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Evaluation of event-free survival as a trial-level surrogate for overall survival for patients with gastric and gastroesophageal junction adenocarcinoma in neoadjuvant/adjuvant settings

J. Xie[1]; A. Valderrama[2]; L.Yin[3]; S. Zhang[4]; C.-S. Shih[5]; C. Gu[3]; P. Bhagia[6]; Z. Wainberg[7]

[1] Economic, Financial, and Strategy Consulting, Analysis Group, Inc., Los Angeles, CA, United States of America; [2] Center for Observational and Real-World Evidence (CORE), Merck & Co., Inc., Kenilworth, NJ, United States of America; [3] Economic, Financial, and Strategy Consulting, Analysis Group, Los Angeles, CA, United States of America; [4] Economic and Data Sciences, Merck & Co., Inc., Kenilworth, NJ, United States of America; [5] Oncology, Merck & Co., Inc., Kenilworth, NJ, United States of America; [6] Oncology, Merck & Co., Inc., Rahway, NJ, United States of America; [7] Medicine, Hematology and Oncology, Ronald Reagan UCLA Medical Center, Los Angeles, CA, United States of America

Background

- Gastric or gastroesophageal junction (GEJ) adenocarcinoma is associated with an incidence of approximately 990,000 cases and 738,000 deaths annually, making it one of the top prevalent and lethal cancers worldwide.[1,2]
- Overall survival (OS) is the standard endpoint in oncology trials but often requires prolonged follow-up.
- A previous meta-analysis evaluated the association between treatment effect on disease-free survival (DFS) and that on OS in esophageal, gastric, and GEJ cancers and found that the R^2 was 0.68 in the subgroup of gastric cancer.[3]
- Event-free survival (EFS) is a well-accepted endpoint in early-stage oncology trials and a common surrogate endpoint for OS in neoadjuvant and adjuvant cancer therapy.
- This study aimed to evaluate the trial-level association between EFS and OS using the most up-to-date studies on neoadjuvant/adjuvant treatments for gastric or GEJ adenocarcinoma.

Methods

Literature Search

- A systematic literature review was conducted to identify clinical trials of the neoadjuvant (with or without adjuvant) treatments for gastric or GEJ adenocarcinoma.
  - Manuscript publications from inception of the databases until December 2020 were searched in the following databases, including MEDLINE®, Embase®, and Cochrane Central Register of Controlled Trials (CENTRAL), via the OVID platform in December 2020.
  - Conference abstracts from 2018 to December 2020 were searched in the following conference proceedings, including American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO), via Ovid Northern Light Life Sciences Conference Abstracts.
- The search included keywords related to "gastric cancer or GEJ adenocarcinoma", "neoadjuvant treatment" and "survival outcomes".
- The eligibility criteria for study inclusion are summarized in **Table 1**.

Table 1. Eligibility Criteria For Study Inclusion *(Main Analyses and Sensitivity Analyses)*

	Eligibility Criteria
Population	Gastric or GEJ adenocarcinoma in the neoadjuvant setting (with or without adjuvant treatment)
Interventions	Any treatment
Study type	Randomized controlled trials (RCTs)
Outcomes	1) Reported the treatment effect on EFS (i.e., hazard ratios [HRs] or Kaplan-Meier [KM] curves of EFS) and the treatment effect on OS (i.e., HRs or KM curves of OS) 2) EFS and OS were measured from the same starting point
Language	English only

Abbreviations: EFS: event-free survival; GEJ: gastroesophageal junction; HR: hazard ratio; KM: Kaplan-Meier; OR: odds ratio; OS: overall survival; RCT: randomized controlled trial

