Angiogenesis Inhibitors for Gastrointestinal Cancers: Update From the 2015 Gastrointestinal Cancers Symposium

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Overview

This CME activity features data from selected presentations on antiangiogenic agents from the 2015 Gastrointestinal Cancers Symposium, chosen for their impact on current clinical practice or because they lay the groundwork for further investigations. Topics include the new approaches to chemotherapy and targeted therapy with antiangiogenic agents for the treatment of gastrointestinal cancers, including colorectal cancer and hepatocellular carcinoma.

Target Audience

This activity is directed toward medical oncologists who treat patients with gastrointestinal malignancies. Fellows, nurses, physician assistants, nurse practitioners, and other healthcare providers are also invited to participate.

Learning Objectives

After participating in this CME activity, learners should be better prepared to:

- Identify key outcomes of selected clinical trials from the 2015 Gastrointestinal Cancers Symposium
- List major adverse events experienced by patients in selected clinical trials from the 2015 Gastrointestinal Cancers Symposium
- Describe the study design of selected clinical trials from the 2015 Gastrointestinal Cancers Symposium

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Angiogenesis Inhibitors for Gastrointestinal Cancers: Update From the 2015 Gastrointestinal Cancers Symposium

The 2015 Gastrointestinal Cancers Symposium, "Bridging Cancer Biology to Clinical Gastrointestinal Oncology," was held January 15-17, 2015, in San Francisco, California. This conference, attended by US and international gastrointestinal (GI) practitioners, focuses on gastroenterology, hepatology, and oncology, and was co-sponsored by the American Gastroenterological Association, the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology. The conference showcased the latest science and research in the screening, diagnosis, treatment, and ongoing management of GI cancers, including those of the colon/rectum, anus, stomach, pancreas, esophagus, liver, and small intestine.

This continuing medical education (CME) activity will focus on selected presentations that address new approaches to chemotherapy and targeted therapy with antiangiogenic agents. The antiangiogenic landscape is becoming increasingly complex, and education is paramount for oncology clinicians to know how to optimally utilize these agents and to know which clinical trial options may be available for their patients.

Second-Line FOLFIRI Regimen for Metastatic Colorectal Cancer: What Effect Can Adding Ramucirumab Have?

With colorectal carcinoma (CRC) being the fourth most common cause of cancer death worldwide,[1] new agents are needed to address treatment-resistant or progressive disease. Agents are being studied that address numerous therapeutic targets to ultimately prolong survival in patients with CRC, including new agents targeted to the angiogenic pathway.

Tabernero and colleagues[2] presented results of the RAISE trial (**Table**), which focused on the efficacy and safety of adding ramucirumab to standard second-line treatment for metastatic CRC (mCRC).[2] The drug is currently approved by the FDA as monotherapy and in combination with paclitaxel for the treatment of gastric cancer, and in combination with docetaxel for non-small cell lung cancer.[3]

Ramucirumab, a recombinant human IgG1 monoclonal antibody against the vascular endothelial growth factor receptor (VEGFR)-2, prevents VEGFR-2–mediated signaling and angiogenesis,[3] thus interfering with CRC tumor growth. RAISE was a randomized, double-blind, multicenter phase 3 trial of FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil) plus ramucirumab or placebo in patients with mCRC progression during or following first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. In the RAISE trial, researchers randomized patients to receive ramucirumab 8 mg/kg and FOLFIRI or placebo and FOLFIRI every 2 weeks per cycle. Treatment continued until disease progression or unacceptable toxicity. Patients were required to have a known *KRAS* mutation status, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1, at least 2 doses of bevacizumab in first-line therapy, and disease progression 6 months or earlier following the last dose of first-line therapy. The study's primary endpoint was overall survival (OS). Secondary endpoints of the study were progression-free survival (PFS), objective response rate (ORR), patient-reported outcomes, safety, pharmacokinetics, and immunogenicity.[2]

A total of 1072 patients were randomized (intent-to-treat population), and 1057 patients received treatment in the trial: 529 in the ramucirumab arm and 528 in the placebo arm. Patients were predominantly male (53.9%, ramucirumab group and 60.8%, placebo group), Caucasian (75.6%, ramucirumab group and 76.5%, placebo group); the median age was 62 years. In the ramucirumab group, 50.2% (269/536) were *KRAS* mutant and 49.8% (267/536) were *KRAS* wild-type. In the placebo group, 48.7% (261/536) were *KRAS* mutant and 51.3% (275/536) were *KRAS* wild-type. Considerably more patients had disease progression 6 months or later following first-line therapy in both groups (when compared with <6 months): 76.7% (411/536) versus 23.3% (125/536) in the ramucirumab group and 75.9% (407/536) versus 24.1% (129/536) in the placebo group. Patients were also stratified according to geographic region: North America (26.7% for both groups), Europe (43.8% for both groups), and other worldwide locations (29.5% for both groups).[2]

