

## Peer Review File

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### Reviewer A:

#### General Comments:

- Abstract: well written
- Overall, this is a very well written study that tackles an extremely broad topic.

#### Specific Comments:

##### Comment 1

- Line 19: grammatical correction: consider changing “would be” to “will be” or “is”

Reply 1: Thank you for careful consideration. We corrected as pointed out.

Changes in the text: Please see the manuscript with yellow label.

##### Comment 2

- Line 47: consider the word opinions/recommendations (or something else) instead of the word “situations.”

Reply 2: Thank you for careful consideration. We rephrased the word “situation” to “circumstances”.

Changes in the text: Please see the manuscript with yellow label.

##### Comment 3

- Line 78: would consider deleting the word future, as this sets up the following paragraphs about the current/past development of therapeutic treatments around the world.

Reply 3: Thank you for careful consideration. We deleted the “future” as suggested.

Changes in the text: Please see the manuscript.

##### Comment 4

- Line 80: would replace the word “with” with “among”

Reply 4: Thank you for careful consideration. We changed the word “with” to “among” as suggested.

Changes in the text: Please see the manuscript.

##### Comment 5

- Line 112: rephrase “were to the category” as the meaning of this is unclear

Reply 5: We apologize for the confusion caused by our previous sentence. We rephrase to clarify the sentences as follow.

Changes in the text: “Herein, we assessed the indication and survival outcomes of perioperative or neoadjuvant chemotherapy mainly based on the phase III trials, with the inclusion of phase II trials in the categories where phase III trials were limitedly available.”

##### Comment 6

- Line 142: delete the phrase “for surgery”; it is not needed as adds confusion

Reply 6: Thank you for careful consideration. We deleted the “for surgery” as suggested.

Changes in the text: Please see the manuscript.

Comment 7

- Line 153: delete the word “other”; or say “the majority of patients with G/GEJ tumors are considered as candidates...”

Reply 7: We apologize for the confusion caused by our previous sentence. This sentence means that in Western countries, all resectable GC except for cases classified as cT1N0 is considered to NAC before surgery. We added this sentence to summarized but, delete the sentence to avoid confusion.

Changes in the text: Please see the manuscript.

Comment 8

- Line 164: first use of the acronym ECX, requires a definition. Add a citation for this sentence.

Reply 8: Thank you for careful consideration. We spelled out.

Changes in the text: Please see the manuscript.

Comment 9

- Line 166: Add a citation for this sentence.

Reply 9: Thank you for careful consideration. We added the two pivotal clinical trial evaluating perioperative ECX to the reference.

Changes in the text: We added the following two articles as reference.

Cunningham D, et al. N Engl J Med 2006 Vol. 355 Issue 1 Pages 11-20

Alderson D, et al. Lancet Oncol. 2017 Sep;18(9):1249-1260.

Comment 10

- Line 167-168: Consider replacing “cannot be used” with something like “were found to be intolerable”. ... “FLOT has therefore become the current...”

Reply 10: Thank you for valuable suggestion. DCF regimen was firstly expected triplet regimen with more potent antitumor activity than ECX or EOX. However, in the metastatic setting, DCF were found to be intolerable. Thus, therapeutic development of DCF was abandoned in the perioperative setting. After that, based on the FLOT-4 trial, FLOT regimen was accepted as standard treatment of perioperative setting. We rephrased sentences combined with the reviewer’s suggestion as follow.

. Changes in the text: The triplet regimen with docetaxel was the most promising, but because of its severe toxicities, docetaxel, cisplatin, and fluorouracil (DCF) was found to be intolerable and abandoned to develop as perioperative setting (37). While perioperative FLOT demonstrated the improved survival with manageable toxic profile in the FLOT-4 trial, FLOT has therefore become the current standard therapy for perioperative chemotherapy (10).

Comment 11

- Line 173: would move this sentence up in the paragraph, to line 171.

Reply 11: Thank you for careful consideration. We moved this sentence.

Changes in the text: Please see the manuscript.

Comment 12

- Line 180: curative-intent resection

Reply 12: Thank you for careful consideration. We changed the word as suggested.

Changes in the text: Please see the manuscript.

Comment 13

- Line 182: “to minimize the number of patients with early-stage disease” doesn’t make sense in this context. Perhaps you meant to minimize the number of patients with recurrence?

Reply13: Thank you for careful consideration. We apologize the confusion. In Japan, early-stage gastric cancer (pT1b - 2N0) comprised almost half of the resected cases. For these cases, surgery alone is the standard of care, and nearly 90% of patients achieved a cure.

We added the sentence more clearly to convey its intent.

Change in the text: Surgery followed by adjuvant chemotherapy is a reasonable approach to eliminate patients with early-stage disease (pT1b-2N0M0) who could achieved a cure by surgery alone.

