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Role of cetuximab in first-line treatment of metastatic colorectal cancer

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Abstract

The treatment of metastatic colorectal cancer (mCRC) has evolved considerably in the last decade, currently allowing most mCRC patients to live more than two years. Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor play an important role in the current treatment of these patients. However, only antibodies directed against EGFR have a predictive marker of response, which is the mutation status of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS). Cetuximab has been shown to be effective in patients with KRAS wild-type mCRC. The CRYSTAL study showed that adding cetuximab to FOLFIRI (regimen of irinotecan, infusional fluorouracil and leucovorin) significantly improved results in the first-line treatment of KRAS wild-type mCRC. However, results that evaluate the efficacy of cetuximab in combination with oxaliplatin-based chemotherapy in this setting are contradictory. On the

other hand, recent advances in the management of colorectal liver metastases have improved survival in these patients. Adding cetuximab to standard chemotherapy increases the response rate in patients with wild-type KRAS and can thus increase the resectability rate of liver metastases in this group of patients. In this paper we review the different studies assessing the efficacy of cetuximab in the first-line treatment of mCRC.

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Key words: Cetuximab; First-line; Metastatic colorectal cancer; Colorectal liver metastases; Elderly patients

Core tip: This article contains updated data regarding biomarkers of response to epidermal growth factor receptor-targeted therapy and reviews the major studies that have evaluated the efficacy of cetuximab in the first-line treatment of metastatic colorectal cancer (mCRC). We have also compiled the most important data supporting the use of cetuximab in the neoadjuvant treatment of colorectal liver metastases. Finally, we review the current evidence regarding the efficacy and safety of cetuximab in the treatment of elderly patients with mCRC.

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INTRODUCTION

Colorectal cancer is the third most common malignancy in men and the second most common in women worldwide. It is the fourth leading cause of cancer death, ac-

counting for 8% of global cancer deaths^[1].

Approximately 35% of patients have metastatic disease at diagnosis and 20%-50% of patients with stages II-III develop metastases in the course of the disease, the liver being the most common site of metastatic spread^[2].

There is a small subset of patients with metastatic disease isolated in the liver or lungs that can be offered potentially curative surgical treatment. Hepatic resection has become the treatment of choice for patients who have liver metastases only and neoadjuvant chemotherapy currently plays a major role in this setting, increasing the resection rate. However, the vast majority of patients with metastatic colorectal cancer (mCRC) are incurable and can only be offered systemic treatment with palliative intent^[3].

In the last decade there have been significant advances in the treatment of mCRC that have changed the natural history of the disease in these patients. Median survival in the era of 5-fluorouracil (5FU) was 6-12 mo^[4]. The introduction of oxaliplatin, irinotecan and subsequently biological agents (bevacizumab, cetuximab, panitumumab, aflibercept and regorafenib) made it possible to prolong the survival of patients with mCRC, reaching median survival times in excess of 20 mo^[5], so that a significant percentage of these patients now live longer than two years.

One of the great challenges of modern oncology is to identify biomarkers to select subsets of patients who will benefit from a particular drug, and thus to develop personalised medicine. In mCRC, the mutation status of v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) predicts response to drugs targeting epidermal growth factor receptor (EGFR)^[6-13].

EGFR is a receptor tyrosine kinase that belongs to the ErbB receptor family, which plays an important role in colorectal cancer progression. The binding of ligands will activate the EGFR, resulting in homodimerization and heterodimerization with other members of the ErbB family, which in turn trigger the activation of downstream signalling pathways, finally resulting in cell growth and proliferation. KRAS is a protein that is an essential component of the EGFR signalling cascade^[5,8]. There are reports that activating mutations in the KRAS gene, which encode this effector protein involved in EGFR-driven signalling, are present in 35%-40% of colorectal cancers^[14,15].

Cetuximab is a chimeric monoclonal antibody that competitively binds to the extracellular domain of EGFR with a higher affinity than its endogenous ligands, blocking EGFR-driven signalling, resulting in inhibition of cell growth and induction of apoptosis^[16-18]. There are also reports that cetuximab can mediate antibody-dependent cellular cytotoxicity against tumour cells^[16,19]. This monoclonal antibody has been proven effective in patients with KRAS wild-type mCRC^[6,7,20,21]. In addition, there is evidence that not only do patients with KRAS mutations not benefit from treatment with cetuximab, but that it could actually have a detrimental effect on them^[7,21].

In this paper we review the most relevant clinical trials that have assessed the role of cetuximab in the first-line treatment of mCRC.

KRAS AND OTHER BIOMARKERS IN COLORECTAL CANCER

KRAS mutation status is a predictor of response to cetuximab that has been validated in several clinical trials. However, the KRAS wild-type status does not guarantee response to cetuximab in all patients^[6-8,10,20,21]. This has led to intensive investigation of mechanisms of primary resistance to anti-EGFR drugs, which has identified potential molecular markers in the complex signalling pathway driven by the EGFR.

While the prognostic value of V-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations in colorectal cancer has been clearly demonstrated^[20,22-26], its role as a predictor of response to EGFR-targeted agents is still controversial^[12,20,22,24]. On the other hand, there is evidence that neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) mutations are associated with a lack of response to anti-EGFR agents^[23,27,28]. In a recent analysis of the PRIME trial, it was found that KRAS and NRAS wild-type mCRC patients showed a significant improvement in progression-free survival (PFS) and overall survival (OS) when treated with FOLFOX-panitumumab compared with FOLFOX alone [hazard ratio (HR) for PFS 0.72, 95%CI: 0.58-0.90, $P < 0.01$; HR for OS 0.78, 95%CI: 0.62-0.99, $P = 0.04$], whereas this benefit was not observed in patients with KRAS or NRAS mutations (HR for PFS 1.28, 95%CI: 0.79-2.07, $P = 0.32$; HR for OS 1.29, 95%CI: 0.79-2.10, $P = 0.31$). In this analysis, the BRAF mutation status was not found to be a predictive marker of response^[28]. Similarly, recent data from the FIRE-3 study showed that in patients with both wild-type KRAS and NRAS, cetuximab-regimen of irinotecan, infusional fluorouracil and leucovorin (FOLFIRI) significantly improved OS compared with bevacizumab-FOLFIRI (33.1 mo *vs* 25.9 mo, HR = 0.69; 95%CI: 0.52-0.92, $P = 0.01$)^[29]. In view of these results, the mutational status of NRAS seems to position itself as a new biomarker that could help us to select responders to anti-EGFR therapies.

Currently, there are data suggesting that in addition to analysis of KRAS mutation status, the evaluation of *EGFR* gene copy number, levels of EGFR ligands, BRAF, NRAS, PIK3CA mutations and PTEN loss could also help us achieve a more accurate selection of patients who may benefit from anti-EGFR targeted drugs^[22,27,30-32], although this needs to be validated in large prospective studies.

CETUXIMAB-BASED THERAPY FOR FIRST-LINE TREATMENT OF MCRC

Cetuximab in combination with irinotecan-based chemotherapy

Data from previous studies that showed an apparent ability of cetuximab to reverse resistance to irinotecan and obtain responses in patients who had previously progressed on irinotecan suggested a potential increased efficiency by combining both drugs^[33-36]. This possible

Table 1 Clinical trials of cetuximab in combination with irinotecan-based chemotherapy

Clinical trial	Type of study	KRAS analysis	Treatment	Response rate	R0 resection rate	PFS (mo)	OS (mo)
Folprecht <i>et al</i> ^[37]	Phase I / II	No	Cetuximab-Irinotecan/ 5FU/FA ¹	67%	19%	9.9	33
Raoul <i>et al</i> ^[38]	Phase I / II	No	Cetuximab-FOLFIRI	48%	19.20%	8.6	22.4
CRYSTAL, Van Cutsem <i>et al</i> ^[6,20]	Phase III	Yes	Cetuximab-FOLFIRI <i>vs</i> FOLFIRI	57.3% <i>vs</i> 39.7% (OR = 2.069, <i>P</i> < 0.001) ²	5.1% <i>vs</i> 2% (OR = 2.65, <i>P</i> = 0.0265) ²	9.9 <i>vs</i> 8.4 (HR = 0.696, <i>P</i> = 0.0012) ²	23.5 <i>vs</i> 20 (HR = 0.796, <i>P</i> = 0.0093) ²
FIRE-3, Heinemann <i>et al</i> ^[41]	Phase III	Yes	Cetuximab-FOLFIRI <i>vs</i> Bevacizumab-FOLFIRI	62 <i>vs</i> 57 (OR = 1.18, <i>P</i> = 0.183)		10 <i>vs</i> 10.3 (HR = 1.06, <i>P</i> = 0.547)	28.7 <i>vs</i> 25 (HR = 0.77, <i>P</i> = 0.017)

¹AIO group regimen of irinotecan, folinic acid and infusional 5FU; ²Results in wild-type KRAS population. PFS: Progression-free survival; OS: Overall survival; FA: Folinic acid; 5FU: 5-fluorouracil; FOLFIRI: Regimen of irinotecan, infusional fluorouracil and leucovorin; AIO: Arbeitsgemeinschaft internistische onkologie; CRYSTAL: CRYSTAL trial (cetuximab combined with irinotecan in first-line therapy for metastatic colorectal cancer); FIRE-3: AIO KRK-0306 trial; KRAS: v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog.

synergistic activity led to combinations of cetuximab and irinotecan-based regimens being assessed in first-line treatment of mCRC (Table 1).

