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Review Article

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Assessment of Efficacy and Safety of Tislelizumab for Esophageal Squamous Cell Carcinoma

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Abstract

Background: Esophageal Squamous Cell Carcinoma (ESCC) is a highly aggressive tumor with limited treatment options and poor global survival rates. The advent of immune checkpoint inhibitors has reshaped therapeutic strategies, with tislelizumab, a humanized PD-1 inhibitor engineered to minimize Fcγ receptor binding, emerging as a promising agent.

Methods: A literature search was performed using PubMed, Embase, Web of Science and ClinicalTrials.gov up to September 2025. Peer-reviewed articles, randomized controlled trials, prospective and retrospective cohort studies, pooled safety analyses, pharmacokinetic reports and real-world studies reporting on tislelizumab in ESCC were included. Abstracts from major oncology congresses (ASCO, ESMO, CSCO) were also reviewed. Evidence was systematically extracted and synthesized to evaluate pharmacologic properties, efficacy outcomes, safety and tolerability, patient-reported outcomes, as well as ongoing investigational trials. Economic analyses and cost-effectiveness reports were screened but summarized separately.

Results: In the second-line setting, tislelizumab monotherapy has demonstrated superior overall survival and a more favorable safety profile compared with chemotherapy, establishing it as a validated treatment option. In the first-line setting, the addition of tislelizumab to platinum–fluoropyrimidine chemotherapy significantly improves overall survival, progression-free survival and objective response rates, with benefits observed across most subgroups. Patient-reported outcomes indicate slower deterioration in global health status and physical functioning compared with chemotherapy alone. Preliminary studies in the neoadjuvant and perioperative settings show promising pathological responses, although long-term survival data are still awaited. Pharmacokinetic and exposure–response analyses support a fixed 200 mg intravenous dose every three weeks, with low immunogenicity and no routine need for dose adjustments in patients with mild-to-moderate hepatic or renal impairment. Safety analyses confirm that tislelizumab is generally well tolerated, with immune-related adverse events manageable through established treatment algorithms.

Conclusion: Tislelizumab has established itself as an effective and tolerable treatment for ESCC, improving both survival outcomes and quality of life of patients. While uncertainties remain regarding biomarker refinement, optimal sequencing and cost-effectiveness outside of China, the current evidence supports tislelizumab as a key component of the evolving treatment paradigm for ESCC underscoring the need for further trials to expand its role in earlier disease stages and broader patient populations. Additionally. generalizability outside Asia remains uncertain due to differences in drug pricing, healthcare access and limited head-to-head data against other PD-1 inhibitors.

Keywords: Tislelizumab, Esophageal squamous cell carcinoma, Malignancies, Cancer, Efficacy, Safety, Tolerability, Cost analysis

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Introduction

Esophageal Squamous Cell Carcinoma (ESCC) is one of the most aggressive malignancies worldwide, contributing substantially to the global cancer burden. According to GLOBOCAN 2020 data, esophageal cancer ranks as the seventh most common cancer and the sixth leading cause of cancer-related death, with ESCC being the predominant histological subtype in Asia and other high-incidence regions [1].

Despite the application of multimodal treatment approaches, including chemotherapy, radiotherapy and surgery, the prognosis for patients with advanced or metastatic ESCC remains poor, with median Overall Survival (OS) generally less than one year [2,3]. Standard chemotherapy regimens often provide limited and short-term benefit and recurrence following definitive chemoradiotherapy is frequent [4,5]. These limitations underscore the need for novel therapeutic approaches.

The introduction of Immune Checkpoint Inhibitors (ICIs) has revolutionized cancer therapy across multiple tumor types. ESCC is characterized by frequent PD-L1 expression and an immunosuppressive tumor microenvironment, supporting the rationale for PD-1–targeted therapy [3,5]. Tislelizumab, a humanized IgG4 monoclonal antibody against PD-1, has emerged as one of the most promising agents in this setting.

The RATIONALE 302 trial demonstrated that tislelizumab significantly improved OS compared with chemotherapy in the second-line treatment of advanced ESCC, leading to its approval and incorporation into clinical practice [5,6]. Furthermore, tislelizumab is now being studied in the first-line metastatic setting, where combinations with chemotherapy have shown encouraging results [3,4]. Pooled analyses have also supported its favorable safety and tolerability profile, with immune-related adverse events being manageable [7].

Beyond clinical outcomes, several pharmacoeconomic evaluations have reported that tislelizumab is a cost-effective alternative to chemotherapy in various healthcare systems [8-10]. This strengthens the case for its widespread adoption. Approval and access vary globally, with availability currently more limited outside Asia.

This review aims to provide a comprehensive and integrated analysis of current evidence regarding the pharmacology, clinical efficacy, safety and cost-effectiveness of tislelizumab in ESCC. The geographic distribution and survival outcomes of ESCC are summarized in Table 1, with the highest prevalence in Asia.