Comment 14

- Line 184: what discussion?

Reply14: Thank you for careful consideration. We apologize the confusion. We should change the sentence as follow.

Change in the text:

(before)

The primary objective of the discussion was to accurately identify patients with a poor prognosis who should undergo surgery as the initial treatment approach.

(after)

The primary objective of the discussion was to accurately identify patients with a poor prognosis who should receive NAC as the initial treatment approach.

Comment 15

- Line 196: patients with “scirrhous GC or GC with extensive...”

Reply 15: Thank you for careful consideration. We changed the word as suggested.

Changes in the text: Please see the manuscript.

Comment 16

- Line 200: I think this references types of GC according to the Borrmann classification, if so, would include this in the subsection heading as “Borrmann Type 4 and large type 3” and perhaps switch the paragraph order to have the paragraph about the Borrmann classification system as the first paragraph in this section.

Reply 16: Thank you for suggestive comment. We changed the title as suggested. However, Borrmann classification is employed as a surrogate diagnosis for scirrhous GC or linitis plastica. Accurate diagnosis the scirrhous GC or linitis plastica, requires pathological examination. To utilization of Borrmann classification to determine the indication of NAC is a unique approach in Japan. Moreover, it is the crucial for clinicians to provide NAC for patient with poor prognosis. While, scirrhous or linitis plastica is well-known for being challenging to treat in the AGC and

addressing this subset is the global concern. Thus, we narrow our focus from the scirrhous GC to specifically emphasize the Borrmann. Thus, we did not switch the order of paragraph. Please kindly understand our intention.

Changes in the text: Please see the manuscript.

Comment 17

- Line 203: consider: "...or having peritoneal metastases at time of surgery"

Reply 17: Thank you for careful consideration. We changed these sentences corresponding to the comment 40. Please see the reply 40.

Changes in the text: Please see the manuscript.

Comment 18

- Line 206: It's unclear how the first half of this sentence relates to the second half of this sentence. What is "ordinal" perioperative chemotherapy?

Reply 18: Thank you for careful consideration. The reviewer's comment is well-taken. Ordinal is not appropriate in this context, and we deleted this word.

Changes in the text: Please see the manuscript.

Comment 19

- Line 216: add citation.

Reply 19: Thank you for careful consideration. We added the reference.

Changes in the text: Please see the manuscript.

Comment 20

- Line 239: add citation if you have one

Reply 20: Progression of peritoneum metastasis cause obstruction of gastrointestinal tract, urinary tract and biliary tract, resulting in being ileus, hydronephrosis and jaundice. It is clinically self-evident that symptomatic disorder caused by peritoneum metastasis deteriorate the QOL of patients. We believe that all reader could accept this sentence without any reference.

Changes in the text: No additional information.

Comment 21, 22, 23

- Line 241: Is this trial being conducted in Japan?

- Line 245: Is this trial being conducted in Japan?

- Line 249: Is this trial being conducted in Japan?

Reply 21, 22, 23: Yes, they are all conducted in Japan.

Comment 24

- Line 251: What does "without non-curative factors" mean?

Reply 24: Thank you for the question. Non-curative factor means distant metastasis such as peritoneum metastasis, liver metastasis and so on. It includes cytology positive as well.

Comment 25

- Line 254: Is all the of information below unique to Japan? If so, please clarify. Might be helpful to note that what JCOG stands for, and clarify that these are trials performed by the Japan Clinical Oncology group. Same for the meaning of OGSG.

Reply 25: We apologize for any confusion caused by the lack of clarity.

As reviewer's pointed out, JCOG means Japanese Clinical Oncology Group. OGSG means Osaka Gastrointestinal cancer chemotherapy Study Group which initiates clinical trials in the Japanese local region. Osaka is the second largest city in Japan.

Changes in the text: We spelled out JCOG and OGSG at the first appearance.

Comment 26

- Line 255: Start this sentence off with "According to XYZ, bulky N2..."

Reply 26: Thank you for the valuable comment. The poor prognosis of AGC with bulky N2 is widely recognized. The several phase II trials were conducted for the patients with extensive LN metastasis (bulky N2/N3) in the Japanese multicenter. However, rationale for these trials was based on the retrospective study conducted at the Japanese tertiary center which was not available in English. We added trials for AGC patients with extensive LN metastasis as reference.

Changes in the text: We added these trials as reference.

Comment 27

- Line 286: Is all the of information below unique to Japan?

Reply 27: Yes, this is the unique category used in Japan.

Comment 28

- Line 304: define DOS

Reply 28: Thank you for careful consideration. We spelled out.

Changes in the text: Please see the manuscript.

Comment 29

- Line 316: Helpful first sentence. Incorporate this within the section above.

