Review Article

Metastatic colorectal cancer-prolonging overall survival with targeted therapies

Satya Dattatreya

Abstract

This review provides an updated overview of the management of metastatic colorectal cancer (CRC). With widespread application of personalized therapy based on specific patient and tumor characteristics, this will enable the oncologists to optimize overall survival while maintaining quality of life. The role of k-ras and braf testing in helping select systemic therapy that includes cetuximab or bevacizumab is clarified. Current management of metastatic CRC is based on careful attention to these finer points, explained in this article.

Key words: Cetuximab, monoclonal antibody, personalized therapy

Introduction

Colorectal cancer (CRC) remains a major public health problem in most developed countries. A global incidence of approximately 1.2 million was reported in 2008.[1] Males and females appear to be equally affected, but there are marked geographical differences, the disease being more common in the Western world and less frequent in Asia and Africa.[2] Despite a decreased incidence of CRC since the mid-1980s, this disease continues to rank as the third most common cancer in incidence and cancer-related death in the United States. CRC is the third most common form of cancer in men and the second most common form of cancer in women in Europe, but it ranks second in frequency of deaths in both men and women.[3]

Within Asia, the incidence rates of CRC vary widely and are uniformly low in all south Asian countries and high in all developed Asian countries. As per currently available data, the incidence rates for CRC in India for males and females are 4.3 per 1,00,000 population and 3.4 per 1,00,000 population, respectively.[4] While the incidence rate of CRC in native Indians has been rising slowly over many decades, the incidence of CRC in immigrant Indians living in the UK and USA has risen rapidly. The absolute burden of CRC has also increased in India during last 3 decades. For example, during a 32-year period (1941–1972), 555 cases of CRC were recorded at the Tata Memorial Hospital, Mumbai. In contrast, a total of 560 cases of CRC were treated at the same institution in 2006 alone.[5]

Department of Medical Oncology, Omega Hospital, Hyderabad, Andhra Pradesh, India

Correspondence to: Dr. Satya Dattatreya,
E-mail: satya_palanki@rediffmail.com

Access this article online

Quick Response Code:

Website: www.sajc.org

DOI: 10.4103/2278-330X.114152

Mortality from CRC has reduced over the past decade due to earlier diagnosis through excellent screening techniques, implementation of clinical practice guidelines for systematising cancer care, increased patient awareness and, particularly, better treatment modalities. Symptoms typically include rectal bleeding and anemia which are sometimes associated with weight loss and changes in bowel habits. Most CRC occurs due to lifestyle and increasing age with only a minority of cases associated with underlying genetic disorders. It typically starts in the lining of the bowel and if left untreated, can grow into the muscle layers underneath, and then through the bowel wall. Screening is effective at decreasing the chance of dying from CRC and is recommended starting at the age of 50 and continuing until a person is 75 years old. Localized bowel cancer is usually diagnosed through sigmoidoscopy or colonoscopy. A significant number of patients present initially with metastatic disease.[1] About 25% of the patients present with *de novo* metastatic colorectal cancer (mCRC). Upto 50% of the patients despite adjuvant treatment after surgery develop mCRC.[6] Thus, the real challenge in management of CRC is mCRC.

Targeted Therapies in Treatment of mCRC

Chemotherapy is indicated for patients with mCRC; the therapeutic aim is to prolong survival, control symptoms, and maintain or improve quality of life. 5-Fluorouracil (5FU), administered systemically with or without folinic acid (LV), has formed the basis of first-line treatment regimens for several decades and has been shown to prolong symptom-free and overall patient survival and improve quality of life. However, more chemotherapeutic agents have become available that have increased response rates, time to disease progression, and survival in patients with mCRC, such as irinotecan and oxaliplatin. In practice, these drugs are used as first- and second-line therapy; although their use increases efficacy outcome in mCRC, there is still an unmet medical need for further improvement in therapy in these patients.[7] In addition to chemotherapy, biological agents such as the

vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab) and epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab and panitumumab) are components of the armamentarium for mCRC.

