nature portfolio

Peer Review File

Cabozantinib and Temozolomide in patients with advanced progressive neuroendocrine tumors: a phase 2 study

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
In the submitted manuscript, Cives and colleagues present the results of a phase 2 trial evaluating the efficacy of cabozantinib in combination with metronomic temozolomide in patients with advanced well-differentiated neuroendocrine tumors originating in gastrointestinal (n=14), pancreatic (n=12), lung (n=9), or unknown primary sites (n=2). The primary endpoint of the trial was objective response rate. The trial was designed with statistical assumptions that a true ORR of >50% would be deemed promising, whereas an ORR of <=25% would not yield further interest. Although the observed ORR of 15% among 33 evaluable patients did not meet the primary endpoint, the high clinical benefit rate, median PFS of 28.5 months, and time to treatment failure of 16.8 months are encouraging.

The manuscript is well written. Although the single-arm nature of the trial limits conclusions that can be drawn, the results add to our understanding of efficacy and safety of combination treatment with chemotherapy plus molecularly targeted therapy for patients with neuroendocrine tumors.

Questions and comments:

1. Page 8, line 203: There is a statement about per protocol assessment of efficacy. Could these criteria also be added to the Methods section?

2. Radiological response: The ORR of 17% observed in patients with pancreatic NET with cabozantinib plus metronomic temozolomide (100 mg/m2 per day on a 7 day on/7 day off cycle) is lower than one would expect from conventional dosing of temozolomide (200 mg/m2 per day x 5 days of each 28-day cycle). Can the authors comment on the potential impact of dosing on response?

3. Were efficacy analyses done to account for patients who discontinued treatment due to symptomatic decline (n=6)? Were these cases felt to represent clinical declines related to progressive disease or other factors?

4. Was lymphopenia observed in any patients? Temozolomide at a dose of 150 mg/m2 per day on a 7 day on/7 day off schedule in patients with neuroendocrine tumors has been associated with lymphopenia and opportunistic infections. Was lymphopenia observed at the dose of temozolomide used in this study (or other studies using this dosing schedule)?

5. Grade 4 thrombocytopenia occurred in 4 patients and led to treatment discontinuation of 4 patients (11%). This rate is somewhat higher than what has been observed with single-agent cabozantinib and temozolomide. Were there any identified risk factors for development of high-grade thrombocytopenia?

6. Page 8, Duration of therapy: Reasons for dose modification and discontinuation of cabozantinib and temozolomide are listed. The last sentence of the paragraph also lists toxicities leading to study treatment discontinuation (n=8). Could the authors clarify whether the patients listed as discontinuing temozolomide (n=5) were able to continue cabozantinib? What was the time to discontinuation of temozolomide for patients who continued cabozantinib?

7. Discussion: Could the authors add more information about potential synergy between metronomic temozolomide and antiangiogenic agents? Including information about results from other studies that have evaluated metronomic

temozolomide and bevacizumab in NET would also enhance the discussion.

Reviewer #2

(Remarks to the Author)
The study reports on a phase II, single-arm trial of temozolomide combined with cabozantinib for the treatment of advanced neuroendocrine tumors (NETs). These tumors include 14 gastrointestinal NETs, 12 pancreatic NETs, nine lung NETs, and two NETs of unknown primary origin. Of the 37 patients enrolled, 33 met the criteria for a per protocol efficacy assessment. The overall response rate was 15%, which fell short of the primary endpoint. Nevertheless, with a median follow-up of 19.2 months, the clinical benefit rate was 100%. The median progression-free survival (PFS) was 28.5 months (95% confidence interval [CI], 16.8–28.5 months), and the median overall survival (OS) had not yet been reached. The estimated three-year OS rate was 68.5% (±9.1%). This study is the first to investigate the temozolomide/cabozantinib combination in the NET setting. While the treatment results are encouraging and suggest potential clinical benefit, further validation in larger, well-controlled studies is clearly needed. Additionally, significant concerns regarding data presentation and outcome assessment currently undermine confidence in the reported findings.

