Gastric Cancer: RAINBOW Subanalysis Shows Paclitaxel-Ramucirumab Efficacy in Western Patients

BY ROBERT H. CARLSON

BARCELONA, Spain—In patients from Western countries, second-line treatment for advanced gastric and gastro-esophageal cancer with the combination of paclitaxel and the VEGF antagonist ramucirumab is safe and efficacious, significantly increasing overall and progression-free survival and response compared with use of paclitaxel alone.

The combination reduced the risk of death by 27 percent and increased survival from 5.9 to 8.6 months compared with paclitaxel alone, according to a subanalysis of 398 patients from Western countries in the randomized placebo-controlled RAINBOW trial who had disease progression on or after use of platinum and fluoropurimidine-containing chemotherapy.

The subanalysis data were presented here at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer (the full analysis of all of RAINBOW's 665 patients was presented earlier this year at the Gastrointestinal Cancers Symposium (***Wilke H et al: Abstract LBA7***).

The results of the subanalysis had been eagerly awaited because some trials have shown significantly different outcomes between patients from Asian and Western countries. In an example cited by several speakers here, the AVAGAST study (***Ohtsu et al: JCO 2011;29:3968-3976***) of bevacizumab plus capecitabine-cisplatin as first-line treatment of patients with gastric cancer, the addition of bevacizumab provided no overall survival benefit for the Asian study population or the study population as a whole, but did improve survival rates in non-Asian patients with diffuse or distal tumors (***Van Cutsem et al: JCO 2012;30:2119-2127***).

In this RAINBOW subanalysis reported at the ESMO meeting, the efficacy and safety of ramucirumab, a vascular endothelial growth factor receptor-2 antagonist, were consistent with the overall study population results, said Eric Van Cutsem, MD, PhD, Professor of Internal Medicine at the University of Leuven and Head of the Digestive Oncology Unit at University Hospital Gasthuisberg in Belgium, first author of this study, and second author of the paper presented at the GI Cancers Symposium.

"Ramucirumab plus paclitaxel should be considered as a new standard in second-line treatment for advanced gastric cancer," he said.

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Regional Differences at Baseline and in Outcome

He acknowledged that the goal of RAINBOW was not to formally compare Western versus Asian patients, but the subanalysis did show some small differences in patient outcomes between the entire RAINBOW cohort and patients in Region 1, comprising Europe (including Israel), Australia, and the United States.

Overall survival for all RAINBOW patients was a median of 9.6 months for the drug combination versus 7.4 months for paclitaxel alone, compared with 8.6 months versus 5.9 months, respectively, for the Western countries of Region 1.

And the objective response rates for all RAINBOW patients was 27.9 percent for the drug combination versus 16.1 percent for paclitaxel alone, compared with 26.8 percent versus 13.0 percent, respectively, for Region 1.

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ERIC VAN CUTSEM, MD, PhD: "We expect that the authorities will also approve the combination of paclitaxel plus ramucirumab, based on the RAINBOW study—That's an important breakthrough in second-line treatment."

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that maintenance therapy with bevacizumab alone is non-inferior to a fluoroupyrimidine-bevacizumab regimen, and that no active maintenance is inferior to either active regimen (***Abstract O-0027***).

Maintenance therapy for patients with metastatic colorectal cancer using fluoroupyrimidine plus bevacizumab after induction is a widely accepted standard, noted Dirk Arnold, MD, Medical Director of the Hubertus Wald Tumor Center, University Cancer Center Hamburg, Germany, who reported the trial that randomly assigned 473 patients to maintenance with fluoroupyrimidine-bevacizumab versus bevacizumab alone versus no maintenance, after a six-month induction with a fluoroupyrimidine-oxaliplatin-bevacizumab regimen.

"Progression-free survival after induction is better with active treatment—either fluoroupyrimidine-bevacizumab or bevacizumab—but preliminary overall survival data show no significant difference between the two active treatments and no treatment," he said.

Time to first progression from the start of induction was 11.7 months for the combination regimen, 10.2 months for bevacizumab alone, and 9.0 months for no maintenance. Overall survival was a median of 23.8 months for fluoroupyrimidine-bevacizumab, 26.2 months for bevacizumab alone, and 23.1 months for no maintenance.

But immediate re-induction with a fluoroupyrimidine-oxaliplatin-bevacizumab regimen after first progression did not work and cannot be recommended, he said. "De-escalation maintenance is confirmed as a standard for most patients, but the lack of a clear overall survival benefit allows individual approaches."

In the future a "moderately active" regimen—either de-escalation or a biologically defined "switch maintenance" strategies–should be evaluated, and that in fact is the next AIO Phase III project, he said.