Bevacizumab is a recombinant, humanized monoclonal antibody against VEGF that is used to inhibit VEGF function in vascular endothelial cells and thereby inhibit tumor angiogenesis, upon which solid tumors depend for growth and metastasis. The addition of bevacizumab to fluoropyrimidine-based chemotherapy, with or without irinotecan or oxaliplatin, in both the first- and second-line treatment of mCRC, significantly increased median progression-free survival (PFS) or time to disease progression in most randomized controlled trials. Bevacizumab was generally, but not always, associated with a survival advantage; in phase III trials, the increase in median overall survival (OS) attributable to bevacizumab was 4.7 months with first-line therapy and 2.1 months with second-line therapy. In some studies, patients experienced clinical improvement without an apparent OS benefit.[8] The chemotherapy regimen used was irinotecan with bolus 5FU and LV (IFL), which is now considered as suboptimal chemotherapy regimen in mCRC.

In a pivotal study, the addition of bevacizumab to irinotecan as first-line therapy for mCRC was associated with a significant increase in median OS, PFS, and duration of response.[9] A pooled analysis of phase II studies showed a median survival of 17.9 months in patients receiving 5FU/LV plus bevacizumab compared with 14.6 months with 5FU/LV or irinotecan (P = 0.008).[10] When bevacizumab was added to oxaliplatin-containing chemotherapy regimens, a significant improvement in PFS (9.4 vs. 8.0 months; P = 0.0023), but not OS (21.3 vs. 19.9 months; P = 0.077), was seen.[11]

Another phase III trial was conducted to compare chemotherapy combined with bevacizumab versus chemotherapy alone in the treatment of patients with mCRC. The patients were treated with LV, 5FU plus irinotecan, with bevacizumab, or without bevacizumab. All patients were stage IV with histologically confirmed adenocarcinoma. The median OS of patients who received bevacizumab was 22.0 months [95% confidence interval (CI): 18.1–25.9] and 25.0 months (CI: 18.1–31.9) for patients without Bevacizumab, however this difference was not statistically significant (P = 0.1391). Thus, there was no statistically significant difference in median OS or in response rates in patients with mCRC treated with bevacizumab plus a combination therapy and those treated with the combination only without bevacizumab.[12]

As second-line therapy in patients who had progressed on a nonbevacizumab-containing regimen, the addition of bevacizumab to oxaliplatin plus infusional 5FU/LV (FOLFOX 4) was associated with a significant increase in OS (12.9 vs. 10.8 months; P = 0.0011).[13]

Recently, a randomized phase III intergroup study has shown that continuing bevacizumab along with chemotherapy in second-line patients of mCRC who have progressed on bevacizumab-containing regimen in the first line, has shown benefits in OS and PFS.[14] With respect to adverse events associated with bevacizumab, the elderly may experience an increased risk of stroke and other arterial events, and the drug is associated with impaired wound healing and, rarely, gastrointestinal perforation.

NO16966 compared efficacy of oxaliplatin-based chemotherapy plus bevacizumab or placebo in 1400 patients.[15] Bevacizumab in combination with oxaliplatin-based therapy led to a significant prolongation of PFS. A retrospective analysis of resection rate was undertaken. In NO16966, a total of 44 out of 699 patients treated with bevacizumab (6.3%) and 34 out of 701 patients treated with placebo (4.9%) underwent R0 metastasectomy (P = 0.24). There were no statistically significant differences in resection rates or OS in patients treated with bevacizumab versus placebo.

Thus, the evolution of therapy for mCRC has undergone a sea change during the last decade [Table 1]. Initially, with chemotherapy alone, the median OS was 18.6 months. With addition of cetuximab it improved to around 19.9 months in unselected populations. A marked improvement to 23.5 months was seen with cetuximab plus chemotherapy in KRAS wild-type (wt) (personalized therapy). Early tumor shrinkage is also emerging as a new treatment marker for identifying patients more likely to respond to cetuximab. Further, in patients with liver-limited disease (LLD), the OS is 36.1 months, which improves to 46.7 months in the patients who undergo resection.

