Targeted therapy in advanced colorectal cancer: more data, more questions

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Colorectal cancer (CRC) remains the third most common malignancy and the third leading cause of cancer death worldwide. The introduction of new chemotherapeutics and monoclonal antibodies into the treatment protocols for advanced CRC has significantly improved the outcomes. Nowadays, oncologists have a wide range of agents to choose for the treatment of advanced CRC; however, their optimal administration remains unclear. This article presents recently published data from the trials evaluating the use of monoclonal antibodies in advanced CRC with a particular emphasis on the predictive and prognostic factors of response to targeted therapy. The results from the CRYSTAL and OPUS studies indicate that the benefit from the addition of cetuximab to first-line chemotherapy is restricted to patients with the wild-type KRAS gene, with the best outcomes observed among those with unmutated forms of both the KRAS and BRAF genes. However, that has not been confirmed in the preliminary data from the COIN trial. Panitumumab has been shown to improve the outcomes when combined with first-line and second-line chemotherapy, but again mostly in patients with wild-type KRAS. The article also describes the detrimental effect of combined anti-vascular endothelial growth factor and anti-epidermal growth factor blockade in the first-line setting observed in the PACCE and the CAIRO-2 trials. Finally, results from the BRiTE registry indicating benefit from continuation of bevacizumab after progression on the first-line regimen are discussed in the context of maintenance therapy. Modern treatment for advanced CRC is based not only on clinical and anatomo-pathological but also molecular tumour characteristics. Our knowledge of the optimal administration of monoclonal antibodies in advanced CRC has extended significantly over the last few years; however, there are still many questions that have to be answered in future trials. *Anti-Cancer Drugs* 21:737–748 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Colorectal cancer (CRC) remains the third most common malignancy and the third leading cause of cancer death worldwide. Early detection of CRC results in radical resection of the tumour in the majority of cases; however, about 40–50% of the patients will present local recurrence and/or distant metastases [1]. Palliative chemotherapy remains the only option for the majority of these patients. Introduction of new chemotherapeutics in recent years has significantly improved their survival. Apart from the typical cytotoxic agents, monoclonal antibodies, such as bevacizumab, cetuximab and panitumumab, are being used in the treatment of advanced CRC, which have significantly improved the efficacy of standard chemotherapy regimens. Results from recent clinical trials deliver new information on their efficacy and optimal administration. Moreover, these data confirm the rightness of personalized therapy in onclogy, wherein not only clinical and anatomo-pathological but also molecular tumour characteristics undoubtedly predict the efficacy of antineoplastic therapy.

Cetuximab in the first-line treatment of metastatic colorectal cancer

Several clinical trials evaluating the combination of cetuximab with the standard first-line and second-line chemotherapy in metastatic CRC (mCRC) showed improvement in treatment efficacy without significant increase in toxicity. In the BOND trial [2], it has been shown that addition of cetuximab to second-line irinotecan-based chemotherapy in patients resistant to this regimen in the first-line setting, significantly improves the outcome. The efficacy of cetuximab as monotherapy in patients treated earlier with fluoropyrimidines, irinotecan and oxaliplatin was observed in the CO.17 study [3]. On the other hand, preliminary data from the CALGB 80203 trial [4] presented at the ASCO meeting in 2006 confirmed improvement in the efficacy of the first-line FOLFIRI and FOLFOX regimens when combined with cetuximab [response rates (RRs) 52% for chemotherapy with cetuximab vs. 38% for chemotherapy without cetuximab; $P = 0.029$]. It is important to notice that in all these studies cetuximab was administered regardless of the KRAS gene status. The additional analysis [5] evaluating the relationship between RR and KRAS status in the population of patients from the CO.17 trial showed that the clinical benefit of cetuximab was restricted to patients with the wild-type KRAS gene; in this group, the median progression-free survival (PFS) was 3.7 months in the case of treatment with cetuximab compared with

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1.9 months in the group treated with the best supportive care only ($P < 0.001$). Median overall survival (OS) was 9.5 months and 4.8 months, respectively ($P < 0.001$). There were no statistically significant differences in median PFS ($P = 0.96$) and OS ($P = 0.89$) among patients with mutated KRAS. Recently published data from other phase III trials confirm earlier observations and add new information on cetuximab use in the first-line treatment of mCRC.

The CRYSTAL study (Cetuximab Combined with Irinotecan in First-Line Therapy for mCRC) [6] enrolled 1198 patients with CRC without earlier treatment for metastatic disease with epidermal growth factor receptor (EGFR) expression and primarily not eligible for curative surgery. Patients were randomized to treatment with the FOLFIRI regimen alone or in combination with cetuximab (599 patients in each group). The aim of the study was to evaluate the efficacy and safety of the combination of cetuximab with the FOLFIRI regimen, also in relation to KRAS status. Median PFS was 8.9 months in the FOLFIRI + cetuximab arm and 8.0 months in the FOLFIRI alone arm ($P = 0.048$), which means a 15% reduction in the risk of disease progression. Median OS was 19.9 months in the FOLFIRI + cetuximab group and 18.6 months in the FOLFIRI alone group; hazard ratio (HR) for death in the FOLFIRI + cetuximab group was 0.93 ($P = 0.31$). Addition of cetuximab to the FOLFIRI regimen significantly improved both the complete and partial RRs (46.9% in the group with cetuximab vs. 38.7% in the group without cetuximab; $P = 0.004$) (Table 1). Consequently, the metastasectomy rate was significantly improved in the FOLFIRI + cetuximab arm (7.0 vs. 3.7%, respectively), including the R0 resections with curative intent (4.8 vs. 1.7%; $P = 0.002$).

The updated data on the treatment efficacy in the CRYSTAL trial according to the KRAS gene status have recently been published [7]. Approximately 63% of the patients had the wild-type KRAS gene, and it has been shown that the benefit of adding cetuximab to the FOLFIRI chemotherapy was restricted to this group of patients (Table 2). Median PFS was 9.9 months when treated with FOLFIRI + cetuximab compared with 8.4 months in the FOLFIRI only group ($P = 0.0012$). In the group with mutated KRAS, there was no benefit from adding cetuximab; median PFS was 7.4 months for FOLFIRI + cetuximab compared with 7.7 months for FOLFIRI alone ($P = 0.2661$). Similar differences were observed in the median OS: in the wild-type KRAS group it reached 23.5 months for FOLFIRI + cetuximab compared with 20.0 months for FOLFIRI alone ($P = 0.0094$), whereas among the patients with mutated KRAS gene, it was 16.2 months compared with 16.7 months, respectively ($P = 0.7551$). Similarly, improvement in RRs after adding cetuximab was observed only in the wild-type KRAS group (57.3% for FOLFIRI + cetuximab vs. 39.7% for FOLFIRI alone; $P < 0.0001$), whereas in patients with mutated KRAS these rates were worse in the cetuximab arm (31.3 vs. 36.1%, respectively; $P = 0.3475$).