In a small phase I / II German study that included 21 patients with EGFR-expressing mCRC who were treated with cetuximab and a combination of irinotecan, infusional 5FU and folinic acid [Arbeitsgemeinschaft internistische onkologie (AIO) group regimen], the response rate (RR) was 67% (two patients achieved complete response), median time to progression (TTP) was 9.9 mo and median OS was 33 mo. It is noteworthy that in this study five of the 21 patients (24%) initially had unresectable liver metastases, which became resectable. Four patients underwent surgery with curative intent, achieving R0 resection, and the fifth patient refused surgery^[37]. Another phase I / II study recruited a total of 52 patients with EGFR-expressing mCRC who were treated with cetuximab in combination with FOLFIRI, showing a RR of 48%, a median PFS of 8.6 mo and a median OS of 22.4 mo. In this study 14 of the 52 patients (27%) with initially unresectable metastatic disease (21% with liver metastases, 2% with lung involvement and 4% with metastasis to other sites) were able to undergo curative surgery, achieving R0 resections in 10 cases^[38].

Based on these results, the CRYSTAL study (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) was conducted, a randomised phase III trial evaluating the efficacy of combining cetuximab-FOLFIRI as compared to FOLFIRI alone in the first-line treatment of mCRC. A total of 1198 patients with EGFR-expressing mCRC were randomised to both arms of the study (599 subjects in each arm). This study conducted a retrospective analysis of KRAS mutation status. Knowing the KRAS mutation status in 89% of the patients, it was observed that the addition of cetuximab to FOLFIRI significantly increased RR (57.3% *vs* 39.7%, OR = 2.069; 95%CI: 1.515-2.826, *P* < 0.001) PFS (9.9 mo *vs* 8.4 mo, HR = 0.696; 95%CI: 0.558-0.867, *P* = 0.0012) and OS (23.5 mo *vs* 20 mo, HR = 0.796; 95%CI: 0.670-0.946, *P* = 0.0093) in the group of patients with wild-type KRAS. It was also noted that in this group there was a significant increase in the R0 resection rate for cetuximab-FOLFIRI (5.1% *vs* 2.0%, OR = 2.650;

95%CI: 1.083-6.490, *P* = 0.0265)^[6,20].

In an analysis of data from the CRYSTAL study, Piesseaux *et al*^[39] observed that in wild-type KRAS patients treated with cetuximab-FOLFIRI early tumour response > 20% was significantly associated with better OS (28.3 mo *vs* 19.6 mo, HR = 0.643; 95%CI: 0.480-0.862, *P* = 0.003) than in patients with early tumour response < 20%; however, this was not observed in patients treated with FOLFIRI alone (21.2 mo *vs* 20.2 mo, HR = 0.814; 95%CI: 0.626-1.059, *P* = 0.125)^[39]. These findings were confirmed in an analysis of data from the CRYSTAL and OPUS studies, which showed a strong association between early tumour response and long-term outcomes in patients with KRAS wild-type mCRC treated with chemotherapy and cetuximab, compared with patients treated with chemotherapy alone^[40]. These results suggest that early tumour response could be useful as a predictor of outcome, although this needs to be confirmed in prospective studies.

Despite the proven benefit of cetuximab in combination with FOLFIRI in the first-line treatment of KRAS wild-type mCRC, the optimal sequence of treatment in these patients has not been established. Whether we should start with an anti-EGFR and upon progression continue with an anti-vascular endothelial growth factor or vice versa is a question that has yet to be answered in randomised clinical trials. In this sense, preliminary results of the randomised FIRE-3 trial have recently been reported. This study conducted by the AIO group in Germany randomised patients in first-line therapy to cetuximab *vs* bevacizumab in combination with FOLFIRI. Of 592 patients with wild-type KRAS, 297 were treated with cetuximab-FOLFIRI and 295 with bevacizumab-FOLFIRI. In the ITT population, the RR was comparable in both arms of the study: 62% with cetuximab-FOLFIRI *vs* 57% with bevacizumab-FOLFIRI (OR = 1.18; 95%CI: 0.85-1.64, *P* = 0.183); however, in the population evaluable for response, there was a significant benefit in favour of the cetuximab arm (72.2% *vs* 63.1%, OR = 1.52; 95%CI: 1.05-2.19, *P* = 0.017). There were no statistically significant differences in PFS (10 mo *vs* 10.3 mo, HR = 1.06; 95%CI: 0.88-1.26, *P* = 0.547); however, cetuximab-FOLFIRI significantly prolonged overall sur-

Table 2 Clinical trials of cetuximab in combination with oxaliplatin-based chemotherapy

Clinical trial	Type of study	KRAS analysis	Treatment	Response rate (%)	R0 resection rate (%)	PFS (mo)	OS (mo)
Arnold <i>et al</i> ^[48]	Phase I b/ II	No	Cetuximab-FUFOX ¹	57%	4%	8.1	28.2
Tabernero <i>et al</i> ^[49]	Phase II	No	Cetuximab-FOLFOX4	72%	21%	12.3	30
OPUS, Bokemeyer <i>et al</i> ^[7,21]	Phase II	Yes	Cetuximab-FOLFOX4 vs FOLFOX4	57% vs 34% (OR = 2.551, <i>P</i> = 0.0027) ²	12% vs 3% (<i>P</i> = 0.0242) ²	8.3 vs 7.2 (HR = 0.567, <i>P</i> = 0.0064) ²	22.8 vs 18.5 (HR = 0.855, <i>P</i> = 0.39) ²
COIN, Maughan <i>et al</i> ^[23]	Phase III	Yes	Cetuximab-mFOLFOX6/XELOX vs mFOLFOX6/XELOX	64% vs 57% (OR = 1.35, <i>P</i> = 0.049) ²	15% vs 13% (<i>P</i> = 0.74) ²	8.6 vs 8.6 (HR = 0.96, <i>P</i> = 0.60) ²	17 vs 17.9 (HR = 1.04, <i>P</i> = 0.67) ²
NORDIC VII, Tveit <i>et al</i> ^[50]	Phase III	Yes	Cetuximab-Nordic FLOX vs Nordic FLOX ³	46% vs 47% (OR = 0.96, <i>P</i> = 0.89) ²	13.4% vs 14.4% ²	7.9 vs 8.7 (HR = 1.07, <i>P</i> = 0.66) ²	20.1 vs 22 (HR = 1.14, <i>P</i> = 0.48) ²

¹FUFOX: AIO group weekly regimen of oxaliplatin, folinic acid and infusional 5FU; ²Results in wild-type KRAS population; ³Nordic FLOX: Biweekly regimen of oxaliplatin, bolus 5FU and folinic acid. KRAS: v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; PFS: Progression-free survival; OS: Overall survival; 5FU: 5-fluorouracil; XELOX: Capecitabine plus oxaliplatin.

vival as compared to bevacizumab-FOLFIRI (28.7 mo *vs* 25 mo, HR = 0.77; 95%CI: 0.62 to 0.96, *P* = 0.017)^[41]. This difference may be explained by various hypotheses.

The deepness of response is the percentage of tumour shrinkage observed at the nadir compared with baseline. It was noted that the deepness of response could be a predictor for OS. A recent analysis of data from the CRYSTAL and OPUS trials observed that the median deepness of response was significantly greater in patients treated with chemotherapy and cetuximab as compared to chemotherapy alone (50.9% with FOLFIRI-cetuximab *vs* 33.3% with FOLFIRI alone, *P* < 0.0001, and 57.9% with FOLFOX4-cetuximab *vs* 30.7% with FOLFOX4 alone, *P* = 0.0008); in addition, a statistically significant association was identified between deepness of response and OS in the CRYSTAL study (*P* < 0.0001) and the OPUS study (*P* < 0.005)^[42,43]. It would be interesting to know about this particular point in the FIRE-3 study as well.

The data available to date show that the presence of BRAF mutations confers a poor prognosis in patients with mCRC^[20,22-26]. A difference in the percentage of patients with mutated BRAF between the two groups in this study may also have contributed to this difference in OS, although this seems unlikely, since the incidence of BRAF mutations is generally low (less than 10%) and not sufficient to explain a difference of four mo in median overall survival.

