Peer Review File

Article Information: http://dx.doi.org/10.21037/jgo-20-593

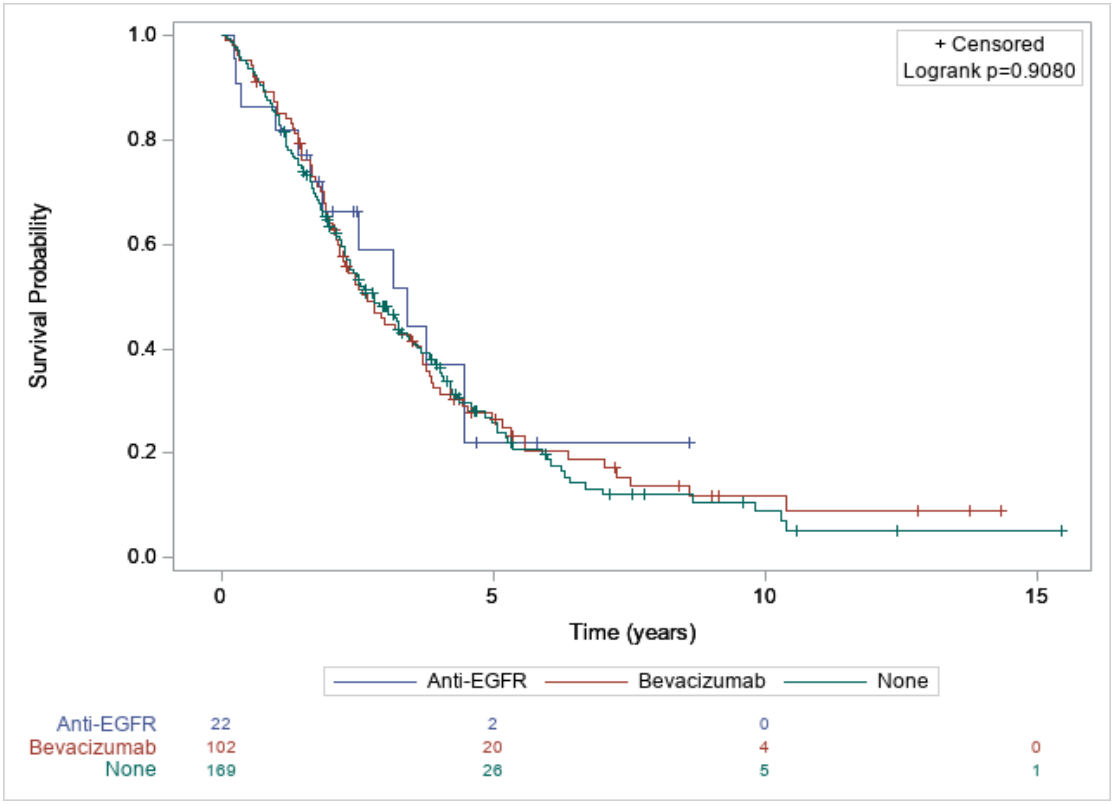
Reviewer A

The main objective of this manuscript was evaluated the impact of different chemotherapy regimens (FOLFIRI vs FOLFOX) on the survival outcomes (PFS and OS) in first line metastatic colorectal setting, depending on primary tumor site. This an interesting clinical question for the oncology community, which has been debated in the last years. However, there are several concerns, which need to be addressed in this communication:

