Systematic Literature Review (SLR) of Disease Burden Related to First-Line (1L) Unresectable, Locally Advanced, or Metastatic Esophageal Squamous Cell Carcinoma (ESCC)

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Conclusions

- **This SLR comprehensively summarizes disease burden associated with 1L treatment of unresectable, locally advanced, or metastatic ESCC**
- **Immuno-oncology agents added to chemotherapy exhibited variability in reported incremental cost-utility ratios (ICURs)[1,2] and was associated with improved HRQoL compared with chemotherapy alone**
- **Important data gaps included few health state utility values (HSUVs), few cost-utility analyses (CUAs) outside of the US and China, and no CUAs comparing IO treatments for insights on relative cost-effectiveness**
- **Few studies outside of CUAs reported healthcare costs and resource use (HCRU) for patients with ESCC, representing another important data gap. Additionally, none of the included studies reported indirect costs, caregiver burden, or productivity loss**

Background

- Esophageal squamous cell carcinoma (ESCC) is the most common form of esophageal cancer (EC), representing approximately 90% of cases globally and accounting for the majority of the burden of disease[3]
- The prognosis for ESCC is poor, with a 5-year survival rate of less than 20%[4]
- The treatment landscape for 1L unresectable, locally advanced recurrent or metastatic ESCC has expanded with the use of immuno-oncology (IO) agents such as tislelizumab, nivolumab, and pembrolizumab
- The objective of this SLR was to identify published evidence reporting on the disease burden associated with 1L treatments of unresectable, locally advanced, or metastatic ESCC, focusing on HSUVs and health-related quality of life (HRQoL), economic evaluations, and HCRU pertaining to treatment

Methods

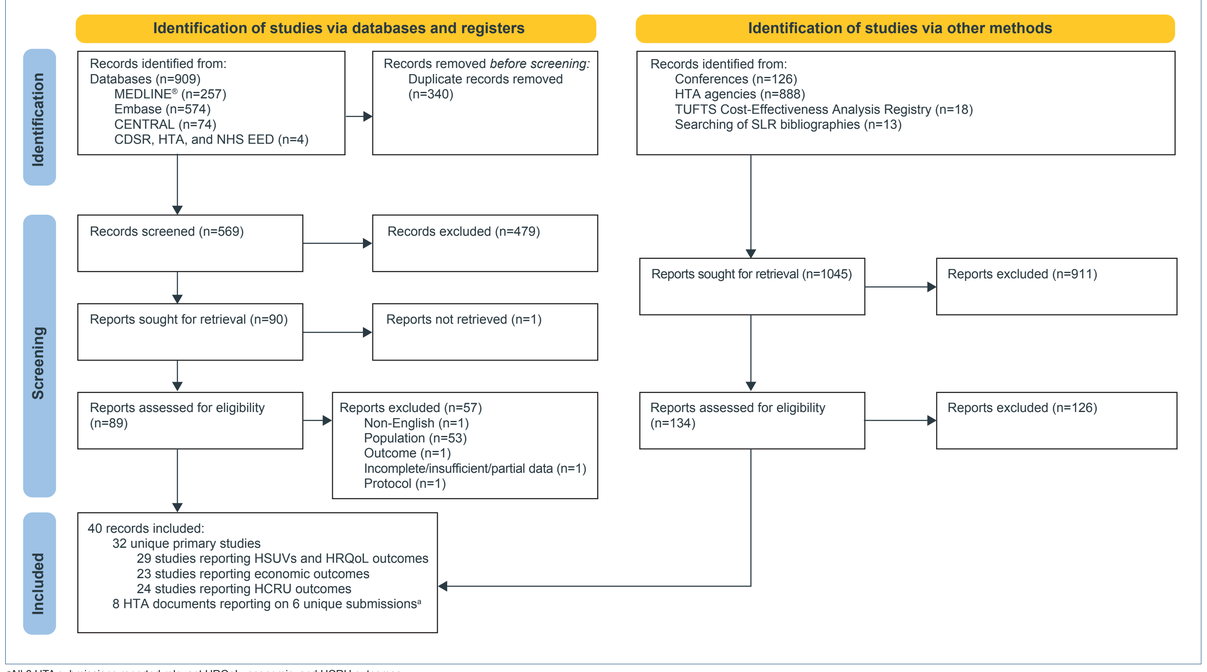
- Embase, MEDLINE® (including Epub Ahead of Print, In-Process, and Other Non-Indexed Citations), Ovid MEDLINE® Daily, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews searches were conducted on October 25, 2023
- Hand searches of key gray literature sources were also conducted to supplement database searches
- Study selection was performed in duplicate and was assessed according to the following eligibility criteria:
  - Adult patients (aged ≥18 years) receiving treatment for 1L unresectable, locally advanced, or metastatic ESCC
  - There was no restriction on intervention or comparator
  - Outcomes of interest included HRQoL outcomes (generic HRQoL measures, HSUVs, patient-reported outcomes), economic outcomes (total costs, life-years, quality-adjusted life-years [QALY], incremental cost-utility ratios [ICURs]), and HCRU outcomes (categorical costs, HCRU frequency, caregiver burden)
- Quality assessment by NICE Quality Assessment Checklist for Health State Utility Values[5] for studies reporting HSUVs and HRQoL instruments (**Supplementary Table 1**†) and Drummond and Jefferson checklist[6] for economic evaluations (**Supplementary Table 2**,† **Supplementary Table 3**†)

