Peer Review File

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Reviewer Comments

I would suggest either to reject the paper or propose a totally rewritten paper taking molecular markers into account when evaluating the results (RAS/BRAF wildtype vs RAS/BRAF mutated, right sided vs left sided vs rectal (3 side groups). Did the MSI cancers receive pembrolizumab and how was the results. It the left sided and rectal groups resemble each other they could be merged.

The intermingling occurs because there is no distinction in the outcome according to RAS or BRAFV600E status or the primary location of the tumor. Separation on these molecular markers would have been the least requirements. As presented now everything is intermingled and of no use for the clinician except the result that the patients tolerate the therapy given. This is in no way surprising as irinotecan is given every 2 weeks in the dose schedule of 85 mg/m2 as is the dose used in the FOLFIRI regimen that at least in the European population is well tolerated. Data on the IRIS+B-mab regimen in the RAS/BRAF mutated group would be interesting.
What was the molecular profiling according to side location with a special focus on RAS/BRAF. The table 1 could be extended with these data that would be interesting.
One could report on median PFS and median OS according to the total population and according to subpopulations divided on RAS/BRAF mutation status.

Reply: We thank you for your comment.
The tumor location was classified as a right-sided group (those in which a tumor was present at the proximal side up to the splenic curve) and a left-side group (from the splenic curve distally). Figure 3 and Table 2 were prepared based on this classification, and discussion were provided.
Due to the health insurance coverage situation in Japan, assays could be conducted for patients after the following periods: RAS: April 2015, BRAF: August 2018, MSI: December 2018.

Therefore, as the treatment period of some patients was outside of the study period, not all patients have assay results.
Specifically, MSI assay was possible in Japan since December 2018. As such, it is not

consistent with the study period of this study. Consequently, we do not have data for pembrolizumab. As presented, BRAF mutation was not observed during the study period. However, considering RAS, we prepared Table 2 for RAS status per location side.

PFS and survival curves and response for these 2 groups would be interesting. In as much as patients in the 2 groups have been treated almost uniformly alike (panitumumab in RAS wildtype and bevacizumab in RAS mutated.
Reply: We thank you for your comment.

Was there a difference according to UG1A1 polymorphism. These data are not mentioned.
Reply: Our data were consistent with the distribution of the polymorphism in Japan. In Asians, it is reported that UGT1A1 *6 is about 30% while *28 is about 15%. The incidence in this study was lower than that previously reported. Comments were made on this matter, as below.
Changes in the text: P16 Line 254-261: The reference (38) was added.

Such an article might be interesting not a paper presenting the intermingling of data as is done her. As done here I would suggest to rejecting the article, but it could be interesting to see efficacy data subdivided as total and on RAS/BRAF data (possibly in the same PFS and OS graphs).
Reply: We prepared Table 2, which includes RAS per location side.

The language should be corrected by a specialist in oncology that should help to clarify and sharpen the oncological descriptions and language.

There are lots of old-fashioned word for combinations denoting chemotherapy that is not used anymore.

It is more than 20 years since the laboratory name for irinotecan was denoted CPT-11 after approval of irinotecan in 2000 and this laboratory name should consequently be omitted.

XELODA was the brand name for capecitabin used by Roche. The regime combining capecitabine and oxaliplatin is named CAPOX as also mentioned in the references. This kind of text without a clear oncological vocabulary is dominating the text. It is very annoying that every time irinotecan is mentioned CPT-11 is mentioned in a bracket.

Reply: We sincerely apologize for this. Per your comment, we have revised the manuscript throughout. The appropriate changes were made in the following parts:
P3 Line 32, P7 Line 101, P8 Line 122, Line 126, P10 Line 162, P11 Line 170, Line 177, P21 Line 344, P22 Line 366, P23 Line 376, Line 379, Line 380, P24 Line 390, Line 391, Line 402, P34 Line 569, P35 Line 586, Line 588.

The Introduction is too long without clear relevance to the present study.
Is there a selection bias since so many patients have rectal cancer and the dominance of males (76%).
Reply: This is a sequential patient study with no selection bias.
Per your comment, P6 Line 89-96, was deleted.