Major comments:
1. Including a CONSORT diagram would enhance the clarity of the manuscript and help readers better understand the flow of participants through the study, including enrollment, allocation, follow-up, and analysis.
2. It would be helpful to include a Swimmer plot illustrating the duration of treatment and response for individual patients who responded to therapy. This visualization would provide readers with a clearer understanding of the heterogeneity in treatment benefit, durability of response, and timing of progression or discontinuation across responders.
3. Biomarker studies are strongly recommended to strengthen and inform the clinical trial evaluating the temozolomide/cabozantinib combination in NETs. Incorporating biomarker analyses could enhance mechanistic understanding and help identify subgroups most likely to benefit. Specific suggestions include:
a) Since methylation of the MGMT promoter silences gene expression and sensitizes tumors to temozolomide, stratifying patients based on MGMT methylation status is critical. Correlating MGMT status with clinical outcomes such as response rate and PFS would add important predictive insight.
b) Evaluate expression levels of cabozantinib-targeted tyrosine kinases (e.g., MET, AXL, VEGFR) by immunohistochemistry or other approaches to explore their potential as predictive biomarkers of response or resistance. Additionally, assessing baseline and on-treatment plasma or serum VEGF levels could provide pharmacodynamic and prognostic information.
c) Given that temozolomide induces DNA damage, tumors with deficient DNA repair mechanisms may be more susceptible. Profiling DNA repair gene alterations (e.g., MMR, ATM, BRCA) and assessing tumor mutational burden could help identify patients more likely to respond to therapy.

Minor comments:
1. The Discussion section should clearly acknowledge the study's limitations. Transparency about the limitations is essential to appropriately contextualize the findings.
2. Typos and grammatical errors can be detected throughout this manuscript.

Reviewer #3

(Remarks to the Author)
Reviewer Report:

This manuscript describes an open-label, single-arm, phase 2 trial that evaluated the combination of cabozantinib and metronomic temozolomide in patients with advanced, progressive, well-differentiated neuroendocrine tumors (NETs). The study addresses an important area of unmet clinical need given the limited treatment options for advanced NETs and is well-conceived. The manuscript is clearly written, and the statistical design and analyses are appropriate and adequately described.

The following minor comments could improve the clarity and transparency of the methodology and results:

1. Clarify the decision rule in the sample size justification.
The sample size calculation is based on a binary decision framework that compares a "favorable" ORR (>50%) to an "unfavorable" ORR (≤25%), with a one-sided alpha of 10% and 90% power. However, the manuscript does not explicitly state the decision rule used to interpret the primary endpoint. For example, it does not specify what threshold number of responses would lead to the conclusion that the regimen is promising. Providing this rule (e.g., "≥X responders out of 33 evaluable patients") would clarify how the trial was designed and guide future research decisions.

2. Report 95% confidence intervals for binary endpoints.
The protocol indicates that 95% confidence intervals (CIs) will be provided for binary endpoints. While the ORR and CBR are reported, their associated 95% CIs are not presented in the abstract or results section. Including the exact CIs for key binary outcomes, such as ORR, CBR, and PR, would enhance interpretability and support reproducibility.

Overall, this is a solid, well-written manuscript that presents promising findings for a difficult-to-treat population. I believe the manuscript is suitable for publication, pending minor revisions that address the above points.

Reviewer #4

(Remarks to the Author)
Drs. Cives and Della Vittoria Scarpati present the results of an open-label, single-arm, phase 2 study to assess the safety and efficacy of cabozantinib and temozolomide in patients with progressive, advanced, well-differentiated pulmonary or GEP-NETs. This study was completed between June 2021 and July 2023. The rationale for the study was based on single agent activity for both cabozantinib and temozolomide and these rare tumors. Of note, cabozantinib achieved FDA approval based on a 13.8-month or 8.8-month PFS in the CABINET study recently (March 2025), hence, that data was maturing while the study was enrolling. Also of note, the dosing of cabozantinib in the study of 40 mg a day is lower than the recent FDA approval monotherapy and the temozolomide 100 mg/m²/day 1 week on 1 week off is not a standard FDA approved dose for any indication to date.

The manuscript is very well-written with clearly laid out details of the study design and execution. The conclusion is that the study did not reach its predefined primary endpoint. The primary endpoint was overall response rate. The overall response rate achieved in the study was 15% across all evaluable patients. The pre-treatment target goal ORR was >50% (this was the target ORR justifying the sample size). Hence, the 15% ORR is far below the target ORR. Hence, this is a negative study for the primary endpoint. That said, the authors are presenting this data because there was a substantial benefit seen in key secondary endpoints including progression free survival and clinical benefit rate paired with a expected side effect profile.

