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Background

- Recent developments in biomarker-directed therapy and immunotherapies for advanced and metastatic gastroesophageal adenocarcinoma (GEA; including gastric cancer [GC], esophageal cancer, and gastroesophageal junction cancer [GEJC]) show promise in improving survival and quality of life[1,2]
- Economic evaluations in GEA are challenged by high treatment costs, inconsistent cost and healthcare resource reporting, variable health-state utility values, regional differences in costs, and difficulties in demonstrating cost-effectiveness[3]

Objective

- To summarize the available economic evidence in unresectable advanced or metastatic GEA, including cost and resource utilization, utilities, and cost-effectiveness of current treatment options to inform future development of robust pharmacoeconomic models

Methods

- We conducted three systematic literature reviews (SLRs) focused on economic evaluations, cost and resource use, and health state utilities
- Comprehensive literature searches covering Embase, MEDLINE®, MEDLINE In-Process, EconLit®, the International Network of Agencies for Health Technology Assessment, and the Centre for Reviews and Dissemination at York University were conducted from January 2014 to July 2024 (PROSPERO ID: CRD42024581806). Relevant conferences from 2022 to 2024 were hand-searched. The SLRs followed the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards[4] and were aligned with the requirements of the National Institute for Health and Care Excellence (NICE) and other global health technology assessment (HTA) agencies[5]
- Records were screened by title/abstract and full text according to predefined population(s), intervention(s), comparator(s), outcome(s), and study design (PICOS) criteria by two independent reviewers, with a third resolving discrepancies. Included studies underwent data extraction into predefined extraction grids, performed by one reviewer with verification by a second reviewer
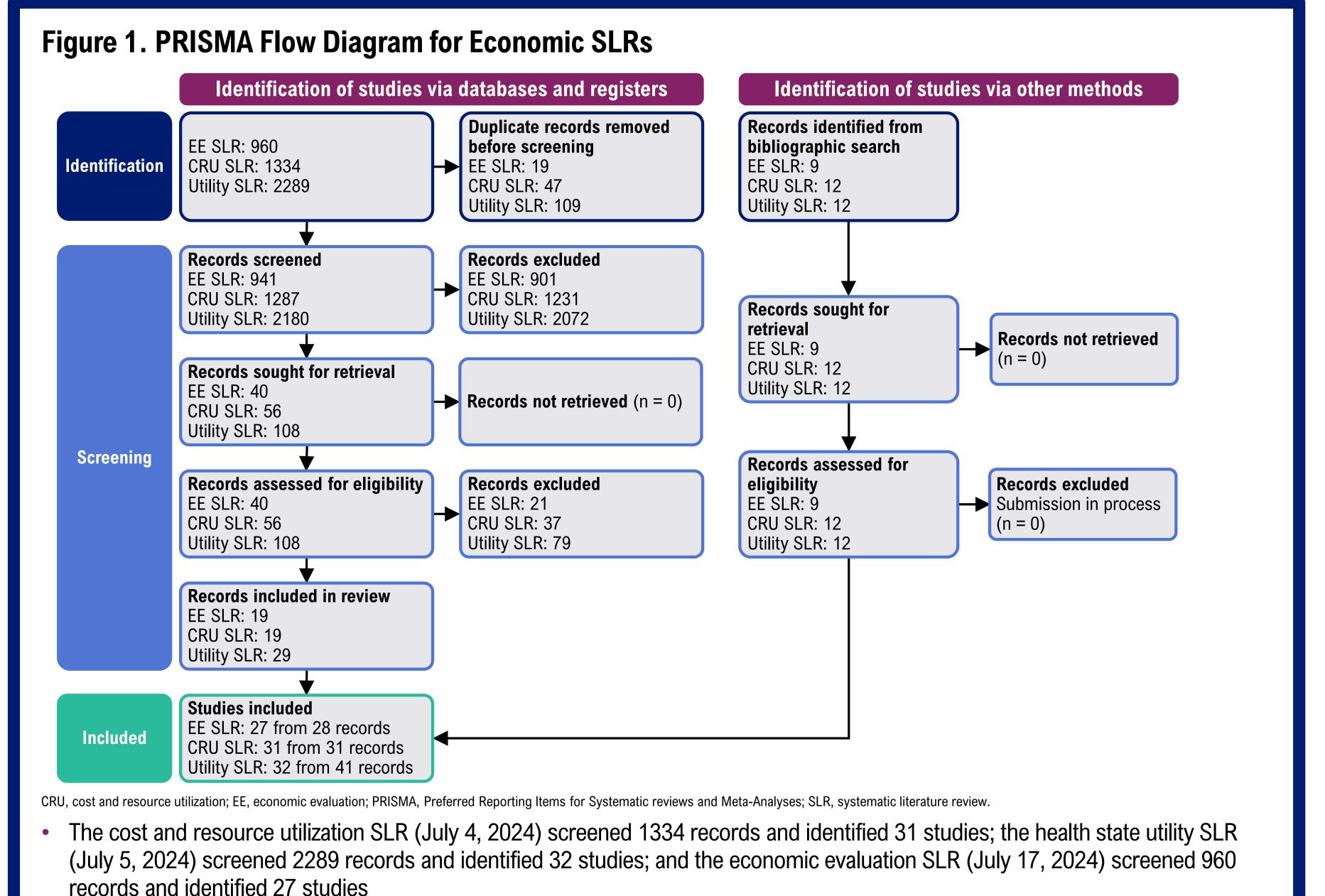
Table 1. PICOS for SLR in Economic Evidence

