Disclosures

- This study is conducted by Evidinno Outcomes Research Inc. in collaboration with Bristol Myers Squibb, which provided financial sponsorship

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Disease-Free Survival as a Surrogate Endpoint for Overall Survival in Adults With Resectable Esophageal or Gastroesophageal Junction Cancer: a Correlation Meta-Analysis

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Background

- Epidemiology
  - Globally, esophageal cancer (EC) is 7th most common cancer and 6th deadliest in cancer-related death[1]
  - In the United States, it is estimated that 19,260 new cases of EC will be diagnosed in 2021, and 15,530 patients with EC will die[2]
  - Prognosis remains poor: five-year relative survival (2010 to 2016) is 20% for EC[2]

- Standard of care is multimodal for locoregional EC and gastroesophageal (GEJ) cancer
  - Practices vary across the globe, but generally involve neoadjuvant chemoradiotherapy followed by surgery (trimodality therapy) or perioperative chemotherapy[3]

1. Bray F, et al. *CA Cancer J Clin* 2018; 68: 394-424. 2. Siegel RL, et al. *CA Cancer J Clin* 2021;71(1):7–33. 3. Al-Batran SE and Lorenzen S. *Hematol Oncol Clin North Am* 2017; 31(3): 441-452.

Background

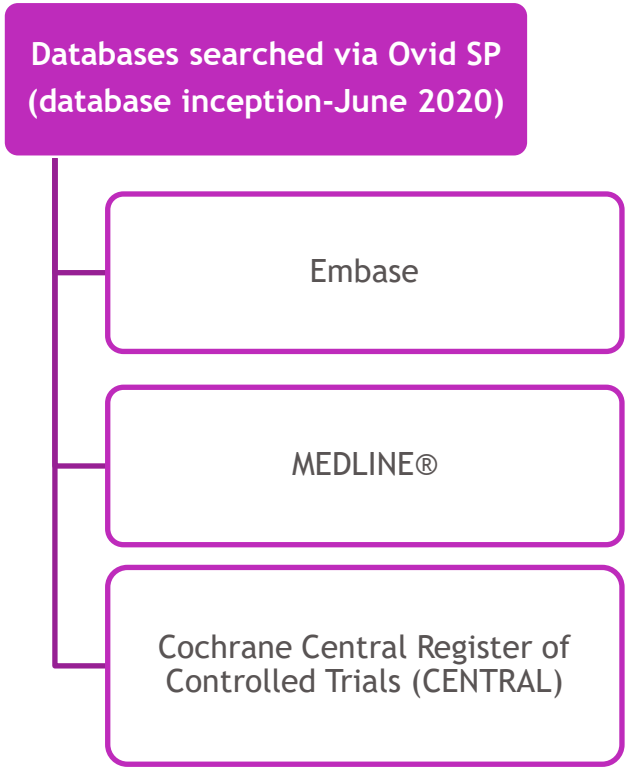
- Rationale for the current study
  - Poor prognosis creates a sense of urgency to develop novel treatments to improve overall survival (OS)
  - OS is generally the gold standard endpoint for oncology trials
  - However, obtaining OS estimates takes longer time than the time to any other event, particularly in early stages of disease
  - Surrogate endpoints may be evaluated in the place of OS
  - Validation of earlier endpoints, such as disease-free survival (DFS), as surrogates of OS can support economic research necessary to achieve timely market access for novel, lifesaving drugs
  - DFS is defined as the time from the date of resective surgery to the date of disease recurrence or death, whichever occurred first
  - DFS and OS are primary and secondary endpoints, respectively, in the ongoing Phase 3 CheckMate 577 trial (NCT02743494)[4]

4. Kelly R, et al. *N Engl J Med* 2021; 384:1191-1203.

Objective

- To investigate the strength of association and to determine and validate the surrogacy relationship between DFS and OS using aggregate-level data from published clinical trials investigating adult patients with resectable EC or GEJ cancer receiving therapies in the (neo)adjuvant and perioperative settings

Methods: Systematic literature review



- Systematic literature review (SLR) of clinical trials evaluating adult patients with EC or GEJ cancer receiving therapies in the (neo)adjuvant and perioperative settings was carried out
- Searches were conducted in 2020 covering several databases

Methods: PICO eligibility criteria

Table 1. PICOS eligibility criteria for the systematic literature review.

