

Peer Review File

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Title: Development of new medical treatment for ovarian cancer recurrence

Reviewer #1

The article is well written and extensively covers all aspects of medical treatment in ovarian cancer recurrent patients. Before the publication I would have some suggestions to make with minor revision:

Comment 1: In introduction section the objective of the study should be declared.

Reply 1: done on paragraph 1

Comment 2: Please report the on-going trial about hipec for recurrent ovarian cancer HORSE NCT01539785.

Reply 2: done on paragraph 5.4

Comment 3: “The addition of bevacizumab to non-platinum, may improve PFS and contribute to reduce ascites, gastro-intestinal symptoms and pleural effusion”. Please specify the PFS improvement as reported in literature.

Reply 3: done on paragraph 2

Comment 4: Correct the punctuation in the following sentence: ‘Several trials have the objective to investigate the role of immune checkpoint inhibitors, some of them in combination with PARP inhibitors, Both in first line and in recurrence setting’. in the 'immunotherapy' section.

Reply 4: I changed the uppercase of the term “Both” and I left the punctuation unchanged.

Comment 5: Write the following acronyms PD-1 / PD-L1 in full the first time they are named in the text.

Reply 5: done on paragraph 5.1

Comment 6: Correct the punctuation in the following sentence: ‘The phase III PAOLA-1 trial has been just closed and showed the advantage of adding olaparib maintenance to Bevacizumab following platinum-based chemotherapy in 1st line OC The median PFS was 22.1 months with olaparib andbevacizumab versus 16.6 months with bevacizumab alone’

Reply 6: done on paragraph 5.3.2

Comment 7: Correct the punctuation in the following sentence: ‘Mortality rates remain high, but during the last years antiangiogenics therapies and PARP-inhibitors have changed the history of this disease and improved the outcome in OC patients: as demonstrated by numerous trials and by a recent meta-analysis (113) PARPi allowed to ...

Reply 7: done on paragraph 6

Comment 8: Correct the format of the citation 43.

Reply 8: done.

Reviewer #2

A very interesting and thorough article. The authors should be commended for their work. Only just minor comments:

Comment 1: Although the term “Carcinoma” refers to epithelial malignancies, I would suggest to change the title and include the word “epithelial” to better clarify the focus of this review.

Reply 1: done.

Comment 2: There are several minor grammatical errors: just few examples

Reply 2: done

- In the last paragraph of the abstract, I suggest to correct to “We reviewed THE literature on the updated treatments for recurrent ovarian cancer, SUMMARIZING all the available drugs and combinations to treat patients with this diagnosis, and focusing the attention on the new approved molecules and the contemporary Clinical Trials, investigating new target therapies and new associations”. → done
- Page 5: Please rephrase the sentence “Particularly from BRCA-mutated patients, we may be expected to have a new response to platinum rechallenge therapy (12), and PARP inhibitors seems to be active both in platinum resistant and in platinum sensitive patients (13)” → done
- Page 6, please correct to: “and AN additional as well as interesting outcome, emerging from this trial, was the possibility of delaying the following line of platinum therapy, assuming that this artificial prolongation of platinum interval could increment the response TO this drug”. → done
- Page 12, please correct to “The three cohorts OF patients”. → done
- Page 14: “WHERE” instead of “were nivolumab” → done
- Page 14: Please rephrase in a better English the sentence “Unfortunately the following RCT had disappointing results of TRINOVA-2 and Trinova-3 trials (68), where neither OS or PFS have been improved, in ROC or in first line of treatment, respectively.”. → done
- Page 19: Please rephrase the sentence “A phase I/II AVANOVA (NC-T02354131) randomized platinum-sensitive ROC to niraparib versus nira-

parib and bevacizumab and has demonstrated an ORR of 45% (84)” to better clarify what does it mean. → done

- Page 20: Please rephrase the sentence “In women with platinum-sensitive ROC, a phase III trial is examining the role of maintenance with olaparib and cediranib versus olaparib alone, after platinum-based chemotherapy, is currently being tested in ICON 9 trial (NCT03278717)” → done
- Page 21: Please correct “Other criticisms are about the low OS of the control group”. → done
- Page 24: Please correct to “Decitabine in combination with Carboplatin versus chemotherapy AT physician’s DISCRETION”. → done
- Page 24: Please correct to “A phase II RCT for patients with resistant/refractory OC, will randomize them to” → no change !
- Page 24: Please correct to “Adavosertib is a WEE1 tyrosine kinase inhibitor” → done
- Page 25: Please correct to “ADC binding antigens” → done

Comment 3: At page 6 please clarify the sentence “Even if the second and the third regimen didn’t demonstrated any differences in OS, their lower toxicity could suggest them as preferable regimens in this population.”. Which are the second and third regimens?

Reply 3: done

Comment 4: Please extend, at least for the first mention, the abbreviation “HRD” (which I do think stands for Homologous Recombination Deficiency).

Reply 4: first mention of “HRD” has been done in paragraph 4, and it is already extended. I changed the three initials in uppercase.

Comment 5: Page 9: What does “PR” stand for? Partial Response? Please extend ALL the abbreviations!

Reply 5: done

Comment 6: The same as above at Page 12 for RR (Response Rate?)

Reply 6: done

Comment 7: Page 16: “TRINOVA-1 was a double-blind, placebo-controlled phase 3 RCT, evaluating patients with recurrent disease <12”. 12 what? Is this 12 months?

Reply 7: done

Comment 8: The chapter on intraperitoneal chemotherapy appears somewhat confusing for two reasons: (1) it mixes standard intraperitoneal chemotherapy and HIPEC without making a clear difference; they are two different things and should be treated separately. (2) It refers mainly to data regarding the treatment at first line (and mainly at IDS) as this is what is available in the literature. However the focus of this review is recurrent ovarian cancer. If you want to make a chapter on intraperitoneal chemotherapy, please clearly distinguish HIPEC from non-HIPEC treatment and make mention only of its use in recurrent ovarian cancer.

Reply 8: your comment is correct. I changed most of the text, leaving only the part concerning recurrent ovarian cancer.

Comment 9: Please make mention of the role of anastrozol and hormonal/anti-hormonal therapies in recurrent LGSOC.

Reply 9: done.

Comment 10: Please verify the numbers of the different chapters/paragraphs because they are incorrect and confusing.

Reply 10: I checked all the numbers and they are correct, corresponding to summary, put at the beginning of the text, after the title page.

Reviewer #3

Comment 1: Only minor language corrections are needed

Reply 1: done