World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i15.4263

World J Gastroenterol 2014 April 21; 20(15): 4263-4275
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Anti-EGFR and anti-VEGF agents: Important targeted therapies of colorectal liver metastases

Qing-Yang Feng, Ye Wei, Jing-Wen Chen, Wen-Ju Chang, Le-Chi Ye, De-Xiang Zhu, Jian-Min Xu

Qing-Yang Feng, Ye Wei, Jing-Wen Chen, Wen-Ju Chang, Le-Chi Ye, De-Xiang Zhu, Jian-Min Xu, Department of General Surgery, Zhongshan Hospital, Fudan University, Shanghai 200032, China

Author contributions: Feng QY and Wei Y wrote the paper; Chen JW, Chang WJ, Ye LC and Zhu DX assisted with data collection, proofreading and in other ways; Xu JM was the invited author and established the theme of this paper; all authors discussed the opinions expressed in this article.

Correspondence to: Jian-Min Xu, MD, PhD, Department of General Surgery, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai 200032, China. xujmin@aliyun.com
Telephone: +86-21-64038038 Fax: + 86-21-64038038
Received: September 26, 2013 Revised: February 7, 2014
Accepted: February 20, 2014
Published online: April 21, 2014

Abstract

Colorectal liver metastasis (CLM) is common worldwide. Targeted therapies with monoclonal antibodies have been proven effective in numerous clinical trials, and are now becoming standards for patients with CLM. The development and application of anti-epidermal growth factor receptor (anti-EGFR) and anti-vascular endothelial growth factor (anti-VEGF) antibodies represents significant advances in the treatment of this disease. However, new findings continue to emerge casting doubt on the efficacy of this approach. The Kirsten rat sarcoma viral oncogene (KRAS) has been proven to be a crucial predictor of the success of anti-EGFR treatment in CLM. Whereas a recent study summarized several randomized controlled trials, and showed that patients with the *KRAS G13D* mutation significantly benefited from the addition of cetuximab in terms of progress-free survival (PFS, 4.0 mo *vs* 1.9 mo, HR = 0.51, *P* = 0.004) and overall survival (OS, 7.6 mo *vs* 5.7 mo, HR = 0.50, *P* = 0.005). Some other studies also reported that the *KRAS G13D* mutation might not be absolutely predictive of non-responsiveness to anti-EGFR therapy. At the same time, "new" RAS mutations, including mutations in neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) and exons 3 and 4 of KRAS, have been suggested to be predictors of a poor treatment response. This finding was first reported by the update of the PRIME trial. The update showed that for patients with non-mutated KRAS exon 2 but other RAS mutations, panitumumab-fluorouracil, leucovorin, and oxaliplatin (FOLFOX)4 treatment led to inferior PFS (HR = 1.28, 95%CI: 0.79-2.07) and OS (HR = 1.29, 95%CI: 0.79-2.10), which was consistent with the findings in patients with KRAS mutations in exon 2. Then, the update of the PEAK trial and the FIRE-Ⅲ trial also supported this finding, which would reduce candidates for anti-EGFR therapy but enhance the efficacy. In first-line targeted combination therapy, the regimens of cetuximab plus FOLFOX was called into question because of the inferior prognosis in the COIN trial and the NORDIC-Ⅶ trial. Also, bevacizumab plus oxaliplatin-based chemotherapy was questioned because of the NO16966 trial. By the update and further analysis of the COIN trial and the NORDIC-Ⅶ trial, cetuximab plus FOLFOX was reported to be reliable again. But bevacizumab plus oxaliplatin-based chemotherapy was still controversial. In addition, some trials have reported that bevacizumab is not suitable for conversion therapy. The results of the FIRE-Ⅲ trial showed that cetuximab led to a significant advantage over bevacizumab in response rate (72% *vs* 63%, *P* = 0.017) for evaluable population. With the balanced allocation of second-line treatment, the FIRE-Ⅲ trial was expected to provide evidence for selecting following regimens after first-line progression. There is still no strong evidence for the efficacy of targeted therapy as a preoperative treatment for resectable CLM or postoperative treatment for resected CLM, although the combined regimen is often administered based on experience. Combination therapy with more than one targeted agent has been proven to provide no benefit, and even was reported to be harmful as first-line treatment by four large clinical trials. However, recent studies reported positive results of erlotinib plus bevacizumab for

maintenance treatment. The mechanism of antagonism between different targeted agents deserves further study, and may also provide greater understanding of the development of resistance to targeted agents.

Key words: Oncology; Colorectal cancer; Liver metastases; Chemotherapy; Targeted therapy

Core tip: Targeted therapy is becoming standard for patients with colorectal liver metastases, but new findings continue to improve our understanding of these therapies. "New" *RAS* mutations, rather than the Kirsten rat sarcoma viral oncogene *G13D* mutation, may be predictive of non-responsiveness to anti-epidermal growth factor receptor therapy. The regimen of cetuximab plus FOLFOX is likely effective, but bevacizumab plus oxaliplatin-based chemotherapy remains controversial. Bevacizumab was suggested to be unsuitable for conversion therapy. Further confirmation is required to demonstrate the effectiveness of targeted therapy as a pre- or post-operative treatment. Combination therapy with more than one targeted agent is not recommended.

Feng QY, Wei Y, Chen JW, Chang WJ, Ye LC, Zhu DX, Xu JM. Anti-EGFR and anti-VEGF agents: Important targeted therapies of colorectal liver metastases. *World J Gastroenterol* 2014; 20(15): 4263-4275 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i15/4263.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i15.4263

INTRODUCTION

Colorectal cancer is one of the most common malignant tumors throughout the world[1,2]. It has the third highest incidence and death rate among all cancers in the United States[3], with 143460 new cases and 51690 deaths in 2012. In China, colorectal cancer was the third most common cancer and had the fifth highest death rate in 2009[4]. Liver metastases are particularly common in patients with colorectal cancer. Almost 50% of patients will eventually develop liver metastases during the natural course of the disease[5,6], and 25% of patients present with liver metastases at diagnosis[7-9]. Autopsies have shown that more than half of patients who died of colorectal cancer had liver metastases, with metastatic liver disease as the cause of death in most patients. However, over the last two decades, the long-term survival of patients with colorectal liver metastases (CLM) has significantly improved. From 1990 to 1997, the median overall survival (OS) was 14.2 mo (95%CI: 13.3-15.2), significantly increased to 29.2 mo (95%CI: 24.3-34.2) from 2004 to 2006 ($P < 0.05$). The 5-year survival rate also rose to 32% (95%CI: 27-38)[10]. These achievements should be attributed to the popularity of early diagnostic techniques, the expansion of indications for liver resection, the introduction of new chemotherapeutic agents (oxaliplatin, irinotecan, *etc.*), and the application of novel targeted agents (cetuximab, panitumumab, bevacizumab, *etc.*).

TARGETED THERAPY AND MOLECULAR PREDICTORS

Targeted biological therapy is becoming a standard personalized medical treatment for patients with CLM. Two options are currently available in routine clinical practice for patients with CLM: anti-epidermal growth factor receptor (anti-EGFR) antibodies and anti-vascular endothelial growth factor (anti-VEGF) antibodies. The anti-EGFR antibodies include cetuximab, a chimeric monoclonal antibody, and panitumumab, a fully human monoclonal antibody. These antibodies are directed against EGFR and inhibit downstream signaling pathways, leading to the inhibition of both cell proliferation and angiogenesis. The humanized monoclonal anti-VEGF antibody bevacizumab exerts its anti-tumor effects by binding VEGF and inhibiting VEGF from binding to its functional receptor, leading to the inhibition of tumor vessel growth and neovascularization and to a decreased permeability in the surviving vasculature.

Currently, no effective predictor of treatment success with angiogenesis inhibitors has been established, although the presence of the Kirsten rat sarcoma viral oncogene (*KRAS*) gene mutation is known to play a crucial role in predicting the success of treatment with anti-EGFR antibodies[11,12]. Three genes in the *RAS* gene family are associated with human tumorigenesis, v-Ha-ras Harvey rat sarcoma viral oncogene homolog (HRAS), KRAS and neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS). Every *RAS* gene has four exons. Past research suggested that RAS mutations were mainly concentrated in KRAS exon 2, codon 12 and 13. Approximately 40% of colorectal cancers are characterized by *KRAS* gene mutations in these two coding regions[13,14].

Many studies have confirmed that KRAS exon 2 mutations are predictive of no benefit from anti-EGFR treatment. The CRYSTAL trial[15] proved that for patients with *KRAS* mutations, the addition of cetuximab to FOLFIRI (irinotecan, fluorouracil and leucovorin) as a first-line therapy did not lead to a significant improvement in median progress-free survival (PFS; median PFS, 7.4 mo *vs* 7.7 mo, hazard ratio, HR = 1.171, $P = 0.260$) and median overall survival (OS; median OS, 16.2 mo *vs* 16.7 mo, HR = 1.035, $P = 0.75$). Another clinical trial[16] of panitumumab also proved that for patients with KRAS mutations, no PFS benefit was associated with panitumumab (median PFS, 7.3 wk *vs* 7.4 wk, HR = 0.99, 95%CI: 0.73-1.36). The subsequent quantitative interaction test compared the magnitude of the relative treatment effect on PFS between wild type and mutant KRAS groups, and showed a statistically significant difference ($P < 0.0001$). A recent meta-analysis[17] also demonstrated the predictive role of the *KRAS* gene in anti-EGFR therapy.