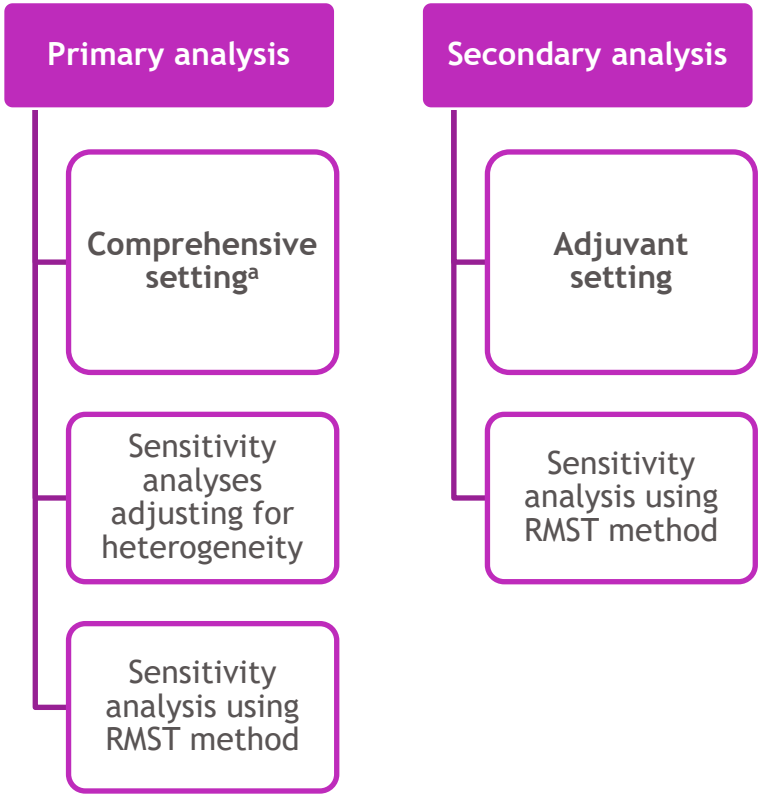
PICO[a] element	Inclusion criteria
Population	• Patients with local/locoregional resectable EC or GEJ • Patients who have had surgery or radiotherapy to remove or shrink tumor • Adults (≥18 years of age)
Intervention	Any (neo)adjuvant (post-operative) or perioperative therapy • Systemic treatment • Radiotherapy • Chemoradiation
Comparator	• Any systemic treatment • Placebo
Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • Disease-free survival (DFS) (or time to disease recurrence/relapse)
Study design	Randomized controlled trials

[a] PICO – Patient, Intervention, Comparator, and Outcome

- Study selection and data extraction of included studies was performed by two independent investigators
- The following items were extracted from each study:
  - Trial characteristics
  - Patient characteristics
  - Treatment characteristics
  - Efficacy outcomes
  - Safety outcomes
- Progression-free survival (PFS) compatible with the definition of DFS was also captured and utilized where DFS was unavailable

Methods: Feasibility assessment and analysis plan

- A feasibility assessment was conducted to determine the optimal approach to the surrogacy analysis
- The following were assessed:
  - Proportionality assumption for hazard ratios of each efficacy outcome using Schoenfeld's test
  - Trial characteristics of the evidence base including study quality (e.g. sample size and study design) and outcome definitions
  - Similarities or heterogeneity of the patient characteristics across the evidence base



[a]Including (neo)adjuvant and perioperative settings
RMST = restricted mean survival time

Methods: Statistical analyses

- Assessment of the association between DFS and OS
  - Using bivariate random-effects meta-analysis (BRMA) framework[5]
    - Includes both within and between study correlation
    - Maintains the individual weighting of each study in the analysis
- Assessment of the strength of trial-level association
  - Based on the National Institute for Health and Care Excellence (NICE) guidelines[6]
    - 95% coverage of the leave-one-out validation implies valid surrogacy

5. Riley RD, et al. *Biostatistics* 2008;9:172-186. 6. Davis S, et al. NICE Decision Support Unit Methods Development. 2012.

