Ramucirumab Slows Progression of Advanced Colorectal Cancer

BY ED SUSMAN

SAN FRANCISCO—The addition of the targeted agent ramucirumab modestly extends the progression-free survival of patients with advanced colorectal cancer when the new drug is administered in a second-line setting, researchers reported here at the Gastrointestinal Cancers Symposium (***Abstract 512***).

The meeting is co-sponsored by the American Gastroenterological Association Institute, American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology.

While the Phase III international trial, called RAISE, which included 1,072 patients, achieved its statistical goal, the actual median survival improvement was just 1.6 months—about six weeks—when ramucirumab was added to FOLFIRI (fluorouracil, leucovorin and irinotecan) when compared with the FOLFIRI treatment alone, Josep Tabernero, MD, PhD, Director of the Vall d'Hebron Institute of Oncology in Barcelona, Spain, said in an ASCO telephone briefing for reporters earlier this week.

"The RAISE study met its primary endpoint. A statistically significant overall survival benefit was observed for ramucirumab plus FOLFIRI versus FOLFIRI in metastatic colorectal cancer after progression on first-line therapy. Ramucirumab is an effective new treatment option for second-line treatment, including patients with poor prognosis."

In the study, which received funding from Eli Lilly, patients assigned to ramucirumab achieved a median overall survival of 13.3 months compared with 11.7 months for patients assigned to the FOLFIRI combination alone. That difference represented a 16 percent reduction in the risk of death and was statistically significant (P=0.0219), he said.

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> "Overall, treatment with ramucirumab plus FOLFIRI was well tolerated, and the adverse events were manageable."

Progression-free survival was also improved with ramucirumab, increasing from a median of 4.5 months with FOLFIRI alone to a median of 5.7 months with the addition of ramucirumab—a difference of 1.2 months.

Tabernero reported that objective responses to treatment were observed in 13.4 percent of the patients assigned to ramucirumab compared with 12.5 percent of patients receiving just the FOLFIRI regimen, but that was not statistically significantly different.

Patients Seen in Everyday Practice

"Advanced colorectal cancer is an incurable disease, and it is particularly difficult to treat after initial therapy stops working," he said. "Our study also

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MODIFIED GEMCITABINE/ NAB-PACLITAXEL

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regimen also results in substantial cost savings—an estimated $5,500 per patient per month of treatment. "That figure does not include the cost for growth factors used in treating neutropenia," Krishna said. "Neulasta [pegfilgrastim] is pretty expensive too. In the clinical trial the rate of growth factor use was 26 percent, but in our experience with the every-other-week regimen, just eight percent of patients required growth factors.

"The combination of gemcitabine and nab-paclitaxel in pancreatic cancer is one of the most recent advances in pancreatic cancer treatment and has been shown to improve survival when compared with gemcitabine alone. But this improved survival comes with increased toxic side effects that can affect quality of life."

Study Specifics

She and her colleagues identified 69 patients with pancreatic cancer who received the modified regimen of gemcitabine and nab-paclitaxel. Forty nine had previously untreated metastatic pancreatic cancer and the remaining 20 had either progressed on other chemotherapy treatments or had locally advanced or borderline resectable disease. The patients' median age was 65.

Overall, less than two percent of patients had severe neurological toxicities compared with 17 percent in the previous Phase III study using the three-week-on, one-week-off schedule; 10 percent of patients had severe low white blood cell counts compared with 38 percent of patients in the Phase III study.

Gives Immune System Time to Recover

The study's senior author, Tanios Bekaii-Saab, MD, Section Chief of Gastrointestinal Oncology at the James and Associate Professor of Medicine, explained that shifting to a regimen of every other week gives the immune system time to recover between chemotherapy sessions and results in less overall toxicity. It is also more convenient for patients since it means fewer visits to the infusion center to receive chemotherapy.

"Pancreatic cancer is an especially difficult diagnosis, so weighing the survival benefit of available treatments against how treatment side effects will impact a patient's remaining life is a critically important part of the treatment planning process," Krishna said.

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included patients with fast-growing tumors, so the findings are relevant to patients that we typically encounter in practice. It is very encouraging that we now have another safe option that adds benefit to standard chemotherapy in this second-line setting."

Consistent tumor effects were found in all treatment groups, he said, including patients with KRAS gene mutations and patients with wild-type KRAS, and in patients who had rapid disease progression with first-line therapy and those who did not progress on first-time treatment for at least six months.

