

2008 GASTROINTESTINAL CANCERS SYMPOSIUM

Highlights from the 2008 Gastrointestinal Cancers Symposium,
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The 2008 Gastrointestinal Cancers Symposium was cosponsored by the American Gastroenterological Association Institute, the American Society of Clinical Oncology, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical Oncology. The meeting brought together experts in the fields of oncology, gastroenterology, and hepatic disease to discuss the latest data and treatment options for a variety of gastrointestinal-related cancers. Here, *G&H* reviews some of the most useful data announced at this meeting.

31 Sunitinib in a Worldwide Treatment-use Trial of Patients With GIST: Safety and Efficacy

Morgan and colleagues reported efficacy and safety results of an ongoing open-label study of sunitinib (Sutent, Pfizer) for the treatment of gastrointestinal stromal tumors (GIST) in patients who are resistant or intolerant to imatinib (Gleevec, Novartis). This trial is aimed at allowing patients around the world access to sunitinib even if they do not qualify for other trials of sunitinib or if sunitinib is not registered for sale in their country of residence. As of April 2007, 1,091 patients received at least 1 dose of sunitinib, planned to be given at 50 mg/day for a cycle of 4 weeks on followed by 2 weeks off therapy. The agent's safety, patients' antitumor response, time to progression (TTP), and overall survival (OS) were assessed. The authors reported that patients started a median of 4 cycles (range, 1–23 cycles), with a median follow-up of 261 days (range, 1–872 days). Furthermore, 39% and 57% of patients required dose reductions and interruptions, respectively. Of these dose reductions and interruptions, 79% were due to adverse events; the most common all-causality adverse events were fatigue (48%), diarrhea (45%), and nausea (35%). The adverse events higher than grade 3 observed were fatigue (10%), abdominal pain (10%), and hand-foot syndrome (9.2%); the hematologic adverse events higher than grade 3 included anemia (8%), neutropenia (8%), and

thrombocytopenia (5%). As of April 2007, 697 patients (64%) were still alive, with a median TTP of 37 weeks (95% confidence interval [CI], 35–44). The median estimated OS was 73 weeks (95% CI, 66–92). The authors concluded that sunitinib was generally tolerated well in patients with imatinib-resistant or -intolerant advanced GIST who were otherwise ineligible to receive sunitinib in other clinical trials. Due to a safety profile consistent with that observed in other trials of sunitinib in patients with GIST, the drug was considered a safe and effective treatment in this population.

128 Final Results From a Phase II, Randomized, Double-blind Study of Sorafenib Plus Doxorubicin Versus Placebo Plus Doxorubicin in Patients (pts) With Advanced Hepatocellular Carcinoma

Abou-Alfa and associates note that therapy with sorafenib (Nexavar, Bayer/Onyx) has achieved prolonged OS and TTP in a phase III study of patients with advanced hepatocellular carcinoma (HCC). They conducted a phase II study of sorafenib in combination with doxorubicin versus doxorubicin plus placebo in advanced HCC patients who were naive to systemic therapy. At the start of therapy, all patients were Child-Pugh Class A, with Eastern Cooperative Oncology Group (ECOG) performance status levels of 0–2. Patients (n=96) received intravenous (IV) doxorubicin every 21 days and were randomized to twice daily oral dosing of either sorafenib or placebo for a maximum of 6 cycles (18 weeks). The primary measured endpoint was TTP with secondary measures of OS and progression-free survival. Interim analysis before crossover from placebo to sorafenib showed encouraging results favoring the sorafenib plus doxorubicin arm. Final results showed an average TTP of 8.6 months for the sorafenib-containing arm versus 4.8 months for doxorubicin alone (Table 1). The only cardiovascular event was 1 case of grade 2/3 left ventricular dysfunction in the sorafenib plus doxorubicin arm. The authors concluded that further research is

Table 1. Endpoint Results in the Trial of Sorafenib Plus Doxorubicin Versus Doxorubicin Alone

	Median Time to Tumor Progression	Median Overall Survival	Median Progression-Free Survival	Response (Complete + Partial), %	Grade 3/4 Fatigue, %	Grade 3/4 Neutropenia, %
Sorafenib + Doxorubicin	8.6 mo	13.7 mo	6.9 mo	4	15	53
Placebo + Doxorubicin	4.8 mo	6.5 mo	2.8 mo	2	15	46

necessary to define a synergistic relationship between sorafenib and doxorubicin.