Region	Proportion of ESCC cases (%)	5-year survival (advanced stage)
China [2]	~50–55% of global cases	<15%
East Asia [3]	70–80% of regional EC cases	<20%
Europe/North America [1]	<20%	15–25% (mostly adenocarcinoma)
Global total [1]	~85% ESCC, 15% adenocarcinoma	<20% (metastatic ESCC)

Table 1: Global epidemiology and outcomes of esophageal squamous cell carcinoma (ESCC).

Mechanism of Action and Clinical Pharmacology of Tislelizumab

Mechanism of action

Tislelizumab is a humanized IgG4 monoclonal antibody that targets the programmed cell death protein-1 (PD-1) receptor. Tislelizumab restores effector T-cell function and promotes anti-tumor immunity by inhibiting PD-1 interaction with its ligands, PD-L1 and PD-L2, which are commonly overexpressed in ESCC tumor microenvironments [3,5]. Figure 1 illustrates tislelizumab's PD-1/PD-L1 blockade and its Fc-engineered mechanism.

Unlike traditional PD-1 antibodies, tislelizumab has an engineered Fc region that reduces Fcγ receptor binding. This reduces macrophages' antibody-dependent phagocytosis of activated T cells, improving immune response durability [3,11]. Although engineered to minimize Fcγ receptor binding, the extent of clinical benefit of this modification compared to other PD-1 inhibitors is uncertain. [3,11].

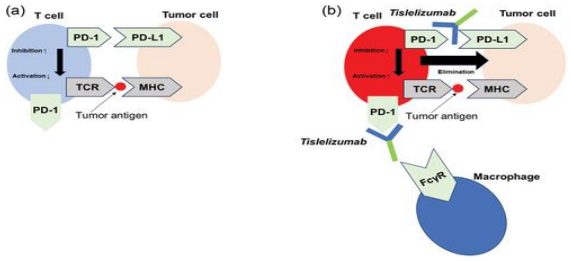

Figure 1: Reproduced from Shiraishi K. et al. Tislelizumab Mechanism of Action in Antitumor activity [12].

Absorption and administration

Tislelizumab is a therapeutic monoclonal antibody that is administered intravenously, eliminating the risk of gastrointestinal absorption. In clinical trials, the recommended regimen was 200 mg IV every three weeks, infused over 30-60 minutes [3,5]. This fixed-dose schedule was supported by pharmacokinetic modeling, which demonstrated consistent exposure across body weight ranges, eliminating the need for weight-based dosing [11]. The key pharmacological characteristics are summarized in Table 2.

Distribution

Tislelizumab has a small volume of distribution, indicating that it is confined to plasma and extracellular fluid compartments, as are other IgG monoclonal antibodies [11]. Population pharmacokinetic (PopPK) analyses show that distribution varies little across demographic groups, implying that the method is applicable to a wide range of ESCC populations [4].

Metabolism and elimination

Tislelizumab is proteolytically degraded into amino acids and peptides in a manner similar to endogenous immunoglobulins [11]. It does not rely on hepatic cytochrome P450 metabolism, which lowers the possibility of metabolic drug–drug interactions. The terminal half-life is approximately 13-17 days, allowing for three-week dosing intervals [3,5].

Elimination occurs *via* systemic catabolic pathways, with a clearance rate of about 0.2–0.3 L/day. Importantly, renal or hepatic

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impairment, sex, age and body weight have no significant effect on clearance [4,11].

Dose Linearity and Population PK Models

Clinical pharmacology studies have shown that pharmacokinetics is linear and dose-proportional over the studied dose range (2–10 mg/kg) [11]. Tislelizumab pharmacokinetics are best described using a two-compartment population PK model with linear elimination. PopPK analyses show that covariates such as ECOG status, tumor type, sex, or body weight have no clinically significant effect on drug disposition [4,11].

Immunogenicity

Tislelizumab has a low incidence of anti-drug antibodies (ADAs) in clinical trials (<2%). Moreover, ADA formation does not seem to affect impact clearance, safety, or efficacy [7]. Because of its low immunogenicity, it is an excellent choice for long-term treatment of ESCC.

Drug–drug interactions

Tislelizumab is not metabolized by cytochrome P450 enzymes, so pharmacokinetic drug-drug interactions are unlikely [11]. Co-administration with chemotherapy agents in combination regimens did not alter exposure or clearance, supporting its use in multimodal treatment strategies [3].

Exposure–response relationship

According to exposure–response modeling, higher trough concentrations of tislelizumab are associated with more complete PD-1 receptor occupancy, increased T-cell activity and better clinical outcomes [11]. However, a plateau effect is observed beyond a threshold exposure, indicating that the 200 mg Q3W fixed-dose regimen is sufficient for maximum efficacy. Notably, increased exposure is not associated with an increase in immune-related adverse events, indicating a favorable therapeutic index [3,5]. Table 2 summarizes the key pharmacological properties of tislelizumab, such as its distribution, metabolism and immunogenicity.