This is particularly notable as the participant enrolled on the study had high risk factors including already having undergone a median of two prior treatments including surgery and 19 of the participants being on an active somatostatin analog concurrent with experimental therapy. In the setting of clinical benefit rate of 100% with sustained responses of greater than 18 months and 12 of 33 participants (highest benefit rate in pancreatic or lung NET) and a durable response rate of 19.5 months all suggest clinical activity that is meaningful for these rare tumors and in this cohort, incurable tumors.

The authors do a nice job of pointing out the limitations of the study which are notable (including the small sample size not allowing any identification of subgroups that benefit from this therapeutic approach and no evidence of any prognostic or predictive markers).
Inclusion of the MGMT and MET analyses that the authors indicate are ongoing would increase interest. MGMT methylation is predictive of clinical benefit with temozolomide in the setting of glioblastoma. In the absence of any other predictive and prognostic markers it would be helpful to see this data relative to the people with prolonged response in the study. Similarly, MGMT methylation with temozolomide is associated with increased toxicities and that relationship could be analyzed in this cohort.

It would be helpful to know what the clinical benefit was in the 18 patients that had at least 1 dose interruption (as well as for the 5 patients that required a dose reduction of cabozantinib or the 10 patients who had a dose interruption of temozolomide; and the 11 patients that had to dose reduce or stop temozolomide). Would be helpful to see if these dose reductions impacted the clinical benefit rate or not. It would also be helpful to know for practical reasons if the dose reductions resolved the AE and allowed patients to continue long-term therapy.

Finally, the discussion could be strengthened by suggesting the specific neck study the authors think is required. Would it be cabozantinib monotherapy (FDA approved based on a PFS of 13.8 months) versus the carbo temozolomide regimen used here (PFS 28.5 months)? With the use PFS is the primary endpoint of that study? Is RECIST the most accurate endpoint for assessing PFS in this population?

A minor critique is it is not clear that table 2 adds much information against table 1 given the lack of any clinical or molecular prognostic or predictive factors

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Thank you for your responses to previous questions and comments. The manuscript is strengthened by the addition of biomarker data and other information.

Minor suggestions:

1- The annual age-adjusted incidence rate of NEN in the U.S. according to the most recent SEER analysis could be updated (8.52 per 100 000) per the following reference:
Dasari A, Wallace K, Halperin DM, Maxwell J, Kunz P, Singh S, Chasen B, Yao JC. Epidemiology of Neuroendocrine Neoplasms in the US. JAMA Netw Open. 2025 Jun 2;8(6):e2515798.
PMID: 40553474; PMCID: PMC12188367.

2. Introduction, Paragraph 2, second and last sentences: The addition of cabozantinib to the treatment landscape for epNET and pNET and approval by the EMA could be mentioned.

Reviewer #2

(Remarks to the Author)
The manuscript quality has been significantly enhanced following thorough revision of the major concerns.

Reviewer #3

(Remarks to the Author)
The authors have addressed my comments (explicit decision rule and the 95% CI for response rates), and I have no further comments / questions.

Reviewer #4

(Remarks to the Author)
I appreciate the authors' efforts to systematically and comprehensively address the reviewer comments. All prior comments have been addressed to satisfaction in my opinion. However, I did note in this review that the results sections mention homogeneous lesion uptake on the DOTA PET in 33/37 patients, and I did not see if this finding was assessed for relationship with any of the endpoints. If this was assessed it would be of clinical value to include. Otherwise, one minor typo in the discussion for the confidence intervals when discussing limitations.

December 5, 2025

Dear Editor,

Thank you very much for your of our manuscript entitled: “A phase 2 study of cabozantinib and temozolomide in advanced neuroendocrine tumors”. We appreciate the reviewers’ thoughtful comments. Our point-by-point response is detailed below:

Reviewer #1

1. Page 8, line 203: There is a statement about per protocol assessment of efficacy. Could these criteria also be added to the Methods section?

We thank the Reviewer for pointing this out. The criteria for per protocol assessment of efficacy have been now detailed in the Methods section (page 8, first paragraph).

2. Radiological response: The ORR of 17% observed in patients with pancreatic NET with cabozantinib plus metronomic temozolomide (100 mg/m2 per day on a 7 day on/7 day off cycle) is lower than one would expect from conventional dosing of temozolomide (200 mg/m2 per day x 5 days of each 28-day cycle). Can the authors comment on the potential impact of dosing on response?

