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# Peer Review File

## LEONARDA-1: Phase III Randomized Study of Lerociclib plus Fulvestrant in Patients with HR+/HER2- Locally Advanced or Metastatic Breast Cancer Who Have Progressed on Prior Endocrine Therapy

REVIEWER COMMENTS

Reviewer #1 - breast cancer, clinical (Remarks to the Author):

Major comments:

Clinical significance is unclear since CDK inhibitors (CDKi) are now given predominantly in first-line setting

Definition of endocrine-resistance is unclear as the PFS in the control arm was almost 6-months. They do not define secondary-resistance.

Discussion is mostly a repeat of their results. The clinical implications of their results need to be stated given that standard of care is a CDKi in the first-line setting.

Abstract:

Please expand on or omit statement ending “typically having poor prognosis” as unclear what this means.

More SAEs were noted in the non-CDKi arm? Might report grade 3 or higher rather than SAEs in the abstract. If reporting SAEs in the abstract would use SAEs attributable to study drug. What is currently stated is misleading.

Methods:

For premenopausal women, where they determined to have postmenopausal estradiol levels before entering the trial? Why was 21-days chosen as in many patients several doses of LHRH agonist are needed to suppress ovarian function.

Why was imaging performed every 8-weeks when standard with ER-positive ABC is generally 12-weeks.

Results:

Please define “secondary drug resistance”.

At what point were DCR and CBR measured?

Discussion

Most is merely repetition of the results

Needs to be completely revised to discuss the clinical implications given than CDKis are used in the first-line setting and these patients were not included in this trial. There is no mention of evaluation lerociclib in the first-line setting.

Discussion of the results of the SONIA trial should be included to support their conclusions.

Reviewer #2 - Biostatistics, phase 3 cancer clinical trials (Remarks to the Author):

General comments:

The results of this phase III trial showed clear benefit of lerociclib + fulvestrant (referred to as treatment below) over placebo + fulvestrant (referred to as control below) in terms of the primary endpoint of progression-free survival (PFS).

Analyses of the secondary endpoints (including subgroup analyses) yielded mostly consistent results with those of the primary endpoint. However, the statistical analysis plan (SAP) for the study specifies a total of 16 subgroup analyses, while the paper reported only 12 of them (Figure 3) and claiming all subgroup analyses yielded improved PFS of the treatment vs control (page 9). It is unclear what the results are for the remaining four subgroup analyses.

Comparison of the OS between groups was not mature yet due to a low number of events (deaths) in the relatively short duration of the trial by the data cut-off date.

While the probability of grade 3 or 4 adverse events (AEs) was clearly higher in the treatment group than the control group, they were mostly manageable (resulting in discontinuation of treatment in only 1 patient out of 137 patients in the treatment group). Also, the probability of serious adverse events (SAEs) was not higher in the treatment group.

While no quantitative comparisons in the probability of AEs and serious adverse events (AEs) between lerociclib and other (multiple) CDK4/6 inhibitors were made, qualitative assertions were made generally in favor of the AE profile of lerociclib relative to other CDK4/6 inhibitors.

A strength of the trial design is that it is a randomized, double-blind, controlled trial. Although there was no pre-planned interim analysis (for futility and/or superiority early stopping), the overall relatively short duration of the trial (due to relatively fast accrual) might have helped justify this design consideration.

The overall results of the trial support lerociclib + fulvestrant as a new treatment option for patients with HR+/HER2- advanced breast cancer patients who have progressed on prior endocrine therapy.

Additional specific comments:

Page 3 (just a style suggestion): the advantages of this therapy lessen over time due to the emergence of resistance -> the efficacy of this therapy decreases over time due to the development of drug resistance;

Page 4 (typo): a phase III trial evaluated -> a phase III trial that evaluated;

Page 6 (typo): every 6 cycle -> every 6 cycles;

Page 7 (typo): (section title) Primary and Secondary Endpoint -> Primary and Secondary Endpoints;

Page 8: Space permitted, please list all pre-specified subgroup analyses in the Statistical Analysis section (or in the supplement of the paper);

Pages 9-10 (Section 'Efficacy'): Please report results from all (16 in total) pre-specified subgroup analyses;

Page 12 (typo): The consistent results -> Consistent results;

Pages 12-13: It is very helpful to describe the patient characteristics in the LEONARDA-1 trial with an intention to compare with those in the previous trials of CDK4/6 inhibitors. In this regard, it would be helpful to be a bit more explicit in terms of what the corresponding characteristics are in the previous trials. This would help to understand better the new information the current trial results have brought.

