/mm ❖ Platelet count ≥100,000 cells/mm^3 ❖ Haemoglobin ≥9 g/dL or ≥5.6 mmol/L ❖ Estimated GFR ≥ 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation ❖ Serum total bilirubin ≤1.5 x ULN ❖ Prothrombin time/international normalised ratio ≤1.5 x ULN unless the patient is receiving anti-coagulant therapy ❖ AST and ALT ≤ 2.5 x ULN (or ≤ 5.0 x ULN in patients with liver metastases) ❖ HBV or HCV infection and meets the following criteria as applicable to the infection type: For patients with inactive/asymptomatic carrier, chronic, or active HBV: HBV DNA <500 IU/mL (or 2500 copies/mL) at screening. For patients with HCV: Patients with detectable HCV RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study ❖ Females of childbearing potential must have a negative serum pregnancy test within 7 days of randomisation and must be willing to have additional pregnancy tests during the study and must be willing to use highly effective methods of birth control for the duration of	❖ Receipt of ≥2 prior lines of systemic treatments for advanced/ metastatic unresectable OSCC ❖ Palliative radiation treatment for OSCC within 14 days of study treatment initiation ❖ History of gastrointestinal perforation and /or fistula or aorto-oesophageal fistula within 6 months prior to randomisation ❖ Tumour invasion into organs located adjacent to the oesophageal disease site at an increased risk of fistula in the study treatment assessed by investigator ❖ Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage (recurrence within 2 weeks of intervention) ❖ Current or past history of severe hypersensitivity reactions to other humanised monoclonal antibodies ❖ Received prior therapies targeting PD-1 or PD-L1 ❖ Has toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk ❖ Prior malignancy active within the previous 2 years before randomisation ❖ Active brain or leptomeningeal metastasis ❖ Has active autoimmune disease or history of autoimmune diseases at high risk for relapse ❖ Has a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days prior to randomisation ❖ Patients who have a history of organ transplant, including stem cell allograft are not permitted to enrol ❖ Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids ❖ Undergone surgery requiring general anaesthesia or epidural anaesthesia within 28 days prior to randomisation ❖ Undergone surgery involving local anaesthesia within 14 days prior to randomisation ❖ Received any radiopharmaceuticals ❖ Has received any chemotherapy, any immunotherapy or any investigational therapies, any Chinese herbal medicine or Chinese patent medicines used to control cancer or boost immunity	❖ Median age: 62.0 years (range, 40-86) vs. 63.0 years (range, 35-81) ❖ Male sex: 84.8% vs. 84.0% ❖ ECOG PS: • 0: 25.8% vs. 23.4% • 1: 74.2% vs. 76.6% ❖ PD-L1 expression: • TAP ≥ 10%: 34.8% vs. 26.6% • TAP < 10%: 45.3% vs. 54.7% • Unknown: 19.9% vs. 18.8% ❖ Smoking status: • Never: 26.6% vs. 24.6% • Former/current: 73.4% vs. 75.0% • Missing: 0.0% vs. 0.4% ❖ Previous therapies: • Surgery: 36.7% vs. 38.7% • Radiotherapy: 66.0% vs. 63.7% • Platinum-based chemotherapy: 97.3% vs. 98.4% ❖ Disease stage at study entry: • Locally advanced: 2.0% vs. 7.8% • Metastatic: 98.0% vs. 92.2%

[2] Paclitaxel was administered as 135-175 mg/m^2 IV once every 3 weeks, or in doses of 80-100 mg/m^2 once weekly as per regional guidelines. In Japan, paclitaxel was administered as 100 mg/m^2 IV in cycles consisting of once weekly dosing for 6 weeks, followed by one week of rest. Docetaxel was administered as 75 mg/m^2 IV once every 3 weeks (70 mg/m^2 IV once every 3 weeks in Japan). Irinotecan 125 mg/m^2 IV was administered on days 1 and 8, every 21 days. Stratified randomisation was used and was stratified by region (Asia, excluding Japan vs. Japan vs. Europe/North America), ECOG PS (0 v 1), and investigator-chosen chemotherapy (paclitaxel vs. docetaxel vs. irinotecan).

