Optimizing the continuum of care in mCRC

Several second-line options can be used in the continuum of metastatic colorectal cancer (mCRC) care. At a Sanofi-sponsored symposium, Professor Alberto Sobrero of the Ospedale San Martino IRCCS, Genoa, Italy, discussed the long-term survival benefits and improved progression-free survival (PFS) and response rates (RR) offered by aflibercept (Zaltrap®, Sanofi) plus FOLFIRI. Dr. Kam-Tong Yuen, Specialist in Clinical Oncology in Hong Kong, discussed his experience with this regimen and its favorable tolerability in local patients, with dose adjustments rarely being required for either aflibercept or chemotherapy over 10 or more cycles.

Prof. Alberto Sobrero

Dr. Kam-Tong Yuen

Rationale behind aflibercept

Unlike bevacizumab, which targets only vascular endothelial growth factor (VEGF)-A, the anti-angiogenic agent aflibercept targets VEGF-A, VEGF-B and placental growth factor (PlGF). [*Expert Rev Anticancer Ther* 2013;13:427-438] This provides a more comprehensive blockade of the multiple signaling pathways involved in angiogenesis, and may help overcome bevacizumab resistance. Evidence that PlGF levels increase significantly after treatment with bevacizumab plus FOLFIRI (irinotecan, leucovorin, 5-FU) and before disease progression further underpins the rationale for using aflibercept as a second-line anti-angiogenic treatment. [*J Clin Oncol* 2010;28:453-459]

Treatment lines in mCRC: Clinical evidence

Clinical trial data can inform the optimum use of biologics during the treatment continuum. (Table) Bevacizumab significantly improved overall survival (OS) and PFS in the first and second lines, but did not improve survival when used as salvage treatment. Aflibercept showed significant OS and PFS benefits and improved RR only in the second line.

Cetuximab improved first-line OS and PFS in patients with wild-type (WT) KRAS and NRAS mCRC. It offered no OS gain in the second line, but good OS and PFS benefits when used in the third and fourth lines. Similar outcomes were obtained with panitumumab, without the OS advantage in salvage lines. The VEGF-receptor inhibitor regorafinib showed survival benefits only in the third and fourth lines.

Optimizing the treatment algorithm

Sobrero explained how these findings should be integrated into clinical practice. "In the continuum of care, we need to focus on the second line and subsequent treatments, as well as the first line," he stated.

"The first question to ask is whether the patients are candidates for intensive treatment," he said. "If not, they should receive either FOLFOX4 [leucovorin, 5-FU, oxaliplatin] plus bevacizumab, fluoropyrimidine, or no treatment."

If patients are candidates for intensive treatment, subsequent treatment decisions should be based on their RAS mutation status, which significantly impacts the OS seen with biological agents. [ASCO 2013, abstract 3511] "Patients with WT RAS should be treated in the first line with FOLFIRI plus cetuximab, or FOLFOX4 plus panitumumab. Recommended second-line treatment is doublet chemotherapy plus bevacizumab or aflibercept, followed in the third line by regorafenib," he suggested.

"If the patient has RAS mutations or their mutation status is not available, determine whether tumor shrinkage is needed," he advised. If not, recommended first-line treatment is capecitabine or doublet chemotherapy plus bevacizumab. If shrinkage is needed, Sobrero's treatment strategy is doublet chemotherapy (or triplet if the patient can tolerate it) plus bevacizumab, with second- and third-line options as for WT-RAS patients.

Table. Outcomes with biological agents across multiple treatment lines in mCRC

	First-line		Second-line		Salvage	
	OS	PFS	OS	PFS	OS	PFS
Bevacizumab[1-5]	✓	✓	✓	✓	-	-
Cetuximab[6-9]*	✓	✓	x	✓	✓	✓
Panitumumab[10-13]*	✓	✓	x	✓	x	✓
Aflibercept[14]	-	-	✓	✓	-	-
Regorafenib[15]	-	-	-	-	✓	✓

✓Significant improvement compared with control
x No significant improvement compared with control
*KRAS wild-type data

