

Decision Letter (JCQ-2026-0028)

From:

To:

CC:

BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0028

Body: 28-Sep-2026

Dear Dr Loke:

Manuscript ID JCQ-2026-0028 entitled "Germline PALB2-mutated triple negative breast cancer treated with Olaparib in a renal transplant patient" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.

1. Access to <https://mc.manuscriptcentral.com/jcq> and log into the site.
 2. Click "Author" at the top left of the screen at "Home" page.
 3. Click "Manuscripts with Decisions" on Author Dashboard page.
 4. Click "create a revision" on the manuscript you are going to revise.
 5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
- IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author

Gabriel C and colleagues report an interesting case entitled "Germline PALB2-mutated triple-negative breast cancer treated with Olaparib in a renal transplant patient." However, several issues should be addressed before the manuscript can be considered for publication.

Major comment:

1. The conclusions should be more cautious. This case suggests that olaparib may be tolerated in a selected kidney transplant recipient, but it does not establish its safety in this population.
2. A timeline summarizing the clinical course, including key events, laboratory findings, and treatments, would improve the presentation. If feasible, Figures 2 and 3 and Table 1 should be integrated into a single figure to facilitate interpretation.
3. The authors should summarize previous studies and case reports on olaparib use in patients with impaired kidney function, preferably in a table, and discuss their relevance to the present case.
4. Please specify the equation used to calculate eGFR and clarify whether serum cystatin C was measured.
5. PARP inhibitors can cause pseudo-AKI by inhibiting tubular creatinine secretion and have also been associated with acute kidney injury. This distinction is particularly relevant in patients with pre-existing kidney impairment. The authors should discuss these possibilities and assess their relevance to the changes in kidney function observed in this patient.
6. Given that this kidney transplant recipient was receiving tacrolimus, were tacrolimus trough concentrations monitored before and during olaparib treatment? Please report any changes in these concentrations and any corresponding dose adjustments.
7. The discussion should acknowledge the limitations of this report, including the lack of reported olaparib plasma concentrations, which limits the assessment of drug exposure.

Minor comment:

Consider replacing "end-stage renal failure" with "kidney failure" to align with current terminology.

Reviewer: 2

Comments to the Author

Case studies such as these provide important insight clinical outcomes in these less studied organ dysfunction populations.

Suggest aligning nomenclature of renal dysfunction to more nephrology appropriate terminology as per KDIGO guidelines i.e., use kidney instead of renal.

Confusing with switching between Creatinine clearance and eGFR halfway through - they aren't the same in terms of estimating kidney function. Also no mention of patient weight which would impact the outcome of creatinine clearance calculation (larger patients may have values that are implying better kidney function than what they really have). Is there reason why measured GFR was not done to get a more accurate picture of the patient's kidney function before the first dose?

Olaparib is extensively metabolised by the liver, are excreted both through the urine and faeces (small fraction of it is unchanged in the urine). Amount renally excreted is about 50% less between mild and moderate kidney dysfunction and exposure was ~24% higher between each kidney function level. Perhaps a little more about the pharmacokinetics would help give context to some of the conclusions (ADEs were very typical of someone on olaparib) and why the dose was chosen at 150mg BD initially. The potential increase in exposure with CYP3A4 or other transporter interactions may also have suggested the initial dose may needed to have been lower (tacro is only moderate inhibitor therefore significance of this interaction could be further discussed). Dialysis doses are not reflective of doses to be given in severe kidney dysfunction as dialysis does remove metabolites that are renally cleared.

Date Sent: 28-Sep-2026

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Author's Response to Decision Letter for (JCQ-2026-0028)

Germline PALB2-mutated triple negative breast cancer treated with Olaparib in a renal transplant patient

Dear Editor and Reviewers,

We sincerely thank the Editor and both reviewers for their careful evaluation of our manuscript and constructive comments. In response, we have revised the manuscript to clarify the clinical findings, strengthen the discussion of pharmacokinetics and safety, and address the limitations of this case report. We have also improved the presentation of the clinical course and incorporated relevant published evidence. Our point-by-point responses are provided below, with the corresponding page numbers in the revised manuscript indicated after each response.

Reviewer 1

Comment 1 The conclusions should be more cautious. This case suggests that olaparib may be tolerated in a selected kidney transplant recipient, but it does not establish its safety in this population.

Response: We thank the reviewer for emphasizing the distinction between an individual clinical observation and evidence of safety. The Clinical Question Box, Abstract, Discussion, and Conclusion now state that the RECIST partial response and eight-month progression-free interval occurred alongside grade 3 anemia requiring transfusions, treatment interruption, and dose adjustments. We explicitly acknowledge that this case cannot establish the safety or optimal dosing of olaparib in kidney transplant recipients with severe kidney impairment. (pp. 2–3, 8–11)

Comment 2 A timeline summarizing the clinical course, including key events, laboratory findings, and treatments, would improve the presentation. If feasible, Figures 2 and 3 and Table 1 should be integrated into a single figure to facilitate interpretation.

