

## No benefit from ramucirumab in first-line chemotherapy?

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Provenance: This is a Guest Editorial commissioned by Section Editor Rulin Miao, MD [Key laboratory of Carcinogenesis and Translational Research (Ministry of education/Beijing), Gastrointestinal Tumor Center, Peking University Cancer Hospital & Institute, Beijing, China].

Comment on: Yoon HH, Bendell JC, Braiteh FS, *et al.* Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. *Ann Oncol* 2016;27:2196-2203.

Received: 18 March 2017; Accepted: 26 March 2017; Published: 21 April 2017.

doi: 10.21037/tgh.2017.03.18

View this article at: <http://dx.doi.org/10.21037/tgh.2017.03.18>

Ramucirumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody targeting human vascular endothelial growth factor receptor-2 (VEGFR-2). It prevents the binding of VEGFR-2 with its ligands including VEGF-A, VEGF-C, and VEGF-D. Thus, receptor activation and vascular endothelial growth factor (VEGF) signal pathways are inhibited, leading to the reduction of tumor neovascularization and growth. Ramucirumab is the only biologic agent targeting angiogenesis that has shown a survival benefit in gastric or gastroesophageal junction adenocarcinoma in phase III trials. Two phase III trials, REGARD and RAINBOW (1,2), demonstrated an improvement in overall survival (OS). The REGARD trial was a phase III, international, randomized, double-blind, placebo-controlled trial (1). Patients were eligible who had metastatic gastric or gastroesophageal junction adenocarcinoma after the failure of first-line platinum or fluoropyrimidine-containing combination therapy; 355 patients were assigned in a 2:1 ratio, to receive best supportive care plus either ramucirumab at 8 mg/kg (n=238) or placebo (n=117) once every 2 weeks. OS was significantly longer in the ramucirumab group: median OS, 5.2 *vs.* 3.8 months; hazard ratio (HR), 0.78; 95% confidence interval (CI), 0.603–0.998; P=0.047. Ramucirumab also significantly prolonged progression-free survival (PFS): median PFS, 2.1 *vs.* 1.3 months; HR, 0.48; 95% CI, 0.38–0.62; P<0.0001. While the objective response rate (ORR) was 3% in both arms, the disease control rate was higher in the ramucirumab arm than in the placebo (49% *vs.* 23%; P<0.0001). The RAINBOW study, a phase III, randomized,

double-blind, placebo-controlled trial, compared the efficacy and safety of ramucirumab plus paclitaxel with that of placebo plus paclitaxel for the second-line treatment of gastric and gastroesophageal junction adenocarcinoma (2). A total of 665 patients were included. OS was significantly longer in the ramucirumab plus paclitaxel group: median OS, 9.6 *vs.* 7.4 months; HR, 0.81; 95% CI, 0.68–0.96; P=0.017. PFS was also longer in the ramucirumab plus paclitaxel group: median PFS, 4.4 *vs.* 2.9 months; HR, 0.64; 95% CI, 0.54–0.75; P<0.0001. The ORR also showed a statistically significant improvement (28% *vs.* 16%; P=0.0001). On the basis of these findings, the combination of ramucirumab and paclitaxel is currently considered a standard of care in second-line treatment. These two positive studies are remarkable since many trials evaluating targeted therapies have failed.

Ramucirumab has also been shown to improve survival outcomes in phase III trials of non-small-cell lung cancer and colorectal cancer (3,4). The REVEL trial examined the efficacy of the addition of ramucirumab to docetaxel in patients receiving second-line treatment for non-small-cell lung cancer (3). There was a significant improvement of OS in docetaxel plus ramucirumab arm (median OS, 10.5 *vs.* 9.1 months; HR, 0.86; 95% CI, 0.75–0.98; P=0.023). For colorectal cancer, the RAISE trial examined the combination of FOLFIRI and ramucirumab compared with FOLFIRI plus placebo in second-line therapy (4). This trial revealed a statistically significant improvement in OS (median OS, 13.3 *vs.* 11.7 months; HR, 0.84; 95% CI, 0.73–0.98; P=0.022). It is notable that all the trials listed above

successfully reached the primary endpoints in second-line setting.