In addition, an imbalance in second-line treatments between the two arms could explain the OS results observed in this study. However, recent data presented by Modest *et al*^[44] at the ESMO 15th World Congress on Gastrointestinal Cancer reject this possible explanation. The percentages of patients receiving oxaliplatin, bevacizumab and anti-EGFR were 63.7%, 46.6% and 15.2% in the cetuximab arm and 62.8%, 17.3% and 41.4% in the bevacizumab arm.

Despite the results of the FIRE-3 trial, there are still doubts about when is the right time to use cetuximab or bevacizumab in the treatment of patients with KRAS

wild-type mCRC. We must wait for the results of the phase III CALGB 80405 trial, which compares chemotherapy (FOLFOX or FOLFIRI) with cetuximab or bevacizumab as first-line treatment in this patient group (clinicaltrials.gov/NCT00265850). It is expected to provide us with definitive data on the efficacy of cetuximab and its role in this setting.

Cetuximab in combination with oxaliplatin-based chemotherapy

Although studies comparing oxaliplatin-based regimens to irinotecan-based regimens in first-line treatment of mCRC have shown that both appear to be equivalent in terms of efficacy^[45-47], there are data suggesting that oxaliplatin-based regimens could produce a greater reduction in the size of metastatic lesions and thereby increase the chances of curative surgery^[47]. These data coupled with the proven benefit of cetuximab alone or in combination with irinotecan^[33-36] make it possible to assess the efficacy of cetuximab in combination with oxaliplatin-based regimens (Table 2).

An I b/ II phase German study assessed the feasibility of treatment with cetuximab in combination with FUFOX regimen (weekly schedule of oxaliplatin, infusional 5FU and folinic acid) in 49 patients with previously untreated EGFR-expressing mCRC, observing an RR of 57%, a median PFS of 8.1 mo and a median OS of 28.2 mo. In this study, four patients (8%) with initially unresectable liver metastases were able to undergo curative surgery, achieving an R0 resection in 2 cases (4%)^[48].

Tabernero *et al*^[49] reported encouraging results from a phase II study which included 43 patients with EGFR-expressing mCRC who were treated with cetuximab in combination with FOLFOX4 as first-line treatment. An RR of 72%, a median PFS of 12.3 mo and a median OS of 30 mo were observed. The most important data from this study include the fact that 10 patients (23%) were able to undergo resection with curative intent of previously unresectable metastatic lesions, achieving an R0 resection in 9 of them (21%).

The randomised phase II OPUS trial (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) assessed the efficacy of cetuximab in combination with FOLFOX4 as first-line treatment of mCRC^[7,21]. This study included a total of 337 patients who were treated with FOLFOX4 with or without cetuximab. The KRAS mutation status was analysed in 315 patients (93%), of which 179 (57%) were wild-type KRAS. Patients with wild-type KRAS treated with FOLFOX4-cetuximab had a significant increase in RR (57% *vs* 34%, OR = 2.551, 95%CI: 1.380-4.717, *P* = 0.0027), PFS (8.3 mo *vs* 7.2 mo, HR = 0.567, 95%CI: 0.375-0.856, *P* = 0.0064) and R0 resection rate (12% *vs* 3%, *P* = 0.0242) as compared to patients with wild-type KRAS treated with FOLFOX4 alone. The OS was higher in the cetuximab-FOLFOX4 arm, although this difference was not statistically significant (22.8 mo *vs* 18.5 mo, HR = 0.855, 95%CI: 0.599-1.219, *P* = 0.39)^[21]. One of the possible causes for this lack of statistical significance is the limited sample size. There was a difference of four mo in median OS in favour of the experimental arm, which is clinically relevant, and it is likely that this difference would have reached statistical significance with a larger sample size. Also, it is noteworthy that the OS for first-line treatment can be affected by therapy received after the study (in this study 23% of patients in the control arm received anti-EGFR treatment after the study).

While both the CRYSTAL and the OPUS studies demonstrate the clinical efficacy of adding cetuximab to standard chemotherapy in first-line treatment of KRAS wild-type mCRC, two phase III randomised trials of cetuximab and oxaliplatin-based chemotherapy did not confirm these results and raise questions about the efficacy of cetuximab in this setting.

In the COIN trial (Continuous Chemotherapy plus Cetuximab or Intermittent Chemotherapy), 2445 patients with mCRC were randomised to the 3 treatment arms (continuous chemotherapy, continuous chemotherapy with cetuximab and intermittent chemotherapy), of which 815 patients were assigned to receive continuous chemotherapy and 815 patients to continuous chemotherapy in combination with cetuximab. Of these 1630 patients, the KRAS mutation status was analysed in tumour samples of 1316 (81%) patients, and 565 (43%) showed KRAS mutations. The cetuximab arm included 357 patients with wild-type KRAS, of whom 117 received mFOLFOX6 and 240 received capecitabine plus oxaliplatin (XELOX). In the KRAS wild-type population, although there was a significant increase in RR in the cetuximab group (64% *vs* 57%, OR = 1.35, 95%CI: 1.00-1.82, *P* = 0.049), no significant differences were found in either resection rate (13% in the control group *vs* 15% in the cetuximab group, *P* = 0.74) or PFS (8.6 mo in the control group *vs* 8.6 mo in the cetuximab group, HR = 0.96; 95%CI: 0.82-1.12, *P* = 0.60) or OS (17.9 mo in the control arm *vs* 17.0 mo in the cetuximab arm, HR = 1.04; 95%CI: 0.87-1.23, *P* = 0.67). However, an exploratory analysis in the KRAS wild-type population showed an improvement in PFS with

cetuximab in patients receiving mFOLFOX6 (HR = 0.72, 95%CI: 0.53-0.98, *P* = 0.037), but not in patients receiving XELOX (HR = 1.02, 95%CI: 0.82-1.26, *P* = 0.88)^[23].

The NORDIC VII trial evaluated the efficacy of cetuximab in combination with a bolus 5FU, folinic acid and oxaliplatin regimen (Nordic FLOX regimen). A total of 566 patients were recruited, who were randomised to 3 treatment arms: Nordic FLOX (arm A), Nordic FLOX with cetuximab (arm B) and Nordic FLOX intermittently with continuous cetuximab (arm C). The KRAS mutation status was evaluated in 498 (88%) patients, of whom 303 were wild-type KRAS (97, 97 and 109 patients in arms A, B and C, respectively). The main comparison to evaluate the efficacy of cetuximab was conducted between arms A and B, showing that adding cetuximab to Nordic FLOX did not provide any benefit in the KRAS wild-type population, the RR being 46% *vs* 47% (OR = 0.96; 95%CI: 0.55-1.69, *P* = 0.89), median PFS 7.9 mo *vs* 8.7 mo (HR = 1.07; 95%CI: 0.79-1.45, *P* = 0.66) and median OS 20.1 mo *vs* 22 mo (HR = 1.14; 95%CI: 0.80-1.61, *P* = 0.48), with Nordic biweekly regimen of oxaliplatin, bolus 5FU and folinic acid (FLOX)-cetuximab and Nordic FLOX, respectively^[50].

It has been suggested that a possible explanation for these discrepant results could be that the chemotherapeutic agents combined with fluoropyrimidines may affect the response to cetuximab in different ways and that irinotecan-based regimens may be more effective than oxaliplatin-based regimens in combination with cetuximab. However, the OPUS study results and preclinical data support the synergistic activity of cetuximab and oxaliplatin^[51-54]. In addition, a phase II study performed by the Central European Cooperative Oncology Group (CECOG) found no significant differences in RR (43% *vs* 45%, OR = 0.93; 95%CI: 0.49-1.77), PFS (8.6 mo *vs* 8.3 mo, HR = 1.06; 95%CI: 0.74-1.52, *P* = 0.7375) or OS (17.4 mo *vs* 18.9 mo, HR = 0.98; 95%CI: 0.67-1.44, *P* = 0.9230) when comparing combinations of cetuximab with FOLFOX6 or FOLFIRI^[55].

Another important observation that can be drawn from these studies is that cetuximab may be more effective with infusional 5FU-based regimens than with bolus 5FU- or capecitabine-based regimens^[54]. In the cetuximab arm of the COIN study, the number of patients receiving XELOX exceeded the number of patients receiving mFOLFOX6, while in the NORDIC VII study all patients were treated with 5FU bolus-based chemotherapy, which may also have contributed to the negative results of both studies.

Furthermore, the COIN study showed increased toxicity when cetuximab was added to XELOX, and the capecitabine dose therefore had to be reduced in that arm of the study. The combination of cetuximab and capecitabine appears to increase the gastrointestinal and dermatological toxicity observed with each of these drugs separately. The reduced intensity of the chemotherapy dose may have contributed to the lack of benefit seen in this study^[23].

