

**Point-by-point response to the Reviewer's comments:**

***Thank you for reviewing our manuscript with critical comments that have improved our manuscript substantially!***

C1) Why histology, grading, TNM, EGFR expression, MSI status, performance status, number of metastatic sites, presence and type of previous adjuvant therapy, types of subsequent therapies, etc. were not considered?

*R1) Thanks for the comment and if I understand correctly, the comment refers to whether or not these factors should be considered predictive of PFS and OS. With respect to TMM stage, indeed all patient included in this study had stage IV disease. We are sorry that EGFR expression was not tested in our cohort and its role has long been superseded by the RAS status. MSI status was also not a standard test for our 2000-2015 cohort and its impact in our study is assumed to be small as the predicted number of patients with MSI-H would be <5 in in cohort. On the other hand, histology grading and previous adjuvant therapy were not reported to affect the outcomes with cetuximab in the presence of known Kras status. The performance status and types of subsequent therapies are reported in Table 2 and 3, and were balanced in both oral and infusion FP groups, and they had no significant interaction for PFS and OS in our cohort. Table 2 has been updated to include the data on performance status. (Please refer to R2) below)*

C2) The sites of tumor should be colon (right and left) and rectum.

*R2) Agree with your comment and the data was updated in Table 2. The percentage of right –sided colon was highlighted in the original submission for quick reference of the readers. The remaining categories of “multiple, colon, and rectum” in the original Table 2 added up to 100% and have no implication on sidedness. Table 2 is now updated according to your comments.*

**Table 2 Baseline characteristics of eligible patients**

	Total (N:95)	Oral (N:57)	Infusional (N:38)	P-value
<b>Gender (%)</b>				
Male	52 (54.7)	32 (56.1)	20 (52.6)	0.900

**Age (Years)**

Median	61.0	61.0	61.0	0.622
Age ≥ 70 (%)	21 (22.1)	12 (21.1)	9 (23.7)	0.960

**ECOG performance status**

0	7 (7.4)	4 (7.0)	3 (7.9)	0.383
1	80 (84.2)	50 (87.7)	30 (78.9)	
2	8 (8.4)	3 (5.3)	5 (13.2)	
3	0 (0)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	

**Site of primary tumor (%)**

Right-sided colon	20 (21.1)	15 (26.3)	5 (13.2)	0.114
Left-sided colon	49 (51.6)	25 (43.9)	24 (63.2)	
Rectum	22 (23.2)	13 (22.8)	9 (23.7)	
Multiple	4 (4.2)	4 (7.0)	0 (0.0)	

**Timing of metastasis (%)**

Synchronous	72 (75.8)	40 (70.2)	32 (84.2)	0.187
Metachronous	23 (24.2)	17 (29.8)	6 (15.8)	

**Extent of the disease (%)**

Primary resected <sup>1</sup>	68 (71.6)	42 (73.7)	26 (68.4)	0.745
Liver-only metastasis	44 (46.3)	26 (45.6)	18 (47.4)	1.000

> 1 site of metastasis	40 (42.1)	24 (42.1)	16 (42.1)	1.000
------------------------	-----------	-----------	-----------	-------

**Site of metastasis (%)**

Liver	67 (70.5)	39 (68.4)	28 (73.7)
Lymph Nodes	28 (29.5)	17 (29.8)	11 (28.9)
Peritoneum	21 (22.1)	11 (19.3)	10 (26.3)
Lung	17 (17.9)	11 (19.3)	6 (15.8)
Bone	3 (3.2)	2 (3.5)	1 (2.6)
Others	8 (8.4)	6 (10.5)	2 (5.3)

C3) Table 2 is incomplete at site of tumor and site of metastasis. Table 3 is incomplete at the CHT backbone. Please give the number of patients (+statistics) for oral and inf. for each row.

*R3) Table 2 and 3 have been updated according to your comments regarding tumor sidedness and chemotherapy backbone with respective number and statistics.*

C4) Please give separately the treatment modifications for patients >70 years old and for AEs.

*R4) For oral fluoropyrimidine-based regimens, 75% dose of the regimen would be used if patients were older than 70 years old and 75% dose of capecitabine if creatinine clearance is less than 50 ml/min.*

*For infusional fluoropyrimidine-based regimens, 75% dose of the regimen would be used if patients were older than 70 years old*

*“Dose modification of chemotherapy due to toxicities were performed according to standard practice. In brief, treatment has to be withheld for grade 2 or above toxicities and to be resumed once recovered to grade 1. Dose reduction was considered for recurrent grade 2, or grade 3 or above toxicities.”*

*The above has been added to the footnote of Table 1.*

C5) Why not all parameters were included in the Cox analysis or what was the reason for selection of variables. Why not the dichotomized age (as significant variable in

factor analysis) was used in Cox analysis?

*R5) As a rule of thumb to maintain the robustness of statistical analysis, our current sample size could not accommodate too many covariates. The selected factors (age, sex, sidedness, primary resected, liver-only disease) are well-known prognostic factors of interest most relevant to our daily practice while the infusion FP was factor being investigated in our study.*

*Regarding using age as the continuous variable in Cox analysis, as the cutoff for dichotomization could be arbitrary. As we would like to explore the effects of age itself, instead of other potential confounders due to age cutoff, age was used as a continuous variable here. For example, if we use 70 years old as cut-off, as patients with age 70 or above, they would receive dose reduction in the chemotherapy regimen, the effects of age may actually reflect more on the effects of dose reduction in this age group.*

C6) Some patients were metachronous for metastases, supposedly they were treated by surgery  $\pm$  (radio)CHT of primary. Please clarify in Table 2 if surgery of primary includes only the palliative surgery of primary (as the Discussion suggests) or includes the previous surgery of nonmetastatic patients? Please also clarify whether metastasectomy was before or after the 1st line treatment, because the latter can be a measure of 1st line efficacy.

