Quantification of Long-term Survival Benefit in a Comparative Oncology Clinical Study

Novel treatments, such as immunotherapies, may have delayed clinical effect\(^1,2\) but may be associated with long-term survival benefit in some patients. The conventional procedure using the log-rank test and hazard ratio (HR) for evaluating the long-term treatment effect on overall survival (OS) can be suboptimal in terms of interpretation and power. As an example, part A of the Figure shows Kaplan-Meier curves for OS comparing chemotherapy plus cetuximab and chemotherapy plus bevacizumab using reconstructed OS data for the expanded RAS wild-type subgroup in Venook et al.\(^3\) The HR was 0.88 (95% CI, 0.72-1.08; \(P = .24\)) in favor of cetuximab numerically. Visually, the Kaplan-Meier curve for cetuximab is almost identical to that for bevacizumab to month 30 but superior to bevacizumab thereafter. This finding suggests that cetuximab might have a relatively long-term OS benefit that was not appropriately captured by HR. Long-term survival benefit is often quantified by comparing survival rates at a specific time point. For instance, at month 60, cetuximab and bevacizumab had observed survival rates of 27% and 17%, respectively. These summaries, however, do not include information on the temporal OS profile before or after month 60. In this study, using these data, we show an alternative, clinically interpretable approach to quantifying long-term survival benefit.

**Methods** | The Kaplan-Meier curve in part A of the Figure provides the OS profile throughout the entire study. The higher the tail part of curve, the better long-term survival associated with the treatment. Therefore, a reasonable quantifier for a long-term survival profile would be the area under

**Figure.** Estimated Survival Curves and the Area Under the Survival Curves

A. Kaplan-Meier curves

B. Areas under Kaplan-Meier curves

Data analysis is based on reconstructed overall survival data for the colorectal cancer study.\(^3\) A, Kaplan-Meier curves for bevacizumab and cetuximab in the expanded RAS analysis. B, The area under the Kaplan-Meier curves within the window of 36 to 72 months for bevacizumab (left) and cetuximab (right) treatment.
the Kaplan-Meier curve beyond a specific time point, for example from months 36 to 72 (shaded areas in Figure, B), which is the restricted mean survival time (RMST) and has been discussed extensively in survival analysis. The difference in RMST can be used to quantify the treatment effect. The CI and P value formulas for this group contrast are given in Zhao et al2 and can be obtained using R-package surv2sampleComp. For this analysis, no author had access to the study data reported by Venook et al3; we reconstructed patient-level overall survival data from published information. This analysis of published data did not require institutional review board approval or informed consent from participants in the colorectal cancer study.

Results | The shaded areas in part B of the Figure correspond to 10.8 months for cetuximab and 8.3 months for bevacizumab. That is, future patients receiving cetuximab would live a mean of 10.8 months from months 36 to 72, which is 2.5 months (95% CI, 0.0-5.0 months; P = .05) longer than survival among bevacizumab-treated patients. This summary provides a clinically interpretable treatment effect associated with longer-term survival.

Another interpretation of the area under the Kaplan-Meier curve is the integrated survival rate. For cetuximab, the average survival rate, 30.0%, can be obtained by dividing 10.8 months by the length of the window (72 − 36 = 36 months). The corresponding survival rate for bevacizumab is 23.1%. The difference of 6.9% (95% CI, 0.0%-13.9%) is more stable than the difference of OS rates at a single time point. One may fit OS data with a parametric Weibull model and estimate RMST without a 72-month ceiling. The RMST beyond 36 months is 15.6 months for cetuximab and 11.3 months for bevacizumab, with a difference of 4.4 months (95% CI, −0.8 to 10.0 months). The OS benefit from cetuximab should be interpreted cautiously because patients might receive another treatment after progression of disease.

Discussion | From the perspective of cost-risk-benefit, using a long-term survival benefit criterion for selecting anticancer therapies may be more appropriate. Although our proposed method does not require modeling assumptions and offers clinical interpretation, the estimate may be sensitive to the choice of the time window. We recommend that this window be selected based on clinical considerations. For instance, we may choose the upper 25th percentile of survival distribution from historical data under standard care as the benchmark for long-term survival evaluation. The proposed summary measure can be useful for identifying high-value subgroups of patients who would gain long-term survival benefit. Unlike the conventional procedure, the proposal herein follows the intent-to-treat analysis principle and provides unbiased assessment for treatment effect. The data analysis is not based on the individual patient data collected from the colorectal cancer study but on those reconstructed from published summary data and the Figure, which represents a limitation of this study.

Miki Horiguchi, BPharm
Lu Tian, ScD
Hajime Uno, PhD
SuChun Cheng, PhD
Dae Hyun Kim, MD
Deb Schrag, MD
Lee-Jen Wei, PhD

Author Affiliations: Division of Biostatistics, Department of Clinical Medicine, Kitasato University Graduate School of Pharmaceutical Sciences, Tokyo, Japan (Horiguchi); Department of Health Research and Policy, Stanford University School of Medicine, Palo Alto, California (Tian); Division of Population Sciences, Department of Medical Oncology, Dana Farber Cancer Institute, Boston, Massachusetts (Uno, Schrag); Department of Biostatistics and Computational Biology, Dana Farber Cancer Institute, Boston, Massachusetts (Cheng); Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts (Kim); Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Wei).

Accepted for Publication: February 7, 2018.

Corresponding Author: Lee-Jen Wei, PhD, Department of Biostatistics, Harvard T. H. Chan School of Public Health, 655 Huntington Ave, Boston, MA 02115 (wei@hsph.harvard.edu).

Published Online: May 3, 2018. doi:10.1001/jamaoncol.2018.0518

Author Contributions: Ms Horiguchi and Drs Tian and Uno contributed equally as first authors. Ms Horiguchi and Dr Wei had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tian, Wei.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Horiguchi, Tian, Uno, Wei.

Critical revision of the manuscript for important intellectual content: Tian, Cheng, Kim, Schrag.

Statistical analysis: Horiguchi, Tian, Uno, Cheng, Wei.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported in part by grants R01 HL089778 from the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), ROO HS022193 from the Agency for Healthcare Research and Quality, NIH; and R21 AG049385 and KOB AG0515587 from the National Institute on Aging, NIH.

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.