Median OS was 13.3 months in the ramucirumab group compared with 11.7 months in the placebo group (overall curve hazard ratio [HR] = 0.84; 95% CI, 0.73–0.98; P =.0219). These results demonstrated a 16% reduction in risk of death with ramucirumab use. Median PFS was 5.7 months and 4.5 months, respectively (HR = 0.79; 95% CI, 0.70–0.90; P =.0005). ORR was comparable between the groups (13.4% for ramucirumab group vs 12.5% for placebo; P = .6336).[2]

Neutropenia (38.4% vs 23.3% for placebo group), fatigue (11.5% vs 7.8% for placebo group), diarrhea (10.8% vs 9.7% for placebo group), and hypertension (10.8% vs 2.8% for placebo group) were the most common grade 3 or higher treatment-emergent adverse events (AEs) in the ramucirumab group. Of note, the rate of febrile neutropenia was comparable between the 2 arms, with the

ramucirumab group at 3.6% and the placebo group at 2.7%. A bleeding or hemorrhage event of any grade was reported in 43.9% of patients in the ramucirumab group and 22.7% in the placebo group, and this AE was grade 3 or higher in 2.5% of the ramucirumab group and 1.7% of the placebo group.[2]

The results of the RAISE trial look promising for ramucirumab in the second-line setting of mCRC. However, further analysis is needed before it is known where the drug, if FDA approved in this setting, will fit into the treatment armamentarium.

Famitinib for Relapsed Metastatic CRC: A Chinese Study

Researchers in China conducted a study from July 2012 to March 2013 to assess famitinib as a treatment option for patients with advanced mCRC who had disease progression following at least 2 lines of chemotherapy (**Table**).[4]

CRC is the fifth deadliest cancer in China and treatment options are limited for patients with advanced mCRC.[5] This study assessed famitnib's efficacy and safety in treating patients with mCRC who progressed following at least 2 lines of chemotherapy.[4]

Famitinib is a small-molecule multikinase inhibitor (VEGFR-2, c–Kit, and PDGFR) that works primarily by interfering with tumor angiogenesis. In this phase 2 trial, Xu and colleagues[4] randomized patients age 18 to 70 years with advanced CRC who progressed after at least 2 prior lines of chemotherapy 2:1 to famitinib 25 mg monotherapy or placebo daily. Patients were required to have recurrent and/or mCRC, experienced progression after at least 2 prior lines of chemotherapy (which must include 5-fluorouracil, irinotecan, and oxaliplatin), and at least 1 measurable lesion according to RECIST

TABLE. Antiangiogenic Agents: Selected Trials from the 2015 Gastrointestinal Cancers Symposium

Author/Abstract No./Trial Name	Trial Description	Primary Outcome Measures/Results	AEs of Note	Therapy Line
Tabernero/#512/RAISE	Randomized, double-blind, phase 3 trial: FOLFIRI + ramucirumab vs FOLFIRI + placebo in patients with mCRC progression following first-line: bevacizumab, oxaliplatin, and a fluoropyrimidine	OS: 13.3 months in the ramucirumab group; 11.7 months in the placebo group (overall curve hazard ratio [HR] = 0.84; 95% CI, .73-.98; *P* = .0219).	Leading grade ≥3 AEs: Neutropenia (38.4% ramucirumab; 23.3% placebo), fatigue (11.5% ramucirumab; 7.8% placebo), diarrhea (10.8% ramucirumab; 9.7% placebo), and hypertension (10.8% ramucirumab; 2.8% placebo)	Second line
Xu/#513	Randomized, double-blind, parallel-group, phase 2 trial in patients with advanced CRC who progressed after at least 2 prior lines of chemotherapy: 2:1 to famitinib monotherapy or placebo	PFS/median PFS: 2.8 months (95% CI, 2.00-2.93) famitinib; 1.5 months (95% CI, 1.47-1.67) placebo (HR = 0.596; 95% CI, 0.414-0.858; *P* = .0053).	Leading grade ≥3 AEs: Hypertension (11.1% famitinib; 1.8% placebo), thrombocytopenia (10.1% famitinib; 1.8% placebo), and hand-foot syndrome (10.1% famitinib; 0% placebo)	Third line
Hochster/#TPS 793/E7208	Randomized phase 2 trial comparing irinotecan plus cetuximab (IC) versus IC plus ramucirumab (ICR) as second-line therapy for patients with *KRAS* wild-type advanced CRC	PFS: Study is ongoing, although less-progressive disease in the ICR group (1/5 in the ICR group vs 8/9 in the IC group)	More-frequent reports of mucositis, diarrhea, neutropenia, and perforation in the ICR group	Second line
Zhu/#232/REACH	Randomized phase 3 trial comparing ramucirumab versus placebo in patients with advanced HCC following first-line sorafenib	OS: 9.2 months (95% CI, 8.1-10.6) ramucirumab; 7.6 months (95% CI, 6.0-9.3) placebo (HR = 0.866; 95% CI, 0.717-1.046; *P* =.1391)	Leading grade ≥3 AEs: AFP ≥400 ng/mL for ramucirumab subgroup (21.8% [26/119] liver injury/failure and 12.6% [15/119] hypertension AFP <400 ng/mL for ramucirumab subgroup 20.8% [32/154] liver injury/failure and 12.3% [19/154] hypertension	Second line