Results

Evidence Identified

- Of 909 records identified in the database/registry searches and 1045 records across gray literature sources, 32 unique studies and 6 unique Health Technology Assessment (HTA) submissions were identified (**Figure 1**)
- Of these, 29 included HRQoL, 23 included economic evaluations, and 24 included HCRU. All 6 HTA submissions included HRQoL, economic, and HCRU outcomes

Figure 1. PRISMA Diagram

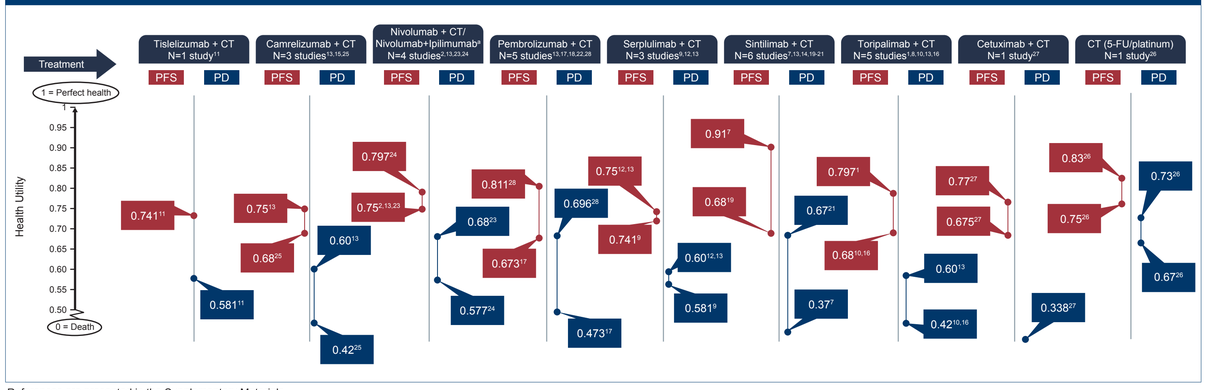


[a]All 6 HTA submissions reported relevant HRQoL, economic, and HCRU outcomes.
CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; HCRU, healthcare costs and resource use; HRQoL, health-related quality of life: HSUV, health state utility value; HTA, Health Technology Assessment; NHS EED, National Health Service Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Health State Utility Values

- There were 23 studies (1 HRQoL[7] and 22 CUAs[1,2,8-27]) and 1 HTA submission[28-30] relating to HSUVs (**Figure 2**)
- The ORIENT-15 trial reported an HSUV of 0.91 for progression-free survival (PFS) and an HSUV of 0.37 for progressive disease (PD) among Chinese patients receiving sintilimab + chemotherapy (CT) for 1L ESCC[7]
- The remainder of the utility values were captured in CUAs; among these, HSUVs were most commonly reported for PFS (range: 0.68[27]-0.80[1]) and PD (range: 0.34[27]-0.73[26]). Importantly, most CUAs utilized HSUVs from published literature in disease areas other than 1L ESCC
- Disutility values were most commonly reported for anemia, decreased neutrophil count, and neutropenia (**Supplementary Table 4**†)

Figure 2. Summary of HSUVs by Treatment Reported by Included Studies



References are presented in the Supplementary Materials.
[a]Ben-Umeh 2023,[4] Liu 2022,[23] and Cao 2022[24] provided single utility values for a model with nivolumab + CT and nivolumab + ipilimumab. Liu 2023[13] provided utility values only for nivolumab + CT.
5-FU, 5-fluorouracil; CT, chemotherapy; HSUV, health state utility value; PD, progressive disease; PFS, progression-free survival.

