Regorafenib in gastric cancer

Elizabeth C. Smyth

Department of Gastrointestinal Oncology and Lymphoma, Royal Marsden Hospital, London, UK

Correspondence to: Elizabeth C. Smyth, MB, BCh, MSc. Department of Gastrointestinal Oncology and Lymphoma, Royal Marsden Hospital, London, UK. Email: elizabeth.smyth@rmh.nhs.uk.

Provenance: This is a Guest Editorial commissioned by Editor-in-Chief Jiafu Ji, MD, FACS (Department of Gastrointestinal Surgery, Peking University School of Oncology & Beijing Cancer Hospital, Beijing, China).

Comment on: Pavlakis N, Sjoquist KM, Martin AJ, *et al.* Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A Multinational Placebo-Controlled Phase II Trial. *J Clin Oncol* 2016;34:2728-35.

Received: 14 December 2016; Accepted: 15 December 2016; Published: 15 March 2017.

doi: 10.21037/tgh.2017.01.07

View this article at: <http://dx.doi.org/10.21037/tgh.2017.01.07>

Gastric cancer is the fifth most common cancer diagnosed and the third most common cause of cancer death globally (1). For patients with operable gastric cancer, complete surgical resection offers the only realistic chance of cure, however up to half of patients treated with optimal multimodality therapy will relapse following potentially curative surgery (2-5). Advanced recurrent or metastatic gastric cancer is associated with a median overall survival of less than 1 year for patients in clinical trials, and only incremental survival benefits have been made with second line therapies (6-12). The anti-HER2 monoclonal antibody trastuzumab and the anti-VEGFR2 antibody ramucirumab represent the totality of currently licensed targeted therapies available for patients with advanced gastric cancer (11-13). Hence, development of alternative treatment options is strongly encouraged.

Regorafenib is a small molecule inhibitor of multiple intracellular tyrosine kinases including angiogenesis related pathways (VEGFR1 and 2), stromal factors (PDGFR β) and oncogenic drivers (BRAF, RET, KIT) (14). Treatment with regorafenib is associated with survival benefits in metastatic colorectal, gastrointestinal stromal and hepatocellular cancers (15-17). The recently published results of the INTEGRATE study, which evaluated the use of regorafenib in previously treated gastric cancer patients, suggest potential efficacy for regorafenib also in this disease (18). In INTEGRATE, patients were recruited from sites in Australia, New Zealand, Canada and Korea and randomized in a 2:1 ratio to either regorafenib (160 mg daily orally, 21 days on with 7 days off schedule) or placebo. The

primary endpoint of the trial was progression free survival. One hundred and forty seven patients were treated on study, and the primary outcome measure demonstrated that patients treated with regorafenib had statistically significantly improved progression free survival compared to patients who received placebo [2.6 *vs.* 0.9 months (HR 0.40; 95% CI, 0.28–0.59; stratified log-rank $P < 0.001$)]. Consistent with the effects of regorafenib in chemorefractory metastatic colorectal cancer, most of the benefit of regorafenib appeared to be in disease control. Radiological responses were infrequent in regorafenib treated patients; 3 of 100 patients had a RECIST response (3%, 95% CI, 1–9%). Toxicity was as expected; rates of serious adverse events were 32% *vs.* 18% in patients treated on the experimental and control arms respectively. The magnitude of benefit derived from regorafenib appeared to be much higher in Korean patients than in non-Asian patients (HR 0.61 non-Asian patients *vs.* 0.12 for Korean patients, P value for interaction < 0.001). This difference remained even when corrected for other pre-specified covariates and interaction terms. Based on the results of the INTEGRATE trial, regorafenib will be assessed in a randomized phase III trial (INTEGRATE II NCT02773524).

The results of the INTEGRATE trial are encouraging, however a phase III trial is indicated in order to fully evaluate the potential benefits of regorafenib in this population. In particular, the progression free survival results in the control arm of INTEGRATE are poor (0.9 months) for a population containing 42% of

patients previously treated with only one prior line of chemotherapy (18). Furthermore, although the radiological response rate associated with regorafenib was low, this is unsurprising for an anti-angiogenic therapy. Despite similarly low radiological response rates in chemorefractory metastatic colorectal cancer patients, regorafenib was associated with a statistically significant improvement in overall survival in the CORRECT trial (15). Also encouraging is that since INTEGRATE was designed, inhibition of angiogenesis has been validated as a clinically useful target for patients with advanced gastric cancer; ramucirumab has become a standard of care in the second line setting, and the small molecule inhibitor apatinib has also been successful in a phase III randomized trial in China, with further confirmatory trials pending. However, as ramucirumab is now established as a standard of care, it is unknown how this may impact on the efficacy of regorafenib in the upcoming INTEGRATE II trial.