Page 13 (typo): 11.07 vs 5.42 months in patients received -> 11.07 vs 5.42 months in patients who received;

Page 13 (typo): These evidence -> This evidence;

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Page 14 (just a style suggestion): These findings suggest that the lerociclib obtains overall advantages in terms of gastrointestinal and hematological toxicity -> These findings suggest that lerociclib reduces overall gastrointestinal and hematological toxicity;

Page 14 (just a style suggestion): exhibits -> has

Page 20: Both panels A and B in Figure 2 show that all patients experienced events in the treatment group by 12 months. This does not seem to be consistent with the results reported in the body of the paper. Please clarify.

Reviewer #3 - Breast cancer, clinical (Remarks to the Author):

This manuscript presents the results of the LEONARDA-1 study, a phase III randomized controlled trial evaluating the efficacy and safety of lerociclib, a novel oral CDK4/6 inhibitor, plus fulvestrant compared to placebo plus fulvestrant in patients with HR+/HER2- advanced breast cancer (ABC) who had progressed on prior endocrine therapy.

There are three FDA approved three CDK4/6 inhibitors, palbociclib, ribociclib, and abemaciclb, which have been practice-changing game changers in ER+/HER2- mBC. The authors evaluated new CDK4/6 inhibitor, lerociclib. This study was conducted exclusively in Chinese patients.

Although, lerociclib plus showed significantly improved progression-free survival (PFS) compared to placebo plus fulvestrant (median PFS 11.07 vs 5.49 months; HR 0.451, $p<0.0001$), there are major limitations and critiques in this study.

1. Even though this study population were not treated with any FDA labeled CDK4/6 inhibitors, maybe associated with drug affordability in China, the authors should explain and discuss about the current standard treatment options globally. Without it, this study could hardly have generalizability.

2. Also, additional studies in diverse patient populations would strengthen the findings.

3. Comparison to other CDK4/6 inhibitors: While the authors discuss the efficacy and safety of lerociclib in the context of other approved CDK4/6 inhibitors, they do not provide a direct comparison. Differences in trial designs, patient characteristics, and inclusion/exclusion criteria make cross-trial comparisons challenging.

4. All the other three approved CDK4/6 inhibitors have showed quite consistent HRs for PFSs (0.42 for PALOAMD-3, 0.59 for MONALEESA-2, and 0.55 for MONARCH-2). However, the HR in this study was 0.49. The authors should discuss more in this regard.

5. The median follow-up time was relatively short (approximately 7.3 months in both arms), and overall survival data were immature at the time of the analysis. Longer follow-up is needed to assess the long-term efficacy and safety of lerociclib plus fulvestrant.

6. While the PFS benefit was consistent across pre-specified subgroups, some of these subgroups had relatively small sample sizes, which may limit the reliability of the subgroup analyses.

7. To reach high-level of evidence, Quality of life assessment should be combined.

**RESPONSE TO REVIEWER COMMENTS**

Reviewer #1 - breast cancer, clinical (Remarks to the Author):

Major comments:

Clinical significance is unclear since CDK inhibitors (CDKi) are now given predominantly in first-line setting
Response: We understand that the CDKi are the SOC in 1L setting. However, the CDKi 1L trials excluded patients whose disease recurred while receiving the endocrine therapy (ET) or within 12 months after completing ET. In LEONADA-1 study, over 60% (67.9% in GB491 arm and 67.4% in placebo arm) of the patients were in the above-mentioned patient population. Therefore, a certain number of patients may not have the opportunity to be treated in the 1L setting.

Definition of endocrine-resistance is unclear as the PFS in the control arm was almost 6-months. They do not define secondary-resistance.
Response: The secondary drug resistance was defined as disease relapsed while on adjuvant ET but after the first 2 years, or relapsed within 12 months of completing adjuvant ET, or PD > 6 months after initiating ET for ABC, while on ET. The PFS in the control arm was 5.49 months. The definition was added in the manuscript.

Abstract:

Please expand on or omit statement ending “typically having poor prognosis” as unclear what this means.
Response: ‘typically having poor prognosis’ was detailed in the discussion session. Due to the limitation of the number of words in the abstract, we didn’t provide details there.