Statistical Methods

- The main analyses evaluated the association between treatment effects on EFS and OS, i.e., HR of EFS and HR of OS between two randomized treatment arms in eligible RCTs.
  - Specific study inclusion criteria for the main analyses were:
    - Population: The population only consisted of patients with distal (or lower) esophagus, gastric or GEJ adenocarcinoma but no proximal/upper esophagus carcinoma
    - Interventions: Patients treated with neoadjuvant therapy regardless of treatment type or whether patients received adjuvant therapy or not
    - Outcomes: 1) Reported the treatment effect on EFS and the treatment effect on OS; 2) EFS and OS were measured from the same starting point;
  - The majority of HRs were directly extracted from publications. If HRs were not reported, pseudo-individual patient-level (IPD) data were reconstructed based on the published KM[4] curves of EFS and/or OS using the algorithm outlined in Guyot et al.[5]
  - HRs and the 95% confidence intervals (CI) were then estimated from the pseudo-IPD data using Cox proportional hazards models.
- Weighted linear regressions were performed with log(HR) of EFS as the independent variable and log(HR) of OS as the dependent variable (natural logarithm was used in the study).
  - The weights were based on the number of patients in each comparison and the analyses were performed without fixed intercept.
  - A positive coefficient for log(HR) of EFS indicated that an increase in the HR of EFS was associated with an increase in the HR of OS.
  - The correlation coefficient (R), coefficients of determination (R^2) and their 95% CI were calculated to measure the trial-level associations between the treatment effects on EFS and OS. The 95% CI for the R and R^2 were estimated using the percentile method with 10,000 bootstrap iterations.
  - The surrogate outcome effect (STE) for HR of EFS was also estimated. The STE was defined as the minimum treatment effect on the surrogate (i.e., EFS) that would be required to predict a statistically significant non-zero effect (i.e., HR<1) on OS.
- In addition to the main analyses, sensitivity analyses were conducted to explore the impact of population, intervention, and definition of outcomes. Three sets of sensitivity analyses were performed for trial-level association between EFS and OS:
  - SA1 - Mixed population (i.e., in addition to gastric/GEJ, studies on proximal/upper esophagus carcinoma were also included)
  - SA2 - Use of chemotherapy (not including chemoradiotherapy) in both neoadjuvant and adjuvant settings (i.e., studies including patients treated with chemotherapy in both neoadjuvant and adjuvant settings were analyzed)
  - SA3 - Starting time of EFS and OS from initiation of neoadjuvant therapy
  - For each set of sensitivity analyses, the same statistical methods as in the main analysis were conducted.
- A leave-one-out cross-validation was used to assess the prediction accuracy of the models described above.
  - The regression model was refit with one observation excluded, and a prediction of HR for OS was made based on the new model and the observed HR for EFS in the excluded observation. This process was repeated for every observation.
  - Consistency in the direction of the observed and predicted HR for OS (e.g., both above or below 1.0) and whether the observed HR fell within the 95% confidence intervals were evaluated.
- All statistical analyses were conducted using R software (version 3.6.3)

Criteria to Evaluate the Strength of Surrogate Outcomes

- Based on Ciani et al. (2017)[6], the threshold indicating a good surrogate outcome is 0.8 for R or 0.65 for R^2.
- In addition, Lassere et al. (2008)[7] reported that an R^2 value close to 1 (greater than 0.9) is an indicator for a strong correlation, a value between 0.9 and 0.75 represents a very good correlation, and an R^2 below 0.25 indicates a weak-poor correlation.
- Institute for Quality and Efficiency in Health Care (IQWiG) also proposed a framework to evaluate the strength of correlation between an intermediate outcome and a long-term outcome.[8] The IQWiG framework considered a high correlation when the lower limit of the 95% CI of R is ≥0.85, a low correlation when the upper limit of the 95% CI of R is ≤0.7, and a medium correlation otherwise.
- All three frameworks were used to evaluate the strength of EFS as a surrogate outcome for OS in the neoadjuvant/adjuvant setting for gastric treatments or GEJ adenocarcinoma.

Study Characteristics

- The search identified 17 RCTs meeting eligibility criteria for trial-level analysis for EFS and OS, which contributed to 18 comparisons (*main analyses and sensitivity analyses*). One RCT used a 2 × 2 factorial design to concurrently evaluate two investigational agents and thus contributed two comparisons.[9]
- The 17 studies enrolled 4,935 patients from year 2006 to 2020, and the median follow-up time of these studies ranged from 9.6 to 126.5 months. (**Table 2**).
- The terminology used for EFS outcomes varied across the included studies; however, the events defining EFS were similar across the studies, which mainly included disease progression, local or distant recurrence, and death.