Preliminary biomarker analysis from INTEGRATE suggest that the benefit of regorafenib was comparable in patients with VEGF-A levels above and below the median (18). Validated biomarkers for anti-angiogenic therapy have been elusive; in a comprehensive translational analysis of the CORRECT trial the benefits of regorafenib were consistent across subgroups of patients ascertained using mutation status, plasma ctDNA concentration, and multiple plasma proteins (19). As many historic studies across tumour types examining circulating and tissue targets putatively associated with the efficacy of anti-angiogenic therapy have failed to consistently identify or validate any such biomarker, it is unlikely that further focus on angiogenesis related biomarkers will be fruitful in this setting (20-22). However, unlike bevacizumab and ramucirumab, regorafenib also targets intracellular drivers of angiogenesis and cell growth such as the FGFR family (14). Preclinical work in gastric and colorectal cancer cell lines demonstrates that *FGFR2* amplified cells are sensitive to growth inhibition using regorafenib at submicromolar concentrations (23). As up to 9% of gastric cancers demonstrate *FGFR2* amplification and highly *FGFR2* amplified cancers demonstrate oncogenic addiction to this pathway, it is possible to speculate that the activity of regorafenib in gastric cancer could relate to inhibition of intracellular tyrosine kinases in addition to antiangiogenic activity (24,25). However, *VEGFR1* and *VEGFR2* dysregulation have also been described in gastric cancer, and less commonly aberrations of *RET* and *KIT*, and it is therefore possible that any, or all, of these regorafenib

targets could play a role in the responses of individual patients to this drug (24).

The ultimate role for regorafenib in the treatment of advanced gastric cancer will be determined by the results of the phase III randomized INTEGRATE II trial. However, it is possible that the divergent benefits of regorafenib in geographically defined subsets of patients could influence the overall outcome of INTEGRATE II. In gastric cancer, regional variation as a confounder of international randomised trial results has precedent, as this occurred in the AVAGAST study (21). Whether regorafenib can be combined with standard cytotoxic chemotherapy is being explored in two early stage studies; REPEAT is a phase Ib study which will examine the activity of regorafenib in combination with paclitaxel (NCT02406170) and a small phase II study which combines regorafenib with FOLFOX chemotherapy for previously untreated patients with gastric cancer is also underway (NCT01913639). Although multitargeted tyrosine kinase inhibitors in general have not been successful in conjunction with chemotherapy to date, proof of concept for efficacy of regorafenib as a single agent has already been demonstrated in INTEGRATE, and it is conceivable that additive benefit could be achieved in these studies. As patients with gastric cancer have limited treatment options, any addition to those currently available is very welcome.

Acknowledgements

Funding: The author acknowledges funding from the Royal Marsden/Institute of Cancer Research National Institute for Health Research Biomedical Research Centre (RM/ICR NIHR BRC).

Footnote

Conflicts of Interest: The author declares honoraria from Five Prime Therapeutics for advisory board participation and from Bristol Meyer-Squibb for honorarium for advisory role.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86.
2. Cunningham D, Allum WH, Stenning SP, et al.

- Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.
3. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;29:1715-21.
 4. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:1389-96.
 5. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011;29:4387-93.
 6. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46.
 7. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991-7.
 8. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncol* 2014;15:78-86.
 9. Thuss-Patience PC, Kretzschmar A, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011;47:2306-14.
 10. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012;30:1513-8.
 11. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014;383:31-9.
 12. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014;15:1224-35.
 13. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-97.
 14. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011;129:245-55.
 15. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381:303-12.
 16. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381:295-302.
 17. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;389:56-66.
 18. Pavlaklis N, Sjoquist KM, Martin AJ, et al. Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A Multinational Placebo-Controlled Phase II Trial. *J Clin Oncol* 2016;34:2728-35.
 19. Tabernero J, Lenz HJ, Siena S, et al. Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial. *Lancet Oncol* 2015;16:937-48.
 20. Custodio A, Barriuso J, de Castro J, et al. Molecular markers to predict outcome to antiangiogenic therapies in colorectal cancer: current evidence and future perspectives. *Cancer Treat Rev* 2013;39:908-24.
 21. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011;29:3968-76.
 22. Fuchs CS, Tabernero J, Tomasek J, et al. Biomarker analyses in REGARD gastric/GEJ carcinoma patients treated with VEGFR2-targeted antibody ramucirumab. *Br J Cancer* 2016;115:974-82.

23. Cha Y, Kim HP, Han SW, et al. Abstract 5484: FGFR2 amplification is predictive of sensitivity to regorafenib in gastric and colorectal cancers. *Cancer Res* 2015;75:5484.
24. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;513:202-9.
25. Pearson A, Smyth E, Babina IS, et al. High-Level Clonal FGFR Amplification and Response to FGFR Inhibition in a Translational Clinical Trial. *Cancer Discov* 2016;6:838-51.

doi: 10.21037/tgh.2017.01.07

Cite this article as: Smyth EC. Regorafenib in gastric cancer. *Transl Gastroenterol Hepatol* 2017;2:16.