Health-Related Quality of Life Measures

- Six clinical trials[31-36] and 3 HTA submissions[37-39] provided HRQoL measures other than HSUVs among patients with 1L ESCC (**Table 1**)
- Across the included HRQoL measures, most active treatments added to CT were associated with improvements in HRQoL over long-term follow-up versus CT
- Of note, treatment with pembrolizumab + CT was associated with decreases in EORTC QLQ-C30 global health status and EORTC QLQ-OES18 pain and dysphagia subscales versus CT[31]

Table 1. Summary of HRQoL Measures

Trial; NCT	Region	Follow-up Times Assessed	Arm(s)	Scale/Category	Summary of Results
CheckMate 648[32, 38]; NCT03143153	Global	Baseline, 49 weeks	NIV + CT NIV + IPI CT	FACT-E, ECS	• Improved HRQoL for NIV + CT versus CT • Improved HRQoL for NIV + IPI versus CT alone, but not NIV + IPI versus NIV + CT
NICE[35]; NCT01249352	Brazil	Visits 1, 9, 17, and 26	NIV + RT + CT RT + CT	FACT-G[a]	• Improved HRQoL for NIV + RT + CT, but not RT + CT
E-DIS[34]; NCT01248299	France	NR	CT (5-FU/platinum) continuation CT (5-FU/platinum) discontinuation	EORTC QLQ-C30,[b] EORTC QLQ-OES18[c]	• Continued CT exhibited longer TUDD
Conroy 2002[36]	EU	Baseline, 6 weeks, and 12 weeks	VIN + CT	EORTC QLQ-C30[b]	• VIN + CDDP improved HRQoL from baseline • Patients with stable disease after treatment reported decline in HRQoL
NCT03671265[33]	China	Q2W for Weeks 3-35	CAM + CT + RT	EORTC QLQ-C30,[b] EORTC QLQ-OES18[c]	• Improved HRQoL for CAM + CT + RT
KEYNOTE-590[31, 37, 39]; NCT03189719	Global	18 weeks	PEM + CT CT	EORTC QLQ-C30,[b] EORTC QLQ-OES18[c]	• Compared with CT, PEM + CT showed decreases in EORTC QLQ-C30 GHS and EORTC QLQ-OES18 pain, dysphagia • For CPS ≥10, PEM + CT improved EORTC QLQ-OES18 versus CT

[a]The FACT-G subscale ranges from 0 to 108, where higher scores reflect better health.
[b]The EORTC QLQ-C30 scale ranges from 0 to 100, where a decrease in global health status implies deterioration.
[c]The EORTC-QLQ OES18 scale ranges from 0 to 100, where an increase in symptom scale scores implies deterioration of symptoms.
5-FU, 5-fluorouracil; CAM, camrelizumab; CDDP, cisplatin; CPS, combined positive score; CT, chemotherapy; ECS, esophageal cancer subscale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Oesophageal Cancer 18-question module; EU, European Union; FACT-E, Functional Assessment of Cancer Therapy-Esophagus; FACT-G, Functional Assessment of Cancer Therapy-General; GHS, global health status; HRQoL, health-related quality of life; IPI, ipilimumab; NIV, nivolumab; NR, not reported; PEM, pembrolizumab; RT, radiotherapy; TUDD, time until definitive deterioration; VIN, vinorelbine.

Economic Evaluations

- 23 primary studies[1,2,7-27,33] and 6 HTA submissions[28-30,37-41] reported economic outcomes of interest (**Table 2**)
- Most included CUAs were conducted using partitioned survival models or Markov models developed from the US or Chinese perspectives and evaluated the cost-effectiveness of IO agents + CT versus CT
- ICURs for IO agents ranged widely from $13,209[1]-$666,832[2] (US$ 2020-2023)
  - The highest ICURs were noted for serplulimab and nivolumab ($104,537[9]-$666,832,[2] US$ 2022)
  - Lower ICURs were noted among tislelizumab, sintilimab, toripalimab, and camrelizumab ($13,209[1]-$46,671,[25] US$ 2020-2022)
  - The widest variation in ICUR was noted for pembrolizumab ($41,805[18]-$550,211[17], US$ 2020-2022)