However, some recent studies raised the possibility that *KRAS* exon 2, codon 13 mutations, mainly G13D, might not be absolutely predictive of non-responsiveness to anti-EGFR therapy. A retrospective study by De Roock *et al*[18] pooled the clinical trials CO.17, BOND, MABEL, EMR202600, EVEREST, BABEL and SALVAGE. The results indicated that in comparison with other *KRAS* mutation, patients with the *KRAS G13D* mutation significantly benefited from the addition of cetuximab in OS (median OS, 7.6 mo *vs* 5.7 mo, HR = 0.50, 95%CI: 0.31-0.81, $P = 0.005$) and PFS (median PFS, 4.0 mo *vs* 1.9 mo, HR = 0.51, 95%CI: 0.32-0.81, $P = 0.004$). There was also a significant interaction between *KRAS* mutation status (*G13D vs* other *KRAS* mutations) and overall survival benefit with cetuximab treatment (adjusted HR = 0.30, 95%CI: 0.14-0.67, $P = 0.003$). No difference was observed between patients with the *KRAS G13D* mutation and wild type KRAS in OS (median OS, $P = 0.79$; median PFS, $P = 0.66$). However, for patients with the *KRAS G13D* mutation, the difference in OS or PFS between cetuximab plus chemotherapy and chemotherapy alone became non-significant in the multivariate analysis (adjusted OS, HR = 0.40, 95%CI: 0.13-1.28, $P = 0.12$; PFS, HR = 0.53, 95%CI: 0.16-1.73, $P = 0.29$). Soon afterwards, Tejpar *et al*[19] pooled the clinical trials CRYSTAL and OPUS, finding that in patients with *G13D* mutant tumors, the addition of cetuximab to chemotherapy significantly improved tumor response (40.5% *vs* 22.0%, odds ratio, OR = 3.38, $P = 0.042$) and PFS (median PFS, 7.4 mo *vs* 6.0 mo, HR = 0.47, $P = 0.039$), but not OS (median OS, 15.4 mo *vs* 14.7 mo, HR = 0.89, $P = 0.68$) after adjusting for differences in baseline variables. Otherwise, in comparison with patients with the KRAS wild type allele, patients with the *KRAS G13D* mutation still had poorer tumor response (OR = 0.50, 95%CI: 0.26-0.97, $P = 0.040$) and OS (HR = 1.61, 95%CI: 1.13-2.29, $P = 0.0085$) with cetuximab. Another meta-analysis by Mao *et al*[20] included 10 studies and 1487 patients, concluding that cetuximab led to significantly higher response rates (relative risk, RR = 1.642, 95%CI: 1.13-2.38) in patients with the *KRAS G13D* mutation than in those with the *KRAS G12* mutation. These studies showed benefits from cetuximab in patients with the *KRAS G13D* mutation, and not worse than KRAS wild type patients. The authors suggested that the *KRAS G13D* mutation should be distinguished from other *KRAS* mutations.

At the same time, other studies supported opposing views. Peeters *et al*[21] conducted a retrospective study assessing the prognostic and predictive impact of individual *KRAS* codon 12 and 13 mutations on panitumumab combined with chemotherapy. They pooled three randomized phase Ⅲ studies including a total of 1053 patients and came to a negative conclusion. The results showed that out of all types of *KRAS* mutations (including G12D, G12V, G12C, G12A, G12S, G12D), only G12A was associated with a negative predictive effect on OS. No other significant differences were observed between panitumumab plus chemotherapy and chemotherapy alone in OS or PFS. Considering the common mechanism of cetuximab and panitumumab, the efficacy of anti-EGFR therapy for patients with *KRAS G13D* mutations remained in doubt. In addition, the above studies are all retrospective and only include a limited number of cases. Thus, the function of the KRAS G13D test should be interpreted and applied conservatively. Further randomized controlled clinical trials should be conducted for confirmation.

In addition to exon 2 mutations, other activating *RAS* mutations may also be negative predictive biomarkers for anti-EGFR therapy, including those in NRAS and exons 3 and 4 of KRAS, which together are called "new" RAS. Douillard *et al*[22] tested the "new" RAS status of the KRAS wild type patients from the PRIME trial. The results showed that in 512 patients without any *RAS* mutations, panitumumab plus FOLFOX4 led to a 2.2 mo improvement in PFS (median PFS, 10.1 mo *vs* 7.9 mo, HR = 0.72, $P = 0.004$) and a 5.8 mo improvement in OS (median OS, 26.0 mo *vs* 20.2 mo, HR = 0.78, $P = 0.04$), a greater improvement than that observed in patients with only wild type KRAS exon 2. A total of 108 patients (17%) with non-mutated *KRAS* exon 2 had other RAS mutations. These mutations were associated with inferior PFS (HR = 1.28, 95%CI: 0.79-2.07) and OS (HR = 1.29, 95%CI: 0.79-2.10) with panitumumab-FOLFOX4 treatment, which was consistent with the findings in patients with *KRAS* mutations in exon 2. At the same time, the head-to-head phase Ⅱ trial PEAK evaluated panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 in patients with previously untreated KRAS exon 2 wild type CLM. The findings from this trial were reported at the 2013 ASCO Annual Meeting[23], with no significant differences observed between panitumumab and bevacizumab in PFS (median PFS, 10.9 mo *vs* 10.1 mo, HR = 0.97, 95%CI: 0.65-1.17) or OS (median OS, not reached *vs* 25.4 mo, HR = 0.72, 95%CI: 0.47-1.11). However, in subgroup analysis of "new" RAS wild type variants, panitumumab led to a significant improvement in PFS (median PFS, 13.1 mo *vs* 9.5 mo, HR = 0.63, $P = 0.02$) and OS (median OS, not reached *vs* 29.0 mo, HR = 0.55, $P = 0.06$). These results indicated that the "new" RAS biomarkers should also be tested when receiving anti-EGFR treatment. This increasing number of predictors is leading to the decreasing number of patients suitable for anti-EGFR therapy, but is also resulting in an enhanced efficacy of the treatment.

As a gene downstream of KRAS, v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) is also a hotspot. Approximately 5% to 9% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene, mainly V600E[14,15]. For all practical purposes, *BRAF* mutations are limited to tumors that do not have *KRAS* mutations. Several studies have confirmed BRAF as a strong prognostic marker[13,15,24,25], but the utility of BRAF status as a predictive marker remains unclear. The subgroup analysis of the CRYSTAL trial[15] showed that in patients with wild type KRAS and mutated BRAF, improvements in PFS (median PFS, 8.0 mo *vs* 5.6 mo, HR = 0.934, $P = 0.87$) and OS (median OS, 14.1 mo *vs* 10.3 mo, HR =

0.908, $P = 0.74$) associated with the addition of cetuximab to FOLFIRI were not statistically significant. Although no evidence was reported of an independent interaction between the treatment approach and the tumor *BRAF* mutation status, BRAF, like KRAS, is expected to become a new predictive factor for treatment efficacy.

TARGETED THERAPY FOR UNRESECTABLE METASTATIC COLORECTAL CANCER

First-line treatment

Anti-EGFR antibody as first-line treatment: Currently, cetuximab plays a major role in the clinical application of anti-EGFR therapeutics. Many clinical trials of cetuximab combined with chemotherapy have demonstrated the significant utility of this agent in treating metastatic colorectal cancer (details in Table 1). The CRYSTAL trial[15,26] involved 1198 patients with unresectable CLM, comparing the addition of cetuximab to irinotecan, fluorouracil, and leucovorin (FOLFIRI) with FOLFIRI alone as the first-line treatment. The results showed that for the intent-to-treat (ITT) population, the cetuximab combined group exhibited a significant increase in the primary end point, PFS (median PFS, 8.9 mo *vs* 8.0 mo, HR = 0.85, $P = 0.048$), but not significant in the secondary end point, OS (median OS, 19.9 mo *vs* 18.6 mo, HR = 0.93, $P = 0.31$). For patients with wild type KRAS, the cetuximab combined group exhibited a greater benefit in terms of PFS (median PFS, 9.9 mo *vs* 8.7 mo, HR = 0.68, 95%CI: 0.50-0.94) and OS (median OS, 23.5 mo *vs* 20.0 mo, HR = 0.796, $P = 0.0093$). The CRYSTAL study thus became a pivotal study in obtaining European Medicines Agency approval of the use of cetuximab as a first-line treatment for metastatic colorectal cancer. Another sizable clinical trial, OPUS[27,28], also proved that for patients with wild type KRAS, cetuximab plus FOLFOX (fluorouracil, leucovorin, and oxaliplatin) significantly improved PFS (median PFS, 8.3 mo *vs* 7.2 mo, HR = 0.567, $P = 0.0064$) but not OS (median OS, 22.8 mo *vs* 18.5 mo, HR = 0.855, $P = 0.39$). Therefore, cetuximab combined with chemotherapy is considered an important part of first-line treatment for unresectable CLM.