Finally, an analysis of combined data from the CRYSTAL and OPUS studies confirms the benefit in all efficacy parameters of adding cetuximab to first-line chemotherapy in patients with KRAS wild-type mCRC. In this combined analysis of 845 patients with KRAS wild-type tumours, it was observed that adding cetuximab to standard chemotherapy in this setting significantly improves the RR (OR = 2.16; $P < 0.0001$), PFS (HR = 0.66; $P < 0.001$) and OS (HR = 0.81; $P = 0.0062$)^[24].

CETUXIMAB-BASED THERAPY FOR SPECIAL SITUATIONS

Cetuximab plus chemotherapy as neoadjuvant treatment of liver-only metastases

In patients with metastatic disease limited to the liver, surgical resection of these metastases is the only potentially curative option, with 5-year survival rates of 45%-55% reported in recent publications^[56-58]. In this setting, there is evidence suggesting that treatment with standard chemotherapy regimens based on oxaliplatin or irinotecan in patients with unresectable liver metastases increases the number of candidates for surgical rescue^[59-66]. As we described previously, resection rates of 8%-23% for initially unresectable liver metastases were reported in phase II studies of patients with an unknown KRAS mutation status, treated with cetuximab and irinotecan or oxaliplatin-based chemotherapy^[37,38,48,49]. Moreover, adding cetuximab to standard chemotherapy has proven to increase the likelihood of response in patients with wild-type KRAS, significantly increasing R0 resection rates^[20,21]. Despite this, no definitive conclusions can be drawn from these studies, since they were not formally designed to assess resection rate. However, these encouraging results have led to studies assessing the role of neoadjuvant cetuximab in the treatment of liver metastases, showing high rates of R0 resections (Table 3).

In the CELIM phase II study, 111 patients with unresectable colorectal liver metastases were randomised to cetuximab in combination with FOLFIRI or FOLFOX6. It was observed that for cetuximab-FOLFOX6 the RR was 68%, while for cetuximab-FOLFIRI the RR was 57%; however, this difference was not statistically significant (OR = 1.62; 95%CI: 0.74-3.59, $P = 0.23$). The R0 resection rate was 34% in the overall population, 38% in the cetuximab-FOLFOX6 group and 30% in the cetuximab-FOLFIRI group. In a retrospective analysis based on KRAS mutation status, a greater RR was observed in patients with wild-type KRAS (70%) as compared to patients with mutated KRAS (41%); this difference was statistically significant (OR = 3.42; 95%CI: 1.35-8.66, $P = 0.0080$), with an R0 resection rate of 33% reported in the KRAS wild-type population. In this study, a team of expert surgeons conducted a retrospective review of resectability, observing that the resectability rate increased significantly, from 32% at baseline to 60% after chemotherapy ($P < 0.0001$)^[67,68]. In the KRAS wild-type population, there were no significant differences

between cetuximab-FOLFOX6 and cetuximab-FOLFIRI in terms of PFS (12.1 mo *vs* 11.5 mo, HR = 1.09; 95%CI: 0.66-1.79) or OS (35.8 mo *vs* 41.6 mo, HR = 1.01; 95%CI: 0.55-1.86)^[68]. It should be noted that patients who underwent R0 liver resection showed a significant improvement in OS as compared to patients without R0 resection (53.9 mo *vs* 27.3 mo, $P = 0.002$)^[69].

In a recent publication by Ye *et al*^[70], 138 patients with KRAS wild-type mCRC and unresectable synchronous liver metastases after resection of the primary tumour were randomised to receive cetuximab plus chemotherapy (mFOLFOX6 or FOLFIRI) or chemotherapy alone. The addition of cetuximab to chemotherapy was associated with a significant increase in RR (57.1% *vs* 29.4%, $P < 0.01$) and R0 resection rate (25.7% *vs* 7.4%, OR = 4.37; $P < 0.01$). Treatment with cetuximab plus chemotherapy significantly prolonged PFS (10.2 mo *vs* 5.8 mo, HR = 0.60; $P = 0.004$) and OS (30.9 mo *vs* 21.0 mo, HR = 0.54; $P = 0.013$) as compared to chemotherapy alone. Furthermore, in the group of patients treated with cetuximab plus chemotherapy, no significant differences were observed between mFOLFOX6 and FOLFIRI in terms of RR (52.8% *vs* 59.1%, $P = 0.31$), PFS (10.1 mo *vs* 9.1 mo, $P = 0.28$) or OS (34.8 mo *vs* 23.1 mo, $P = 0.24$). The study also found that patients who underwent a liver resection had a significant improvement in OS *vs* patients who did not undergo surgery, both in the cetuximab plus chemotherapy group (46.4 mo *vs* 25.7 mo, $P = 0.007$) and in the chemotherapy alone group (36.0 mo *vs* 19.6 mo, $P = 0.016$).

A higher response rate has been shown to be associated with a higher probability of resection with curative intent^[71], and it has been seen that triple- *vs* double-agent chemotherapy significantly increases the RR and R0 resection rate^[72]. Based on these assumptions, the association of cetuximab with a triple combination of chemotherapeutic agents (5FU, irinotecan and oxaliplatin) was also assessed in order to increase the resectability of colorectal liver metastases.

Garufi *et al*^[73] conducted the POCHER phase II trial, which assessed the combination of cetuximab with chronomodulated infusion of irinotecan, 5FU, leucovorin and oxaliplatin (chrono-IFLO regimen) as neoadjuvant treatment in 43 patients with unresectable colorectal liver metastases. KRAS mutation analysis was performed in 37 patients, showing a high incidence of wild-type KRAS (80%). In the overall population, the RR was 79.1%, reaching a rate of 60% for R0 resections. With a median follow-up of 22 mo, the estimated median OS was 37 mo, with a 2-year survival rate of 68.2% in the overall population, 80.6% in patients who underwent R0 resection and 47.1% in patients who did not undergo resection of metastases ($P = 0.01$).

In a phase II study, 42 patients with mCRC received cetuximab in combination with 5FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX regimen) as first-line treatment. Of 40 patients evaluated for KRAS mutation status, 60% were KRAS wild-type. The RR was 80.9% in the overall population, 83.3% in patients with wild-

Table 3 Clinical trials of neoadjuvant cetuximab in the treatment of liver metastases

Clinical trial	Type of study	KRAS analysis	Treatment	Response rate	R0 resection rate	PFS (mo)	OS (mo)
CELIM, Folprecht <i>et al</i> ^[67,68]	Phase II	Yes	Cetuximab-FOLFOX6 vs cetuximab-FOLFIRI	68% vs 57% (OR = 1.62, <i>P</i> = 0.23)	38% vs 30%	11.2 vs 10.5 (HR = 1.15, NS)	35.7 vs 29.0 (HR = 1.09, NS)
			Wild-type KRAS vs mutated KRAS	70% vs 41% (OR = 3.42, <i>P</i> = 0.008)	33% vs 30%	11.9 vs 9.9 (HR = 1.31, NS)	36.1 vs 27.4 (HR = 1.48, NS)
Ye <i>et al</i> ^[70]	Phase IV	Yes	Cetuximab-mFOLFOX6/FOLFIRI vs mFOLFOX6/FOLFIRI	57.1% vs 29.4% (<i>P</i> < 0.01)	25.7% vs 7.4% (<i>P</i> < 0.01)	10.2 vs 5.8 (HR = 0.6, <i>P</i> = 0.004)	30.9 vs 21 (HR = 0.54, <i>P</i> = 0.013)
			Cetuximab-mFOLFOX6 vs Cetuximab-FOLFIRI	52.8% vs 59.1% (<i>P</i> = 0.31)		10.1 vs 9.1 (<i>P</i> = 0.28)	34.8 vs 23.1 (<i>P</i> = 0.24)
POCHER, Garufi <i>et al</i> ^[73]	Phase II	Yes	Cetuximab-Chrono-IFLO ¹	79.1	60	14	37
Saridaki <i>et al</i> ^[75]	Phase II	Yes	Cetuximab-FOLFIRINOX	70	37 ² 62 ³	10.2	30.3

¹Chronomodulated infusion of irinotecan, 5FU, leucovorin and oxaliplatin; ²R0 resection rate in overall population; ³R0 resection rate in the subgroup of patients with metastatic disease limited to the liver. KRAS: v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; PFS: Progression-free survival; OS: Overall survival; NS: Not significant; 5FU: 5-fluorouracil; FOLFIRI: Regimen of irinotecan, infusional fluorouracil and leucovorin.

type KRAS and 81.3% in patients with mutated KRAS, with no statistical differences between groups. In the overall population, median PFS was 9.5 mo and median OS was 24.7 mo. In the KRAS population, median PFS was slightly higher in the wild-type KRAS group as compared to mutated KRAS group (9.9 mo *vs* 7.8 mo); the median OS in the mutated KRAS group was 23.1 mo, while it was not reached in the wild-type KRAS group^[74]. These promising results have led to the commencement of the PRODIGE 14 randomised phase II trial, which is currently ongoing. It will assess resectability in patients with unresectable colorectal liver metastases who will be treated with targeted therapy in combination with a triple-agent (FOLFIRINOX) or double-agent (FOLFOX or FOLFIRI) chemotherapy. The targeted therapy will be chosen according to KRAS mutation status: cetuximab in patients with wild-type KRAS and bevacizumab in mutated KRAS patients (clinicaltrials.gov/NCT01442935).