The combination FOLFIRI + cetuximab was characterized by a higher percentage of adverse reactions grade 3 and 4 (79.3 vs. 61.0%; $P < 0.001$), mainly because of the more frequent skin reactions (19.7 vs. 0.2%; $P = 0.001$), acne-like skin rash (16.2 vs. 0.0%; $P < 0.001$), diarrhoea (15.7 vs. 10.5%; $P = 0.008$) and infusion-related reaction (2.5 vs. 0.0%; $P < 0.001$). Although toxicity grade 3 and 4 was more common in the FOLFIRI + cetuximab arm, there was no difference in the treatment duration between both the groups; however, it has been noticed that the median PFS correlated with the intensity of the skin rash.

The CRYSTAL trial proved that the addition of cetuximab to the first-line FOLFIRI regimen in the treatment of mCRC significantly prolongs the median PFS; however, this effect is restricted to patients with the wild-type KRAS gene. Only in this population of patients, the addition of cetuximab to the FOLFIRI regimen significantly prolonged the median OS for almost 4 months. This survival advantage is similar to the results of trials evaluating the combinations of chemotherapy with bevacizumab in mCRC and results of the trials described below that examined the combination of cetuximab with oxaliplatin-based chemotherapy.

The results from the phase II ACROBAT trial [8] published in 2007 that examined the efficacy and safety of the combination FOLFOX4 + cetuximab in the first-line

Table 1 Treatment efficacy in the CRYSTAL trial – entire population

	FOLFIRI + cetuximab	FOLFIRI alone	*P*
Median PFS (months)	8.9	8.0	0.048
Median OS (months)	19.9	18.6	0.31
Response rate (%)	46.9	38.7	0.004

OS, overall survival; PFS, progression-free survival.

Table 2 Treatment efficacy in the CRYSTAL trial according to the KRAS status (ECCO 15 – ESMO 34, 2009, Abstract No. 6077)

	Wild-type KRAS			Mutated KRAS		
	FOLFIRI + cetuximab	FOLFIRI	*P*	FOLFIRI + cetuximab	FOLFIRI	*P*
Median PFS (months)	9.9	8.4	0.0012	7.4	7.7	0.2661
Median OS (months)	23.5	20.0	0.0094	16.2	16.7	0.7551
Response rate (%)	57.3	39.7	<0.0001	31.3	36.1	0.3475

OS, overall survival; PFS, progression-free survival.

setting in mCRC were encouraging. In this study the RR was as high as 72%, median PFS was 12.3 months and median OS reached 30.0 months. Twenty-three percent of patients with primary inoperable metastases have undergone resections with curative intent and all this with acceptable treatment toxicity. These data required further confirmation. Recently, the results of the OPUS (The Oxaliplatin and Cetuximab in First-Line Treatment of mCRC) trial [9] have been published. The study enrolled patients with mCRC without earlier treatment for metastatic disease and directly compared the efficacy and tolerability of the FOLFOX4 + cetuximab combination with FOLFOX4 alone. The primary endpoint of the study was the best confirmed overall RR; secondary endpoints were rate of curative metastasectomies, duration of response to therapy, PFS, OS and treatment tolerance. Retrospectively, treatment efficacy in relation to the KRAS gene status was analysed. Three hundred and thirty-seven patients were enrolled into the study (169 to the FOLFOX4 + cetuximab group and 168 to the FOLFOX4 alone group). Similar to the CRYSTAL trial, they had primarily nonresectable, EGFR-expressing mCRC. In the entire study population, the RR reached 46% in the FOLFOX4 + cetuximab group and 36% in the FOLFOX4 group ($P = 0.064$). PFS did not differ between the groups (median PFS was 7.2 moths in both groups). However, in the group treated with FOLFOX4 + cetuximab, there was a longer duration of response to the treatment (9 vs. 5.7 months), and similar to the CRYSTAL trial, the addition of cetuximab doubled the percentage of R0 metastasectomies (2.4% in the FOLFOX4 group vs. 4.7% in the FOLFOX4 + cetuximab group) (Table 3).

Around 57% of the patients had the wild-type KRAS gene. Updated data on the treatment efficacy according to the KRAS status are presented in Table 4 [7]. Among patients with wild-type KRAS, the combination of FOLFOX4 + cetuximab significantly improved the RR (57.3 vs. 34.0% in the FOLFOX4 alone), but in patients with mutated KRAS these rates were lower in the FOLFOX4 + cetuximab arm (33.8 vs. 52.5%, respectively). In the group of patients with wild-type KRAS, R0 resections in the FOLFOX4 + cetuximab arm were more than twice of that observed in the FOLFOX4 alone arm (9.8 vs. 4.1%, respectively). Again, this difference was not observed among patients with mutated KRAS. It was also found that among patients with wild-type KRAS treated with the FOLFOX4 + cetuximab regimen, there was a statistically significant improvement in PFS (median PFS were 8.3 months in the FOLFOX4 + cetuximab group and 7.2 months in the FOLFOX4 group; $P = 0.0064$). Median OS was also improved in the FOLFOX4 + cetuximab arm (22.8 vs. 18.5 months, respectively), but that difference did not reached statistical significance which may be due to the small sample size. By contrast, the addition of cetuximab to the FOLFOX4 among patients with mutated KRAS had detrimental effects on both PFS (5.5 months in the FOLFOX4 + cetuximab arm vs. 8.6 months in the FOLFOX4 alone arm; $P = 0.0153$) and OS (13.4 vs. 17.5 months, respectively; $P = 0.2004$).

There was no significant difference in toxicity grade 3 and 4 between the groups (76% in the FOLFOX4 + cetuximab arm vs. 70% in the FOLFOX4 arm). The main difference in toxicity was noted for skin rash (11 vs. 0.6%, respectively) and palmar-plantar erythrodysesthesia (4 vs. 0.6%, respectively).

