Decision Letter (JCQ-2026-0013)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0013

Body: 30-May-2026

Dear Dr Lee:

Manuscript ID JCQ-2026-0013 entitled "Case Report of Tumour Response to Capivasertib after Exposure to Alpelisib" 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 minor 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.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

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
This manuscript reports a case of a heavily pre-treated patient with HR+/HER2−/PIK3CA-mutated metastatic breast cancer who achieved a partial response to fulvestrant plus capivasertib following prior exposure to fulvestrant plus alpelisib. The clinical question is relevant, as the CAPItello-291 trial excluded patients with prior PI3K/mTOR/AKT inhibitor or fulvestrant exposure, leaving a knowledge gap regarding sequential PI3K/AKT pathway targeting. Several points require revision as outlined below.

1. Discrepancy Between CT Imaging Dates and Text
The text (line 104) states "interval imaging after 3 months of treatment," but the Figure 2 legend indicates CT A was obtained on 2025/1/24 and CT B on 2025/2/22—an interval of approximately one month. The authors should verify and clarify: if the figure legend dates are erroneous, please correct them; if the text description is inaccurate, please revise accordingly.
2. Absence of Standardized Response Criteria
No standardized response assessment criteria (e.g., RECIST 1.1) are referenced in the manuscript. Terms such as "good partial response" and "stable disease" are used without quantitative support. For a case report whose central conclusion rests on imaging-demonstrated treatment response, the authors should provide baseline and post-treatment measurable lesion dimensions per RECIST 1.1 and include specific measurement values in the Figure 2 legend.
3. AKT1/PTEN Alteration Status Not Reported
The capivasertib approval encompasses PIK3CA, AKT1, and PTEN as qualifying biomarkers. This report documents only the PIK3CA H1047R mutation, without mentioning whether AKT1 or PTEN alterations were assessed. Reporting the complete molecular profile would strengthen the mechanistic discussion. The authors should supplement these data or explain why testing was not performed.
4. Mechanistic Discussion Could Be Expanded
The statement that differences in pathway targeting may explain capivasertib efficacy after alpelisib progression (lines 138–139) would benefit from further elaboration:
Alpelisib selectively inhibits the p110α isoform, whereas AKT activation can be driven by multiple upstream inputs (including other PI3K isoforms and RTK bypass pathways). AKT-level blockade may therefore circumvent resistance mechanisms operating at the PI3K level.
Whether PIK3CA mutation persistence was confirmed before capivasertib initiation (e.g., via repeat liquid biopsy) should be discussed.
Potential alpelisib resistance mechanisms that remain susceptible to AKT-level inhibition (e.g., PTEN loss, acquired AKT amplification) deserve mention.
Additionally, the patient achieved approximately 18 months PFS on fulvestrant plus alpelisib (April 2020 to October 2021), substantially exceeding the median PFS of 11 months in the SOLAR-1 trial. This prolonged response to PI3K inhibition may reflect high tumour dependency on the PI3K/AKT pathway, providing biological plausibility for subsequent AKT inhibitor responsiveness. This point could be developed to strengthen the discussion.
5. Writing and Editorial Corrections
Line 24: "...remains poorly described," — the comma should be a period.
Line 103: "successfully cessation" should read "successful cessation."
Line 103: Missing end-of-sentence punctuation.
"Meaningful response" in the abstract is vague; specify as PR or SD per RECIST.
The treatment narrative between January 2017 and June 2019 is dense due to the rapid succession of regimens. Consider streamlining and ensuring full concordance with the Figure 1 timeline.

Reviewer: 2

Comments to the Author
Dear authors,
Thank you for this interesting case report. As this is a rare case report, this makes it valuable for the literature. But I have some recommendations as follows:
1- I recommend usage of term ‘metastatic breast cancer’ in the title.
2- There are some spelling mistakes. I recommend revision and correction.
3- I recommend revision of the abbreviations in the abstract and main text.
4- Keywords in alphabetical order would be better. I recommend revision.
5- A brief explanation of current case report in the last paragraph of ‘introduction’ section would be better. I recommend revision.
6- I wish to know the pathological findings at the time of first diagnosis; I recommend addition of this data. In addition, I wish to know levels of estrogen and progesterone positivity.
7- A more detailed definition of prior systemic treatments would be better. I recommend addition of this data.
8- The ‘discussion’ section might be developed more detailed with data supporting the current case report.
9- I recommend revision and correction of the references (e.g. some references were given as 1120-1125, but some as 1120-5).
10- Legend for ‘Figure 2’ needs revision and correction.
I wish to read the final version of your report after your revision.
Best regards...