Parameter	Findings
Route [3,5]	IV infusion, 200 mg Q3W
Distribution [11]	Confined to plasma & extracellular fluid
Metabolism [11]	Proteolytic catabolism, not CYP450 dependent
Elimination half-life [3,5]	13–17 days
Clearance [4,11]	~0.2–0.3 L/day; not affected by renal/hepatic function, age, or sex
Dose proportionality [11]	Linear PK (2–10 mg/kg range)
Population PK [4,11]	Two-compartment linear model; minimal covariate effects
Immunogenicity [7]	ADA incidence <2%; no effect on PK/efficacy
Drug–drug interactions [3]	Minimal; safe in combinations
Exposure–response [5,11]	Higher trough → better PD-1 occupancy; plateau effect at therapeutic doses

Table 2: Pharmacological Profile of Tislelizumab in ESCC.

Clinical Efficacy of Tislelizumab in Esophageal Squamous Cell Carcinoma

Overview

Esophageal Squamous Cell Carcinoma (ESCC) has traditionally been associated with a poor prognosis, particularly in the advanced and metastatic stages. Standard treatment paradigms relied on chemotherapy, which had limited survival benefit. The development of immune checkpoint inhibitors (ICIs) that target the PD-1/PD-L1 axis has altered the therapeutic landscape. Tislelizumab has emerged as one of the most extensively studied PD-1 inhibitors in ESCC, with efficacy shown in first-line, second-line, neoadjuvant and combination therapy settings [3-5]. It is important to note that nivolumab, pembrolizumab, camrelizumab and sintilimab have all demonstrated activity in ESCC and tislelizumab is one of several effective PD-1 inhibitors rather than a single global standard.

Tislelizumab in second-line therapy

RATIONALE-302 (Phase III)

Tislelizumab was first approved as a second-line option in ESCC in the global randomized Phase-III RATIONALE-302 study (NCT03430843). In the full intent-to-treat population, tislelizumab monotherapy significantly improved overall survival compared to investigator-chosen chemotherapy (median OS roughly 8.6 *vs* 6.3 months; Hazard Ratio (HR) ≈ 0.70), with higher objective response rates and more durable responses (longer median duration of response) [5,13,14].

The pivotal RATIONALE-302 trial compared tislelizumab to investigator's choice chemotherapy (paclitaxel, docetaxel, or irinotecan) in previously treated advanced or metastatic ESCC, with the clinical efficacy being compared as follows:

- **Primary endpoint:** Overall Survival (OS).
- **Results:** Tislelizumab significantly improved OS (median 8.6 months *vs*. 6.3 months; HR ~0.70) [5]. (HR= Hazard Ratio)
- **1-year OS rate:** 37% with tislelizumab *vs*. 23% with chemotherapy.
- **Subgroup analyses:** Benefits were consistent across PD-L1 subgroups, geographic regions and baseline characteristics.
- **Safety:** Fewer grade ≥3 adverse events (46% *vs*. 68%) with tislelizumab.

RATIONALE-302 established tislelizumab as a second-line standard by showing superior survival compared to chemotherapy, with consistent benefits across subgroups.

Tislelizumab in first-line therapy

RATIONALE-306 (Phase III)

RATIONALE-306 evaluated tislelizumab + chemotherapy (platinum + fluoropyrimidine) versus chemotherapy alone in previously untreated advanced ESCC.

- **Primary endpoint:** Overall Survival (OS).
- **Results:** Combination significantly improved OS (median 17.2 months *vs*. 10.6 months; HR 0.70) [4].
- **PFS (Progression-Free Survival):** Improved with tislelizumab (median 7.3 months *vs*. 5.6 months).

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- **Response rates:** Objective Response Rate (ORR) of 63% with tislelizumab-chemotherapy *vs*. 42% with chemotherapy alone
- **Subgroups:** Benefit observed irrespective of PD-L1 status.

The RATIONALE-306 trial demonstrated that first-line tislelizumab plus chemotherapy significantly improved survival in advanced or metastatic ESCC, establishing this approach as a new standard of care [15]. As a result, for unresectable/advanced ESCC, randomized phase-3 evidence supports first-line tislelizumab combined with chemotherapy as an effective option that improves Progression-Free Survival (PFS) and Overall Survival (OS) while also preserving quality of life; multiple country-level economic models suggest it can be cost-effective under typical Chinese thresholds, though results depending on cost and modelling choices [3,16-18].

Tislelizumab as neoadjuvant therapy

Several early-phase studies have evaluated tislelizumab in the neoadjuvant setting for locally advanced resectable ESCC.

- Tislelizumab in combination with chemotherapy or chemoradiotherapy resulted in high pathological Complete Response (pCR) rates, with pCR of 18–30% and Major Pathological Response (MPR) rates exceeding 40% [3].
- Safety: Immune-related toxicity was manageable, with no significant increase in surgical delays or complications reported.