AE indicates adverse event; AFP, α-fetoprotein; CI, confidence interval; CRC, colorectal cancer; FOLFIRI, irinotecan, folinic acid, and 5-fluorouracil; HR, hazard ratio; IC, irinotecan plus cetuximab; ICR, irinotecan, cetuximab, and ramucirumab; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival.

1.1. Exclusion criteria included prior therapy with a tyrosine kinase inhibitor that targets VEGFR, insufficient hepatic, renal, cardiac, or hematologic functions, uncontrolled hypertension, proteinuria, or central nervous system metastases. The primary endpoint of the study was PFS. Secondary endpoints included OS, ORR, disease control rate (DCR), and quality of life.[4]

A total of 154 patients (median age, 55.6 years in the famitinib group, 54.3 years in the placebo group; 56.6% male in the famitinib group, 60.0% in the placebo group) were randomized: 99 to the famitinib group and 55 to the placebo group. Study treatment was greater than third-line therapy for 59.6% of patients in the famitinib group and 63.6% in the placebo group. Most patients had undergone surgery for the primary tumor. A history of antibody therapy was comparable across the 2 treatment groups (over 40%).[4]

Famitinib improved the PFS of these patients by 1.3 months. Median PFS was 2.8 months (95% CI, 2.00-2.93) in the famitinib group and 1.5 months (95% CI, 1.47-1.67) in the placebo group (HR = 0.596; 95% CI, 0.414-0.858; *P* =.0053). PFS results were statistically better for the famitinib group compared with the placebo group when examined for male gender (but not female), younger patient age (≤60 years, but not >60 years), and less severe disease (≤2 metastatic sites, but not >2). OS was similar between the treatment groups. Patients in the famitinib group had a DCR of 59.8% compared with 31.4% in the placebo group (*P* =.0016), with 2 patients achieving partial responses and 53 with stable disease. None of the patients in the placebo group achieved an objective response and 16 had stable disease.[4]

Drug-related AEs of grade 3 or higher were reported by 46.5% of patients (46/99) in the famitinib group versus 20.0% (11/55) in the placebo group. Thirteen patients (13.1%) in the famitinib group discontinued treatment due to drug-related AEs; three patients (5.5%) in the placebo group discontinued for this reason. Drug-related serious AEs were reported by 5.1% of patients (5/99) in the famitinib group and 3.6% (2/55) in the placebo group. The most common AEs of any grade in the famitinib group were proteinuria (42.4%; 16.4% in the placebo group), neutropenia (41.4%; 1.8% in the placebo group), hypertension (38.4%; 7.3% in the placebo group), and leukopenia (36.4%; 1.8% in the placebo group). The most commonly reported AEs grade 3 or higher in the famitinib group were hypertension (11.1%; 1.8% in the placebo group), thrombocytopenia (10.1%; 1.8% in the placebo group), and hand-foot syndrome (10.1%; 0% in the placebo group).[4]

The results of this trial are encouraging, as there are limited treatment options for mCRC beyond second line in many countries (regorafenib and aflibercept are approved for this purpose in the US but not available in China at the time of the trial). However, the benefit-to-risk ratio for patients would need to be considered if this agent becomes available.

