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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SUPPLEMENTARY METHODS

Supplementary Table 1. NICE Quality Assessment Checklist for Health State Utility Values

Trial; NCT Reference	Sample Size	Respondent Selection and Recruitment	Inclusion/ Exclusion Criteria	Response Rates to Instruments Used	Loss to Follow-up	Missing Data	Any Other Problems With the Study
498-Babu-2018[1]	n=67 enrolled; n=65 analyzed	All patients enrolled in the trial were eligible for analysis. Patients were enrolled from Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. Recruitment methodologies were not described.	Major exclusion criteria were previous chemotherapy for metastatic or locally advanced disease, congestive heart failure, concurrent second malignancy, and evidence of brain metastases.	Data not explicitly provided. Tables 3 and 4 indicate n=8 patients in the ECF arm were not evaluable at 6 months; while all patients were evaluable at all timepoints for the DCF arm.	No mention of loss to follow-up.	n=2 patients did not complete the QoL questionnaires and were excluded from the analysis. Methods of handling missing data were not further described.	Single-center, nonrandomized design restricted to the patients treated only in one department may effect the generalizability of the results. Posttreatment QoL parameters were assessed only after three and six cycles of chemotherapy, therefore there might be significant undetected variations of HRQoL in between the treatment cycles. The sample size was not very large to draw any robust conclusion.
CheckMate 649; NCT028721166 3255-Moehler-2023[2]	ITT: n=1581 PRO population: n=1360	Patients were recruited from CheckMate 649. All patients from the trial were eligible. Recruitment methodology was not described.	All randomly assigned patients with an evaluable PRO assessment at baseline and ≥1 evaluable postbaseline PRO assessment were included.	In the CPS ≥5 and overall PRO analysis populations, >95% of patients had an evaluable baseline assessment. EQ-5D and FACT-Ga questionnaire completion rates were >80% on most on-treatment assessments with ≥10 patients (until week 133) in both treatment arms; EQ-5D completion rates during follow-up were slightly lower.	Loss to follow-up appears balanced between arms. Progression of disease was the primary reason for discontinuation of treatment in both arms, followed by adverse events related to treatment, adverse events not related to treatment, patient request for consent withdrawal and other (See CONSORT diagram in Suppl. Fig. 1).	For the GaCS, further analyses of missing data patterns were performed to investigate missing at random assumptions. Assessments with ≥10 patients per treatment arm were included for most PRO scales/ subscale; for the EQ-5D and FACT-G7, assessments with ≥20 patients per treatment arm in the overall PRO analysis population were included to achieve model convergence. Missing PRO assessment data were not imputed.	Sample sizes in the chemotherapy arm were smaller than those in the nivolumab plus chemotherapy arm at later timepoints. This study was limited by an open-label trial design, which might have potentially influenced patient responses to questionnaires. PROs were prespecified exploratory endpoints.
FLAGS; NCT00400179 641-Bodoky-2015[3]	Randomized: n=1053 FACT (any item): n=1002 FACT Ga: n=997	Patients were recruited from FLAGS. All patients from the trial were eligible. Recruitment methodology was not described.	The analysis population for the PRO analysis consisted of all patients who completed at least one PRO assessment in any language. Patients were excluded for serious comorbid conditions, prior palliative chemotherapy, or any previous therapy for malignancy other than gastric cancer within the past 5 years or had received concomitant drugs known to interact with S-1.	Compliance to questionnaire fulfillment was more than 80% through cycle 9. After cycle 9, good compliance was observed despite less than 10% of patients remaining on study.	Less than 10% of patients remaining on study after cycle 9. Reasons for discontinuation were not provided.	All PRO end points (TOI, PWB, SWB, EWB, FWB, GaCS, and CCSQ scales) were described using longitudinal summary statistics with no imputation for missing data. The probability of missing data (missingness) was not significantly related to the previously obtained TOI score (*P*=0.11, odds ratio for 7-point MID decrease=1.04), nor was it related to PWB, SWB, EWB, FWB, or GaCS scores.	Open-label according to CT.gov (NCT00400179). Outcome reporting may be biased.
