Commentary

# Variations in outcome for advanced gastric cancer between Japanese and Western patients: a subgroup analysis of the RAINBOW trial

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Received: 08 April 2016; Accepted: 23 April 2016; Published: 27 May 2016.
doi: 10.21037/tgh.2016.05.06
**View this article at:** http://dx.doi.org/10.21037/tgh.2016.05.06

Two large, global phase 3 trials have confirmed the efficacy of the vascular endothelial growth factor receptor 2 monoclonal antibody ramucirumab in the second-line treatment of advanced gastric cancer (GC) and gastro-oesophageal junction cancer (GOJ) (1,2). The RAINBOW trial evaluated its use in conjunction with paclitaxel chemotherapy and reported significant improvements in overall survival (OS), progression free survival (PFS) and response rates (RR); however differentials in outcome based on geographical area were noted. For patients from the Asia geographical area (consisting of Japan, South Korea, Hong Kong, Singapore and Taiwan) addition of ramucirumab resulted in improvements in PFS and RR, but no significant improvement in OS (2). The majority of patients from the Asian geographical group were recruited from Japan (140 out of 223). This additional subgroup analysis gives further information about geographical differences in outcome between Japanese patients in comparison to 'Western' patients from Australia, Europe, Israel and the USA (3).

Considering the baseline characteristics of the Japanese (n=140) and Western (n=398) patient groups there are some clear and clinically important differences between them. The Japanese group of patients had a better performance status and a shorter time to progression after first line therapy. They also had a higher proportion of diffuse type histology, 0–2 metastatic sites (compared to >3) and a lower incidence of ascites, suggesting a lower burden of metastatic disease compared to the Western patient group. These findings are consistent with previous subgroup analyses of trials of targeted agents in GC, where Japanese patients have also been found to be comparatively fitter than their Western counterparts (4). The median duration of study therapy was notably longer in the Japanese population compared to the Western population (22.5 *vs.* 16.1 weeks) with less treatment discontinuation due to adverse events (7.4% *vs.* 13.6%). Data was also suggestive of a longer time to deterioration of ECOG performance status in the Japanese group (HR for deterioration 0.64 *vs.* 0.89), although these hazard ratios did not meet significance. This all indicates a generally improved tolerance and longer exposure to treatment among the Japanese patient group. The combination treatment was associated with higher rates of grade ≥3 neutropaenia across both geographical groups, with a higher incidence amongst the Japanese population (66.2% *vs.* 32.1%). Rates of febrile neutropaenia and serious adverse events however were similar, suggesting that this could be safely managed. Again this finding is consistent with previous studies reporting higher incidences of neutropaenia associated with paclitaxel chemotherapy in Japanese compared to Western patient cohorts (5).

When comparing outcomes, OS, PFS and RR were superior across both arms of the trial in Japanese as compared to Western patients. Within the Japanese group the addition of ramucirumab did not lead to a significant difference in median OS [11.4 *vs.* 11.5 months, HR 0.88 (95% CI: 0.60–1.28)] but did lead to significant improvements in both PFS and RR. This is in contrast to the Western population where median OS [8.6 *vs.* 5.9 months, HR 0.73 (95% CI: 0.58–0.91)], PFS and RR were all significantly improved. When quantifying the magnitude of benefit seen with the addition of ramucirumab, the improved HR for progression on combination therapy within the Japanese cohort when compared to the Western cohort (0.50 *vs.* 0.63) reflected a greater relative

improvement in PFS gained.

A key explanatory factor in the difference in OS benefit found between the two groups is likely to be in the rate of uptake of further lines of post-discontinuation therapy. This was markedly higher in the Japanese population than in the Western population (75.0% *vs.* 37.2%), with a higher proportion of Japanese patients receiving fourth line or beyond therapy. It should also be noted that the median survival of 11.5 months recorded in this unplanned subgroup analysis in the Japanese paclitaxel/placebo group is substantially better than any outcomes previously reported, comparing favourably to the median OS of 9.5 months in the paclitaxel arm of the WJOG trial: so far the best outcome achieved in a second-line chemotherapy trial (6). In a further exploratory analysis included in the paper the magnitude of effect on OS seen with the addition of ramucirumab appeared to be greater across both geographical groups for patients who did not go on to receive any further lines of treatment. The high uptake of further lines of treatment and relatively long survival is likely to have led to a 'dilution' of OS benefit seen with the addition of ramucirumab to second-line therapy in the Japanese patient group (7).

It is instructive to compare these findings to other trials of targeted agents in advanced GC. The AVAGAST study compared first line cisplatin/fluoropyrimidine with bevacizumab or placebo (8). Despite significant improvements in PFS and RR with the addition of bevacizumab, the numerically longer median OS seen was not statistically significant. A subgroup analysis revealed patients in the Pan-American subgroup showed a statistically significant benefit in OS whereas those in the European and Asian subgroups did not, with 90% of the Asian subgroup being drawn from Japan and South Korea. In contrast to RAINBOW, the subset of Asian patients in AVAGAST also did not show any improvement in either PFS or RR. There were again differences in this study between the Asian and non-Asian populations that may go some way to explaining these results: the Asian group had fewer GOJ primaries, a lower frequency of liver metastases and received second-line chemotherapy more often. Such findings are not restricted to anti-angiogenic trials: in a subset analysis of the TOGA study addition of trastuzumab to first-line chemotherapy again did not significantly influence OS in Asia but produced a marked influence in South America where second-line therapies are rarely used (9). There have also been differences in outcome noted within Asian populations. For example in the TYTAN study evaluating the addition of lapatinib to paclitaxel for second-line treatment, there were significant improvements in OS and PFS seen for the Chinese population, but not for the Japanese population (10).

