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CORRESPONDENCE

Gastric cancer drug trials—are women second class citizens?

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We read with interest the News & Views article by Manish A. Shah (Targeted therapies in gastric cancer—the dawn of a new era. *Nat. Rev. Clin. Oncol.* **11**, 10–11; 2014)[1] that focused on a recently published study by Fuchs and colleagues.[2] We agree with the author that the anti-VEGF monoclonal antibody ramucirumab represents a new biological therapy for gastric cancer; however, we disagree with the statement that ramucirumab has been shown to be efficacious in most subgroups of patients. The lack of efficacy of several new drugs in six recent large phase III clinical trials that include this agent and one prospective randomized trial in women with this disease is concerning.[2–8]

Our concerns are based on two facts. First, in Figure 3 in the article by Fuchs and colleagues,[2] the hazard ratio (HR) in women is 1.431 (0.852–2.405, 95% CI), whereas for men the HR is 0.676 (0.499–0.916, 95% CI). Because the total number of research participants of men and women in this study are both more than 100 (248 and 107, respectively), the results for both men and women seem statistically trustworthy. Therefore, from these data, we can conclude that the drug is not effective in women. Second, we searched PubMed for the results of clinic trials published from January 2011 to February 2014, using the key words 'gastric cancer trial phase' or 'gastro-oesophageal junction trial phase' or 'gastroesophageal adenocarcinoma trial phase'. We identified six studies—in addition to the article by Fuchs *et al.*[2]—that included ≥100 patients and that had analysed the HR separately for men and for women.[3–8] Notably, the HR for women in five of these six trials was higher than the HR for men (Table 1). The only exception is the median overall survival (months) in the trial noted for those patients treated with capecitabine and cisplatin with or without cetuximab who had previously untreated advanced-stage gastric cancer;[6] the HR for men and women was similar, 1.04 versus 1.00, respectively. However, the study reported a negative result, indicating that addition of cetuximab to capecitabine and cisplatin provided no additional benefit to chemotherapy alone. Furthermore, the median overall survival durations for women in both treatment arms (7.2 and 8.7 months, for those receiving capecitabine and cisplatin with or without cetuximab, respectively) in this trial are lower than the respective results seen in men (10.9 and 11.0 months, respectively).

The lack of efficacy observed in women with gastric cancer compared with men in these trials is most likely due to incidence and mechanistic differences that are related to gender differences. Although the molecular mechanisms for gender differences in gastric cancer are not well understood, there are data that strongly support the existence of such differences. First, it is known that there is a gender difference in the incidence of this disease.[9] Incidence of gastric cancer in women is much less than that in men.[10] Second, differences have been

Table 1 | Gender differences in efficacy of drugs in major clinic trails in recent years

Clinic trial	*n*	Number of women	Gender difference data
Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD trial)[2]	355	107	HR (95% CI) for overall survival M: 0.676 (0.499–0.916) W: 1.431 (0.852–2.405)
A randomized phase III trial of adjuvant chemotherapy with mitomycin-C in combination with either short-term doxifluridine or long-term doxifluridine plus cisplatin after curative D2 gastrectomy (AMC0201 trial)[3]	855	267	HR (95% CI) for RFS M: 1.05 (0.82–1.34) W: 1.24 (0.84–1.85)
Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer[4]	244	63	HR (95% CI) for risk of development of surgical-site infection M: 1.03 (0.61–1.75) W: 1.19 (0.33–4.31)
Intraoperative versus extended antimicrobial prophylaxis after gastric cancer surgery[5]	355	115	Odds ratios for surgical-site infection M: 0.436 (0.162–1.177) W: 0.881 (0.120–6.481)
Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced-stage gastric cancer (EXPAND trial)[6]	904	231	HR (95% CI) for median PFS M: 1.08 (0.89–1.31) W: 1.22 (0.87–1.71) HR (95% CI) for median overall survival M: 1.04 (0.88–1.23) W: 1.00 (0.75–1.34)
Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced-stage oesophagogastric cancer (REAL3)[7]	553	95	HR (95% CI) for overall survival M: 1.34 (1.01–1.76) W: 1.52 (0.85–2.72)
Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC trial)[8]	1,035	304	HR (95% CI) for 3-year DFS M: 0.49 (0.36–0.66) W: 0.83 (0.54–1.27)

Abbreviations: DFS, disease-free survival; HR, hazard ratio; M, men; PFS, progression-free survival; RFS, recurrence-free survival; W, women.

reported in the survival rates between men and women with metastatic gastric cancer.[11] These data indicate that in women and men, biological and genetic components contribute differently to the susceptibility and to the progression of the disease. For example, in the trials of doxifluridine,[3] perioperative enteral immunonutrition,[4] postoperative antimicrobial prophylaxis,[5] and the combination of capecitabine and oxaliplatin (Table 1),[8] the outcome of treatment of gastric cancer with these drugs showed gender differences. Furthermore, for some drugs, there are gender differences in terms of how the pathways targeted by these agents are regulated. For example, the monoclonal antibody ramucirumab directed against VEGFR-2, and the anti-EGFR antibodies panitumumab and cetuximab show hormonal differences and gender-related differential expression.[12,13] Therefore, to a certain degree, the outcome of gender differences from treatments with these drugs is expected.

Another concern is that the protocols in the trials are the same for men and women, and do not consider these gender differences. The effect of a drug treatment is based on a complicated network of interactions between the drug, tumour tissues and the whole human body. Theoretically, for the drugs showing gender specificity, research on the gender differences should be done before starting the clinical trial, to optimize the conditions for both men and women. All the factors that can influence the effect of drugs, such as body mass, hormonal levels, and age, should be considered. We feel that neglecting the subgroup of women in the biomedical community of patients with gastric cancer is a serious problem. Undoubtedly, the incidence of the disease is greater in men; should the drugs then be designed and developed exclusively for the benefit of the male population? If that is the case, should women be excluded from such trials? What is the benefit for a woman to be enrolled in a trial for a drug that has not been developed to target 'her particular disease'? The inclusion of patients in general in clinical trials, and women in this specific situation, should be based on scientific knowledge.

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Competing interests
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