Similar to the CRYSTAL trial, the OPUS study confirmed the improved efficacy of front-line chemotherapy when administered with cetuximab, but this effect is restricted to patients with wild-type KRAS gene. Moreover, the OPUS study clearly shows that adding cetuximab to the FOLFOX4 regimen in patients with a mutated KRAS gene significantly worsens the outcomes. This phenomenon was not observed in the CRYSTAL trial, but in the CAIRO-2 study [10] the addition of cetuximab to the combination of capecitabine + oxaliplatin + bevacizumab in patients with mutated KRAS had a detrimental impact on the treatment outcomes. It is, therefore, possible that cetuximab diminishes the activity of oxaliplatin in tumours harbouring mutated KRAS, but that observation requires confirmation and explanation in future studies.

Recently, the preliminary results from the phase III COIN trial [11] evaluating the addition of cetuximab to the fluoropyrimidine + oxaliplatin chemotherapy in the

Table 3 Treatment efficacy in the OPUS trial – entire population

	FOLFOX + cetuximab	FOLFOX alone	*P*
Median PFS (months)	7.2	7.2	0.6170
Duration of response to treatment (months)	9.0	5.7	NA
Response rate (%)	46	36	0.064
R0 metastasectomies rate (%)	4.7	2.4	NA

NA, not available; PFS, progression-free survival.

Table 4 Treatment efficacy in the OPUS trial according to the KRAS status (ECCO 15 – ESMO 34 2009, Abstract No. 6077)

	Wild-type KRAS			Mutated KRAS		
	FOLFOX + cetuximab	FOLFOX	*P*	FOLFOX + cetuximab	FOLFOX	*P*
Median PFS (months)	8.3	7.2	0.0064	5.5	8.6	0.0153
Median OS (months)	22.8	18.5	0.3854	13.4	17.5	0.2004
Response rate (%)	57.3	34.0	0.0027	33.8	52.5	0.0290

OS, overall survival; PFS, progression-free survival.

first-line setting for mCRC patients have been presented. The patients in the COIN trial were randomized to one of the three arms: continuous chemotherapy (arm A), continuous chemotherapy + cetuximab (arm B) and intermittent chemotherapy (arm C). The choice of the fluoropirymidine [either 5-fluorouracil (5FU) or capecitabine] depended on the treating physician and patient before randomization; two-thirds of the patients received XELOX. The trial prospectively analysed the data for KRAS status. Although among the wild-type KRAS patients there was an increase in the RR when treated with chemotherapy + cetuximab compared with chemotherapy alone, the COIN trial did not meet its primary endpoint of OS. In the wild-type KRAS group, the OS reached 17 months for chemotherapy + cetuximab and 17.9 months for chemotherapy alone; $P = 0.68$). OS in patients with KRAS mutation was 14.8 months with chemotherapy alone and 13.6 months with the addition of cetuximab. The investigators conclude that the lack of improvement in OS might have resulted from the significantly increased toxicity seen in the cetuximab group, especially when combined with capecitabine. The safety data during the first 12 weeks of treatment for the first 804 patients randomized to the trial have already been published [12]. Of these, 203 (25%) patients received a combination of *l*-folinic acid [175 mg intravenously (i.v.) over 2 h] or *d,l*-folinic acid (350 mg i.v. over 2 h), concurrent administration of oxaliplatin (85 mg/m^2 i.v. over 2 h) plus bolus 5FU (400 mg/m^2) followed by a 46-h i.v. infusion of 5FU 2400 mg/m^2 repeated every 2 weeks (OxMdG), 102 (13%) patients received OxMdG + cetuximab (OxMdG + C), 333 (41%) patients were treated with oxaliplatin 130 mg/m^2 i.v. for 2 h on day 1 along with capecitabine 1000 mg/m^2 twice daily, orally on days 1–14 repeated every 3 weeks (XELOX) and 166 (21%) patients received XELOX + cetuximab (XELOX + C). The addition of cetuximab to both the OxMdG and XELOX regimens significantly increased the overall toxicity grade 3/4 ($P < 0.001$). Neutropenia was most frequent in the 5FU arms (17% in OxMdG vs. 2% in XELOX vs. 26% in OxMdG + C vs. 1% in XELOX + C), and the same was true for febrile neutropenia (4 vs. 1 vs. 5 vs. 0%, respectively). However, gastrointestinal toxicity was most frequent in the XELOX + cetuximab arm: for nausea and vomiting 3% vs. 7% vs. 7% vs. 14%, respectively and for diarrhoea 6% vs. 15% vs. 13% vs. 25%, respectively. On account of toxicity, at least one dose reduction was necessary in 28% of the patients in the OxMdG arm, 44% in the OxMdG + C arm, 22% in the XELOX arm and 49% in the XELOX + cetuximab arm. The doubling of dose reductions when chemotherapy was given with cetuximab was highly statistically significant ($P < 0.001$). Moreover, the oxaliplatin dose in the XELOX + cetuximab arm was reduced in 33% of the patients compared with 15% in the XELOX alone arm ($P < 0.001$). According to the investigators in the COIN trial, all these factors might have influenced the final efficacy outcomes.

Panitumumab in the first-line and second-line treatment

Another anti-EGFR antibody used in the treatment of mCRC is panitumumab, which is a fully human anti-epidermal monoclonal antibody approved to be used as monotherapy in wild-type KRAS patients after the failure of standard chemotherapy ± bevacizumab or cetuximab. Preliminary data on panitumumab activity in the first-line treatment of mCRC are encouraging. The phase III PRIME study [13] enrolled 1183 patients with metastatic adenocarcinoma of the colon or rectum, with no history of chemotherapy for metastatic disease and no earlier oxaliplatin, and they were randomized to treatment with FOLFOX4 + panitumumab or FOLFOX4 alone. Six hundred and fifty-six patients (60%) had wild-type KRAS. The treatment efficacy data are presented in Table 5. Among the wild-type KRAS patients, addition of panitumumab to the standard FOLFOX4 regimen significantly improved median PFS [9.6 months vs. 8.0 months; HR = 0.8 (95% confidence interval)] and RR (55 vs. 48%). On the other hand, similar to the OPUS and CAIRO-2 studies, in the population of patients with mutated KRAS, the combination of the anti-EGFR antibody plus oxaliplatin-based chemotherapy was inferior compared with chemotherapy alone.