These findings support ongoing phase II/III trials exploring tislelizumab as part of multimodal treatment.

Combination Therapy Strategies

Tislelizumab is increasingly being explored in combination regimens to enhance outcomes in esophageal and gastric cancers [7,16,19,20].

With chemotherapy

- In both first- and second-line settings, tislelizumab has shown synergistic effects with chemotherapy, improving tumor response rates and delaying progression [4].
- Toxicity profiles were manageable, with no unexpected adverse events compared to chemotherapy alone.

With chemoradiotherapy (CRT)

- Early-phase studies suggest tislelizumab enhances response when added to definitive chemoradiotherapy in unresectable ESCC [3].
- Trials are ongoing to define its role in this setting.

With targeted agents

- Exploratory studies are evaluating tislelizumab in combination with anti-angiogenic agents and novel immunotherapy combinations. Preliminary findings indicate enhanced immune infiltration and tumor control, though confirmatory results are awaited. Results from pivotal phase II/III trials, including RATIONALE-302 and RATIONALE-306, are detailed in Table 3.

Real-world evidence

Real-world studies have supported clinical trial findings:

- In retrospective analyses, patients who received tislelizumab after chemotherapy failure had OS outcomes comparable to RATIONALE-302, with manageable toxicity [5].
- Expanded access programs in Asia showed comparable response rates and safety in diverse patient populations, including the elderly and those with comorbidities [3].

Trial	Phase	Setting	Intervention	Comparator	Main outcomes
RATIONALE-302 [5]	III	2nd line	Tislelizumab	Chemo (taxane/irinotecan)	OS ↑ (8.6 *vs*. 6.3 mo), ORR 20% *vs*. 10%, fewer grade ≥3 AEs
RATIONALE-306 [4]	III	1st line	Tislelizumab + chemo	Chemo alone	OS ↑ (17.2 *vs*. 10.6 mo), ORR 63% *vs*. 42%, PFS ↑
Neoadjuvant studies [3]	II	Resectable ESCC	Tislelizumab ± chemo/CRT	—	pCR 18–30%, MPR >40%, safe surgery
Combination CRT [3]	II (ongoing)	Unresectable ESCC	Tislelizumab + CRT	CRT alone	Early efficacy signals, safety acceptable

Table 3: Key Clinical Trials of Tislelizumab in ESCC. **Note:** ORR: Objective Response Rate, CRT: Chemo Radio Therapy.

Summary

- **Second-line (RATIONALE-302):** Tislelizumab is superior to chemotherapy, establishing it as the new standard.
- **First-line (RATIONALE-306):** Tislelizumab + chemotherapy improved survival, approved globally as first-line therapy.
- **Neoadjuvant setting:** Early evidence shows encouraging pCR/MPR with acceptable safety.
- **Combination strategies:** Synergy with chemotherapy and CRT; trials ongoing with novel partners.
- **Real-world data:** Confirms trial efficacy and safety in broader populations.

Safety and Tolerability Profile of Tislelizumab in Esophageal Squamous Cell Carcinoma (ESCC)

Overall safety findings

Tislelizumab has been consistently shown to have a better safety profile than chemotherapy in multiple phase II and III trials for esophageal squamous cell carcinoma (ESCC) [5]. In the pivotal RATIONALE-302 study, 46% of patients on tislelizumab experienced grade ≥3 Treatment-Related Adverse Events (TRAEs), while 68% received chemotherapy, resulting in fewer treatment discontinuations in the immunotherapy group [5]. Similarly, in the first-line RATIONALE-306 trial, adding tislelizumab to platinum-

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fluoropyrimidine chemotherapy increased the overall frequency of Adverse Events (AEs), but there were no new toxicities associated with tislelizumab [4]. A meta-analysis of phase II/ III studies confirmed that tislelizumab has lower hematologic toxicity and better tolerability than chemotherapy [21]. Real-world neoadjuvant cohorts also demonstrated that tislelizumab did not increase perioperative complications or surgical delays, suggesting a manageable toxicity profile in the curative setting [3].

Common adverse events

The spectrum of AEs with tislelizumab reflects the known class effects of PD-1 inhibitors.

- **Grade 1-2 events** (mild to moderate): fatigue, decreased appetite, nausea, rash, pruritus, pyrexia, arthralgia, mild hypothyroidism and mild diarrhea [4,5].
- **Grade 3 events** (severe): anemia, neutropenia, elevated liver transaminases, pneumonitis and severe diarrhea/colitis [3-5].
- **Grade 4-5 events** were rare but included life-threatening immune-related pneumonitis or hepatitis, with occasional treatment-related deaths reported [5,7].

