

HEM/ONC News

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284 Efficacy, Safety and Impact on Quality of Life of a Treatment With Sorafenib in Elderly Cancer Patients With Advanced Hepatocellular Carcinoma. Preliminary Results of a Phase II Study

Sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor, which to date is the only systemic therapy able to prolong survival and time to progression in hepatocellular carcinoma patients, was assessed in this prospective, nonrandomized, phase II study conducted by Mantovani and colleagues. The study evaluated the safety and efficacy of sorafenib in elderly patients who had not received previous systemic therapy. Quality of life (using SF-36 questionnaire) and changes in interleukin-6 (IL-6) serum levels were also assessed. Prior to receiving treatment, patients underwent multidimensional geriatric assessment (MGA) and were assigned to 3 different categories: fit, intermediate, and frail. Sorafenib 800 mg/day was administered until disease progression or unacceptable toxicity. Efficacy assessments (objective clinical response according to response evaluation criteria in solid tumors [RECIST] and disease control rate [DCR]) were done every 3 months. DCR was defined as the percentage of patients who had a best response (complete response [CR], or partial response [PR], or stable disease [SD]); it had to be maintained for at least 28 days after the first response evaluation. From January to October 2008, 12 patients were enrolled (mean age, 70.3 years; range, 66–76; 11 males 1 female). Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0 in 25%, PS 1 in 66.7%, and PS 2 in 8.3% of patients. According to the MGA, 2 patients were fit, 8 intermediate, and 2 frail. At the 3-month evaluation, no patients had CR/PR, 7 of 11 patients had SD, 4 of 11 patients had progressive disease, and 1 had died (from progressive disease). The DCR was 85.7%. Adverse events were moderate, with grade 3 hand-foot and skin reactions (25%) being the most frequently reported events. Hypertension (16.7%), diarrhea (16.7%), nausea/vomiting (8.3%), and asthenia (8.3) were also reported. Treatment was stopped (for a mean of 7 days) and restarted with a dose reduction

(400 mg) due to toxicities in 81.8% of patients; mean dose was 581 mg/day. Changes in quality of life parameters were not significant, but there was a trend toward improvement after 3 months of treatment; serum IL-6 levels were high at enrollment, but did not change thereafter. Study findings showed that sorafenib, given to hepatocellular carcinoma patients, demonstrated a good DCR, moderate toxicity at the higher dose, and optimal acceptability at the lower dose.

382 XELOX-1/NO16966, a Randomized Phase III Trial of First-line XELOX Compared With FOLFOX4 for Patients With Metastatic Colorectal Cancer (MCR): Updated Survival and Tolerability Results

Updated overall survival (OS) results of the NO16966 study, originally presented at the 2007 meeting of the American Society of Clinical Oncology (ASCO) by Cassidy and colleagues, confirmed that XELOX is still noninferior to FOLFOX4 in terms of median OS. In the original study, 634 patients received either XELOX (oxaliplatin 130 mg/m², capecitabine 1,000 mg on days 1–14 every 3 weeks) or FOLFOX4 (oxaliplatin, 5 fluororacil [5-FU], and leucovorin). However, in the updated study, the design was changed to a 2 × 2 partially blinded study by adding either bevacizumab (7.5 mg/kg every 3 weeks for XELOX and 5 mg/kg every 2 weeks for FOLFOX4) or placebo to both regimens. The updated study recruited an extra 1,400 patients to the original 634, with an additional 14 months of follow up compared to the primary analysis. The secondary analysis determined that XELOX was noninferior to FOLFOX4 in terms of median OS. Safety was consistent with previous findings for the 2 treatment groups (non-bevacizumab-containing arms). Grade 3/4 adverse events occurred less frequently in the pooled XELOX versus the pooled FOLFOX4 group (71.5% vs 78.1%) and the incidence of hematologic adverse events was also lower in patients treated with XELOX as compared to FOLFOX4. Grade 3/4 gastrointestinal adverse events were, however, more common with XELOX (33% vs 25.8%), as was hand-foot syndrome (grade 3; 6.1%

vs 1.2%). Updated study findings showed a similar safety profile for both regimens, and confirmed that XELOX is noninferior to FOLFOX4 for OS when given as first-line treatment to patients with MCRC.

