Impact of PD-1 and PD-L1 Inhibitors on Patient-Reported Outcomes in Esophageal Squamous Cell Carcinoma: A Systematic Review of Clinical Trials

Philip O. Buck, PhD, MPH[1], Wesley Wong, PharmD[1], Jason Allaire, PhD[1,2]*

[1]Generativity Solutions Group, USA, [2]North Carolina State University, USA

Contact Information: Jason.Allaire@generativitysg.com

Background

- Esophageal cancer includes both adenocarcinoma, which is the most common histologic type in the United States (US), and squamous cell carcinoma (ESCC), which represents approximately 90% of all cases globally[1]
- Symptoms of esophageal cancer include difficulty swallowing, chest pain or heartburn, weight loss, chronic cough, vomiting after meals, all of which can adversely affect nutritional status, physical functioning, and daily activities[2-4]
- As a result, esophageal cancer substantially impairs patients' health-related quality of life (HRQoL); improving patients' self-reported symptoms, as well as HRQoL, are key treatment goals in this population[3,4]
- Patients with ESCC treated programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, alone or in combination with chemotherapy, have shown significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) compared with those treated with chemotherapy alone[5-7]
- Beyond survival benefits, treatment with PD-1 and PD-L1 inhibitors have shown significant improvements in patient-reported outcomes (PROs) such as dysphagia and pain symptoms, as well as HRQoL[8]

Objective

- To comprehensively evaluate PROs, including HRQoL, among ESCC patients treated with PD-1/PD-L1 inhibitors across clinical trials

Methods

Study Design	• Systematic literature review (SLR)
Search Period	• All publications available up to July 20, 2025
Search Strategy	• A systematic literature search was conducted in the PubMed, Embase, and the Cochrane Library databases, supplemented by Elicit (an AI-assisted systematic literature review tool), to identify clinical trials evaluating the effects of PD-1 or PD-L1 checkpoint inhibitors on PROs in patients with ESCC • Search terms and free-text keywords related to PD-1/PD-L1 inhibitors, ESCC, PROs, HRQoL, and clinical trials were used
Study Selection	• Studies were included if they met the following criteria: 1) Conducted in patients with ESCC 2) Reported PROs, including HRQoL, as part of a clinical trial investigating PD-1 or PD-L1 checkpoint inhibitors 3) Published as full-text, peer-reviewed manuscripts in English • Two independent reviewers (SC and WW) screened all titles and abstracts to determine study eligibility. Studies with any discrepancies between reviewers were re-evaluated by a third reviewer (JA) • Studies were excluded if they were duplicates, abstracts, conference proceedings, review articles, meta-analyses, case reports, or non-clinical trial studies (e.g., real-world data studies)
Data Extraction	• First author, publication year, NCT number, trial name, trial phase, study population, study design, intervention and comparator(s), number of patients, PRO measures, follow-up duration, and key PRO results

References:
1. Jiang W et al. *Cancer Commun (Lond)*. 2025.
2. American Cancer Society. *Esophageal Cancer*. 2025.
3. Farnqvist K et al. *Dis Esophagus*. 2025.
4. Liu Q et al. *Cancer Med*. 2018.
5. Ren W et al. *Front Immunol*. 2025.
6. Yang F et al. *Front Immunol*. 2024.
7. Leone AG et al. *ESMO Open*. 2022
8. Gupta K et al. *Healthcare (Basel)*. 2024.

Results

Search Results

- At the time of the literature search (July 20, 2025), 475 relevant publications were identified
- After removing 133 duplicate records and 324 publications that did not meet the inclusion criteria, 18 full-text publications reporting PROs from 13 clinical trials were included in the systematic review (**Table 1**)
- PROs were assessed using the EORTC QLQ-C30 and QLQ-OES18, EQ-5D-5L, EQ-5D-3L, and FACT-E instruments, all of which are validated questionnaires

PROs by Treatment Settings

- In the first-line setting, evidence from phase 3 trials indicates that nivolumab-, camrelizumab-, sintilimab-, or pembrolizumab-based regimens in combination with chemotherapy generally maintained overall HRQoL and/or provided modest but favorable improvements in key ESCC-related symptoms, such as swallowing-related difficulties, eating difficulties, and pain, with limited separation from chemotherapy alone
- Additional benefits were observed with camrelizumab plus chemotherapy in eating difficulties and with sintilimab plus chemotherapy in social functioning, fatigue, and constipation