Table 2. Study Characteristics

Author Year	Trial Name	Treatment arms	Sample size	Follow-up Time	Neoadjuvant therapy	Adjuvant therapy	HR of EFS (Experimental vs. control)	HR of OS (Experimental vs. control)
Shapiro 2015 and van Hagen 2012[10,11]	CROSS	Neoadjuvant chemoradiotherapy + surgery	178	Minimum follow-up of 60 months for all included patients	Carboplatin, paclitaxel + 41.4 Gy	NR	0.64	0.68
		Surgery alone	188		NR			
Klevebro 2016 and von Dobeln 2018[12,13]	NeoRes	Neoadjuvant chemotherapy + surgery	91	All patients were followed until death or until 60 months after randomization	Cisplatin, fluorouracil (cisplatin could be replaced by carboplatin or oxaliplatin)	NR	1.05	0.99
		Neoadjuvant chemoradiotherapy + surgery	90		Cisplatin, fluorouracil (cisplatin could be replaced by carboplatin or oxaliplatin) + 40 Gy			
Iwasaki 2020 and Iwasaki 2018[14,15]	JCOG0501	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	151	4.5 years (Median)	S-1, cisplatin	S1	0.98	0.92
		Surgery + adjuvant chemotherapy	149		NR			
Monti 2020[16]	GASTRODOC	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	45	55 months (Median)	Docetaxel, oxaliplatin, capecitabine	Docetaxel, oxaliplatin, capecitabine	1.25	1.05
		Neoadjuvant chemotherapy + surgery	46			NR		
Al-Batran 2019, Al-Batran 2017, and Homann 2017[17-19]	FLOT4	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	356	43 months (Median follow-up for surviving patients)	Fluorouracil, leucovorin, oxaliplatin, docetaxel	Fluorouracil, leucovorin, oxaliplatin, docetaxel	0.75	0.77
		Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	360		Epirubicin, cisplatin, fluorouracil; epirubicin, cisplatin, capecitabine	Epirubicin, cisplatin, fluorouracil; epirubicin, cisplatin, capecitabine		
Steur 2020 and Cats 2018[20,21]	CRITICS	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	393	7 years (Median)	Epirubicin, cisplatin, capecitabine; epirubicin, oxaliplatin, capecitabine	Epirubicin, cisplatin, capecitabine; epirubicin, oxaliplatin, capecitabine	1.01	0.95
		Neoadjuvant chemotherapy + surgery + adjuvant chemoradiotherapy	395		Epirubicin, cisplatin, capecitabine; epirubicin, oxaliplatin, capecitabine	Cisplatin, capecitabine + 45 Gy		
Ma 2015[22]	NR	Neoadjuvant chemotherapy + surgery	40	All patients were followed up for 3 years	Docetaxel, oxaliplatin, calcium folinate, 5-FU	NR	1.71	1.04
		Neoadjuvant chemotherapy + bevacizumab + surgery	40					
Cunningham 2017 and Cunningham 2015[23,24]	ST03	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	533	36.2 months (Median)	Epirubicin, cisplatin, capecitabine	Epirubicin, cisplatin, capecitabine	0.95	0.92
		Neoadjuvant chemotherapy + bevacizumab + surgery + adjuvant chemotherapy	530	39.1 months (Median)	Epirubicin, cisplatin, capecitabine, bevacizumab	Epirubicin, cisplatin, capecitabine, bevacizumab		
Zhao 2017[25]	NR	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	50	9.6 months (Median)	S-1, oxaliplatin	S-1, oxaliplatin	0.76	0.45
		Surgery + adjuvant chemotherapy	52		NR			
Stahl 2017 and Stahl 2009[26,27]	POET	Neoadjuvant chemotherapy + surgery	59	126.5 months (Median)	Fluorouracil/folinic acid, cisplatin	NR	1.56	1.54
		Neoadjuvant chemoradiotherapy + surgery	60		Fluorouracil/folinic acid, cisplatin, etoposide + 30 Gy			
Fazio 2015[28]	SAKK 43/99	Neoadjuvant chemotherapy + surgery	34	10 years	Docetaxel, cisplatin, fluorouracil	NR	0.79	0.81
		Surgery + adjuvant chemotherapy	35		NR	Docetaxel, cisplatin, fluorouracil		
Cunningham 2006 and Smyth 2016[29,30]	MAGIC	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	250	49 months (Median)	Epirubicin, cisplatin, fluorouracil	Epirubicin, cisplatin, fluorouracil	0.66	0.75
		Surgery alone	253	47 months (Median)	NR	NR		
Schuhmacher 2010[31]	EORTC 40954	Neoadjuvant chemotherapy + surgery	72	4.7 years (Median)	Cisplatin, d-L-folinic acid, fluorouracil	NR	0.76	0.84
		Surgery alone	72	4.1 years (Median)	NR			
Stahl 2018 and Moehler 2015[32,33]	AIO/CAO STO-0801	Neoadjuvant chemotherapy + surgery + adjuvant therapy	80	34.9 months (Median)	Epirubicin, cisplatin, capecitabine	Epirubicin, cisplatin, capecitabine	0.84	0.73
		Neoadjuvant chemotherapy + panitumumab + surgery + adjuvant therapy	80		Epirubicin, cisplatin, capecitabine, panitumumab			
Hayashi 2020[9]	COMPASS-D	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	31	47.6 months (Median)	2 courses of cisplatin and S-1	S-1	1.1	0.94
		Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	31	51.5 months (Median)	4 courses of cisplatin and S-1			
		Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	33	50.5 months (Median)	2 courses of S-1, cisplatin, and docetaxel		2.64	2.09
		Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	32	53.8 months (Median)	4 courses of S-1, cisplatin, and docetaxel			
Lorenzen 2013[34]	FLOT 65 +	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	21	22.4 months (Median)	5-FU, leucovorin, oxaliplatin, docetaxel	5-FU, leucovorin, oxaliplatin, docetaxel	0.5	0.52
		Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	22		5-FU, leucovorin, oxaliplatin	5-FU, leucovorin, oxaliplatin		
Eveno 2019[35]	PRODIGE 19	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	40	43 months (95% CI: 36.5–48.3)	Epirubicin, cisplatin, 5-fluorouracil; epirubicin, cisplatin, Xeloda	Epirubicin, cisplatin, 5-fluorouracil; epirubicin, cisplatin, Xeloda	0.64	0.71
		Surgery + adjuvant chemotherapy	43		NR			