> How can it be that the 80405 and FIRE-3 trials had different overall survival results with the same treatments?

DIRK ARNOLD, MD, said that in the future a "moderately active" regimen—either de-escalation or a biologically defined "switch maintenance" strategies—should be evaluated, and that in fact is now being planned for the next AIO Phase III project.

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Van Cutsem said these differences were possibly due to differences in baseline characteristics. For example, more patients in the overall trial received doublet rather than triplet chemotherapy as first-line therapy—75 vs. 24.5 percent, while in Region 1 the mix was 62.1 vs. 37.2 percent.

Patients globally had shorter times to disease progression, 66.8 percent during first-line therapy versus 58.0 percent for Region 1; and more patients had gastric versus gastro-esophageal junction cancer globally—79.4 and 20.6 percent, while in Region 1 the mix was 69.3 and 30.7 percent, respectively.

Gastric cancer of all types is more common in Asian countries but the outcomes are typically better—thought to be due to more extensive screening.

In April the U.S. Food and Drug Administration approved ramucirumab as a single agent for second-line treatment of metastatic gastric cancer and gastro-esophageal adenocarcinoma, following the outcome of the placebo-controlled Phase III REGARD trial of 355 patients (***Fuchs et al: Lancet 2014;383:31-39***). "We expect that the authorities will also approve the combination of paclitaxel plus ramucirumab, based on the RAINBOW study," Van Cutsem said in an interview. "That's an important breakthrough in second-line treatment."

Era of New Targeted Therapies in GEJ Cancer

Another speaker, Manish A. Shah, MD, Director of the Department of Gastrointestinal Cancer and Co-director of the Research Center for Advanced Digestive Care at Weill Cornell Medical College, called the RAINBOW study the most recent success story in GI cancer.

"We're in an era of new therapies for gastric cancer and gastroesophageal junction adenocarcinoma," he said in an interview. "Many new targets are available and validated, we're seeing positive results targeting antiangiogenesis and HER2, and new targets are being evaluated such as MET inhibition."

He said that HER2 is now a validated target for first-line gastric cancer, and that targeting the angiogenesis pathway in gastric and gastroesophageal adenocarcinoma is also validated.

In his own presentation he expanded on data he published recently, including that of tumor heterogeneity, discussed in a review paper he wrote in *Nature Reviews Clinical Oncology* (***2014;11:10-11***).

"Historically all the different gastric diseases have been lumped together—proximal stomach cancer, distal stomach cancer, diffuse stomach cancer," he said. "We put them all together, but their biology might be different and so they may not all respond to the same targets the same way—which may explain why some of the previous studies didn't work," he said. "But we still need to learn who would benefit most from antiangiogenic therapy."

On July 23, researchers from the Cancer Genome Atlas published results in *Nature* identifying four subtypes of gastric tumors based on shared mutations and other molecular abnormalities (*see page 29*).

At the World Congress, Shah said that researchers are beginning to understand the difference in outcomes between Western and Asian populations. Because Asians, particularly in Korea and Japan, have regular screening, they typically present with earlier disease—"so most of the time when patients have metastatic disease, their stomach is already removed. Whereas in the West, patients present with metastatic disease with their primary tumor in place and so the disease burden is different and they need to get second-line and third-line therapy."

Differences in molecular subtypes are also being found between geographic regions. The most exciting studies now are in inhibition of MET, the STAT-3 oncogene, and the immune checkpoint inhibitors PD1/PDL1 pathways.

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History of the World Congress

The World Congress on Gastrointestinal Cancer began in 1999 as Perspectives in Colorectal Cancer, founded by Mario Dicato, MD, and Eric Van Cutsem, MD, PhD, along with Jacques Wils, MD, of Laurentius Hospital in The Netherlands, who retired as chair following the 2003 Congress. Dicato and Van Cutsem remain as Chairs, and Vice-Chair is Josep Tabernero, MD, PhD, of Vall d'Hebron University Hospital and the Institute of Oncology in Barcelona.

An agreement was reached in 2004 between the organizers and the European Society for Medical Oncology to collaborate on the development of the Congress with the goal of increasing the educational value, and expanding the reach to a wider audience.

The meeting originally focused only on colorectal cancer, but after partnering with ESMO the program was expanded to include sessions on gastric cancer, pancreatic cancer, esophageal, pancreas and bile duct, neuro-nephrotic and upper GI cancers, liver, and gastrointestinal stromal tumors.

"Knowing the right people, having good networking, and being on top of the science has helped the Congress evolve," Van Cutsem said. This year it attracted 2,500 attendees.