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P-56 Estimating endpoint correlation between surrogate measures and overall survival using reconstructed survival data: Case studies from adjuvant and metastatic gastric cancer trials

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Background: Validation of intermediate endpoints such as disease-free survival (DFS) and progression-free survival (PFS) as surrogate predictors for overall survival (OS) in randomized controlled trials (RCTs) requires establishing their association at the individual-level. In the absence of individual-level patient data (IPD), this study developed an analytical framework to estimate this association between DFS/PFS and OS using reported Kaplan-Meier (KM) curves from the RCTs and demonstrated its predictive performance in adjuvant and metastatic gastric cancer (GC) treatment settings.

Methods: Assuming a three-state illness-death model for cancer survival, we developed a linear optimization model to elicit the underlying pre-progression death probability as well as post-progression survival (PPS) distribution using pseudo-patient level DFS/PFS and OS data reconstructed from the published KM curves. In the adjuvant setting, pre-progression death probability was bounded below by the cure rates which were estimated by fitting mixture cure models (MCMs) to the DFS data. In the MCMs, time-to-event outcomes for the uncured subpopulation were modeled using parametric survival functions suggested by National Institute for Health and Care Excellence (NICE) and non-disease-related mortality rates were derived from the age- and sex-adjusted local life-table data from World Health Organization. Reconstructed DFS/PFS distributions were extrapolated via parametric- and spline-based models suggested by NICE and adjusted with estimated background mortality rates whereas elicited PPS distributions were extrapolated assuming constant hazard rate over time. Estimated pre-progression death probabilities and modeled DFS/PFS/PPS distributions governed a Monte-Carlo simulation framework which generated paired pseudo pre- and post-progression data to predict Spearman's rank and Pearson's product moment correlation coefficients. Model performance was tested on two correlation meta-analyses in GC (14 RCTs with 3371 patients on adjuvant chemotherapy; 20 RCTs with 4069 patients on metastatic treatments) published in 2013 by the GASTRIC group. For each test case, model-predicted OS rates and Spearman rank correlation coefficients were compared against their reported counterparts and corresponding 95% CIs.

Results: Predicted OS curves laid within the 95% CIs of the reported OS KM-curves 96% and 100% of the time in the adjuvant and metastatic setting, respectively, where the average deviation between the restricted mean survival times under the model-predicted OS curves and the statistically best-fitting OS curves to the reported data was $<$ 1% in both settings. Average deviation between the estimated and reported Spearman rank correlation coefficients was no more than 0.01 (reported: 0.97 [95% CI:0.97-0.98] vs. predicted: 0.96 [95% CI:0.96-0.96]) and 0.13 (reported: 0.85 [95% CI:0.85-0.85] vs. predicted: 0.72 [95% CI:0.71-0.72]) in both settings. Predicted Pearson correlation coefficients were 0.95 [95% CI:0.95-0.95] and 0.94 [95% CI:0.94-0.95] in the adjuvant and metastatic setting, respectively.

Conclusions: Our study offers a useful approach for an indirect endpoint correlation assessment in the absence of IPD. Results indicate the model to be precise in adjuvant but conservative in metastatic GC setting which should be approached with caution due to independent simulation of paired DFS/PFS and PPS durations from the illness-death model and the lack of data-driven lower bounds on pre-progression death probability in the metastatic setting.

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P-57 An observational/translational study of BRAF inhibitor combination therapy for BRAF-mutant metastatic colorectal cancer including biomarker research: BEETS trial (JACCRO CC-18)

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Background: BRAF inhibitor combination therapy became the standard of care for BRAF -mutated metastatic colorectal cancer (mCRC) based on the BEACON CRC trial, which showed a survival benefit of the three-drug combination regimen with BRAF and MEK inhibitors plus anti-EGFR antibody as well as the two-drug combination regimen with BRAF inhibitor and anti-EGFR antibody over standard chemotherapy. The two-drug combination regimen is approved in Europe and the US, while both three- and two-drug combination regimens are approved in Japan. These two regimens have not been directly compared in terms of efficacy and the patients and disease factors that guides regimen selection are not clearly established.

Trial design: This is a multicenter observational/translational study to prospectively evaluate the efficacy and safety of BRAF inhibitor combination therapy as a second- or third-line treatment in patients with BRAF -mutant mCRC in clinical practice. Two hundred patients will be assigned to either two- or three-drug combination therapy arm based on physician's choice. Clinical data from the three- and the two-drug combination therapies will be compared to identify factors associated with the benefit of each treatment. Eligibility criteria are (1) patients with colorectal cancer confirmed as adenocarcinoma on pathological examination and with BRAF mutation on tumor tissue-based genomic testing, (2) patients planning to receive BRAF inhibitor combination therapy as second or third-line treatment, (3) patients with ECOG Performance Status (PS) of 0-2, (4) patients must be at least 20 years of age at the time of consent, and (5) patients have measurable or evaluable lesions in RECIST v1.1. The primary endpoint is overall survival. The secondary endpoints include response rate, disease control rate, tumor volume reduction, time to response, duration of response, progression-free survival, and safety. In addition, blood samples of patients will be prospectively collected before and after treatment, which will be used for liquid biopsy research including circulating tumor-DNA (ctDNA) and RNA analyses using next-generation sequencers to explore novel predictors of response and resistance mechanisms to BRAF inhibitor combination therapy. In the translational study part, the primary endpoint is to analyze the association between clinical outcome of BRAF inhibitor combination therapy and tumor genomic data from ctDNA and RNA analysis at pre-treatment. The secondary endpoints are to analyze the association between clinical outcome of BRAF inhibitor combination therapy and liquid biopsy data after failure or intolerance to the treatment; to analyze tumor dynamics by comparing genomic data before and after BRAF inhibitor combination therapy; and to evaluate the association between liquid biopsy data and patient background factors (PS, number of metastatic organs, CRP, presence of primary tumors). Blood-based tumor genomic measurements will be performed by DNA Chip Research Inc (Tokyo, Japan). ctDNA exome analysis will be performed for plasma and tumor-educated blood platelets (TEP)-Seq RNA analysis will be performed for tumor-related platelets which are extracted from blood samples. Enrollment opened in October 2021.

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