However, the efficacy of cetuximab combined with FOLFOX was called into question by recent studies. In the COIN trial[24], the addition of cetuximab to oxaliplatin-based chemotherapy did not result in a significant improvement in the primary end point OS (median OS, 17.0 mo *vs* 17.9 mo, $P = 0.68$), or the secondary end point PFS (median PFS, 8.6 mo in both arms, $P = 0.60$). Only the response rate was significantly increased by the addition of cetuximab (64% *vs* 57%, $P = 0.049$). Then in the NORDIC-Ⅶ trial[29], patients with wild type KRAS derived no benefit from cetuximab plus FLOX (fluorouracil, leucovorin, and oxaliplatin) in the primary end point PFS (median PFS, 8.7 mo *vs* 7.9 mo, $P = 0.66$), or in the secondary end point OS (median OS, 22.0 mo *vs* 20.1 mo, $P = 0.48$). Considering these two clinical trials, the national comprehensive cancer network (NCCN) guidelines have removed the regimen of cetuximab plus FOLFOX from first-line treatment since the 2012 version. However, the 2012 European Society for Medical Oncology (ESMO) guidelines retained this regimen and assigned its highest level of recommendation (Recommendation +++) because of defects in the COIN trial and the NORDIC-Ⅶ trial. In the COIN trial[24], cetuximab plus capecitabine and oxaliplatin (XELOX) induced more severe diarrhea, and the dose of capecitabine had to be reduced by 15%. Additionally, in recent subgroup analysis, a significant improvement in PFS with cetuximab was observed in all-wild-type (KRAS, NRAS, BRAF) patients treated with fluorouracil-based therapy (HR = 0.72, 95%CI: 0.53-0.98, $P = 0.037$) but not in those treated with capecitabine-based therapy (HR = 1.02, 95%CI: 0.82-1.26, $P = 0.88$). Patients with no more than one metastatic site also exhibited improved PFS with cetuximab (HR = 0.73, 95%CI: 0.55-0.97, $P = 0.03$). In the NORDIC-Ⅶ trial[29], fluorouracil was given as a bolus infusion instead of a continued infusion, which was not exactly the same as the FOLFOX regimen. In conclusion, the regimen of cetuximab combined with FOLFOX has been proven to be reliable as a first-line treatment for CLM.

Panitumumab combined with chemotherapy is also an important first-line treatment for CLM (details in Table 1). The PRIME trial showed that panitumumab plus FOLFOX4 significantly improved PFS in KRAS exon 2 wild type patients[30] (median PFS, 9.6 mo *vs* 8.0 mo, HR = 0.80, $P = 0.02$) and all RAS wild type patients (mentioned above). However, the regimen of panitumumab plus FOLFIRI was not analyzed in a reliable randomized controlled clinical trial as a first-line treatment, and its efficacy was mainly inferred from the results of clinical trials where it was used as a second-line treatment. Therefore, panitumumab plus FOLFIRI was only listed as an alternative in the NCCN guidelines (V. 2013) and was not recommended in ESMO guidelines (V. 2012). Taking into account the differences between populations receiving first-line and second-line treatment, the combination of chemotherapy with panitumumab should be carefully chosen when used in first-line treatment.

Anti-VEGF antibody as a first-line treatment: The anti-VEGF antibody bevacizumab has been widely used as a first-line treatment for CLM, and achieves good effects (details in Table 1). Kabbinavar *et al*[31] pooled data from patients receiving bevacizumab plus fluorouracil/leucovorin from three clinical trials, and reported significant improvements in response rate (34.1% *vs* 24.5%, $P = 0.019$), PFS (median PFS, 8.8 mo *vs* 5.6 mo, HR = 0.63, $P < 0.0001$) and OS (median OS, 17.9 mo *vs* 14.6 mo, HR = 0.74, $P = 0.008$). The pivotal AVF2107g trial[32] proved that the addition of bevacizumab to IFL (irinotecan, fluorouracil, and leucovorin) resulted in a statistically significant and clinically meaningful improvement in the primary end point, OS (median OS, 20.3 mo *vs* 15.6 mo, HR = 0.66, $P < 0.001$), and the secondary end point, PFS (median PFS, 10.6 mo *vs* 6.2 mo, HR = 0.54, $P < 0.001$).

Table 1 Phase Ⅱ/Ⅲ clinical trials of targeted agents in combination with chemotherapy as first-line treatments for metastatic colorectal cancer

Clinical trial (reporters)	Year	Primary end point	Population	Regimen	Patient number	Median PFS (mo)	HR *P* value (95%CI)	Median OS (mo)	HR *P* value (95%CI)	Response rates	OR *P* value (95%CI)
CRYSTAL[26]	2009	PFS	ITT	FOLFIRI + Cet	599	8.9	HR = 0.85	19.9	HR = 0.93	46.90%	OR = 1.403
				FOLFIRI	599	8.0	[a]*P* = 0.048	18.6	*P* = 0.31	38.70%	[a]*P* = 0.0038
			KRAS WT	FOLFIRI + Cet	316	9.9	HR = 0.696	23.5	HR = 0.796	57.30%	OR = 2.069
			subgroup	FOLFIRI	350	8.4	[a]*P* = 0.0012	20	[a]*P* = 0.0093	39.70%	[a]*P* < 0.001
			KRAS MT	FOLFIRI + Cet	214	7.4	HR = 1.171	16.2	HR = 1.035	31.30%	OR = 0.822
			subgroup	FOLFIRI	183	7.7	*P* = 0.26	16.7	*P* = 0.75	36.10%	*P* = 0.35
OPUS[27]	2009	Response rates	ITT	FOLFOX4 + Cet	169	7.2	HR = 0.931	18.3	HR = 1.015	46%	OR = 1.516
				FOLFOX4	168	7.2	*P* = 0.62	18.0	*P* = 0.91	36%	*P* = 0.064
			KRAS WT	FOLFOX4 + Cet	82	8.3	HR = 0.567	22.8	HR = 0.855	57%	OR = 2.551
			subgroup	FOLFOX4	97	7.2	[a]*P* = 0.0064	18.5	*P* = 0.39	34%	[a]*P* = 0.0027
			KRAS MT	FOLFOX4 + Cet	77	5.5	HR = 1.72	13.4	HR = 1.290	34%	OR = 0.459
			subgroup	FOLFOX4	59	8.6	[a]*P* = 0.0153	17.5	*P* = 0.20	53%	[a]*P* = 0.029
COIN[24]	2011	OS	KRAS WT	FOLFOX/XELOX + Cet	362	8.6	HR = 0.96	17.0	HR = 1.04	64%	OR = 1.35
							P = 0.60		*P* = 0.68		[a]*P* = 0.049
				FOLFOX/XELOX	367	8.6		17.9		57%	
			KRAS WT	FOLFOX + Cet	117	9.0	HR = 0.77	-	-	-	-
				FOLFOX	127	9.2	*P* = 0.056				
			KRAS WT	XELOX + Cet	245	8.4	HR = 1.06	-	-	-	-
				XELOX	240	8.0	*P* = 0.56				
			KRAS MT	FOLFOX/XELOX + Cet	297	-	-	13.6	HR = 0.98	-	-
									P = 0.80		
				FOLFOX/XELOX	268			14.8			
NORDIC-Ⅶ[29]	2012	PFS	ITT	FLOX + Cet	194	8.3	HR = 0.89	19.7	HR = 1.06	49%	OR = 1.35
							P = 0.31		*P* = 0.67		*P* = 0.15
				Intermittent FLOX + Cet	187	7.3	Not reported	20.3	HR = 1.03	47%	Not report
									P = 0.79		
				Nordic FLOX	185	7.9	Control	20.4	Control	41%	Control
			KRAS WT	FLOX + Cet	97	7.9	HR = 1.07	20.1	HR = 1.14	46%	OR = 0.96
			subgroup				*P* = 0.66		*P* = 0.48		*P* = 0.89
				Intermittent FLOX + Cet	109	7.5	Not reported	21.4	HR = 1.08	51%	OR = 0.96
									P = 0.66		*P* = 0.89
				Nordic FLOX	97	8.7	Control	22.0	Control	47%	Control
			KRAS MT	FLOX + Cet	72	9.2	HR = 0.71	21.1	HR = 1.03	49%	OR = 1.44
			subgroup				*P* = 0.07		*P* = 0.89		*P* = 0.31
				Intermittent FLOX + Cet	65	7.2	Not reported	20.5	HR = 1.04	42%	Not report
									P = 0.84		
				Nordic FLOX	58	7.8	Control	20.4	Control	40%	Control
PRIME[30]	2010	PFS	KRAS WT	FOLFOX4 + Pan	325	9.6	HR = 0.80	23.9	HR = 0.83	55%	OR = 1.35
				FOLFOX4	331	8.0	[a]*P* = 0.02	19.7	*P* = 0.072	48%	*P* = 0.068
			KRAS MT	FOLFOX4 + Pan	221	7.3	HR = 1.29	15.5	HR = 1.24	40%	-
				FOLFOX4	219	8.8	[a]*P* = 0.02	19.3	*P* = 0.068	40%	
AVF2107g[32]	2004	OS	ITT	IFL + Bev	402	10.6	HR = 0.54	20.3	HR = 0.66	44.80%	[a]*P* = 0.004
				IFL	411	6.2	[a]*P* < 0.001	15.6	[a]*P* < 0001	34.80%	
NO16966[33]	2008	PFS	ITT	FOLFOX4/ XELOX + Bev	699	9.4	HR = 0.83	21.3	HR = 0.89	38%	OR = 1.00
							[a]*P* = 0.0023		*P* = 0.0769		*P* = 0.99
				FOLFOX4/ XELOX	701	8.0		19.9		38%	
			Subgroup	FOLFOX4 + Bev	349	9.4	HR = 0.89	21.2	HR = 0.94	-	-
				FOLFOX4	351	8.6	97.5%CI: 0.73-1.08	20.3	97.5%CI: 0.75-1.16		
			Subgroup	XELOX + Bev	350	9.3	HR = 0.77	21.4	HR = 0.84	-	-
				XELOX	350	7.4	97.5%CI: 0.63-0.94	19.2	97.5%CI: 0.68-1.04		
CAIRO-2[67]	2009	PFS	ITT	XELOX + Bev + Cet	368	9.4	HR = 1.22	19.4	HR = 1.15	52.70%	*P* = 0.49
							[a]*P* = 0.01		*P* = 0.16		
				XELOX + Bev	368	10.7		20.3		50%	
			KRAS WT	XELOX + Bev + Cet	158	10.5	*P* = 0.30	21.8	*P* = 0.64	61.40%	*P* = 0.06
			subgroup								
				XELOX + Bev	156	10.6		22.4		50.00%	
			KRAS MT	XELOX + Bev + Cet	98	8.1	[a]*P* = 0.003	17.2	[a]*P* = 0.03	45.90%	[a]*P* = 0.03
			subgroup								
				XELOX + Bev	108	12.5		24.9		59.20%	