Toxicity was comparable across the study arms, except for the rate of adverse events specific for the anti-EGFR therapy like skin toxicity, paronychia, diarrhoea, stomatitis and hypomagnesaemia, which occurred significantly more often in the panitumumab-containing arm.

Panitumumab has also proved activity in the second-line therapy of mCRC when combined with the standard FOLFIRI regimen. In a randomized, multicentre, phase III study [14] of FOLFIRI + panitumumab versus FOLFIRI alone in mCRC patients with one earlier chemotherapy regimen for metastatic disease, combined therapy with anti-EGFR antibody significantly improved the outcomes in the group of patients with wild-type KRAS. Patients with a history of anti-EGFR antibody therapy or treatment with small molecule EGFR inhibitors were excluded from the study. The median PFS was 5.9 months for the FOLFIRI + panitumumab arm and 3.9 months for the FOLFIRI alone arm ($P = 0.004$), median OS reached 14.5 versus 12.5 months, respectively ($P = 0.115$), and RRs were 35 versus 10%, respectively. Contrary to the results from the studies evaluating the combination of oxaliplatin-based chemotherapy with anti-EGFR blockade, there was no difference in PFS, OS, or RR among patients with mutated KRAS who received FOLFIRI + panitumumab versus FOLFIRI alone. Again, as in the PRIME trial, the rate of adverse events between the arms was comparable except for the known anti-EGFR toxicities such as skin rash, diarrhoea and hypomagnesaemia.

The results of the trials presented above are the next step into the era of the tailored therapy in mCRC; testing of the KRAS status is now considered a routine procedure

Table 5 Treatment efficacy in the PRIME study according to the KRAS status

	Wild-type KRAS			Mutated KRAS		
	FOLFOX4 + panitumumab	FOLFOX4	HR	FOLFOX4 + panitumumab	FOLFOX4	HR
Median PFS (months)	9.6	8.0	0.8	7.3	8.8	1.29
Response rate (%)	55	48	NA	40	40	NA

HR, hazards ratio; NA, not available; PFS, progression-free survival.

allowing many patients to avoid unnecessary treatment potentially associated with significant toxicity. In addition, the routine testing of the KRAS status results in significant cost savings [15]. The annual cost savings for the United States healthcare system from using KRAS testing to select patients for anti-EGFR monoclonal antibodies is estimated to be $740 million. It is believed that the routine KRAS evaluation will result in cost savings also in cases of cetuximab use in the second-line and third-line therapy in which treatment duration is much shorter than in the first-line setting.

Beyond KRAS: BRAF mutational status plays a prognostic role

KRAS is a low molecular-weight GTP-binding protein that initiates intracellular transmission of EGFR activation. The downstream effectors of KRAS are the serine/threonine kinases RAF: c-RAF-1, ARAF and BRAF, with the latest being the main effector of KRAS. Eventually, BRAF activates the pathway of the mitogen-activated protein kinase.

Cetuximab and panitumumab are approved for the treatment of advanced CRC patients with the wild-type KRAS gene; however, not all these patients will respond to the treatment. It has been hypothesized that mutations of the other members of the RAS-RAF-mitogen-activated protein kinase pathway may be responsible for resistance to anti-EGFR antibodies. It has been reported that BRAF-mutated CRCs are more aggressive [16] and that KRAS and BRAF mutations are mutually exclusive [17,18]. Italian investigators evaluated retrospectively the impact of the specific V600E mutation in the BRAF gene on the efficacy of cetuximab or panitumumab in 113 patients with mCRC [19]. Eleven of the 79 patients with wild-type KRAS had mutation V600E in BRAF. None of the patients with mutated BRAF responded to treatment, whereas those who responded, were free of mutation in BRAF ($P = 0.029$). BRAF mutation also correlated with worse prognosis: patients with a mutated form of BRAF had a much shorter PFS ($P = 0.11$) and OS ($P < 0.0001$). The study suggested that wild-type forms of both KRAS and BRAF are necessary for cetuximab and panitumumab activity; however, at present, testing of the BRAF mutational status is not required before the administration of these antibodies (the newest NCCN guidelines recommend considering the testing of BRAF status). The study also proved that the blockade of mutated BRAF with sorafenib may restore cetuximab and panitumumab activity. Combined sorafenib and cetuximab therapy in mCRC is currently being evaluated in a phase II trial [20].

More data on the BRAF significance in the treatment of mCRC come from the recently presented updated analyses from the CRYSTAL and OPUS studies [21–23]. In the CRYSTAL study, the BRAF status was mutated in 6% of the 83% of patients evaluated for the BRAF mutation and in 9% of the wild-type KRAS patients. In the OPUS study, the BRAF mutation was discovered in 4% of the 92% of tumours available for BRAF evaluation and in 6% of tumours harbouring wild-type KRAS. Both separate analyses from CRYSTAL and OPUS and the combined meta-analysis from these two studies have shown that the best outcomes are observed among patients with KRAS wild-type and BRAF wild-type tumours (KRASwt/BRAFwt), irrespective of the treatment arm. On the other hand, the worst outcomes were reported for the wild-type KRAS/mutated BRAF (KRASwt/BRAFmt) patients treated with chemotherapy alone and they were inferior to the results achieved in the same group treated with chemotherapy plus cetuximab (Table 6). These data suggest that the cetuximab treatment effect does not vary according to the BRAF mutation status and patients with mutated BRAF also seem to benefit from cetuximab. The investigators of the CRYSTAL study acknowledge that the BRAF status plays a more prognostic than predictive role in wild-type KRAS tumours.

Combined blockade of VEGF and EGFR in the first-line therapy

If bevacizumab, cetuximab or panitumumab added separately to the standard first-line chemotherapy in advanced CRC significantly improves outcomes, combining the two classes of monoclonal antibodies could theoretically have additive or synergistic efficacy. In a phase II BOND-2 trial [24], patients resistant to the first-line therapy were simultaneously administered bevacizumab and cetuximab with or without irinotecan and the treatment efficacy was surprisingly high with an acceptable toxicity profile. Unfortunately, interim analysis from the phase III PACCE trial [25] showed that addition of panitumumab to the standard first-line oxaliplatin-based chemotherapy + bevacizumab worsens the outcomes. Recently, the final data from the PACCE trial and the CAIRO-2 study have been published [10], which evaluated the efficacy of the combination of bevacizumab and cetuximab.

