FOLFOX Plus Bevacizumab With or Without Irinotecan in Advanced Colorectal Cancer: CHARTA—Final Results and Multivariate Prognostic Factor Analysis

- Hans-Joachim Schmoll, MD, Halle University Clinic, Halle, Germany

CHARTA trial results have demonstrated that a four-drug combination including irinotecan offers benefit to patients with advanced colorectal cancer (CRC) compared with the most commonly used first-line, three-drug regimen. In a late-breaking clinical trial oral presentation, Dr. Schmoll said that the activity of the standard three-drug combination is limited and that the addition of irinotecan might be superior.

The regimens compared in CHARTA were the triplet therapy of fluorouracil plus leucovorin and oxaliplatin (FOLFOX) plus bevacizumab (Avastin, Genentech) (BEV) and the four-drug combination of fluorouracil plus leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus BEV.

The trial investigators included 250 patients with advanced unresected CRC, stratifying them according to ESMO groups: group 1, potentially resectable metastatic disease with curative intention; group 2, disseminated disease, technically never or unlikely to be resectable—intermediate intensive treatment; and group 3, never-resectable metastatic disease—nonintensive/sequential treatment. Other stratifications included risk score, mutation status, and primary tumor side (left or right).

The patients were randomized 1:1 to six-month induction of standard FOLFOX/BEV (control group) or FOLFOXIRI/BEV, each followed by maintenance with capcitabine plus BEV until progression or a maximum of 12 months. Progression was followed by reinduction upon investigator decision. Dose reductions of 25% were allowed in cycles 1 and 2 at the investigator’s discretion, with escalation in subsequent cycles. The primary endpoint was progression-free survival (PFS) at nine months.

After a median follow-up of 38.8 months among 241 evaluable patients, nine-month PFS was 57% in the control arm and 68% for FOLFOXIRI/BEV (P = 0.085), meeting the predetermined significance boundary. PFS duration was 10.3 months for the control group and 12 months for FOLFOXIRI/BEV (P = 0.17).

Overall survival (OS) was 24 months for the control arm and 28 months for the four-drug arm (P = 0.39). “The lack of significant PFS and OS improvement is likely due to the low patient numbers,” Dr. Schmoll explained.

Best response rates (complete plus partial responses) were 60% for the control group and 68% for FOLFOXIRI/BEV (P = 0.16), and secondary responses (after reinduction) and PFS duration showed nonsignificant gains for the FOLFOXIRI/BEV arm. OS was 45.3 months for patients in the control arm and 44.2 months for those receiving FOLFOXIRI/BEV (P = NS).

Patients with synchronous tumors receiving the four-drug combination had a significant PFS benefit of 11.76 months versus 10.05 months (hazard ratio [HR], 0.72; P = 0.027). Median OS was similar between the groups with a nonsignificant benefit for FOLFOXIRI/BEV (22.47 months versus 27.96 months; HR, 0.78; P = 0.12). No advantage was observed in patients with metachronous tumors.

Dr. Schmoll reported a further significant benefit for FOLFOXIRI/BEV in patients with primary synchronous tumors that had been resected. For them, median PFS was 15.225 months. For those without resection, median PFS was 10.45 months (HR, 0.63; P = 0.032). PFS results reflected nonsignificant trends favoring the four-drug arm in subgroups defined by sidedness, RAS and BRAF mutations, and combinations of these factors.

Analysis of ESMO groups showed nonsignificant trends favoring the addition of irinotecan for groups 1 and 3, but not group 2.

Finally, univariate prognostic factor analysis identified only two factors favoring FOLFOXIRI/BEV: carcinoembryonic antigen (CEA) levels of less than 20 ng/mL versus greater than 20 ng/mL (P = 0.01) and synchronous versus metachronous primary tumors (P = 0.03). In multivariate analysis, only CEA levels less than 20 ng/mL were significant (P = 0.02).

There were no clinically relevant increases in toxicity, Dr. Schmoll noted, likely due to dose reductions in cycles 1 and 2. Quality of life, he added, was comparable between the two treatment arms. “CHARTA supports the benefit of the four-drug combination,” he concluded.