In an article published recently in *Annals of Oncology*, Yoon *et al.* reported a phase II trial from the United States examining ramucirumab as first-line therapy in patients with metastatic or locally-advanced adenocarcinoma originating from the esophagus, stomach or gastroesophageal junctions (5).

Patients were randomly assigned 1:1 to receive modified FOLFOX6 (mFOLFOX6) plus ramucirumab (8 mg/kg) or mFOLFOX6 plus placebo every 2 weeks. The primary endpoint was PFS. The secondary endpoints included ORR and OS. A total of 84 patients were enrolled in each arm, all of whom were randomized and included in the efficacy analysis. Esophageal cancer patients accounted for almost half of the patients. The baseline patient characteristics were generally well balanced between groups. The trial did not meet its primary endpoint of superiority in the intention-to-treat population in PFS (median PFS, 6.4 *vs.* 6.7 months; HR, 0.98; 95% CI, 0.69–1.37; *P*=0.886) or OS (median OS, 11.7 *vs.* 11.5 months; HR, 1.08; 95% CI, 0.73–1.58; *P*=0.712). Although the best overall response of stable disease favored the ramucirumab arm (39.3% *vs.* 20.2%), the ORRs were similar (45.2% *vs.* 46.4%). Although a few types of adverse events such as neutropenia, fatigue, and hypertension occurred more frequently in the ramucirumab arm, the rates of most grade-3 or greater toxicities did not significantly differ between the two arms. The reasons for discontinuation of treatment were disease progression (43% ramucirumab *vs.* 69% placebo), patient or investigator decision (27% ramucirumab *vs.* 10% placebo), adverse events (21% ramucirumab *vs.* 6% placebo), and death (1% ramucirumab *vs.* 4% placebo). Thus, discontinuation of study treatment for reasons other than disease progression was more common in the ramucirumab arm. In this study, several post hoc analyses were performed. In the analysis that censored for premature discontinuation, the HR for PFS favored the ramucirumab arm (HR, 0.76; 95% CI, 0.50–1.15; *P*=0.194). The preplanned subgroup analysis indicated a benefit of ramucirumab in gastric or gastroesophageal junction cancer (*n*=88; median PFS 9.3 *vs.* 7.6 months; HR, 0.53; 95% CI, 0.29–0.97; *P*=0.036). Exploratory pharmacokinetic analyses also indicated that a higher concentration of ramucirumab following the first dose was associated with a better prognosis compared with the placebo arm.

In this study of Yoon *et al.*, the addition of ramucirumab to mFOLFOX6 did not result in a survival benefit as shown in PFS and OS. The improvement of ORR was not

observed either. Even though this study is a phase II trial and does not totally deny the usefulness of ramucirumab in first-line therapy, ramucirumab in first-line therapy does not seem to be promising, since even a better trend in the ramucirumab arm was not observed.

Then, what made this trial negative? As described in this article, there are several possible reasons.

