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Answering reviewers

Reviewer's code: 02849903

In this review, Ohhara et al provide a clear summary of the role of targeted therapy in metastatic colorectal cancer. Overall, the text is clear and this review should be valuable for both World Journal of Gastroenterology readers not particularly familiar with targeted therapies and specialists in the field. My suggestions to further improve the quality of the paper are;

Major: 1. According to the title of this review, it would be better to briefly summarize clinical studies of targeted therapy other than EGFR and VEGF (e.g. "A randomized, placebo-controlled phase 2 study of ganitumab or conatumumab in combination with FOLFIRI for second-line treatment of mutant KRAS metastatic colorectal cancer", Ann Oncol, 2013).

Response: We thank the reviewer for this pertinent comment.

In accordance with the reviewer's comment, we included other targeted agents like gefitinib, erlotinib, ganitumab, conatumumab, trastuzumab, and lapatinib in our text and references.

- ✓ Kuo T, et al. Phase II study of gefitinib, fluorouracil, leucovorin, and oxaliplatin therapy in previously treated patients with metastatic colorectal cancer. J Clin Oncol 2005; 23: 5613-5619
- ✓ Santoro A, et al. A phase II randomized multicenter trial of gefitinib plus FOLFIRI and FOLFIRI alone in patients with metastatic colorectal cancer. Ann Oncol 2008; 19: 1888-1893
- ✓ Kozuch P, et al. Phase II trial of erlotinib and capecitabine for patients with

previously untreated metastatic colorectal cancer. Clin Colorectal Cancer 2009; 8: 38-42

- ✓ Cohn AL, et al. A randomized, placebo-controlled phase 2 study of ganitumab or conatumumab in combination with FOLFIRI for second-line treatment of mutant KRAS metastatic colorectal cancer. Ann Oncol 2013; 24: 1777-1785
- ✓ Sartore-Bianchi A, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016; 17: 738-746

2. The paper by Hong et al ("A phase II study of bevacizumab, oxaliplatin, and capecitabine in patients with previously untreated metastatic colorectal cancer: a prospective, multicenter trial of the Korean Cancer Study Group", Am J Clin Oncol, 2014) should be included as reference.

Response: We wish to thank the reviewer for this comment.
As the reviewer noted, we include the paper by Hong et al as the reference, no 11.

3. As the authors mentioned, KRAS status is a well-described biomarker for the EGFR-targeted therapy. Although the survival of patients with wild type KRAS is better than with mutant KRAS, the tumor eventually relapse regardless of EGFR inhibition. Thus, it is really important to elucidate the mechanism of acquired resistance to targeted therapies. A seminal report in Nature (Diaz et al, "The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers", 2012) has shown that the emergence of mutant KRAS from wild type KRAS is a mediator of acquired resistance. I suggest the authors to include this paper in this review to strengthen the point that

mutant KRAS is a valid biomarker in EGFR inhibitor treatment.

Response: We strongly appreciate the reviewer's comment on this point.
As the reviewer noted, we have added the following text in the cetuximab part;
''Moreover, recently, some reports revealed that use of anti-EGFR drugs for mCRC contributed to acquisition of a KRAS mutation. Misale et al. offered two possible explanations for the discordant results of KRAS: heterogeneity of KRAS status within the primary tumor; and clonal selection during the process of metastasis. In this report, among 10 patients with KRAS wild type who acquired resistance to anti-EGFR therapy, 6 patients had the KRAS mutation after progression on anti-EGFR therapy. In the six patients for whom sufficient pre-treatment tumor samples were available for KRAS testing, KRAS mutations were found to be absent at pre-treatment. Similarly, Diaz et al. showed that emergence of mutant KRAS from wild type KRAS was a mediator of acquired resistance to anti-EGFR antibodies. These results indicate that treatment with anti-EGFR antibodies is associated with the acquisition of secondary KRAS mutations.''

- ✓ Misale S, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature 2012; 486: 532-536
- ✓ Diaz LA Jr, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature 2012; 486: 537-540

4. Most of the inhibitor, which are currently available in clinic, are antibody-based reagents. Santoro et al has shown that gefitinib (EGFR TKI) did not improve the efficacy of FOLFIRI in mCRC (Santoro et al, Ann Oncol, 2008). Is this because of the bioactivity of antibody such as ADCC and CDC?

Response: We wish to thank the reviewer for this comment.