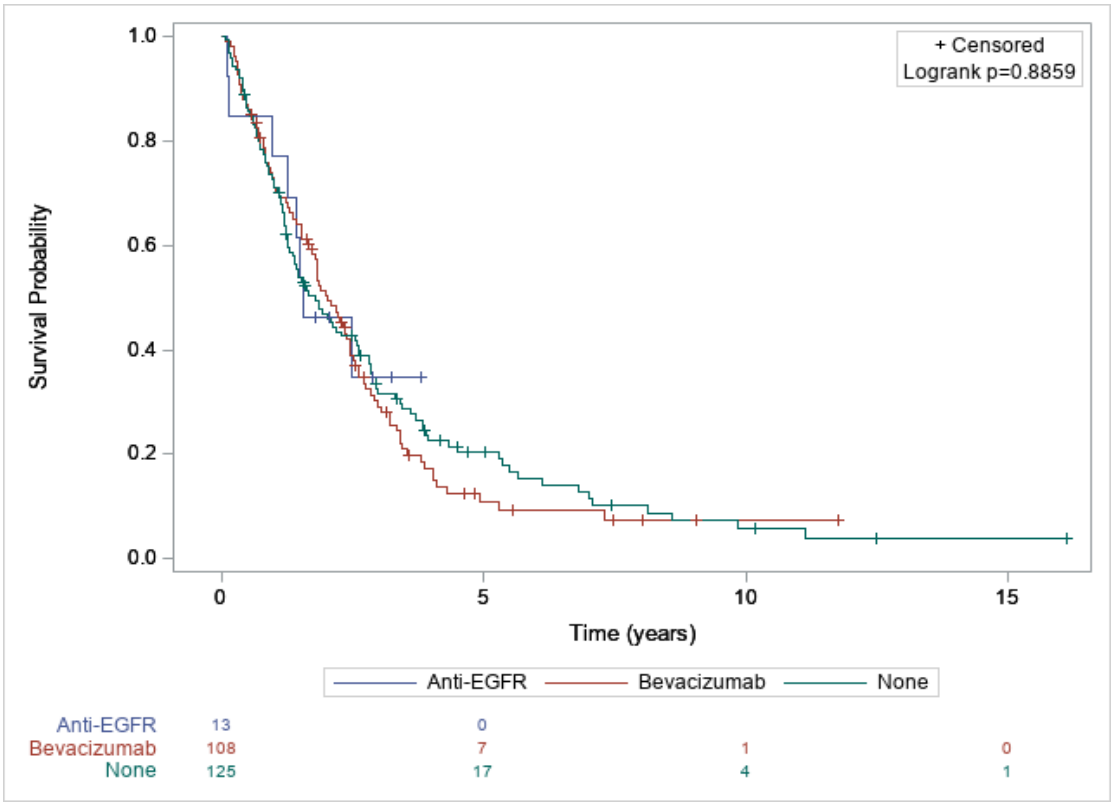
Questions 1. As authors have mentioned in the introduction, the combination of monoclonal antibodies plus chemotherapy have proved their efficacy. In statistical analyses section, primary end.point was "to evaluate whether there was a benefit in favor of either FOLFIRI or FOLFOX plus target therapies as first line of metastatic in terms of PFS for patients depending PTL". So the comparison should be by full regimens of treatment, including specifically the target therapy, not only if it were based on FOLFOX or FOLFIRI, due to the potential different impact of the biological therapy dependent of primary tumor site. Discussed in several manuscripts (doi:10.7150/jca.34550, doi: 10.18632/oncotarget.22396)

Response: Our study include mainly patients treated in first line with bevacizumab ("Only 8% of patients received anti EGFR in first line while 59% received bevacizumab in first line"). So our main idea was to determine if in patients treated with chemotherapy with or without bevacizumab, the sidedness influence the response to irinotecan or oxaliplatin. According to reviewer request we performed subgroup analysis in function of the type of target therapy anti EGFR vs VEGF and the sidedness. We did not observed influence of target therapies in function of sidedness. We may suspect a lack of power in our study
Accordingly, we add the two references in the discussion.

Modification of the text: No difference in term of OS was observed between patients treated in first line with bevacizumab and anti EGFR whatever the sideness (not shown). We did not confirm previously reported influence of sidedness on efficacy of anti EGFR vs antiangiogenic in our cohort (doi:10.7150/jca.34550, doi: 10.18632/oncotarget.22396).



Left side tumors



Right side tumors

Question 2. An statistical analysis, examine if classic prognostic factors are balanced between FOLFOX vs FOLFIRI treated patients should be added.

Response: According to reviewer request we compared prognostic factor in the FOLFOX and FOLFIRI group an did not observe particular differences.

Modification of the text: No particular clinical differences were seen between the FOLFOX and the FOLFIRI group for classical prognostic factors (not shown)