Date Sent: 30-May-2026

Author's Response to Decision Letter for (JCQ-2026-0013)

Case Report of Tumour Response to Capivasertib after Exposure to Alpelisib

Response Letter
Dear Editor and Reviewers,
We sincerely thank the reviewers for their careful reading of our manuscript and for their constructive comments. We have revised the manuscript accordingly and provide a point-by-point response below. All changes have been incorporated into the revised manuscript.

Reviewer 1
Comment 1. The text (line 104) states "interval imaging after 3 months of treatment," but the Figure 2 legend indicates CT A was obtained on 2025/1/24 and CT B on 2025/2/22—an interval of approximately one month. The authors should verify and clarify: if the figure legend dates are erroneous, please correct them; if the text description is inaccurate, please revise accordingly.
Response: We thank the reviewer for identifying this discrepancy. We have reviewed the imaging dates and corrected the manuscript accordingly. The timing of the interval imaging has been clarified in the Case Report section and the Figure 2 legend has been revised to ensure concordance between the text and figure as one month.

Comment 2. No standardized response assessment criteria (e.g., RECIST 1.1) are referenced in the manuscript. Terms such as "good partial response" and "stable disease" are used without quantitative support. For a case report whose central conclusion rests on imaging-demonstrated treatment response, the authors should provide baseline and post-treatment measurable lesion dimensions per RECIST 1.1 and include specific measurement values in the Figure 2 legend.

Response: We agree with the reviewer that standardized response assessment is important, particularly because the clinical significance of this case is based on the radiological response to capivasertib. We have revised the manuscript to specify that treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), and have added the corresponding assessment details to both the manuscript text and the Figure 2 legend.
Comment 3. The capivasertib approval encompasses PIK3CA, AKT1, and PTEN as qualifying biomarkers. This report documents only the PIK3CA H1047R mutation, without mentioning whether AKT1 or PTEN alterations were assessed. Reporting the complete molecular profile would strengthen the mechanistic discussion. The authors should supplement these data or explain why testing was not performed.
Response: We thank the reviewer for this helpful suggestion. We have expanded the molecular profiling information in the Case Report section. The available molecular testing confirmed a PIK3CA exon 21 c.3140A>G (p.H1047R) mutation. We have clarified whether AKT1 and PTEN alterations were assessed in the available next-generation sequencing report. Where complete AKT1/PTEN status was unavailable, this limitation has been explicitly acknowledged in the manuscript.

Comment 4. The statement that differences in pathway targeting may explain capivasertib efficacy after alpelisib progression (lines 138–139) would benefit from further elaboration: Alpelisib selectively inhibits the p110α isoform, whereas AKT activation can be driven by multiple upstream inputs (including other PI3K isoforms and RTK bypass pathways). AKT-level blockade may therefore circumvent resistance mechanisms operating at the PI3K level. Whether PIK3CA mutation persistence was confirmed before capivasertib initiation (e.g., via repeat liquid biopsy) should be discussed. Potential alpelisib resistance mechanisms that remain susceptible to AKT-level inhibition (e.g., PTEN loss, acquired AKT amplification) deserve mention. Additionally, the patient achieved approximately 18 months PFS on fulvestrant plus alpelisib (April 2020 to October 2021), substantially exceeding the median PFS of 11 months in the SOLAR-1 trial. This prolonged response to PI3K inhibition may reflect high tumour dependency on the PI3K/AKT pathway, providing biological plausibility for subsequent AKT inhibitor responsiveness. This point could be developed to strengthen the discussion.

Response: We agree and have expanded the Discussion section. We now discuss the biological rationale for sequential PI3K/AKT pathway inhibition, including the difference between selective p110α inhibition by alpelisib and pan-AKT inhibition by capivasertib. We have added discussion of potential bypass mechanisms and downstream pathway activation that may permit sensitivity to AKT-level inhibition despite prior PI3Kα inhibitor exposure. We have also addressed whether persistence of the PIK3CA mutation was confirmed before capivasertib initiation and acknowledged this as a limitation if repeat molecular testing was not performed. In addition, we have highlighted that the patient's prolonged disease control on fulvestrant plus alpelisib may suggest dependence on the PI3K/AKT pathway, providing biological plausibility for subsequent response to capivasertib.

