Article:
Hall, PS, Cairns, DA orcid.org/0000-0002-2338-0179 and Seymour, MT orcid.org/0000-0002-2441-9629 (2021) Quantifying and Interpreting Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Cancer Control for Advanced Gastroesophageal Cancer Among an Older Population—Reply. JAMA Oncology, 7 (11). 1725. ISSN 2374-2437

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Reply to Wang et al. and Mizutani, June 2021

We thank Mizutani for his description of GO2 as a modern trial tailored to reflect the preferences and clinical needs of older and frailer patients. He is of course right that patient selection included an element of subjectivity: the limits of what constitutes *"unsuitable for full-dose combination chemotherapy because of advanced age and/or frailty"* varies between individual clinicians, between cultures and over time. However, we should remember that every trial report we read has been subject to the same or greater subjectivity; since, no matter how apparently objective are the eligibility criteria written in a protocol, the decision to approach or not approach a potential participant who meets those criteria is one of clinical judgement. Similarly, clinical decisions about the application of 'standard' dosing schedules to individuals is a matter of judgement, and national surveys during the preparation for both FOCUS2 in colorectal cancer[1] and GO2 in gastroesophageal cancer[2] showed marked inconsistency in those decisions. By contrast, GO2 was exceptionally inclusive, embracing real-world clinical judgment in patient selection, but then applied a careful multidimensional baseline health assessment, which has allowed us to define the trial population far more objectively than in other trials, and to look for interactions between different dimensions of baseline fitness and treatment.

We also thank Wang et al. for their interest in the statistical aspects of GO2 and for highlighting their own methodology in this area. Their point reflects the fact that while conversations with patients about the non-inferiority margins or superiority increments of treatments are usually expressed in absolutes (days, weeks), the statistical estimates of individual time-points (eg medians) are intrinsically unstable and do not fairly assess the impact of treatment across the whole population. Our design followed regulatory guidance in Europe[3] and the United States,[4] basing statistical inference on the hazard ratio as a '*relative metric*' approach. This reflects the importance to all patients of demonstrating non-inferiority over the expected patient-lifetime; so converting an absolute value (agreed at our patient forum) into a hazard ratio (used in the trial's statistical design) is not a *"detour"*, but an important step to keep the trial result relevant for the whole patient population. Importantly for this, we found no evidence of violation of the proportional hazards assumption underpinning the Cox model.[2]

We agree that the alternative approach proposed by Dr Wei's group,[5] based on differences in restricted mean survival time (RMST), may more directly reflect the absolute differences important to patients while retaining statistical relevance across the whole population. Following their methodology, we estimated differences in RMST, adjusting for stratification factors, as 12.3 days (95%CI: -7.8, 32.3) for Level A vs. B, and 11.2 days (95%CI: -8.5, 31.0) for Level A vs. C (similar values to those derived from our curves by the letter authors). Although, as for any *post-hoc* secondary analysis, this must be interpreted with caution, it provides further support for our non-inferiority conclusions which were based on excluding differences of greater than 34 days.

References

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