1615-Glimelius-1997[4]	ITT: n=61	Patients were recruited from the Regional Oncological Centre in Uppsala, Sweden. Recruitment methodology was not described.	All patients enrolled were eligible for analysis. Excludes patients >75 years old	The number of patients who replied to the questionnaires declined during follow-up. This decline was more rapid in the best supportive care group. Number evaluable available in Table 2. The reasons for not replying to a questionnaire after 2 and 4 months were usually either death or that the patient was terminally ill. Consequently, treatment effects may be underestimated and biased towards the null. This decline was more rapid in the best supportive care group. Response rates were not provided.	Two patients in each group did not complete the questionnaire at randomization because of rapidly progressing disease. The reasons for not replying to a questionnaire after 2 and 4 months were usually either death or that the patient was terminally ill. After the first interview, one patient in the best supportive care group refused further interviews.	Data not provided.	Conducted in Sweden - may not be generalizable to broader population. Small sample size - conclusions should be interpreted with caution.
GATAC trial; 1698-Gubanski-2014[5]	Enrolled: n=81 Treated: n=78 (T arm, n=39; C arm, n=39) Entire treatment duration: n=47 (T arm, n=25; C arm, n=22)	Patients were recruited from the GATAC trial. Recruitment methodology was not described.	Designed to include 80 patients with histologically verified metastatic or unresectable adenocarcinoma of the stomach or the cardia and radiologically measurable lesions according to the response evaluation criteria in solid tumors (RECIST). All patients had a good performance status (WHO ≤2) and adequate hematological, renal, and liver functions at baseline.	One hundred ninety-one completed QoL questionnaires were collected. The compliance rate in answering questionnaires was 96% at baseline, 85% after four courses, and 64% after eight courses of treatment.	Reasons for lack of QoL assessment, n (%): Missing baseline questionnaire: 3 (9) Disease progression: 10 (31) Death: 6 (19) Toxicity: 7 (22) Missing questionnaire: 6 (19) Many participants excluded from analysis were due to incomplete response following AE, in addition to some excluded participants due to missing baseline or follow-up questionnaire. Exclusion of those with incomplete response due to AE may bias the null to overestimate the reported QoL during follow-up.	Patients with missing questionnaires were excluded from the analysis, as suggested by the text "47 patients had completed all three assessments." The uncompleted assessments classified as missing questionnaire could not be connected to disease progression or severe toxicity, suggesting missing data is unlikely to significantly bias the results.	Based in Sweden - may not be generalizable.
2506-Korkeila-2017[6]	Total: n=53 Evaluable for QoL analyses: n=46	All patients enrolled in the trial were eligible for inclusion in analysis. Recruitment methodology was not described.	Prerequisites for inclusion in the analyses of (a change in) physical functioning score consisted of at least one given treatment cycle as well as QLQ-questionnaire filled at baseline and after the first treatment cycle.	The number of patients with assessable QoL questionnaires at baseline was 46 (45 for global health status and STO 22 questionnaires), after the first and subsequent four cycles, the number of patients was 45, 37, 30, 27, and 20, respectively.	No mention of reasons for loss to follow-up.	Data not provided.	This study did not have a control arm; results should be analyzed with caution. Based in Finland - may not be generalizable.
3975-Roth-2007[7]	Randomized: n=121 Analyzed: n=119	Patients were recruited from the Swiss Group for Clinical Cancer Research Coordinating Center. Recruitment methodology was not described.	All patients enrolled were eligible for analysis. No exclusion criteria provided. Of 121 patients, two were not treated (renal failure, n=1; and ineligibility, n=1) and were excluded.	Of all expected QoL forms before treatment failure, 120 (100%) were received at baseline, and 175 (71%) were received under treatment.	No mention of loss to follow-up.	n=2 patients were not treated (renal failure, n=1; and ineligibility, n=1) and were excluded from the analysis. Data were not further provided.	QoL evaluation was not powered for a formal treatment comparison. Conducted in Sweden - may not be generalizable to broader population.