A pooled long-term safety analysis of over 3000 patients found that tislelizumab monotherapy had a lower incidence of grade ≥3 TRAEs than other PD-1 inhibitors, confirming its favorable tolerability [7]. Treatment-related mortality was low (<1%), primarily due to immune-related pneumonitis or hepatic failure [7].

Immune-related adverse events (irAEs)

Immune-related Adverse Events (irAEs) associated with tislelizumab are consistent with PD-1 inhibitors and involve multiple organ systems [5].

- The most common irAEs are thyroid dysfunction (hypothyroidism and hyperthyroidism), rash and hepatitis [4,5].
- Less common irAEs include pneumonitis, colitis, adrenal insufficiency, hypophysitis and nephritis [7].
- Most irAEs are grade 1-2, manageable with corticosteroids and treatment interruption; grade ≥3 irAEs occur less frequently but require high-dose corticosteroids or additional immunosuppression [5].
- Fatal irAEs were rare but have been documented in post-marketing pharmacovigilance datasets [9].

Hematologic and non-hematologic toxicities

Hematologic toxicities such as anemia (8-12%), neutropenia (3-6%) and thrombocytopenia (2-5%) were more common when tislelizumab was combined with chemotherapy, reflecting cytotoxic effects rather than immunotherapy-specific toxicities [4]. Non-hematologic toxicities included fatigue, rash, diarrhea and liver enzyme elevations, which were generally reversible [5]. Importantly, compared to chemotherapy alone, tislelizumab monotherapy significantly reduced the risk of alopecia, peripheral neuropathy and gastrointestinal toxicities [21].

Combination therapy safety

When combined with chemotherapy, tislelizumab primarily adds immune-related toxicities to chemotherapy-related adverse events [4]. In neoadjuvant settings, tislelizumab with chemotherapy or chemoradiotherapy did not delay significantly surgery or increase postoperative complications [3]. No new immune-related complications were reported in these perioperative studies [3].

Safety in special populations

Pharmacokinetic and safety modeling has shown that mild to moderate hepatic or renal impairment has no significant effect on tislelizumab clearance, allowing for use without dose adjustments in these populations [11]. Subgroup analyses from RATIONALE-302 revealed a consistent safety profile across all age groups, including elderly patients (>65 years) [5]. Patients with active autoimmune diseases or prior organ transplantation were excluded from pivotal trials and safety data for these groups is limited [7].

Post-marketing surveillance

Additional real-world safety signals, such as pneumonitis, myocarditis and severe hepatitis, were discovered through an analysis of the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), which is consistent with PD-1 inhibitor class effects [9]. Importantly, the overall safety profile of tislelizumab in post-marketing surveillance was consistent clinical trial findings, with no new unexpected safety concerns identified [9].

Treatment discontinuation and dose modification

The rate of treatment discontinuation due to AEs in RATIONALE-302 was lower with tislelizumab than chemotherapy [5]. In first-line combination therapy (RATIONALE-306), the majority of discontinuations were due to chemotherapy-related toxicities, with tislelizumab accounting for only a small proportion [4]. Temporary treatment interruptions were used for irAE management and most patients were able to resume therapy after resolution [7]. Table 4 summarizes the incidence of treatment-related adverse events observed across pivotal trials.

Adverse Event	Grade 1–2 (%)	Grade 3-4 (%)
Fatigue [4,5]	10–20	<2
Rash / Pruritus [3,5]	8–15	<1
Diarrhea [5]	5–8	<1
Hypothyroidism [4,7]	5–7	<1
Hyperthyroidism [4]	2–4	<1
Hepatitis [5,7]	<2	1–2
Pneumonitis [7]	2–4	1–2
Anemia [4]	8–12	3–5
Neutropenia [4]	5–10	3–6
Fatal AEs [7,9]	—	<1 (pneumonitis, hepatic failure, myocarditis)

Table 4: Incidence of Key Adverse Events with Tislelizumab in ESCC.

Long-term data (>4 years) remain limited and rare but severe immune-related toxicities (pneumonitis, myocarditis) continue to warrant vigilance.

Cost analysis

The introduction of immune checkpoint inhibitors has prompted important discussions about affordability and sustainability within various healthcare systems. Tislelizumab, a newer PD-1 inhibitor, has been the subject of numerous pharmacoeconomic studies in ESCC.

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Several cost-effectiveness analyses have been conducted in China, where ESCC is especially prevalent. Using partitioned survival models, studies have consistently demonstrated that tislelizumab is associated with an increase in Quality-Adjusted Life Years (QALYs) compared to standard chemotherapy, albeit at a higher upfront cost [10]. Second-line tislelizumab monotherapy was estimated to have an Incremental Cost-Effectiveness Ratio (ICER) of around USD 11,073.85 per QALY, which was deemed cost-effective under China's willingness-to-pay thresholds [10].

