Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: Dear Editor, thank you so much for inviting me to revise this manuscript about biliary tract cancer. The overall limited survival benefit provided by systemic therapies in this setting, with most patients reporting a survival rate of less than a year from the moment of diagnosis, has led to notable efforts towards the identification of novel targets and agents that could modify the natural history of these aggressive hepatobiliary malignancies. In fact, the massive use of next-generation sequencing (NGS) has led to the identification of previously unknown molecular features of CCA, including the presence of specific genetic aberrations that have been suggested to be distinctive features of iCCA and eCCA. Among these druggable alterations, fibroblast growth factor receptor (FGFR)2 gene fusions and rearrangements, isocitrate dehydrogenase-1 (IDH-1) mutations, and BRAF mutations have been widely described in CCA patients, reporting important differences between iCCA and eCCA. In addition, immunotherapy has recently shown interesting results, as witnessed by the TOPAZ-1 trial, which has the potential to "open" the immunotherapy era for BTC. Based on these premises, the paper addresses a timely topic. The manuscript is quite well written and organized. Tables are comprehensive and clear. The introduction explains in a clear and coherent manner the background of this study. We suggest the following modifications: • Although the authors correctly included important papers in this setting, we believe the background of emerging medical treatments as well as locoregional therapies should be better discussed and some recently published papers should be added, only for a matter of consistency (PMID: 32396398 ; PMID: 33611090 ; PMID: 32824407; PMID: 33645367) • In addition, we believe some issues deserve further discussion. In everyday clinical practice, we know that the pathologic confirmation of diagnosis is necessary before any non-surgical treatment and can be challenging in BTC, particularly in patients affected by primary sclerosing cholangitis and biliary strictures. In fact, decisions to undertake biopsies should follow a multidisciplinary discussion, especially in potentially resectable tumors. Moreover, endoscopic imaging and tissue sampling are useful but, sadly, biopsy samples are often inadequate for molecular profiling, and in addition, tissue sampling has reported high specificity but low sensitivity in diagnosis of malignant biliary strictures. Finally, the highly desmoplastic nature of BTC limits the accuracy of cytological and pathological approaches. On the basis of these premises, in this scenario, it is urgent to develop new strategies in order to anticipate the diagnosis identifying BTC at an early, resectable stage, and to obtain sufficient material with which to perform genomic analysis. Among these strategies, liquid biopsy has received growing attention over the years, given the

promising applications in cancer patients. More specifically, several studies have shown the potential role of liquid biopsy, and the authors should discuss this point, also reporting recent studies in this setting (doi: 10.3390/cells9030721; doi: 10.21873/cgp.20203). Moreover, the timeline should be enlarged and the type of systemic treatment specified, in order to help readability. The discussion should be also expanded, and a more personal perspective included. - Reference number 17 out of context. I suggest to remove it. In addition, the sentence "while the BRCA1 positivity was the rationale for taxane-based therapy" is wrong. Platinum-based chemo has a stronger rationale, why the authors talk about taxane? Please revise accordingly. We believe that major revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides clear answers, with some limitations. We suggest and the addition of some references for a matter of consistency. Moreover, the authors should better clarify some points and should add some details and studies, as suggested.

Thank you for your suggestion, we have revised it according to your comments. The current condition of the diagnosis and treatment of cholangiocarcinoma has been added, some recently published papers have been added, and relevant content has been added for early diagnosis and liquid biopsy. The timeline has been enlarged to make the time criteria clearer and to indicate the drugs and types of systemic therapy. Reference number 17 has been removed.

Reviewer #2:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: The author described a case of intrahepatic cholangiocarcinoma with germline BRCA1 mutation who had no response to first line chemotherapy GemCis but had complete response to paclitaxel + anti-PD-1. The case presentation was clear and summary of literature was up to date. Some minor revision will make it better. 1. Please add more

information about initial surgical plan in a patient with stage IV intrahepatic cholangiocarcinoma. In my opinion, the lung metastasis was too tiny (according to Figure 2B) to confirm it was true metastasis or non-specific nodule. Surgical resection based on initial CT scan was reasonable but the author had better to give more information about initial decision making process. 2. The initial course was confusing. "The intrahepatic mass was subsequently excised." But according to the subsequent description and image, the tumor excision was only planned but not actually excised, right? 3. The case had image evaluation after 2 cycles of first line GemCis, approximately only 6 weeks. Is image evaluation every 6 weeks a routine practice in your institute or due to clinical signs of progression? Please describe in the case presentation section. 4. I will recommend the author to add a line graph of the dynamic change of CA199 in Figure 1A, so that readers will have more insight about the clinical course. 5. Please give a brief information about the NGS assay. Is that an approved panel or home-made panel?

Thank you for your suggestion, we have revised it according to your comments. 1. Intraoperative observations have been added, and the final decision not to proceed was made based on the intraoperative situation. 2. The sentence "The intrahepatic mass was subsequently excised." was misrepresented and has been revised. 3. The patient became symptomatic after 2 cycles of treatment and CA199 did not decrease significantly, so the assessment was refined. 4. A trend line for CA199 changes has been added. 5. It is an NGS panel approved by our hospital.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under

Thank you for your suggestion, we have revised it according to your comments. The title of the manuscript has been revised and shortened to 18 words. Original images have been edited using PowerPoint to ensure that all graphics or arrows or text sections are edited for reprocessing. Tables have been revised to a standard three-line table as required. Highlights of the latest cutting-edge research have been added and refined.