NCT01567618 5106-Xiao-2015[8]	Enrolled, n=39. Analyzed, n=38. One patient withdrew consent after the first cycle.	All the patients were treated in the Sixth Affiliated Hospital of Sun Yat-sen University. Recruitment methodology was not described.	All patients enrolled were eligible for analysis. Eligible patients had histologically confirmed gastric adenocarcinoma and measurable unresectable or metastatic lesions, were 18-80 years of age with ECOG of 0-2. No prior chemotherapy was allowed. Patients had adequate hematological, hepatic and renal functions, life expectancy >3 months. Patients were excluded due to receipt of certain treatments before entering the trial. Patients with bone-only metastasis, symptomatic brain metastasis, other simultaneous systemic anticancer treatments, uncontrolled hypertension, unstable coronary syndrome, cardiac arrhythmia, concurrent malignancies, or active infection were also ineligible.	Sixty out of 78 expected questionnaires were completed (76.9 %), 30 (76.9 %) patients finished the baseline assessment, and 30 (76.9 %) patients finished the second assessment. Given limited context/justification for response rates, it is difficult to ascertain its threat to validity.	One patient withdrew consent after the first cycle.	Patients with missing data were excluded from analysis. While small sample size might threaten the study's statistical power, no significant threat to the estimate's validity is expected. See text: "Nine subjects were excluded from the analysis because of insufficient data leaving 30 patients for evaluation."	Only 23 (59%) were chemo-naive patients. No comparator treatment arm. All patients were enrolled from China; may not be generalizable to broader population. Open-label trial.
5105-Xiao-2023[9]	Total recruited, n=995; HER2 status was negative or unknown and receiving active 1L treatment, n=682 EQ-5D-3L: 672 EQ-VAS: 675 FACT: Physical well-being: 679 FACT: Social/family well-being: 678 FACT: Emotional well-being: 679 FACT: Functional well-being: 680 FACT-Ga: 677 FACT: Trial outcome index: 602 FACT-G: 296 FACT: Gastric total: 281 Katz index: 611 Interference with daily activities: 682 Interference with social life: 682	To be invited to participate in the survey, clinical oncologists and gastroenterologists must have been practicing for more than 5 and less than 35 years and been involved in treatment decisions for a minimum of 10 patients with GC/GEJC/EAC per typical calendar month. Sampling was conducted in a stratified random fashion within regions, with caps applied to reduce bias of oversampling at any given site or region, and to maximize representativeness of the sample. Clinicians included in the survey were invited to recruit up to 12 consecutively consulting patients.	Excludes participants receiving 1L active drug treatment from clinical trials. Otherwise, see text for eligibility criteria: "To be eligible, patients had to be aged 18 years or over, have a clinician confirmed diagnosis of unresectable advanced or metastatic GC/GEJC/EAC, an Eastern Cooperative Oncology Group (ECOG) score of ≤2, and be receiving 1L active drug treatment (excluding clinical trials) or best supportive care (BSC) at point of consultation."	Response rates are reported and vary for each QoL measure, but no significant threat to validity is expected.	No loss of follow-up as this is a cross-sectional study.	Missing data in the patient questionnaire were not imputed, and the base (n) for each variable is reported, thereby enabling the calculation of the number of patients excluded from analysis due to missing values.	From text: "A limitation of this approach (ie, clinicians providing data for differing numbers of patients depending on the size of the advanced GC/ GEJC/ EAC consulting patient population) may be that the patient sample was not evenly distributed across the sites and might be weighted towards those sites with a large population of patients with advanced GC/GEJC/EAC patients. Furthermore, participants were encouraged, but not required, to complete all forms. As a result of the dependence on accurately completed questionnaires, the base sizes fluctuated across different variables. Finally, eligible patients were selected by physicians on a consecutive basis from the point of physician enrollment into the study, and it is therefore likely that patients who visited their physician more frequently were also more likely to have been included in the study."
ATTRACTION-4 Part 2; NCT02746796 G-BIB-413-Kang-2022[10]	Randomized, n=724 (n=362 [NIV+CHEMO]; n=362 [CHEMO]) Received treatment: n=359 (NIV+CHEMO); n=358 (CHEMO) EQ-5D-3L completed at baseline: n=358 (NIV+CHEMO); n=357 (CHEMO) FACT Ga completed at baseline: n=357 (NIV+CHEMO); n=355 (CHEMO)	Patients were enrolled from 130 centers across Japan, South Korea, and Taiwan in the ATTRACTION-4 trial. No further recruitment methodology was described.	Patients with HER2-positive or indeterminate gastric cancer, malnutrition, multiple cancers, various other lung/heart/gastric diseases, autoimmune diseases, unable to take oral medications or previous treatment with certain medications. Patients with no baseline data were censored to day 1 (randomization) and patients with baseline data, but no subsequent data were censored to day 2 (1 day post randomization) in both analyses.	EQ-5D-3L at baseline: 99% for both arms FACT-Ga at baseline: NIV+chemo: 99% and chemo: 98% Completion of both questionnaires were both >90% at following assessments during study treatment.	Reasons for treatment discontinuation are available in Fig 1. Reasons for treatment discontinuation included disease progression, apparent worsening of clinical symptoms, AEs, discontinuation based on physician's decision, and other. Loss to follow-up appears to be comparable between arms and no threat to validity is expected.	Data not provided. Patients with missing baseline data appear to have been excluded from the analysis.	Results may not be generalizable outside of Asia.