More SAEs were noted in the non-CDKi arm? Might report grade 3 or higher rather than SAEs in the abstract. If reporting SAEs in the abstract would use SAEs attributable to study drug. What is currently stated is misleading.
Response: Yes, more SAEs were reported in the placebo arm. Treatment related serious AEs were reported for 4.4% and 4.3% in lerociclib plus fulvestrant arm and placebo plus fulvestrant arm, respectively. The grade 3 or higher TEAEs were reported in the abstract. Due to the number of wording restriction in the abstract, we removed the SAE related description.

Methods:

For premenopausal women, where they determined to have postmenopausal estradiol levels before entering the trial? Why was 21-days chosen as in many patients several doses of LHRH agonist are needed to suppress ovarian function.
Response: The estradiol levels were tested at the study sites/local laboratory. According to the ZOLADEX (goserelin) label, serum estradiol is suppressed to levels similar to those observed in postmenopausal women within 3 weeks following initial administration. Therefore, at least 21 days of LHRH agonists before the study treatment was chosen.

Why was imaging performed every 8-weeks when standard with ER-positive ABC is generally 12-weeks.
Response: The every 8-week imaging (rather than 12-week) was to ensure that the clinical efficacy be captured timely and was adopted by other CDKi trials as well.

Results:

Please define “secondary drug resistance”.
Response: The secondary drug resistance was defined as disease relapsed while on adjuvant ET but after the first 2 years, or relapsed within 12 months of completing adjuvant ET, or PD > 6 months after initiating ET for ABC, while on ET. The definition was added in the manuscript.

At what point were DCR and CBR measured?
Response: DCR and CBR was calculated based on the RECIST assessment of tumor imaging. The data cut-off was the same as the final analysis.

Discussion

Most is merely repetition of the results

Needs to be completely revised to discuss the clinical implications given than CDKis are used in the first-line setting and these patients were not included in this trial. There is no mention of evaluation lerociclib in the first-line setting.
Response: The lerociclib 1L trial data was just analyzed and will be presented at ASCO 2024. The clinical significance of 2L setting was added (see below).

Discussion of the results of the SONIA trial should be included to support their conclusions.
Response: added as below.
Even though the current CDK4/6 inhibitors have moved to the first-line setting as the standard of care, CDK4/6 inhibitors still provide patients treatment benefits in the second-line setting due to the below considerations. Firstly, the

CDK4/6 inhibitor first-line trials excluded patients whose disease recurred while receiving the ET or within 12 months after completing ET. In LEONADA-1 study, over 60% (67.9% in GB491 arm and 67.4% in placebo arm) of the patients were in the above-mentioned patient population. Therefore, a certain number of patients not having the opportunity to be treated in the first-line setting may obtain clinical benefit from the second-line setting. Secondly, according to the MAINTAIN and P-REALITY X studies, CDK4/6 inhibitor switching or cross-line treatment may also improve clinical outcomes. Thirdly, the SONIA study demonstrated that first-line use of CDK4/6 inhibitor + ET does not provide statistically significant, nor clinically meaningful PFS benefit compared to second-line use in women with HR+, HER2- ABC; use in first-line prolongs the time on CDK4/6i by 16.56 months and increases toxicity and costs; second-line use may thus be a preferred option for the majority of patients.

Reviewer #2 - Biostatistics, phase 3 cancer clinical trials (Remarks to the Author):

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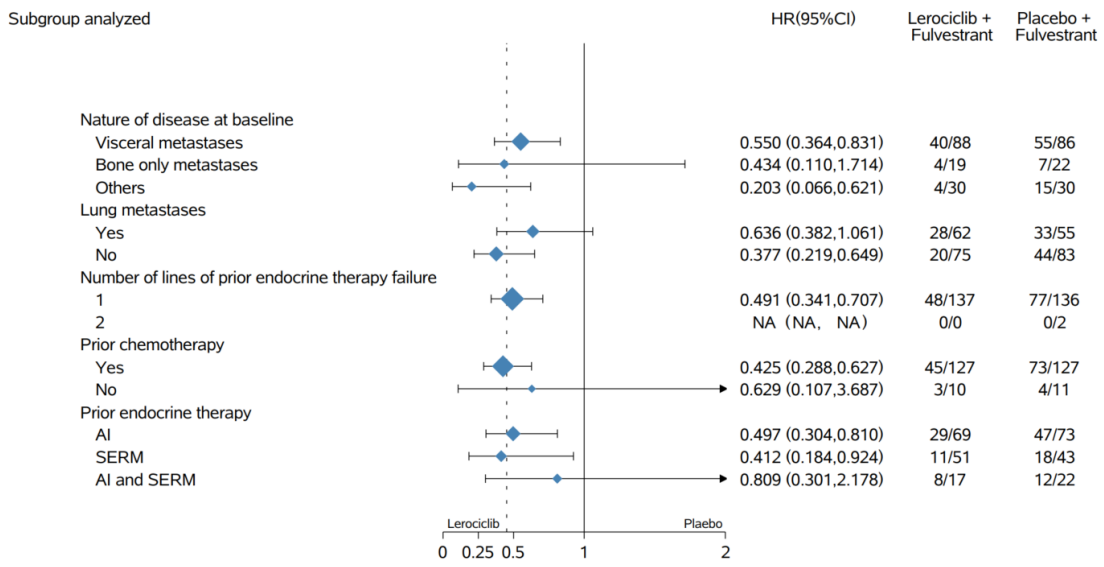
Response: We included 11 subgroups in the original manuscript. The 5 subgroups not included are in the below figure.