Tislelizumab in combination with chemotherapy has also been tested as a first-line treatment. In patients with advanced gastric or gastroesophageal junction cancer, first-line tislelizumab plus chemotherapy improved quality-adjusted survival by 0.3 years compared to chemotherapy alone and was deemed cost-effective in China [19]. It was also effective in patients with higher PD-L1 levels [19]. Another study in China found that first-line tislelizumab plus chemotherapy for advanced esophageal squamous cell carcinoma increased quality-adjusted life years by about 0.5 compared to chemotherapy alone and was cost-effective [22]. A recent analysis suggested that tislelizumab plus chemotherapy resulted in more QALYs than chemotherapy alone, with ICERs ranging between USD 20,000 and 25,000 per QALY depending on assumptions, putting it within acceptable limits for the Chinese health system [17]. Similarly, a study modeled first-line tislelizumab-based regimens and reported that they offered favorable cost-effectiveness profiles compared with chemotherapy in most scenarios [23].

In the second-line setting, it is more cost-effective than camrelizumab, yielding more QALYs at a lower cost, implying a potential economic advantage over other checkpoint inhibitors [9]. A lifetime simulation model demonstrated that, for patients with advanced ESCC, combining tislelizumab with chemotherapy results in greater clinical benefit compared to chemotherapy alone, albeit at a higher treatment cost. Nevertheless, given the willingness-to-pay threshold currently applied in China, tislelizumab in combination with chemotherapy appears to be a cost-effective option [24]. Compared to chemotherapy alone, tislelizumab plus chemotherapy had an ICER of USD 27,896/QALY, added 0.414 QALYs and 0.751 life-years and increased the cost by USD 11,560 [8]. From the Chinese healthcare perspective, tislelizumab plus chemotherapy is more cost-effective than chemotherapy alone as a first-line therapy for OSCC [8,10,17,23-25].

Beyond China, the generalizability of these findings is uncertain. Cost structures, drug pricing and willingness-to-pay thresholds differ significantly across health systems. For example, a pharmacoeconomic model conducted in Europe suggested that, while tislelizumab improved outcomes compared to chemotherapy, its cost-effectiveness was heavily influenced by local reimbursement policies and negotiated drug prices [10]. Taken together, these findings suggest that tislelizumab, either alone or in combination with chemotherapy, may be an economically viable option in certain healthcare settings, particularly where drug costs are offset by increased survival and quality of life. However, widespread adoption in low- and middle-income countries will most likely necessitate price adjustments, increased health insurance coverage, or inclusion on national reimbursement lists.

Quality of life

In advanced ESCC, survival gains must be balanced against treatment burden, making Patient-Reported Outcomes (PROs) and Quality of Life (QoL) assessments essential in evaluating new therapies. While chemotherapy has long been considered standard, it is frequently associated with significant toxicity and deterioration in both physical and psychosocial domains [4]. In contrast, recent trials suggest that tislelizumab may help maintain or improve QoL in patients with advanced ESCC [8-10,17,23,24] which is supported by Table 5.

The pivotal RATIONALE-302 study found that tislelizumab monotherapy improved not only overall survival in the second-line setting compared to chemotherapy, but also slowed the decline in global health status and functional scores, as well as fewer treatment-related symptoms [4,5]. Importantly, patients receiving tislelizumab reported better physical and role functioning, as well as less fatigue and appetite loss, compared to those receiving chemotherapy [4]. [4,5].

In the first-line setting, the addition of tislelizumab to chemotherapy produced promising QoL outcomes. Preliminary analyses from the RATIONALE-306 trial revealed that patients receiving combination therapy experienced slower worsening of global health status and had better overall symptom control compared with those on chemotherapy alone [3]. These findings are consistent with pooled analyses indicating that the use of PD-1 inhibitors may mitigate some chemotherapy-induced declines in health-related QoL [26]. Table 5 shows the patient-reported quality of life outcomes with tislelizumab.

Real-world reports back up these findings. In an Asian cohort, patients treated with tislelizumab had stable global health status scores over time, though fatigue remained a significant symptom [27]. In the RATIONALE-302 trial, patients who received tislelizumab maintained their overall quality of life and physical functioning, whereas chemotherapy patients deteriorated [2]. Improvements were also observed in ESCC-related symptoms such as reflux and fatigue control, highlighting tislelizumab's beneficial role in patient well-being [2]. In Japanese patients with advanced ESCC, tislelizumab as a second-line treatment improved overall survival (median 9.8 *vs*. 7.6 months) and progression-free survival compared with chemotherapy [28]. Patients also experienced fewer severe side effects and a higher quality of life [28]. In patients with locally advanced, resectable ESCC, perioperative tislelizumab in combination with neoadjuvant chemotherapy resulted in a high rate of complete tumor removal (R0 resection 96%) and a promising pathological complete response rate (44%). The treatment was generally well tolerated, with manageable severe side effects [29]. These findings suggest that, while tislelizumab can help to preserve QoL, supportive care measures are still essential to address persistent treatment-related symptoms.