129 Clinical Benefit of Sorafenib in Hepatitis C Patients With Hepatocellular Carcinoma: Subgroup Analysis of the SHARP Trial

The phase III SHARP study was the first to show a benefit with sorafenib therapy in terms of HCC OS. As hepatitis C virus (HCV) is a primary risk factor for HCC, accounting for 50–70% of cases in Europe and North America, Bolondi and colleagues conducted a subgroup analysis to determine the efficacy and safety of sorafenib in SHARP trial participants with both HCV and HCC. The overall study population was randomized to either placebo or sorafenib. Subanalysis included only those patients with serologic evidence of HCV infection. Primary endpoints were OS and time to symptomatic progression. Secondary endpoints were TTP, disease control rate (complete or partial response or stable disease confirmed 28 days after initial evaluation), and safety. Of the original cohort of 602 patients, 178 were HCV-positive (93 in the sorafenib group and 85 in the placebo group). Median OS was 14 months in the sorafenib group and 7.9 months in the placebo group, whereas time to symptomatic progression was similar in both arms. Median TTP was 7.59 months in the sorafenib group versus 2.76 months for placebo. Disease control rate was higher in the sorafenib than the placebo group (44% and 31%, respectively). Grade 3/4 adverse events included hand/foot skin reactions (12.9% vs 0%), diarrhea (10.8% vs 2.4%), hyperbilirubinemia (9.7% vs 2.4%), ascites (6.5% vs 9.4%), and fatigue (6.5% vs 8.2%), in the sorafenib and placebo groups, respectively. Adverse events led to dose reduction in 32% of sorafenib and 8% of placebo patients. The authors concluded that results in HCV-positive patients are consistent with those in the overall SHARP population, confirming the benefit of sorafenib in this subset of patients.

273 An Updated Analysis of Safety and Efficacy of Oxaliplatin/Bevacizumab ± Panitumumab for First-line Treatment of Metastatic Colorectal Cancer From a Randomized, Controlled Trial (PACCE)

Hecht and coauthors presented the results of a trial that evaluated the benefit of adding panitumumab (Vectibix, Amgen) to a first-line FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin [Eloxatin, Sanofi-Aventis]) regimen containing bevacizumab (Avastin, Genentech) in patients with metastatic colorectal cancer. In the previously reported PACCE trial, a total of 823 patients received bevacizumab plus FOLFOX alone (n=410) or with panitumumab (another arm administered bevacizumab plus an irinotecan-based regimen with or without panitumumab). The findings reported at this symposium represent updated results from this arm of the trial, which was discontinued because addition of the fully human monoclonal antibody panitumumab did not improve progression-free survival and was associated with significant toxicities. The patients, whose ECOG performance status was 0 or 1, were randomized to receive either panitumumab 6 mg/kg every 2 weeks or no panitumumab concomitant with bevacizumab plus FOLFOX until disease progression or intolerability. The primary objective was to assess progression-free survival, and tumor assessments were performed every 12 weeks. At the data cutoff on May 31, 2007, 94% of patients had completed first-line treatment, with a median follow-up of 12.2 months (range, 0–26.3 months). The median progression-free survival was 9.5 versus 11 months (95% CI, 8.7–10.9 vs 10.3–11.9) for patients who did and did not receive panitumumab, respectively. The median time to treatment failure was 5.7 versus 5.9 months (95% CI, 5.5–6.0 vs 5.7–6.2) for patients who did and did not receive panitumumab, respectively. No patients who received panitumumab achieved complete response, and 186 patients each achieved partial response. Grade 3/4 adverse events were significantly worse among patients who received panitu-

mumab and included diarrhea (24% vs 13%), infections (19% vs 10%), dehydration (18% vs 6%), skin toxicity (39% vs 2%), hypokalemia (10% vs 4%), and pulmonary embolism (6% vs 4%). Grade 5 adverse events were infections (1% vs 1%) and pulmonary embolism (1% vs 0%). There were 140 (36%) death events reported among patients who received panitumumab as compared to 107 (26%) in the cohort who did not receive panitumumab. The authors reported that, in exploratory analyses, patients with worse ECOG status and elderly age (>80 years) who received panitumumab appeared to experience worse outcomes. Overall, panitumumab plus FOLFOX with bevacizumab was associated with shorter progression-free survival and increased toxicity. This combination is thus considered unsuitable in the general population of patients with metastatic colorectal cancer. Further data collection and analyses are ongoing.