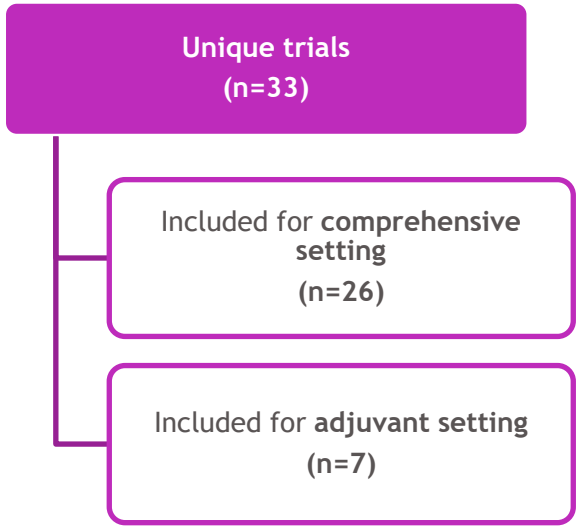
Methods: Statistical analyses

- Estimation of surrogacy equations using weighted linear regression (WLR)
  - Main analyses used trial sample sizes as weights; inverse-variance weights of the OS HR estimate were used as an alternative
- Calculation of surrogate threshold effect
  - Defined as the minimum value of the hazard ratio for DFS (HR_{DFS}) necessary to predict a positive treatment effect on the hazard ratio for OS (HR_{OS})[7]
- Leave-one-out cross-validation approach
  - For every trial included in the meta-analysis, the specific trial of interest was removed, and a new regression model was fit with the remaining trials' data
  - Goodness of fit was assessed by comparing the observed HR_{OS} for the left-out trial with the 95% prediction interval of the predicted HR_{OS} from the new regression model

7. Burzykowski T, Buyse M. *Pharm Stat* 2006;5(3):173–186.

Results: Evidence base

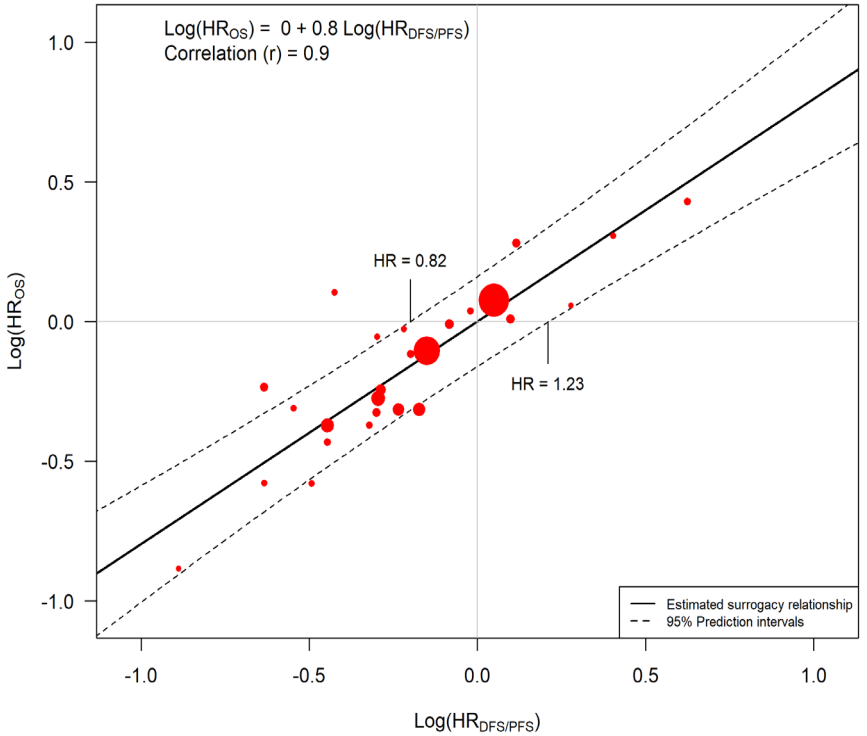
- 33 unique trials in SLR completion
  - 7 trials were excluded for analyses due to evidence of non-proportional hazard ratios
- 26 unique trials included for comprehensive setting (primary analysis)
  - 27 comparisons in total due to three treatment arms in one trial
- 7 unique trials included for adjuvant setting only (secondary analysis)
- The main findings present results from the comprehensive setting



Results: Correlations

- Results obtained from BRMA
  - Correlation = 0.83 (95% confidence interval [CI], 0.70–0.90)
- Results obtained from WLR
  - Correlation = 0.90 (95% CI, 0.77–0.96) using sample size as weights (**Fig 1**)
  - Correlation = 0.89 (95% CI, 0.76–0.95) using inverse variance as weights

Weighted linear regression to estimate the association between the log-transformed disease-free survival/progression-free survival and overall survival hazard ratios using trial sample sizes as weights.