Table 2. Summary of Included Economic Evaluations

Intervention[a]	Region	Currency (Cost Year)	ICUR Range[b]
TIS + CT[11]	China	US$ (2022)	$18,846
CAM + CT[13,15,25]	China	US$ (2020-2022)	$29,771-$46,671
NIV + CT[2,13,23,24,38,40]	Scotland, UK	£ (NR)	£31,363-£33,272
	Global, US, China	US$ (2021-2022)	$282,307-$597,522
NIV + IPI[2,23,24]	Global, US, China	US$ (2021-2022)	$155,160-$666,832
PEM + CT[13,17,18,22,28-30,37,39,41]	Canada	CA$ (NR)	$142,861; Dominated by Blended CT
	Scotland, UK	£ (NR)	£32,051-£43,225
	Australia	AU$ (NR)	Redacted[c]
	Global, US, China	US$ (2020-2022)	$41,805-$550,211
SER + CT[9,13]	China	US$ (2022-2023)	$104,537-$176,432 (PFS)
SIN + CT[7,13,14,19-21]	China	US$ (2021-2022)	$18,622-$30,409
TOR + CT[1,8,9,13,16]	China	US$ (2021-2022)	$13,209-$43,405
CET + CT[27]	Netherlands	€ (2009)	€252,203
CT (5-FU/platinum) continuation[26,d]	France	€ (2018)	€-30,958

[a]Comparators for these models are CT or PBO + CT. [b]Results for base case analyses are presented unless otherwise specified. [c]Redacted value lies between $95,000 and <$115,000 per QALY.
[d]The comparator for this study was CT (5-FU/platinum) discontinuation.
5-FU, 5-fluorouracil; AU$, Australian dollar; £, British pound sterling; CA$, Canadian dollar; CAM, camrelizumab; CET, cetuximab; CT, chemotherapy; €, euro; ICUR, incremental cost-utility ratio; IPI, ipilimumab; NIV, nivolumab; NR, not reported; PBO, placebo; PEM, pembrolizumab; PFS, progression-free survival; QALY, quality-adjusted life-year; SER, serplulimab; SIN, sintilimab; TIS, tislelizumab; TOR, toripalimab; US$, US dollar.

Healthcare Resource Use Outcomes

- 24 studies (21 CUAs,[1,8-27] 1 retrospective cohort study,[42] 1 prospective cohort study,[43] and 1 retrospective non-interventional cross-sectional study[44]) and 6 unique HTA submissions[28,37-41] reported HCRU outcomes of interest
- Healthcare resource use costs associated with IO agents versus CT were underreported
- For China, total direct costs reported for IO treatments across a 10-year horizon ranged from $12,969.06[1]-$89,759.94[23] US$ for patients with PFS and from $1,628.02[23]-$6,942.32[25] US$ for patients with PD
- Hospitalizations, length of stay, and emergency room (ER) visits are noted in **Table 3**

Table 3. Summary of Hospitalizations, LOS, and ER Visits

Treatment	Region (Studies, n)	Summary
CUAs[a]		
PEM + CT[22]	US (n=1)	• Monthly inpatient hospital stays more frequent for PFD (1.26) versus PD (1.90) • ER visit, per patient: $177.20 (US$ 2020)
SER + CT[12]	China (n=1)	• Hospitalization per day: $19.86 (US$ 2023)
SIN + CT[20]	China (n=1)	• Hospitalization per day: $19.86 (US$ 2021)
CET + CT[27]	Netherlands (n=1)	• 6 hospitalizations can be combined with CT
CT (5-FU/platinum) continuation[26]	France (n=1)	• Cost per hospitalization (CT session), per patient: €407.00 (€ 2018)
Cohort and Cross-Sectional Studies		
CT + RT versus nutritional support + CT + RT[42]	China (n=1)	• Mean LOS higher for CT + RT (51.57 days) versus nutritional support + CT + RT (48.26 days)
Self-expanding metal stent versus intraluminal radioactive stent[43]	China (n=1)	• Mean LOS higher for radioactive stents (10.1 days) versus metal stents (8.9 days)
Platinum + fluoropyrimidine doublet therapy[44]	Global (n=1)	• Average number of AE-related hospitalizations per patient higher in Asia (11.8) than North America and Europe (7.3)

[a]For CUAs, resource use outcomes are reported as model parameters and are applicable to both intervention and comparator.
5-FU, 5-fluorouracil; AE, adverse event; CET, cetuximab; CT, chemotherapy; CUA, cost-utility analysis; ER, emergency room; €, euro; LOS, length of stay; PD, progressive disease; PEM, pembrolizumab; PFD, progression-free disease; RT, radiotherapy; SER, serplulimab; SIN, sintilimab; US$, US dollar.

References

Provided in Supplementary Material (view using Supplementary Material QR code)†

†Supplementary Material Download
Please scan the QR code to the left to view and download supplementary materials.

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Presenter Disclosures

Eugenia Priedane is employed by BeiGene and may hold stock or other ownership.

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