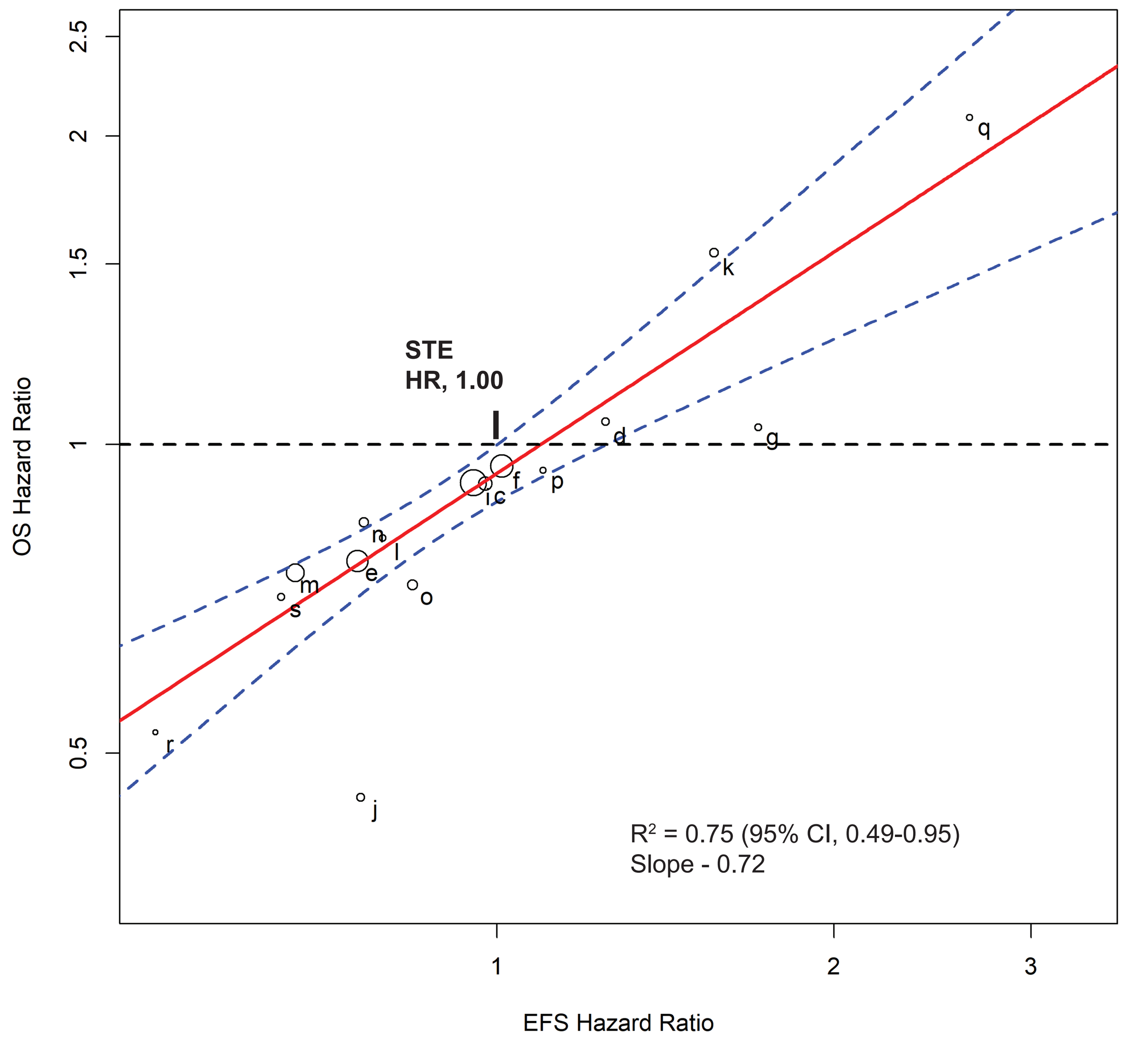
Note: * One study (i.e., Hayashi 2020[9]) contributed two observations. All other studies contributed a single observation.