Biomarkers to Optimize Clinical Outcome in mCRC

The survival of the patients has dramatically improved with the progress in chemotherapeutic regimens as new routes of administration and introduction of more potent cytotoxic agents administered in sequential 5FU-LV-irinotecan (FOLFIRI)/5FU-LV-oxaliplatin strategies (FOLFOX) has achieved median OS up to 20 months.[16] Biologic therapies targeting two

Table 1: Efficacy of targeted therapies in metastatic colorectal cancer patients

	Bevacizumab	Cetuximab	
	ITT population	ITT population	Kras wild-type population
Overall survival (months)	20.3	20 (CRYSTAL) 18.5 (OPUS)	23.5 (CRYSTAL) 22.8 (OPUS)
Response rates (%)	44.8	40 (CRYSTAL) 34 (OPUS)	57 (CRYSTAL) 57 (OPUS)
Progression-free survival (months)	10.6	8.4 (CRYSTAL) 7.2 (OPUS)	9.9 (CRYSTAL) 8.3 (OPUS)

ITT=Intent to treat

different mechanisms, angiogenesis (bevacizumab) and EGFRs (cetuximab and panitumumab) have been developed.

In the EGFR signalling pathway, K-Ras is a key central downstream effector. K-Ras gene status, wt versus mutated, highly influences the efficacy of the two drugs, cetuximab and panitumumab, targeting EGFR. Most patients (up to 60%) present with a wt K-Ras tumor. The K-Ras mutation confers a modified conformation to the K-Ras protein that prevents its inactivation.[17] EGFR inhibitors do not affect the pathway in case of a K-Ras mutation.[18] This resistance was indicated in single-arm studies retrospectively analyzed with regard to K-Ras status. Basically, no response to cetuximab or panitumumab was noted in patients with mutated K-Ras tumors.[19,20]

The randomized cetuximab combined with irinotecan in first-line therapy for mCRC (CRYSTAL) and oxaliplatin and cetuximab in first-line treatment of mCRC (OPUS) trials demonstrated large differences between wt and mutated tumors, particularly in response rate, PFS and OS. In CRYSTAL and OPUS, the improvement in OS in the overall patient population was 8-10%.[21] When patients were categorized into KRAS wt population the response rate jumped to 17%-23%. This also translated to a better OS of 3.5 months in the KRAS wt population compared to a difference of 1.3 months in the general population. The hazard ratio (HR) was 0.80, meaning a 20% reduction of death with a combination of cetuximab with FOLFIRI over FOLFIRI alone. Thus, personalized treatment is a better approach than the "one treatment fits all"approach.[22,23] American Society of Clinical Oncology (ASCO) in 2008 acknowledged the identification of the KRAS status as one of the top oncology research and clinical advances. KRAS status is an important biomarker of cetuximab efficacy.

KRAS versus BRAF

Among the various biomarkers in mCRC, KRAS and BRAF have been studied extensively. The clinical activity of cetuximab in the CRYSTAL study was shown in a retrospective analysis to be limited to those patients whose tumors were wt at codons 12 and 13 of the KRAS gene, a group comprising 64% of the KRAS evaluable population.[21] The benefit in patients with KRAS wt tumors was apparent in relation to a significantly reduced risk of disease progression (HR, 0.696, $P = 0.012$) and significantly increased odds of response in favor of the cetuximab plus FOLFIRI arm (odds ratio, 2.069 $P \leq 0.001$). The addition of cetuximab to FOLFIRI in patients with KRAS wt disease resulted in significant improvements in OS (median, 23.5 vs. 20.0 months; HR, 0.796; $P = 0.0093$), PFS (median, 9.9 vs. 8.4 months; HR, 0.696; $P = 0.0012$), and response (rate 57.3% vs. 39.7%; odds ratio, 2.069; $P < 0.001$) compared with FOLFIRI alone. Significant interactions between KRAS status and treatment effect were noted for all key efficacy end-points. KRAS mutation status was confirmed as a powerful predictive biomarker for the efficacy of cetuximab plus FOLFIRI. BRAF tumor mutation was a strong indicator of poor prognosis.[21,24] In a follow-up analysis, researchers pooled data from both CRYSTAL and OPUS populations (which included 1,645 patients, though only 1,378 of the samples were evaluable) and assessed outcomes based on both KRAS and BRAF gene mutation status. It was found that adding cetuximab to chemotherapy improved outcomes for all patients with normal forms of KRAS, regardless of BRAF status, but that those with normal forms of both the KRAS and BRAF genes benefited most. Median survival for patients with normal KRAS and BRAF treated with chemotherapy and cetuximab was 24.8 months, versus 21.1 months for chemotherapy alone. For patients with normal KRAS and BRAF mutations, adding cetuximab increased median survival from 9.9 months to 14.1 months.[25] These data demonstrate that BRAF mutations are prognostic; patients whose tumors harbor BRAF mutations have significantly shorter PFS and OS. However, patients with a normal KRAS gene and a BRAF mutation still seem to benefit from cetuximab, and the decision regarding the use of cetuximab should not be based on the presence of BRAF mutations.[26]