Randomized Phase 3 Study of Fluoropyrimidine (FP) Plus Bevacizumab Versus FP Plus Irinotecan and Bevacizumab as First-Line Therapy for Metastatic Colorectal Cancer

- Dominik P. Modest, MD, University Hospital Grosshadern, Munich, Germany

Reduced initial treatment intensity for patients with untreated, unresectable metastatic colorectal cancer (mCRC) failed to meet noninferiority limits compared with initial standard-of-care, full-intensity treatment in the phase 3 German AI0 KRK-0110 trial. The study compared an experimental lesser-intensity initial treatment of fluoropyrimidine (FP) plus bevacizumab with metachronous tumors.

This year’s 19th annual European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer gathered more than 3,600 medical and scientific professionals in Barcelona, Spain, from June 23 to 28. The meeting brought particular attention to the influence of primary tumor sidedness in colorectal cancer as it affects prognosis and treatment outcomes to meet the growing interest in this theory.

The author is a freelance writer living in New York City.
(Avastin, Genentech) (BEV) followed by irinotecan (IRI) plus FP plus BEV at first progression (arm A) with standard full-intensity initial therapy with FP plus IRI plus BEV (arm B). In the subgroup of patients with RAS-mutant mCRC, however, more intensive first-line chemotherapy did not lead to better outcomes, Dr. Modest said in an oral presentation.

The primary endpoint in the study was noninferiority of arm A to arm B in time to failure of strategy (TFS). The noninferiority margin was set to a hazard ratio (HR) of 0.8, requiring 378 events. The primary safety outcome was symptomatic toxicities (National Cancer Institute grades 2–5) per treatment cycle.

Study investigators enrolled 434 patients, 421 of whom were ultimately evaluable (arm A, n = 212; arm B, n = 209). Similar numbers of patients in both groups also received capecitabine (arm A, 71.2%; arm B, 65.1%). The median patient age was 70 years, and approximately 67% were men. Dr. Modest noted that the trial population was somewhat older than in other mCRC clinical trials. In addition, RAS mutations were distributed evenly between the groups: arm A had 48.4% of patients with RAS wild-type tumors and 51.6% with RAS mutations, and arm B had 47.3% of patients with RAS wild-type tumors and 52.7% with RAS mutations. Escalation with irinotecan in patients with progressive disease occurred in only 37.7% of arm A patients, Dr. Modest noted.

After a median follow-up of 35.7 months in arm A and 32.9 months in arm B, TFS was 9.6 months and 9.9 months, respectively (HR, 0.86; 95% confidence interval, 0.73–1.02; P = 0.16). Among patients with RAS wild-type tumors, TFS was 8.6 months for arm A and 11.8 months for arm B, meeting the noninferiority margin (HR, 0.65; P = 0.01). “We found something that personally I did not expect—a three-month gain for arm B in terms of TFS,” Dr. Modest said. Among patients with RAS-mutant tumors, however, differences were not significant (arm A, 10.0 months versus arm B, 9.4 months; HR, 1.08; P = 0.62).

Overall survival (OS) was similar at 21.9% for arm A and 23.5% for arm B (HR, 0.84; P = 0.14). Dr. Modest pointed to a plateau in the OS curves in favor of the irinotecan-containing upfront therapy. “We see, though, that it is not statistically significant,” he added. Analysis according to mutation group, however, showed a significant five-month advantage for the more intensive first-line treatment in wild-type tumors (arm A, 23.5 months, versus arm B, 28.5 months; HR, 0.64; P = 0.02). With RAS-mutant tumors, OS was similar at 21.3 months for arm A and 23.2 months for arm B (HR, 0.90; P = 0.54).

While the overall toxicity analysis revealed no substantial advantage for less-intensive induction, the analysis of symptomatic toxicity (e.g., bleeding, vomiting) did show a small but expected advantage for the sequential treatment arm (P = 0.03).

“Noninferiority was not proven in the full analysis set. Superiority was shown for initial FP plus irinotecan and bevacizumab in RAS wild-type tumors, and noninferiority was shown for the RAS mutation tumors,” Dr. Modest said. He underscored that sequential escalation of therapy was feasible only in a minority of mCRC patients.

Dr. Modest concluded that more intensive first-line chemotherapy was not associated with a substantial improvement of outcome in patients with RAS-mutated mCRC. “Sequential therapy starting with FP plus bevacizumab may be considered specifically in the context of RAS-mutant mCRC,” he added.

The Left Versus Right Colon Cancer Story: What Is the Truth?

