Specific Comments to Authors: In this submission from Sung Yong Han's group, the authors report that when the first-line chemotherapy is considered in very elderly patients with metastatic pancreatic cancer, gemcitabine monotherapy is superior for the management of metastatic pancreatic cancer in very elderly patients. This is a potentially interesting report that may affect the first-line chemotherapy in very elderly patients with metastatic pancreatic cancer. But there are some issues to be discussed more. The authors should consider the following comments.

1) The authors reported that the gemcitabine mono group in the elderly group had fewer chemotherapy cycles and a lower second-line chemotherapy transition rate compared with the combination chemotherapy group. The authors should explain why such a result occurred.

Response:

Thank you for your comment. FFX is different from other regimens as regards chemotherapy interval days. To correct this, the total cycle was converted to chemotherapy days. In the G mono group of the elderly group, the proportion of patients who died within 2 months was high. Most of these patients died from cancer progression, and this is thought to be the cause of the difference in total chemotherapy days and the rate of receiving 2nd chemotherapy. We have shown this information in the Discussion section as follows:

(lines 249-253) "In the G mono group in elderly patients, more people died within 2 months compared to the combination group (32% vs. 4%, p=0.009), and most of them died from cancer progression. Due to this phenomenon, chemotherapy days, PFS, and OS are considered to be shorter in this group than in the combination group."

2) The authors, like other tables, should classify adverse events into the elderly group and the very elderly group and described in Table 4.

Response:

Thank you for your comment. We have added Table 5 to compare adverse events between the elderly and very elderly. We have also added the following sentence in the Results section:

(lines 240-244) "Adverse events associated with each age group are listed in Table 5. Neutropenia (36.0% vs. 77.6% in the elderly, p=0.000) (45.0% vs. 90.0% in the very elderly, p=0.038) and neuropathy (0% vs. 46.9% in the elderly, p=0.000) (0% vs. 50.0% in the very elderly, p=0.001) were significantly difference between the two chemotherapy group in the elderly and very elderly groups."

Specific Comments to Authors: The manuscript entitled, "First-line chemotherapy in very elderly

patients with metastatic pancreatic cancer: Gemcitabine monotherapy versus Combination chemotherapy" is interesting. The authors have retrospectively evaluated the clinical responses of gemcitabine monotherapy (i.e., G mono) and combination chemotherapy (i.e., gemcitabine plus nab-paclitaxel and FOLFIRINOX) in the elderly (i.e., 65–74 years old) and very elderly (i.e., ≥75 years old) pancreatic ductal adenocarcinoma cancer (PDAC) patients. The primary outcomes of assessing the clinical responses of these therapies were progression-free survival (PFS) and overall survival (OS). The median PFS and OS in the elderly patients were found to be longer in the combination chemotherapy group compared to very elderly patients. Consistent with the findings of other clinical studies, the adverse events were more frequently observed in the combination chemotherapy group than in the G mono group. While the combination therapy was found to be more effective than G mono in elderly patients, G mono was superior for the management of metastatic pancreatic cancer in very elderly patients. Overall, the current studies provided the rationale of exploring G mono in very elderly patients, which also strengthened the previously published data demonstrating that G mono should be used in older patients or those with low Eastern Cooperative Oncology Group (ECOG) performance status. I have a few minor comments.

1. Please use "0" before point (.) wherever applicable. For example, use p=0.020 instead of p=.020.

Response:

Thank you for your comment. We have revised the representation of the p-values, as recommended.

2. The reference style should be consistent. For example, in reference 1, the first author's name is bold.

Response:

Thank you for your comment. Following your comment, we have ensured consistency in the reference style.

Reviewer #3:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Rejection
Specific Comments to Authors: The manuscript by Han et al analyzes 104 patients over age 65 with pancreatic cancer, comparing those over 75 years of age with those between 65 – 74. Fifty-nine patients were treated with combination chemotherapy (gemcitabine versus gemcitabine plus nab-paclitaxel and FOLFIRINOX) and 45 with monotherapy. Primary outcomes included PFS and OS. Unsurprisingly, the baseline characteristics were significantly different between the two chemotherapy groups and two age groups. Two-thirds of those patients between 65 – 74 years old were treated with combination therapy (49/74) versus 1/3 of 30 patients in 75 years and older. In attempt to compare outcomes between the two groups, you have done propensity score matching. Unfortunately, it has led to very few patients in either group: (50 total patients 65 – 74 years, 25 Rx with monotherapy and 25 with combination Rx versus 20 patients 75 years and older, 10 in each group. This makes statistical comparisons fraught with the potential for a beta error.

Response:

Thank you for your comment. We agree with you. We already mentioned this as part of the study limitations.

1. There seems to be a significant discordance in CA 19-9 between the 65 – 74 year-old group and those ≥ 75 years. Given that biliary obstruction alone can be a cause of CA 19-9 elevation, did any of these patients have jaundice?

a. Had any of these patients, particularly those with a head lesion, undergone biliary bypass or endoscopic stenting?

Response:

Thank you for your comment. Some patients underwent endoscopic stenting. We evaluated the laboratory findings, such as ca19-9 and TB, after appropriated biliary drainage. We have included biliary stenting due to obstruction as a variable in Tables 1 and 2.

b. Did any of these patients have previous pancreatic resection?

Response:

Thank you for your comment. We excluded patients who had previously undergone pancreatic resection. We added the following sentence in the Materials and Methods section to clarify this:

(lines 113-114) "…those who had previously undergone surgical resection were excluded."

2. You mention that neutrophil-lymphocyte ratio, CA 19-9, ECOG status, and tumor burden are all associated with pancreatic cancer prognosis, yet you fail to mention that infectious complications related to neutropenia or cholangitis from an obstructed biliary prosthesis are factors associated with survival.