We have commented on the potential impact of temozolomide dosing on tumor response (page 17, second paragraph).

3. Were efficacy analyses done to account for patients who discontinued treatment due to symptomatic decline (n=6)? Were these cases felt to represent clinical declines related to progressive disease or other factors?

We thank the Reviewer for this comment. We have now performed sensitivity analyses to account for the patients who discontinued treatment due to symptomatic decline (page 10, last paragraph; page 11, last paragraph). In all cases, clinical decline was felt to be related to overall functional deterioration and comorbid conditions rather than progressive disease.

4. Was lymphopenia observed in any patients? Temozolomide at a dose of 150 mg/m2 per day on a 7 day on/7 day off schedule in patients with neuroendocrine tumors has been associated with lymphopenia and opportunistic infections. Was lymphopenia observed at the dose of temozolomide used in this study (or other studies using this dosing schedule)?

We are deeply grateful to the Reviewer for this comment. We observed lymphopenia in 9 patients, as now clarified in Table 3. Among the 6 patients who developed grade 3 lymphopenia, 2 had lymphocyte counts already below the LLN at baseline (1 patient with grade 1 lymphopenia, 1 patient with grade 2 lymphopenia). All grades were assigned according to the absolute CTCAE v5.0 thresholds, without considering changes relative to baseline. No opportunistic infections occurred during the study. All cases of grade 3 lymphopenia were asymptomatic, without clinical consequences and were not perceived as clinically significant by treating physicians. The text has been appropriately edited (abstract; page 12, last paragraph).

5. Grade 4 thrombocytopenia occurred in 4 patients and led to treatment discontinuation of 4 patients (11%). This rate is somewhat higher than what has been observed with single-agent cabozantinib and temozolomide. Were there any identified risk factors for development of high-grade thrombocytopenia?

We thank the Reviewer for this comment. Several conditions recurred in patients who developed grade 4 thrombocytopenia: i) prior treatment with chemotherapy or ^{177}Lu-dotatate

(4/4) and ii) extensive skeletal involvement (3/4). We have briefly discussed this point in the revised manuscript (page 12, last paragraph; page 13, first paragraph).

6. Page 8, Duration of therapy: Reasons for dose modification and discontinuation of cabozantinib and temozolomide are listed. The last sentence of the paragraph also lists toxicities leading to study treatment discontinuation (n=8). Could the authors clarify whether the patients listed as discontinuing temozolomide (n=5) were able to continue cabozantinib? What was the time to discontinuation of temozolomide for patients who continued cabozantinib?

The number of patients who permanently discontinued temozolomide was 4 (neutropenia: 3; nausea: 1). We have now edited the typo in the text. All patients who discontinued temozolomide were able to continue cabozantinib. The median time to temozolomide discontinuation was 2.6 months (95% CI, 1.7-4.3 months). We have now included these data in the text (page 10, first paragraph; Figure 2).

7. Discussion: Could the authors add more information about potential synergy between metronomic temozolomide and antiangiogenic agents? Including information about results from other studies that have evaluated metronomic temozolomide and bevacizumab in NET would also enhance the discussion.

We have added information on the potential synergy between metronomic alkylator therapy and antiangiogenic agents. Studies evaluating metronomic temozolomide plus antiangiogenic agents in NET patients have been discussed (page 16, second paragraph; page 17, first paragraph).

Reviewer #2

1. Including a CONSORT diagram would enhance the clarity of the manuscript and help readers better understand the flow of participants through the study, including enrollment, allocation, follow-up, and analysis.

We have now included a CONSORT diagram (Figure 1; page 9, last paragraph), as requested.

2. It would be helpful to include a Swimmer plot illustrating the duration of treatment and response for individual patients who responded to therapy. This visualization would provide readers with a clearer understanding of the heterogeneity in treatment benefit, durability of response, and timing of progression or discontinuation across responders.

We have included a Swimmer plot illustrating the duration of treatment response (Figure 2; page 10, first paragraph), as requested.