CheckMate 649; NCT02872116 G-BIB-412-Shitara-2022[11]	Enrolled: n=3185 patients Randomized: n=2031 FACT Ga evaluable: PD-L1 CPS ≥5: NIV+CHEMO, n=412; CHEMO, n=386 Overall population: NIV+CHEMO, n=679; CHEMO, n=639	Patients were recruited from CheckMate 649. No further recruitment methodology was described.	No exclusion criteria provided.	Among patients who were eligible for PRO assessments, the proportion completing the FACT-Ga questionnaire in both treatment arms was 90% or more at baseline and 80% or more at most subsequent assessments for which at least 10 patients were eligible (until week 133).	The primary reason for treatment discontinuation was disease progression. Loss to follow-up appear to be balanced between groups.	Data not provided.	Open-label trial - outcome reporting may be biased.
FAST; NCT01630083 2921-Lordick-2021[12]	FAS: n=161 (EOX: n=84; ZOL/EOX: n=77) PPS: n=143 (EOX: n=74; ZOL/EOX: n=69). PPS, EORTC QLQ-C30 at cycle 1 (ZOL/EOX; EOX): n=68; n=74 PPS, EORTC QLQ-STO22 at cycle 1 (ZOL/EOX; EOX): n=68; n=74	Patients were recruited from the FAST trial. All patients from the trial were eligible for PRO assessment. Recruitment methodology was not described.	The PRO analysis was conducted on the FAS and the PPS set. The FAS included all patients randomized who received at least one dose of any study drug. The PPS comprised all patients without major protocol violations who received at least two complete cycles of therapy according to the protocol and had a second tumor evaluation after baseline.	A similar proportion of patients completed both instruments in the two arms up to cycle 8 of EOX. The proportion of patients who completed the EORTC QLQ-C30 at cycle 8 was 82% in the ZOL/EOX group and 77% in the EOX group. For the EORTC QLQ-STO22, this proportion was 66% and 60%, respectively. From the end of the EOX treatment onwards, the proportion of patients completing the questionnaire remained high in the ZOL/EOX arm but markedly decreased in the EOX arm (<=20%). See Table 2. Reasons for non-responses are unknown, and therefore difficult to determine the potential threat to validity.	No mention of loss to follow-up.	For MMRM, the model included all data available and assumed that the missing observations were missing at random. No mention of imputation.	The add-on setting (zolbetuximab as add-on to first-line EOX) and the expected different duration of the EOX and zolbetuximab therapies rendered a blinded study design difficult. While the limitation of the open-label nature of PROs collection in FAST cannot be discarded, this limitation is mitigated by the fact that the control arm (EOX) was an active therapy and considered part of the standard of care. Another limitation is the marked decrease in the number of patients completing the PRO instruments after the end of EOX treatment in both arms. While the number of patients completing the questionnaires remained high during EOX treatment, this number dropped rapidly in both arms thereafter.