Improved outcomes among Japanese GC patients have been well recognized for a number of years. Whether this reflects differences in cancer epidemiology and biology, or societal and healthcare provision factors such as improved diagnosis and medicines access is a matter of some debate (11). There has been some argument that tumours in Asian populations represent a biologically distinct and less aggressive entity, however studies published to date have failed to find clear genetic or biological differences to support this. In a recent landmark analysis by the Cancer Genome Atlas in which they analysed 295 gastric tumours, no systematic differences in the distribution of the proposed molecular subtypes between East Asian and Western patients was found (12). More specific to the use of anti-angiogenic agents, a biomarker analysis of the AVAGAST study demonstrated that high baseline circulating VEGFA levels and low tumour NRP1 expression appeared to correlate with bevacizumab benefit. In Asian patients however this trend was not seen: this group showed lower levels of VEGFA overall and even those with higher levels still did not gain benefit from bevacizumab (13). These findings have been implicated in the poorer responses to the drug apparently seen in Asian patients, but again it is not clear whether geographic region is a surrogate for differences in disease biology potentially influencing sensitivity to specific anti-angiogenic agents.

Despite a lack of clear evidence of genetic heterogeneity, there are well-recognised differences between Eastern and Western GC populations in terms of epidemiology, histology, and diagnostic and treatment patterns. Western countries have a higher incidence of tumours of the proximal stomach and GOJ, with the incidence of such proximal cancers increasing even whilst the overall incidence of GC in the West declines (14). Proximal tumours are known to be associated with worse outcomes, however even when compared by tumour location survival differences between East and West persist (15). In Japan mass screening programmes have led to substantial stage-shift, with significantly more cancers being diagnosed and treated at an early stage (16). Even in the context of advanced disease, the earlier diagnosis and treatment in Japanese patients is potentially reflected in the generally lower burden of metastatic or measurable disease found. There are also variations of GC presentation and survival

 

within Europe. Eastern European countries have been found to have higher incidence rates and poorer survival than Western European countries (17). There is also some evidence that the pattern of overall decline in incidence is not being seen in Eastern Europe, perhaps related to epidemiological factors such as high prevalence of *H. Pylori* infection (18).

The lack of demonstration of an OS benefit in Asian patients within RAINBOW is consistent with previous trials of targeted agents in advanced GC. In contrast to AVAGAST however, the PFS and RR improvements seen in the Japanese population do provide evidence for biological effect with the addition of ramucirumab. The use of PFS as an effective surrogate endpoint is a contentious issue in most tumour types and in GC has been questioned, with the results of several large patient and trial-level meta-analyses showing a poor correlation between PFS and OS for chemotherapy in both first and second line treatment settings (19,20). Whether the improvements in PFS seen with Japanese patients in RAINBOW correlate to a more tangible OS benefit remain to be seen. There are a number of ongoing studies looking at ramucirumab use in combinations and sequences that are more standard to Japanese and East Asian practice and which may aid in further clarifying its role in treatment (NCT02359058, NCT02539225).

The advantage of large global studies such as RAINBOW is that nuanced interpretations of geographical differences in outcome can be made, and pre-planned subgroup analyses based on geographical area are important components in the design and interpretation of such trials. This was an unplanned subgroup analysis with relatively small numbers in the Japanese patient group limiting its interpretation; however it does appear to add to the existing evidence of disparity between Eastern and Western GC outcomes. This is likely to be due to a complex mixture of both disease-related, epidemiological, diagnostic and treatment factors. Ramucirumab appears to have a clear benefit in the second-line treatment of GC in Western patients both as monotherapy and in combination with paclitaxel chemotherapy, reflected in its recent FDA and EMA licensing. The benefit for Japanese and East Asian patients is less pronounced, however this is in the context of a treatment landscape where utilisation of greater numbers of effective therapies is leading to incrementally improved survival outcomes in general. In spite of this the uptake of ramucirumab in Japan has been high, and the results of further trials are awaited with interest. In the emerging era of genomics it is hoped that approaches in GC will start to shift from describing regional differences in treatment to more individualised management based on the molecular profile of the tumour and validated prognostic and treatment biomarkers. Such research may well help to further define the role of ramucirumab and its place amongst other emerging targeted and immunotherapeutic treatments in the future, and that perhaps this more personalized approach will go some way towards overcoming regional variations in outcome seen.

## Acknowledgements

None.

## Footnote

*Provenance:* This is a Guest Commentary commissioned by the Section Editor Dr. Rulin Miao (Department of Gastrointestinal Surgery, Peking University Cancer Hospital & Institute, Beijing, China).
*Conflicts of Interest:* The authors haves no conflicts of interest to declare.

*Comment on:* Shitara K, Muro K, Shimada Y, *et al.* Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer. Gastric Cancer 2015.

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doi: 10.21037/tgh.2016.05.06
**Cite this article as:** Davidson M, Chau I. Variations in outcome for advanced gastric cancer between Japanese and Western patients: a subgroup analysis of the RAINBOW trial. Transl Gastroenterol Hepatol 2016;1:46.

 