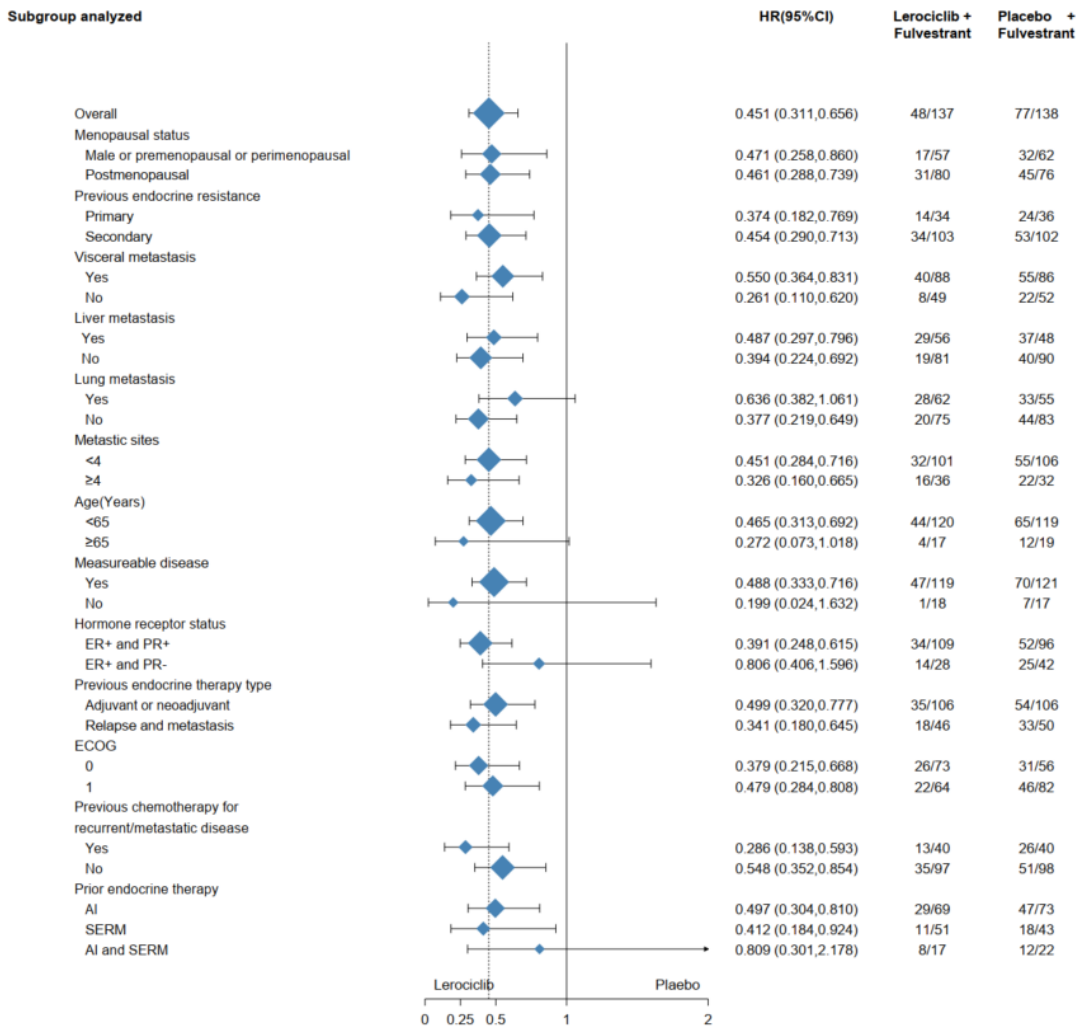

As per the suggestion, we revised the figure and included ‘Lung metastases’ and ‘Prior endocrine therapy’. The other 3 subgroups were not included due to below considerations.