EXELOX; NCT02395640 5534-Zhu-2022[13]	Randomized: n=448 (XELOX, n=222; EOX, n=226) ITT population: XELOX, n=222, EOX, n=226 Per Protocol and Safety population: n=428 (XELOX, n=213; EOX, n=215)	Patients were recruited from the EXELOX trial. All patients from the trial were eligible for PRO assessment. Recruitment methodology was not described.	Key exclusion criteria included HER2-positive patients who were able to afford and willing to receive trastuzumab treatment, and symptomatic brain or leptomeningeal metastases. All patients enrolled in the trial were eligible for QoL assessment.	At baseline and at the beginning of cycles two, four, six, and eight, the rates of compliance to the QoL questionnaire were 86.9%, 75.3%, 68.1%, 48.8%, and 15.0% in the XELOX arm, and 83.2%, 81.8%, 74.1%, 45.9%, and 12.1% in the EOX arm, respectively.	Discontinuations appear comparable between treatment arms (see CONSORT diagram). XELOX: ineligible (n=1), no response evaluation (n=6); EOX: ineligible (n=1), withdrew due to personal reason (n=1), no response evaluation (n=6).	We also used the last observation carried forward (LOCF) method and mean-value method to fill in the missing data.	Open-label trial - outcome reporting may be biased. Conducted at seven sites in China - may not be generalizable to broader population.
KEYNOTE-062; NCT02494583 4778-Van Cutsem-2021[14]	Randomized: n=763 (PEM, n=256; PEM plus chemotherapy, n=257; chemotherapy, n=250). Present analysis (PEM monotherapy and chemotherapy arms only): n=495 (PEM, n=252; chemotherapy, n=243) EORTC QLQ-C30 evaluable, (pembrolizumab, chemotherapy): n=239, n=234	Patients were recruited from the KEYNOTE-062 trial. All patients from the trial were eligible for PRO assessment. Recruitment methodology was not described.	The HRQoL analysis population comprised all patients who received >=1 dose of study treatment and completed >=1 HRQoL questionnaire. Trial exclusion criteria not described.	Compliance rates at week 18 were similar in the pembrolizumab arm and the chemotherapy arm for EORTC QLQ-C30 (87.9% and 81.9%), EORTC QLQ-STO22 (87.9% and 81.3%), and EQ5D-3L (87.9% and 82.5%) questionnaires, respectively. Completion rates of all three questionnaires decreased from baseline because of treatment discontinuation attributed to disease progression, death, or AEs. Despite the potential bias towards the null due to non-responders' reasons for exclusion (AE, disease progression, death), similar decrease in response rates between arms likely minimize any potential threats to validity.	Completion rates of all three questionnaires decreased from baseline because of treatment discontinuation attributed to disease progression, death or AEs. Despite the potential bias towards the null due to non-responders' reasons for exclusion (AE, disease progression, death), similar decrease in response rates between arms likely minimize any potential threats to validity.	Change in LSM score from baseline to week 18 was assessed using a constrained longitudinal data analysis model based on the missing-at-random assumption. Statistically valid and acceptable method to handle missing data; threat to validity is not expected.	HRQoL outcomes reported here were prespecified secondary and exploratory endpoints from KEYNOTE-062. One limitation of these HRQoL analyses is the partially blinded design of the study. Patients were not fully blinded to pembrolizumab monotherapy because only one type of study treatment was administered in that arm of the trial. Conversely, administration of pembrolizumab or placebo was blinded in the combination chemotherapy arms.
REQUEST; 2395-Kim-2019[15]	Enrolled, n=532; Analyzed, n=527; Five of these patients were ultimately excluded because they were participating in other investigational studies	Patients were enrolled from 26 sites in Korea. Recruitment methodology was not described.	Eligibility criteria align well with the PICOS defined for this SLR. See text: "The inclusion criteria for patients (who were all aged >20 years) were having histologically confirmed unresectable locally advanced or metastatic/ recurrent gastric adenocarcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, an expected survival of >3 months, and no prior palliative chemotherapy for GC. The exclusion criteria were having participated in a clinical trial with any investigational drug within the 30 days prior to study entry or having comorbidities or organ dysfunctions unsuitable for systemic chemotherapy."	Participants' compliance with completing the QoL questionnaires decreased from 95.07% (501/527 patients) to 75.76% (25/33 patients) by the end of the 12-month study period. However, authors note "This trend was similar to the compliance observed for the QLQ-C30 scale in the RAINBOW study [30]." Considering this, there is no significant threat to validity expected.	62, 62, 20, 16 patients were lost to follow-up at month 3, 6, 9, and 12, respectively. (Fig 1)	Data not provided.	Participants received varying chemotherapy regimens, which may have heterogenous effects on QoL results and potentially bias the null towards no effect. With respect to this concern, the authors note "However, to ensure that the conditions of this study were as realistic as possible, we did not limit the chemotherapy regimens included." Additionally, patients were recruited from Korea; may not be generalizable.