Another small phase II study also assessed the first-line effectiveness of cetuximab in combination with FOLFIRINOX in 30 unselected patients with KRAS wild-type mCRC, showing an RR of 70% (with 13.3% complete responses), median TTP of 10.2 mo and a median OS of 30.3 mo. Of all the patients, 11 (37%) underwent R0 secondary resection (10 patients with liver lesions and one patient with metastatic lung disease). In this study, 16 patients had metastatic disease limited to the liver, with a rate of R0 secondary resection in this subgroup of 62% (10/16)^[75].

While triple-agent chemotherapy in combination with cetuximab could generate a high response rate and consequently increase the resectability rate, it also appears to be associated with a high incidence of grade 3-4 toxicity^[73-75], so we must wait for results of randomised studies with a larger sample size, such as the PRODIGE 14 study, to confirm the efficacy of this combination and obtain further details about its toxicity profile and tolerability.

Treatment with cetuximab in elderly patients

The goals of chemotherapy in elderly patients with un-

resectable mCRC are the same as in younger patients, namely to control symptoms and prolong survival. However, elderly patients often have comorbidities and may have impaired organ function associated with age, so we must carefully evaluate the risks and benefits expected from chemotherapy^[76,77].

In several clinical trials the number of elderly patients included was small and few have been conducted specifically in this population, so the best available evidence on the efficacy and toxicity of treatment in this patient group mainly derives from subgroup analysis of large phase III trials and extrapolating data from the non-elderly population.

Studies carried out in the elderly and analysis of combined data and subgroups of phase III studies suggest that the benefits of elderly patients with mCRC being treated with combination therapy are similar to those observed in younger patients^[78-83]. Data also show that the efficacy of cetuximab-based therapy in elderly patients with previously treated mCRC appears to be similar to that of younger patients, with acceptable tolerability^[84,85]. The role of cetuximab in first-line treatment of mCRC in this population has been evaluated in two phase II clinical trials conducted by the Spanish Cooperative Group for the Treatment of Digestive Tumours.

The first phase II study evaluated the efficacy and safety of cetuximab monotherapy as first-line treatment for elderly patients with mCRC. There were a total of 41 patients \geq 70 years, with the KRAS mutation analysis only being possible in 23 of them, showing five KRAS mutated patients and 18 wild-type KRAS. In the overall population, there was a low RR of 14.6%, with a median TTP of 2.5 mo and a median OS of 11.1 mo. In the KRAS population, five KRAS wild-type patients had an objective response, whereas KRAS mutated patients showed no objective response; in addition, seven patients with wild-type KRAS were progression-free at week 12, whereas only one patient with mutated KRAS was progression-free at the same time point; however, these differences were not statistically significant, probably be-

cause of the small sample size^[86].

In another phase II study, Sastre *et al.*^[87] evaluated the combination of cetuximab with capecitabine in the same setting with the aim of increasing RR. A total of 66 patients ≥ 70 years were included, performing KRAS mutation analysis in 58 (88%) of them, which showed an incidence of 50% for both wild-type and mutated KRAS. After 27 patients were included the protocol had to be amended for safety reasons, reducing the dose of capecitabine from 1250 to 1000 mg/m² per 12 h. In the overall population, the RR was 31.8%, median PFS was 7.1 mo and median OS was 16.1 mo. The RR and median PFS were significantly higher in the KRAS wild-type as compared to the KRAS mutated group (48.3% *vs* 20.7%, $P = 0.027$, and 8.4 mo *vs* 6.0 mo, $P = 0.024$), while only a non-significant trend toward a longer OS was observed for KRAS wild-type patients (18.8 mo *vs* 13.5 mo, $P = 0.107$). It is important to mention that before dose reduction, the incidence of grade 3-4 toxicity was high, mainly paronychia (29.6%), acneiform rash (29.6%), hand-foot syndrome (22.2%) and diarrhoea (18.5%); however, after dose reduction, the incidence of paronychia and diarrhoea decreased (7.7% and 12.8%, respectively), although the incidence of acneiform rash and hand-foot syndrome was similar (28.2% and 20.5%, respectively). As described previously, the combination of cetuximab and capecitabine appears to increase the toxicity associated with each of these drugs; thus, the high incidence of grade 3-4 toxicity observed in this study may be explained by the additive toxic effect of the combination, rather than the age of patients.

Although no definitive conclusions can be drawn from these studies, in elderly patients with KRAS wild-type mCRC, the results appear to be comparable to those observed in younger patients. Therefore, it seems advisable to use cetuximab in combination with chemotherapy, choosing the regimen based on the toxicity profile and assessing each patient individually.

CONCLUSION

KRAS is a biomarker that has proved useful in selecting patients eligible to receive cetuximab. Currently, NRAS is presented as a new biomarker that could help identify responders to anti-EGFR drugs. However, further studies are still needed to identify new biomarkers that, in combination with KRAS, can help us make a more precise selection of suitable patients for EGFR-targeted therapy.

The benefit of cetuximab in combination with FOLFIRI as first-line treatment in patients with KRAS wild-type mCRC has been clearly demonstrated in the CRYSTAL study, so this combination could be considered as standard. While there is evidence supporting the use of cetuximab in combination with FOLFOX in patients with KRAS wild-type mCRC, given the conflicting results observed in the COIN and NORDIC VII trials, the use of cetuximab combined with oxaliplatin plus capecitabine or bolus 5FU cannot be recommended. Given the high

response rates and high rates of R0 resection observed in selected population studies, cetuximab in combination with standard chemotherapy doublets should be a therapeutic option to consider in patients with unresectable liver-only metastases from KRAS wild-type colorectal cancer. In this setting, the use of triple-agent chemotherapy in combination with cetuximab has shown encouraging results; however, we expect results from studies with a larger sample size to provide more data on efficacy and toxicity.

There is evidence that treatment with cetuximab in combination with chemotherapy in elderly patients appears to have similar efficacy to that observed in younger patients, with acceptable tolerability, so that its use should be considered in elderly patients with KRAS wild-type mCRC, who are in good general health without relevant comorbidities.

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 Field K, Lipton L. Metastatic colorectal cancer-past, progress and future. *World J Gastroenterol* 2007; **13**: 3806-3815 [PMID: 17657834]
- 3 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]
- 4 Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. *J Clin Oncol* 2005; **23**: 4553-4560 [PMID: 16002847 DOI: 10.1200/JCO.2005.17.749]
- 5 Broadbridge VT, Karapetis CS, Price TJ. Cetuximab in metastatic colorectal cancer. *Expert Rev Anticancer Ther* 2012; **12**: 555-565 [PMID: 22594891 DOI: 10.1586/era.12.25]
- 6 Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pinter 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]
- 7 Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, Donea S, Ludwig H, Schuch G, Stroh C, Loos AH, Zube 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]
- 8 Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; **359**: 1757-1765 [PMID: 18946061 DOI: 10.1056/NEJMoa0804385]
- 9 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: 17657834]