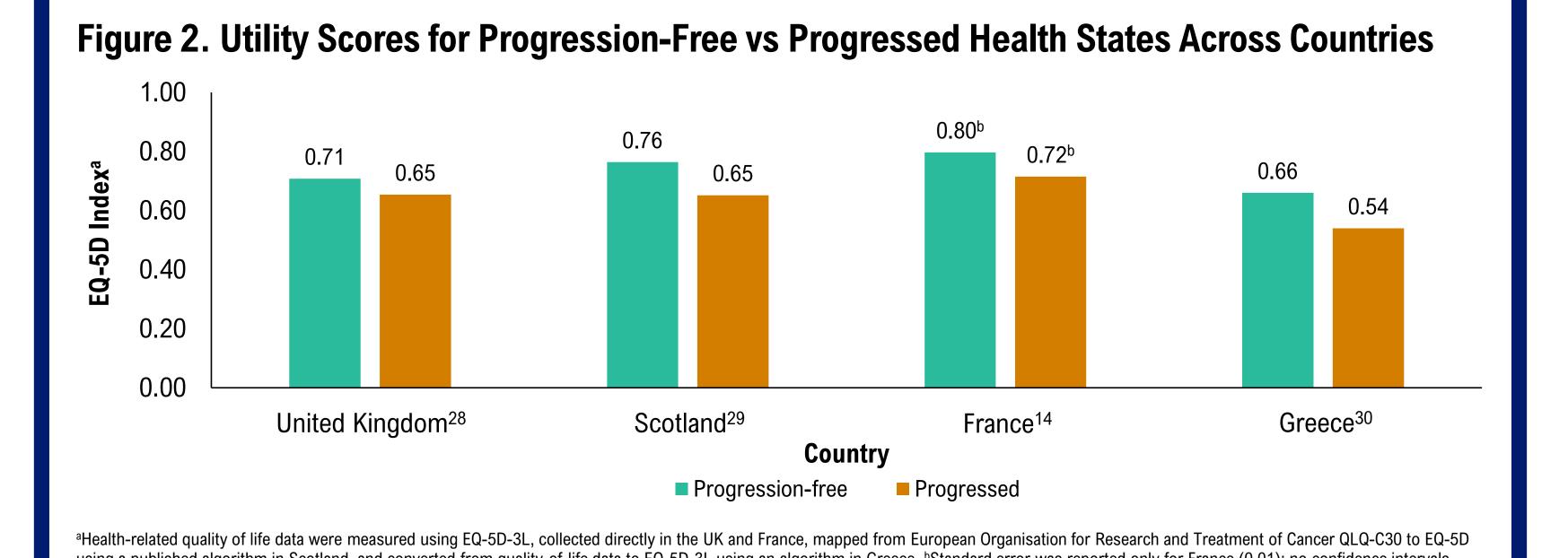| Category	Cost and Resource Utilization SLR	Health State Utility SLR	Economic Evaluation SLR
Population	Adults (≥18 years) with treatment-naïve or first-line-treated unresectable/inoperable advanced or metastatic GEA, including gastric, and GEJ subtypes, irrespective of HER2 status	Adults (≥18 years) with unresectable/inoperable, advanced or metastatic GEA, including gastric, esophageal, and GEJ subtypes, irrespective of HER2 status	Adults (≥18 years) with treatment-naïve or first-line-treated unresectable/inoperable advanced or metastatic GEA, including gastric, and GEJ subtypes, irrespective of HER2 status
Intervention	No restrictions	No restrictions	No restrictions
Comparator	No restrictions	No restrictions	No restrictions
Outcomes	Direct medical, nonmedical, and indirect costs; unit costs; health care resource utilization; budget impact	Utility data (EQ-5D, SF-6D, HUI, EQ-5D VAS); mapped utilities; health state utilities and disutilities	ICERs, QALYs (including incremental), DALYs (including incremental), LYs (including incremental), total costs, HRQoL outcomes (utility and QALY)
Study type	Cost, resource use, and combined cost-resource studies; economic evaluations reporting costs/resource use; systematic reviews/meta-analyses on relevant population[a]	Studies reporting utility/disutility data (any treatment); systematic reviews/meta-analyses on relevant population[a]	Primary and model-based economic evaluations: cost-consequence, cost-minimization, cost-effectiveness, cost-utility, cost-benefit, budget impact; systematic reviews/meta-analyses[a]
Country	US, Canada, EU (4 countries), UK, Japan	No restrictions	No restrictions
Time limit	Last 10 years	Last 10 years	Last 10 years