V-325 Study Group Trial; NCT00811447 304-Ajani-2007[16]	Enrolled, n=445	Patients were recruited from the V325 phase 3 trial from 72 centers in 16 countries. Recruitment methodology was not described.	Very elderly (>75 years) were ineligible for study inclusion. To be considered assessable for PRO (patient-reported outcomes) analysis, a questionnaire must have been completed ≤15 days before random assignment for the baseline assessment and more than 10 days after the start of the latest infusion for assessments during the treatment period; this allowed assessment of the patient's QoL after recovery from potential acute toxicities of the drug. Questionnaires without an assessment date or those completed after the cutoff date or after further antitumor therapy were not assessable. If more than one questionnaire was received from a patient within a defined window, the mean of the assessable values was taken.	Response rates were decreased with time, but there were no differences reported between groups and similar response rates were observed between groups. See text: "The proportion of patients with assessable QLQ-C30 questionnaires at baseline was 86.0% with DCF and 89.7% with CF. The rate of assessable questionnaires decreased over time (Table 2), as expected. The availability of forms was similar between the two treatment groups. ... The proportion of patients with assessable EQ-5D questionnaires at baseline was 78.7% with DCF and 92.8% with CF (Table 2). There were no differences between the groups at baseline in the QLQ-C30 global health status/QoL, functional, or symptom subscales or in the EQ-5D (Table 3)."	No mention of loss to follow-up.	Data are not provided but can be calculated using the number of respondents. Nonetheless, adequate handling of missing data was described. See text: "We chose the parameter of time to definitive deterioration of global health status/QoL by 5% as the primary endpoint of the QoL analysis following the methodology described by Awad et al. Because a definitive deterioration can often be captured before a patient's deterioration in physical status affects compliance, this methodology is less affected by missing data than the classical repeated-measures analysis of variance. This methodology is similar to other time-to-event analyses, such as time to progression, but has been adapted to the analysis of QoL and is less impacted by missing data than a classical analysis of variance. It allows keeping patients in the analysis even if some of their questionnaires are missing as long as they have assessable questionnaires afterwards. In addition, if a patient died within 12 weeks of the last assessment, the death was considered an event, and missing questionnaires afterwards were not considered as missing values, which is in contrast to an analysis of variance. When a patient deteriorated and did not have an assessment after that point, the patient was considered as definitively deteriorated because it is assumed that the reason for the missing data was the worsening of the patient's QoL. This approach has been shown to be sensitive when true differences in QoL exist."	Open label per ct.gov https:// clinicaltrials.gov/study/NCT00811447
FLOT65+; NCT00737373 324-Al-Batran-2013[17]	Enrolled, n=143; ITT, n=143; safety analysis, n=142. One patient was excluded from the safety analysis because of consent withdrawal before study treatment.	All patients from the trial were eligible for analysis. Recruitment methodology was not described.	Only very elderly patients (65+ years old) were eligible. See text: "Patients aged ≥65 years with histologically confirmed and measurable locally advanced or metastatic adenocarcinoma of the stomach or oesophagogastric junction were eligible. Patients with locally advanced disease (as determined by CT scans and endoscopic ultrasound) had to have lymph node involvement (>2 cm) in order to enable adequate response evaluation. Patients must have had no prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, sufficient bone marrow and kidney function, and no concurrent uncontrolled medical illness. Participants gave written informed consent, which was approved by the ethics committees of the participating institutions."	Response rates decreased over time, but no significant differences in response rates and QoL scores were observed between groups. Therefore, decreased response rates are unlikely to threaten validity of results. See text: "The proportions of patients with assessable QoL questionnaires at baseline, 8, 16, and 24 weeks were 123/143 (87%), 91/122 (75%), 51/76 (67%) and 21/31 (68%), respectively, and were similar in both arms."	No mention of loss to follow-up.	Data not provided.	Open label per ct.gov: NCT00737373
3653-Park-2017[18]	Enrolled, n=250; enrolled and received study treatment, n=247; randomized to continuous or stop and go arm (confirmed disease stabilization), n=121	All patients from the trial were eligible for analysis. Recruitment methodology was not described.	Patients were eligible for the induction phase if they were aged ≥18 years and had histologically confirmed recurrent or metastatic gastric adenocarcinoma, no previous palliative chemotherapy, measurable or evaluable lesion(s), ECOG performance status ≤2, and adequate major organ functions. Patients were eligible for the maintenance phase if they had an ECOG performance status ≤2 and had completed six cycles of induction SOX with documented radiographical evidence of a complete response (CR), partial response (PR), stable disease (SD), or incomplete response (IR).	More than 90% of the patients in each arm completed the randomization questionnaire and at least one post-randomisation questionnaire. Low threat to validity is expected.	Continuous arm: progressive disease: 46 Patient's refusal: 5 Physician's discretion: 3 AE: 3 Stop and go arm, no resuming SOX at PD: Physician discretion: 5 Patient's refusal: 5 Poor performance status: 1 Grade 3 neuropathy: 1 Surgery: 1	Data not provided.	Study consisted of a non-randomized induction phase, followed by randomized maintenance phase. Open label per ct.gov. Conducted solely in Korean patients, may not be generalizable.