As the subgroup of ‘Nature of disease at baseline’ was already presented as ‘Visceral Metastasis’, in which ‘No’ includes ‘Bone only metastases’ and ‘Others’, we didn’t include ‘Nature of disease at baseline’ to avoid duplication.

In the subgroup of ‘Number of lines of prior endocrine therapy failure’, only 2 patients were enrolled in ‘2’, therefore the analysis couldn’t be conducted appropriately and this subgroup was not included.

Regarding the subgroup of ‘Prior chemotherapy’, we consider the already included ‘Previous chemotherapy for recurrent/metastatic disease’ is more meaningful.

The corresponding figure was revised as below.




Comparison of the OS between groups was not mature yet due to a low number of events (deaths) in the relatively short duration of the trial by the data cut-off date.

While the probability of grade 3 or 4 adverse events (AEs) was clearly higher in the treatment group than the control group, they were mostly manageable (resulting in discontinuation of treatment in only 1 patient out of 137 patients in the treatment group). Also, the probability of serious adverse events (SAEs) was not higher in the treatment group.

While no quantitative comparisons in the probability of AEs and serious adverse events (AEs) between lerociclib and other (multiple) CDK4/6 inhibitors were made, qualitative assertions were made generally in favor of the AE profile of lerociclib relative to other CDK4/6 inhibitors.

A strength of the trial design is that it is a randomized, double-blind, controlled trial. Although there was no pre-planned interim analysis (for futility and/or superiority early stopping), the overall relatively short duration of the trial (due to relatively fast accrual) might have helped justify this design consideration.

The overall results of the trial support lerociclib + fulvestrant as a new treatment option for patients with HR+/HER2- advanced breast cancer patients who have progressed on prior endocrine therapy.

Additional specific comments:

Page 3 (just a style suggestion): the advantages of this therapy lessen over time due to the emergence of resistance -> the efficacy of this therapy decreases over time due to the development of drug resistance;
Response: revised.

Page 4 (typo): a phase III trial evaluated -> a phase III trial that evaluated;
Response: revised.

Page 6 (typo): every 6 cycle -> every 6 cycles;
Response: revised.

Page 7 (typo): (section title) Primary and Secondary Endpoint -> Primary and Secondary Endpoints;
Response: revised.

Page 8: Space permitted, please list all pre-specified subgroup analyses in the Statistical Analysis section (or in the supplement of the paper);
Response: should the previous response regarding the subgroup analysis satisfy, we may not need to add the list. We certainly open to list it in the supplement as necessary.

Pages 9-10 (Section ‘Efficacy’): Please report results from all (16 in total) pre-specified subgroup analyses;
Response: revised (please see details in the previous response).

Page 12 (typo): The consistent results -> Consistent results;
Response: revised.

Pages 12-13: It is very helpful to describe the patient characteristics in the LEONARDA-1 trial with an intention to compare with those in the previous trials of CDK4/6 inhibitors. In this regard, it would be helpful to be a bit more explicit in terms of what the corresponding characteristics are in the previous trials. This would help to understand better the new information the current trial results have brought.
Response: LEONADA-1 included patients received first-line chemotherapy in the recurrent and metastatic stage (29.1%), which were not included in

MONALEESA-3, MONARCH-2 and MONARCH Plus. This point was mentioned in the original manuscript.

Page 13 (typo): 11.07 vs 5.42 months in patients received -> 11.07 vs 5.42 months in patients who received;
Response: revised.

Page 13 (typo): These evidence -> This evidence;
Response: revised.

Page 13 (typo): palbociclib and dalpiciclib has -> palbociclib and dalpiciclib have yielded (or something like that);
Response: revised as ‘palbociclib and dalpiciclib have induced…’

Page 14 (just a style suggestion): These findings suggest that the lerociclib obtains overall advantages in terms of gastrointestinal and hematological toxicity -> These findings suggest that lerociclib reduces overall gastrointestinal and hematological toxicity;
Response: prefer to keep the original wording to avoid potential misunderstanding.