Comment 5. Line 24: "...remains poorly described," — the comma should be a period. Line 103:

"successfully cessation" should read "successful cessation." Line 103: Missing end-of-sentence punctuation. "Meaningful response" in the abstract is vague; specify as PR or SD per RECIST.
The treatment narrative between January 2017 and June 2019 is dense due to the rapid succession of regimens. Consider streamlining and ensuring full concordance with the Figure 1 timeline.

Response: We thank the reviewer for these detailed editorial comments. We have corrected the punctuation error in the abstract, revised “successfully cessation” to “successful cessation,” and added missing punctuation. We have also replaced vague wording such as “meaningful response” with more specific response terminology. The treatment narrative has been streamlined to improve readability, and we have checked the text against Figure 1 to ensure consistency in treatment sequence and timing.

Reviewer 2
Comment 1. I recommend usage of the term “metastatic breast cancer” in the title.
Response: We thank the reviewer for this suggestion. We have revised the title to include “metastatic breast cancer.”

Comment 2. There are some spelling mistakes. I recommend revision and correction.
Response: We agree and have carefully proofread the manuscript. Spelling, grammar, and typographical errors have been corrected throughout.

Comment 3. I recommend revision of the abbreviations in the abstract and main text.
Response: We thank the reviewer for this comment. We have reviewed all abbreviations in the abstract and main text. Abbreviations are now defined at first use and used consistently throughout the manuscript.

Comment 4. Keywords in alphabetical order would be better. I recommend revision.
Response: We have revised the keywords and arranged them in alphabetical order.

Comment 5. A brief explanation of the current case report in the last paragraph of the Introduction section would be better. I recommend revision.
Response: We thank the reviewer for this helpful suggestion. We have revised the final paragraph of the Introduction to briefly summarize the current case, including the patient’s prior benefit from fulvestrant plus alpelisib and subsequent partial response to fulvestrant plus capivasertib. This revision clarifies the clinical relevance and novelty of the case before the Case Report section.

Comment 6. I wish to know the pathological findings at the time of first diagnosis; I recommend addition of this data. In addition, I wish to know levels of estrogen and progesterone positivity.
Response: We thank the reviewer for this helpful suggestion. We have added the available pathological information from the initial diagnosis. As detailed pathology records from the initial diagnosis were unavailable for review, this has been stated in the manuscript. We have also clarified the receptor status at the time of pleural recurrence, which showed oestrogen receptor-positive, progesterone receptor-negative, and HER2-negative disease.

Comment 7. A more detailed definition of prior systemic treatments would be better. I recommend addition of this data.
Response: We agree with the reviewer. We have expanded the Case Report section to provide a more detailed account of the patient’s prior systemic therapies, including treatment sequence, treatment periods, and best response or reason for treatment discontinuation where available. We have also reviewed the text for consistency with the treatment timeline presented in Figure 1.

Comment 8. The Discussion section might be developed in more detail with data supporting the current case report.
Response: We thank the reviewer for this valuable suggestion. We have expanded the Discussion section to further contextualise the current case, including the eligibility criteria and outcomes of the CAPItello-291 trial, available retrospective data, and the limited published experience of capivasertib after prior alpelisib exposure. We also added a discussion of the biological rationale for sequential PI3K/AKT pathway inhibition, including potential mechanisms through which AKT inhibition may retain activity after PI3Kα inhibitor progression. Finally, we discuss the patient’s prolonged clinical benefit from fulvestrant plus alpelisib as a possible indication of dependence on PI3K/AKT pathway signalling, while acknowledging the limitations of this inference.

Comment 9. I recommend revision and correction of the references, for example, some references were given as 1120–1125, but some as 1120–5.
Response: We have revised the reference list for consistency and corrected formatting discrepancies, including page ranges and journal style requirements.

Comment 10. Legend for Figure 2 needs revision and correction.
Response: We agree and have revised the Figure 2 legend. The corrected legend now includes accurate imaging dates, clarifies that the images show liver computed tomography before and after fulvestrant plus capivasertib, and includes lesion measurements where available to support the radiological response assessment.

We again thank the reviewers for their thoughtful and constructive comments, which have helped improve the clarity and scientific value of the manuscript.

Sincerely,
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