Systematic Literature Review of Disease Burden Related to First-Line Unresectable, Locally Advanced, or Metastatic Gastric Cancer and Gastroesophageal Junction Adenocarcinoma

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INTRODUCTION

- Gastric cancer arises from cells lining the stomach and is the fifth most common cancer worldwide and the third leading cause of cancer related deaths.[1,2] Gastroesophageal junction adenocarcinoma occurs at the junction between the esophagus and stomach; incidence ranges from 2.0 to 2.2 per 100,000 in North America and from 0.6 to 1.7 per 100,000 in East Asia.[3]
- First-line (1L) treatments for advanced or metastatic GC/GEJ adenocarcinoma have historically included fluoropyrimidine- or platinum-based chemotherapies, although these regimens are associated with a poor median overall survival (OS) of less than one year.4 For both GC and GEJ adenocarcinoma, PD-1 inhibitors such as tislelizumab, nivolumab, pembrolizumab, and sintilimab have shown promising results in clinical trials
- 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 GC/GEJ adenocarcinoma. In particular, the SLR aimed to identify literature reporting HSUVs, HRQoL, HCRU, and costs pertaining to treatment

METHODS

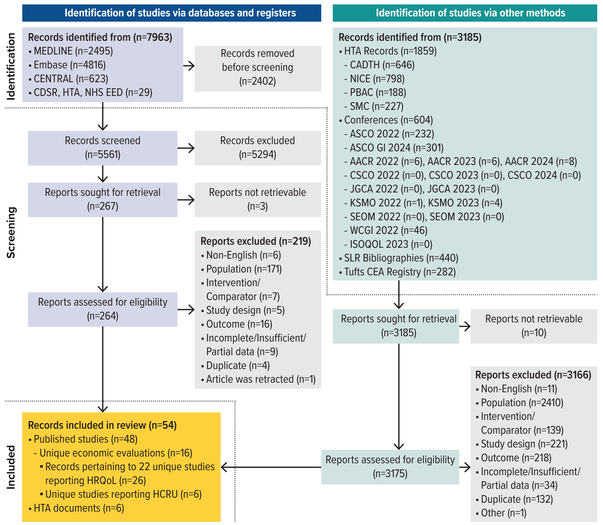
- Searches of Embase, MEDLINE® (including Epub Ahead of Print, In-Process, and Other Non-Indexed Citations), Ovid MEDLINE® Daily, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were conducted on February 14, 2024
- Hand searches of key grey literature 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 GC/GEJ adenocarcinoma
  - There was no restriction on intervention or comparator
  - Outcomes of interest included HRQoL outcomes (generic HRQoL measures, HSUVs, patient-reported outcomes) and HCRU outcomes (healthcare costs, HCRU frequency, caregiver burden)
  - Study types of interest included clinical trials, observational studies, surveys, and economic evaluations; no restrictions were applied to captured studies based on country of origin
- Quality assessment was performed using the following instruments:
  - National Institute for Health and Care Excellence (NICE) Quality Assessment Checklist for Health State Utility Values5 for studies reporting HSUVs and HRQoL instruments (**Supplementary Table 1**)
  - Drummond and Jefferson checklist6 for economic evaluations reporting HSUVs (**Supplementary Table 2**)

RESULTS

Evidence Identified

- Of 7,963 records identified in the database/registry searches and 3,185 records across grey literature sources, 54 records reporting on 44 unique studies (16 economic evaluations[12,17-19,22,26,30,31,34,37,38,42,46,48,49,51], 22 unique studies from 26 records reported HRQoL outcomes[7-31], 19 studies and economic evaluations reported on HCRU[32-50]) and six health technology assessment (HTA) documents reporting on 6 unique submissions (six reported economic evaluations[51-56], two reported HRQoL outcomes[58,59], and six reported HCRU outcomes[51-56]) were included in this review (**Figure 1**)[7-60]

Figure 1. PRISMA Diagram



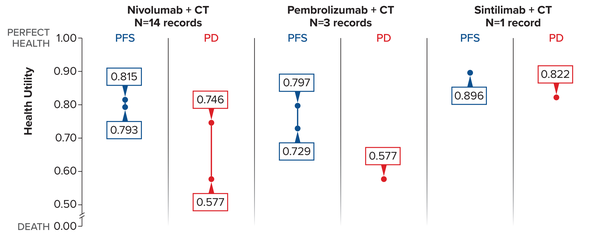
Adapted from: MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. doi: 10.1136/bmj.n71

