Reviewer’s report

Title: Biweekly cetuximab in combination with FOLFOX-4 in the first-line treatment of wild-type KRAS metastatic colorectal cancer: final results of a phase II, open-label, clinical trial (OPTIMIX-ACROSS Study)

Version: 2
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Reviewer: Jaw-Yuan Wang

Reviewer’s report:

Fernandez-Plana et al. conducted a multicentre, single-arm, open-label, phase II study to evaluate the efficacy and safety of biweekly cetuximab in combination with oxaliplatin, leucovorin, and fluorouracil (FOLFOX-4) as first line treatment of metastatic KRAS wild-type colorectal cancer in 99 ITT patients between July 2009 and December 2011. They found that the ORR was 60.6%, with a median follow-up of 17.8 months, the median OS and PFS were 20.8 and 10.1 months, respectively. Metastases from colorectal cancer were surgically resected in 26 (26.3%) patients, with complete resection achieved in 18 (69.2%) patients. Median PFS and OS in patients undergoing metastatic resection were 12.6 and 29.5 months, respectively. The most common grade 3-4 toxicities were neutropenia (32.3%), acne-like rash (15.2%) and diarrhoea (11.1%). The results seem informative; however, there are a lot of criticisms and have several issues that the authors need to address before the manuscript is suitable for publication.

Major Compulsory Revisions:

1. The major point that authors have to elucidate is that a sample size of 98 patients was calculated to detect a 95% confidence interval (CI) for the ORR of 50-70%, assuming an estimated rate of 60% according to previous studies and on the basis of anticipated loss to follow-up of 10% of patients. The above sample size was based one-arm or two-arms sample size estimation? Additionally, the intention to treat population (ITT) included all patients that received at least one dose of the four drugs and had at least one radiological assessment at 8 weeks. If the patients just received one dose of the four drugs could be considered as a candidate for the evaluation of ORR?

2. There were 16 patients received prior chemotherapy in the current study, what was the regimen used should be present in the text.

3. For mCRC treatment, the median OS was actually over 24 months and the current study was only based a median follow-up of 17.8 months. Apparently, the relatively shorter follow-up time was another limitation for further interpretations.

4. From the data from OPUS study, the combination of FOLFOX4 and cetuximab for mCRC, only a better ORR and PFS but no OS advantage was found. Why did authors try to conduct the study design? Moreover, the issue regarding weekly vs. biweekly cetuximab administration for mCRC is actually approved and widely used in the real world.
5. In the Results section, authors must provide the detailed information about how many cycles of regimen was administrated to the studied patients and the definition of relative dose intensity (RDI). The relatively high incidence of 31 patients (39.4%) had at least one cetuximab dose reduction, if it would affect the clinical outcome? Furthermore, the most common adverse events grade 3 or 4 were neutropenia (32.3%) and diarrhoea (13.1%). The AE was prominently different from previous reports; especially the constipation was the major GI AE.

Minor Essential Revisions:
1. In table 1, authors have to look up their data again, Prior therapy, n (%) Chemotherapy 9 (56.3%); Chemotherapy and radiotherapy 7 (43.8%); Surgery 48 (48.5%). Also uniform UK and missing data.
2. Please correct the typo, this phase II study was design with…(designed)

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.