3. Biomarker studies are strongly recommended to strengthen and inform the clinical trial evaluating the temozolomide/cabozantinib combination in NETs. Incorporating biomarker analyses could enhance mechanistic understanding and help identify subgroups most likely to benefit. Specific suggestions include:
a) Since methylation of the MGMT promoter silences gene expression and sensitizes tumors to temozolomide, stratifying patients based on MGMT methylation status is critical. Correlating MGMT status with clinical outcomes such as response rate and PFS would add important predictive insight.
b) Evaluate expression levels of cabozantinib-targeted tyrosine kinases (e.g., MET, AXL, VEGFR) by immunohistochemistry or other approaches to explore their potential as predictive biomarkers of response or resistance. Additionally, assessing baseline and on-treatment plasma or serum VEGF levels could provide pharmacodynamic and prognostic information.
c) Given that temozolomide induces DNA damage, tumors with deficient DNA repair mechanisms may be more susceptible. Profiling DNA repair gene alterations (e.g., MMR,

ATM, BRCA) and assessing tumor mutational burden could help identify patients more likely to respond to therapy.

We thank the Reviewer for this comment. We have now incorporated biomarker analyses, with specific regards to:

a) **Assessment of MGMT promoter methylation status through methylation-specific PCR;**
b) **Assessment of MGMT expression status through immunohistochemistry;**
c) **Assessment of c-MET, AXL and VEGFR2 expression through immunohistochemistry;**
d) **Assessment of plasma VEGF-A levels at baseline, best response and treatment discontinuation through ELISA.**

Biologic data have been correlated through univariate analysis with patients' clinical outcomes (mainly response rate and PFS), as requested. The independence of the association between biologic data and clinical outcomes was not assessed through multivariable analysis, as low numbers would have rendered the multivariable model highly unstable.
We have not profiled DNA repair gene alterations. While the point raised by the Reviewer is in our opinion well taken, there is no evidence to date that MMR or TMB predict clinical outcomes in response to temozolomide or cabozantinib, and the heterogeneity of our cohort (primarily in terms of primary sites) does not make it ideal for testing this concept at this time.

4. The Discussion section should clearly acknowledge the study's limitations. Transparency about the limitations is essential to appropriately contextualize the findings.

We have strengthened the study's limitations section following this Reviewer recommendation (page 20, first paragraph).

5. Typos and grammatical errors can be detected throughout this manuscript.

We have carefully reviewed the manuscript and corrected all typos and grammatical errors.

Reviewer #3

1. Clarify the decision rule in the sample size justification.
The sample size calculation is based on a binary decision framework that compares a "favorable" ORR (>50%) to an "unfavorable" ORR (≤25%), with a one-sided alpha of 10% and 90% power. However, the manuscript does not explicitly state the decision rule used to interpret the primary endpoint. For example, it does not specify what threshold number of responses would lead to the conclusion that the regimen is promising. Providing this rule (e.g., "≥X responders out of 33 evaluable patients") would clarify how the trial was designed and guide future research decisions.

We thank the Reviewer for this comment. The decision rule has been now explicitly included in the Methods section of the manuscript (page 6, third paragraph).

2. Report 95% confidence intervals for binary endpoints.
The protocol indicates that 95% confidence intervals (CIs) will be provided for binary endpoints. While the ORR and CBR are reported, their associated 95% CIs are not presented in the abstract or results section. Including the exact CIs for key binary outcomes, such as ORR, CBR, and PR, would enhance interpretability and support reproducibility.

We have now reported 95% confidence intervals for all proportions of interest, both in the abstract and in the Results section.

Reviewer #4

1. Inclusion of the MGMT and MET analyses that the authors indicate are ongoing would increase interest. MGMT methylation is predictive of clinical benefit with temozolomide in the

setting of glioblastoma. In the absence of any other predictive and prognostic markers it would be helpful to see this data relative to the people with prolonged response in the study. Similarly, MGMT methylation with temozolomide is associated with increased toxicities and that relationship could be analyzed in this cohort.

We thank the Reviewer for this comment. We have now performed the requested analyses and reported the correlation between MGMT/MET status and clinical benefit (page 13, last paragraph; page 14; page 15, first paragraph). No association has been observed between MGMT status and toxicities (page 13, last line).

2. It would be helpful to know what the clinical benefit was in the 18 patients that had at least 1 dose interruption (as well as for the 5 patients that required a dose reduction of cabozantinib or the 10 patients who had a dose interruption of temozolomide; and the 11 patients that had to dose reduce or stop temozolomide). Would be helpful to see if these dose reductions impacted the clinical benefit rate or not. It would also be helpful to know for practical reasons if the dose reductions resolved the AE and allowed patients to continue long-term therapy.