PACCE[68]	2009	PFS	ITT	Ox-CT + Bev + Pan	413	10.0	HR = 1.27 95%CI: 1.06-1.52	19.4	HR = 1.43 95%CI: 1.11-1.83	46%	OR = 0.92 95%CI: 0.70-1.22
				Ox-CT + Bev	410	11.4		24.5		48%	
			KRAS WT subgroup	Ox-CT + Bev + Pan	201	9.8	HR = 1.36 95%CI: 1.04-1.77	20.7	HR = 1.89 95%CI: 1.30-2.75 ^aP = 0.045	50%	-
				Ox-CT + Bev	203	11.5		24.5		56%	
			KRAS MT subgroup	Ox-CT + Bev + Pan	135	10.4	HR = 1.25 95%CI: 0.91-1.71	19.3	HR = 1.02 95%CI: 0.67-1.54	47%	-
				Ox-CT + Bev	125	11.0		19.3		44%	
			ITT	Iri-CT + Bev + Pan	115	10.1	HR = 1.19 95%CI: 0.79-1.79	20.7	HR = 1.42 95%CI: 0.77-2.62	43%	OR = 1.11 95%CI: 0.65- 1.90
				Iri-CT + Bev	115	11.7		20.5		40%	
			KRAS WT subgroup	Iri-CT + Bev + Pan	57	10.0	HR = 1.50 95%CI: 0.82-2.76	NE	HR = 1.28 95%CI: 0.50-3.25 P = 0.445	54%	-
				Iri-CT + Bev	58	12.5		19.8		48%	
			KRAS MT subgroup	Iri-CT + Bev + Pan	47	8.3	HR = 1.19 95%CI: 0.65-2.21	17.8	HR = 2.14 95%CI: 0.82-5.59	30%	-
				Iri-CT + Bev	39	11.9		20.5		38%	

^aP < 0.05. PFS: Progress-free survival; OS: Overall survival; ITT: Intent to treat; WT: Wild type; MT: Mutant type; NE: Not estimatable; KRAS: KRAS exon 2, codons 12 and 13; FOLFOX: Fluorouracil, leucovorin, and oxaliplatin; XELOX: Capecitabine and oxaliplatin; FLOX: Fluorouracil, leucovorin, and oxaliplatin; Ox-CT: Oxaliplatin-based chemotherapy; FOLFIRI: Irinotecan, fluorouracil, and leucovorin; IFL: Irinotecan, fluorouracil, and leucovorin; Iri-CT: Irinotecan-based chemotherapy; Cet: Cetuximab; Pan: Panitumumab; Bev: Bevacizumab.

However, the regimen of bevacizumab combined with oxaliplatin-based chemotherapy remains controversial. The large, double-blind, placebo- controlled clinical trial NO16966[33] involved 1401 patients with unresectable CLM, and compared bevacizumab-plus-oxaliplatin-based chemotherapy (FOLFOX, XELOX) with chemotherapy alone. The addition of bevacizumab was associated with a more modest increase in the primary end point, PFS, of 1.4 mo (median PFS, 9.4 mo *vs* 8.0 mo, HR = 0.83, P = 0.0023). But no benefit was observed in the secondary end point OS (median OS, 21.3 mo *vs* 19.9 mo, HR = 0.89, P = 0.077). More attention should be paid on the results of the subgroup analysis, which indicated that bevacizumab was only associated with significant improvements in PFS when added to XELOX (HR = 0.77, P = 0.0026) but not FOLFOX (HR = 0.89, P = 0.1871). Another recent meta-analysis[34] came to a similar conclusion. This meta-analysis included six randomized clinical trials with a total of 3060 patients, and found that bevacizumab resulted in significant improvements in PFS (HR = 0.72, 95%CI: 0.66-0.78, P < 0.00001) and OS (HR = 0.84, 95%CI: 0.77-0.91, P < 0.00001). However, the advantage in OS was limited to irinotecan-based regimens (HR = 0.78, 95%CI: 0.68-0.89, P = 0.0002). Neither fluorouracil nor oxaliplatin-based treatments presented statistically significant data. Thus, bevacizumab combined with oxaliplatin-based chemotherapy is not currently the best choice as a first-line treatment.

Conversion therapy

Approximately 80%-90% of patients with CLM have unresectable metastatic liver disease at presentation[35]. However, some of these patients might become resectable after response to conversion chemotherapy. Such patients are referred to as Group 1 patients in the ESMO guidelines. For these patients, the treatment aim should be achieving maximum tumor shrinkage to create an opportunity for radical surgery[36]. Therefore, short-term indicators should be set as the end points of conversion therapy, such as resection rate, response rate, and rate of early tumor shrinkage (ETS).

ETS is a novel short-term indicator suitable for conversion therapy. The shrinkage of tumor size is directly associated with the ability to operate, and has also been proven to be associated with long-term survival. Giessen *et al*[37] defined ETS as a ⩾ 20% decrease in maximum tumor diameter between baseline and seven weeks of treatment, and found that patients with ETS had a more favorable outcome in terms of PFS (9.9 mo *vs* 6.1 mo, P = 0.029) and OS (27.5 mo *vs* 17.8 mo, P = 0.002). Modest *et al*[38] observed ETS ⩾ 20% in 59% of patients with KRAS wild type tumors and indicated that patients with ETS ⩾ 20% exhibited increases in their overall response rate (82% *vs* 19%, P < 0.001), PFS (8.9 mo *vs* 4.7 mo, P < 0.001) and OS (31.6 mo *vs* 15.8 mo, P = 0.005). These studies suggested that ETS was an effective predictor of the success of conversion therapy.

In conversion therapy, the clinical application of anti-EGFR treatment is also common and effective. In the CRYSTAL trial[15,26], patients in ITT population had a higher response rate (46.9% *vs* 38.7%, P = 0.004) and a higher R0 resection rate (4.8% *vs* 1.7%) with the addition of cetuximab. For patients with hepatic-only metastases, cetuximab plus FOLFIRI was associated with a 77% response rate. The OPUS trial[27,28] also showed that for patients with wild type KRAS, cetuximab plus FOLFOX4 was associated with significantly higher best overall response (57% *vs* 34%, OR = 2.551, P = 0.0027). A recent study by Ye *et al*[39] compared cetuximab plus chemotherapy with chemotherapy alone as a first-line treatment for patients with initially unresectable CLM. In this trial, the primary end point was set as the rate of patient conver-

sion to resection for liver metastases. The results showed that for ITT population, cetuximab plus chemotherapy significantly improved the rate of patient conversion to resection (28.6% *vs* 13.2%, $P = 0.027$), R0 resection rate (25.7% *vs* 7.4%, $P = 0.004$) and response rate (57.1% *vs* 29.4%, $P = 0.001$). Long-term outcomes were also improved, such as PFS (median PFS, 10.2 mo *vs* 5.8 mo, $P = 0.004$) and OS (median OS, 30.9 mo *vs* 21.0 mo, $P = 0.013$).