*R6) Thanks for the comment and The footnote 1 has been added to Table 2 to explain that “primary resected” included both palliative surgery of primary and previous surgery of nonmetastatic patients with status known before the start of palliative chemotherapy. “Metastasectomy of curative intent” in Table 3 of our study refers to those performed as a result of the 1<sup>st</sup> line palliative chemotherapy with cetuximab.*

C7) Please eventually summarize the extent of disease (presence of primary, multiple metastatic sites, size of metastases, etc.) in order to have a comparison of tumor burden of the subgroups.

*R7) Thanks for your comment and the data on the extent of disease in different subgroups are available in Table 2. Size of metastases were not available but I am afraid it's impact on clinical outcomes and toxicity has not been consistently highlighted in the reported literature.*

C8) Please give the number of patients in Table 6 for grade 3-4 AND any grade (or grade 1-2) for each AE for both treatments.

*R8) Revision of Table 6 has been performed accordingly to your comment.*

C9) It would be useful to see a stratified analysis (survival and AEs) based on backbone CHT, because almost certain the survival (and moreover the AE pattern) of e.g. capecitabine+cetuximab vs. FOLFOX+cetuximab significantly differs.

*R9) Thank you for pointing out the significance of chemotherapy backbone other than the fluoropyrimidine component. While separate analysis of capecitabine/ 5FU alone + cetuximab was not performed due to small sample size, the comparison of oxaliplatin-based vs irinotecan-based regimens was not significant. The data was not included in the manuscript as comparison between oral vs infusional FP remains the primary objectives of the study and there is limitation in number of table. Nevertheless, we have prepared a summary table for your kind reference:*

**Survival and adverse events experienced by our patients grouped by chemotherapy backbone**

	<b>CAPOX (N:43)</b>	<b>CAPIRI (N:9)</b>	<b>CAP (N:5)</b>	<b>FOLFOX (N:26)</b>	<b>FOLFIRI (N:12)</b>
<b>mPFS (months)<sup>1</sup></b>	11.8	9.36	6.47	11.1	9.33
<b>mOS (months)<sup>1</sup></b>	28.9	23.3	7.20	31.2	26.3
<b>G3 or above Adverse Events (%)</b>	15 (34.9)	2 (22.2)	2 (40.0)	6 (23.1)	2 (16.7)
<b>Hematologic (%)</b>					
Anaemia	25 (58.1)	7(77.8)	4 (80.0)	19 (73.1)	9 (75.0)
G3 or above	3 (7.0)	0 (0)	1 (20.0)	0 (0)	0 (0)
Leucopenia	20 (46.5)	3 (33.3)	2 (40.0)	14 (53.8)	5 (41.7)
G3 or above	1 (2.3)	0 (0)	0 (0)	1 (3.8)	1 (8.3)
Neutropenia	19 (44.2)	5 (55.6)	2 (40.0)	18 (69.2)	5 (41.7)
G3 or above	3 (7.0)	1 (11.1)	1 (20.0)	4 (15.4)	1 (8.3)
Thrombocytopenia	32 (74.4)	2 (22.2)	3 (60.0)	13 (50.0)	3 (25.0)
G3 or above	4 (9.3)	0 (0)	1 (20.0)	0 (0)	0 (0)

**Biochemistry (%)**

Raised AST	39 (90.7)	6 (66.7)	2 (40.0)	14 (53.8)	7 (58.3)
G3 or above	1 (2.3)	0 (0)	0 (0)	1 (3.8)	0 (0)
Raised bilirubin	10 (23.3)	2 (22.2)	2 (40.0)	5 (19.2)	2 (16.7)
G3 or above	1 (2.3)	0 (0)	0 (0)	1 (3.8)	0 (0)

**Non-hematologic (%)**

Acneiform rash	29 (67.4)	5 (55.6)	2 (40.0)	13 (50.0)	9 (75.0)
G3 or above	1 (2.3)	0 (0)	0 (0)	1 (3.8)	1 (8.3)
Diarrhoea	13 (30.2)	4 (44.4)	0 (0)	5 (19.2)	3 (25.0)
G3 or above	2 (4.7)	0 (0)	0 (0)	0 (0)	0 (0)
HFS <sup>2</sup>	0 (0)	1 (11.1)	1 (20.0)	0 (0)	0 (0)
G3 or above	0 (0)	1 (11.1)	1 (20.0)	0 (0)	0 (0)

<sup>1</sup> 95% CI is not calculated because the sample sizes of some groups are too small.

<sup>2</sup> It refers to hand-foot syndrome.

*The above table summarized the survival and adverse events experienced by our patients grouped by chemotherapy backbone. Patients using only capecitabine as chemotherapy backbone has poorest mPFS and mOS as expected. Patients using oxaliplatin appears to have better mPFS and mOS, compared with patients using irinotecan.*

C10) In the discussion you are reporting that “we could not answer the underlying mechanism linking ethnicity and FP tolerability”, but the literature for pharmacogenomics of FP and difference in allele frequencies for ethnicities may give you some idea in this regard.

*R10) Thanks for enlightening us with relevant literature! While your suggested data with the pharmacogenomics of FP may underline the mechanism linking ethnicity and FP tolerability, our study could not answer this due to the nature of our retrospective analysis on clinical outcomes without incorporating pharmacogenomics study. Nevertheless, I believe this would be a potential topic for future study in a larger cohort of patients of different ethnicities.*