• Axel Grothey, MD, Mayo Clinic, Rochester, Minnesota

In contrast to current ESMO and National Comprehensive Cancer Network (NCCN) recommendations, Dr. Grothey stated that, for treatment of right-sided colon RAS/RAF wild-type tumors, epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) may be considered in later lines of therapy.

Dr. Grothey, who is on the guidelines committee that established the latest version of NCCN’s Clinical Practice Guidelines in Oncology, Colon Cancer, noted that the ESMO recommendation for left-side primary tumors allows EGFR mAbs as the standard of care in first-line treatment and allows them to “be considered in first line if response is goal” on the right. In contrast, the NCCN recommendation for left-side primaries states no clear preference between EGFR mAbs or bevacizumab (Avastin, Genentech) in first-line treatment, but states “no EGFR mAbs in first line and potentially not in any line” for right-sided tumors.

Studies demonstrating strikingly divergent outcomes based on tumor sidedness, however, dislodged Dr. Grothey’s confidence in the conventional wisdom. In Brulé et al., among 399 patients with KRAS wild-type tumors, progression-free survival (PFS) was similar for treatment with best supportive care (BSC) versus BSC plus cetuximab (Erbitux, Eli Lilly) (1.9 months versus 1.8 months) in patients with right-sided tumors, but 1.9 months versus 5.4 months in those with left-sided tumors.1 In a second study by Loupakis et al. among 2,503 unscreened colorectal cancer (CRC) patients, median overall survival (OS) ranged between 14.6 months and 24.8 months for three different bevacizumab-containing regimens for right-sided tumors and between 34.0 months and 42.0 months in left-sided tumors.2

Similarly, in the Heinemann et al. presentation of FIRE-3 data, for those receiving fluorouracil plus leucovorin and irinotecan (FOLFIRI) plus cetuximab, OS was 36.7 months in left-sided tumors and 16.1 months for right-sided tumors (P < 0.0001). For the arm receiving FOLFIRI plus bevacizumab, OS was 28.0 months for left-sided tumors and 22.7 months for right-sided tumors (P = 0.034).3

In patients with metastatic CRC (mCRC) in the CRYSTAL trial of FOLFIRI with or without cetuximab, OS was 28.7 months versus 21.7 months for FOLFIRI alone in left-sided mCRC (P = 0.002), and 18.5 months and 15.0 months, respectively, with and without cetuximab in right-sided mCRC (P = 0.76).1

Presenting further evidence, Dr. Grothey cited the presentation of Venook et al. of CALGB/SWOG 80405 data, in which median event-free survival was 35.2 months and 21.9 months for RAS wild-type tumors (P = 0.009), and OS was 39.3 months and 13.6 months, respectively, for left- and right-sided tumors (P = 0.001). Treatment with bevacizumab, however, was not affected by sidedness, with median OS of 32.6 months and 29.2 months for the left and right sides, respectively (hazard ratio, 0.88; P = 0.50).5

Finally, tumor responses were sharply differentiated for left-sided tumors in the recent Arnold et al. analysis of six
MEETING HIGHLIGHTS: ESMO World Congress on Gastrointestinal Cancer

Table 1 Comparison of EGFR mAb Treatment Recommendations for Wild-Type RAS/RAF Left- and Right-Sided Colon Cancer

<table>
<thead>
<tr>
<th>Primary Location</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>ESMA: EGFR mAbs are standard of care in first line</td>
</tr>
<tr>
<td></td>
<td>NCCN: No clear preference for EGFR mAbs or bevacizumab (Avastin, Genentech) in first line</td>
</tr>
<tr>
<td></td>
<td>Axel Grothey: EGFR mAbs are preferred; bevacizumab can be used in select patients in first line</td>
</tr>
<tr>
<td>Right</td>
<td>ESMA: EGFR mAbs can be considered in first line if response is goal</td>
</tr>
<tr>
<td></td>
<td>NCCN: No EGFR mAbs in first line and potentially not in any line</td>
</tr>
<tr>
<td></td>
<td>Axel Grothey: No EGFR mAbs in first line (if response is goal, consider triplet), but allow EGFR mAbs in later line</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; mAb = monoclonal antibody; NCCN = National Comprehensive Cancer Network.

Adapted with permission from Axel Grothey.