Thus, KRAS mutation status is a powerful predictive biomarker, whereas BRAF mutation is a prognostic biomarker [Table 2].

Basis, Evidence to Strategize Treatment Plan

In multicenter phase 3 trial, CRYSTAL, the efficacy and safety of irinotecan in combination with a simplified regimen of 5FU and LV (FOLFIRI) plus cetuximab in the initial treatment of mCRC was evaluated. A retrospective subgroup analysis to investigate the influence of the tumor KRAS mutation status on outcome was also conducted. This trial was a randomized, open-label, multicenter study comparing 14-day cycles of cetuximab plus FOLFIRI and FOLFIRI alone and randomly assigned patients (in a 1:1 ratio) to one of the two treatment groups. The primary end-point was PFS, whereas secondary end-points included the OS time, the rate of best overall response and safety end-points.[22]

The CRYSTAL study met its primary end-point in demonstrating that the addition of cetuximab to FOLFIRI statistically significantly reduced the risk of progression of mCRC compared with chemotherapy alone. This study showed significant benefit in OS (23.5 vs. 19.5 months; HR = 0.796, $P = 0.0093$) with cetuximab-containing regimen, in addition to clinical benefits in PFS and response rates in KRAS wt patients.

In the OPUS study, the biomarker analysis was extended through the use of additional DNA samples extracted from stained tissue sections. Patients were randomly assigned to receive FOLFOX-4 (oxaliplatin 85 mg/m2; folinic acid 200 mg/m2, followed by 5-FU, as a 400 mg/m2 intravenous bolus then a 600 mg/m2 infusion over 22 h,

Table 2: Stratification of patients, treatment goals-European Society for Medical oncology guidelines

Clinical situation	Goal	What is needed	Treatment intensity[15,16]
Patients with liver (lung) metastasis Potentially resectable	Cure as the goal	Maximal Tumor shrinkage	Upfront combination, multidrug regimen
Patients with multiple metastasis Rapid progression Tumor-related symptoms Risk for rapid Deterioration	Symptom relief as the goal	Control of progressive disease	
Patients with unresectable metastasis No options for resection No symptoms Comorbidity Risk for rapid deterioration	More lifetime as the goal	Tumor shrinkage less relevant Control of further progression Prevention from toxicity	A single agent (sequential approach) or with doublets

days 1 and 2 of a 14-day cycle) with or without cetuximab (initial dose 400 mg/m2 and 250 mg/m2/week, thereafter), until the occurrence of progressive disease or unacceptable toxicity, as first-line treatment for mCRC. Response was assessed radiologically every 8 weeks. The primary end-point was response, as evaluated by an independent review committee according to modified World Health Organization criteria. Secondary end-points included PFS, OS and safety.[27]

Clinical outcome was reassessed according to mutation status. The addition of cetuximab to FOLFOX-4 significantly improved PFS (HR 0.567, $P = 0.0064$) and response (odds ratio 2.551, $P = 0.0027$) in patients with KRAS wt tumors. A favorable effect on survival was also observed (4 months), though this was not statistically significant. This could be because this was a phase II study and the KRAS-wt patient were not covered to look at the OS benefit.[28]

