Peer Review File

Article information: https://dx.doi.org/10.21037/gpm-23-50

Comment 1: Consider adding a short introductory paragraph to provide background information. This will help readers better understand the context of the article.
Reply 1: We added a paragraph at the beginning of the short commentary. This should help to understand the rest of the article. (See page 1, Lines 9-18)
Changes in the text: Low-grade serous ovarian carcinoma (LGSOC) is a distinct subtype of ovarian cancer that presents unique challenges in terms of treatment due to intrinsic chemoresistance. LGSOC, in comparison to high-grade serous ovarian carcinoma, has a high prevalence of mutations in KRAS (20-40%), NRAS (26%) and BRAF (5-10%) (1,2). Patients with activating mutations in canonical MAPK pathway components are reported to respond more frequently to targeted agents, such as MEK inhibitors, compared to patients without a mutation in the MAPK pathway (3,4). MEK inhibitors are a class of targeted therapies designed to block the activity of MEK1 and MEK2. These are proteins that play a crucial role in the MAPK signaling cascade and can contribute to uncontrolled cell growth, resistance to apoptosis and increased angiogenesis (5).

Comment 2: Maintain consistency in the structure of paragraphs to facilitate easier information retrieval for readers. This includes details such as the name of the clinical trial, the drug used, patient characteristics, significant endpoints of the trial, and key findings related to MAPK biomarkers for MEK1/2 inhibition.
Reply 2: Thank you for this comment. To facilitate reading we worked on consistency and specified the drug type.
Changes in the text: For example: page 1 line 20: ENGOT-ov11/MILO study, page 1 line 26 KRAS mutation (KRASmut), page 1 line 28 without a KRAS mutation (KRASwt), page 1 line 45-46 the In the GOG-281/LOGS phase 2/3 trial, patients with recurrent LGSOC were treated with trametinib, a MEK1/2 inhibitor, versus PCC., page 2 line 52-53: ENGOT-ov60/GOG-3052/RAMP201 study including patients with recurrent LGSOC etc. All changes are highlighted in the reviewed manuscript in yellow.

Comment 3: Clarify the nature of trametinib at line 38 by providing additional information, such as describing trametinib as a specific inhibitor (e.g., trametinib, a [target of inhibitor] inhibitor).
Reply 3: We understand that for a broader audience the nature of trametinib is not common knowledge. We added this into the text.
Changes in the text: page 1 line 46 In the GOG-281/LOGS phase 2/3 trial, patients with recurrent LGSOC were treated with trametinib, a MEK1/2 inhibitor, versus PCC. PFS and overall response rate (ORR) were both markedly higher in patients with KRAS, BRAF and NRAS mutations compared to patients with wild-type KRAS, BRAF and NRAS(3).

Comment 4: Reevaluate the conclusion at the statement "Binimetinib could be an effective treatment option for LGSOC ~." Consider replacing "Binimetinib" with a broader term like "MEK inhibitors" for a more suitable conclusion.
Reply 4: We understand the comment of the reviewer. Our original idea was to limit the

conclusion to binimetinib, as this is a commentary on the paper of Grisham et al. As the conclusion can be generalized to MEK inhibitors as a group and therefore we adapted the conclusion.
Changes in the text: Page 2 line 60-65: In conclusion, this post-hoc analysis identifies alterations in the MAPK pathway as possible biomarkers to select patients for MEK1/2 inhibitor treatment in the future. MEK inhibitors could be an effective treatment option for LGSOC patients with alterations in the MAPK pathway and not limited to KRAS. Biomarker research is crucial in identifying the right patient population to select for targeted agents, making this type of translational research important in LGSOC.

Comment 5: The manuscript requires proofreading. I've provided a few examples below, but I recommend a thorough proofread for additional improvements.
Reply 5: We appreciate the comments. We conducted a comprehensive proofreading of the commentary. We implemented almost all the comments and in the manuscript and highlighted the changes in the text. Here we give some examples of the changes.
Changes in the text:

- Consistency in Terminology: page 1 line 26-30: The study found that patients with a KRAS mutation (KRASmut) treated with binimetinib were 3.4 times more likely to respond (complete remission (CR) or partial remission (PR)) compared to patients without a KRAS mutation (KRASwt) (95% CI: 1.57 - 7.67). Among patients treated with binimetinib, 44% of KRASmut patients achieved a CR/PR compared to 19% of KRASwt patients. Other changes are highlighted in yellow in the text.
- Clinical Trials Code: page 2 line 52-53: Similar impact of a KRAS mutation on ORR were described in the ENGOT-ov60/GOG-3052/RAMP201 study including patients with recurrent LGSOC(12).
- Abbreviations: page 2 line 26-28: The study found that patients with a KRAS mutation (KRASmut) treated with binimetinib were 3.4 times more likely to respond (complete remission (CR) or partial remission (PR)) compared to patients without a KRAS mutation (KRASwt) (95% CI: 1.57 - 7.67).
- English grammar improvement: Page 1 line 32-34: The study also found that patients who harbor MAPK pathway alterations (NRAS, BRAF, NF1, RAF1 mutations) and are treated with binimetinib have longer progression-free survival (PFS) compared to those without MAPK pathway alterations (hazard ratio (HR) 0.50; 95% CI: 0.31 - 0.79).
- Confidence interval: We used dashes instead of commas: e.g. Page 1 Line 28 (95% CI: 1.57 - 7.67).
- Eloboration of sentence: We adapted the sentence as follows: page 1 line 40-43: In vitro and in vivo data indicate that patients harboring the KRAS G12V mutation may be more sensitive to MEK inhibition compared to other KRAS variants. Despite this, the study found no difference in PFS in patients with KRAS G12V mutation (n= 19) versus patients with other KRAS variants (n= 26).
- Defined abbreviations: Thank you for this remark, we changed this to ORR page 2 line 53-56: The initial results of this study showed that avutometinib, a dual RAF/MEK inhibitor, in monotherapy or in combination with defactinib, a FAK inhibitor, had a higher ORR in KRASmut patients (monotherapy 10% - combination 60%) compared to KRASwt patients (monotherapy 6% - combination 29%).

-Parenthesis placement: Thank you for noticing this, we adapted the sentence: page 2 line 53-56: The initial results of this study showed that avutometinib, a dual RAF/MEK

inhibitor, in monotherapy or in combination with defactinib, a FAK inhibitor, had a higher ORR in KRASmut patients (monotherapy 10% - combination 60%) compared to KRASwt patients (monotherapy 6% - combination 29%)