OS = overall survival; PFS = progression-free survival

Adapted from: 1) N Engl J Med 2004;350:2335-2342; 2) J Clin Oncol 2008;26:2013-2019; 3) J Clin Oncol 2005;23:3697-3705; 4) J Clin Oncol 2010;28:3191-3198; 5) J Clin Oncol 2007;25:1539-1544; 6) J Clin Oncol 2011;29:2011-2019; 7) Ann Oncol 2011;22:1535-1546; 8) Ann Oncol 2008;19(suppl 8):abstract 385P; 9) N Engl J Med 2008;359:1757-1765; 10) J Clin Oncol 2011;29(suppl):abstract 3510; 11) J Clin Oncol 2012;30(suppl 4):abstract 383; 12) J Clin Oncol 2011;29(suppl):abstract 3523; 13) J Clin Oncol 2008;26:1626-1634; 14) Ann Oncol 2011;22(suppl 5):abstract O-0024; 15) J Clin Oncol 2012;30(suppl 4):abstract LBA385.

Second-line strategies: Which is best?

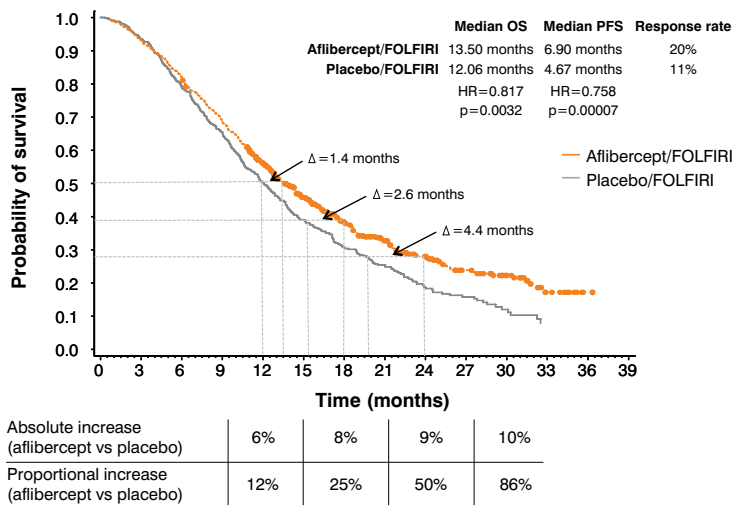
Sobrero compared the data from several pivotal studies of second-line mCRC treatment. The Kaplan-Meier OS data in the E3200 study of FOLFOX4 plus bevacizumab and the TML (Treatment through Multiple Lines) study of FOLFIRI plus bevacizumab resembled what Sobrero termed 'banana curves'. [Giantonio BJ, et al, ASCO 2005; *J Clin Oncol* 2007;25:1539-1544; *J Clin Oncol* 2012;30(15S):abstract CRA3503] "There is no long-term survival benefit," he explained. "By 30 months, the initial OS advantage with bevacizumab is lost." Study 181 of FOLFIRI with or without panitumumab did not show long-term OS benefits with panitumumab either. [*J Clin Oncol* 2012;30(suppl 4):abstract 38]

"The most impressive efficacy data are seen in the VELOUR study," said Sobrero. The largest study of second-line mCRC treatment to date, VELOUR compared FOLFIRI with or without aflibercept in more than 1,200 patients. [*J Clin Oncol* 2012;30:3499-3506]

"The OS curves show that survival benefit with aflibercept is maintained over time, similar to what is seen with adjuvant treatment," noted Sobrero. (Figure 1) At 30 months, the absolute increase in survival was 10 percent, which equated to a proportional increase of 86 percent. These positive findings are further supported by the internal consistency of the data, namely the significantly increased RR and PFS with aflibercept. "The OS benefit with aflibercept was not influenced by further treatment, as the proportions of patients receiving subsequent biologics and/or chemotherapy were similar in both study arms," Sobrero added.