For anti-VEGF treatment, the AVF2107g trial[32] showed a significant improvement in response rate (44.8% *vs* 34.8%, $P = 0.004$) with bevacizumab plus IFL. But the NO16966 trial[33] came to a negative conclusion that bevacizumab plus oxaliplatin-based chemotherapy did not improve the response rate (47% *vs* 49%, OR = 0.90, 97.5%CI: 0.71 to 1.14, $P = 0.31$). The meta-analysis[34] mentioned previously also suggested no improvement in response rate (OR = 1.12, 95%CI: 0.94-1.33, $P = 0.21$) with the addition of bevacizumab as a first-line treatment. Based on these results, some researchers held that bevacizumab was not suitable for conversion therapy. To investigate this suspicion, a phase Ⅲ clinical trial FIRE-Ⅲ comparing FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab as first-line treatment was reported at the 2013 ASCO Annual Meeting[40]. For ITT population, there was no significant difference between the cetuximab group and the bevacizumab group in primary endpoint response rate (62% *vs* 58%, $P = 0.183$). But for the evaluable population, cetuximab led to a significant advantage over bevacizumab (72% *vs* 63%, $P = 0.017$). At the secondary end point no difference was observed in PFS, but a 3.7 mo improvement in OS was observed in the cetuximab group (28.7 mo *vs* 25 mo, $P < 0.017$). In this clinical trial, cetuximab exhibited an advantage over bevacizumab in conversion therapy. However, the evaluable population decreased by 66 patients (11.1%) compared with the ITT population. The final results on exit bias should be emphasized. And in an update presented at the 2013 ESMO Annual Meeting[41], the "new" *RAS* mutations were tested. The results showed that all RAS wild-type patients had a longer median OS with FOLFIRI plus cetuximab, leading to a more significant improvement of 7.5 mo (33.1 mo *vs* 25.6 mo, HR = 0.70, $P = 0.011$), compared with 3.7 mo in patients with only KRAS exon 2 wild type. This study again confirmed the predictive role of "new" RAS. All previous clinical trials came to a conclusion that bevacizumab was not preferred for conversion therapy. However, bevacizumab is still considered acceptable because it cannot be known in advance whether resectability will be achieved, and bevacizumab provided a benefit in terms of long-term survival.

Targeted therapy after progression

Numerous clinical trials have proven the benefits of second-line targeted therapy for patients who had first-line progression and did not receive targeted agents as first-line treatment[42-46]. However, for patients who received first-line targeted therapy, it is unclear whether and how to use targeted agents continuously.

Some studies have suggested that the continuation of bevacizumab following progression on first-line bevacizumab could provide benefits. In the TML trial[47], patients with CLM who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy with or without bevacizumab. The results showed that continuing on bevacizumab led to a modest improvement in OS (median OS, 11.2 mo *vs* 9.8 mo, HR = 0.81, $P = 0.0062$). PFS was also improved by 1.6 mo (median PFS, 5.7 mo *vs* 4.1 mo, HR = 0.68, $P < 0.0001$). Another study[48] retrospectively analyzed 573 patients from the US Oncology iKnowMed electronic medical record system and showed that continuous bevacizumab after progression was associated with longer OS (HR = 0.76, 95%CI: 0.61-0.95) and longer post-progression OS (HR = 0.74, 95%CI: 0.60-0.93) in multivariate analysis. Some single-arm studies[49,50] also showed a median post-progression PFS of 5 to 5.6 mo and a median OS of 13.9 to 15.4 mo with continuous bevacizumab.

For anti-EGFR antibodies, NCCN guidelines (V. 2013) concluded that if cetuximab or panitumumab were used as the initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy. This conclusion might be hasty because of the lack of evidence from related clinical trials. The ongoing clinical trial CAPRI was the first study to investigate a treatment strategy of continuing cetuximab after first-line progress. KRAS wild type patients with CLM were given first-line cetuximab plus FOLFIRI and were randomized at progression (1:1) to receive FOLFOX alone or in combination with cetuximab. The results of this trial were expected to resolve this controversy.

The FIRE-Ⅲ trial also provided evidence for selecting second-line treatments. After first-line progression, 48.2% patients in cetuximab group received bevacizumab instead, and 14.4% patients continued on cetuximab. In bevacizumab group, 42.9% patients changed into cetuximab, and 17.6% patients continued on bevacizumab. The allocation of second-line treatment was balanced ($P = 0.347$). As previously mentioned, cetuximab plus FOLFIRI had advantages in terms of OS (28.7 mo *vs* 25 mo, $P < 0.017$), but not PFS. This anomaly might be explained that cetuximab and bevacizumab were similar as first-line treatment in PFS and OS. The benefits in terms of OS in cetuximab group mainly came from the second-line bevacizumab treatment, which didn't prolong PFS. This explanation suggested that first-line cetuximab followed by second-line bevacizumab was better than first-line bevacizumab followed by second-line cetuximab. Considering that the FIRE-Ⅲ trial was not over, the final results were expected.

For patients failed with targeted therapy as first-line treatment, the major difficulty lies in identifying the resistance arises from whether cytotoxic chemotherapy or targeted monoclonal antibodies. Although it is reasonable to replace only part of the regimen, delays in treatment and unnecessary economic waste must be taken into account. The selection of second-line or subsequent treatment is a severe test of the experience and judgment of physicians.

PREOPERATIVE CHEMOTHERAPY COMBINED WITH TARGETED AGENTS FOR RESECTABLE METASTATIC COLORECTAL CANCER

Preoperative chemotherapy is believed to be advantageous because of the earlier treatment of micro metastatic disease, the determination of responsiveness to chemotherapy, and the avoidance of local therapy for those patients with early disease progression. However, only a few large randomized clinical trial provided evidence on neoadjuvant chemotherapy for patients with upfront resectable CLM, aside from additional reports from some small-sample and/or single-arm studies[51-53]. The large randomized clinical trial EORTC 40983[54] involved 364 potentially resectable patients with up to four liver metastases and compared FOLFOX4 as perioperative chemotherapy with surgery alone. The results showed a significantly higher 3-year PFS rate (35.4% *vs* 28.1%, HR = 0.79, $P = 0.058$) in patients receiving perioperative chemotherapy. However, a recent update of this trial[55] reported that the difference of OS after a median follow up of 8.5 years was not significant, with a 5-year OS of approximately 50% in both groups. In addition to the lack of benefit for long-term survival, this trial was not designed to compare preoperative chemotherapy alone, which made it difficult to prove the effect of preoperative chemotherapy. Adam *et al*[56] also reported the negative result that preoperative chemotherapy for metachronous CLM provided no benefit in long-term OS and PFS.

In terms of preoperative chemotherapy combined with targeted agents, the NCCN and ESMO guidelines gave no strong evidence. Only a few small-sample, single-arm studies were available. Gruenberger *et al*[57] reported a non-randomized clinical trial evaluating bevacizumab plus XELOX as a preoperative therapy for patients with potential resectable CLM. After preoperative therapy with bevacizumab, they observed a complete response rate of 8.9%, a partial response rate of 64.3%, and a progressive disease rate of only 5.4%. No interference in liver regeneration was found after resection. There are also a number of studies concentrating on locally advanced rectal cancer[58-62], but these results were not suitable for patients with common colon cancer, because of the differences between colon and rectal cancer in route of metastasis, surgical strategy, application of radiotherapy and so on.

The risks of preoperative targeted therapy should be taken into account. These risks mainly lie in missing the window of opportunity for resection; the achievement of a complete response, making it difficult to identify areas for resection; and potential liver toxicity, making resection impossible. It is also difficult to determine the best cycles of preoperative therapy. The results of EORTC 40983 and a number of other trials suggested that preoperative chemotherapy plus targeted agents might be useful. More detailed evidences are needed to enable physicians to weigh the advantages and disadvantages of this approach.

CHEMOTHERAPY COMBINED WITH TARGETED AGENTS AS POSTOPERATIVE ADJUVANT TREATMENT

For patients with resected stage Ⅱ/Ⅲ colorectal cancer, postoperative adjuvant treatment with targeted agents has been proven to be useless or even harmful. In the N0147 trial[63], cetuximab plus FOLFOX significantly increased grade 3/4 adverse events (72.5% *vs* 52.3%, odds ratio, OR = 2.4, $P < 0.001$), providing no benefit in primary end point 3-year PFS rate (65.0% *vs* 67.1%, HR = 1.12, $P = 0.38$). In the interim analysis of the ongoing PETACC-8 trial reported at the 2012 ESMO Annual Meeting, cetuximab plus FOLFOX provided no benefit for KRAS wild-type patients in disease-free survival (DFS, HR = 1.047, $P = 0.6562$) or OS (HR = 1.092, $P = 0.5583$). Worse DFS was observed with cetuximab in patients aged > 70 years ($n = 149$, HR = 1.97, $P = 0.051$), in females ($n = 666$, HR = 1.45, $P = 0.031$) and in patients with right-sided colon cancer ($n = 570$, HR = 1.40, $P = 0.043$). The NSABP C-08 trial[64] reported negative results with the addition of bevacizumab to FOLFOX in 3-year DFS (77.4% *vs* 75.5%, HR = 0.89, $P = 0.15$). The results of the AVANT trial[65] also failed to show benefits from bevacizumab plus oxaliplatin-based chemotherapy in DFS, with an even worse outcome for the FOLFOX-combined regimen in terms of OS (HR = 1.27, 95%CI: 1.03-1.57, $P = 0.02$). The four large randomized clinical trials above came to a conclusion that targeted agents had no role in the adjuvant treatment of resected stage Ⅱ/Ⅲ colorectal cancer.

For resected CLM, the role of postoperative adjuvant chemotherapy remains unclear[36]. However, postoperative chemotherapy with FOLFOX plus bevacizumab is often administered despite the lack of data supporting this regimen. In the interim analysis of the Dutch HEPATICA trial[66] reported at the 2011 ASCO Annual Meeting, bevacizumab plus capecitabine and oxaliplatin (CAPOX) as postoperative adjuvant chemotherapy provided no significant benefit compared with CAPOX alone in 2-year DFS rate (70% *vs* 52%, $P = 0.074$), and exhibited no significant differences in toxicity. For patients who received targeted therapy and responded before surgery, it is reasonable to continue targeted therapy as a postoperative adjuvant treatment. However, for upfront resected CLM without preoperative targeted therapy, postoperative targeted therapy is not recommended, based on the negative results of trials N0147, PETACC-8, NSABP C-08 and AVANT.