Results

Main Analyses

- For main analysis, **Figure 1** shows the relationship between treatment effects on EFS and treatment effects on OS using all 16 comparisons (15 studies) involving 4,388 patients from the included RCTs.
- The estimated correlation coefficient between treatment effects on EFS and OS was 0.87 (95% CI: 0.70-0.98). Results of the weighted linear regression model indicated that the log(HR) of EFS was a significant predictor and a good surrogate outcome for the log(HR) of OS with an estimated coefficient of 0.72 (p < 0.001) and an R^2 of 0.75 (95% CI: 0.49 - 0.95), based on the criterion published by Ciani et al. (2017)[6]. When it was compared to Lassere et al. (2008)[7], (i.e., very good: R^2 = 0.9-0.75), the association between EFS and OS represents a very good correlation.
- The STE for OS corresponded to an EFS HR of 1.00 (**Figure 1**). Thus, to predict a nonzero treatment effect on OS in a future trial with a similar treatment type, an EFS HR of at least 1.00 would need to be ascertained. Although such thresholds provide useful guidance, there will always be clinical and other judgements involved in the decision process.

Figure 1. Trial-Level Association between Treatment Effects on EFS and OS in the Main Analysis



Note: Treatment effects are expressed as HRs for EFS and HRs for OS. Every circle represents a comparison of the experimental group versus the control group, with the size of the circles representing the weight of the comparison, proportional to the number of patients in the sample. The red straight line represents the weighted linear regression, which shows the effect on OS predicted by the observed effects on EFS. The blue curved lines represent the 95% prediction limits for the regression line. The horizontal dashed line provides a reference where HR equals to 1. The STE of EFS for predicting a significant OS effect in the main analysis is presented in the figure.

