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REPLY

Gastric cancer drug trials—are women second class citizens?

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I would like to thank Wang and colleagues for their comments (Gastric cancer drug trials—are women second class citizens? *Nat. Rev. Clin. Oncol.* doi:10.1038.nrclinonc.2013.231-c1)[1] on the News & Views (Targeted therapies in gastric cancer—the dawn of a new era. *Nat. Rev. Clin. Oncol.* **11**, 10–11; 2014),[2] regarding the apparent limited activity of ramicirumab in women.

They question the lack of benefit of ramicirumab in this subgroup of patients, as suggested from the data reported in Figure 3 in the article by Fuchs *et al.*[2] I believe that this observation illustrates one of the key limitations of subgroup analyses and multiple testing in trials. Phase III clinical trials are usually powered for a primary end point, such as overall survival, as noted in the REGARD study. However, additional patient and tumour characteristics are commonly evaluated individually to confirm broad applicability and for further hypothesis development. Multiple hypotheses testing in this regard is associated with a false discovery proportion, resulting in the possibility of identifying a difference that could also occur randomly.[3,4] Specifically the Forest plot represented in Figure 3 reported the results of an analysis on 33 individual variables.[2] At a 5% significance level, one would have expected at least one of these variables to suggest a false difference in efficacy.

Wang and colleagues point to additional studies in support of the hypothesis that women benefit less than men from the investigational or experimental treatment. These studies, however, are difficult to interpret given their heterogeneity—they include perioperative studies involving antibiotics or immunotherapies, adjuvant chemotherapy, and new targeted drugs. Owing to such heterogeneity, it is difficult to identify a plausible biological rationale for the gender difference observed in the outcome of these studies. Notably, the investigational drug was not superior to standard of care in several of these studies, thus the apparent difference in lack of efficacy according to gender does not seem so meaningful. Furthermore, the number of women recruited in these studies is less than half of the total number of patients enrolled (closer to one-third in each study cited by Wang *et al.* in Table 1), consistent with the epidemiology of the disease. This small sample size of women is more likely to lead to spurious findings with wide confidence limits, as demonstrated by the hazard ratios provided in Table 1 (Wang *et al.*),[1] which crossed the equivalency point of 1.0, suggesting that there is no real difference in outcome according to gender.

It is, however, an interesting quandary whether there might be a specific interaction between antiangiogenic therapy and oestrogen, which would warrant further investigation. When considering the potential gender difference effect on the efficacy on an antiangiogenic therapy, two other studies might also need consideration. The first study, AVAGAST, evaluated the use of chemotherapy with and without bevacizumab in the first-line metastatic setting for advanced-stage gastric cancer.[5] The second study, RAINBOW, examined the use of second-line chemotherapy with and without ramicirumab in patients with advanced-stage gastric cancer.[6] Of note, both studies did not show any gender-related differences in the outcome, thereby reinforcing the idea that the gender bias highlighted in the REGARD study is likely to be spurious.

Nonetheless, I entirely agree with Wang and colleagues on the importance of identifying a subpopulation of patients who may benefit from antiangiogenic therapy. Numerous reports have examined a variety of potential biomarkers to predict the efficacy of antiangiogenic therapy. In patients with gastric cancer, the AVAGAST study included a comprehensive analysis of biomarkers in over 90% of the study population, and found two candidate biomarkers—plasma VEGF-A and neuropilin 1, which were associated with a potential benefit from antiangiogenic therapy.[7] Specifically, high levels of VEGF-A in plasma or the presence of tumours with low neuropilin-1 staining were associated with greater benefit from antiangiogenic therapy (HR 0.72, 95% CI 0.57–0.93 and HR 0.75, 95% CI 0.59–0.97, respectively). The test for interaction for each of the examined candidate biomarkers was of borderline significance ($P = 0.07$, and $P = 0.06$, respectively for plasma VEGF-A and for tumour neuropilin-1), suggesting that additional validation is required. A biomarker analysis of ramicirumab is ongoing and these results are eagerly awaited in light of determining a subpopulation of patients who will benefit most from this therapy.

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Competing interests
The author declares no competing interests.

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