The PACCE trial enrolled 1053 patients with CRC without earlier therapy for metastatic disease. They were randomized to oxaliplatin-based (823 patients) or irinotecan-based (230 patients) chemotherapy + bevacizumab; in the experimental arms, panitumumab was also added. In the oxaliplatin-based therapy, median PFS was 10 months for the arm with additional panitumumab as compared with 11.4 months for the arm without panitumumab (HR = 1.27). For the irinotecan-based therapy, median PFS was 10.1 months in the case of panitumumab administration and 11.7 months for those treated without panitumumab (HR = 1.19). Median OS in the oxaliplatin group was 19.4 months with panitumumab and 24.5 months without panitumumab (HR = 1.43); in the irinotecan group, median OS was 20.7 months and 20.5 months, respectively (HR = 1.42). Addition of panitumumab did not increase the RR in any of the treatment arms (Table 7). The negative effects of panitumumab were independent of the KRAS status. Panitumumab significantly increased the treatment toxicity, particularly the skin toxicity, diarrhoea and the rate of pulmonary embolism, in both the oxaliplatin-based and irinotecan-based groups.

The exacerbated toxicity observed in the panitumumab arms increased the frequency of dose delays, dose reductions, and therefore, diminished the dose intensity. It might have negatively impacted the treatment efficacy. The investigators of the study also acknowledge the pharmacodynamic interactions between the study drugs that might have worsened the efficacy of therapy with two monoclonal antibodies. The EGFR blockade may inhibit the intracellular signaling pathways and therefore diminish bevacizumab and/or cytotoxics activity; it can also lead to cell-cycle arrest and resistance to chemotherapeutics.

On the other hand, the CAIRO-2 study [10] evaluated the efficacy and safety of cetuximab addition to the standard front-line chemotherapy capecitabine + oxaliplatin + bevacizumab in mCRC. It has been shown that the addition of cetuximab results in a shorter median PFS (10.7 months without cetuximab vs. 9.4 months with cetuximab; $P = 0.01$; Table 8). HR for progression or death in the group treated with cetuximab was 1.22. Median OS for patients treated without cetuximab reached 20.3 months as compared with 19.4 months for those receiving cetuximab ($P = 0.16$). It has also been proved that the addition of cetuximab to the standard first-line therapy does not significantly increase the RR (50% for those treated without cetuximab vs. 52.7% for those receiving cetuximab; $P = 0.49$).

The treatment efficacy according to the KRAS mutation status is presented in Table 9. It clearly shows that the addition of cetuximab in patients with mutated KRAS significantly worsens the outcomes; in the cetuximab-containing arm, patients with mutated KRAS had a significantly shorter median PFS than those with the wild-type gene (8.1 vs. 10.5 months; $P = 0.04$). Moreover, patients with mutated KRAS in the cetuximab group had a much shorter median PFS (8.1 vs. 12.5 months; $P = 0.003$) and median OS (17.2 vs. 24.9 months; $P = 0.03$) compared with those with mutated KRAS but not having received cetuximab. The updated analysis from this study refers also to the BRAF status; it shows that patients with mutated BRAF tumours had a

Table 8 Treatment efficacy in the CAIRO-2 trial: the entire population

	CAP + OXA + BEV + CET	CAP + OXA + BEV	*P*
Median PFS (months)	9.4	10.7	0.01
Median OS (months)	19.4	20.3	0.16
Response rate (%)	52.7	50.0	0.49

BEV, bevacizumab; CAP, capecitabine; CET, cetuximab; OS, overall survival; OXA, oxaliplatin; PFS, progression-free survival.

Table 6 Treatment efficacy in the CRYSTAL and OPUS studies according to the BRAF status in KRAS wild-type population (Gastrointestinal Cancers Symposium 2010, Abstract No. 406)

	KRASwt/BRAFwt			KRASwt/BRAFmut		
	CTH + cetuximab	CTH	*P*	CTH + cetuximab	CTH	*P*
Median PFS (months)	10.9	7.7	<0.0001	7.1	3.7	0.2301
Median OS (months)	24.8	21.1	0.0479	14.1	9.9	0.0764
Response rate (%)	60.7	40.9	<0.0001	21.9	13.2	0.4606

CTH, chemotherapy; KRASwt/BRAFmut, patients with wild-type KRAS and mutated BRAF gene; KRASwt/BRAFwt, patients with both wild-type KRAS and BRAF genes; OS, overall survival; PFS, progression-free survival.

Table 7 Treatment efficacy in the PACCE trial

	Oxaliplatin-based chemotherapy			Irinotecan-based chemotherapy		
	+ BEV	+ BEV and PAN	HR	+ BEV	+ BEV and PAN	HR
Median PFS (months)	11.4	10	1.27	11.7	10.1	1.19
Median OS (months)	24.5	19.4	1.43	20.5	20.7	1.42
Response rate (%)	48	46	NA	40	43	NA

BEV, bevacizumab; HR, hazards ratio; NA, not available; OS, overall survival; PAN, panitumumab; PFS, progression-free survival.

Table 9 Treatment efficacy in the CAIRO-2 trial according to the KRAS status

	Wild-type KRAS			Mutated KRAS		
	CAP + OXA + BEV + CET	CAP + OXA + BEV	*P*	CAP + OXA + BEV + CET	CAP + OXA + BEV	*P*
Median PFS (months)	10.5	10.6	0.3	8.1	12.5	0.003
Median OS (months)	21.8	22.4	0.64	17.2	24.9	0.03
Response rate (%)	61.4	50.0	0.06	45.9	59.2	0.03

BEV, bevacizumab; CAP, capecitabine; CET, cetuximab; OS, overall survival; OXA, oxaliplatin; PFS, progression-free survival.

decreased median PFS compared with patients with wild-type BRAF, irrespective of the treatment arm (5.9 vs. 12.2 months; $P = 0.003$ in the chemotherapy + bevacizumab arm, and 6.6 vs. 10.4 months; $P = 0.010$ in the chemotherapy + bevacizumab + cetuximab arm, respectively). The median OS was also decreased in patients with mutated BRAF as compared with wild-type tumours in both the arms (15.0 vs. 24.6 months in the chemotherapy + bevacizumab arm; $P = 0.002$, and 15.2 vs. 21.5 months in the chemotherapy + bevacizumab + cetuximab arm; $P = 0.001$) [26]. Another analysis evaluated the relationship between the RR and the expression of the EGFR. It has been shown that even among patients with high EGFR expression, median PFS is shorter when treated with cetuximab (9.8 months for cetuximab group vs. 12.2 months for treated without cetuximab; $P = 0.003$). It has also been shown that in females the addition of cetuximab to the standard chemotherapy significantly shortens median PFS (8.6 vs. 12.5 months; $P < 0.001$) and median OS (18.8 vs. 20.1 months; $P = 0.02$). Interestingly, these differences were not observed among males.