Adverse Events

Treatment with ramucirumab resulted in more Grade 3 and 4 adverse events than with FOLFIRI alone. The most common toxicities experienced by patients in the ramucirumab arm of the trial were neutropenia, fatigue, diarrhea, and hypertension; and those Grade 3 or 4 adverse events occurred in at least five percent of patients.

"Although the rate of neutropenia was greater in the ramucirumab arm, the rate of febrile neutropenia—a clinically significant toxicity—were similar between the two arms," he said. About 3.6 percent of patients receiving ramucirumab experienced febrile neutropenia compared with 2.7 percent of the patients taking just FOLFIRI.

> "Ramucirumab is an effective new treatment option for second-line treatment, including patients with poor prognosis."

"Overall, treatment with ramucirumab plus FOLFIRI was well tolerated, and the adverse events were manageable," he said.

> "The RAISE trial clearly demonstrates that sustained inhibition of angiogenesis from first-line to second-line metastatic colorectal cancer therapy improves survival in a clinically representative population."

'Want to Offer All We Can to Our Patients'

Commenting on the results in the teleconference, the moderator, Smitha Krishnamurthi, MD, Associate Professor of Hematology and Oncology at Case Western Reserve University School of Medicine, in response to a question, said: "We would have liked to have seen that these results were stronger, but what we have found is that as our patients get exposed to all our active drugs, it does translate into them living longer.

"It's true that 1.6 months is not a long time, but we want to offer everything that we can to our patients especially because these agents tend to be well tolerated and can be combined with chemotherapy."

Tabernero explained that the trial evaluated the concept of whether using the new agent to attack the vascular endothelial growth factor receptor (VEGF) signaling pathway could impact the progression of colorectal cancer. Ramucirumab is a recombinant human IgG1 monoclonal antibody that binds to the extracellular domain of VEGF-2, preventing ligand binding and receptor activation. The VEGF signaling pathway and angiogenesis are keys to promoting colorectal cancer growth, he said, adding that ramucirumab is currently FDA approved only for the treatment of stomach cancer, but it is being studied in a range of other cancers.

Patients were eligible for the study if they had been diagnosed with advanced colorectal cancer and had disease progression after treatment with bevacizumab, oxaliplatin, and a fluoropyrimidine. The 1,072 patients were randomly assigned to receive ramucirumab at 8 mg/kg with FOLFIRI or to placebo plus FOLFIRI.

The 536 patients in each group received treatment every two weeks until disease progression or the development of unacceptable toxicity.

The FOLFIRI regimen that was given to all patients in the study included irinotecan at 100 mg/m^2, folinic acid (leucovorin) at 400 mg/m^2, fluorouracil in a 400 mg/m^2 bolus, followed by 2,400 mg/m^2 administered intravenously over 46 to 48 hours continuously.

Should Not Be Extrapolated to Other Regimens and Schedules

Tabernero cautioned that while this study shows that ramucirumab adds benefit to FOLFIRI chemotherapy, the findings should not be extrapolated to other chemotherapy regimens and schedules without formal investigation in clinical trials. Further research is also needed to explore the potential benefits of ramucirumab after first-line treatment with the EGFR inhibitor cetuximab.

"The RAISE trial clearly demonstrates that sustained inhibition of angiogenesis from first-line to second-line metastatic colorectal cancer therapy improves survival in a clinically representative population," he said.

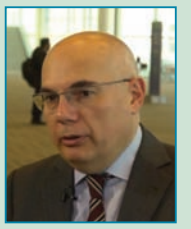
Krishnamurthi agreed: "It's good news that ramucirumab, an angiogenesis inhibitor with proven activity against gastric cancer and lung cancer, has now been found to be active against metastatic colorectal cancer. Now, when a patient's colorectal cancer has progressed, second-line FOLFIRI chemotherapy can be combined with a continuation of bevacizumab or with a change to ziv-aflibercept or, possibly, ramucirumab.

"All of these approaches have had a similar effect upon survival. Further studies are needed to determine the activity of ramucirumab against colorectal cancer in first-line or other settings," she said.

Bevacizumab and ziv-aflibercept are FDA approved for use in combination with chemotherapy, whereas regorafenib is approved as a standalone therapy for patients with previously treated metastatic colorectal cancer.

iPad Extra!

VIDEO: Watch a video of Dr. Tabernero elaborate on his findings on the iPad edition of this issue with *OT* reporter Sarah Maxwell in an interview conducted at the symposium.



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