Peer Review File

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Reviewer A

Smith et al document a case report of PARPi to a somatic BRCA1 LOF mutation
The case report is relevant and well written,
There does need to be more information in the case presentation,

Comment 1: Specifically there should be more information on the somatic mutation, was this from NGS profiling? What co-occurring alterations were present, TMB, etc
Reply 1: We have provided additional details about the genetic testing performed including specifying the type of NGS platform, listing co-occurring genetic alterations, and addressing microsatellite stability and TMB.
Changes in the text: In the "Case Presentation" section, we have added the above details in lines 101-105.

Comment 2: Was germline profiling performed
Reply 2: Germline profiling was performed and was negative for any mutation.
Changes in the text: We have specified that germline testing was performed and was negative in line 105 in the "Case Presentation" section.

Comment 3: Is there more information on the pathology? Differentiation or grade?
Reply 3: We have added more details regarding tumor histopathology including differentiation and grade.
Changes in the text: In the "Case Presentation" section, we have specified that the tumor was a G2 moderately differentiated adenocarcinoma (line 97).

Comment 4: What was the volume of disease at recurrence?
Reply 4: In the body of the text within the "Case Presentation" section we have provided more specific information about radiographic measurements of disease recurrence within the retroperitoneal lymph nodes.
Changes in the text: In lines 99-100 we have clarified that at the time of recurrence there were four index lesions among the retroperitoneal lymph nodes, with the largest being an interaortocaval node measuring 13.8 x 40.9 mm.

Minor
Comment 5: Remove infrigatinib – no longer in development
Reply 5: We have removed our description of infigratinib from the text as well as the associated reference.
Changes in the text: In line 74 the infigratinib description has been removed and Javle et al., 2021 reference has been removed from the reference section (previously #10).

Comment 6: Grade the anaemia

Reply 6: The patient's anemia was Grade 2 by Common Terminology Criteria for Adverse Events, and the text has been updated to reflect this.
Changes in the text: In line 112 we have specified that the patient developed a Grade 2 anemia.

Reviewer B

This case report discusses a 79-year-old male patient diagnosed with metastatic extrahepatic cholangiocarcinoma (CCA) harboring a somatic BRCA1 mutation. Instead of opting for chemotherapy, the patient received first-line treatment with the PARP inhibitor talazoparib. Remarkably, he exhibited a rapid and complete radiographic response to talazoparib monotherapy, with a significant reduction in his CA19-9 tumor marker levels. Even more noteworthy, the patient has remained on talazoparib for over three years without any signs of disease recurrence. This case underscores the potential effectiveness of PARP inhibitors in treating BRCA-mutated extrahepatic CCA. While retrospective studies have suggested clinical activity in this context, large-scale prospective trials are essential to confirm these findings conclusively. Importantly, this case report is the first to document the use of talazoparib as a frontline treatment for this specific condition. The authors emphasize ongoing trials exploring combination therapies involving PARP inhibitors in CCA, highlighting the need for further research to establish their role in clinical practice. This exceptional response to talazoparib represents an encouraging development in the pursuit of improved treatments for cholangiocarcinoma patients with BRCA mutations.

Certainly, there are several issues and areas for improvement in the article:

Comment 1: Page 2, line 43, the full name and abbreviation of PARP are repeated unnecessarily.
Reply 1: We have removed the redundant unabbreviated version of PARP.
Changes in the text: In the abstract (now line 42), we have removed the redundant unabbreviated version of PARP.

Comment 2: Page 2, line 47, the gene "BRCA" should be in italics for proper formatting.
Reply 2: We have italicized this instance of "BRCA" to align with proper formatting.
Changes in the text: In the abstract (now line 46), this instance of "BRCA" is now italicized.

Comment 3: In the introduction, the author should consider adding citations to review articles to provide readers with a clearer understanding of the current treatment advancements and future directions in cholangiocarcinoma. For instance, adding references to the following two articles would be beneficial: 1) The study mentioned by Halder, Ritika et al. in the 2022 publication "Hepatobiliary Surgery and Nutrition". 2)The research discussed by Brindley, Paul J et al. in the September 9, 2021 issue of "Nature Reviews Disease Primers".
These references will help furnish readers with a more comprehensive background regarding current treatment modalities and prospective research areas.
Reply 3: We agree with reviewer's comment that citing a review article would be beneficial in providing readers with additional background. In the introduction section we have now cited the most comprehensive and recent review article we could find which is entitled

"Cholangiocarcinoma – novel biological insights and therapeutic strategies" published by Ilyas et al., in *Nature Reviews Clinical Oncology* in July 2023. Due to reference limitations, we are unable to cite additional review articles.
Changes in the text: In line 70-71 of the "Background" section we have cited the above review article, which has also been added to the Reference list as #8.

Comment 4: Figures or data illustrating the patient's sequencing results should be included to provide a more comprehensive overview. Are there any mutations in other target genes? For example, it's worth exploring if there are any IDH mutations since they are also related to PARP inhibitors.
Reply 4: We have expanded the case description to include more details regarding the results of next-generation sequencing. We have listed the additional genetic alteration – however, none of these were feasible targets for treatment. No *IDH* mutations were detected.
Changes in the text: Lines 101-105 in the "Case Description" section now provide a more comprehensive overview of the next-generation sequencing results including specific platform utilized, additional mutations, microsatellite stability, and tumor mutational burden.

Comment 5: Page 9, the units for CA19-9 in line 267 should be consistent throughout the article.
Reply 5: We have updated the units for CA19-9 here to be consistent with other instances in the article.
Changes in the text: In line 298, the U is now capitalized to be more consistent with previous instances.