[3] For detailed in- and exclusion criteria, please see trial protocol.

the study, and for at least 120 days after the last dose of tislelizumab and 180 days after the last dose of ICC ❖ Non-sterile males who have female sexual partner(s) of childbearing potential must use highly effective form of birth control for the duration of the study, and for at least 120 days after the last dose of tislelizumab and 180 days after the last dose of ICC	❖ Any serious or unstable pre-existing medical conditions, psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures ❖ Known history of, or any evidence of interstitial lung disease, non-infectious pneumonitis, pulmonary fibrosis diagnosed based on imaging or clinical findings, or uncontrolled systemic diseases ❖ Has severe chronic or active infection requiring systemic antibacterial, antifungal or antiviral therapy, within 14 days prior to Cycle 1 Day 1 ❖ Known history of HIV ❖ Cardiovascular risk factors (please see trial protocol) ❖ Severe malnutrition despite enteral or parenteral nutritional supplementation ❖ Known, active alcohol or drug abuse or dependence ❖ Pregnant or breastfeeding woman	

Efficacy (I vs. C)	**Safety** (I vs. C)
Data cutoff 1 December 2020 (median follow-up 8.5 months vs. 5.8 months): **Death**: 77.0% vs. 83.2% **Median OS**: 8.6 months (95% CI, 7.5-10.4) vs. 6.3 months (95% CI, 5.3-7.0); HR for death 0.70, 95% CI, 0.57-0.85; one-sided p=0.0001 **12-month OS rate**: 37.4% (95% CI, 31.4-43.4) vs. 23.7% (95% CI, 18.5-29.3) **Patients who received anti–PD-1 or anti–PD-L1 therapy after discontinuation of study treatment**: 4.3% vs. 21.5% **Median OS in patients with TAP ≥10%:** 10.3 months (95% CI, 8.5-16.1) vs. 6.8 months (95% CI, 4.1-8.3); HR 0.54; 95%CI, 0.36-0.79; one-sided p=0.0006 Survival benefits also in patients with **TAP <10%** (HR 0.82; 95%CI, 0.62 to 1.09) and **TAP unknown** (H, 0.67; 95% CI, 0.41-1.12) Patients who **had disease progression or died at data cutoff**: 87.1% vs. 70.3% **Median PFS:** 1.6 months (95% CI, 1.4-2.7) vs. 2.1 months (95% CI, 1.5-2.7); HR 0.83; 95% CI, 0.67-1.01 **Estimated PFS rates at 6 months**: 21.7% vs. 14.9% **Estimated PFS rates at 12 months:** 12.7% vs. 1.9% Patients who achieved an **objective response**: 20.3% (95% CI, 15.6-25.8) vs. 9.8% (95% CI, 6.4-14.1) Patients with a **complete response**: 2.0% vs. 0.4% **Median duration of response**: 7.1 months (95% CI, 4.1-11.3) vs. 4.0 months (95% CI, 2.1-8.2)	**TRAEs:** 73.3% vs. 93.8% **TRAEs grade ≥3:** 18.8% vs. 55.8% **Serious TRAEs:** 14.1% vs. 19.6% **Discontinued due to TRAEs:** 6.7% vs. 13.8% **Death due to disease progression:** 59.8% vs. 66.0% **Deaths attributed to TRAEs:** 2.0% vs. 2.9%

Patient-reported outcomes (PROs) [10]

Completion rates:

- For the QLQ-C30, QLQ-OES18, and EQ-5D-5L, the adjusted completion rate at baseline was ≥93.8% across all assessments.
- At week 12, the completion rate for all PRO instruments dropped to 57% vs. 30%. At week 18, the completion rate for all PRO instruments continued to decline to 39% vs.15%.
- The adjusted completion rates remained >90% for both arms at week 12 and week 18.