These findings led Sobrero to recommend the treatment strategy shown in Figure 2. "Whenever we can, we try to use all agents to improve survival. We want to reduce the number of treatment lines lost," he said. In WT-RAS patients with rapid disease progression, the choice of second-line treatment should be based on whether the patient is likely to be a candidate for fourth-line treatment. If so, Sobrero suggested that aflibercept plus FOLFIRI be given in the second line, followed by an epidermal growth factor receptor inhibitor, and then regorafinib.

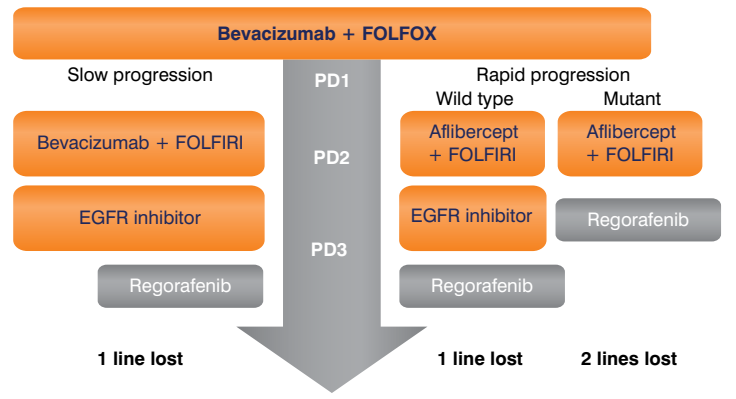
Figure 1. Survival analysis in VELOUR: Second-line aflibercept/FOLFIRI vs placebo/FOLFIRI in mCRC



Absolute increase (aflibercept vs placebo)	6%	8%	9%	10%
Proportional increase (aflibercept vs placebo)	12%	25%	50%	86%

FOLFIRI = irinotecan, leucovorin, 5-FU; HR = hazard ratio; OS = overall survival; PFS = progression-free survival
Adapted from J Clin Oncol 2012;30:3499-3506.

Figure 2. Treatment strategies for mCRC patients who do not require initial tumor shrinkage



EGFR = epidermal growth factor receptor; FOLFIRI = irinotecan, leucovorin, 5-FU; FOLFOX = leucovorin, 5-FU, oxaliplatin; PD = progressive disease
Adapted from Sobrero S, 2014.

"In terms of data consistency and long-term survival benefit, VELOUR shows that aflibercept plus FOLFIRI offers the most solid option for second-line treatment in mCRC," concluded Sobrero.

HK experience with aflibercept

Yuen shared cases of mCRC patients who received second-line treatment with aflibercept plus FOLFIRI at his hospital.

A 62-year-old man with stage IV, WT-KRAS mCRC of the sigmoid colon and bilobar liver metastases was initially treated with eight cycles of XELOX (capecitabine and oxaliplatin) until his carcinoembryonic antigen (CEA) levels rebounded. He then received 12 cycles of aflibercept (4 mg/kg) plus FOLFIRI, which were well tolerated. His ECOG (Eastern Cooperative Oncology Group) performance status remained at 1 throughout. Grade 1 diarrhea occurred at cycles 4, 5 and 11; the FOLFIRI dose was reduced to 80 percent due to grade 3 neutropenia at cycle 10, but there was no need to reduce the aflibercept dose. Urine protein remained normal throughout treatment and grade 1 hypertension was seen at cycle 11, but not 12. At follow-up after cycle 12, the primary tumor was enlarged but liver metastases remained static.

A 44-year-old man, ECOG 0, who had undergone low anterior resection for rectosigmoid carcinoma and received eight cycles of adjuvant capecitabine followed by six cycles of XELOX after recurrence, showed enlargement of a pre-sacral mass and an increase in peritoneal metastases. He was started on aflibercept (4 mg/kg) plus FOLFIRI. Over 10 cycles, no dose modifications were required, and the only aflibercept-related adverse event was grade 1 hypertension at cycle 5, which resolved. Treatment was continued after cycle 12 with regular follow-up.

"Aflibercept plus FOLFIRI is active in patients with good performance status who have failed prior oxaliplatin-based chemotherapy, and is well tolerated," concluded Yuen. (ot)