Abbreviations: AE, adverse event; BSC, best supportive care; CCSQ, Chemotherapy Convenience and Satisfaction Questionnaire; CPS, combined positive score; CT, chemotherapy; DCF, docetaxel, cisplatin plus 5-FU; EAC, esophageal adenocarcinoma; ECF, epirubicin, cisplatin plus 5-FU; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach; EOX, epirubicin + oxaliplatin + capecitabine; EQ-5D, EuroQol 5 Dimension; EQ-5D-3L, EuroQol 5 Dimension 3 Level; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-G7, abbreviated 7-item version of FACT-G; FACT-Ga, Functional Assessment of Cancer Therapy-Gastric; FAS, full analysis set; FWB, functional well-being; GaCS, gastric cancer subscale; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; ITT, intention-to-treat; LSM, least square means; MID, minimum important difference; MMRM, mixed-effects model for repeated measures; NIV, nivolumab; PD-L1, programmed death-ligand 1; PEM, pembrolizumab; PICOS, population, intervention, comparison, outcome; PPS, per-protocol set; PRO, patient-reported outcomes; PWB, physical well-being; QoL, quality of life; S-1, tegafur/gimeracil/oteracil; SLR, systematic literature review; SOX, S-1/oxaliplatin; SWB, social/family well-being; TOI, trial outcome index; VAS, visual analog scale; WHO, World Health Organization; XELOX, oxaliplatin plus capecitabine; ZOL, zolbetuximab.

Supplementary Table 2. Drummond and Jefferson Checklist for Economic Evaluations

	4268-Shu-2022[19]	2175-Jiang-2022[20]	2293-Kashiwa-2022[21]	3695-Peng-2018[22]	1998-Huang-2023[23]	5400-Zhang-2023[24]	5536-Zhu-2023[25]	3109-Marupuru-2023[26]	3305-Morimoto-2023[27]	757-Cao-2023[28]	2600-Lang-2023[29]	5017-Wen-2020[30]
Study Design												
The research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The economic importance of the research question is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The viewpoint(s) of the analysis are clearly stated and justified	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The rationale for choosing the alternative programs or interventions compared is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The alternatives being compared are clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The form of economic evaluation used is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data Collection												
The source(s) of effectiveness estimates used are stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Details of the design and results of effectiveness study are given (if based on a single study)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Details of the methods of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA	NA
The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods to value benefits are stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Details of the subjects from whom valuations were obtained are given?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
The relevance of productivity changes to the study question is discussed	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Quantities of resources are reported separately from their unit costs	No	No	No	No	No	No	No	No	No	No	No	No
Methods for the estimation of quantities and unit costs are described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Currency and price data are recorded	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Details of currency of price adjustments for inflation or currency conversion are given	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Details of any model used are given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The choice of model used and the key parameters on which it is based are justified	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No
Analysis and Interpretation of Results												
Time horizon of costs and benefits is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The discount rate(s) is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
The choice of discount rate(s) is justified	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes
An explanation is given if costs and benefits are not discounted	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	No
Details of statistical tests and confidence intervals are given for stochastic data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
The approach to sensitivity analysis is given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The choice of variables for sensitivity analysis is justified	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No
The ranges over which the variables are varied are justified	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Incremental analysis is reported	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Major outcomes are presented in a disaggregated as well as aggregated form	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	Yes
The answer to the study question is given	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusions follow from the data reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conclusions are accompanied by the appropriate caveats	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Abbreviation: NA, not applicable.

