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

Sotelo MJ *et al* Cetuximab in first-line 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 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. 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 metastatic colorectal cancer.

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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, accounting 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 hepatic 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 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 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-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 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 (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%, odds ratio (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, Piessevaux *et al* 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 versus 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 survival 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 Ib/II phase German study assessed the feasibility of treatment with cetuximab in combination with a weekly schedule of oxaliplatin, infusional 5FU and folinic acid (AIO group FUFOX regimen) 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 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 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 versus patients who did not undergo surgery, both in the cetuximab plus chemotherapy group (46.4 mo *vs* 25.7 mo, *P* = 0007) 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- versus 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-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 unresectable 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 ≥ 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 because 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 per12 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.

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**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 *et al*[37] | Phase I/II | No | Cetuximab-Irinotecan/5FU/FA1 | 67% | 19% | 9.9 | 33 |
| Raoul *et al*[38] | Phase I/II | No | Cetuximab-FOLFIRI | 48% | 19.2% | 8.6 | 22.4 |
| CRYSTAL, Van Cutsem *et al*[6,20] | Phase III | Yes | Cetuximab-FOLFIRI *vs* FOLFIRI | 57.3% *vs* 39.7% (OR = 2.069, *P* < 0.001)2 | 5.1% *vs* 2% (OR 2.65, *P* = 0.0265) 2 | 9.9 *vs* 8.4 (HR = 0.696, *P* = 0.0012)2 | 23.5 *vs* 20 (HR = 0.796, *P* = 0.0093)2 |
| FIRE-3, Heinemann *et al*  [41] | Phase III | Yes | Cetuximab-FOLFIRI *vs* Bevacizumab-FOLFIRI | 62 *vs* 57 (OR = 1.18, *P* = 0.183) |  | 10 *vs* 10.3 (HR = 1.06, *P* = 0.547) | 28.7 *vs* 25 (HR = 0.77, *P* = 0.017) |

1AIO group regimen of irinotecan, folinic acid and infusional 5FU; 2 Results in wild-type KRAS population. PFS: Progression-free survival; OS: Overall survival; FA: Folinic acid.

**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 *et al*[48] | Phase Ib/II | No | Cetuximab-FUFOX1 | 57% | 4% | 8.1 | 28.2 |
| Tabernero *et al*[49] | Phase II | No | Cetuximab-FOLFOX4 | 72% | 21% | 12.3 | 30 |
| OPUS, Bokemeyer *et al*[7,21] | Phase II | Yes | Cetuximab-FOLFOX4 *vs* FOLFOX4 | 57% *vs* 34% (OR = 2.551, *P* = 0.0027)2 | 12% *vs* 3% (*P* = 0.0242)2 | 8.3 *vs* 7.2 (HR = 0.567, *P* = 0.0064)2 | 22.8 *vs* 18.5 (HR = 0.855, *P* = 0.39)2 |
| COIN, Maughan *et al*[23] | Phase III | Yes | Cetuximab-mFOLFOX6/XELOX *vs* mFOLFOX6/XELOX | 64% *vs* 57% (OR = 1.35, *P* = 0.049) 2 | 15% *vs* 13 % (*P* = 0.74)2 | 8.6 *vs* 8.6 (HR = 0.96, *P* = 0.60) 2 | 17 *vs* 17.9 (HR = 1.04, *P* = 0.67) 2 |
| NORDIC VII, Tveit *et al*[50] | Phase III | Yes | Cetuximab-Nordic FLOX *vs* Nordic FLOX3 | 46% *vs* 47% (OR = 0.96, *P* = 0.89)2 | 13.4% *vs* 14.4%2 | 7.9 *vs* 8.7 (HR = 1.07, *P* = 0.66) 2 | 20.1 *vs* 22 (HR = 1.14, *P* = 0.48) 2 |

1AIO group weekly regimen of oxaliplatin, folinic acid and infusional 5FU; 2 Results in wild-type KRAS population;3 Biweekly regimen of oxaliplatin, bolus 5FU and folinic acid. PFS: Progression-free survival; OS: Overall survival.

**Table 3Clinical 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 *et al*[67,68] | Phase II | Yes | Cetuximab-FOLFOX6 *vs* cetuximab-FOLFIRI  Wild-type KRAS *vs* mutated KRAS | 68% *vs* 5%7 (OR = 1.62, *P* = 0.23)  70% *vs* 41% (OR = 3.42, *P* = 0.008) | 38% *vs* 30%  33% *vs* 30% | 11.2 *vs* 10.5 (HR = 1.15, NS)  11.9 *vs* 9.9 (HR = 1.31, NS) | 35.7 *vs* 29.0 (HR = 1.09, NS)  36.1 *vs* 27.4 (HR = 1.48, NS) |
| Ye *et al*[70] | Phase IV | Yes | Cetuximab-mFOLFOX6/FOLFIRI *vs* mFOLFOX6/FOLFIRI  Cetuximab-mFOLFOX6 *vs* Cetuximab-FOLFIRI | 57.1% *vs* 29.4% (*P* < 0.01)  52.8% *vs* 59.1% (*P* = 0.31) | 25.7% *vs* 7.4 % (*P* < 0.01) | 10.2 *vs* 5.8 (HR = 0.6, *P* = 0.004)  10.1 *vs* 9.1 (*P* = 0.28) | 30.9 *vs* 21 (HR = 0.54, *P* = 0.013)  34.8 *vs* 23.1 (*P* = 0.24) |
| POCHER, Garufi *et al*[73] | Phase II | Yes | Cetuximab-Chrono-IFLO1 | 79.1 | 60 | 14 | 37 |
| Saridaki *et al*[75] | Phase II | Yes | Cetuximab-FOLFIRINOX | 70 | 372  623 | 10.2 | 30.3 |

1Chronomodulated infusion of irinotecan, 5FU, leucovorin and oxaliplatin; 2R0 resection rate in overall population; 3 R0 resection rate in the subgroup of patients with metastatic disease limited to the liver. PFS: Progression-free survival; OS: Overall survival; NS: Not significant.