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; ASCO GI, American Society of Clinical Oncology Gastrointestinal Cancers Symposium; CADTH, Canadian Agency for Drugs and Technologies in Health; CDSR, Cochrane Database of Systematic Reviews; CEA, cost-effectiveness analysis; CSCO, Chinese Society of Clinical Oncology; EED, Economic Evaluation Database; HCRU, healthcare resource use; HRQoL, health-related quality of life; HTA, health technology assessment; ISOQOL, International Society for Quality of Life Research; JGCA, Japanese Gastric Cancer Association; KSMO, Korean Society of Medical Oncology; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; RCT, randomized controlled trial; SEOM, Sociedad Espanola de Oncologia Medica; SLR, systematic literature review; SMC, Scottish Medicines Consortium; WCGI, World Congress on Gastrointestinal Cancer.

Health State Utility Values

- Seventeen studies (one cross-sectional study,[30] two clinical trials,[7,18,60] 14 published cost-utility analyses [CUAs][38-50,59]), and three HTA submissions[52,54,55] provided information relating to HSUVs
- Two clinical trials (ATTRACTION-4 (Part 2)[60] and CheckMate 649[27,28]) reported data for EQ-5D:
  - Nivolumab plus chemotherapy had a significantly longer time to symptom deterioration (TTSD) (hazard ratio [HR]: 0.81, 95% CI: 0.67, 0.99)[60] and time until definitive deterioration (TUDD) (HR: 0.67; 95% CI: 0.52, 0.86) compared to chemotherapy alone[17]
- One cross-sectional study derived EQ-5D-3L scores for patients in the US, the UK, France, Germany, China, and Japan.30 The total mean EQ-5D-3L score across all countries was 0.701, with mean scores of 0.510 in France, 0.696 in Germany, 0.726 in the UK, 0.750 in the US, 0.757 in Japan, and 0.940 in China
- Among CUAs of PD-1 inhibitors, HSUVs for progression-free survival (PFS) ranged from 0.729 to 0.896 and from 0.577 to 0.822 for progressive disease (PD) (**Figure 2**).
- Disutility values were most commonly reported for neutropenia, anemia, fatigue, and nausea/vomiting (**Supplementary Table 3**)

Figure 2. HSUVs Reported by CUAs and HTA Publications for PD-1 Inhibitors



Abbreviations: CT, chemotherapy; CUA, cost-utility analysis; HSUV, health state utility value; HTA, health technology assessment; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival.

Health-Related Quality of Life Measures

- Twenty clinical trials,[7-29] two observational studies,[30,31] and two HTA submissions[54,55] provided HRQoL measures other than HSUVs in patients with 1L GC/GEJ adenocarcinoma
- HRQoL results among PD-1 inhibitors and other targeted therapies are presented in **Table 1**
  - Tislelizumab plus chemotherapy, nivolumab plus chemotherapy, and bemarituzumab plus chemotherapy were associated with maintained or improved HRQoL compared to chemotherapy alone
  - Pembrolizumab plus chemotherapy and zolbetuximab plus chemotherapy demonstrated mixed results across HRQoL scales and trials. Pembrolizumab monotherapy demonstrated similar HRQoL to chemotherapy alone

Table 1. Summary of HRQoL Measures Among PD-1 Inhibitors and Other Targeted Therapies