Supplementary Table 3. AE Disutility Values Reported by Economic Evaluations and HTAs

Region/ Perspective	Reference	Intervention	Comparators	Utility Input Source	AE Disutility
Published CUAs					
US/ US third-party payer perspective	757-Cao-2023[28]	NIV + CT (CAPOX or FOLFOX)	CT (CAPOX or FOLFOX)	Shiroiwa et al. 2011[31]	Neutropenia: 0.46
US/ US payer perspective	3109-Marupuru-2023[26]	NIV + CT (CAPOX or FOLFOX)	CT (CAPOX or FOLFOX)	Soni et al. 2021[32] Shiroiwa et al. 2011[31]	Grade 4 Neutropenia: 0.163 Neutrophil count decreased: 0.163 Lipase increased: 0.17 Grade 3 Diarrhea: 0.11 Neutropenia: 0.163 Neutrophil count decreased: 0.163 White blood cell count decreased: 0.163 Nausea: 0.26 Peripheral neuropathy: 0.014 Vomiting: 0.11 Fatigue: 0.20 Anemia: 0.119 Decreased appetite: 0.038 Thrombocytopenia: 0.108 Platelet count decreased: 0.108 Peripheral sensory neuropathy: 0.014 Lipase increased: 0.17 Palmar-plantar erythrodysesthesia syndrome: 0.326
China/ Chinese healthcare system perspective	1998-Huang-2023[23]	ZOL + CT (mFOLFOX6)	PBO + CT (mFOLFOX6)	SPOTLIGHT[33]	Nausea/Vomiting: 0.12 Neutropenia: 0.20 Anemia: 0.07 Neutrophil count decrease: 0.20 Fatigue: 0.07
China and US/ Chinese and US payer perspectives	2600-Lang-2023[29]	PEM or PEM + CT (CIS + 5-FU or CIS + CAP)	CT (CIS + 5-FU or CIS + CAP)	Cao et al. 2023[28] Shu et al. 2022[19] Zhou et al. 2017[34] Chen et al. 2017[35] Shabaruddin et al. 2013[36]	US CT-related AE: 0.044
US, UK, and China/ National healthcare system perspectives	5536-Zhu-2023[25]	PEM + CT (CAPOX)	NIV + CT (CAPOX)	Shu et al. 2022[19]	NIV + CT vs CT AE: 0.013 PEM + CT vs CT AE: 0.007
HTAs					
UK/ NHS and Personal Social Services perspective	G-HTA-656-NICE-2023[37]	NIV + CT (CAPOX or FOLFOX)	CT (CAPOX or FOLFOX)	CheckMate 649[38]	Anemia: 0.115 Diarrhea: 0.0468 Fatigue: 0.119 Nausea: 0.103 Neutropenia: 0.08973 Vomiting: 0.103 Thrombocytopenia: 0.11
UK/ NHS and Personal Social Services perspective	G-HTA-1297-NICE-2024[39]	PEM + CT (FP or CAPOX)	PBO + CT (FP or CAPOX)	KEYNOTE-859[40]	Anemia: 0.11500 Neutropenia: 0.08973 Diarrea: 0.04680 Vomiting: 0.10300 Fatigue: 0.11900 Nausea: 0.10300 Hypokalemia: 0.00000 Palmar-plantar erythrodysesthesia syndrome: 0.04320 Peripheral neuropathy: 0.21600

Abbreviations: 5-FU, fluorouracil; AE, adverse event; CAP, capecitabine; CAPOX, capecitabine, oxaliplatin; CIS, cisplatin; CT, chemotherapy; CUA, cost-utility analysis; FOLFOX, leucovorin, fluorouracil, oxaliplatin; FP, 5-FU, cisplatin; HTA, health technology assessment; mFOLFOX6, modified folinic acid, fluorouracil, and oxaliplatin regimen; NIV, nivolumab; PBO, placebo; PEM, pembrolizumab; UK, United Kingdom; US, United States; ZOL, zolbetuximab.

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