The clinical benefit rate observed in this study was 100%, and was not impacted by cabozantinib dose reduction/interruption or temozolomide dose reduction/interruption/discontinuation. We have now included in the text the findings from exploratory analyses assessing the impact of dose reduction, treatment interruption or discontinuation on PFS (page 11, last paragraph; Supplementary Figure 1). Cabozantinib dose reductions always resolved the adverse event, allowing patients to continue the treatment. Temozolomide dose reductions resolved the adverse event in 2/6 cases (page 10, first paragraph). The text has been implemented accordingly.

3. Finally, the discussion could be strengthened by suggesting the specific next study the authors think is required. Would it be cabozantinib monotherapy (FDA approved based on a PFS of 13.8 months) versus the cabo temozolomide regimen used here (PFS 28.5 months)? With the use PFS as the primary endpoint of that study? Is RECIST the most accurate endpoint for assessing PFS in this population?

We have briefly oulined the type of study that we think is required to corroborate the results observed in this phase 2 trial. As pointed out by this Reviewer, a logical next step might be a phase 3 randomized trial comparing cabozantinib monotherapy versus cabozantinib plus temozolomide in patients with pancreatic and extra-pancreatic advanced NETs. PFS should serve as the primary endpoint and stratification by MGMT status, among other relevant factors, might be incorporated into the study design. While we acknowledge that RECIST v1.1 criteria have many limitations in the assessment of NET patients, their use will remain standard until robust evidence establishes the superiority of alternative assessment methods (page 20, second paragraph).

4. A minor critique is it is not clear that table 2 adds much information against table 1 given the lack of any clinical or molecular prognostic or predictive factors

We thank the Reviewer for this comment. He have now added biologic information to Table 2. We believe that this synoptic view of the clinical-biologic characteristics of patients who responded to the investigational treatment may help understanding the importance of biologic information in appropriately pre-selecting patients most likely to respond to the combination of cabozantinib and temozolomide.

February 26, 2026

Dear Editor,

Thank you very much for your of our manuscript entitled: “A phase 2 study of cabozantinib and temozolomide in advanced neuroendocrine tumors”. We appreciate the reviewers’ thoughtful comments. Our point-by-point response is detailed below:

Reviewer #1

1. The annual age-adjusted incidence rate of NEN in the U.S. according to the most recent SEER analysis could be updated (8.52 per 100 000) per the following reference:
   Dasari A, Wallace K, Halperin DM, Maxwell J, Kunz P, Singh S, Chasen B, Yao JC. Epidemiology of Neuroendocrine Neoplasms in the US. JAMA Netw Open. 2025 Jun 2;8(6):e2515798.
   PMID: 40553474; PMCID: PMC12188367.

We have updated the annual-age adjusted incidence rate of NEN, as requested.

2. Introduction, Paragraph 2, second and last sentences: The addition of cabozantinib to the treatment landscape for epNET and pNET and approval by the EMA could be mentioned.

We have now mentioned the EMA approval of cabozantinib, as suggested. This establishes cabozantinib as an important addition to the treatment landscape for epNETs and pNETs.

Reviewer #2

1. The manuscript quality has been significantly enhanced following thorough revision of the major concerns.

Thank you very much for your positive feedback.

Reviewer #3

1. The authors have addressed my comments (explicit decision rule and the 95% CI for response rates), and I have no further comments / questions.

Thank you very much for your positive feedback.

Reviewer #4

1. I appreciate the authors' efforts to systematically and comprehensively address the reviewer comments. All prior comments have been addressed to satisfaction in my opinion. However, I did note in this review that the results sections mention homogeneous lesion uptake on the DOTA PET in 33/37 patients, and I did not see if this finding was assessed for relationship with any of the endpoints. If this was assessed it would be of clinical value to include. Otherwise, one minor typo in the discussion for the confidence intervals when discussing limitations.

We thank the Reviewer for this comment. SSTR positivity on imaging was already evaluated in relation to several endpoints including ORR (Table 2) and clinical/radiological benefit (Supplementary Table 2). To avoid any ambiguity, we specified in the main text that SSTR positivity, when present, was homogeneous on DOTA PET scans. No cases of heterogeneous SSTR expression were observed. We have now corrected the typo in the discussion (limitations paragraph).