Reply 29: Thank you for the suggestive comment. We followed the instruction from reviewer.

Changes in the text: Please see the manuscript.

Comment 30

- Line 317: delete "or postoperative", the word peri-operative implies both pre and post-operative.

Reply 30: Thank you for the comment. We agree that perioperative generally means pre and postoperative. However, RESOLVE trial has three arms, one control arm; postoperative CAPOX and two experiment arms: perioperative SOX and postoperative SOX. Thus, we have to distinguish between perioperative arm and postoperative arm.

Changes in the text: No change in the revised manuscript.

Comment 31

- Line 327: fix this grammar: "analysis of survival analysis"

Reply 31: Thank you for careful consideration. We rephrased this sentence.

Changes in the text: An updated survival analysis revealed a significant improvement in 5-year OS...

Comment 32

- Line 347-357: Perhaps this section and 2.2.6 should fall under a "Global" categorization? As I read through these two sections I still thought that I was in the East section. Or consider breaking

up the immunotherapy sections to their respective East/West/Japan/Global (or International) sections (since some of these studies seem to be china-specific).

Reply 32: Thank you for the valuable suggestion. We changed the title as suggested.

Changes in the text: Title and title numbers

(before) 2.2.5 Combination with immune therapy

2.2.6 Biomarker-driven personalized therapy

2.2.6.1 HER2-positive G/GEJ cancer

2.2.6.2 Microsatellite-instability-high (MSI-H) or deficient-mismatch-repair (dMMR) G/GEJ cancer

3. Future perspectives

(after) 2.2.5 Global collaboration with East and West

3.1 Biomarker-driven personalized therapy

3.1.1 HER2-positive G/GEJ cancer

3.1.2 Microsatellite-instability-high (MSI-H) or deficient-mismatch-repair (dMMR) G/GEJ cancer

4. Future perspectives

Comment 33

- Line 383: Where did these trials take place?

Reply 33: NEOHX was conducted at the multicenter in Spain.

HerFLOT was conducted at the multicenter in Germany and this study was initiated by the investigators of AIO.

Changes in the text: No change in the revised manuscript.

Comment 34

- Line 415: Where did this trial take place?

Reply 34: DANTE was conducted at the multicenter in Germany and Swiss. This study was initiated by the investigators of AIO and SAKK.

Changes in the text: No change in the revised manuscript.

Comment 35

- Line 423: Where did this trial take place?

Reply 35: INFINITY was conducted at the multicenter in Italy.

Changes in the text: No change in the revised manuscript.

Comment 36

- Line 460: SPOTLIGHT AND GLOW, were these discussed above?

Reply 36: Thank you for the important question. We apologize the confusion. The SPOTLIGHT and GLOW were phase III trial targeting CLDN18.2 positive and HER2-negative **unresectable advanced or recurrent** GC. We added the unresectable advanced or recurrent to avoid the confusion.

Changes in the text: Recently, the successful results of the SPOTLIGHT and GLOW trials showed that CLDN18.2 highly expressed G/GEJ cancer as an independent therapeutic subset in HER2-negative **unresectable advanced or recurrent** G/GEJ cancer (94) (95).

Comment 37

Tables/Figures:

- Figure 1: helpful, typo in the spelling of the word patients. Need to include DOS, FLOT, SOX, CAPOX, XP/FP and several others in the legend
- Table 1: helpful, matches nicely if you make a formal section for Global/International, as noted above

Consider a table like this that captures EVERY study mentioned within the text:

	Stage II	Stage II/III	Stage III	Stage III/IV	Stage IV
JCOG0501			Neoadjuvant SP		
FLOT-4		FLOT			
PRODIGY			Anti-PD-1 inhibitor dostarlimab		
FOCUS					
...					
...					
...					
...					
...					
SPOTLIGHT					
GLOW					

Country color code: Japan (red), Germany (blue), Korea (green), China (yellow), global (purple)...

In the box: Chemotherapy, immunotherapy, targeted therapy, XRT

Could use a \* (as in trastuzumab\*) to denote studies that are ongoing

Reply 37: Thank you for the suggestion, but we deeply apologize not to accept the instructive suggestion.

The results could not be summarized according to the Stage because stage classification was changed over the years. Further, only interim results were available yet on some studies. Some studies of HER2 targeted therapy were terminated due to poor accrual. In the response above, SPOTLIGHT and GLOW were not clinical trial for the resectable GC.

### Reviewer B:

The authors have prepared a very thorough review of perioperative gastric cancer management that covers difference in practice in Japan, East Asia and Western Europe + North America. They provide a comprehensive review of major trials and highlight newer areas of research and some on-going studies.

The paper only requires minor edits in my opinion.