[a]Recent systematic reviews/meta-analyses (last 3 years) were screened to identify new studies but excluded at secondary screening. Cost-minimization analyses and budget impact analyses were included and identified at the full-text screening stage, but data from these studies were not extracted with other modeling studies. The relevant cost and resource utilization data from these studies deemed relevant for the cost and resource utilization review.
DALY, disability-adjusted LY; European Union; LY, GEA, gastroesophageal adenocarcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; LY, life-year; PICOS, population(s), intervention(s), comparator(s), outcome(s), and study design; QALY, quality-adjusted LY; SF-6D, Short Form-6 Dimension; SLR, systematic literature review; VAS, visual analog scale.

Results

Figure 1. PRISMA Flow Diagram for Economic SLRs

- The cost and resource utilization SLR (July 4, 2024) screened 1334 records and identified 31 studies; the health state utility SLR (July 5, 2024) screened 2289 records and identified 32 studies; and the economic evaluation SLR (July 17, 2024) screened 960 records and identified 27 studies

Table 2. Evidence From Cost and Resource Utilization Studies

Component	US (n = 12)	Europe (n = 12)	Canada (n = 2)	Japan (n = 2)
Resource utilization	• Inpatient admissions: 21%[4]–65%[7] had ≥1 admission; mean stay: 3.4[8]–13[7] days • 30-day readmissions: 16%[8]–21%[9] • ED visits: 16%[7]–56%[9] had ≥1 visit • Outpatient visits: 90%[10]–100%[9,11] had ≥1 visit • Pharmacy use: 9%[7]–91%[8]	For UK • Inpatient/ED use: <1%[12] • Outpatient visits: every 3–6 weeks[13] • GP home visits: every 2 weeks[13] • Nurse home visits: weekly 20-minute nurse visits during progression[13] • Concomitant medication use: 1.76/year[12]	NR	NR
Drug cost	• Nivo: $6,638[14]–$21,601[15]/cycle • Pembro: $21,566/cycle[15] • Chemo: $74[16]–$727[2]/cycle	For UK • Pembro: €104,513[16] • €144,188[17]/year (Germany); $12,658/cycle[15] (UK) • Tras (Herceptin): €42,462/year[17] (Germany) • Nivo + XELOX: £3,950/cycle (UK)[13] • Nivo + FOLFOX, €2,633/cycle[13] (UK) For France • Pembro: €104,513[16]–€144,188[17]/year (Germany) • Nivo + chemo: €42,462/year[17] (Germany)	• Nivo + chemo: CA$5,651–CA$8,345/cycle[18] • Chemo: CA$1,676–CA$2,368/cycle[18] • Pembro + tras + chemo: CA$13,968–CA$15,092/cycle[19]	• Progression-free per month: Nivo: $8,259 Chemo: $1,780–$2,162[20] • Post-progression per month: Chemo: $1,992–$3,144[20]

Chemo, chemotherapy; ED, emergency department; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; GP, general practitioner; nivo, nivolumab; NR, not reported; pembro, pembrolizumab; tras, trastuzumab; XELOX, capecitabine and oxaliplatin.

- A total of 31 studies were included that reported cost and resource utilization data in patients with GEA across multiple countries
- The review identified 12 cost and/or resource use analyses, eight utility analyses, and 11 submissions to various HTA agencies. Most evidence originated from studies conducted in the US (n = 12) and Europe (n = 12), with fewer studies from Japan (n = 2) and Canada (n = 2). Three international studies encompassed multiple regions

Figure 2. Utility Scores for Progression-Free vs Progressed Health States Across Countries

[a]Health-related quality of life data were measured using EQ-5D-3L, collected directly in the UK and France, mapped from European Organisation for Research and Treatment of Cancer QLQ-C30 to EQ-5D using a published algorithm in Scotland, and converted from quality-of-life data to EQ-5D-3L using an algorithm in Greece. [b]Standard error was reported only for France (0.01); no confidence intervals, ranges, standard errors, or standard deviations were reported for the other countries.

- A total of 32 studies reporting health state utility data in patients with advanced or metastatic GEA, including both HER2-positive and HER2-negative populations, were identified across multiple countries
- The highest number of studies were multicenter international studies (n = 13), followed by those conducted in Europe (n = 9), Japan (n = 3), China (n = 3), and Canada (n = 2). One study each was conducted in the Republic of Korea (n = 1) and Iran (n = 1)
- Health utility was most measured using EQ-5D instruments, with valuation methods such as time trade-off, standard gamble, or country-specific value sets
- Across all countries, progression-free states consistently showed higher utility scores than progressed states, indicating the unmet need for treatments that delay progression
- In China, EQ-5D index scores were lower among patients with more advanced disease and varied depending on whether the 2014 or 2018 China-specific tariffs were applied. Using the 2014 tariff, scores were 0.79 for stage III and 0.60 for stage IV disease, whereas with the 2018 tariff, they were higher at 0.90 and 0.81, respectively.[26] EQ-5D scores were also higher in females (0.91) compared with males (0.79)[27]