- 17664471 DOI: 10.1200/JCO.2006.10.5437]
- 10 **Lièvre A**, Bachet JB, Boige V, Cayre A, Le Corre D, Buc E, Ychou M, Bouché O, Landi B, Louvet C, André T, Bibeau F, Diebold MD, Rougier P, Ducreux M, Tomasic G, Emile JF, Penault-Llorca F, Laurent-Puig P. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol* 2008; **26**: 374-379 [PMID: 18202412 DOI: 10.1200/JCO.2007.12.5906]
 - 11 **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]
 - 12 **De Roock W**, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, Kalogeris KT, Kotoula V, Papamichael D, Laurent-Puig P, Penault-Llorca F, Rougier P, Vincenzi B, Santini D, Tonini G, Cappuzzo F, Frattini M, Molinari F, Saletti P, De Dosso S, Martini M, Bardelli A, Siena S, Sartore-Bianchi A, Tabernero J, Macarulla T, Di Fiore F, Gangloff AO, Ciardiello F, Pfeiffer P, Qvortrup C, Hansen TP, Van Cutsem E, Piessevaux H, Lambrechts D, Delorenzi M, Tejpar S. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 2010; **11**: 753-762 [PMID: 20619739 DOI: 10.1016/S1470-2045(10)70130-3]
 - 13 **Di Fiore F**, Blanchard F, Charbonnier F, Le Pessot F, Lamy A, Galais MP, Bastit L, Killian A, Sesboüé R, Tuech JJ, Queuniet AM, Paillot B, Sabourin JC, Michot F, Michel P, Frebourg T. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy. *Br J Cancer* 2007; **96**: 1166-1169 [PMID: 17375050 DOI: 10.1038/sj.bjc.6603685]
 - 14 **Lea IA**, Jackson MA, Li X, Bailey S, Peddada SD, Dunnick JK. Genetic pathways and mutation profiles of human cancers: site- and exposure-specific patterns. *Carcinogenesis* 2007; **28**: 1851-1858 [PMID: 17693665 DOI: 10.1093/carcin/bgm176]
 - 15 **Normanno N**, Tejpar S, Morgillo F, De Luca A, Van Cutsem E, Ciardiello F. Implications for KRAS status and EGFR-targeted therapies in metastatic CRC. *Nat Rev Clin Oncol* 2009; **6**: 519-527 [PMID: 19636327 DOI: 10.1038/nrclinonc.2009.111]
 - 16 **Li S**, Schmitz KR, Jeffrey PD, Wiltzius JJ, Kussie P, Ferguson KM. Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. *Cancer Cell* 2005; **7**: 301-311 [PMID: 15837620 DOI: 10.1016/j.ccr.2005.03.003]
 - 17 **Vincenzi B**, Santini D, Tonini G. New issues on cetuximab mechanism of action in epidermal growth factor receptor-negative colorectal cancer: the role of vascular endothelial growth factor. *J Clin Oncol* 2006; **24**: author reply 1957-1958 [PMID: 16622275 DOI: 10.1200/JCO.2005.05.0450]
 - 18 **Jean GW**, Shah SR. Epidermal growth factor receptor monoclonal antibodies for the treatment of metastatic colorectal cancer. *Pharmacotherapy* 2008; **28**: 742-754 [PMID: 18503402 DOI: 10.1592/phco.28.6.742]
 - 19 **Kurai J**, Chikumi H, Hashimoto K, Yamaguchi K, Yamasaki A, Sako T, Touge H, Makino H, Takata M, Miyata M, Nakamoto M, Burioka N, Shimizu E. Antibody-dependent cellular cytotoxicity mediated by cetuximab against lung cancer cell lines. *Clin Cancer Res* 2007; **13**: 1552-1561 [PMID: 17332301 DOI: 10.1158/1078-0432.CCR-06-1726]
 - 20 **Van Cutsem E**, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, Shchepotin I, Maurel J, Cunningham D, Tejpar S, Schlichting M, Zube 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]
 - 21 **Bokemeyer C**, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zube 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]
 - 22 **Di Nicolantonio F**, Martini M, Molinari F, Sartore-Bianchi A, Arena S, Saletti P, De Dosso S, Mazzucchelli L, Frattini M, Siena S, Bardelli A. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 5705-5712 [PMID: 19001320 DOI: 10.1200/JCO.2008.18.0786]
 - 23 **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]
 - 24 **Bokemeyer C**, Van Cutsem E, Rougier P, Ciardiello F, Heeger S, Schlichting M, Celik I, Köhne CH. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. *Eur J Cancer* 2012; **48**: 1466-1475 [PMID: 22446022 DOI: 10.1016/j.ejca.2012.02.057]
 - 25 **Richman SD**, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, Taylor G, Barrett JH, Quirke P. KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial. *J Clin Oncol* 2009; **27**: 5931-5937 [PMID: 19884549 DOI: 10.1200/JCO.2009.22.4295]
 - 26 **Ogino S**, Nosho K, Kirkner GJ, Kawasaki T, Meyerhardt JA, Loda M, Giovannucci EL, Fuchs CS. CpG island methylator phenotype, microsatellite instability, BRAF mutation and clinical outcome in colon cancer. *Gut* 2009; **58**: 90-96 [PMID: 18832519 DOI: 10.1136/gut.2008.155473]
 - 27 **De Roock W**, De Vriendt V, Normanno N, Ciardiello F, Tejpar S. KRAS, BRAF, PIK3CA, and PTEN mutations: implications for targeted therapies in metastatic colorectal cancer. *Lancet Oncol* 2011; **12**: 594-603 [PMID: 21163703 DOI: 10.1016/S1470-2045(10)70209-6]
 - 28 **Oliner KS**, Douillard J-Y, Siena S, Tabernero J, Burkes RL, Barugel ME, Humblet Y, Bodoky G, Cunningham D, Jassam J, Rivera F, Kocakova I, Ruff P, Blasinska-Morawiec M, Smakal M, Williams RT, Rong A, Wizezorek JS, Sidhu R, Patterson SD. Analysis of KRAS/NRAS and BRAF mutations in the phase III PRIME study of panitumumab (pmab) plus FOLF-FOX versus FOLFOX as first-line treatment (tx) for metastatic colorectal cancer (mCRC). *J Clin Oncol* (ASCO Meeting Abstracts) 2013; **31** Suppl: abstr 3511
 - 29 **Stintzing S**, Jung A, Rossius L, Modest DP, Fischer von Weikersthal L, Decker T, Möhler M, Scheithauer W, Kirchner T, Heinemann V. 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 (Sep 27-Oct 1, 2013; Amsterdam, The Netherlands). *European Cancer Congress* 2013; **2013**: abstract 17
 - 30 **Jacobs B**, De Roock W, Piessevaux H, Van Oirbeek R, Biesmans B, De Schutter J, Fieuws S, Vandesompele J, Peeters M, Van Laethem JL, Humblet Y, Penault-Llorca F, De Hertogh G, Laurent-Puig P, Van Cutsem E, Tejpar S. Amphiregulin and epiregulin mRNA expression in primary tumors predicts outcome in metastatic colorectal cancer treated with cetuximab. *J Clin Oncol* 2009; **27**: 5068-5074 [PMID: 19738126 DOI: 10.1200/JCO.2008.21.3744]
 - 31 **Di Bartolomeo M**, Pietrantonio F, Perrone F, Dotti KF,