Trial NCT	Region	Follow-up Times Assessed	Treatments	Scale/Category	Summary of Results
RATIONALE-305 NCT03777657[29]	Global	Baseline; Cycles 4, 6	TIS + CT vs PBO CT	EORTC-QLQ-C30 EORTC-QLQ-STO22	TIS+CT showed a significantly lower risk for deterioration compared to PBO+CT
ATTRACTION-4 (Pt 2) NCT02746796[60]	Asia	NR	NIV + CT vs PBO + CT	FACT-Ga	NIV+CT had longer median TTSD compared to PBO+CT
CheckMate 649; NCT02872116[55,18,17]	Global	Baseline; Week 7, then every 6 weeks to 36 months	NIV + CT vs CT	EQ-5D-3L VAS FACT-G FACT-Ga GaCS	Patients who received NIV+CT reported more clinically meaningful improvements in HRQoL compared to those who received chemotherapy alone
KEYNOTE-062; NCT02494583[22]	Global	Baseline; Weeks 9, 12, 18, 42, 48	PEM vs PBO + CT	EQ-5D-3L VAS EORTC-QLQ-C30 EORTC-QLQ-STO22	No statistically significant differences between PEM monotherapy and PBO+CT
KEYNOTE-859; NCT03675737[16,54]	Global	Baseline; Week 18	PEM + CT vs PBO + CT	EQ-5D-3L VAS EORTC-QLQ-C30 EORTC-QLQ-STO22	Smaller deterioration in EQ-5D VAS from baseline to Week 18 in patients treated with PEM+CT vs PBO+CT No statistically significant differences observed between treatment arms for TTTD in EORTC-QLQ-C30 Statistically significant decrease in TTTD in the pain subscale of EORTC-QLQ-STO22 in patients treated with PEM+CT vs PBO+CT
FIGHT; NCT03694522[23,24]	Global	Baseline; every 8 weeks from Weeks 6 to 46	BEM + CT vs PBO + CT	EQ-5D VAS EORTC-QLQ-C30	BEM+CT showed improvements in HRQoL and longer time to deterioration compared to PBO+CT
FAST; NCT01630083[14]	EU	Baseline; Cycle 1, Cycle 5, every 12 weeks to disease progression	ZOL + CT vs PBO + CT	EORTC-QLQ-C30 EORTC-QLQ-STO22	Significantly delayed deterioration in EORTC QLQ-C30 GHS for patients receiving ZOL+CT vs PBO+CT No statistically significant differences between treatments for any EORTC QLQ-STO22 subscale
SPOTLIGHT; NCT03504397[15]	Global	Baseline; Cycles 9, 17	ZOL + CT vs PBO + CT	EORTC-QLQ-C30	No clinically meaningful deterioration in HRQoL in either arm. Results were similar between arms

Abbreviations: BEM, bemarituzumab; CT, chemotherapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; EORTC QLQ-OES18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Oesophagus18; EORTC-QLQ-STO22, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Stomach22; EQ-5D-3L VAS, EuroQol 5 Dimensions 3 Level Visual Analogue Scale; EU, European Union; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; GaCS, Gastric Cancer Subscale; GHS, global health status; HRQoL, health-related quality of life; NIV, nivolumab; NR, not reported; PBO, placebo; PD-1, programmed cell death protein 1; PEM, pembrolizumab; TIS, tislelizumab; TTSD, time to sustained deterioration; TTTD, time to treatment discontinuation; ZOL, zolbetuximab.

Healthcare Resource Use and Costs Outcomes

- Four studies reported resource use related to hospitalizations, emergency room (ER) visits, and outpatient visits.[32,33,35,36] The proportions of patients experiencing each HCRU outcomes during 1L treatment for GC/GEJ is reported in **Table 2**
- All studies reported HCRU in a chemotherapy context. No studies were identified that provided HCRU data for targeted therapies, including PD-1 inhibitors
- Among hospitalized patients, mean length of stay ranged from 7 days[35] to 8.7 days[32]
- In the US, 44.1% of patients experienced a cancer related inpatient admission, with a mean of 1.5 hospitalizations per patient and 8.7 days per stay.[32] Among Mexican patients, 63.3% of visits were for GC-related surgery, 14.3% were for disease symptom management, and 6.1% were for adverse events or toxicity[36]
- Hospitalizations per patient ranged from 0.2736 in Mexico to 1.632 in the US
- In Brazil, reasons for ER visits included adverse event/toxicity (18.5%), pain (2.9%), comorbidities (1.2%), and cancer symptoms (5.2%)[35]