Cetuximab significantly exacerbated the treatment toxicity: adverse events grade 3 and 4 were observed in 73.2% of the patients treated without cetuximab compared with 81.7% of those receiving cetuximab ($P = 0.006$). When grade 3 cetuximab-related skin toxicity was excluded, the incidence of adverse events was similar. Patients treated without cetuximab had a much better improvement in the quality of life ($P = 0.007$) and global health ($P = 0.03$).

The investigators of the study acknowledge that worse outcomes observed in the cetuximab group cannot result only from the more frequent treatment-related adverse events because the toxicity was generally manageable and the percentage of patients who prematurely stopped the treatment because of toxicity was comparable in both groups. The investigators refer to the results from the PACCE trial in which significant differences in survival after the addition of panitumumab to the standard chemotherapy + bevacizumab were observed only in the oxaliplatin arm; these differences were not noticed for the irinotecan arm. Eventually, the results of the BOND-2 trial confirm high activity of the combination of irinotecan, cetuximab and bevacizumab in patients resistant to irinotecan, which seems to be higher than the activity of the combination irinotecan + cetuximab observed in the identical population of patients in the BOND study. Is it, therefore, possible that cetuximab is more potent in combination with irinotecan than with oxaliplatin? Future studies will have to respond to this question.

The investigators in the CAIRO-2 study also claim the negative relationship between bevacizumab and cetuximab resulting in significantly less frequent occurrence of arterial hypertension in the cetuximab arm. Italian investigators proved in a small study of 39 patients with mCRC that occurrence of arterial hypertension during bevacizumab administration may be an interesting prognostic factor of responsiveness to therapy with this antibody [27]. They observed partial remission of disease in 75% of the patients who experienced arterial hypertension grade 2 and 3 compared with 32% of the patients without hypertension ($P = 0.04$). Similarly, the median PFS was significantly longer in the arm with hypertension (14.5 vs. 3.1 months; $P = 0.04$). Although in the hypertension group median OS has not been reached yet, it was 15.1 months in the group without hypertension ($P = 0.11$). These data await confirmation in larger trials.

However, the concept of the combined blockade of both the vascular endothelial growth factor (VEGF) and EGF pathways in mCRC has not been completely abandoned. Erlotinib is an oral inhibitor of the EGFR tyrosine kinase. The administration of bevacizumab concurrently with erlotinib is being investigated in various solid tumours and the primary data show meaningful antitumoural activity with an acceptable toxicity profile. This concept is being evaluated also in mCRC. In the GERCOR-C04-2 phase III 2×2 factorial design trial, patients with potentially unresectable mCRC are randomized to standard chemotherapy of FOLFOX or XELOX with bevacizumab or with bevacizumab and erlotinib [28]. After six courses, patients without progression are treated with bevacizumab and erlotinib with the reintroduction of the front-line regimen at the disease progression.

The ACT (ML 19033) trial evaluates the efficacy and safety of bevacizumab with erlotinib in patients with mCRC who did not progress during the 18 weeks of standard first-line chemotherapy consisting of bevacizumab, fluoropirymidine and oxaliplatin or irinotecan [29].

Uncertainties on the optimal anti-EGFR strategy

Both cetuximab and panitumumab are approved for the treatment of advanced CRC with the wild-type KRAS gene. The current NCCN guidelines recommend

administration of cetuximab or panitumumab in combination with standard first-line chemotherapy in the wild-type KRAS mCRC patients, although so far the equal efficacy of these monoclonal antibodies has not been proved in randomized clinical trials. Are cetuximab and panitumumab really interchangeable? In fact, their molecular mechanism of action differs significantly. First, panitumumab is a fully human monoclonal antibody and does not trigger anti-chimeric antibody reactions that may occur to neutralize cetuximab. Second, cetuximab, being a class IgG1 antibody, produces antibody-dependent cell-mediated cytotoxicity, which is not seen with panitumumab, a class IgG2 antibody. Finally, the mechanism of resistance to fully human panitumumab may be different from the resistance to chimeric cetuximab. The head-to-head comparison of these antibodies is being evaluated in a phase III trial ASPECCT that randomizes patients with chemorefractory mCRC to monotherapy with cetuximab or panitumumab [30]. Another uncertainty is regarding the administration of cetuximab and panitumumab in a sequential manner. The NCCN guidelines do not recommend the use of one of these agents after therapeutic failure of the other. There are, however, individual case reports in the literature describing the safety and efficacy of panitumumab in patients who experienced hypersensitivity reactions to cetuximab or progressed on cetuximab. An interesting retrospective analysis from the Memorial Sloan Kettering Cancer Center presents 22 patients with earlier cetuximab treatment who subsequently received panitumumab monotherapy [31]. The reasons for cetuximab discontinuation were hypersensitivity reactions (32%), disease progression (14%), convenience of a bi-weekly schedule (23%), preceding surgery (18%) and no evidence of disease after resection of metastases (9%). None of the patients who experienced a hypersensitivity reaction to cetuximab developed a subsequent hypersensitivity reaction to panitumumab. The analysis also showed that the majority of patients (89%) who responded to cetuximab continued to respond to panitumumab. There was one patient, however, whose tumour progressed on cetuximab and responded to subsequent panitumumab. Although this phenomenon is not clearly understood, the investigators of the analysis claim that molecular differences in these monoclonal antibodies may be responsible for their non-cross-resistance. A planned phase II study exploring the efficacy of a single agent panitumumab after progression on cetuximab-containing chemotherapy in KRAS wild-type CRC patients will verify this hypothesis [32].