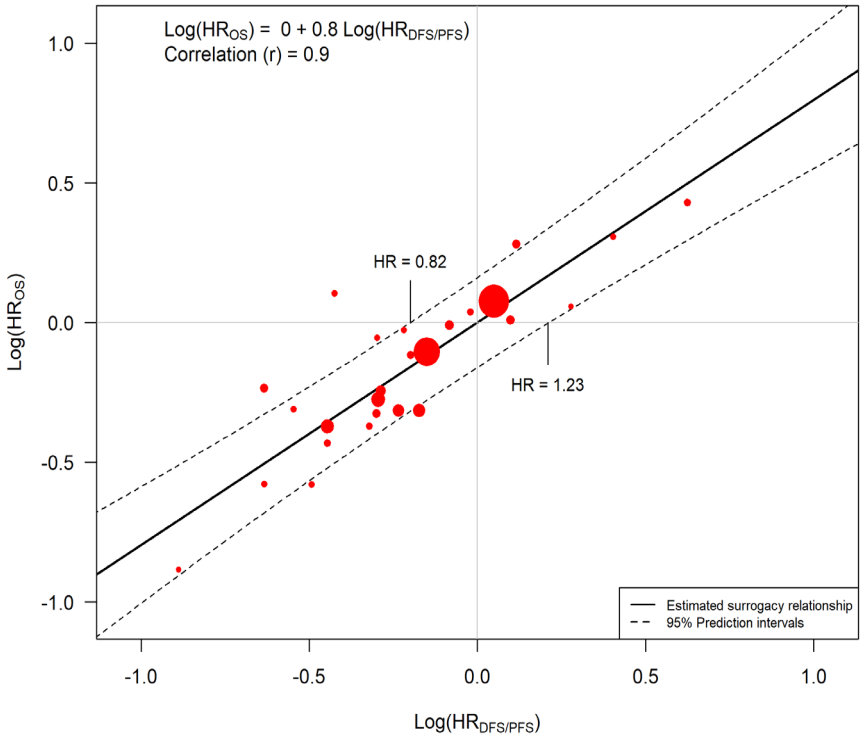


Each dot represents a trial; Sizes of the dots correspond to the weights associated within the surrogacy equation.

Results: Surrogate threshold effects

- STE of 0.82 indicates that a reported $HR_{DFS/PFS}$ of 0.82 or less would lead to a statistically significant protective effect on the HR_{OS} of the treatment
- STE value is relatively close to 1, indicating the likely utility of the surrogacy equation

Weighted linear regression to estimate the association between the log-transformed disease-free survival/progression-free survival and overall survival hazard ratios using trial sample sizes as weights.