Cetuximab and Results of CRYSTAL, OPUS, COIN Studies

In patients with KRAS wt tumor, CRYSTAL and OPUS studies have shown a response rate of 57%; whereas in COIN study it was observed to be 59%, with cetuximab and chemotherapy regimen. Thus, response rates with cetuximab in CRYSTAL, OPUS, and COIN studies have shown consistent benefit as compared to chemotherapy alone. Also, OS and PFS have shown significant benefits with cetuximab-containing regimen in CYRSTAL and OPUS studies but not in COIN study.[29] One of the reasons for results of COIN study may be the imbalance in dose reductions between treatment arms and imbalance in poststudy treatment.

Cetuximab + FOLFIRI Versus Cetuximab + FOLFOX

The ASCO 2012 update compared the pooled analysis of OPUS (FOLFOX regimen) and COIN (OxMdg subgroup) with CRYSTAL (FOLFIRI regimen). In one of the pooled analysis, the pooled *KRAS wt* population included 179 patients from the OPUS study and 244 from the OxMdG subgroup of the COIN study. A benefit for the addition of cetuximab to infusional 5-FU/FA and oxaliplatin was suggested for response (odds ratio 1.87, 95% CI 1.07-3.28) and PFS (HR, HR 0.69, 95% CI 0.52-0.92), but OS did not show a statistically significant improvement (HR 0.90, 95% CI 0.73-1.11). These response and PFS data are similar to those of the *KRAS* wt population of the CRYSTAL study investigating infusional 5-FU/FA and irinotecan +/- cetuximab (response: Odds ratio 2.07, 95% CI 1.52-2.83; PFS: HR 0.70, 95% CI 0.56-0.87) whereas the improvement in OS was statistically significant in that study (HR 0.80, 95% CI 0.67-0.95).[30] The CECOG CORE and CELIM study did a head to head comparison of cetuximab with FOLFOX and FOLFIRI. It showed that with both the regimens the response rate, PFS and OS were similar. Thus, cetuximab works equally well with FOLFOX or FOLFIRI.

Anti-EGFR Therapy with Cetuximab and Outcome in mCRC-Evidences

A look at 10 studies shows an improvement in overall response rate in KRAS evaluable patients receiving cetuximab in first-line mCRC with KRAS wt population. The improvement is shown in almost all the studies. This benefit also translates into a PFS and OS benefit as shown in a meta-analysis of six trials which showed that the PFS HR is 0.77 and the OS HR is 0.86 and both the values are statistically significant. Thus, based on the analysis of individual trials, pooled analysis as well as meta-analysis improvement in patients of mCRC having KRAS wt, is demonstrated with anti-EGFR treatment [Figure 1].[22,27]

Importance of Subdividing Patients of mCRC

There is a "Limited Liver Disease"−this is a subset in the existing LLD but with less than five metastases. The CELIM trial showed that in such disease the DFS jumps to 16.8 months when less than five metastases compared to 8.2 months when more than five metastases.[31] In the 2nd subset of patients with never resectable metastases,

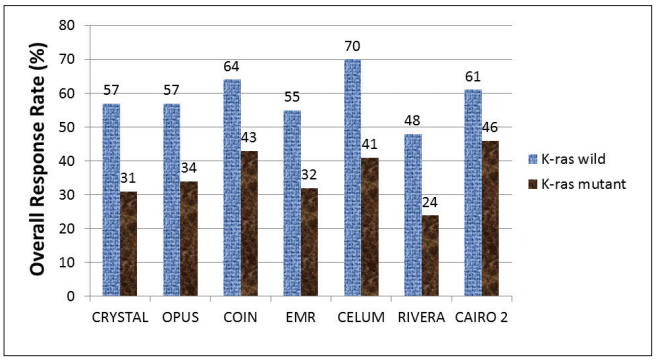

Figure 1: Outcome of various studies of cetuximab in metastatic colorectal cancer patients

high tumor burden or tumor-related symptoms the goal of treatment is to induce tumor shrinkage because this would increase the chance of resecting metastases, promote symptom relief, and improve long-term outcomes. With cetuximab and FOLFIRI 52% of the patients showed response.[26] More importantly, the patients who responded to cetuximab and FOLFIRI had a rapid relief of symptoms within 8 weeks, whereas patients on FOLFIRI took 16 weeks to respond. Thus, best outcomes are seen in KRAS wt LLD.