Table 2. Summary of HCRU Across Regions

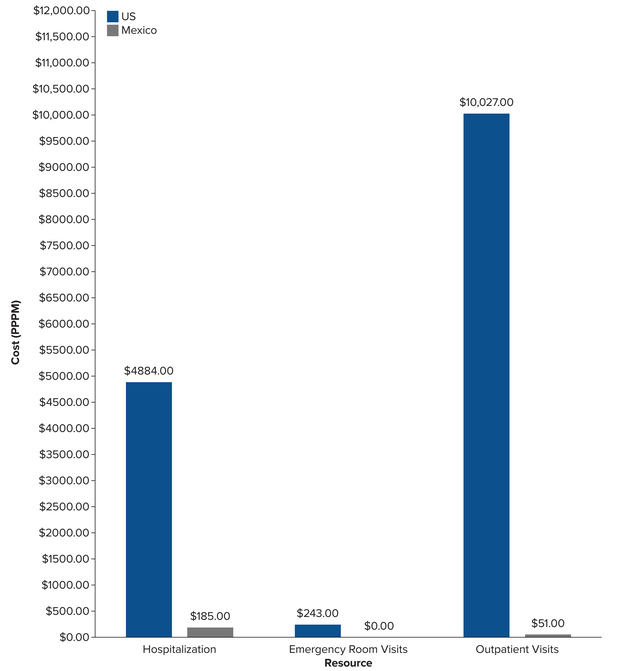
Region	Hospitalizations (Proportion of Patients)	ER Visits (Proportion of Patients)	Outpatient Visits (Proportion of Patients)
US[32,33]	39% to 46.2%	25.3% to 28%	92%
Brazil[35]	39%	42.6%	NR
Mexico[36]	22.2%	NR	14.4%

Abbreviations: ER, emergency room; HCRU, healthcare resource use; NR, not reported; US, United States.

Healthcare Cost Outcomes

- Four studies reported costs related to hospitalizations, ER visits, and outpatient visits.[32-34,36] All studies reported costs in a chemotherapy context. No studies were identified that provided cost data for targeted therapies, including PD-1 inhibitors
- Mean per patient per month (PPPM) costs for hospitalization, ER visits, and outpatient visits were reported in 3 studies,[32-34,36] and are summarized in **Figure 3**
- Mean hospitalization costs in Argentina across all treatment cycles of 1L therapy were $107.6 using public unit costs and $664 using private unit costs[34]
- Physician office visit costs in the US ranged from $31332 to $3,04933 PPPM

Figure 3. Mean Per Patient Per Month Costs Associated With HCRU Across Regions



Abbreviations: ER, emergency room; HCRU, healthcare resource use; PPPM, per patient per month; US, United States.

CONCLUSIONS

- This systematic literature review (SLR) represents the most comprehensive available summary of disease burden associated with first-line (1L) treatment of unresectable, locally advanced, or metastatic gastric cancer (GC)/gastroesophageal junction (GEJ) adenocarcinoma
- The addition of tislelizumab and nivolumab to chemotherapy was associated with maintained or improved health-related quality of life (HRQoL) outcomes compared to chemotherapy alone, while pembrolizumab demonstrated mixed results. Nivolumab plus chemotherapy was also associated with longer time to deterioration in EQ-5D compared to chemotherapy alone
- Data for healthcare resource use (HCRU) and costs related to hospitalizations, ER visits, and outpatient visits were limited by a small number of studies reporting these outcomes. A substantial number of patients experienced hospitalizations and ER visits, though these proportions and associated costs varied by country.
- Important data gaps included few studies reporting on health state utility values (HSUVs) derived from patients with 1L GC/GEJ, and a notable lack of health care resource use HCRU outcomes associated with emerging immunotherapies such as PD-1 inhibitors
- Only one study provided information about patient and caregiver burden, and showed that a GC/GEJ diagnosis had impacts on work, income, and activity for both patients and caregivers

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References 11-60 can be found in the supplemental material by scanning the QR code here.

DISCLOSURES

ES: Grants: Bristol Myers Squibb (BMS), AstraZeneca (institution); Consulting: AstraZeneca, Astellas BeiGene, BMS, Gilead, Novartis, Pfizer, TCypherBio, Viracta, Zymeworks; Honoraria: Amgen, AstraZeneca, Astellas, BeiGene, BMS, MSD, Merck, Mirati, Novartis; Travel: Amgen, Mirati, BeiGene; Participation on Data Safety Monitoring Board or Advisory Board: AstraZeneca, Amgen, Daiichi Sankyo, Jazz, Zymeworks; Leadership: EORTC GI Trials Group Chair, ESMO Guidelines Committee Chair, UKIOG Trustee; **WT, LZ:** Employees of BeiGene and report stock or other ownership; **AS, VD, SC:** Employees of EVERSANA, who received consulting fees.

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