Healthcare Resource Utilization

- Patients with advanced GEA face a significant healthcare burden, marked by longer and more frequent hospitalizations and emergency department visits, particularly in the US
- Reported hospitalization frequency and duration demonstrated significant variability across studies, as did the number of emergency department visits. Disease-related symptoms were the main drivers of acute care in the US, accounting for 81.8% of emergency department visits and 61.5% of inpatient admissions[6]
- Patients with advanced GEA need frequent outpatient care, particularly in the US where first-line with chemotherapy containing regimens involves multiple monthly visits and additional appointments for management of adverse events (AEs). In Europe, patients generally have a low number of oncologist and physician visits, supplemented by brief weekly nurse visits during disease progression
- The primary reasons for outpatient visits in the US were staging assessment and follow-up (93.5% each). Visits were also for treatment administration (71.0%) and imaging (62.9%), with 38.7% addressing disease-related symptoms[6] (visits could be coded for multiple reasons)
- Pharmacy use among patients with advanced GEA varied widely in the US, with 9%[7]–91%[8] of patients with advanced GEA requiring medications. In Europe, concomitant medication use was estimated at 1.76 times per year (0.03 per week),[12] indicating different treatment patterns and needs between Europe and the US

AE Costs

- In the US, neutropenia accounted for the highest AE cost at $17,181 per patient per episode,[21] followed by anemia at $4,368[22] and diarrhea at $3,340[23] (all USD); costs for peripheral neuropathy, thrombocytopenia, vomiting, nausea, fatigue, hypokalemia, hand-foot syndrome, and stomatitis were not reported
- In the UK, neutropenia had the highest cost per patient per episode (£2,257),[12] followed by peripheral neuropathy (£1,868),[12] thrombocytopenia (£783),[13] fatigue (£780),[12] anemia (£770),[12] and hypokalemia (£754)[12] had moderate costs, while diarrhea, vomiting, and nausea (£522 each),[12] hand-foot syndrome (£267),[12] and stomatitis (£209)[24] had the lowest costs (all GBP)
- In Canada, peripheral neuropathy had the highest cost at CA$10,839 per patient per episode, followed by neutropenia and thrombocytopenia at CA$8,780 each. Anemia and fatigue each cost CA$6,214, diarrhea CA$5,018, and vomiting and nausea CA$4,234 each[18]; costs for hypokalemia, hand-foot syndrome, and stomatitis were not reported
- Severe AEs (anemia, nausea/vomiting, and thrombocytopenia) are associated with considerably high costs in the US, reaching $31,000–$49,000 for patients with commercial insurance compared with $9,000–$17,000 for patients with Medicare (all USD). Cost of severe AEs are pronounced with further lines of therapy[25]
- In the US, during first-line therapy, pembrolizumab plus chemotherapy was associated with AE costs of $6,311 per cycle and nivolumab plus chemotherapy incurred $6,050 per cycle (all USD). In the UK, the corresponding costs were £351 and £132 per cycle, respectively (all GBP)[15]

Table 3. Cost-Effectiveness of Immunotherapy and Targeted Therapies in Advanced/Metastatic GEA

