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Title: FOLFIRI3-aflibercept as Second or Later-line Therapy in Patients with Metastatic Colorectal Cancer

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Dear Fang-Fang Ji,

We sincerely thank you for your supplementary comments on our manuscript. We addressed all the remarks in the provided, edited version of the manuscript and wish to re-submit it for further consideration in the journal. The requested pdf files of the statements (conflict of interest, data sharing, informed consent) and audio core tip file are provided together with the re-submitted manuscript.

Detailed responses to all comments addressed by reviewers point by point are given below.

We look forward to the outcome of your assessment.

Yours sincerely,

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2 Peer-review report

Reviewer #1: This is unique study evaluation the efficacy and safety of FOLFIRI3 plus aflibercept in ordinal clinical setting that may encourage future prospective trial with the relatively high response rate. However, there are some points authors may re-consider.

#1. Authors should provide the reasons for discontinuation of the prior irinotecan treatment in irinotecan pre-exposed population.

The reasons for prior lines treatment discontinuation were not collected in this retrospective study. Of course, that will be done case in the planned prospective trial.

Authors cannot conclude FOLFIRI3＋aflibercept is promising for irinotecan pre-exposed patients if those patients were not refractory to irinotecan.

The signal of promising efficacy results even in patients with prior exposition to irinotecan is shown in Table 3 (in the manuscript). Among 7 patients with disease progression as best response to prior irinotecan regimen, 3 (43%) patients were controlled (either response or stabilization) with the FOLFIRI3-aflibercept regimen. Among 10 patients with stabilization as best response to prior irinotecan regimen, 4 (40%) patients had tumor response (CR or PR).

Table 3. Contingency table of tumor response with FOLFIRI3-aflibercept according to prior tumor response with irinotecan (n=35)

		FOLFIRI3-aflibercept				
		CR/PR *n* (%)	SD *n* (%)	PD *n* (%)	NE *n* (%)	All *n* (%)
Prior irinotecan-based regimen	CR/PR	5	3	7	0	15 (42.8)
	SD	4	4	2	0	10 (28.6)
	PD	1	2	3	1	7 (20.0)
	NE	2	0	1	0	3 (8.6)
	All	12 (34.3)	9 (25.7)	13 (37.1)	1 (2.8)	35

#2. There were too many toxicity related discontinuation of therapy (46.7%) despite dose reductions in this study. In VELOUR study, the proportion of adverse event related discontinuation was 26.8%. This may be attributed to specific UGT1A1 genotype, namely

*28/*28, which leads to higher incidence of serious toxicity with irinotecan. Can author reveal the patients UGT1A1 status?

The UGT1A1 status is not available in this retrospective study, but will be assessed in the planned prospective trial.

#3. Can authors provide detailed profile of prior treatment in both groups? In VELOUR sub-group study (Chau, et al. BMC Cancer 2014), they suggested adjuvant fast relapse is a favorable predictive factor for FOLFIRI plus aflibercept.

Please find below detailed information for prior therapies in both groups.

		Irinotecan-naïve, n=30		Prior irinotecan, n=35	
		N	%	N	%
Prior systemic therapy	Adjuvant only	4	13.3	0	0.0
	Metastatic only	22	73.3	26	74.3
	Both	4	13.3	9	25.7
Prior lines (met. disease)	0	5	16.7	0	0.0
	1	25	83.3	15	42.8
	2	-	-	13	37.1
	3	-	-	6	17.1
	4	-	-	1	2.8
Prior drugs	Oxaliplatin	29	96.7	35	100.0
	Irinotecan	-	-	35	100.0
	Anti-angiogenic agents	18	60.0	29	82.8
	Bevacizumab	18	60.0	29	82.8
	Anti-EGFR	2	6.7	4	11.4
Adjuvant regimen	No	22	73.3	26	74.3
	FOLFOX	7	23.3	9	25.7
	Capecitabine	1	3.3	0	0.0

Prior No of line with irinotecan	0	30	100.0	-	-
	1	-	-	29	82.8
	2	-	-	6	17.1
Prior irinotecan regimen	FOLFIRI	-	-	10	28.6
	FOLFIRI3	-	-	4	11.4
	FOLFOXIRI/FOLFIRINOX	-	-	19	54.3
	FOLFIRI then FOLFIRINOX			2	5.7

The sample size of this study does not allow multiple subgroups analysis.

Reviewer #2: This is a retrospective, small sample size study using modofied chemotherapy+ targeted therapy in patients with metastatic CRC. The results are promising, indicating that the combination is effective in irinotecan naive and pre-treated patients. The manuscript is well written, the english is good and no corrections are needed. The tabels, graphs are clear, the literature is cited well. The statistics is appropriate. I agree with authors that randomised trial on bigger sample size would be the next step.

Reviewer #3: There is one question for the authors：Is there a dose finding stage for FOLFIRI3-aflibercept regime? What is the basis for determining the dosage of this regime?

The dose of aflibercept is the standard dose (4 mg/kg) recommended in the SPCs. The total dose of irinotecan is the standard 180 mg/m ²q2w, separated in two injections per cycle (90 mg/m ²on day 1 and 90 mg/m ²on day 3).