EORTC QLQ-C30

- Results from the mixed-effect model for repeated measurements indicated that the tislelizumab-treated patients maintained QLQ-C30 GHS/QoL scale scores at both week 12 (LS mean change: 0.0; 95% CI, -2.5 to 2.4) and week 18 (LS mean change: -0.8; 95% CI, -3.5 to 2.0), whereas the ICC arm experienced worsening at both week 12 (LS mean change: -5.8; 95% CI, -8.8 to -2.8) and week 18 (LS mean change: -8.9; 95% CI, -12.8 to -4.9)
- There was a difference in change from baseline between the two arms at week 12 (difference in LS mean change: 5.8; 95% CI, 2.0 to 9.5, p= 0.0028) and week 18 (difference in LS mean change: 8.1; 95% CI, 3.4 to 12.8, p= 0.0008)
- There were no differences in change from baseline between the arms at week 12 in physical functioning (difference in LS mean change: 2.6; 95% CI, -0.07 to 6.0, p=0.1266); however, at week 18 the reduction in physical functioning from baseline was less in the tislelizumab arm (LS mean change: -4.6; 95% CI, -7.1 to -2.1) compared with the ICC arm (LS mean change: -8.9; 95% CI, -12.1 to -5.6) and there was a difference in decline (difference in LS mean change: 4.2; 95% CI, 0.4 to 8.1, p= 0.0327).
- Finally, fatigue symptoms worsened at week 12 for both the tislelizumab arm (LS mean change: 3.5; 95% CI, 0.4 to 6.6) and the ICC arm (LS mean change: 11.3; 95% CI, 7.5 to 15.1) and remained consistent at week 18 for the tislelizumab arm (LS mean change: 1.0; 95% CI, -2.1 to 4.2) while continuing to increase for the ICC arm (LS mean change: 6.4; 95% CI, 2.0 to 10.9)

- The worsening of fatigue was less in the tislelizumab arm at week 12 (difference in LS mean change: -7.8; 95% CI, -12.6 to -3.1, p=0.0014) and week 18 (difference in LS mean change: -5.4; 95% CI: -10.5 to -0.3, p=0.0379).