Study	Country	Comparator	Population/Subgroups	Incremental Cost	Incremental QALY	ICER/QALY	WTP Threshold/QALY[a]	Cost-Effectiveness
Immunotherapies								
1. Nivolumab + chemotherapy								
Zhang 2023[22]	US	Chemo alone	Overall GEA; PD-L1 CPS ≥5	$217,141; NR	0.23; NR	$944,090; $649,647	$100,00	Not cost-effective
NICE 2023[11]	UK	Chemo alone	Overall GEA; PD-L1 CPS ≥1; PD-L1 CPS ≥5	Data redacted	Data redacted	$34,110–£47,840; £42,803; £37,694	£50,00	Potentially cost-effective
HAS 2022[14]	France	Chemo alone	Overall GEA	NR	NR	€181,128	€350,00[b]	Not cost-effective
Kashiwa 2022[21] & Morimoto 2022[20]	Japan	Chemo alone	Overall GEA; PD-L1 CPS ≥1; PD-L1 CPS ≥5	$92,185–$139,210; $166,321; $144,049	0.132–0.30; 0.46; 0.34	$458,114–$699,907 (¥74,750,097); $424,698; $359,134	¥15,000,000 & $75,000	Not cost-effective
Jiang 2022[2] & Zhang 2023[22]	China	Chemo alone	Overall GEA	$98,943	0.23	$191,266–$430,185	$33,436–$37,653	Not cost-effective
CDA-AMC 2022[18]	Canada	Chemo alone	Overall GEA	CA$88,768	0.223	CA$398,312	CA$50,000	Not cost-effective
2. Pembrolizumab + chemotherapy								
Lang 2024[2]	China	Chemo alone	Overall GC/GEJC; PD-L1 CPS ≥1; PD-L1 CPS ≥10	$16,627; $22,777; $16,684	0.23; 0.32; 0.51	$72,462; $70,200; $32,779	$35,865	Only PD-L1 CPS ≥10 cost-effective
NICE 2024[12]	UK	Standard chemo	GEA CPS ≥1 licensed population	Data redacted	1.09	Data redacted	£30,000	Cost-effective
CDA-AMC 2024[19,a]	Canada	Trastuzumab + chemo	Overall GC/GEJ	CA$142,868	0.75	CA$191,271	CA$50,000	Not cost-effective
3. Sintilimab + chemotherapy								
Xiang 2024[34]	China	Chemo alone	Overall GC/GEJC; PD-L1 CPS ≥5; PD-L1 CPS <5	$7,988; $12,980; $3,391	0.32; 0.49; 0.19	$25,239; $26,341; $17,658	$38,223	Cost-effective
4. Tislelizumab + chemotherapy								
Li 2024[35]	China	Chemo alone	Overall GC/GEJC	$7,361	0.38	$19,371	$18,625	Low probability at base WTP; >50% if WTP >$23,000
Targeted therapies								
1. Trastuzumab-based chemotherapy								
Franchi 2020[36]	Italy	Standard chemo	Overall GC HER2-positive	NR	NR	€43,998/LYG	€50,000–€100,000	Cost-effective
2. Zolbetuximab + chemotherapy								
Huang 2023[37]	China	Chemo alone	Overall GC/GEJC CLDN18.2+, HER2−	$75,799	0.41	$185,353	$38,201	Not cost-effective