COMBINATION THERAPY WITH MORE THAN ONE TARGETED AGENT

As anti-EGFR antibodies and anti-VEGF antibodies exert their anti-tumor effects in different mechanisms, their combination should theoretically lead to greater effects. Preclinical trials also demonstrated that the com-

bination of more than one targeted agent led to stronger inhibition of the downstream signaling pathways compared with single treatment. However, most clinical trials showed no advantages and in some cases even showed disadvantages of the combination of anti-EGFR and anti-VEGF antibodies as first-line treatment. The CAIRO-2 trial[67] compared cetuximab plus bevacizumab with bevacizumab alone based on the XELOX regimen. For the ITT population, the combination of cetuximab with bevacizumab led to shorter PFS (median PFS, 9.4 mo *vs* 10.7 mo, $P = 0.01$). There was no differences in OS (median OS, 19.4 mo *vs* 20.3 mo, $P = 0.16$) or response rates (52.7% *vs* 50.0%, $P = 0.49$). Subgroup analysis also showed no difference for KRAS wild type patients in response rate (61.4% *vs* 50%, $P = 0.06$), PFS (median PFS, 10.5 mo *vs* 10.6 mo, $P = 0.30$) or OS (median OS, 21.8 mo *vs* 22.4 mo, $P = 0.64$). Similar results were observed in the PACCE trial[68] with the addition of panitumumab to regimens containing bevacizumab and oxaliplatin/irinotecan. In patients receiving panitumumab plus bevacizumab and oxaliplatin-based chemotherapy, the addition of panitumumab significantly decreased the PFS (median PFS, 10.0 mo *vs* 11.4 mo, HR = 1.27, 95%CI: 1.06-1.52) and OS (median OS, 19.4 mo *vs* 24.5 mo, HR = 1.43, 95%CI: 1.11-1.83). In patients receiving irinotecan-based chemotherapy, no differences were observed between the two groups in their PFS or OS.

The combination of more than one targeted agent as a maintenance treatment is also controversial. The GERCOR-DREAM trial[69], reported at the 2012 ASCO Annual Meeting, provided positive results that the addition of erlotinib to bevacizumab as a maintenance treatment significantly improved the duration of maintenance PFS (median MT-PFS, 5.8 mo *vs* 4.6 mo, HR = 0.73, $P = 0.005$) after first-line treatment in CLM. Although the OS data were not mature, they were promising and warranted continuation of the trial. However, the similar Nordic ACT trial[70] reported opposite results that the addition of erlotinib to bevacizumab as a maintenance treatment did not significantly improve PFS (median PFS, 5.73 mo *vs* 4.23 mo, HR = 0.79, $P = 0.19$) or OS (median OS, 21.5 mo *vs* 22.8 mo, HR = 0.88, $P = 0.51$). Despite their conflicting results, these two trials provided novel research ideas.

The clinical trials described above raise the questions that whether cytotoxic agents interfere with targeted agents, in which phase combinations of targeted agents should be used, and what are the differences between experiments in vivo and in vitro. Although it is not presently recommended to combine more than one targeted agent, more mechanistic research is meaningful and valuable. This could also lead to a breakthrough in understanding the development of resistance to targeted agents.

CONCLUSION

Surgical resection undoubtedly remains the gold standard for the treatment of resectable CLM. However, a well-coordinated multidisciplinary approach is more important to achieving optimal outcomes for patients with CLM. Targeted therapy with monoclonal antibodies is becoming increasingly important for patients with CLM, with new findings and doubts continuing to emerge regarding these relatively new agents. For patients with the *KRAS G13D* mutation, anti-EGFR therapy might have positive effects. The "new" RAS mutations were considered to be predictors of poor responsiveness to anti-EGFR therapy. The efficacy of cetuximab plus FOLFOX is likely to be reliable, but bevacizumab plus oxaliplatin-based chemotherapy remains controversial. Studies suggest that bevacizumab is not suitable for conversion therapy. More evidence is needed to confirm the utility of targeted therapy for neoadjuvant and adjuvant treatment. Combination therapy with more than one targeted agent is not currently recommended.

In the era of personalized cancer medicine, current research goals should be focused on further defining the roles of targeted agents at different stages of disease and treatment, as well as optimizing their sequencing with other treatments. More clinical trials are necessary to answer the remaining questions. Treatment regimens should be more accurate and personalized based on novel molecular markers. The growing number of molecular predictors has led to the conjecture that tumor classification will soon be based on molecular markers rather than localization or histology. In the future, every patient will be genotyped for several markers and treated with appropriate targeted agents. This may be the best way to approach the tumor heterogeneity among patients. However, some studies[71] remind us that heterogeneity also exists within a single tumor, which makes it difficult to describe the molecular characteristics of the whole tumor based on the part of the tissue analyzed by biopsy. A map of all tumor heterogeneity may be useful and necessary. In this increasingly complex era, surgeons and physicians will play central roles in making decisions by collecting, evaluating and using evidence, rather than based on their personal experience.

REFERENCES

1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **Ferlay J**, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010; **46**: 765-781 [PMID: 20116997 DOI: 10.1016/j.ejca.2009.12.014]

3 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]

4 **Chen W**, Zheng R, Zhang S, Zhao P, Li G, Wu L, He J. Report of incidence and mortality in China cancer registries, 2009. *Chin J Cancer Res* 2013; **25**: 10-21 [PMID: 23372337 DOI: 10.3978/j.issn.1000-9604.2012.12.04]

5 **Van Cutsem E**, Nordlinger B, Adam R, Köhne CH, Pozzo C, Poston G, Ychou M, Rougier P. Towards a pan-European consensus on the treatment of patients with colorectal liver

metastases. *Eur J Cancer* 2006; **42**: 2212-2221 [PMID: 16904315 DOI: 10.1016/j.ejca.2006.04.012]
6 **Yoo PS**, Lopez-Soler RI, Longo WE, Cha CH. Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. *Clin Colorectal Cancer* 2006; **6**: 202-207 [PMID: 17026789 DOI: 10.3816/CCC.2006.n.036]
7 **Wang CC**, Li J. An update on chemotherapy of colorectal liver metastases. *World J Gastroenterol* 2012; **18**: 25-33 [PMID: 22228967 DOI: 10.3748/wjg.v18.i1.25]
8 **Muratore A**, Zorzi D, Bouzari H, Amisano M, Massucco P, Sperti E, Capussotti L. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? *Ann Surg Oncol* 2007; **14**: 766-770 [PMID: 17103261 DOI: 10.1245/s10434-006-9146-1]
9 **Hayashi M**, Inoue Y, Komeda K, Shimizu T, Asakuma M, Hirokawa F, Miyamoto Y, Okuda J, Takeshita A, Shibayama Y, Tanigawa N. Clinicopathological analysis of recurrence patterns and prognostic factors for survival after hepatectomy for colorectal liver metastasis. *BMC Surg* 2010; **10**: 27 [PMID: 20875094 DOI: 10.1186/1471-2482-10-27]
10 **Kopetz S**, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, Grothey A, Vauthey JN, Nagorney DM, McWilliams RR. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009; **27**: 3677-3683 [PMID: 19470929 DOI: 10.1200/jco.2008.20.5278]
11 **Baselga J**, Rosen N. Determinants of RASistance to anti-epidermal growth factor receptor agents. *J Clin Oncol* 2008; **26**: 1582-1584 [PMID: 18316790 DOI: 10.1200/jco.2007.15.3700]
12 **Khambata-Ford S**, Garrett CR, Meropol NJ, Basik M, Harbison CT, Wu S, Wong TW, Huang X, Takimoto CH, Godwin AK, Tan BR, Krishnamurthi SS, Burris HA, Poplin EA, Hidalgo M, Baselga J, Clark EA, Mauro DJ. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol* 2007; **25**: 3230-3237 [PMID: 17664471 DOI: 10.1200/jco.2006.10.5437]
13 **Roth AD**, Tejpar S, Delorenzi M, Yan P, Fiocca R, Klingbiel D, Dietrich D, Biesmans B, Bodoky G, Barone C, Aranda E, Nordlinger B, Cisar L, Labianca R, Cunningham D, Van Cutsem E, Bosman F. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol* 2010; **28**: 466-474 [PMID: 20008640 DOI: 10.1200/jco.2009.23.3452]
14 **Tol J**, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. *N Engl J Med* 2009; **361**: 98-99 [PMID: 19571295 DOI: 10.1056/NEJMc0904160]
15 **Van Cutsem E**, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zubel A, Celik I, Rougier P, Ciardiello F. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; **29**: 2011-2019 [PMID: 21502544 DOI: 10.1200/jco.2010.33.5091]
16 **Amado RG**, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD, Chang DD. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 1626-1634 [PMID: 18316791 DOI: 10.1200/jco.2007.14.7116]
17 **Dahabreh IJ**, Terasawa T, Castaldi PJ, Trikalinos TA. Systematic review: Anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer. *Ann Intern Med* 2011; **154**: 37-49 [PMID: 21200037 DOI: 10.7326/0003-4819-154-1-201101040-00006]
18 **De Roock W**, Jonker DJ, Di Nicolantonio F, Sartore-Bianchi A, Tu D, Siena S, Lamba S, Arena S, Frattini M, Piessevaux H, Van Cutsem E, O'Callaghan CJ, Khambata-Ford S, Zalcberg JR, Simes J, Karapetis CS, Bardelli A, Tejpar S. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA* 2010; **304**: 1812-1820 [PMID: 20978259 DOI: 10.1001/jama.2010.1535]
19 **Tejpar S**, Celik I, Schlichting M, Sartorius U, Bokemeyer C, Van Cutsem E. Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. *J Clin Oncol* 2012; **30**: 3570-3577 [PMID: 22734028 DOI: 10.1200/jco.2012.42.2592]
20 **Mao C**, Huang YF, Yang ZY, Zheng DY, Chen JZ, Tang JL. KRAS p.G13D mutation and codon 12 mutations are not created equal in predicting clinical outcomes of cetuximab in metastatic colorectal cancer: a systematic review and meta-analysis. *Cancer* 2013; **119**: 714-721 [PMID: 22972628 DOI: 10.1002/cncr.27804]
21 **Peeters M**, Douillard JY, Van Cutsem E, Siena S, Zhang K, Williams R, Wiezorek J. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. *J Clin Oncol* 2013; **31**: 759-765 [PMID: 23182985 DOI: 10.1200/jco.2012.45.1492]
22 **Douillard JY**, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Williams R, Rong A, Wiezorek J, Sidhu R, Patterson SD. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013; **369**: 1023-1034 [PMID: 24024839 DOI: 10.1056/NEJMoa1305275]
23 **Schwartzberg L**, Rivera F, Karthaus M, Fasola G, Canon J, Yu H, Oliner K, Go W. Analysis of KRAS/NRAS mutations in PEAK: A randomized phase II study of FOLFOX6 plus panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC). *J Clin Oncol* 2013; **31** Suppl 15: Abstract 3631
24 **Maughan TS**, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, Idziaszczyk S, Harris R, Fisher D, Kenny SL, Kay E, Mitchell JK, Madi A, Jasani B, James MD, Bridgewater J, Kennedy MJ, Claes B, Lambrechts D, Kaplan R, Cheadle JP. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; **377**: 2103-2114 [PMID: 21641636 DOI: 10.1016/s0140-6736(11)60613-2]
25 **Samowitz WS**, Sweeney C, Herrick J, Albertsen H, Levin TR, Murtaugh MA, Wolff RK, Slattery ML. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. *Cancer Res* 2005; **65**: 6063-6069 [PMID: 16024606 DOI: 10.1158/0008-5472.can-05-0404]
26 **Van Cutsem E**, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 1408-1417 [PMID: 19339720 DOI: 10.1056/NEJMoa0805019]
27 **Bokemeyer C**, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zubel A, Koralewski P. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; **27**: 663-671 [PMID: 19114683 DOI: 10.1200/jco.2008.20.8397]
28 **Bokemeyer C**, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zubel A, Celik I, Schlichting M, Koralewski P. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal

cancer: the OPUS study. *Ann Oncol* 2011; **22**: 1535-1546 [PMID: 21228335 DOI: 10.1093/annonc/mdq632]
29 **Tveit KM**, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, Sigurdsson F, Kure E, Ikdahl T, Skovlund E, Fokstuen T, Hansen F, Hofsli E, Birkemeyer E, Johnsson A, Starkhammar H, Yilmaz MK, Keldsen N, Erdal AB, Dajani O, Dahl O, Christoffersen T. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J Clin Oncol* 2012; **30**: 1755-1762 [PMID: 22473155 DOI: 10.1200/jco.2011.38.0915]
30 **Douillard JY**, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; **28**: 4697-4705 [PMID: 20921465 DOI: 10.1200/jco.2009.27.4860]
31 **Kabbinavar FF**, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005; **23**: 3706-3712 [PMID: 15867200 DOI: 10.1200/jco.2005.00.232]
32 **Hurwitz H**, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335-2342 [PMID: 15175435 DOI: 10.1056/NEJMoa032691]
33 **Saltz LB**, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; **26**: 2013-2019 [PMID: 18421054 DOI: 10.1200/jco.2007.14.9930]
34 **Macedo LT**, da Costa Lima AB, Sasse AD. Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. *BMC Cancer* 2012; **12**: 89 [PMID: 22414244 DOI: 10.1186/1471-2407-12-89]
35 **Adam R**. Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases. *Ann Oncol* 2003; **14** Suppl 2: ii13-ii16 [PMID: 12810452]
36 **Schmoll HJ**, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Köhne CH, Labianca R, Price T, Scheithauer W, Sobrero A, Tabernero J, Aderka D, Barroso S, Bodoky G, Douillard JY, El Ghazaly H, Gallardo J, Garin A, Glynne-Jones R, Jordan K, Meshcheryakov A, Papamichail D, Pfeiffer P, Souglakos I, Turhal S, Cervantes A. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Ann Oncol* 2012; **23**: 2479-2516 [PMID: 23012255 DOI: 10.1093/annonc/mds236]
37 **Giessen C**, Laubender RP, Fischer von Weikersthal L, Schalhorn A, Modest DP, Stintzing S, Haas M, Mansmann UR, Heinemann V. Early tumor shrinkage in metastatic colorectal cancer: retrospective analysis from an irinotecan-based randomized first-line trial. *Cancer Sci* 2013; **104**: 718-724 [PMID: 23480146 DOI: 10.1111/cas.12148]
38 **Modest DP**, Laubender RP, Stintzing S, Giessen C, Schulz C, Haas M, Mansmann U, Heinemann V. Early tumor shrinkage in patients with metastatic colorectal cancer receiving first-line treatment with cetuximab combined with either CAPIRI or CAPOX: an analysis of the German AIO KRK 0104 trial. *Acta Oncol* 2013; **52**: 956-962 [PMID: 23244709 DOI: 10.3109/0284186x.2012.752580]
39 **Ye LC**, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, Ye QH, Yu Y, Xu B, Qin XY, Xu J. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013; **31**: 1931-1938 [PMID: 23569301 DOI: 10.1200/jco.2012.44.8308]
40 **Heinemann V**, Fischer von Weikersthal L, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S, Heintges T, Lerchenmueller J, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Mueller S, Schaefer B. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). *J Clin Oncol* 2013; **31** Suppl 18: Abstract LBA3506
41 **Stintzing S**, Jung A, Rossius L. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients (September 27-October 1, 2013; Amsterdam, The Netherlands). *European Cancer Congress* 2013; **2013**: Abstract LBA17
42 **Cunningham D**, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**: 337-345 [PMID: 15269313 DOI: 10.1056/NEJMoa033025]
43 **Sobrero AF**, Maurel J, Fehrenbacher L, Scheithauer W, Abubakr YA, Lutz MP, Vega-Villegas ME, Eng C, Steinhauer EU, Prausova J, Lenz HJ, Borg C, Middleton G, Kröning H, Luppi G, Kisker O, Zubel A, Langer C, Kopit J, Burris HA. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 2311-2319 [PMID: 18390971 DOI: 10.1200/jco.2007.13.1193]
44 **Seymour MT**, Brown SR, Middleton G, Maughan T, Richman S, Gwyther S, Lowe C, Seligmann JF, Wadsley J, Maisey N, Chau I, Hill M, Dawson L, Falk S, O'Callaghan A, Benstead K, Chambers P, Oliver A, Marshall H, Napp V, Quirke P. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. *Lancet Oncol* 2013; **14**: 749-759 [PMID: 23725851 DOI: 10.1016/s1470-2045(13)70163-3]
45 **Giantonio BJ**, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; **25**: 1539-1544 [PMID: 17442997 DOI: 10.1200/jco.2006.09.6305]
46 **Bennouna J**, Borg C, Delord JP, Husseini F, Trillet-Lenoir V, Faroux R, François E, Ychou M, Goldwasser F, Bouché O, Senellart H, Kraemer S, Douillard JY. Bevacizumab combined with chemotherapy in the second-line treatment of metastatic colorectal cancer: results from the phase II BEVACOLOR study. *Clin Colorectal Cancer* 2012; **11**: 38-44 [PMID: 21803002 DOI: 10.1016/j.clcc.2011.05.002]
47 **Arnold D**, Andre T, Bennouna J, Sastre J, Osterlund PJ, Greil R, Van Cutsem E, Von Moos R, Reyes-Rivera I, Bendahmane B, Kubicka S. Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV plus CT: Results of a randomized phase III intergroup study (TML study). *J Clin Oncol* 2012; **30** Suppl 18: Abstract CRA3503

48 **Cartwright TH**, Yim YM, Yu E, Chung H, Halm M, Forsyth M. Survival outcomes of bevacizumab beyond progression in metastatic colorectal cancer patients treated in US community oncology. *Clin Colorectal Cancer* 2012; **11**: 238-246 [PMID: 22658457 DOI: 10.1016/j.clcc.2012.05.005]

49 **Hong YS**, Lee J, Kim KP, Lee JL, Park YS, Park JO, Park SH, Kim SY, Baek JY, Kim JH, Lee KW, Kim TY, Kim TW. Multicenter phase II study of second-line bevacizumab plus doublet combination chemotherapy in patients with metastatic colorectal cancer progressed after upfront bevacizumab plus doublet combination chemotherapy. *Invest New Drugs* 2013; **31**: 183-191 [PMID: 22782485 DOI: 10.1007/s10637-012-9853-3]