First, these results raise the possibility that the efficacy of ramucirumab in second-line treatment demonstrated in two trials [RAINBOW and REGARD (1,2)] may not be applicable to first-line treatment. All the previous trials that added VEGF-targeting agents to first-line therapy produced negative results, which are consistent with the results of this trial. The AVAGAST trial is a phase III, international, randomized, double-blind, placebo-controlled trial examining fluoropyrimidine-cisplatin plus bevacizumab compared with fluoropyrimidine-cisplatin plus placebo in first-line therapy (6). There was no difference in OS between the two treatment groups, whereas median progression-free survival (6.7 *vs.* 5.3 months; HR, 0.80; 95% CI, 0.68–0.93; *P*=0.0037) and overall response rate (46.0% *vs.* 37.4%; *P*=0.0315) were significantly improved. AVATAR, which is another phase III trial similar to AVAGAST in study design, was conducted on Chinese patients with gastric cancer (7). In the AVATAR trial, bevacizumab also failed to yield a survival benefit in OS (median 10.5 *vs.* 11.4 months; HR, 1.11; 95% CI, 0.79–1.56; *P*=0.56). Furthermore, ST03 trial, UK phase II/III trial, assessing the addition of bevacizumab to perioperative epirubicin, cisplatin, and capecitabine chemotherapy, revealed that bevacizumab did not improve OS (8). Three-year OS was 50.3% in the chemotherapy alone arm and 48.1% in the chemotherapy plus bevacizumab arm (HR, 1.08; 95% CI, 0.91–1.29; *P*=0.36). On the other hand, apatinib, an oral small molecular of VEGFR-2 tyrosine kinase inhibitor, significantly prolonged OS (median OS 6.5 *vs.* 4.7 months; *P*=0.016) in patients with gastric or gastroesophageal cancer and HR for OS of 0.71 (95% CI, 0.54–0.94) was less than that in the REGARD and RAINBOW trial (0.78 and 0.81) (1,2,9). The same is true for colorectal cancer. All the studies using bevacizumab in perioperative setting such as AVANT, NSABP C-08, and QUASAR2 are negative (10–12). Moreover, the NO16966 trial comparing the efficacy of currently used oxaliplatin-based first-line chemotherapy (FOLFOX or capecitabine plus oxaliplatin) plus bevacizumab or placebo did not show the benefit in OS, whereas PFS favored the addition of bevacizumab (13). However, positive data were obtained

in second- or later-lines of chemotherapy. The addition of bevacizumab in second-line chemotherapy improved OS in phase III trials. Although the E3200 trial recruited patients who had not been treated with bevacizumab and the ML18147 trial included patients who had received bevacizumab, favorable OS in bevacizumab arm was consistent (14,15). As mentioned before, the RAISE trial was conducted in second-line setting (4). Regorafenib is a tyrosine kinase inhibitor targeting a wide range of kinase including VEGFR. The CORRECT trial compared regorafenib and placebo for heavily pre-treated colorectal cancer patients, showing that regorafenib increased OS (median OS 6.4 *vs.* 5.0 months; HR, 0.77; 95% CI, 0.64–0.94;  $P=0.0052$ ) (16). These results suggested that the development of anti-VEGF in front-line therapy is more difficult than later-lines chemotherapy.

Second, this study included patients with esophageal adenocarcinoma. The HR for PFS was more favorable in patients with gastric or gastroesophageal junction cancer than in patients with esophageal cancer. The reasons for the lesser efficacy of ramucirumab in esophageal cancer remain unclear. No successful targeted therapy for esophageal cancer has yet been developed. As one example, the SCOPE1 trial aimed to investigate the addition of cetuximab to cisplatin and fluoropyrimidine-based definitive chemoradiotherapy in patients with localized esophageal squamous-cell cancer and adenocarcinomas (17). This study was a phase II/III trial, but stopped before the continuation to phase III because the trial met criteria for futility. In addition, the COG trial is a phase III trial comparing gefitinib with placebo in previously treated advanced esophageal squamous-cell cancer and adenocarcinomas (18). Further, this is also a negative trial that did not meet its primary endpoint, OS. Although these two studies included both adenocarcinoma and squamous cell carcinoma patients, subgroup analyses did not reveal a difference in pathological type. It is indicated that the development of targeted therapies is challenging regardless of pathological findings, particularly for esophageal cancer. It is uncertain whether or not the difficulties are caused by genetic background. Further studies are necessary in this regard.

Third, a high proportion of patients stopped treatment for reasons other than disease progression. In the ramucirumab arm in particular, only 46% of patients (36 of 78) were able to continue the treatment until disease progression. Discontinuation of treatment for reasons other than disease progression occurred more frequently in the ramucirumab arm. Reduction of the chemotherapy

dose might lower the efficacy of chemotherapeutic agents. It is possible that the addition of ramucirumab induced an increase of toxicities, resulting in early withdrawal from treatment because there were more adverse events in the ramucirumab arm. It should be taken into account that oxaliplatin is associated with cumulative neurotoxicity. In the NO16966 trial, the treatment discontinuation due to toxicities were frequently observed, which is thought to be one of the reasons to fail to show a superior OS (13). Nonetheless, the proportion of toxicities shown in this article indicated the treatment is considered to be well tolerated. Perhaps the protocol criteria were too strict to allow the continuation of treatment.