Response: We appreciate this suggestion. Figure 2 now presents an integrated two-panel display: panel A summarizes key clinical events and the olaparib treatment course, while panel B shows the longitudinal trends in cancer antigen 15-3, creatinine clearance, and hemoglobin. This allows dose changes, treatment interruption, and laboratory findings to be considered together. Figure 1 remains separate to display the radiographic response. Table 1 is retained as a comparison of previously published cases rather than incorporated into the patient-specific timeline. (pp. 15–17)

Comment 3 The authors should summarize previous studies and case reports on olaparib use in patients with impaired kidney function, preferably in a table, and discuss their relevance to the present case.

Response: Thank you for recommending a clearer comparison with prior evidence. Table 1 summarizes reports by Baum et al., Goon et al., and Yoshida et al., together with the present case, including malignancy, kidney status, olaparib regimen, outcome, adverse events, and availability of pharmacokinetic assessment. The Discussion addresses the relevance and limitations of these cases, particularly the difficulty of extrapolating experience from patients already receiving hemodialysis to a patient initiating olaparib before dialysis. (pp. 9–10, 13–15)

Comment 4 : Please specify the equation used to calculate eGFR and clarify whether serum cystatin C was measured.

Response: We appreciate the opportunity to clarify the method of kidney-function assessment. The manuscript reports creatinine clearance (CrCl) calculated using the Cockcroft–Gault equation for women; it does not report a calculated estimated glomerular filtration rate (eGFR). CrCl was 13 mL/min at olaparib initiation and remained below 25 mL/min during treatment. Serum cystatin C was not measured. These distinctions, and the resulting limitations in assessing true glomerular filtration, are now stated explicitly. (5, 7, 9–10)

Comment 5 PARP inhibitors can cause pseudo-AKI by inhibiting tubular creatinine secretion and have also been associated with acute kidney injury. This distinction is particularly relevant in patients with pre-existing kidney impairment. The authors should discuss these possibilities and assess their relevance to the changes in kidney function observed in this patient.

Response: We thank the reviewer for highlighting this clinically important distinction. The Discussion now explains that olaparib can cause an apparent decline in creatinine-based kidney-function estimates by inhibiting tubular creatinine secretion, without a corresponding reduction in true filtration; it also acknowledges that true acute kidney injury has been reported with PARP inhibitors. In our patient, pre-existing progressive allograft dysfunction, acute-on-chronic kidney injury during therapy, chronic infection, and subsequent reduction of immunosuppression provide competing explanations. Because cystatin C and a measured glomerular filtration rate were unavailable, pseudo-acute kidney injury could not be reliably distinguished from genuine deterioration, and we have avoided attributing the kidney course solely to olaparib. (pp. 9–10)

Comment 6 Given that this kidney transplant recipient was receiving tacrolimus, were tacrolimus trough concentrations monitored before and during olaparib treatment? Please report any changes in these concentrations and any corresponding dose adjustments.

Response: We agree that tacrolimus monitoring is important in this setting. As reported in the Case Description, tacrolimus trough concentrations were monitored during concomitant olaparib treatment, and no tacrolimus dose adjustment was required specifically in response to olaparib initiation. The later reduction of immunosuppression occurred in the setting of chronic infection and allograft failure. However, numerical trough concentrations before and during olaparib treatment were not available for reporting, so we cannot provide the requested quantitative comparison. We now acknowledge this limitation explicitly and do not substitute a general therapeutic target for patient-specific measurements. (pp. 6–7, 9–10)

Comment 7 : The discussion should acknowledge the limitations of this report, including the lack of reported olaparib plasma concentrations, which limits the assessment of drug exposure.

Response: We appreciate this recommendation. The Discussion now states that olaparib plasma concentrations were unavailable, precluding an exposure–toxicity assessment in this patient. It also identifies the lack of cystatin C measurements, a reported measured glomerular filtration rate, patient weight, and numerical tacrolimus trough concentrations. Together with the single-patient design and complex course of allograft dysfunction, these limitations prevent firm conclusions about causality, safety, or optimal dosing. (p. 10)

Comment 8 Consider replacing “end-stage renal failure” with “kidney failure” to align with current terminology.

Response: Thank you for this terminology recommendation. We have standardized the clinical terminology to use 'kidney failure' and 'kidney impairment' where appropriate, including in Table 1. The original titles of cited publications have been preserved in the reference list. (pp. 3–10, 15)

Reviewer 2

Comment 1: Case studies such as these provide important insight clinical outcomes in these less studied organ dysfunction populations.