Uncertainties on the optimal anti-VEGF strategy

In 2004, based on the positive results from the phase III randomized trials, the US Food and Drug Administration approved bevacizumab to be used in combination with the standard first-line and second-line chemotherapy in advanced CRC [33,34]. As the optimal duration of treatment has not yet been defined, it is unclear whether bevacizumab should be maintained with second-line chemotherapy after progression with bevacizumab plus first-line regimen. The BRiTE registry (the Bevacizumab Regimens: Investigation of Treatment Effects and Safety) [35] is a large, observational study that was started in the United States to evaluate the efficacy and tolerability of bevacizumab in an unselected population of patients with advanced CRC. Chemotherapy-naive patients with metastatic disease were treated with bevacizumab in combination with one of the standard chemotherapy regimens chosen at the discretion of the treating physician. FOLFOX was the most common standard chemotherapy regimen, whereas less frequent ones were FOLFIRI, IFL, bolus FU/LV, XELOX, protracted infusion of FU/LV and finally FLOX. The primary end-points of the study included treatment tolerance, median PFS, RRs and median OS. In the BRiTE registry, median PFS was 10.0 months and median OS reached 25.1 months. Although the median PFS observed in the BRiTE registry was comparable with the results from the earlier randomized trials assessing the efficacy of adding bevacizumab to the standard first-line chemotherapy in mCRC, the median OS was significantly longer than expected. The additional analysis of the BRiTE registry was aimed at finding factors responsible for the apparent discordance between PFS and OS. One thousand, four hundred and forty-five patients who experienced disease progression were divided into three groups: no treatment continuation after progression (17.5%), treatment continuation with no bevacizumab (no-BBP) (36.7%) and treatment continuation with bevacizumab (BBP) (44.4%). Treatment continuation was described as any systemic anticancer therapy using cytotoxic and/or biological agents (19 patients who continued bevacizumab alone were excluded from the analysis as this group was too small to be considered separately). There were no significant differences in the baseline characteristics between the no-BBP and BBP groups, except for the slightly higher percentage of patients with ECOG ≥ 1 in no-BBP group. Median time to first progression during front-line therapy was almost identical in both the groups (8.7 months in the no-BBP group and 8.9 months in BBP group). Median OS among patients who continued bevacizumab after first progression (BBP) reached 31.8 months and was statistically longer than that in no-BBP group (19.9 months; $P < 0.001$) and in the group of patients without any treatment continuation (12.6 months; $P < 0.001$). In addition, median survival beyond progression was significantly longer in the group that continued bevacizumab (19.2 vs. 9.5 vs. 3.6 months, respectively). In the multivariate analysis, it has been shown that continuing bevacizumab after first progression is an independent factor that predicts survival beyond progression. This positive effect of bevacizumab continuation after disease progression was observed regardless of whether bevacizumab was administered continuously or if there was any break in bevacizumab treatment (even longer than 2 months). Continuation of bevacizumab after

disease progression was not associated with a significant increase in treatment toxicity; the only significant difference related to the higher percentage of patients with primary or aggravating arterial hypertension observed in the BBP group compared with no-BBP group and the entire patient population in the BRiTE registry.

This study suggests the potential survival advantage from bevacizumab continuation after progression on the first-line therapy in mCRC. Progression of the disease during cytotoxic treatment generally implies resistance to chemotherapeutics, which results from the genetic instability of cancer cells. However, the mechanism of resistance to bevacizumab is not completely understood; this may be independent of the resistance to chemotherapeutics. Moreover, besides inhibiting neoangiogenesis, bevacizumab 'normalizes' aberrant tumour microvasculature and potentiates cytotoxics delivery into the tumour, which means that continuing bevacizumab in combination with second-line or even third-line cytotoxic chemotherapy in mCRC may continue to improve its efficacy. However, the BRiTE registry was only an observational study with all its limitations that might have influenced the final results and as such bevacizumab should not be used in the second-line regimen after progression on bevacizumab-containing front-line therapy. Currently, the hypothesis generated in the BRiTE registry is being evaluated in two prospective, randomized phase III trials. In a European trial AIO 0504/AGMT, patients who progressed on first-line regimens composed of fluoropyrimidine plus oxaliplatin or irinotecan with bevacizumab were randomized to receive the second-line chemotherapy of fluoropyrimidine plus oxaliplatin (for those with irinotecan-based front-line regimen) or plus irinotecan (for those with oxaliplatin-based first-line treatment) with or without bevacizumab. The safety analysis from this study shows that extended bevacizumab does not increase the rate of serious adverse events [36]. In the United States, bevacizumab beyond progression is being investigated in a randomized SWOG/NCCTG/NCIC iBET S0600 study in which patients who progressed on first-line bevacizumab with FOLFOX or XELOX are randomized to second-line treatment with irinotecan-based chemotherapy plus cetuximab with or without bevacizumab (5 or 10 mg/kg every 2 weeks) [37].

Another concept currently intensively investigated in clinical trials is maintenance therapy with bevacizumab in patients who achieved disease response to the induction therapy with cytotoxics plus bevacizumab. Inhibiting tumour regrowth during the 'maintenance phase' with the antiangiogenic therapy may lower the frequency of adverse events occurring as a result of prolonged exposition to cytotoxic regimens. In the CAIRO-3 study, patients with advanced CRC untreated earlier, receive the induction therapy of XELOX + bevacizumab for six cycles. Those who obtain response to the treatment are subsequently randomized to the maintenance therapy with low-dose capecitabine with bevacizumab or no further treatment. Upon progression of the disease, the initial cytotoxic regimen of XELOX + bevacizumab will be reintroduced in both the arms. Similar is the AIO KRK 0207 study in which patients who respond to the initial 24-week regimen of fluoropyrimidine, oxaliplatin and bevacizumab are randomized to no further therapy, bevacizumab alone or bevacizumab combined with a fluoropirymidine. The reintroduction of the initial first-line regimen is planned upon disease progression. The SAKK 41/06 study is a phase III non-inferiority trial that evaluates the maintenance therapy with bevacizumab versus no further treatment in patients with mCRC without progression on the standard first-line chemotherapy plus bevacizumab. The efficacy and safety of the maintenance therapy with bevacizumab and erlotinib is being evaluated in two trials mentioned earlier, GERCOR-C04-2 [28] and ACT (ML 19033) [29].