Gunnar Folprecht and colleagues (CELIM study) studied tumor response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: The CELIM randomized phase 2 trial. Patients with nonresectable liver metastases (technically nonresectable or ≥ 5 metastases) were randomly assigned to receive cetuximab with either FOLFOX6 (oxaliplatin, fluorouracil, and folinic acid; group A) or FOLFIRI (irinotecan, FU, and folinic acid; group B). They were assessed for response every 8 weeks by compute tomography (CT) or magnetic resonance imaging. A local multidisciplinary team reassessed resectability after 16 weeks, and then every 2 months up to 2 years. Patients with resectable disease were offered liver surgery within 4–6 weeks of the last treatment cycle. The primary end-point was tumor response assessed by Response Evaluation Criteria In Solid Tumours, analyzed by modified intention to treat. A retrospective, blinded surgical review of patients with radiological images at both baseline and during treatment was done to assess objectively any changes in resectability. A confirmed partial or complete response was noted in 36 (68%) of 53 patients in group A, and 30 (57%) of 53 patients in group B. In a retrospective analysis of response by KRAS status, a partial or complete response was noted in 47 (70%) of 67 patients with KRAS wt tumors versus 11 (41%) of 27 patients with KRAS-mutated tumours. According to the retrospective review, resectability rates increased from 32% (22 of 68 patients) at baseline to 60% (41 of 68) after chemotherapy ($P < 0.0001$). Chemotherapy with cetuximab yields high response rates compared with historical controls and leads to significantly increased resectability.[32]

Early Tumor Shrinkage and Correlation with OS

Early tumor shrinkage is defined as reduction of more than 20% regression on a CT scan at 8 weeks. Early tumor shrinkage with cetuximab correlates with prolonged OS as was shown in the CRYSTAL and the OPUS trial in which 64%-69% patients had early tumor shrinkage and this correlated with increased median OS of 26 - 28 months.[33,34] Survival benefit was not seen in patient achieving early tumor shrinkage with FOLFO × 4 and FOLFIRI regimen only.

In patients with never resectable metastases asymptomatic and with less aggressive disease. The ESMO 2010 guidelines also recommends, in such patients, treatment with single agent (sequential approach) or with doublets. Even in these patients the CRYSTAL data showed that in non-LLD patients the median OS increases by 5.1 months and similar benefit was shown in the OPUS data.[35]

Cetuximab Once a Week Versus Cetuximab Once in 2 Weeks

Cetuximab has been evaluated, in few studies, for biweekly regimen. Patients with KRAS wt mCRC were randomized to q1w cetuximab (400 mg/m^2 initial dose then 250 mg/m^2/week) or q2w cetuximab (500 mg/m^2 every 2 weeks). Both arms received FOLFOX4 (folinic acid 200 mg/m^2, then 5-FU 400 mg/m^2 bolus, then 5-FU 600 mg/m^2 over 22 h on days 1 + 2, plus oxaliplatin 85 mg/m^2 on day 1 q2w). Primary end-point was objective response rate (ORR). Secondary efficacy end-points were disease control rate (DCR), PFS and OS. 152 patients with KRAS wt tumors (22 centers in 12 countries) were randomized to arm A (n = 75) and arm B (n = 77). Baseline characteristics were well-balanced. Median follow-up for PFS analysis was 16.5 months. Overall ORR (55% vs. 59%) and PFS (9.5 mo vs. 9.3 mo) were similar in patients with EGFR detected and nondetectable tumors. OS data are not yet mature. Based on current data most common (≥10% in either arm), grade 3/4 treatment emergent adverse events were comparable in FOLFOX + q1w cetuximab and FOLFOX + q2w cetuximab: Neutropenia/neutrophil decrease (32% vs. 34%), rash (15% vs. 16%), diarrhea (7% vs. 10%). G3/4 composite adverse events categories specific to cetuximab or FOLFOX showed no difference between treatment arms: Infusion-related reactions (2.7% vs. 2.6%), skin reactions (24% vs. 26%), neurotoxicities (0% vs. 1.3%). These data suggest that in terms of ORR, DCR, PFS and safety, cetuximab q2w is a convenient alternative to the standard q1w regimen when combined with FOLFOX4.[36]