In the RATIONALE-305 trial, patients with advanced gastric or gastroesophageal junction adenocarcinoma who received first-line tislelizumab plus chemotherapy showed sustained improvements in quality of life compared with placebo plus chemotherapy. At cycle 6, the global health status/quality of life difference was 2.52 points, with improved physical functioning (2.46 points), decreased fatigue (–3.01 points) and improved gastrointestinal symptoms and pain scores. Tislelizumab also reduced the risk of deterioration in these domains, with hazard ratios ranging from 0.64 to 0.77 [16]. In first-line treatment for advanced ESCC, combining PD-1 inhibitors with chemotherapy significantly improved survival over chemotherapy alone, increasing median overall survival from 11.3 to 15.6 months. Toripalimab, tislelizumab and sintilimab outperformed the other PD-

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1 inhibitors in terms of overall survival, with tislelizumab and sintilimab also having the lowest risk of disease recurrence [30]. In a phase II trial for elderly patients with inoperable locally advanced ESCC, the addition of tislelizumab to concurrent chemoradiotherapy (S-1 + radiotherapy) is being investigated for improved progression-free survival, overall survival and response rates when compared to chemoradiotherapy alone. The combination is expected to improve efficacy while keeping a manageable safety profile [31].

Overall, available data suggest that tislelizumab— used alone or in combination— provide not only a survival benefit but also a quality-of-life advantage over standard chemotherapy (Table 5). Nonetheless, longer follow-up and larger real-world datasets are required to confirm the long-term efficacy of these benefits across diverse patient populations. While RATIONALE-302 and 306 provide ESCC-specific quality-of-life outcomes, results from gastric/GEJ adenocarcinoma (RATIONALE-305) should be interpreted as supportive proxy data rather than direct ESCC evidence.

Study / Setting	Intervention	Global health/QoL	Physical function	Fatigue	Appetite/GI symptoms	Reference
2L RATIONALE-302	Tislelizumab	Slower decline	Better preserved	Less deterioration	–	[2,4,5]
1L RATIONALE-306	Tislelizumab + Chemo	Delayed worsening	Maintained	–	–	[3]
1L RATIONALE-305 (G/GEJ)	Tislelizumab + Chemo	2.52	2.46	–3.01	Improved GI symptoms & pain	[16]
Notes: Quality-of-life outcomes are based on patient-reported measures from pivotal RATIONALE studies (302, 306, 305) and real-world cohorts of advanced or metastatic esophageal squamous cell carcinoma (ESCC) and gastroesophageal junction adenocarcinoma (G/GEJ) patients. Higher scores indicate better global health, preserved physical function and fewer symptoms such as fatigue or gastrointestinal issues. Improvements or slower declines in these domains with tislelizumab (monotherapy or in combination with chemotherapy) reflect the therapy's potential to maintain overall well-being compared with standard chemotherapy, though results may vary across study populations and follow-up periods.						

Table 5: Patient-reported quality-of-life outcomes with tislelizumab in advanced esophageal and gastroesophageal cancers.

Discussion

This narrative review summarizes the clinical and pharmacologic evidence supporting tislelizumab in esophageal squamous cell carcinoma. In randomized phase III studies, tislelizumab monotherapy improved OS compared to chemotherapy in the second-line setting (RATIONALE-302), while the tislelizumab plus platinum–fluoropyrimidine chemotherapy improved OS compared to chemotherapy alone in the first-line setting (RATIONALE-306) [3,5]. Across trials and pooled analyses, responses to tislelizumab were durable in a subset of patients and the agent had a generally manageable toxicity profile compared to conventional cytotoxic regimens [5,7]. Population pharmacokinetic analyses support a fixed 200 mg intravenous Q3W dosing schedule with low immunogenicity, predictable exposure-response and no routine dose adjustments for mild to moderate organ impairment [5,11].

Clinical implications

The available evidence supports two practical clinical implications. First, for patients with advanced ESCC who have progressed on first-line therapy, single-agent tislelizumab is a validated second-line option that improves survival while producing fewer high-grade treatment-related adverse events than standard chemotherapy [5]. Second, in previously untreated advanced ESCC, the addition of tislelizumab to platinum-fluoropyrimidine chemotherapy significantly improves OS, PFS and objective response rates and it is now the standard first-line treatment in RATIONALE-306 populations [3]. Health-related quality of life data show that tislelizumab regimens deteriorate more slowly than chemotherapy, which is an important factor to consider when selecting treatment for this symptomatic disease [2,3]. Finally, several country-level cost-effectiveness models indicate that, under commonly used Chinese willingness-to-pay thresholds, tislelizumab (monotherapy or in combination) can be cost-effective — though generalizability beyond China depends on local pricing and reimbursement structures [8,10,17].