Page 14 (just a style suggestion): exhibits -> has
Response: revised.

Page 20: Both panels A and B in Figure 2 show that all patients experienced events in the treatment group by 12 months. This does not seem to be consistent with the results reported in the body of the paper. Please clarify.
Response: In both Panel A and Panel B of Figure 2, the Kaplan Meier (KM) survival curve shows the last event occurred at 12 months, that is, in GB491 arm, the only patient reached 12 months of PFS follow-up progressed at the 12th month. Patients who have not yet experienced the PFS event are denoted by a '+' symbol on the curve, indicating censoring.

These graphical representations are in agreement with the results detailed in the main text of the paper.

Reviewer #3 - Breast cancer, clinical (Remarks to the Author):

This manuscript presents the results of the LEONARDA-1 study, a phase III randomized controlled trial evaluating the efficacy and safety of lerociclib, a novel oral CDK4/6 inhibitor, plus fulvestrant compared to placebo plus fulvestrant in patients with HR+/HER2- advanced breast cancer (ABC) who had progressed on prior endocrine therapy.
There are three FDA approved three CDK4/6 inhibitors, palbociclib, ribociclib,

and abemaciclb, which have been practice-changing game changers in ER+/HER2- mBC. The authors evaluated new CDK4/6 inhibitor, lerociclib. This study was conducted exclusively in Chinese patients.
Although, lerociclib plus showed significantly improved progression-free survival (PFS) compared to placebo plus fulvestrant (median PFS 11.07 vs 5.49 months; HR 0.451, p<0.0001), there are major limitations and critiques in this study.
1. Even though this study population were not treated with any FDA labeled CDK4/6 inhibitors, maybe associated with drug affordability in China, the authors should explain and discuss about the current standard treatment options globally. Without it, this study could hardly have generalizability.
Response: please refer to the previous response to Reviewer#1 regarding first-line as SOC.

2. Also, additional studies in diverse patient populations would strengthen the findings.
Response: agree. The LEONADA-1 study results were in line with a ph2 study conducted in the western population. No ph3 study was done in western patients. In the discussion session, it was mentioned as 'Even though the efficacy and safety data were in line with the results of the phase 2 study[18] conducted in western patients, further evaluation of the efficacy and tolerability of lerociclib plus fulvestrant in diverse populations may be considered.'

3. Comparison to other CDK4/6 inhibitors: While the authors discuss the efficacy and safety of lerociclib in the context of other approved CDK4/6 inhibitors, they do not provide a direct comparison. Differences in trial designs, patient characteristics, and inclusion/exclusion criteria make cross-trial comparisons challenging.
Response: agree. We revised the wording as 'These findings suggest that the lerociclib may obtain overall advantages in terms of gastrointestinal and hematological toxicity although cross-trial comparisons are challenging and may introduce bias.'

4. All the other three approved CDK4/6 inhibitors have showed quite consistent HRs for PFSs (0.42 for PALOAMD-3, 0.59 for MONALEESA-2, and 0.55 for MONARCH-2). However, the HR in this study was 0.49. The authors should discuss more in this regard.
Response: The HR in this study was 0.45. Numerically, HRs of these studies were in the level of 0.4, 0.5. As no H2H studies were conducted, it is hard to compare the HR directly. Therefore, we didn't discuss in details and described as 'The clinical efficacy of lerociclib in combination with fulvestrant was in line with other CDK4/6 inhibitors in combination with fulvestrant…' in the manuscript.

5. The median follow-up time was relatively short (approximately 7.3 months in both arms), and overall survival data were immature at the time of the analysis. Longer follow-up is needed to assess the long-term efficacy and safety of lerociclib plus fulvestrant.
Response: This manuscript presents the pre-planned final analysis.

6. While the PFS benefit was consistent across pre-specified subgroups, some of these subgroups had relatively small sample sizes, which may limit the reliability of the subgroup analyses.
Response: agree, this is the limitation of subgroup analysis.

7. To reach high-level of evidence, Quality of life assessment should be combined.
Response: Unfortunately, the QOL data were not collected in this study.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

Overall the authors have addressed prior concerns. However, concerns remain about not confirming estradiol suppression on goserelin and the time line for CBR which is usually reported at 6-months

Reviewer #2 (Remarks to the Author):

All my comments have been adequately addressed.

Reviewer #3 (Remarks to the Author):

The revision was well responsed and revised accordingly.

It would be acceptable for the publication in Nature Comminications.