[a]WTP thresholds reported in the publications and applied in decision-making and recommendations. [b]The WTP value reflected a probabilistic analysis (80% probability of cost-effectiveness). It was not an official threshold, and HAS did not validate the ICER or cost-effectiveness results due to methodological uncertainties. [c]The CDA-AMC 2024 study in Canada compared pembrolizumab + trastuzumab + chemotherapy with trastuzumab + chemotherapy. CDA-AMC, Canada's Drug Agency; Chemo, chemotherapy; CLDN18.2, claudin 18.2; CPS, combined positive score; GC, gastric cancer; GEA, gastroesophageal adenocarcinoma; GEJC, gastroesophageal junction cancer; HAS, Haute Autorité de Santé; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; LYG, life-year gained; NICE, National Institute for Health and Care Excellence; NR, not reported; PD-L1, programmed death-ligand 1; QALY, quality-adjusted life-year; WTP, willingness to pay.

- A total of 27 studies reported economic evaluation data in advanced or metastatic GEA, including 24 cost–utility analyses, 2 cost-effectiveness analyses, and 1 cost-minimization analysis
- Nivolumab was assessed in 13 studies and pembrolizumab in 5. Most studies were conducted in China (n = 10), followed by Europe (n = 7), the US (n = 3), Japan (n = 3), and Canada (n = 2). Two studies were conducted across multiple countries
- Economic evaluations were performed mainly from a healthcare payer perspective (n = 9)[18,21,23,31,35,36,39] or societal perspective (n = 17),[12-15,22,24,32-34,36,37,40-45] with one study[14] not reporting the perspective

Nivolumab

- In the US, nivolumab plus chemotherapy showed improvements in quality-adjusted life years (QALYs) but was associated with high incremental costs, resulting in incremental cost-effectiveness ratios (ICERs) that far exceeded the commonly accepted willingness-to-pay (WTP) threshold
- In the UK, ICERs for nivolumab plus chemotherapy approached the WTP threshold, indicating potential cost-effectiveness in programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥1 and ≥5 subgroups. Incremental cost and QALY data were not reported for this regimen
- Across France, Japan, China, and Canada, ICERs for nivolumab + chemotherapy compared with chemotherapy remained well above local WTP thresholds, including subgroups with confirmed PD-L1 expression in Japan