The CORE 2 data on the use of cetuximab every week versus every 2 weeks at a dose of 500 mg/m^2 showed equivalent response rates and PFS benefits and this was shown in all treatment lines-first-, second-, or third-line treatment. Thus, cetuximab once every 2 weeks is as

effective as cetuximab once a week, but at this point of time preferably every week schedule is in practice.

Conclusion

OS in metastatic colorectal cancer patient has seen a significant improvement with personalized approach in therapy, which has developed in last decade. Cetuximab in KRAS wt metastatic colorectal cancer patients has shown clinical benefits, which are noteworthy. Thus, it would be ideal to test all patients of mCRC for KRAS status and if it is KRAS wt, then cetuximab should be an integral part of the therapy. Thus, the ideal strategy would be the personalized approach for the patients of metastatic colorectal cancer through KRAS testing on "test-tailor-treat" basis.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. Noronha V, Tsomo U, Jamshed A, Hai MA, Wattegama S, Baral RP, *et al*. A fresh look at oncology facts on south central Asia and SAARC countries. South Asian J Cancer 2012;1:1-4.
3. Boyle P, Ferlay J. Cancer incidence and mortality in Europe, 2004. Ann Oncol 2005;16:481-8.
4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
5. Mohandas K. Colorectal cancer in India: Controversies, enigmas and primary prevention. Indian J Gastroenterol 2011;30:3-6.
6. Ribes J, Navarro M, Clèries R, Esteban L, Pareja L, Binefa G, *et al.* Colorectal cancer mortality in Spain: Trends and projections for 1985 – 2019. Eur J Gastroenterol Hepatol 2009;21:92-100.
7. Reynolds NA, Wagstaff AJ. Cetuximab: In the treatment of metastatic colorectal cancer. Drugs 2004;64:109-18.
8. McCormack PL, Keam SJ. Bevacizumab: A review of its use in metastatic colorectal cancer. Drugs 2008;68:487-506.
9. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
10. Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: The addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol 2005;23:3706-12.
11. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, *et al.* Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol 2008;26:2013-9.
12. Stathopoulos GP, Batziou C, Trafalis D, Koutantos J, Batzios S, Stathopoulos J, *et al*. Treatment of colorectal cancer with and without bevacizumab: A phase III study. Oncology 2010;78:376-81.
13. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, *et al.* Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539-44.
14. Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, *et al*. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): A randomised phase 3 trial. Lancet Oncol. 2013;14:29-37.
15. Saltz L, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, *et al*. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer. J Clin Oncol 2007;25(suppl):4028.
16. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. J Clin Oncol 2004;22:229-37.
17. 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;6:519-27.
18. Stites EC, Trampont PC, Ma Z, Ravichandran KS. Network analysis of oncogenic Ras activation in cancer. Science 2007;318:463-7.
19. Lièvre A, Bachet JB, Boige V, Cayre A, Le Corre D, Buc E, *et al*. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008;26:374-9.
20. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, Zanon C, Moroni M, Veronese S, *et al.* Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 2007;67:2643-8.
21. Van Cutsem E, Köhne CH, Láng I, Folprecht G, Nowacki MP, Cascinu S, *et al.* 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;29:2011-9.
22. Van Cutsem E, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, *et al.* Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-17.
23. Van Cutsem E, Lang I, Folprecht G, Nowacki M, Barone C, Shchepotin I, *et al*. Cetuximab plus FOLFIRI: Final data from the CRYSTAL study on the association of KRAS and BRAF biomarker status with treatment outcome. J Clin Oncol 2010:28:15s (suppl; abstr 3570)
24. Bokemeyer C, Van Cutsem E, Rougier P, Ciardiello F, Heeger S, Schlichting M, *et al*. 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;48:1466-75.
25. Kris MG, Benowitz SI, Adams S, Diller L, Ganz P, Kahlenberg MS, *et al*. Clinical Cancer Advances 2010: Annual report on progress against cancer from the american society of clinical oncology. J Clin Oncol 2010;28:5327-47.
26. Bokemeyer C, Kohne C, Rougier P, Stroh C, Schlichting M, Van Cutsem E. Cetuximab with chemotherapy (CT) as first-line treatment for metastatic colorectal cancer (mCRC): Analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation status. J Clin Oncol 2010;15s: abs3506.
27. Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, *et al.* Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27:663-71.
28. Bokemeyer C, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zubel A, *et al*. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: The OPUS study. Ann Oncol 2011;22:1535-46.
29. Sullivan KM, Kozuch PS: Impact of KRAS Mutations on Management of Colorectal Carcinoma. Patholog Res Int 2011;2011:219303.
30. Taïeb J, Maughan T, Bokemeyer C, Van Cutsem E, Brodowicz T, Folprecht G, *et al*. Cetuximab combined with infusional 5-fluorouracil/folinic acid (5-FU/FA) and oxaliplatin in metastatic colorectal cancer (mCRC): A pooled analysis of COIN and OPUS study data. J Clin Oncol 2012;30, abstr 3574.
31. Folprecht G, Gruenberger T, Bechstein WO, Rabb HR, Lordick F, Hartmann JT, *et al*. 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.
32. Piessevaux H, Bokemeyer C, Schlichting M, Heeger S, Tejpar S. Impact of early tumor shrinkage on long-term outcome in metastatic colorectal cancer (mCRC) treated with FOLFOX4 with or without cetuximab: Lessons from the OPUS trial. J Clin Oncol 2011;29:abstr 398.
33. Piessevaux H, Buyse M, De Roock W, Prenen H, Schlichting M, Van Cutsem E, *et al*. Radiological tumor size decrease at week 6 is a potent predictor of outcome in chemorefractory metastaticcolorectal cancer treated with cetuximab (BOND trial). Ann Oncol 2009;20:1375-82.
34. Van Cutsem E, Bokemeyer C, Heeger S, Sartorius U, Rougier P,