- Lampis A, Bertan C, Beretta E, Rimassa L, Carbone C, Biondani P, Passalacqua R, Pilotti S, Bajetta E; on behalf of Italian Trials in Medical Oncology (ITMO) Group. Lack of KRAS, NRAS, BRAF and TP53 mutations improves outcome of elderly metastatic colorectal cancer patients treated with cetuximab, oxaliplatin and UFT. *Target Oncol* 2013 Jul 3; Epub ahead of print [PMID: 23821376 DOI: 10.1007/s11523-013-0283-8]
- 32 **Pentheroudakis G**, Kotoula V, De Roock W, Kouvatseas G, Papakostas P, Makatsoris T, Papamichael D, Xanthakis I, Sgouros J, Televantou D, Kafiri G, Tsamandas AC, Razis E, Galani E, Bafaloukos D, Efstratiou I, Bompolaki I, Pectasides D, Pavlidis N, Tejpar S, Fountzilas G. Biomarkers of benefit from cetuximab-based therapy in metastatic colorectal cancer: interaction of EGFR ligand expression with RAS/RAF, PIK3CA genotypes. *BMC Cancer* 2013; **13**: 49 [PMID: 23374602 DOI: 10.1186/1471-2407-13-49]
 - 33 **Saltz LB**, Meropol NJ, Loehrer PJ, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 2004; **22**: 1201-1208 [PMID: 14993230 DOI: 10.1200/JCO.2004.10.182]
 - 34 **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]
 - 35 **Lenz HJ**, Van Cutsem E, Khambata-Ford S, Mayer RJ, Gold P, Stella P, Mirtsching B, Cohn AL, Pippas AW, Azarnia N, Tsuchihashi Z, Mauro DJ, Rowinsky EK. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. *J Clin Oncol* 2006; **24**: 4914-4921 [PMID: 17050875 DOI: 10.1200/JCO.2006.06.7595]
 - 36 **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, Zube 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]
 - 37 **Folprecht G**, Lutz MP, Schöffski P, Seufferlein T, Nolting A, Pollert P, Köhne CH. Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. *Ann Oncol* 2006; **17**: 450-456 [PMID: 16303861 DOI: 10.1093/annonc/mdj084]
 - 38 **Raoul JL**, Van Laethem JL, Peeters M, Brezault C, Hussein F, Cals L, Nippgen J, Loos AH, Rougier P. Cetuximab in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) in the initial treatment of metastatic colorectal cancer: a multicentre two-part phase I/II study. *BMC Cancer* 2009; **9**: 112 [PMID: 19366444 DOI: 10.1186/1471-2407-9-112]
 - 39 **Piessevaux H**, Schlichting M, Heeger S, Van Cutsem E, Tejpar S. Early tumor shrinkage for the prediction of efficacy of cetuximab in metastatic colorectal cancer (mCRC): analysis from the CRYSTAL study. *Ann Oncol* 2010; **21** Suppl 8: viii189-viii224 [DOI: 10.1093/annonc/mdq521]
 - 40 **Piessevaux H**, Van Cutsem E, Bokemeyer C, Schlichting M, Heeger S, Tejpar S. Early tumor shrinkage and long-term outcome in metastatic colorectal cancer (mCRC): Assessment of predictive utility across treatment arms in the CRYSTAL and OPUS studies. *J Clin Oncol* (ASCO Meeting Abstracts) 2011; **29** Suppl: abstr 3572
 - 41 **Heinemann V**, Fischer von Weikersthal L, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S-E, Heintges T, Lerchenmüller J, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Mueller S, Schaefer B, Modest DP, Jung A, Stintzing S. 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* (ASCO Meeting Abstracts) 2013; **31** Suppl: abstr LBA3506
 - 42 **Mansmann UR**, Sartorius U, Laubender RP, Giessen CA, Esser R, Heinemann V. Quantitative analysis of the impact of deepness of response on postprogression survival time following first-line treatment in patients with mCRC. *J Clin Oncol* (ASCO Meeting Abstracts) 2013; **31** Suppl: abstr 3630
 - 43 **Mansmann U**, Sartorius U, Laubender R, Giessen C, Esser R, Heinemann V. Quantitative analysis of the impact of deepness of response on post-progression survival time following first-line treatment in patients with mCRC. *Ann Oncol* 2013; **24** Suppl 4: iv14-iv15 [DOI: 10.1093/annonc/mdt201.9]
 - 44 **Modest D**, Fischer von Weikersthal L, Stintzing S, Decker T, Kiani A, Vehling-Kaiser U, Al Batran S-E, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Schaefer B, Jung A, Heinemann V. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS-wildtype metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). *Ann Oncol* 2013; **24** Suppl 4: iv22-iv23 [DOI: 10.1093/annonc/mdt201.29]
 - 45 **Punt CJ**. Irinotecan or oxaliplatin for first-line treatment of advanced colorectal cancer? *Ann Oncol* 2005; **16**: 845-846 [PMID: 15890668 DOI: 10.1093/annonc/mdi196]
 - 46 **Colucci G**, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, Carteni G, Agostara B, Pezzella G, Manzione L, Borsellino N, Misino A, Romito S, Durini E, Cordio S, Di Seri M, Lopez M, Maiello E, Montemurro S, Cramarossa A, Lorusso V, Di Bisceglie M, Chiarenza M, Valerio MR, Guida T, Leonardi V, Piscanti S, Rosati G, Carozza F, Netti G, Valdesi M, Filippelli G, Fortunato S, Mancarella S, Brunetti C. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005; **23**: 4866-4875 [PMID: 15939922 DOI: 10.1200/JCO.2005.07.113]
 - 47 **Tournigand C**, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; **22**: 229-237 [PMID: 14657227 DOI: 10.1200/JCO.2004.05.113]
 - 48 **Arnold D**, Höhler T, Dittrich C, Lordick F, Seufferlein T, Riemann J, Wöll E, Herrmann T, Zube A, Schmoll HJ. Cetuximab in combination with weekly 5-fluorouracil/folinic acid and oxaliplatin (FUFOX) in untreated patients with advanced colorectal cancer: a phase Ib/II study of the AIO GI Group. *Ann Oncol* 2008; **19**: 1442-1449 [PMID: 18441330 DOI: 10.1093/annonc/mdn150]
 - 49 **Tabernero J**, Van Cutsem E, Díaz-Rubio E, Cervantes A, Humblet Y, André T, Van Laethem JL, Soulié P, Casado E, Verslype C, Valera JS, Tortora G, Ciardiello F, Kisker O, de Gramont A. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2007; **25**: 5225-5232 [PMID: 18024868 DOI: 10.1200/JCO.2007.13.2183]
 - 50 **Tveit KM**, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pylhonen S, Sigurdsson F, Kure E, Ikeda T, Skovlund E, Fokstuen T, Hansen F, Hofslie 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]
 - 51 **Balin-Gauthier D**, Delord JP, Rochaix P, Mallard V, Thomas F, Hennebelle I, Bugat R, Canal P, Allal C. In vivo and in vitro antitumor activity of oxaliplatin in combination with

- cetuximab in human colorectal tumor cell lines expressing different level of EGFR. *Cancer Chemother Pharmacol* 2006; **57**: 709-718 [PMID: 16320055 DOI: 10.1007/s00280-005-0123-3]
- 52 **Prewett M**, Deevi DS, Bassi R, Fan F, Ellis LM, Hicklin DJ, Tonra JR. Tumors established with cell lines selected for oxaliplatin resistance respond to oxaliplatin if combined with cetuximab. *Clin Cancer Res* 2007; **13**: 7432-7440 [PMID: 18094427 DOI: 10.1158/1078-0432.CCR-07-1768]
 - 53 **Balin-Gauthier D**, Delord JP, Pillaire MJ, Rochaix P, Hoffman JS, Bugat R, Cazaux C, Canal P, Allal BC. Cetuximab potentiates oxaliplatin cytotoxic effect through a defect in NER and DNA replication initiation. *Br J Cancer* 2008; **98**: 120-128 [PMID: 18182978 DOI: 10.1038/sj.bjc.6604134]
 - 54 **Woo J**, Palmisiano N, Tester W, Leighton JC. Controversies in antiepidermal growth factor receptor therapy in metastatic colorectal cancer. *Cancer* 2013; **119**: 1941-1950 [PMID: 23504768 DOI: 10.1002/cncr.27994]
 - 55 **Ocvirk J**, Brodowicz T, Wrba F, Ciuleanu TE, Kurteva G, Beslija S, Koza I, Pápai Z, Messinger D, Yilmaz U, Faluhelyi Z, Yalcin S, Papamichael D, Wenczl M, Mrcic-Krmpotic Z, Shacham-Shmueli E, Vrbanc D, Esser R, Scheithauer W, Zielinski CC. Cetuximab plus FOLFOX6 or FOLFIRI in metastatic colorectal cancer: CECOG trial. *World J Gastroenterol* 2010; **16**: 3133-3143 [PMID: 20593498 DOI: 10.3748/wjg.v16.i25.3133]
 - 56 **Dexiang Z**, Li R, Ye W, Haifu W, Yunshi Z, Qinghai Y, Shenyong Z, Bo X, Li L, Xiangou P, Haohao L, Lechi Y, Tianshu L, Jia F, Xinyu Q, Jianmin X. Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases. *Ann Surg Oncol* 2012; **19**: 2860-2868 [PMID: 22526903 DOI: 10.1245/s10434-012-2356-9]
 - 57 **Saiura A**, Yamamoto J, Hasegawa K, Koga R, Sakamoto Y, Hata S, Makuuchi M, Kokudo N. Liver resection for multiple colorectal liver metastases with surgery up-front approach: bi-institutional analysis of 736 consecutive cases. *World J Surg* 2012; **36**: 2171-2178 [PMID: 22547015 DOI: 10.1007/s00268-012-1616-y]
 - 58 **Nanji S**, Cleary S, Ryan P, Guindi M, Selvarajah S, Grieg P, McGilvary I, Taylor B, Wei A, Moulton CA, Gallinger S. Up-front hepatic resection for metastatic colorectal cancer results in favorable long-term survival. *Ann Surg Oncol* 2013; **20**: 295-304 [PMID: 23054102 DOI: 10.1245/s10434-012-2424-1]
 - 59 **Adam R**, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, Kunstlinger F, Levi F, Bismuth F. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001; **8**: 347-353 [PMID: 11352309]
 - 60 **Adam R**, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giachetti S, Paule B, Kunstlinger F, Ghémar D, Levi F, Bismuth H. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; **240**: 644-657; discussion 657-658 [PMID: 15383792 DOI: 10.1097/01.sla.0000141198.92114.f6]
 - 61 **Pozzo C**, Basso M, Cassano A, Quirino M, Schinzari G, Trigila N, Vellone M, Giuliani F, Nuzzo G, Barone C. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004; **15**: 933-939 [PMID: 15151951 DOI: 10.1093/annonc/mdh217]
 - 62 **Alberts SR**, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, Levitt R, Rowland K, Nair S, Sargent DJ, Donohue JH. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005; **23**: 9243-9249 [PMID: 16230673 DOI: 10.1200/JCO.2005.07.740]
 - 63 **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]
 - 64 **Nordlinger B**, Van Cutsem E, Rougier P, Köhne CH, Ychou M, Sobrero A, Adam R, Arvidsson D, Carrato A, Georgoulas V, Giulianti F, Glimelius B, Golling M, Gruenberger T, Tabernero J, Wasan H, Poston G. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur J Cancer* 2007; **43**: 2037-2045 [PMID: 17766104 DOI: 10.1016/j.ejca.2007.07.017]
 - 65 **Nuzzo G**, Giuliani F, Ardito F, Vellone M, Pozzo C, Casano A, Giovannini I, Barone C. Liver resection for primarily unresectable colorectal metastases downsized by chemotherapy. *J Gastrointest Surg* 2007; **11**: 318-324 [PMID: 17458605 DOI: 10.1007/s11605-006-0070-2]
 - 66 **Adam R**, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, Ducreux M, Azoulay D, Bismuth H, Castaing D. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 2009; **27**: 1829-1835 [PMID: 19273699 DOI: 10.1200/JCO.2008.19.9273]
 - 67 **Folprecht G**, Gruenberger T, Bechstein WO, Raab HR, Lordick F, Hartmann JT, Lang H, Frilling A, Stoehlmacher J, Weitz J, Konopke R, Stroszczyński C, Liersch T, Ockert D, Herrmann T, Goekkurt E, Parisi F, Köhne CH. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010; **11**: 38-47 [PMID: 19942479 DOI: 10.1016/S1470-2045(09)70330-4]
 - 68 **Folprecht G**, Gruenberger T, Bechstein W, Lordick T, Lang H, Weitz J, Suedhoff T, Hartmann J, Liersch T, Koehne C. Progression free and overall survival after neoadjuvant treatment of colorectal liver metastases with cetuximab plus FOLFOX or FOLFIRI - Results of the CELIM study. *Eur J Cancer* 2011; **47** Suppl 1: S394 [DOI: 10.1016/S0959-8049(11)71654-9]
 - 69 **Folprecht G**, Gruenberger T, Bechstein W, Raab H-R, Weitz J, Lordick F, Hartmann JT, Lang H, Trarbach T, Stoehlmacher-Williams J, Liersch T, Ockert D, Jaeger D, Steger U, Suedhoff T, Kohne CH. Cetuximab and chemotherapy in the treatment of patients with initially "nonresectable" colorectal (CRC) liver metastases: Long-term follow-up of the CELIM trial. *J Clin Oncol* (ASCO Meeting Abstracts) 2013; **31** Suppl: abstr 3538
 - 70 **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]
 - 71 **Folprecht G**, Grothey A, Alberts S, Raab HR, Köhne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005; **16**: 1311-1319 [PMID: 15870084 DOI: 10.1093/annonc/mdi246]
 - 72 **Falcone A**, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; **25**: 1670-1676 [PMID: 17470860 DOI: 10.1200/JCO.2006.09.0928]
 - 73 **Garufi C**, Torsello A, Tumolo S, Ettorre GM, Zeuli M, Campanella C, Vennarecci G, Mottolese M, Sperduti I, Cognetti F. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer* 2010; **103**: 1542-1547 [PMID: 20959822 DOI: 10.1038/sj.bjc.6605940]
 - 74 **Assenat E**, Desseigne F, Thezenas S, Viret F, Mineur L,

