Combination with fluoropyrimidines and platinum-based agents have been used as first-line therapy for metastatic gastric/gastroesophageal junction cancer (GC) resulting in a median progression-free survival (PFS) of 5–6 months and a median overall survival (OS) of 10–15 months. Trastuzumab, a monoclonal antibody against human epidermal growth factor receptor 2 (HER2), significantly improved the OS of HER2-positive GC patients, which consists of around 15% of patients (1). However, other randomized studies failed to show benefits of several molecular targeting agents for GC in first-line (2-7), thus development of more effective combination is important.

Ramucirumab, a fully human immunoglobulin G1 monoclonal antibody to the extracellular binding domain of vascular endothelial growth factor receptor 2 (VEGFR-2), become one of the standard treatment for pretreated GC based on two pivotal trials (RAINBOW and REGARD). Ramucirumab monotherapy in REGARD improved OS compared with placebo (8). Additionally, ramucirumab plus paclitaxel in RAINBOW was more effective than paclitaxel alone as second-line treatment for GC (9). To move effective agents from second-line to first-line is a formula in Oncology field and efficacy of ramucirumab in first-line is anticipated.

In the issue of Annals of Oncology, the result of a randomized phase-2 study of first-line ramucirumab were reported (10). This trial failed to show improvement in PFS when ramucirumab was combined with FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) in comparison with FOLFOX plus placebo (6.4 vs. 6.7 months, hazard ratios; HR 0.98). OS (median 11.7 vs. 11.5 months) or ORRs (45.2% versus 46.4%) as secondary endpoints were also similar. Higher proportion of patients in the ramucirumab arm discontinued study treatment because of reasons other than progressive disease (48% vs. 16%). Although most grade ≥3 toxicities did not differ significantly between two arms, slightly higher incidence of mild grade toxicities in ramucirumab arm might contribute to this difference of treatment discontinuation. Overall, this trial did not show any benefit of ramucirumab, so is this the end of development of ramucirumab in first-line? The answer is “NO” since there are several issued to be addressed. First, the treatment might not be delivered adequately in ramucirumab arm. According to post hoc exploratory analysis which censored treatment discontinuation due to reasons other than progressive disease (on-treatment PFS), HR favored the ramucirumab arm (0.76). This phenomenon was in line with previous randomized study of anti-VEGF-A monoclonal antibody bevacizumab plus FOLFOX for colorectal cancer, which showed better HR in on-treatment PFS (0.63) rather than analysis by usual PFS definition (0.83) due to discontinuation of entire protocol treatment by low grade toxicities such as sensory neuropathy (11). In this first-line ramucirumab trial, treatment duration of all compounds seems to be similar (10). So, not a few patients are suspected to stop entire treatment due to side effects with chemotherapy. In previous AVAGAST trial of bevacizumab in combination with fluoropyrimidines and cisplatin for GC, more
than half of patients continued fluoropyrimidines and bevacizumab after completion of 6 cycles of cisplatin combination (2), and rates of treatment discontinuation due to adverse events were similar between two arms (21% in bevacizumab vs. 19% in placebo). Second, this study included both esophageal adenocarcinoma and GC. The HR for PFS favored the ramucirumab arm in GC subgroup (HR 0.53), but not in the esophageal cancer subgroup (10). Although the exact reason of different outcome between esophageal and GC is not clear, previous independent two meta-analyses showed prognostic impact of VEGFR expression in GC but this was not observed in esophageal adenocarcinoma (12,13). Biomarker analysis in REGARD study also showed a trend of worse outcome in GC patients with higher VEGFR2 expression, although predictive impact of ramucirumab efficacy remains unclear due to small sample size (14). Further study is necessary to compare detailed tumor profile between esophageal adenocarcinoma and GC. Finally, an exploratory exposure-response analysis indicated that patients with higher ramucirumab exposure had longer OS as same as previous analysis in REGARD and RAINBOW (15). At this time, exact impact of higher dose of ramucirumab to improve efficacy is unknown, and higher dose of trastuzumab did not result in superior outcome of HER2 positive GC patient than standard doses (16), despite the fact that exposure–response analysis showed patients with the high exposure had better OS than patient with low exposure with trastuzumab (17). These questions should be answered in ongoing randomized phase 3 trials to evaluate capecitabine/5-fluorouracil and cisplatin with or without ramucirumab as first-line therapy in patients with metastatic GC (RAINFALL, NCT02314117), which used cisplatin based regimen and intensive dose of ramucirumab (at a dose of 8 mg/kg day 1 and day 8 of a 3 weeks cycle). We should stay tuned for RAINFALL, whether it can show benefit of ramucirumab in first-line as same as antecedent RAINBOW in second-line.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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