Response: We thank the reviewer for recognizing the potential value of this observation in an underrepresented clinical population. The revised manuscript presents the RECIST partial response and eight-month progression-free interval together with the clinically important, transfusion-requiring anemia. We emphasize the case's educational value for individualized treatment and monitoring, while avoiding conclusions about general safety or efficacy in patients with severe kidney impairment.

Location in revised manuscript: pp. 8, 11

Comment 2: Suggest aligning nomenclature of renal dysfunction to more nephrology appropriate terminology as per KDIGO guidelines i.e., use kidney instead of renal.

Response: We appreciate this recommendation. The manuscript now consistently uses kidney-focused terminology, including 'kidney impairment' and 'kidney failure', in its clinical narrative and Table 1. Published article titles have been left unchanged. (pp. 3–10, 15)

Comment 3 Confusing with switching between Creatinine clearance and eGFR halfway through - they aren't the same in terms of estimating kidney function. Also no mention of patient weight which would impact the outcome of creatinine clearance calculation (larger patients may have values that are implying better kidney function than what they really have). Is there reason why measured GFR was not done to get a more accurate picture of the patient's kidney function before the first dose?

Response: We agree that Cockcroft–Gault creatinine clearance, eGFR, and measured GFR are distinct measures. The Case Description now states the Cockcroft–Gault equation used for CrCl and reports a pretreatment CrCl of 13 mL/min. The patient's weight, which is required to independently verify that estimate, was not available for reporting and is identified as a limitation. No measured GFR result was available in the case documentation, and the reason for its absence could not be established from the available records. We have not inferred an explanation. The Discussion also notes that cystatin C was not measured, limiting interpretation of creatinine-based changes during treatment. (pp. 5, 10)

Comment 4 Olaparib is extensively metabolised by the liver, are excreted both through the urine and faeces (small fraction of it is unchanged in the urine). Amount renally excreted is about 50% less between mild and moderate kidney dysfunction and exposure was ~24% higher between each kidney function level. Perhaps a little more about the pharmacokinetics would help give context to some of the conclusions (ADEs were very typical of someone on olaparib) and why the dose was chosen at 150mg BD initially.

Response: Thank you for these pharmacokinetic observations. The revised Discussion notes that olaparib is predominantly metabolized through CYP3A, with approximately 44% of drug-related material recovered in urine and 42% in feces, largely as metabolites. Relative to normal kidney function, exposure increases by approximately 24% in mild and 44% in moderate kidney impairment. The recommended tablet dose of 200 mg twice daily applies to CrCl 31–50 mL/min, whereas evidence below 30 mL/min remains insufficient. Accordingly, the initial 150 mg twice-daily dose in this patient (CrCl 13 mL/min) is described as an empirical, individualized reduction rather than an established regimen. We also discuss grade 3 anemia and the possible contribution of underlying allograft dysfunction. (pp. 3, 6, 8–9)

Comment 5 The potential increase in exposure with CYP3A4 or other transporter interactions may also have suggested the initial dose may needed to have been lower (tacro is only moderate inhibitor therefore significance of this interaction could be further discussed).

Response: We appreciate the reviewer's concern regarding potential drug interactions. The updated Discussion distinguishes tacrolimus as primarily a CYP3A substrate, rather than an established moderate CYP3A inhibitor. It also notes that olaparib may weakly inhibit CYP3A and potentially alter tacrolimus exposure, while the reciprocal effect of tacrolimus on olaparib exposure remains uncertain. We therefore

describe the 150 mg twice-daily starting dose as an empirical reduction principally reflecting severe kidney impairment, with additional caution concerning possible interactions, rather than as a validated tacrolimus-specific adjustment. Tacrolimus trough concentrations were monitored, and no olaparib-related tacrolimus dose adjustment was required. (pp. 6, 9)

Comment 6 Dialysis doses are not reflective of doses to be given in severe kidney dysfunction as dialysis does remove metabolites that are renally cleared.

Response: We agree that dosing experience in patients receiving hemodialysis cannot be directly applied to patients with severe kidney impairment who have not yet started dialysis. The revised Discussion compares the published cases and highlights differences in residual kidney function, metabolite handling, drug formulation, and availability of pharmacokinetic measurements. Table 1 documents the individual regimens and outcomes. Our patient began olaparib with CrCl 13 mL/min and only later resumed hemodialysis; we therefore avoid proposing a dose for severe predialysis kidney impairment on the basis of dialysis case reports. The extent to which dialysis alters parent-drug or metabolite exposure cannot be established from this case. (pp. 9–10, 15)

We appreciate the reviewers' valuable suggestions, which have helped improve the clarity and scientific rigor of our manuscript. We hope that the revisions adequately address their concerns and that the revised manuscript will be considered favorably for publication.

Sincerely,
Daniel Jia Ming Ang

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