EORTC QLQ-OES18

- Results from the mixed-effect model for repeated measurements indicated that the QLQ-OES18 symptom index scale scores in the tislelizumab arm were maintained at both week 12 (LS mean change: 0.9; 95% CI, -0.7 to 2.5) and week 18 (LS mean change: 0.3; 95% CI, -1.4 to 2.0), whereas the ICC arm experienced worsening at both week 12 (LS mean change: 3.0; 95% CI, 1.0-5.1) and week 18 (LS mean change: 3.0; 95% CI, 0.6-5.5).
- There was no difference in change from baseline, however, between the two arms at either week 12 (difference in LS mean change: -2.1; 95% CI, -4.6 to 0.4, p=0.0929) or week 18 (difference in LS mean change: -2.7; 95% CI, -5.6 to 0.2, p=0.0678)
- Dysphagia symptoms at week 12 worsened less in the tislelizumab arm (LS mean change: 2.7; 95% CI, -1.7 to 7.1) than in the ICC arm (LS mean change: 7.7; 95% CI, 2.2 to 13.2); however, there was no significant difference between the two arms (difference in LS mean change: -4.9; 95% CI; -11.8 to 1.9, p=0.1581)
- At week 18, the tislelizumab arm (LS mean change: 1.6; 95% CI, -3.5 to 6.6) and the ICC arm (LS mean change: 1.9; 95% CI, -5.5 to 9.2) also experienced similar changes from baseline in dysphagia symptoms, and there was no significant difference between the arms (difference in LS mean change: -0.3; 95% CI, -9.1 to 8.5, p=0.9528)
- With regards to eating symptoms, patients in the tislelizumab arm maintained their scores at week 12 (LS mean change: 0.0; 95% CI, -2.8 to 2.8), whereas the ICC arm experienced worsening in problems with eating (LS mean change: 2.7; 95% CI, -0.8 to 6.2); however, there was no significant difference between the arms (difference in LS mean change: -2.7 ; 95% CI, -7.0 to 1.6, p=0.2218)
- At week 18, there was a difference change from baseline in eating problems (difference in LS mean change -5.2; 95% CI, -10.3 to 0.0, p=0.0487), with the tislelizumab arm experiencing fewer eating problems than at baseline (LS mean change: -0.5; 95% CI, -3.6 to 2.6) compared with the ICC arm (LS mean change: 4.7; 95% CI, 0.3 to 9.1)
- For reflux symptoms at week 12, there was a difference in change from baseline (difference in LS mean change: -4.1; 95% CI, -7.6 to -0.6, p=0.0229) with the tislelizumab arm experiencing fewer reflux symptoms than at baseline (LS mean change: -2.3; 95% CI, -4.6 to -0.1) compared with the ICC arm which experienced a worsening in reflux symptoms (LS mean change: 1.8; 95% CI, -1.1 to 4.7)
- At week 18, both arms experienced similar slight reduction from baseline in reflux symptoms, but the differences in change between the two arms was not significant (difference in LS mean change: -0.6; 95% CI, 5.7 to 4.5, p=0.8034)
- Finally, for pain symptoms, tislelizumab-treated patients consistently maintained their scores at both week 12 (LS mean change: -1.6; 95% CI, -3.4 to 0.2) and week 18 (LS mean change: -1.4; 95% CI, -3.9 to 1.0) as did the chemotherapy-treated patients at both week 12 (LS mean change: -1.1; 95% CI, -3.6 to 1.3) and week 18 (LS mean change: 0.2; 95% CI, -3.6 to 4.1)
- There were no significant differences, however, in change from baseline between the two arms at either week 12 (difference in LS mean change: -0.5; 95% CI, -3.4 to 2.5, p=0.7660) or week 18 (difference in LS mean change: -1.7; 95% CI, -6.1 to 2.8, p=0.4573)

EQ-5D-5L

- According to the EQ-5D-5L at week 12, the tislelizumab arm experienced less of a decrease in health status according to the VAS score of the EQ-5D-5L (mean change: 0.2 vs. -1.8)
- At week 18, the tislelizumab arm continued to experience less decline in health status (mean change: -0.6 vs. -5.9)

TTD

- The stratified HR (95% CI) showed that risk of experiencing a deterioration event was lower for the patients in the tislelizumab arm in comparison with the ICC arm for physical functioning (0.67; 95% CI, 0.45-1.00, p=0.0239) and reflux (0.50; 95% CI, 0.32-0.80, p=0.0014)
- There were no differences in the risk of deterioration for the GHS/QoL scale for the dysphagia, eating, and pain symptoms between the two arms

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS: +2.3 months	0.70 (0.57-0.85)	HR ≤0.65 AND gain ≥2.0-<3 months	3	-	Improvement in I vs. C[4]	+1[5]	4
Adapted	NC	2a	≤12 months	OS: +2.3 months	0.70 (0.57-0.85)	HR >0.65-0.70 AND gain ≥1.5 months	2	-37% TRAEs ≥ grade 3	-	+1[6]	3

Risk of bias (RCT) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**

[4] Differences were not statistically significant.
[5] Upgrade due to improvement of QoL.
[6] Upgrade due to 37% less TRAEs ≥ grade 3.

unclear[7] unclear risk	-	no[8] high risk	yes low risk	yes[9] high risk	High risk

Ongoing trials [13]

NCT number/trial name	Description	Estimated study completion date
NCT03957590	A phase 3, randomised, double-blind, placebo-controlled study of tislelizumab (BGB-A317) vs. placebo in combination with concurrent chemoradiotherapy in patients with localized OSCC	12/2024
NCT05919030/ RENMIN-236	Chemoradiation vs. chemotherapy in combination with tislelizumab as first-line treatment for advanced OSCC with low PD-L1 expression: multicentre, randomised, phase 3 trial	07/2027
NCT04973306/ iCROSS	Neoadjuvant immunotherapy combined with chemoradiotherapy vs. neoadjuvant chemoradiotherapy for locally advanced resectable OSCC (cII-III stage): a multicentre prospective randomised clinical trial	07/2027

Available assessments

- In October 2021, NIHR published a Health Technology Briefing "Tislelizumab for oesophageal cancer – second line" [14].
- No further assessments were identified.