	FOLFIRI	FOLFOX	pValue
Age			0,2736
N	137	358	
Mean (std)	63.5 (10.5)	64.5 (10.9)	
Median [min - max]	65.0 [24.0 - 86.0]	66.0 [28.0 - 89.0]	
Sex			0,4577
Male	85 (62.0%)	209 (58.4%)	
Female	52 (38.0%)	149 (41.6%)	
Tumor location			0,3885
Left colon + sigmoid	58 (42.3%)	159 (44.4%)	
Right colon + transverse colon	55 (40.1%)	122 (34.1%)	
Rectum	24 (17.5%)	77 (21.5%)	
WHO performance status			0,0553
0-1	93 (93.0%)	232 (85.6%)	
2-4	7 (7.0%)	39 (14.4%)	
Missing values	37	87	
Number of metastatic sites			0,4711
1	79 (57.7%)	220 (61.5%)	
2	43 (31.4%)	93 (26.0%)	
> 2	15 (10.9%)	45 (12.6%)	
metastatic sites			
liver			0,1341
No	47 (34.3%)	98 (27.5%)	
Yes	90 (65.7%)	259 (72.5%)	
Missing values	0	1	
lung			0,8483
No	95 (69.3%)	250 (70.2%)	
Yes	42 (30.7%)	106 (29.8%)	
Missing values	0	2	

peritoneum			0,9391
No	105 (76.6%)	274 (77.0%)	
Yes	32 (23.4%)	82 (23.0%)	
Missing values	0	2	
KRAS mutation			0,4462
No	60 (54.5%)	127 (50.2%)	
Yes	50 (45.5%)	126 (49.8%)	
Missing values	27	105	
BRAF mutation			0,6785
No	75 (90.4%)	192 (91.9%)	
Yes	8 (9.6%)	17 (8.1%)	
Missing values	54	149	
LDH			0,4395
<= 254	53 (58.2%)	154 (62.9%)	
> 254	38 (41.8%)	91 (37.1%)	
Missing values	46	113	
Alkalin phosphatase > 300			0,0523
No	85 (90.4%)	203 (81.9%)	
Yes	9 (9.6%)	45 (18.1%)	
Missing values	43	110	
Primary tumor resection			0,0548
No	23 (16.8%)	89 (24.9%)	
Yes	114 (83.2%)	269 (75.1%)	
surgery of metastasis			0,0642
No	103 (75.2%)	237 (66.6%)	
Yes	34 (24.8%)	119 (33.4%)	
Missing values	0	2	

Question 3. The OS comparison between patients treated with FOLFOX vs FOLFIRI stratified by tumor location has already published with almost 4000 patients doi:10.1016/j.clcc.2019.01.005. Please include this reference and discuss with your results.
Response: According to reviewer request we add this reference in the discussion.
Modification of the text: In a retrospective study from SEER-Medicare similar OS were observed in patients treated with FOLFOX and not FOLFIRI in the era before target therapies. In this cohort sidedness did not impact the effect of chemotherapy doublet

Question 4. Are there other potential prognostic factors in the rectal metastatic population, which they could explain the potential benefit for FOLFIRI regimens? Due to this is a retrospective study, a multivariable analsys should be done, adding other potential prognostic factors (CEA levels, ECOG, number of metastasic site….) or describe as a limitation in the discussion.
Response: According to reviewer request we compared prognostic factor in rectal cancer group vs colon cancer and did not observe particular differences.
Modification of the text:
No particular differences were seen between rectal and colon cancer for classical prognostic factors (not shown)

5. Same comment for the comparison for mono vs doublet vs triplet.
Response: According to reviewer request we compared prognostic factor in mono vs doublet vs triplet treatment and did not observe particular differences.
Modification of the text:
No particular differences were seen between patients treated with monotherapy, doublet or triplet for classical prognostic factors (not shown)

Reviewer B

In the Discussion, it is convenient to include in the study limitations section that the population described is not only very heterogeneous (synchronous, metachronous, resectable, unresectable, mutant, wt, left / right / rectum) but also other aspects such as:
- Most of the patients have been treated with Folfox (72,4 %)
- For some comparisons the number of patients and the retrospective nature of the study limits any conclusions like that of ....."FOLFIRI and FOLFIRINOX regimens might be preferred for metastatic rectal carcinoma"....
- The low number of patients limits also any comparisons based on mutational status and sidedness.

Response: According to reviewer we make the appropriate modification in the discussion

Modification of the text:

Other limitations to our study are that it compared a highly heterogeneous (synchronous, metachronous, resectable, unresectable, various genetic mutational status, left / right / rectum) but also other aspects such as an enrichment in FOLFOX treated patients. The choice of the chemotherapy regimen was physician dependent and some differences in patients could have not been detected by our data collection. Finally, the low number of patients limits also comparisons based on mutational status and sidedness. The selection of therapy based on the conclusion of this study may be taken with caution because of the low number of patients and the retrospective design.