431 Efficacy and Safety of the First-line Treatment with a Combination of Bevacizumab and Biweekly XELIRI in Metastatic Colorectal Cancer Without Previous Treatment

Bevacizumab—the cornerstone of first-line treatment of colorectal cancer—in combination with XELIRI (capecitabine and irinotecan) was analyzed by Alfonso and colleagues in this unicenter, observational, retrospective study. The objectives of the study were to evaluate the safety and efficacy of bevacizumab with a combination of biweekly XELIRI. The study enrolled 43 patients (median age, 65 years; range, 45–78). In 33% of patients, the primary tumor was in the rectum, 65% of patients had hepatic metastases, and 23% of patients had received adjuvant treatment. Patients received a median of 11 cycles of bevacizumab and 12 cycles of irinotecan and capecitabine (39.5% and 37% of patients needed at least one dose reduction of capecitabine and irinotecan, respectively). Asthenia, diarrhea, and nausea/vomiting (all 7%) were the most frequently reported grade 3/4 adverse events, and hand-foot syndrome was the most frequent grade 1-2/3-4 toxicity reported in 34.9%/2.3% of patients. A response rate of 62.8% was observed in 27 patients, of which 2 patients (4.7%) experienced CR and 25 patients (58.1%) PR. Disease stabilization was seen in 30% of patients, and 23.3% of patients underwent resection of metastases (14% in the liver). Median OS and progression-free survival (PFS) were 19 months and 10.3 months, respectively. The study demonstrated promis-

ing results in regard to response rates and PFS with the combination of biweekly XELIRI plus bevacizumab. This regimen also showed a tolerable safety profile with a low incidence of bevacizumab-related adverse events.

445 Effect of Tumor KRAS Mutation Status on Second-line Treatment with Panitumumab (Pmab) and FOLFIRI: Interim Results From the Pmab Regimen Evaluation in Colorectal Cancer to Estimate Primary Response to Treatment (PRECEPT) Study

A prospective analysis, performed by Cohn and colleagues, evaluated the efficacy and safety of second-line panitumumab plus FOLFIRI (5-FU, leucovorin, irinotecan) by KRAS Status. Panitumumab, which is a fully human antibody to the epidermal growth factor receptor, is effective as monotherapy in the treatment of MCRC. The phase II, open-label, single-arm study enrolled patients who failed first-line treatment with oxaliplatin-based chemotherapy plus bevacizumab. Enrolled patients had unresectable, measurable disease, ECOG status 0 or 1, and had to have tumor samples evaluable for KRAS testing. Patients were administered 6 mg/kg of panitumumab plus FOLFIRI every 2 weeks until disease progression or intolerability. Tumor assessments were made at weeks 8, 16, 24, 32, and every 12 weeks thereafter. Real-time polymerase chain reaction (PCR) or DNA extracted from fixed tumor sections was used to evaluate tumor KRAS status. Efficacy (including objective response rate), PFS, OS, and safety were evaluated by KRAS status. The study enrolled 115 patients who received at least 1 dose of panitumumab (safety set). Of all patients, 109 had tumors with known KRAS status: 64 (59%) patients had wild-type KRAS tumors

Best Objective Response*, n (%)	Pts w/ wt KRAS	Pts w/ mt KRAS
Complete response	1 (2)	1 (2)
Partial response	14 (24)	10 (23)
Stable disease	21 (36)	14 (33)
Disease Progression	12 (20)	13 (30)
Unable to evaluate/not done	11 (19)	5 (12)
Objective response rate*, patients, n	15	11
Crude rate, % (95% CL)	25 (14–37)	26 (13–39)
Other Efficacy†	Pts w/ wt KRAS	Pts w/ mt KRAS
Progression-free survival‡, patients, n	30	32
Median weeks (95% CI)	26 (15–34)	16 (9–24)
Overall survival‡, patients, n	19	17
Median weeks (95% CL)	39 (32–unk)	31 (24–51)

Table 1. Interim Efficacy Outcomes

*Response rate set (n=102) with 59 pts with wild-type KRAS and 43 pts with mutant KRAS.