Other aspects and conclusions

- In July 2023, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Tevimbra® as monotherapy for the treatment of adult patients with unresectable, locally advanced, or metastatic OSCC after prior platinum-based chemotherapy. Marketing authorisation was issued on 15 September 2023. This indication is **not approved**, but currently under review **by the FDA**.
- **RATIONALE-302 study (NCT03430843)** is an open-label, randomised, phase 3 clinical study evaluating tislelizumab vs. chemotherapy as second-line treatment for advanced or metastatic ESCC. Eligible patients were adults with histologically confirmed ESCC who had advanced or metastatic disease that progressed after first-line systemic treatment. Patients who had tumour progression within 6 months after definitive chemoradiotherapy, neoadjuvant, or adjuvant therapy were also eligible; patients were required to have an ECOG PS of 0 or 1, at least one measurable/evaluable lesion by RECIST v1.1, and adequate hematologic, hepatic, renal, and coagulation function. Exclusion criteria included patients who had received prior therapies targeting PD-1 or PD-L1, active brain or leptomeningeal metastasis, active autoimmune disease, or other prior malignancies active within 2 years before random assignment.
- The **primary endpoint** was **OS in all patients**. Final analysis showed that **OS was significantly longer** with tislelizumab vs. chemotherapy in all patients (median, 8.6 vs 6.3 months; HR 0.70; 95% CI, 0.57-0.85; one-sided p=0.0001).
- Analysis of **patient-reported outcomes** showed that HRQoL, including fatigue symptoms and physical functioning, was **maintained i**n patients with advanced or metastatic ESCC receiving tislelizumab compared with patients who received chemotherapy.
- The original and adapted **ESMO-MCBS** was applied and resulted in a **final adjusted clinical benefit grade of 4 and 3,** respectively.
- The **risk of bias** of RATIONALE-302 was considered **high,** it increased due to the lacking information about the randomisation process, the open-label design of the trial and its industry-funded background.
- **3 ongoing phase 3 trials**, assessing the efficacy and safety of tislelizumab in patients with OSCC, were identified via ClinicalTrials.gov.
- To confirm the promising results of the RATIONALE-302 trial, more phase 3 data (gained from double-blind trials) is required.

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Abbreviations: AE=adverse event, AJ=adjustment, ANC=absolute neutrophil count, ALT=alanine aminotransferase, AST=aspartate transaminase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CPS=combined positive score, DNA=deoxyribonucleic acid, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EORTC-QLQ-C30= Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items, EQ-5D-5L= EuroQoL Five-Dimensions Five-Levels ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GFR=glomerular filtration rate, GHS=global health status, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HR=hazard ratio, HRQoL= health-related quality of life, I=intervention, ICC=investigator-chosen chemotherapy Int.=intention, ITT=intention-to-treat, IV=intravenous, LS=least square, MG=median gain, n=number of patients, NIHR=National Institute for Health Research, OSCC= oesophageal squamous cell carcinoma, OS=overall survival, PD-1= programmed cell death protein 1, PD-L1= programmed death-ligand 1 , PD-L2= programmed death-ligand 2, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QLQ-OES18=Quality of Life Questionnaire Oesophageal Cancer Module 18 items, QoL=quality of life, RNA=ribonucleic acid, SAE=serious adverse event, ST=standard treatment, TAP=tumour abnormal protein, TRAE=treatment-related adverse event, TTD=time to deterioration, ULN=upper limit of normal, VAS=visual analogue scale

[7] No information was found regarding the randomisation process.
[8] Open-label trial.
[9] Industry-funded.

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