Figure 1. Characteristics of the Studies Included in the Systematic Review

Trial Name	Trial Number	Phase	Cancer Type and Population	Treatment Arms	PD-1/PD-L1 Inhibitor Line of Therapy	Primary Endpoint	PRO Measures	Follow-up Duration for PRO Measures
CheckMate 648	NCT03143153	Phase 3	• Previously untreated, unresectable advanced, recurrent, or metastatic ESCC	1) Nivolumab + CT 2) Nivolumab + Ipilimumab 3) CT	1L	OS, PFS	• FACT-E	49 weeks
ATTRACTION-3	NCT02569242	Phase 3	• Unresectable advanced or recurrent ESCC	1) Nivolumab 2) CT	2L	OS	• EQ-5D-3L	42 weeks
RAMONA	NCT03416244	Phase 2	• Advanced ESCC with disease progression/recurrence after first-line therapy	1) Nivolumab 2) Nivolumab + Ipilimumab	2L	OS	• EORTC QLQ-C30	6 months
RATIONALE 302	NCT03430843	Phase 3	• Advanced or metastatic ESCC with disease progression after first-line therapy	1) Tislelizumab 2) CT	2L	OS	• EORTC QLQ-C30 • EORTC QLQ-OES18 • EQ-5D-5L	18 weeks
ESCORT	NCT03099382	Phase 3	• Advanced, recurrent, or metastatic ESCC with disease progression after first-line therapy	1) Camrelizumab 2) CT	2L	OS	• EORTC QLQ-C30 • EORTC QLQ-OES18	8 weeks
ESCORT-1st	NCT03691090	Phase 3	• Previously untreated, unresectable advanced, recurrent, or metastatic ESCC	1) Camrelizumab + CT 2) Placebo + CT	1L	OS, PFS	• EORTC QLQ-C30 • EORTC QLQ-OES18	36 weeks
GASTO1056	ChiCTR2000028900[a]	Phase 2	• Previously untreated, resectable ESCC	1) Neoadjuvant camrelizumab + nab-paclitaxel + carboplatin	1L	Safety, feasibility	• EORTC QLQ-C30 • EORTC QLQ-OES18	*
N/A	NCT03671265	Phase 1b	• Previously untreated, locally advanced ESCC	1) Camrelizumab + CT + radiotherapy	1L	Safety, tolerability, HRQoL	• EORTC QLQ-C30 • EORTC QLQ-OES18	35 weeks
ORIENT-15	NCT03748134	Phase 3	• Previously untreated, unresectable advanced, recurrent, or metastatic ESCC	1) Sintilimab + CT 2) Placebo + CT	1L	OS	• EORTC QLQ-C30 • EORTC QLQ-OES18 • EQ-5D-5L	60 weeks
ORIENT-2	NCT03116152	Phase 2	• Advanced or metastatic ESCC with disease progression after first-line therapy	1) Sintilimab 2) CT	2L	OS	• EORTC QLQ-C30 • EQ-5D-5L	42 weeks
CY-NICE	ChiCTR2200056558[a]	Phase 2	• Previously untreated, resectable locally advanced ESCC	1) Neoadjuvant sintilimab + CT	1L	pCR	• EORTC QLQ-C30 • EORTC QLQ-OES18	**
KEYNOTE-181	NCT02564263	Phase 3	• Unresectable locally advanced or metastatic ESCC or adenocarcinoma with disease progression after one prior line of therapy	1) Pembrolizumab 2) CT	2L	OS	• EORTC QLQ-C30 • EORTC QLQ-OES18 • EQ-5D-3L	9 weeks
KEYNOTE-590	NCT03189719	Phase 3	• Previously untreated, unresectable locally advanced or metastatic ESCC or adenocarcinoma	1) Pembrolizumab + CT 2) Placebo + CT	1L	OS, PFS	• EORTC QLQ-C30 • EORTC QLQ-OES18 • EQ-5D-5L	18 weeks

[a] Chinese Clinical Trial Registry identifier
*PROs were assessed at the start of neoadjuvant therapy and again before surgical resection. Patients received two 21-day cycles of neoadjuvant therapy before surgical resection 21 to 42 days after the first day of the 2nd cycle
**PROs were assessed at baseline and post-neoadjuvant therapy. Patients received at least two 21-day cycles of neoadjuvant therapy before being evaluated for surgical resection within 4 to 6 weeks after completing last cycle

Abbreviations: 1L, first-line; 2L, second-line; CT, chemotherapy; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EORTC QLQ-OES18, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Cancer Module 18 items; EQ-5D-5L, EuroQol Five-Dimension Five-Level Questionnaire; EQ-5D-3L, EuroQol Five-Dimension Three-Level Questionnaire; ESCC, esophageal squamous cell carcinoma; FACT-E, Functional Assessment of Cancer Therapy-Esophageal Questionnaire; HRQoL, health-related quality of life; OS, overall survival; pCR, pathological complete response rate; PFS, progression-free survival

PROs by Treatment Settings (Cont.)

- In the second-line setting, phase 3 trials showed that nivolumab, tislelizumab, camrelizumab, and pembrolizumab were associated with maintenance or improvement in global HRQoL compared with chemotherapy, with tislelizumab and camrelizumab also demonstrating delayed deterioration and reduced symptom burden
- Tislelizumab demonstrated particularly robust benefits, including attenuated declines in physical functioning and fatigue, as well as fewer eating problems, with significant differences versus chemotherapy emerging early and sustained over time (up to 18 weeks)

Presented at ISPOR, Philadelphia, PA, USA, May 17-20, 2026

Conclusions

- ✓ **Clinical trials have demonstrated that PD-1/PD-L1 inhibitor-based regimens maintained or improved PROs compared with chemotherapy in patients with ESCC**
- ✓ **Evidence of PRO benefit was reported more frequently in the second-line setting, where PD-1/PD-L1 inhibitors were used as monotherapy and directly compared with chemotherapy**
- ✓ **Overall, PD-1 and PD-L1 inhibitors had a positive impact on global health status, functional domains, and key disease-related symptoms**
- ✓ **Evaluating long-term follow-up of PROs in future clinical research will be essential to ensure that novel immune checkpoint inhibitors translate into meaningful benefits for patients**

Limitations

- This study was restricted to peer-reviewed clinical trial publications. Data from conference abstracts, gray literature, and real-world studies were excluded
- Substantial heterogeneity existed across the included clinical trials with respect to PRO instruments, assessment schedules, follow-up durations, and treatment settings. Therefore, the statistical thresholds for clinical meaningful difference in PROs may differ across studies
- All included trials assessed PROs within one year of baseline and thus it was difficult to draw conclusions about the long-term effects of PD-1/PD-L1 inhibitors on PROs in ESCC patients

Sponsor: Generativity Solutions Group

Learn more about Generativity