Kohne C. Outcome according to metastatic site in patients with KRAS wild-type tumors: Analysis from the CRYSTAL and OPUS studies. J Clin Oncol 2011;29:abstr 472.
35. Kohne C, Bokemeyer C, Heeger S, Sartorius U, Rougier P, Van Cutsem E. Efficacy of chemotherapy plus cetuximab according to metastatic site in KRAS wild-type metastatic colorectal cancer (mCRC): Analysis of CRYSTAL and OPUS studies. J Clin Oncol 2011;29:3576.
36. Ciuleanu T, Nikolic V, Shmueli E, Vrbanec D, Plate S, Krmpotic ZM, *et al*. Cetuximab weekly (q1w) versus every two weeks (q2w) plus FOLFOX4 as first-line therapy in patients (pts) with KRAS wild-type (wt) metastatic colorectal cancer (mCRC). J Clin Oncol 2011;29:3580.

How to cite this article: Dattatreya S. Metastatic colorectal cancer-prolonging overall survival with targeted therapies. South Asian J Cancer 2013;2:179-85.
Source of Support: Nil. **Conflict of Interest:** None declared.

Letter to Editor

Extrauterine mixed endometrial stromal-smooth muscle tumor: Report of an unusual entity

Neena Elizebeth Luke, Gayatri Ravikumar, Julian A. Crasta

Correspondence to: Dr. Gayatri Ravikumar
E-mail: gayatri.ravikumar@gmail.com

Access this article online

Quick Response Code:

Website: www.sajc.org

DOI: 10.4103/2278-330X.114153

News

29th ICON Meeting Jaipur.
The 29th ICON meeting is scheduled from 13th to 15th Sept 2013 at Jaipur.
Contact: Dr Hemant Malhotra
for further details on: drmalhotrahemant@gmail.com