279 Interim Results From PACCE: Irinotecan/Bevacizumab ± Panitumumab as First-line Treatment for Metastatic Colorectal Cancer

In related findings, Hecht and associates reported on the cohort from the PACCE study who received bevacizumab plus leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI) with or without panitumumab. The characteristics of the study population reported in this analysis were similar to those reported in the analysis of the patients who received oxaliplatin-based therapy, as were the endpoints. In an exploratory analysis, *K-Ras* status (wild-type or mutant [ie, activating mutations in exon 2]) was determined by polymerase chain reaction on DNA from tumor samples and correlated with panitumumab response. A total of 230 patients received bevacizumab plus FOLFIRI with or without panitumumab (115 each). The median follow-up for all patients was 8.9 months (range, 0.2–24.1 months). The median progression-free survival among those who did and did not receive panitumumab, respectively, was 10.6 versus 10.7 months (95% CI, 8.3–13.7 vs 9.0–13.2), and the median time to treatment failure was 6.6 versus 6.0 months (95% CI, 5.9–8.0 vs 4.8–6.9). Forty-six patients (40%) who received panitumumab achieved partial response as compared to 42 (37%) patients who received only FOLFIRI plus bevacizumab. Higher response rates were reported by investigators among patients who received panitumumab (55% vs 46%). Grade 3/4 adverse events included diarrhea (28% vs 9%), infections (17% vs 9%), dehydration (14% vs 6%), pulmonary embolism (11% vs 5%), hypokalemia (11% vs 4%), and skin toxicities (40% vs 2%). Grade 5 adverse events were infections (2% vs 0%) and pulmonary embolism (1% vs 0%); 24 (22%) deaths on study were

reported in the panitumumab-receiving cohort versus 18 (16%) in the cohort who did not receive panitumumab. Overall, progression-free survival times were similar between the cohorts, with higher investigator-reported response rates in the panitumumab-receiving cohort. Increased toxicity was also observed among patients who received panitumumab. The authors noted that analyses are ongoing, including the response rates stratified by *K-Ras* mutational status, to be reported in the future.

350 Preliminary Efficacy of Bevacizumab with first-line FOLFOX, XELOX, FOLFIRI, and fluoropyrimidines for mCRC: First BEAT

Berry and colleagues reported preliminary results of research intended to assess the safety profile of bevacizumab in combination with a variety of first-line chemotherapeutic regimens for metastatic colorectal cancer. It is already known that the addition of bevacizumab improves OS and progression-free survival when added to irinotecan- and oxaliplatin-based regimens. The First BEAT trial allowed physicians to choose a preferred chemotherapeutic regimen in 41 countries; 1,965 patients were enrolled. Bevacizumab was added to first-line chemotherapy at a dose of either 5 mg/kg for 2 weeks for patients receiving 5-fluorouracil-based chemotherapy or 7.5 mg/kg for 3 weeks for patients receiving capecitabine (Xeloda, Roche)-based chemotherapy until disease progression. Regimens included FOLFOX (29%), FOLFIRI (26%), capecitabine plus oxaliplatin (XELOX; 18%) or capecitabine/5-fluorouracil monotherapy (15%). Patients (median age, 59 years) had ECOG performance status of 0 or 1. The median follow-up was 21.4 months, with a 60-day mortality rate of 2.5%. Overall, 52% of patients were treated until disease progression, and patients who received capecitabine or 5-fluorouracil monotherapy appeared to have a poorer prognosis in comparison to those who received combination regimens plus bevacizumab. The median progression-free survival was 10.8 months (95% CI, 10.4–11.3) based on 1,396 events. The median time to progression was 11.2 months (95% CI, 10.7–11.6) based on 1,312 events. Grade 3–5 adverse events included bleeding (3.2%), gastrointestinal perforation (1.8%), arterial thromboembolism (1.3%), hypertension (5.1%), proteinuria (1.0%), and wound healing complications (1.0%), which is a profile consistent with bevacizumab-based therapy in other trials. The authors concluded that the efficacy and safety of first-line bevacizumab plus standard chemotherapy in this community-based trial was consistent with that seen in previous phase III trials.