Pembrolizumab

- In the UK, for advanced GC/GEJC, pembrolizumab + doublet chemotherapy was cost-effective for the CPS ≥1 licensed population, though uncertainty persisted for CPS ≥10[12]
- In Canada, for patients with advanced GC/GEJC, pembrolizumab + trastuzumab and chemotherapy showed ICER well above the WTP threshold[19]

In China

- In China, pembrolizumab + chemotherapy demonstrated potential cost-effectiveness only in patients with PD-L1 CPS ≥10, while ICERs in the overall GC/GEJC and CPS ≥1 subgroups remained above the WTP threshold[33]
- The primary driver of cost-effectiveness varies across countries; predominantly being drug acquisition costs in Canada, treatment- and AE-related costs and overall disease management in the UK, and treatment- and AE-related costs, health state utilities, body surface area, and use of subsequent therapies in China

Sintilimab

- In China, sintilimab + chemotherapy was cost-effective for advanced GC/GEJC, with ICERs well below the WTP threshold and probabilistic sensitivity analyses indicating >97% probability of cost-effectiveness across overall GC/GEJC and PD-L1 CPS ≥5 and <5 subgroups[34]
- Cost-effectiveness was mainly driven by the medication cost of sintilimab and capecitabine, supportive care, and progression-free utility[34]

Tislelizumab

- In China, tislelizumab + chemotherapy for advanced GC/GEJC demonstrated limited cost-effectiveness, with a low probability of being cost-effective at the base WTP threshold. This was mainly influenced by progression-free utility, chemotherapy costs, and best supportive care[35]

Trastuzumab

- In China, trastuzumab + single-agent chemotherapy for HER2-positive GC/GEJC had similar average costs when compared with trastuzumab monotherapy (RMB ¥165,195 vs ¥153,137) but had a numerically longer median PFS (11.0 months vs 7.9 months)[46]
- The key factor impacting the ICERs across all countries was the cost of nivolumab, with additional influential factors being progression-free survival (PFS)/progressive disease utilities in China, baseline age/utilities in the UK, and drug administration/subsequent treatment costs in Canada
- In Italy, trastuzumab-based chemotherapy improved survival and demonstrated favorable cost-effectiveness vs standard chemotherapy for advanced HER2-positive GC[36]

Zolbetuximab

- In China, zolbetuximab + chemotherapy for claudin 18.2-positive, HER2-negative advanced gastric/GEJ adenocarcinoma showed no probability of cost-effectiveness at current pricing. Key drivers of cost-effectiveness were zolbetuximab cost, body surface area, and PFS utility. At the current price, the intervention was estimated to not be cost-effective[37]

Conclusions

- This SLR highlights the high overall treatment cost of advanced GEA
- Evidence from this SLR demonstrated that factors such as care setting, resource use, and patient health state significantly influenced costs, indicating their role in determining the cost of advanced GEA treatment
- Hematologic AEs represented the highest-cost toxicities, whereas gastrointestinal AEs ranked among the lowest-cost AEs. This pattern was evident despite differences in healthcare systems and costing methodologies
- Disease progression was associated with worse patient-reported quality of life, reinforcing the value of maintaining progression-free states

- This SLR is limited by inconsistent reporting of resource use and cost data and scarce economic evidence, especially for the US. Variability in model assumptions, extrapolation of survival estimates beyond observed trial data, and exclusion of key comparators further impact these findings. These gaps highlight the need for standardized, locally relevant, and payer-specific models to better reflect real-world practice
- Despite advances in investigational therapies for GEA, many are associated with high treatment costs, which emphasizes an unmet need for therapies that deliver both superior clinical efficacy and economic efficiency

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