50 **Tsutsumi S**, Ishibashi K, Uchida N, Ojima H, Hosouchi Y, Yashuda N, Kigure W, Yamauchi S, Asao T, Ishida H, Kuwano H. Phase II trial of chemotherapy plus bevacizumab as second-line therapy for patients with metastatic colorectal cancer that progressed on bevacizumab with chemotherapy: the Gunma Clinical Oncology Group (GCOG) trial 001 SILK study. *Oncology* 2012; **83**: 151-157 [PMID: 22889925 DOI: 10.1159/000337992]

51 **Bathe OF**, Ernst S, Sutherland FR, Dixon E, Butts C, Bigam D, Holland D, Porter GA, Koppel J, Dowden S. A phase II experience with neoadjuvant irinotecan (CPT-11), 5-fluorouracil (5-FU) and leucovorin (LV) for colorectal liver metastases. *BMC Cancer* 2009; **9**: 156 [PMID: 19457245 DOI: 10.1186/1471-2407-9-156]

52 **Chiappa A**, Bertani E, Makuuchi M, Zbar AP, Contino G, Viale G, Pruneri G, Bellomi M, Della Vigna P, Zampino MG, Fazio N, Travaini ML, Trifirò G, Corbellini C, Andreoni B. Neoadjuvant chemotherapy followed by hepatectomy for primarily resectable colorectal cancer liver metastases. *Hepatogastroenterology* 2009; **56**: 829-834 [PMID: 19621711]

53 **Gruenberger B**, Scheithauer W, Punzengruber R, Zielinski C, Tamandl D, Gruenberger T. Importance of response to neoadjuvant chemotherapy in potentially curable colorectal cancer liver metastases. *BMC Cancer* 2008; **8**: 120 [PMID: 18439246 DOI: 10.1186/1471-2407-8-120]

54 **Nordlinger B**, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; **371**: 1007-1016 [PMID: 18358928 DOI: 10.1016/s0140-6736(08)60455-9]

55 **Nordlinger B**, Sorbye H, Glimelius B, Poston G, Schlag P, Rougier P. EORTC liver metastases intergroup randomized phase III study 40983: long-term survival results. *J Clin Oncol* 2012; **30** Suppl 15: Abstract 3508

56 **Adam R**, Bhangui P, Poston G, Mirza D, Nuzzo G, Barroso E, Ijzermans J, Hubert C, Ruers T, Capussotti L, Ouellet JF, Laurent C, Cugat E, Colombo PE, Milicevic M. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg* 2010; **252**: 774-787 [PMID: 21037433 DOI: 10.1097/SLA.0b013e3181fcf3e3]

57 **Gruenberger B**, Tamandl D, Schueller J, Scheithauer W, Zielinski C, Herbst F, Gruenberger T. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 1830-1835 [PMID: 18398148 DOI: 10.1200/jco.2007.13.7679]

58 **Dewdney A**, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, Tait D, Brown G, Wotherspoon A, Gonzalez de Castro D, Chua YJ, Wong R, Barbachano Y, Oates J, Chau I. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). *J Clin Oncol* 2012; **30**: 1620-1627 [PMID: 22473163 DOI: 10.1200/jco.2011.39.6036]

59 **Gasparini G**, Torino F, Ueno T, Cascinu S, Troiani T, Ballestrero A, Berardi R, Shishido J, Yoshizawa A, Mori Y, Nagayama S, Morosini P, Toi M. A phase II study of neoadjuvant bevacizumab plus capecitabine and concomitant radiotherapy in patients with locally advanced rectal cancer. *Angiogenesis* 2012; **15**: 141-150 [PMID: 22212406 DOI: 10.1007/s10456-011-9250-0]

60 **Helbling D**, Bodoky G, Gautschi O, Sun H, Bosman F, Gloor B, Burkhard R, Winterhalder R, Madlung A, Rauch D, Saletti P, Widmer L, Borner M, Baertschi D, Yan P, Benhattar J, Leibundgut EO, Bougel S, Koeberle D. Neoadjuvant chemoradiotherapy with or without panitumumab in patients with wild-type KRAS, locally advanced rectal cancer (LARC): a randomized, multicenter, phase II trial SAKK 41/07. *Ann Oncol* 2013; **24**: 718-725 [PMID: 23139259 DOI: 10.1093/annonc/mds519]

61 **Landry JC**, Feng Y, Cohen SJ, Staley CA, Whittington R, Sigurdson ER, Nimeiri H, Verma U, Prabhu RS, Benson AB. Phase 2 study of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: ECOG 3204. *Cancer* 2013; **119**: 1521-1527 [PMID: 23288663 DOI: 10.1002/cncr.27890]

62 **Uehara K**, Ishiguro S, Sakamoto E, Maeda A, Inoue M, Tojima Y, Kobayashi S, Omiya N, Ishizuka N, Nakao A, Goto H, Nagino M. Phase II trial of neoadjuvant chemotherapy with XELOX plus bevacizumab for locally advanced rectal cancer. *Jpn J Clin Oncol* 2011; **41**: 1041-1044 [PMID: 21803876 DOI: 10.1093/jjco/hyr084]

63 **Alberts SR**, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, Smyrk TC, Sinicrope FA, Chan E, Gill S, Kahlenberg MS, Shields AF, Quesenberry JT, Webb TA, Farr GH, Pockaj BA, Grothey A, Goldberg RM. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. *JAMA* 2012; **307**: 1383-1393 [PMID: 22474202 DOI: 10.1001/jama.2012.385]

64 **Allegra CJ**, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Colangelo LH, Atkins JN, Seay TE, Fehrenbacher L, Goldberg RM, O'Reilly S, Chu L, Azar CA, Lopa S, Wolmark N. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J Clin Oncol* 2011; **29**: 11-16 [PMID: 20940184 DOI: 10.1200/jco.2010.30.0855]

65 **de Gramont A**, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, Cunningham D, Cartwright TH, Hecht JR, Rivera F, Im SA, Bodoky G, Salazar R, Maindrault-Goebel F, Shacham-Shmueli E, Bajetta E, Makrutzki M, Shang A, André T, Hoff PM. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. *Lancet Oncol* 2012; **13**: 1225-1233 [PMID: 23168362 DOI: 10.1016/s1470-2045(12)70509-0]

66 **Voest EE**, Snoeren N, Schouten SB, Bergman AM, van Werkhoven E, Loosveld OJL, van Gulik TM, Smit JM, Cats A, Boven E, Hesselink E, Rijken A, Tol M, Dalesio O, Verheul HM, Tollenaar RA, van der Sijp J, Borel Rinkes I, van Hillegersberg R. A randomized two-arm phase III study to investigate bevacizumab in combination with capecitabine plus oxaliplatin (CAPOX) versus CAPOX alone in post radical resection of patients with liver metastases of colorectal cancer. *J Clin Oncol* 2011; **29** Suppl 15: Abstract 3565

67 **Tol J**, Koopman M, Cats A, Rodenburg CJ, Creemers GJ, Schrama JG, Erdkamp FL, Vos AH, van Groeningen CJ, Sinnige HA, Richel DJ, Voest EE, Dijkstra JR, Vink-Börger ME, Antonini NF, Mol L, van Krieken JH, Dalesio O, Punt CJ. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009; **360**: 563-572 [PMID:

19196673 DOI: 10.1056/NEJMoa0808268]
68 **Hecht JR**, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, McCollum D, Stella P, Deeter R, Shahin S, Amado RG. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009; **27**: 672-680 [PMID: 19114685 DOI: 10.1200/jco.2008.19.8135]
69 **Tournigand C**, Samson B, Scheithauer W, al. e. Bevacizumab (Bev) with or without erlotinib as maintenance therapy, following induction first-line chemotherapy plus Bev, in patients (pts) with metastatic colorectal cancer (mCRC): efficacy and safety results of the International GERCOR DREAM Phase III trial. *J Clin Oncol* 2012; **30** Suppl 18: Abstract LBA3500
70 **Johnsson A**, Hagman H, Frödin JE, Berglund A, Keldsen N, Fernebro E, Sundberg J, De Pont Christensen R, Garm Spindler KL, Bergström D, Jakobsen A. A randomized phase III trial on maintenance treatment with bevacizumab alone or in combination with erlotinib after chemotherapy and bevacizumab in metastatic colorectal cancer: the Nordic ACT Trial. *Ann Oncol* 2013; **24**: 2335-2341 [PMID: 23788755 DOI: 10.1093/annonc/mdt236]
71 **Gerlinger M**, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, Martinez P, Matthews N, Stewart A, Tarpey P, Varela I, Phillimore B, Begum S, McDonald NQ, Butler A, Jones D, Raine K, Latimer C, Santos CR, Nohadani M, Eklund AC, Spencer-Dene B, Clark G, Pickering L, Stamp G, Gore M, Szallasi Z, Downward J, Futreal PA, Swanton C. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012; **366**: 883-892 [PMID: 22397650 DOI: 10.1056/NEJMoa1113205]

P- Reviewers: Deutsch JC, Mocellin S, Ramia JM
S- Editor: Gou SX **L- Editor**: A **E- Editor**: Wu HL

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327

9 771007 932045