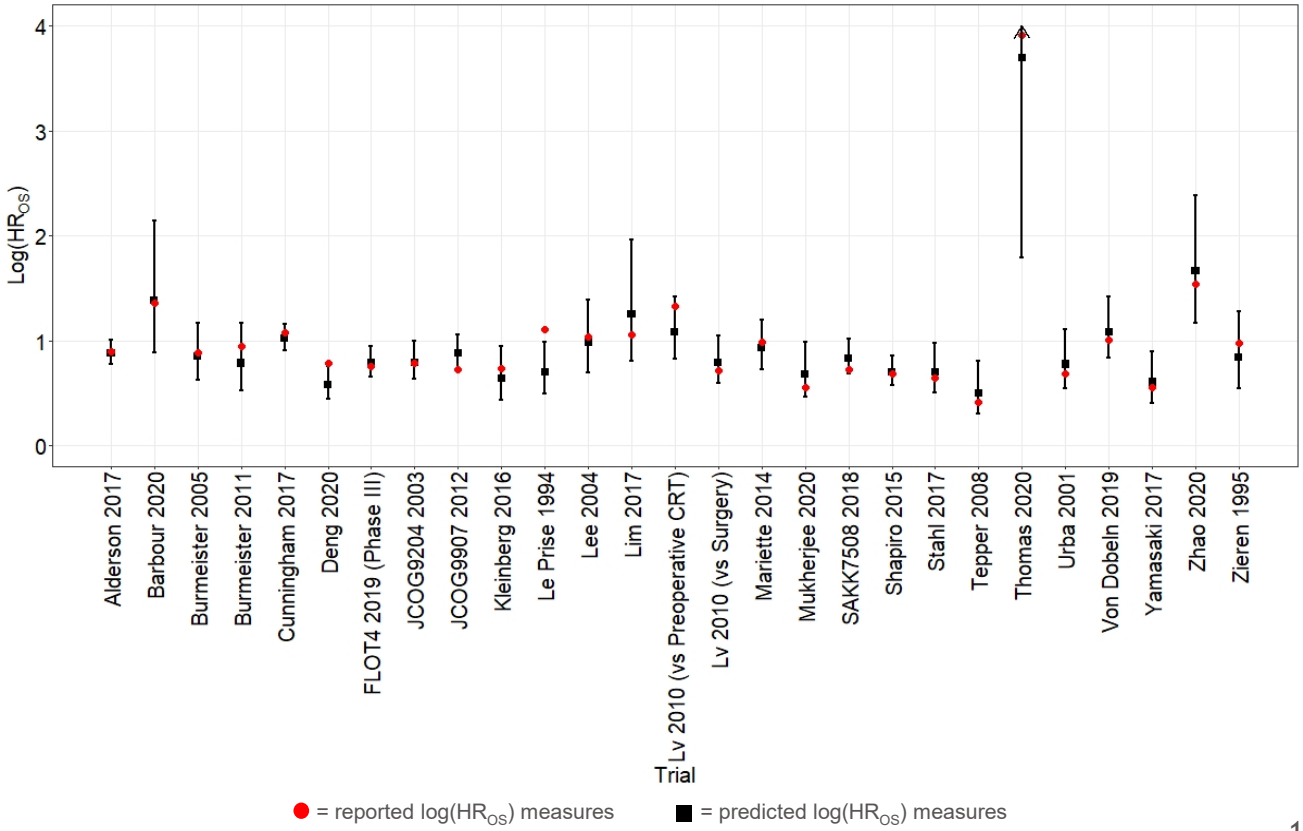


Each dot represents a trial; Sizes of the dots correspond to the weights associated within the surrogacy equation.

Results: Leave-one-out cross validation

- Reported HR_{OS} fell within the 95% prediction intervals of their corresponding predicted OS HRs for 26 out of 27 comparisons
- DFS/PFS was deemed to be a valid surrogate endpoint in the comprehensive setting
- One outlying phenomenon (Thomas 2020)
  - Estimated prediction interval extended upwards past the graph
  - Reported HR_{OS} still remains within the prediction interval

Leave-one-out cross validation in the comprehensive setting.



Results: Estimation of surrogacy equations

- The surrogacy equations were obtained using weighted linear regression
  - $\log (HR_{OS}) = 0.80 \times \log (HR_{DFS/PFS})^{a}$
  - Intercept was approximately 0, indicating that HR_{DFS} of 1 predicts HR_{OS} of 1
- The use of predictive surrogacy equation was compared with two pivotal trials (CROSS and FLOT4) and the ongoing CheckMate 577
  - HR_{OS} in CheckMate 577 is expected to be statistically significant
  - Predicted OS HRs for CROSS and FLOT4 trials contain a maximum absolute difference of no more than 0.03

Reported HR_{OS} and predicted HR_{OS} from the predictive surrogacy equation for three recent major RCTs.

Reported efficacy measures	CROSS	FLOT4	CM 577
	HR_{PFS} = 0.64 (0.49, 0.82) HR_{OS} = 0.69 (0.53, 0.89)	HR_{PFS} = 0.74 (0.58, 0.95) HR_{OS} = 0.76 (0.62, 0.94)	HR_{DFS} = 0.69 (0.56, 0.86) HR_{OS} = NR
Predicted HR_{OS} in comprehensive setting	0.70 (0.58, 0.85)	0.79 (0.66, 0.94)	0.75 (0.65, 0.85)

Abbreviations: CM 577 – CheckMate 577 trial, NR – Not reported. Values in parentheses indicate the 95% CI of the for reported HRs or 95% prediction interval of the predicted HR_{OS}. [a] Intercept in the surrogacy equation was negligibly small (approximately 0) and was omitted from the equation

Conclusion

- The results and their validation point out a correlation between DFS and OS in EC and GEJ cancer
  - The estimated surrogacy equation had a high STE of 0.82, which suggests that the equation has strong predictive utility
  - Leave-one-out cross validation confirmed its validity

- The estimated surrogacy equation and the corresponding surrogate threshold effect can enable HR_{DFS} as a surrogate predictor of HR_{OS} in the (neo)adjuvant and perioperative setting among adult patients with EC and GEJ cancer

- Limitations
  - The analysis was restricted to aggregate-level data - using individual patient data could improve the correlation estimation to provide additional support through further statistical models
  - The findings of this research only apply to early-stage EC/GEJ and can not be generalized to other types of cancer
  - Analysis shown is based on a mix of therapy settings and regimens

Thank you!

Presenter Contact Information
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