Ramucirumab in Second-Line Treatment of *KRAS* Wild-Type CRC

Hochster and ECOG colleagues[6] reported results of the E7208 randomized phase 2 trial comparing irinotecan plus cetuximab (IC) versus IC plus ramucirumab (ICR) as second-line therapy for patients with *KRAS* wild-type, advanced CRC (**Table**). The primary endpoint of the study was PFS; secondary endpoints were response rate and grade 3-4 AE rate. Patients were required to have received at least 1 prior regimen of bevacizumab (more than 28 days prior to start of study) with fluoropyrimidine and oxaliplatin, and to have evidence of disease progression and measurable disease. The study randomized patients to receive cetuximab 500 mg/m^2 and irinotecan 180 mg/m^2 with or without ramucirumab 8 mg/kg every 2 weeks. A total of 35 patients enrolled in the study between October 2010 and June 2012 with 33 in the interim analysis (16 in the IC group and 17 in the ICR group). Results on this portion of the trial are as follows: grade 3-5 toxicity (17% in the IC group, 75% in the ICR group); 2 grade 5 events in the ICR group (perforation); more-frequent reports of mucositis, diarrhea, neutropenia, and perforation in the ICR group, and less-progressive disease in the ICR group (1/5 in the ICR group vs 8/9 in the IC group). The study reopened in July 2014 with a planned accrual of an additional 100 patients for 85% power to detect median PFS from 4.5 to 7.65 months. ICR drug dosages were decreased to reflect actual doses received: irinotecan was decreased to 150 mg/m^2, cetuximab was decreased to 400 mg/m^2, and ramucirumab was decreased to 6 mg/kg every 2 weeks. IC arm doses remain as the original protocol. At the time of the poster presentation, there were 7 new accruals and no serious AEs.[6]

Advanced Hepatocellular Carcinoma: Is Ramucirumab an Emerging Option?

A study evaluating second-line ramucirumab in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline α-fetoprotein (AFP) showed a significant improvement in OS compared with placebo (**Table**).[7]

HCC is the second most common cause of cancer death.[1] Treatments providing survival benefit in the second-line setting are needed, especially for patients with elevated AFP, which is associated with a poor prognosis.[7]

Zhu and colleagues[7] conducted a phase 3 trial (REACH) to evaluate the safety and efficacy of ramucirumab in patients with advanced HCC who have received first-line sorafenib. Patients were required to have Barcelona Clinic Liver Cancer stage B/C, Child-Pugh score A, and an ECOG PS of 0 or 1. Researchers randomized patients 1:1 to one of 2 groups: ramucirumab 8 mg/kg or placebo every 2 weeks per cycle, both with best supportive care. Treatment continued until disease progression or unacceptable toxicity. The primary endpoint was OS, and secondary endpoints included PFS, time to progression, ORR, safety, and patient-reported outcomes.[7]

A total of 544 patients enrolled in the trial (272 in each arm). OS in the ramucirumab group was 9.2 months (95% CI, 8.1-10.6) and 7.6 months (95% CI, 6.0-9.3) in the placebo group (HR = 0.866; 95% CI, 0.717-1.046; *P* =.1391). A post-hoc trial analysis revealed that

treatment with ramucirumab improved OS in patients with higher baseline AFP values (≥400 ng/mL) compared with placebo: median of 7.8 months versus 4.2 months (HR = 0.674; 95% CI, 0.508–0.895; *P* =.0059). The median OS for those patients with AFPs less than 400 ng/mL was longer than the higher AFP group at 10.1 months in the ramucirumab group and 11.8 months in the placebo group (HR = 1.093; 95% CI, 0.836-1.428; *P* =.5059). Safety data were reported for the 2 subgroups (AFP ≥400 ng/mL and AFP <400 ng/mL). Liver injury or failure and hypertension were the leading grade ≥3 AEs for both ramucirumab subgroups (21.8% [26/119] liver injury/failure and 12.6% [15/119] hypertension for AFP ≥400 and 20.8% [32/154] liver injury/failure and 12.3% [19/154] hypertension for AFP <400). Liver injury or failure and bleeding/hemorrhage were the most common AEs for both placebo subgroups (30.5% [39/128] liver injury/failure and 9.4% [12/128] bleeding/hemorrhage for AFP ≥400, and 17.7% [26/147] liver injury/failure and 6.1% [9/147] bleeding/hemorrhage for AFP <400).[7]

Conclusion

Multiple new antiangiogenic agents are being tested in multiple tumor types. In a recent interview following the 2015 Gastrointestinal Cancers Symposium, Wafik S. El-Deiry, MD, PhD, of the Fox Chase Cancer Center, commented that "progress is being made with the development of new antiangiogenic agents. The landscape of targets would appear to have more opportunities to exploit the targets, as well as for testing novel sequences and combinations."[8]

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