We are sorry not to have enough answer for reviewer question. As the reviewer mentioned, gefitinib combination chemotherapy showed no improvement of the ORR or PFS. Moreover, adding gefitinib occurred severe toxicities like skin rash and diarrhea. On the other hand, multi-kinase inhibitor, regorafenib, demonstrated the efficacy in mCRC as salvage setting. In addition, recent study showed that trastuzumab plus lapatinib effected to mCRC patients with HER2 positive status tumor. From these results, some of tyrosine-kinase inhibitors have clinical benefits, but most of the inhibitor for mCRC are antibodies. As the reviewer noted, it may influence the ADCC or CDC, but we do not know the reason.

Minor: Typo in the title of Table 1.

Response: We thank the reviewer's detection.
We have changed the mistype in the title of Table 1. We have collected 'anti-antiangiogenic' to 'anti-angiogenic'.

Reviewer's code: 00505466

The authors provide a very comprehensive and extended overview of targeted therapy for metastatic colorectal cancer. It is a very long exhaustive) summation of data from clinical trials. A few comments are to be made. This manuscript seems to me more suitable for a (medical) oncology journal and not for a gastroenterology journal.

I would like to ask the authors to discuss whether there are differences in outcome for colon versus rectal cancer metastases.

Response: We thank the reviewer for this comment.

We are sorry that we have enough answer for the reviewer's question. However, one observation study compared right-side colon with left-side colon in 17,641 patients with colon carcinomas. In this study, hepatic and pulmonary metastases were more frequently found in left-sided carcinomas, and peritoneal metastasis in right-sided carcinomas. Survival was significantly worse in patients with right-sided carcinomas than left-side ones. The differences between right-side and left-side carcinomas are associated with differentiation of tumor biology. Smith et al. reported that KRAS mutations were more common in CRCs from the right colon as compared to those from the left colon, and BRAF mutations were more common in CRCs from the transverse and right colon as compared to those from the left colon. KRAS mutations were associated with lung-only metastases, BRAF mutations with peritoneal and nodal-only metastases, and microsatellite instability was associated with nodal-only metastases.

According to the reviewer comment, we add the following sentences in the cetuximab section.

"In the COIN trial, exploratory analyses were conducted in order to identify somatic molecular profile of the EGFR pathway, and its relationship to the site of the primary and metastases [69]. KRAS mutations were more common in the right colon as compared to those from the left colon, and BRAF mutations were more common from the transverse and right colon as compared to those from the left colon. KRAS mutations were associated with lung-only metastases, BRAF mutations with peritoneal and nodal-only metastases, and microsatellite instability was associated with nodal-only metastases. At the point of differences between primary cites, other study reported that hepatic and pulmonary metastases were more frequently found in left-sided carcinomas, and peritoneal metastasis in right-sided carcinomas in the analyses based on 17,641 patients with mCRC."

- ✓ Benedix F, et al; Colon/Rectum Carcinomas (Primary Tumor) Study Group. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum. 2010 Jan;53(1):57-64.
- ✓ Smith CG, et al. Somatic profiling of the epidermal growth factor receptor pathway in tumors from patients with advanced colorectal cancer treated with chemotherapy ± cetuximab. Clin Cancer Res. 2013 Aug 1;19(15):4104-13.

In these days of economic crisis, the additional treatment costs for a survival benefit of a few months has to be discussed.

Response: We wish to thank the reviewer for this comment

As the reviewer noted, we need to consider the cost effectiveness of targeted therapy in mCRC. We should select the treatment option based on not only evidence but also patient background like age, performance status, or economic conditions by countries. However, our review article focused on the benefit of targeted therapy in patients with mCRC. So, we did not add the information about cost effectiveness of targeted therapy. We are sorry, but we strongly appreciate with the reviewer comment.

Page 8. 'IFL' should be explained as 'irinotecan, fluorouracil, and leucovorin' at first appearance.

Response: We thank the reviewer for this pertinent comment. As the reviewer noted, we added the explanation for 'IFL' as 'irinotecan, fluorouracil, and leucovorin' at first appearance.

Reviewer's code: 00503404

A comprehensive, well written review paper

Response: We thank the reviewer for this pertinent comment.

Reviewer's code: 00041966

This is a comprehensive review on the use of biologic in conjunction with cytotoxic drugs in metastatic colorectal cancer patients. The manuscript is nicely written and provides an overview of the current literature on the subject. In the tables summarizing the principal results of the reported studies it could be useful to report the regimen of both arms with significative differences.

Response: We strongly appreciate with the reviewer comment.