Sensitivity Analyses

- The sensitivity analyses suggested similar association between EFS and OS as in the main analysis, which supported the robustness of the main analysis findings (**Table 3**).
- The R^2 ranged from 0.76 to 0.89 and R ranged from 0.87 to 0.95. Results from SA3, i.e., including RCTs that reported the starting time of both EFS and OS from the initiation of neoadjuvant therapy, yielded the strongest association between treatment effects on EFS and OS, with an R^2 of 0.89 (95% CI: 0.66 - 0.98).

Table 3. Trial-Level Association between Treatment Effects on EFS and OS in the Sensitivity Analyses

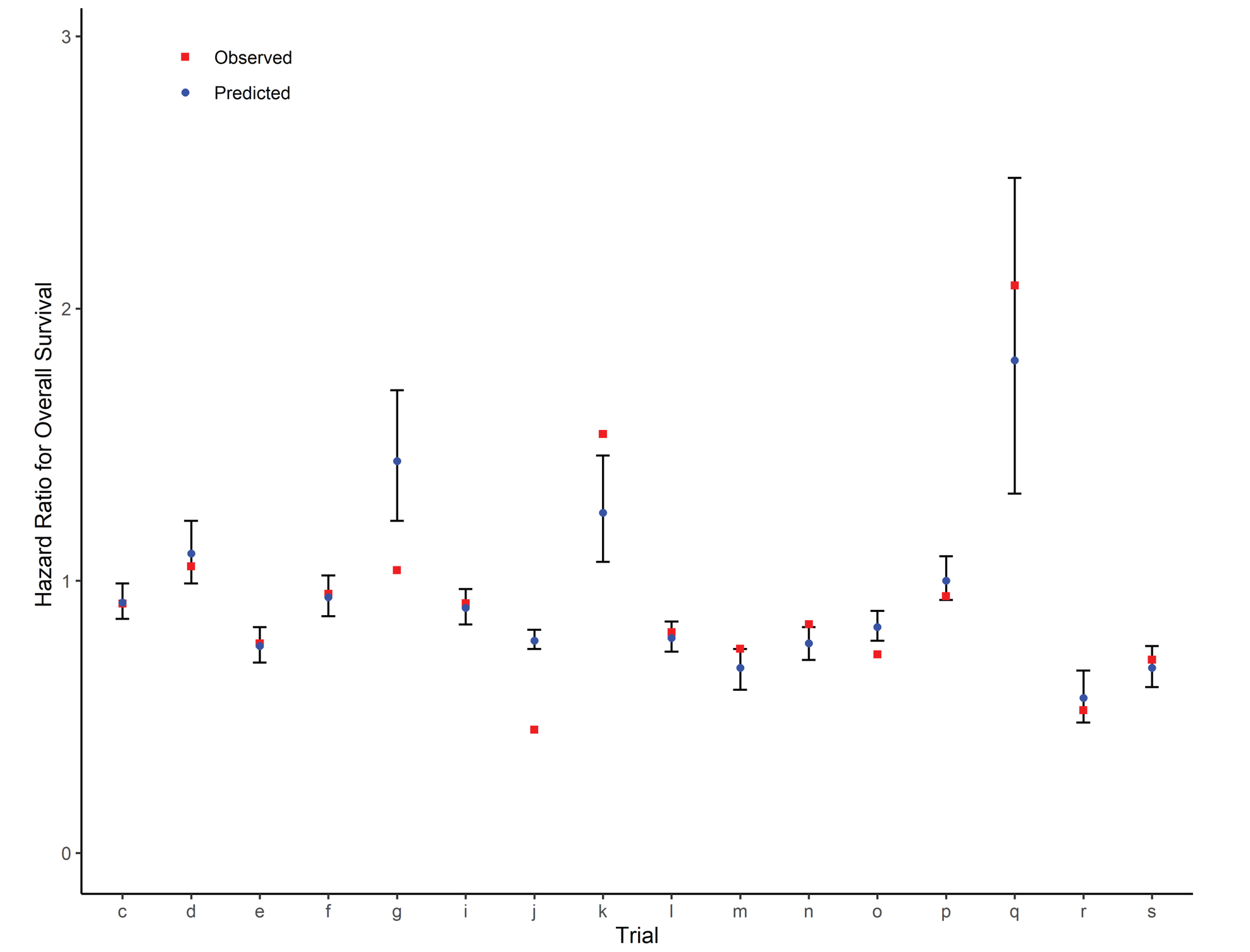
	# of observations *	# of patients	Coefficient for log(HR) of EFS (p-value)	R (95% CI)	R^2 (95% CI)
SA1 - Mixed population	18	4,935	0.72 (<0.001)	0.88 (0.73, 0.98)	0.78 (0.53, 0.96)
SA2 - Use of chemotherapy in both neoadjuvant and adjuvant settings	12	3,976	0.74 (<0.001)	0.87 (0.66, 0.99)	0.76 (0.43, 0.98)
SA3 - Starting time of EFS and OS as from initiation of neoadjuvant therapy	11	3,960	0.63 (<0.001)	0.95 (0.82, 0.99)	0.89 (0.66, 0.98)