Fourth, mFOLFOX6 was used as the backbone regimen in this study. Many of the targeted agents that have been examined in combination with FOLFOX, such as onartuzumab, panitumumab and rilotumumab, have failed to improve the clinical outcomes in first-line chemotherapy for gastric or gastroesophageal adenocarcinoma (19,20). Onartuzumab and rilotumumab are anti-MET antibodies that inhibit HGF binding and receptor activation. The efficacy and safety of mFOLFOX6 and onartuzumab were examined in the first-line setting for metastatic, human epidermal receptor 2 (HER2)-negative patients (19). The enrollment of this trial was stopped early due to negative results from a randomized phase II trial. It was revealed that the addition of onartuzumab to mFOLFOX6 did not improve PFS in either an unselected population or in MET-positive patients as defined by immunohistochemistry. The PRODIGE 17 ACCORD 20 MEGA assessed mFOLFOX6 in combination with panitumumab or rilotumumab as the first-line treatment of patients (20). This study did not reach the endpoint. Moreover, adding panitumumab or rilotumumab seemed more toxic and less effective than the placebo arm. Interestingly, the placebo arm in both trials, namely, mFOLFOX6 alone provided relatively better outcomes with median OS being 11.3–13.1 months. Better outcomes in control arms make it more difficult to reach the endpoint in general. Actually, the AVAGAST trial showed poorer outcomes with bevacizumab in Asian patients whose outcomes were better compared with those from Pan-America: median OS was 13.9 *vs.* 12.1 months (HR, 0.97; 95% CI, 0.75–1.25) for Asian patients while median OS was 11.5 *vs.* 6.8 months (HR, 0.63; 95% CI, 0.43–0.94) for Pan-American patients (6). Anti-MET antibodies may be ineffective since rilotumumab also failed to improve the survival outcomes in association with epirubicin, cisplatin and capecitabine (21). However, we cannot exclude the

possibility that favorable outcomes in the placebo arm made these trials negative. The efficacy of bevacizumab is sometimes characterized by ceiling effect which means that patients with better prognosis are less likely to gain the benefits.

It is of interest that ziv-aflibercept, a recombinant fusion protein that binds VEGF-A, VEGF-B and placental growth factor with high affinity, failed to improve outcomes. Ziv-aflibercept was also evaluated in combination with mFOLFOX6 as first-line therapy for esophageal, gastric and gastroesophageal junction (22). The trial setting was quite similar to the study of Yoon *et al.* at several points.

At present, two randomized trials of ramucirumab are ongoing. The RAINFALL, a global phase III trial, compares fluoropyrimidines (capecitabine or 5-FU) plus cisplatin with and without ramucirumab as first-line treatment. This study is directed only to HER2-negative gastric and gastroesophageal junction cancers. The primary endpoint is PFS and OS is the key secondary endpoint. The RAINSTORM trial is an Asian global phase II trial comparing S-1 plus oxaliplatin with and without ramucirumab as the first-line treatment. Notably, ramucirumab is administered at a higher dose of 8 mg/kg on days 1 and 8 in these trials, since it has been reported that a higher concentration of ramucirumab is correlated with a better prognosis. In both trials, the patient recruitment has already been completed. There is no doubt that these two trials would be a pivotal trial. However, not only the results for the endpoints but also biomarker analyses are probably important to answer unsolved questions. A robust biomarker has not yet been identified for anti-angiogenic agents such as ramucirumab or bevacizumab even after various candidates have been tested. The establishment of biomarker is a key to breakthrough certainly. Anyway, the results of these two studies are eagerly awaited.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* K Muro has received research funding from MSD, Daiichi Sankyo, Ono, Kyowa Hakko Kirin, Shionogi, and Gilead Sciences; and he has also received honoraria for lectures from Chugai, Takeda, Eli Lilly, Merck Serono, Taiho, and Yakult honsha. S Mitani has no conflicts of interest to declare.

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doi: 10.21037/tgh.2017.03.18

**Cite this article as:** Mitani S, Muro K. No benefit from ramucirumab in first-line chemotherapy? *Transl Gastroenterol Hepatol* 2017;2:30.