- Kramar A, Samalin E, Portales F, Bibeau F, Crapez-Lopez E, Bleuse JP, Ychou M. Cetuximab plus FOLFIRINOX (ERBIRINOX) as first-line treatment for unresectable metastatic colorectal cancer: a phase II trial. *Oncologist* 2011; **16**: 1557-1564 [PMID: 22016477 DOI: 10.1634/theoncologist.2011-0141]
- 75 **Saridaki Z**, Androulakis N, Vardakis N, Vamvakas L, Kabouraki E, Kalbakis K, Hatzidaki D, Voutsina A, Mavroudis D, Georgoulas V, Souglakos J. A triplet combination with irinotecan (CPT-11), oxaliplatin (LOHP), continuous infusion 5-fluorouracil and leucovorin (FOLFOXIRI) plus cetuximab as first-line treatment in KRAS wt, metastatic colorectal cancer: a pilot phase II trial. *Br J Cancer* 2012; **107**: 1932-1937 [PMID: 23169296 DOI: 10.1038/bjc.2012.509]
- 76 **Balducci L**, Extermann M. Management of cancer in the older person: a practical approach. *Oncologist* 2000; **5**: 224-237 [PMID: 10884501 DOI: 10.1634/theoncologist.5-3-224]
- 77 **Honecker F**, Köhne CH, Bokemeyer C. Colorectal cancer in the elderly: is palliative chemotherapy of value? *Drugs Aging* 2003; **20**: 1-11 [PMID: 12513112]
- 78 **Sastre J**, Marcuello E, Masutti B, Navarro M, Gil S, Antón A, Abad A, Aranda E, Maurel J, Valladares M, Maestu I, Carrato A, Vicent JM, Díaz-Rubio E. Irinotecan in combination with fluorouracil in a 48-hour continuous infusion as first-line chemotherapy for elderly patients with metastatic colorectal cancer: a Spanish Cooperative Group for the Treatment of Digestive Tumors study. *J Clin Oncol* 2005; **23**: 3545-3551 [PMID: 15908665 DOI: 10.1200/JCO.2005.03.004]
- 79 **Feliu J**, Salud A, Escudero P, Lopez-Gómez L, Bolaños M, Galán A, Vicent JM, Yubero A, Losa F, De Castro J, de Mon MA, Casado E, González-Barón M. XELOX (capecitabine plus oxaliplatin) as first-line treatment for elderly patients over 70 years of age with advanced colorectal cancer. *Br J Cancer* 2006; **94**: 969-975 [PMID: 16552438 DOI: 10.1038/sj.bjc.6603047]
- 80 **Mitry E**, Douillard JY, Van Cutsem E, Cunningham D, Magherini E, Mery-Mignard D, Awad L, Rougier P. Predictive factors of survival in patients with advanced colorectal cancer: an individual data analysis of 602 patients included in irinotecan phase III trials. *Ann Oncol* 2004; **15**: 1013-1017 [PMID: 15205193 DOI: 10.1093/annonc/mdh267]
- 81 **Goldberg RM**, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, Rothenberg ML, Green E, Sargent DJ. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 2006; **24**: 4085-4091 [PMID: 16943526 DOI: 10.1200/JCO.2006.06.9039]
- 82 **Sastre J**, Aranda E, Massutí B, Tabernero J, Chaves M, Abad A, Carrato A, Reina JJ, Queralt B, Gómez-España A, González-Flores E, Rivera F, Losa F, García T, Sanchez-Rovira P, Maestu I, Díaz-Rubio E. Elderly patients with advanced colorectal cancer derive similar benefit without excessive toxicity after first-line chemotherapy with oxaliplatin-based combinations: comparative outcomes from the 03-TTD-01 phase III study. *Crit Rev Oncol Hematol* 2009; **70**: 134-144 [PMID: 19111473 DOI: 10.1016/j.critrevonc.2008.11.002]
- 83 **Jackson NA**, Barrueco J, Soufi-Mahjoubi R, Marshall J, Mitchell E, Zhang X, Meyerhardt J. Comparing safety and efficacy of first-line irinotecan/fluoropyrimidine combinations in elderly versus nonelderly patients with metastatic colorectal cancer: findings from the bolus, infusional, or capecitabine with camptostar-celecoxib study. *Cancer* 2009; **115**: 2617-2629 [PMID: 19382200 DOI: 10.1002/cncr.24305]
- 84 **Bouchahda M**, Macarulla T, Spano JP, Bachet JB, Lledo G, Andre T, Landi B, Tabernero J, Karaboué A, Domont J, Levi F, Rougier P. Cetuximab efficacy and safety in a retrospective cohort of elderly patients with heavily pretreated metastatic colorectal cancer. *Crit Rev Oncol Hematol* 2008; **67**: 255-262 [PMID: 18400508 DOI: 10.1016/j.critrevonc.2008.02.003]
- 85 **Jehn CF**, Böning L, Kröning H, Possinger K, Lüftner D. Cetuximab-based therapy in elderly comorbid patients with metastatic colorectal cancer. *Br J Cancer* 2012; **106**: 274-278 [PMID: 22215062 DOI: 10.1038/bjc.2011.554]
- 86 **Sastre J**, Aranda E, Grávalos C, Massutí B, Varela-García M, Rivera F, Soler G, Carrato A, Manzano JL, Díaz-Rubio E, Hidalgo M. First-line single-agent cetuximab in elderly patients with metastatic colorectal cancer. A phase II clinical and molecular study of the Spanish group for digestive tumor therapy (TTD). *Crit Rev Oncol Hematol* 2011; **77**: 78-84 [PMID: 20042346 DOI: 10.1016/j.critrevonc.2009.11.005]
- 87 **Folprecht G**, Gruenberger T, Bechstein W, Lordick T, Lang H, Weitz J, Suedhoff T, Hartmann J, Liersch T, Koehne C. Progression free and overall survival after neoadjuvant treatment of colorectal liver metastases with cetuximab plus FOLFOX or FOLFIRI - Results of the CELIM study. *Oncologist* 2012; **17**: 339-345 [PMID: 22363067 DOI: 10.1634/theoncologist.2011-0406]

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