Note: * One study (i.e., Hayashi 2020[9]) contributed two observations. All other studies contributed a single observation.

Cross-validation

- The prediction results from the cross-validation analyses are shown in **Figure 2**. The observed and predicted HRs for OS were consistent in the direction of treatment effect on OS (e.g., both HRs were either above or below HR = 1.0) for all comparisons. The observed HRs fell within the 95% confidence intervals of the predicted HRs in 68.8% (11 of 16) of the comparisons.

Figure 2. Cross-validation of Trial-level Surrogate Outcome Analysis Between EFS and OS in the Main Analysis



Note: The observed HRs for OS for each comparison are plotted against their corresponding predicted HRs and 95% confidence intervals calculated from a weighted linear regression model with leave-one-out validation. Red rectangles represent the observed HRs and blue circles indicate the predicted HRs, with the black bars denoting the 95% confidence intervals.

Conclusions

- Using published RCTs on neoadjuvant treatment (with or without adjuvant treatment) for gastric or GEJ adenocarcinoma, the study found a statistically significant association between the treatment effect on EFS and the treatment effect on OS.
  - With an R^2 of 0.75 for OS in the main analysis, EFS was a good surrogate endpoint for OS in gastric or GEJ adenocarcinoma based on the criterion published by Ciani et al[6]. (i.e., good: R^2 >0.65).
  - When it was compared to Lassere et al. (2008) criteria[7] (i.e., very good: R^2 = 0.9-0.75), the association between EFS and OS represents a very good correlation.
  - When using the IQWiG framework[8], which is mainly used in Germany, we found that the association between EFS and OS (R = 0.87; 95% CI, 0.70-0.98) qualified as a medium correlation.
  - Sensitivity analysis results were consistent with the findings from the main analysis, suggesting that the strong correlation was not affected by study population, treatment or the way in which outcomes were evaluated.
- The findings suggest that EFS is a good surrogate for OS in gastric or GEJ adenocarcinoma in neoadjuvant/adjuvant settings.

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Conflicts of interest

A. Valderrama, S. Zhang, C.-S. Shih, and P. Bhagia are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and reported financial interest in Merck & Co., Inc., Kenilworth, NJ, USA. J.Xie, L.Yin, and C.Gu are employees of Analysis Group, Inc., who have received funding from Merck and Co., Inc for the conduct of this research. Z. Wainberg reports personal fees for consulting or advisory boards from Amgen, Astra Zeneca, Daiichi, Bayer, BMS, Merck, Ipsen, Five Prime, Gilead, Arcus, Astellas, Molecular Templates, Array; Honoraria from Amgen, Astra Zeneca, Daiichi, Bayer, BMS, Merck, Ipsen, Five Prime, Gilead, Arcus, Astellas, Molecular Templates, Array; Research Grant/Funding (Institution)from Amgen, Astra Zeneca, Daiichi, Bayer, BMS, Merck, Ipsen, Five Prime, Gilead, Arcus, Astellas, Molecular Templates, Roche/Genentech, Array/Pfizer

Sponsorship: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

Presented at the ESMO 2021 Virtual Congress; 16–21 September 2021