Dr. Grothey’s recommendation for primary tumors on the left side of the colon: EGFR mAbs are preferred. Bevacizumab, however, can be used in select patients in the first line, specifically for those with low-volume disease in whom no rapid anatomic response is needed and for elderly patients who are not candidates for oxaliplatin- or irinotecan-based chemotherapy. His recommendation for right-sided tumors: no EGFR mAbs are recommended for the first line, although if response is the goal, triplet therapy can be considered. EGFR mAbs can be allowed in later lines of treatment (Table 1).

“I personally have patients who actually responded to EGFR mAbs therapy single-agent with right-sided RAS wild-type tumors. So I don’t think we should eliminate this treatment option,” he commented. “We now have a much better understanding of who the ideal patient is for first-line EGFR mAb therapy.”

A negative selection cascade, he continued, excludes patients with KRAS/NRAS, HRAS exon 2, 3, 4 wild-type BRAFV600E mutations, and HER-2 amplification. Beyond that, an overlay of other criteria eliminates right-sided cancers and those with low EGFR ligand expression.

“I am treating more patients with first-line EGFR mAbs now that I am more sure of who these patients are that benefit from this therapy,” he concluded.

Overall Survival Analysis of the FOXFIRE-SIFL OX-FOXFIRE Global Prospective Randomized Studies of First-Line Selective Internal Radiotherapy (SIRT) in Patients With Liver Metastases From Colorectal Cancer

• Harpreet S. Wasan, MD, Hammersmith Hospital, Imperial College London, London, United Kingdom

A combined analysis of three studies (FOXFIRE, SIFL OX, and FOXFIRE Global), each with similar designs evaluating first-line selective internal radiation therapy (SIRT) using yttrium (Y)-90 resin microspheres (SIR-Spheres, Sirtex Medical, Inc.) plus first-line chemotherapy in patients with unresectable metastatic colorectal cancer (mCRC), found no overall survival (OS) benefit and no progression-free survival (PFS) benefit. Liver-specific PFS and rates of radiologic response, however, were superior with the addition of SIRT, according to Dr. Wasan.

SIRT with Y-90 microspheres was approved by the Food and Drug Administration in 2002 for unresectable liver tumors, Dr. Wasan noted, adding that 40% to 50% of the more than one million patients with CRC diagnosed each year develop liver metastases. SIRT plus fluorouracil plus leucovorin and oxaliplatin (FOLF OX) has been shown in the SIFL OX trial to improve local control of liver metastases. In the three combined trials, 1,103 patients (median age, 63 years; 86% male) were randomized 1:1 to standard oxaliplatin-based chemotherapy, bevacizumab, or another biologically targeted agent (at investigators’ discretion) or the same systemic therapy (with a dose modification of oxaliplatin for three cycles) plus a single SIRT treatment.

Dr. Wasan pointed out that about 35% of patients had extrahepatic metastases, and about 53% had unresected primary tumors in situ.

The primary endpoint of OS was similar for both treatment arms at 23.3 months for chemotherapy alone and 22.6 months for chemotherapy plus SIRT (hazard ratio [HR], 1.04; P = 0.609). PFS was also similar between groups at 10.3 months for chemotherapy alone and 11.0 months for chemotherapy plus SIRT (HR, 0.90; 95% confidence interval [CI], 0.79–1.02; P = 0.108). The only subgroup showing significant benefit for one of the treatments was the group with right-sided primary tumors receiving SIRT plus chemotherapy (HR, 0.67; 95% CI, 0.48–0.92).

First radiological progression within the liver occurred sooner in the chemotherapy-alone arm (HR, 0.51; 95% CI, 0.43–0.62; P < 0.001). First extrahepatic progression or death without documented radiological progression had a higher cumulative incidence in the SIRT arm (HR, 1.76; 95% CI, 1.47–2.11; P < 0.001). In addition, a greater number of patients in the chemotherapy-alone arm had subsequent post-protocol systemic therapy (74.0% versus 67.9%; P = 0.026).

Toxicities, especially hematologic, occurred at a greater incidence in the SIRT plus chemotherapy arm.

Dr. Wasan noted that an exploratory subgroup analysis of data from the SIFL OX and FOXFIRE Global trials had shown a greater OS of 4.9 months among patients with right-sided primary tumors receiving SIRT (HR, 0.64; P = 0.007). The possibility that benefits are poorer from conventional systemic...
treatment in tumors arising from right-sided colonic tumors, Dr. Wasan said, needs to be explored further.