Why use the terms midgut hindgut etc instead of a separation on the actual location of the primary tumor? Table 1 nicely depicts the side of location with 11 patients with a right sided tumor (coecum, ascending, transverse) with only one patient a location in the transverse, 13 patients had a left sided tumor (descending, sigmoid, rectosigmoid) and 17 had a rectal tumor.
Reply: We conducted an additional analysis in which tumors proximal to the splenic curve were defined as right-sided while those distal to the splenic curve were defined as left-sided.
Changes in the text: P13 197-200.

I would guess there are only a little number of BRAF unknown assuming RAS and BRAF mutation to be mutual exclusive. In table II BRAF is unknown in 24/41 patients but RAS is known in all patients.
Reply: Due to health insurance coverage status in Japan, some patients did not have BRAF assay.
Changes in the text: P12 Line 188-192.

I see no reason to present survival data on 6, 12 and 36 months. Just keep to median PFS and OS.
Reply: We modified the descriptions per your comment.
Changes in the text: P13 Line 200-202, P14 Line 218-226

It will be too time-consuming to correct and clarify and sharpen the oncological language.
Reply: We modified the descriptions per your comment.

As examples:
Line 32: Modified regimen. The modification is not mentioned in the abstract. I think one should mention the doses of irinotecan and S-1, beva panitumumab and cetuximab aimed at being used i.e the modified regime used.
Reply: Detailed dose information was added to main text on P11, Line 169-179, rather than the Abstract (Line 32-).
Changes in the text: P11 Line 169-179

Line 34 why waste words using the term MTA´s in the abstract when all MTA´s are either bevacizumab or panitumumab of cetuximab. Especially not in the abstract. Later in the article it is relevant.
Reply: We deleted the descriptions per your comment.
Changes in the text: P3 Line 33-35

line 37: advanced recurrent colorectal cancer. One could mentione how many advanced and how many recurrent they are two groups. As seen in table 1 58.5 % are advanced (stage VI) at diagnosis the rest are recurrent. How long was the time from primary diagnosis to recurrence and what was the definition of primary advanced - 3 or 6 months after the primary diagnosis. Did the 2 groups differ in outcome?
Reply: Median (IQR) from the start of the second line through to the confirmation of the exacerbation was 222.0 days (155.0–347.5). There were 4 patients without recurrence. US and CT scans were used for assessing the target lesion according to RECIST, and used to judge and adopt PD.

Data on treatment after second line is missing.
Reply: Treatment after the third line followed Clinical Guidelines.

Line 167: I thought all patients received irinotecan in second line, did anyone receive FOLFOX since it is mentioned in this section.
Reply: No patient received prior treatment with FOLFOX.

Genomic RAS BRAF analysis. What method was used? Second generation testing for what RAS mutations (reference) and was extended RAS status evaluated in all patients? It should be clearly stated that the only BRAF mutation considered is BRAFV600E.

Reply: MEBGEN RASKET-B kit was used to assess BRAF gene mutation, including BRAFV600E.

In the results section one could mention the numbers located on the right, left and rectal site.
How many patients with an advanced cancer at the primary diagnosis had their primary removed (if any).
Reply: Patient characteristics including cancer stages, in all patients, are shown in Table 1. The primary locations were as follows: Right colon: 11 patients, left colon: 30 patients. There were more patients whose primary colorectal cancer was left sided. The most common location of the primary tumor was the rectum, followed by the ascending colon. The majority of patients were stage IV cancer (24/41 patients, 58.5%) at the initial diagnosis. The primary tumor was resected in 7/24 patients (29.2%).

In table 4. Rash is reported in 10 patients. The percentage is then 10/41 = 24% but I guess rash is only seen in patients treated with an EGFR inhibitor thus yielding 10/17 = 58.8%. The table could be depicted more clearly by omitting the 0(0) and instead use
Reply: We modified the descriptions per your comment.

I made minor changes from “A single-center retrospective analysis of the efficacy and safety of a modified irinotecan plus S-1 (IRIS) regimen with molecular targeting agents as second-line chemotherapy in Japanese patients with recurrent or nonresectable colorectal cancer” to “A single-center retrospective analysis of the efficacy and safety of a modified regimen of irinotecan plus S-1 (IRIS) ~~regimen~~ with molecular targeting agents as second-line chemotherapy in Japanese patients with recurrent or nonresectable colorectal cancer”.