Response:

Thank you for your comment. We agree with you. However, in our study, biliary drainage was not associated with prognosis in the Cox regression analysis.

3. In the Discussion, you state: "We demonstrated that G mono has similar efficacy to combination chemotherapy…" Actually, your study shows the opposite. Combination therapy appears to have better outcomes in patients between 65 – 74 years and comparable outcomes in older patients, likely because of underlying health issues, intolerance of side effects, baseline ECOG status, and inability to infuse full doses of chemotherapy.

Response:

Thank you for your comment. This must have been overlooked during English language proofreading. We could not find this unclear sentence during the final proofreading before submission. However, following your comment, we have edited this paragraph.

(*lines* 247-257) "In this study, we evaluated the efficacy of G mono and combination chemotherapy in elderly and very elderly groups. In the elderly group, the median PFS and OS were significantly longer for combination chemotherapy than for G mono. In the G mono group in elderly patients, more people died within 2 months compared to the combination group (32% vs. 4%, p=0.009), and most of them died from cancer progression. Due to this phenomenon, chemotherapy days, PFS, and OS are considered to be shorter in this group than in the combination group. Moreover, combination

chemotherapy had a significantly more pronounced effect on tumor burden before and after chemotherapy. However, G mono had similar efficacy to that of combination chemotherapy in the very elderly group. Furthermore, the rate of severe adverse events was significantly lower in the G mono group than in the combination chemotherapy group."

Reviewer #4:

Scientific Quality: *Grade D (Fair)*

Language Quality: *Grade C (A great deal of language polishing)*

Conclusion: *Major revision*

Specific Comments to Authors: *This was retrospective cohort study to compare the effectiveness of first-line chemotherapy in very elderly patients with metastatic pancreatic cancer, specially emphasis on gemcitabine monotherapy versus combination chemotherapy. Contrary to the results in the elderly group, the effect of combination chemotherapy was similar to that of gemcitabine monotherapy in the very elderly group, while the incidence of adverse event was lower in the gemcitabine treatment arm. The author concluded that gemcitabine monotherapy may be superior for choice in very elderly patients compared to treat metastatic pancreatic adenocarcinoma. The study concept, methods for analysis, statistical procedures, and description were generally considered appropriate except for several parts, as being described below with page number 1 from the title page.*

Page 4, lines 24; "dp" must be forgotten to delete. Correct appropriately.

Response:

Thank you for your comment. We have deleted it.

Page 4, lines 26; The author is required to mention why to defined elderly as 65-74 years old and very elderly as ≥75 years old, for example by citing domestic or international guidelines regarding to the geriatrics.

Response:

Thank you for your comment. We have added the following sentence in the Introduction section:

(lines 98-100) "In the Joint Committee of the Japan Gerontological Society and the Japan Geriatrics Society, 75 years was defined as old age and 65-74 as the pre-old age range."

Page 10, lines 2-; The first paragraph seemed to be confusing, as I think the results are interpreted in reverse.

Response:

Thank you for your comment. This must have been overlooked during English language proofreading. We could not find this unclear sentence during the final proofreading before submission. However, following your comment, we have edited this paragraph.

(lines 247-257) "In this study, we evaluated the efficacy of G mono and combination chemotherapy in elderly and very elderly groups. In the elderly group, the median PFS and OS were significantly longer for combination chemotherapy than for G mono. In the G mono group in elderly patients, more people died within 2 months compared to the combination group (32% vs. 4%, p=0.009), and most of them died from cancer progression. Due to this phenomenon, chemotherapy days, PFS, and OS are considered to be shorter in this group than in the combination group. Moreover, combination chemotherapy had a significantly more pronounced effect on tumor burden before and after chemotherapy. However, G mono had similar efficacy to that of combination chemotherapy in the very elderly group. Furthermore, the rate of severe adverse events was significantly lower in the G mono group than in the combination chemotherapy group."

Page 12, lines 11-; Since table 4 showed the appearance of AE but not conducted in the analysis for each of the two groups as elderly vs. very elderly, it is not possible to conclude "gemcitabine monotherapy may be superior for managing metastatic pancreatic cancer in very elderly patients compared with combination therapy in terms of adverse event" based only on the dose reduction rate in whole cohort including elderly and very elderly.

Response:

Thank you for your comment. We have added Table 5 for comparison between the elderly and very elderly. In the very elderly, even though dose reduction was more in the combination group, the rate of adverse events was similar between both groups or higher in the combination group than in the G mono group.

(lines 240-244) "Adverse events associated with each age group are listed in Table 5. Neutropenia (36.0% vs. 77.6% in the elderly, p=0.000) (45.0% vs. 90.0% in the very elderly, p=0.038) and neuropathy (0% vs. 46.9% in the elderly, p=0.000) (0% vs. 50.0% in the very elderly, p=0.001) were significantly difference between the two chemotherapy group in the elderly and very elderly groups."

Furthermore, it may be necessary to show by multivariate cox regression analysis that gemcitabine monotherapy was not a poor prognostic factor in the very elderly.

Response:

Thank you for your comment. We have added Supplementary Table 1 (cox regression analysis). In the multivariate Cox regression analysis, CA19-9 and NL ratio were significant prognostic factors in the very elderly. Gemcitabine monotherapy was not associated with poor prognosis.

We have added the following sentence in the Materials and Methods section to clarify this:

(line 154-156) "Supplementary Table 1 shows that Ca19-9 and NL ratio were the most important prognostic factors. Hence, we especially tried to adjust for these variables similarly."