Strengths of the evidence

The clinical program for tislelizumab in ESCC is notable for:

- Large, randomized, global phase III data (RATIONALE-302, RATIONALE-306) addressing both second- and first-line settings [3,5].
- Supportive subgroup and health-quality analyses that demonstrate consistency of effect across regions and patient-reported outcomes [2,4].
- Pooled long-term safety and efficacy datasets that document durability of benefit and a stable safety profile across indications [7]. Pharmacologic characterization (PopPK, exposure–response, immunogenicity) is robust and supports the approved dosing strategy [11].

Limitations and knowledge gaps

Despite the breadth of studies, several limitations constrain interpretation and application:

1. **Heterogeneity of trial populations and PD-L1 assays:** Trials used differing PD-L1 assays and cut-points (e.g., TAP, CPS), complicating cross-trial comparisons and biomarker-based patient selection [3,5]. The predictive value of PD-L1 remains inconsistent and does not fully explain who derives durable benefit.
2. **Limited head-to-head comparisons among PD-1 agents:** While other PD-1 inhibitors (e.g., pembrolizumab, nivolumab) have demonstrated efficacy in ESCC, direct randomized comparisons between tislelizumab and other

PD-1 agents are lacking; cross-trial comparisons are confounded by population and design differences [32,33].

3. **Neoadjuvant and perioperative data are preliminary:** Single-arm phase II and small prospective cohorts show promising pathological responses, but randomized data demonstrating long-term survival benefit and impact on surgical morbidity remain absent [3,29].
4. **Real-world evidence and broader generalizability:** Most large pivotal data were generated in multi-regional trials with heavy Asian representation; further real-world data from diverse health systems are necessary to confirm external validity and safety in excluded populations (e.g., active autoimmune disease, organ transplant recipients) [7,12].
5. **Post-marketing safety signals:** Pharmacovigilance datasets have identified rare but severe immune-related events (e.g., pneumonitis, myocarditis); systematic characterization of risk factors, optimal monitoring and management in routine practice is needed [9].
6. **Economic uncertainty outside China:** Cost-effectiveness studies largely model Chinese healthcare inputs; applicability to other regions with different drug prices and willingness-to-pay thresholds is uncertain [8,17].

Recommendations for future research

To address these gaps and refine clinical use, we recommend the following priorities:

1. **Biomarker development:** Prospective studies harmonizing PD-L1 assays and exploring integrated multi-omic biomarkers (TMB, gene expression immune signatures, circulating tumor DNA) to better predict responders and guide de-escalation or escalation strategies.
2. **Head-to-head and platform trials:** Direct comparative trials or adaptive platform studies comparing different PD-1 agents (including tislelizumab) combined with chemotherapy or other agents would clarify relative efficacy, toxicity and value.
3. **Randomized neoadjuvant trials:** Phase III trials comparing neoadjuvant tislelizumab combinations versus standard neoadjuvant regimens with long-term survival and functional outcomes as endpoints are required to establish curative-intent roles.
4. **Mechanistic and resistance studies:** Translational research to define mechanisms of primary and acquired resistance (tumor immune microenvironment, macrophage interactions, Fc engineering effects) could inform rational combination strategies (e.g., anti-angiogenics, CTLA-4, or macrophage-targeted agents).
5. **Real-world safety registries and pharmacovigilance:** Prospective registries capturing under-represented populations (autoimmune disease, organ dysfunction, elderly frail patients) would improve safety characterization and guide monitoring algorithms.
6. **Health-economic analyses across regions:** Independent cost-effectiveness evaluations using local pricing and health system parameters outside China (Europe, North America, low-middle income countries) should inform reimbursement and access planning.
7. Fc-engineering's clinical impact remains speculative, requiring further translational and comparative studies.

Conclusion

Tislelizumab has emerged as a transformative therapy in the management of esophageal squamous cell carcinoma. Evidence from pivotal clinical trials and supporting studies consistently demonstrates that it can extend survival, provide long-term disease control in a subset of patients and have a manageable safety profile when compared to conventional chemotherapy. Beyond clinical efficacy, tislelizumab offers meaningful improvements in quality of life, which is particularly important in a disease associated with high symptom burden and poor prognosis.

As research advances, the role of tislelizumab is likely to expand into earlier disease stages and more diverse patient populations. The challenge ahead is to improve patient selection, optimize treatment combinations and ensure global accessibility. With these advances, tislelizumab represents not only a significant advancement in ESCC treatment but also a foundation for more personalized and effective therapeutic strategies can be built. Future efforts should focus on biomarker-driven patient selection, evaluation in neoadjuvant/CRT settings and independent health-economic studies across diverse healthcare systems. Future research should prioritize biomarker-driven selection and expanding global accessibility of tislelizumab in ESCC.

Author Contributions

All authors assisted in formatting, editing and revising the manuscript; all authors interpreted the data and wrote the first and final draft of the manuscript; all authors revised the article critically for important intellectual content and they gave final approval of the article to be published.

Competing Interests

The authors declare no conflict of interests for this article.

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