Comment 38

introduction

Line 91: Perhaps it is worth noting that neither study has demonstrated a difference in OS to date.

Reply 38: Thank you for the suggestion. The updated analysis of PRODIGY and RESOLVE showed NAC DOS and perioperative SOX improved the survival comparing to surgery followed by adjuvant chemotherapy (S-1 and CAPOX).

Changes in the text: No change in the revised manuscript.

Comment 39

Concept of review

Line 111/112 – please revise language to make it clear that some Ph II studies were high quality, but I don't think you can say they were equal quality as Ph III studies.

Reply 38: Thank you for the comment. We apologized our original sentence make misunderstanding for reader. We rephrased this sentence above mentioned. Please see the reply5.

Thank you for the careful consideration. We corrected the spelling of durvalumab.

(Table 1: “dulva” should Durva)

Comment 40

2.2.3 Line 196, scirrhous GC is not a term all GI oncologists will be familiar with, I suggest defining it and clarifying its relation with linitis plastica. (done below, you can ignore)

Reply 40: Thank you for the important question. We agree that the difference between scirrhous GC and LP is unclear and confusing. Scirrhous GC mainly focusing on the histologically wide spread of tumors with rigid fibrous proliferation, typically exhibiting wall thickness and luminal narrowing. Scirrhous GC referred not only limited or IIC-like AGC but also to lesions with extensive infiltration like Borrmann type IV. LP indicate the wall thickness with sclerosis of the gastric body. Originally, Brinton et al. described belt-like shape GC in 1865 (Lectures on the Diseases of the Stomach: with an Introduction on Its Anatomy and Physiology. 2nd edition. Philadelphia (PA): Lea and Blanchard; 1865). It was currently used almost the same as scirrhous GC. However, definition of scirrhous or LP is mainly discussed by the endoscopist or pathologist. Vivier-Chicoteau et al described in their paper that there was no consensual definition for gastric linitis plastica (GLP) and they suggested the novel diagnostic score to clarify the GLP (Gastric Cancer 23:639 – 647. 2020). We could not understand whether there was a global consensus in this definition scirrhous GC. We believe this review should be given in terms of clinical aspect. Taking into consideration on the complicated situation, we added the following sentences.

Changes in the text: Scirrhous GC mainly focusing on the histologically wide spread of tumors with rigid fibrous proliferation, typically exhibiting wall thickness and luminal narrowing. Scirrhous GC referred not only limited or IIC-like AGC, but also to lesions with extensive infiltration like Borrmann type IV. LP indicate the wall thickness with sclerosis of the gastric body and LP is currently used



quite similar as the scirrhous GC (47). However, a global consensus on the definition of LP has not yet been reached (48). In terms of the pharmacological treatment, it would be acceptable not to precisely distinguish between these two categories. Due to its infiltrative and invasive nature, scirrhous GC or LP has a high likelihood of not achieving negative surgical margins or presenting peritoneal metastasis during laparotomy.

Comment 41

Line 447: “countriesare” needs a space.

Reply 41: Thank you for careful consideration. We corrected the sentences as pointed out.

Changes in the text: Please see the manuscript.

Comment 42

Line 459: you could add the FIGHT study and FGFR, similar level of benefit from similar level of data

Reply 42: Thank you for your suggestive comment. As the reviewer commented, FGFR2b might be a promising target in the resectable stage GC in future. We referred to the FGFR2b as potential candidate for next biomarker in the treatment of resectable AGC.

Changes in the text: We added the following sentences. Furthermore, bemarituzumab, a novel targeting agent for fibroblast growth factor receptor 2 isoform IIb (FGFR2b) demonstrated the promising results in the randomized phase II (FIGHT) trial for patients with FGFR2b-selected unresectable advanced or recurrent AGC (99).

Comment 43

Table 1, acronyms need defined.

Reply 43: Thank you for careful consideration. We spelled out.

Changes in the text: Please see the text.

Comment 44

The TOPGEAR study could be added, as it does not include any patients with SCC, and only ¼ patients had GEJ tumours.

Reply 43: Thank you for the informative suggestion. The TOPGEAR study is also pivotal trial to assess the optimal perioperative therapy for adenocarcinoma of gastric or gastroesophageal junction. We referred to this trial as suggested.

Changes in the text: We added the sentences in the section of “4. Future perspective”.

Trimodal approach using chemotherapy, radiation therapy and surgery is another anticipating therapeutic strategy to improve the prognosis of patients with resectable AGC. The TOPGEAR trial is the international randomized phase III trial of perioperative ECF or FLOT with or without perioperative chemoradiation for resectable AGC (101). The interim analysis of TOPGEAR demonstrated the feasibility and safety of adding chemoradiation to perioperative chemotherapy (102). Further investigation on survival benefit is awaited.