Other antiangiogenic agents in the treatment of mCRC

Cediranib is a highly potent tyrosine kinase inhibitor that selectively blocks all three VEGFRs. In a phase II study HORIZON I [38], it has shown activity in combination with the FOLFOX6 regimen in the second-line treatment of mCRC. The median PFS times for the combination of FOLFOX6 + cediranib were 5.8 months (cediranib at a dose 20 mg daily) and 7.2 months (cediranib at a dose 30 mg daily) and were comparable with the median PFS of 7.8 months for the combination FOLFOX6 + bevacizumab. Currently, there are two ongoing phase III studies that evaluate cediranib in combination with FOLFOX chemotherapy in the first-line setting in mCRC. The HORIZON II study [39] randomly compares oxaliplatin-based chemotherapy (FOLFOX or XELOX) with cediranib or placebo, and the HORIZON III [40] is a randomized comparison of the mFOLFOX6 chemotherapy plus cediranib (20 mg daily) with mFOLFOX6 plus bevacizumab (5 mg/kg i.v. every 2 weeks) in the front-line setting in mCRC. The preliminary data from the HORIZON III trial show that the efficacy did not meet the prespecified criteria for the primary endpoint of non-inferiority in PFS.

Vatalanib is an oral tyrosine kinase inhibitor targeting all three VEGFRs. The studies of FOLFOX plus vatalanib versus FOLFOX alone in the first-line (CONFIRM-1 trial) [41] and second-line (CONFIRM-2 trial) [42] setting in mCRC failed to show a significant improvement in PFS.

Sunitinib, another oral tyrosine kinase inhibitor that blocks VEGFR2, platelet-derived growth factor receptor b and c-kit, inhibits angiogenesis and cell proliferation. The phase III study (SUN 1122) evaluating sunitinib in combination with the FOLFIRI regimen versus FOLRIRI alone has been prematurely stopped when an Independent Data

Monitoring Committee found that the addition of sunitinib to FOLFIRI did not result in better PFS among patients with mCRC.

Aflibercept is a recombinant fusion protein of VEGR-1 and VEGFR-2 extracellular domains and the Fc portion of human IgG. It is currently being evaluated in combination with FOLFIRI in a phase III trial of a second-line treatment after the failure of the oxaliplatin-based chemotherapy [43].

Brivanib, a dual kinase inhibitor of VEGFR-2 and fibroblast growth factor, is being evaluated in a phase III trial in combination with cetuximab versus cetuximab alone in wild-type tumours refractory to combination chemotherapy [44].

Anti-EGFR or anti-VEGF strategy?

The data from prospective randomized trials presented above clearly prove that both cetuximab and panitumumab improve treatment efficacy of the front-line regimens used in mCRC; however, their activity is restricted to the wild-type KRAS tumours. As it was stated earlier, bevacizumab has also been shown to improve the outcomes in combination with first-line chemotherapy. Thus, which monoclonal antibody should be chosen to achieve the greatest benefit? For about 40% of the patients with mutated KRAS gene, bevacizumab is the only option. For the remaining 60% with wild-type KRAS tumours, clinicians may choose between anti-VEGF and anti-EGFR monoclonal antibodies. The results from the CRYSTAL [6], OPUS [9] and PRIME [13] trials indicate that the efficacy (measured as median PFS, median OS and overall RR) of the front-line cytotoxic regimens combined with anti-EGFR antibodies in wild-type KRAS mCRC are similar to the results from prospective, randomized studies evaluating the same cytotoxic combinations with bevacizumab (Table 10). However, these are not the head-to-head comparisons and cannot be interpreted as evidence of equal efficacy of these antibodies in the front-line setting. Currently, the head-to-head comparison of these agents is being conducted in the CALGB 80405 phase III study which randomizes patients with mCRC to the front-line FOLFOX or FOLFIRI with bevacizumab or cetuximab or the combination of bevacizumab and cetuximab [49]. However, the study has already been amended after publications regarding the predictive significance of KRAS and after publications of the results from the PACCE and CAIRO-2 studies indicating worse outcomes in combined anti-EGFR and anti-VEGF therapy. It is, therefore, possible that these amendments will confound the final results.

Summary

The results of the recent studies presented above evaluating the use of monoclonal antibodies in the treatment of advanced CRC expand our knowledge on their optimal administration. First, the trials evaluating the use of the EGFRs inhibitors clearly proved that cetuximab and panitumumab maintain activity mostly in patients with the wild-type KRAS gene. Moreover, mutation of the BRAF kinase, an effector for KRAS, is a negative prognostic factor in mCRC and the best outcomes are observed among patients with unmutated forms of both the KRAS and BRAF genes. Testing the KRAS status allows avoiding unnecessary, potentially toxic therapy in many patients and, what is also very important, results in significant cost savings in health care systems around the world. Contrary to the logical presumption that two monoclonal antibodies with different mechanism of action will improve the treatment efficacy, two randomized clinical trials clearly showed that simultaneous blockade of VEGF and EGFR worsens the outcomes. Many interactions between chemotherapeutics and biological agents still remain not totally understood; the higher activity of cetuximab in combination with irinotecan than with oxaliplatin is just one example. The detrimental effects from the addition of cetuximab to the combination of chemotherapy with bevacizumab observed in females but not males in the CAIRO-2 study, needs a more detailed explanation. Finally, maintenance therapy with targeted agents in patients responding to the front-line combined cytotoxic regimens is being evaluated in ongoing phase III trials.

Table 10 Efficacy of front-line regimens containing cetuximab or panitumumab or bevacizumab

	Regimen	mPFS (months)	mOS (months)	ORR (%)
Anti-EGFR containing regimens in wild-type KRAS mCRC				
CRYSTAL study [6]	FOLFIRI + cetuximab	9.9	23.5	57.3
	FOLFIRI + cetuximab (wtKRAS/wtBRAF)	10.9	25.1	61.0
OPUS study [9]	FOLFOX4 + cetuximab	8.3	22.8	57.3
PRIME study [13]	FOLFOX4 + panitumumab	9.6	NA	55
Bevacizumab containing regimens				
TREE study [45]	mFOLFOX6 + bevacizumab	9.9	26.1	52
	CapeOx + bevacizumab	10.3	27.0	46
NO 16966 study [46]	FOLFOX4 or XELOX + bevacizumab	9.4	21.3	47
BICC-C study [47]	FOLFIRI + bevacizumab	11.2	Not reached	57.9
MEXICO study [48]	FOLFIRI + bevacizumab	9.0	23.0	46
	XELIRI + bevacizumab	9.0	23.0	42

EGFR, epidermal growth factor receptor; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; ORR, overall response rate.

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