Impact of Primary Tumor Location on Survival In Patients With Metastatic Colorectal Cancer Receiving Selective Internal Radiation Therapy And Chemotherapy as First-Line Therapy

• Guy Van Hazel, MD, University of Western Australia, Perth, Australia

The right-sided primary tumor metastatic colorectal cancer (mCRC) population is one that is relatively resistant to standard-of-care systemic chemotherapy regimens, Dr. Van Hazel said. Improvements in overall survival (OS) in these mCRC patients, however, are significant and clinically meaningful when they also receive selective internal radiation therapy (SIRT) using yttrium (Y)-90 resin microspheres (SIR-Spheres, Sirtex Medical, Inc.), compared with chemotherapy alone, he added.

Primary tumors arising from the left and right sides of the splenic flexure differ clinically and molecularly, and they have divergent blood supplies. Right-sided primaries are associated with inferior response to treatment and worse prognosis compared with left-sided primary tumors. Dr. Van Hazel cited the CRYSTAL study of cetuximab (Erbitux, Eli Lilly) plus fluorouracil, leucovorin, and irinotecan (FOLFIRI) versus FOLFIRI alone, with median OS of 23% for right-sided primaries and 76% for the left. Median OS was 18.5 months and 28.7 months, respectively, for right- and left-sided primaries with cetuximab plus FOLFIRI.

Dr. Van Hazel examined the impact of sidedness on OS and progression-free survival (PFS) in the SIRFLOX and FOXFIRE Global trials in first-line SIRT using Y-90 resin microspheres with fluorouracil plus leucovorin and oxaliplatin (FOLFIRI)-based chemotherapy in liver-only or liver-dominant mCRC. His intention-to-treat analysis of 739 patients found similar tumor burden in both groups, but with left-sided primary tumor patients in the mFOLFOX6 arm more likely to receive bevacizumab (Avastin, Genentech).

An OS advantage for SIRT plus chemotherapy in the right-sided primary group was significant (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.46–0.89; P = 0.007). SIRT conferred no advantage to patients with left-sided primary tumors (HR, 1.12; 95% CI, 0.92–1.36; P = 0.279). The treatment interaction by location for OS was highly significant (P = 0.002).

SIRT plus chemotherapy conferred a nearly statistically significant PFS benefit (P = 0.053) at 10.8 months versus 8.7 months. PFS was similar for both treatments in left-sided primary tumor patients (11.4 months versus 10.8 months; P = 0.426). Rates of hepatic response for the overall population were higher for mFOLFOX6 plus SIRT (71.8%) than for mFOLFOX6 alone (67.6%; P = 0.004). Sidedness did not affect adverse event rates, Dr. Van Hazel noted. He concluded, “The observed OS improvement may support a side-based approach to first-line selection for SIRT.”

Are there plausible explanations for the lack of OS benefit for SIRT plus chemotherapy in these clinical trials? In an interview, Harpreet S. Wasan, MD, presenter of the SIRT study that is summarized directly before this report, offered speculations:

“We thought a few small lung metastases or in lymph nodes outside the liver—or leaving the primary tumor in for a while and treating the secondaries (we could go back later if needed) would not make a difference. But in fact it probably did make a difference. If we could do it over, we would make sure that all primaries were resected and that patients had no extrahepatic disease at all.”

The discussant for both Dr. Van Hazel’s and Dr. Wasan’s presentations, John Zalcberg, MD, of Monash University in Melbourne, Australia, pointed out that, in an as-yet unpublished ARCAD (Aide et Recherche en Cancérologie Digestive) database analysis from van Rooijen et al., resection of synchronous tumors in mCRC added 5.8 months to OS. Approximately 50% of patients in Dr. Wasan’s SIRT study had in situ unresected primary tumors, and about 35% had extrahepatic metastases. Dr. Zalcberg cited another unpublished ARCAD-based analysis by Sjoquist et al. that found the presence of two or more metastatic sites had as strong an impact on OS (HR, 1.204) as sites in the liver (HR, 1.198).

Dr. Zalcberg concluded that first-line use of SIRT should be considered in patients with symptomatic, extensive, and unresectable liver-dominant metastatic disease who are not fit enough for triplet or doublet chemotherapy plus biologicals. The right-sided primary tumor findings, while intriguing, remain hypothesis-generating until randomized studies are conducted, he said.

REFERENCES