ICON8: Response to Ludmir et Al and da Costa et al

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We would like to thank Ludmir and colleagues, and da Costal et al for their interest and comments on the ICON8 Progression Free Survival results, published by Clamp and colleagues[1].

Ludmir et al discuss the merits of using restricted mean survival time (RMST) to describe survival data, as opposed to the usual hazard ratio (HR) and median progression free survival (mPFS). We agree that in the context of non-proportional hazards (that is, the HR varying over time), RMST is more appropriate to describe these data, and would concur with their recommendation that clinical investigators should consider reporting RMST when summarising survival data, and certainly when there is evidence of non-proportional hazards. However, we would like to correct the authors with regards to the mPFS times, as the interval reported was the interquartile range not 97.5% confidence intervals. The two measures cannot be compared, while the confidence interval reflects the uncertainty in the estimate of mean survival the interquartile range is a simple measure of spread of the data. Nonetheless, we do still advocate the use of RMST when analysing survival data.

Da Costa et al raise the possibility that any potential benefit from weekly dose-dense paclitaxel in ICON8 might have been lost as 50% of women who entered the trial received neoadjuvant chemotherapy. They postulate that both the large bulk of disease present at trial entry and the break in chemotherapy caused by interval cytoreductive surgery might have negatively impacted on activity, in particular any anti-angiogenic effect of dose-dense paclitaxel. We acknowledge this hypothesis but do not agree that the results of ICON8 suggest any difference in the activity of dose-dense paclitaxel dependent on surgical approach. Our pre-planned subgroup analysis did not detect any heterogeneity in treatment effect by surgical timing. Moreover, for those patients who underwent immediate primary surgery, the volume of residual disease was a stratification factor used during randomisation, preventing any imbalance in this well-established prognostic factor between treatment arms.

Although our subgroup analyses lack the full power of the overall trial analysis to detect a benefit from dose-dense paclitaxel, they are substantially larger than the cohort of 112 patients who did not receive bevacziumab in the GOG262 trial. We believe that ICON8 provides the most robust evidence available on the use of dose-dense paclitaxel in a non-Japanese patient group and does not support this approach irrespective of the surgical strategy adopted during first-line treatment.

References

1. Clamp AR, James EC, McNeish IA et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *The Lancet* 2019; **394**(10214): 2084-2095