†All pts receiving ≥1 dose of panitumumab with evaluable KRAS status (n=109).

CI=confidence interval; CL=confidence level; mt=mutation; pts=patients; unk=unknown; w/=with; wt=wild-type.

and 45 (41%) had mutated KRAS tumors. First tumor assessments were performed in 102 patients (response rate set). Efficacy outcomes based on KRAS status are described in Table 1. Panitumumab-related adverse events were observed in 93% of patients; 87 (76%) patients had grade 3 or higher adverse events. Study results from this early analysis showed differences in PFS and OS in favor of patients with wild-type KRAS, and suggested that panitumumab was well tolerated, with safety findings in line with other FOLFIRI/panitumumab trials.

462 Bevacizumab (B) Plus Everolimus (E) in Refractory Metastatic Colorectal Cancer (MCR)

Phase I data in patients with refractory MCR demonstrated that a bevacizumab/everolimus combination was safe and activity was seen in several patients. In this study by Bullock and coauthors, 20 patients (median age, 57 years; range, 35–78) with refractory MCR were enrolled in an expanded cohort of bevacizumab/everolimus. Bevacizumab was administered at a dose of 10 mg/kg

every 2 weeks and everolimus at a dose of 10 mg every day. Blood, skin, and tumor biopsies pre- and on treatment were collected for markers of response and resistance. At present, 18 patients are evaluable for safety and 16 for efficacy. Patients had a median of 3 prior regimens and all patients had prior bevacizumab exposure, 16 of which had progressive disease. Adverse events reported during the study are presented in Table 2. Of the 16 patients evaluable for response, 6 had SD as best response; 3 minor responses in patients who progressed on bevacizumab were also observed. No CR or PR was seen. Study findings suggest that the combination of bevacizumab/everolimus may overcome resistance to bevacizumab. Patient accrual is ongoing and updated data will be presented.

LBA381 KRAS Status and Efficacy of First-line Treatment of Metastatic Colorectal Cancer Patients with FOLFOX6 + Cetuximab or FOLFIRI + Cetuximab: The CECOG/CORE1.2.001 Experience

The Central European Cooperative Oncology Group (CECOG) performed a retrospective analysis on a previously reported phase II study comparing FOLFOX6 plus cetuximab (FX+C) and FOLFIRI plus cetuximab (FF+C). In the analysis, CECOG evaluated the effect of KRAS status on PFS, overall response rate (ORR), OS, and safety. Genomic DNA was isolated from archival tumor material and the KRAS mutation status of codons 12/13 was determined by a quantitative PCR-based assay. The patient population for which tissue samples were available (117/151; 77%) represented the overall intent-to-treat population. KRAS wild-type status was observed in 62 of 117 (53%) patients with evaluable tissue (34/57 and 28/60 in the FX+C and FF+C groups, respectively). Patients with KRAS wild-type had a significantly improved PFS compared to patients with KRAS mutation (8.9 vs 7.8 months; hazard ratio [HR]=1.83; $P=.0051$). KRAS wild-type patients also had a strong inclination toward improved OS (median 24.4 vs 16.7 months; HR=1.61; $P=.05740$). The difference in the rates of PFS and OS between the mutation and wild-type KRAS patients increased over time. For KRAS wild-type and mutation patients, the ORR was 53% and 63%, respectively. When analysis stratified results by treatment group, a statistically significant difference was seen in favor of KRAS wild-type patients for PFS (median 9.1 vs 7.2 months; HR=2.04; $P=.0196$) and OS (HR=2.92; $P=.0019$) in the FX+C arm; no significant differences were observed in the FF+C arm. Safety findings were similar both in patients with KRAS wild-type and mutated tumors.

Table 2. Treatment-related Adverse Events and Other Events of Interest

	Adverse Event	Number of Patients (n)
Grade 4	Hypokalemia	1
Grade 3	Bowel perforation/fistula	2
	Hyperglycemia	3
	Hypokalemia	3
	Hypertension	2
	Fatigue	1
	Alkaline phosphatase elevation	1
	Hypoalbuminemia	1
	Volume depletion	1
Grades 1 and 2	Mucositis (grades 1 and 2)	10
	Hyperlipidemia (grade 1)	11