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Systematic or Meta-analysis Studies

Parp inhibitors as maintenance treatment in platinum sensitive recurrent ovarian cancer: An updated meta-analysis of randomized clinical trials according to BRCA mutational status☆

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ABSTRACT

Objective: This meta-analysis investigated the effectiveness of PARP inhibitors (PARPis) as maintenance treatment in platinum sensitive recurrent ovarian cancer (ROC), stratifying results based on BRCA mutational status into five different categories: whole population, germ-line BRCA mutated patients, somatic BRCA mutated patients, HRD patients and wild type population.

Methods: PubMed, Medline, Scopus, EMBASE and clinicaltrials.gov, as well as meeting proceedings were searched for eligible studies that described RCTs testing the efficacy of PARPis as maintenance treatment in platinum sensitive ROC. Data were extracted independently and analysed using RevMan statistical software version 5.3. Primary end-point was progression free survival (PFS).

Results: The analysis confirmed the positive effect of PARPis in patients with platinum sensitive ROC in case of germinal or somatic BRCA mutations. Specifically, HR for PFS was 0.26, 95% CI 0.21–0.31, $p < 0.00001$ for the mutation of BRCA gene and 0.24, 95%, CI 0.12–0.48, $p < 0.0001$ for the somatic alteration. In addition, in the HRD population, studies that analysed the efficacy of PARPis reported a PFS improvement with HR 0.34, 95% CI 0.26–0.43, $p < 0.00001$. Finally, our analysis confirms the role of these drugs in prolonging PFS in the whole population with HR 0.36, 95% CI 0.32–0.42, $p < 0.00001$, although to a lesser extent, with a significant improvement even in wild type cancers with HR 0.49, 95%, CI 0.41–0.59, $p < 0.00001$).

Conclusions: PARPis are effective regardless of BRCA mutational status. Future investigations are necessary to explore the use of different PARPis as monotherapy, comparing them among each other in terms of efficacy and toxicity, and exploring their potential re-use.

Introduction

It is by now widely recognized that ovarian cancer (OC) harbours a remarkable degree of genomic disarray and instability and presents with a wide range of mutations [1,2]. Indeed, around 50% of all high-grade serous ovarian tumours are estimated to have a deficiency in the homologous recombination (HR) DNA repair mechanism, with about 15% of carcinomas harbouring a germline and 6% a somatic Breast Related Cancer Antigens (BRCA) 1–2 mutation. These mutations confer to the cell a disability to repair DNA through the HR pathway, leading to a condition defined as homologous recombination deficiency (HRD) [1,3]. HRD as a condition, is not exclusively defined by deleterious BRCA 1 and 2 mutations, but by genomic alterations and/or epigenetic silencing of other pathway genes as well, including ATR, ATM, RAD51/54, CHK1/2, NBS1, PTEN and PALB2 [1,3,4]. These genetic and epigenetic aberrations grant the so-called "BRCA-ness" profile, resulting in a disability of affected cells to correctly repair DNA double strand breaks, much like a BRCA mutation. Consequently, a "BRCA-ness" profile encompasses a susceptibility to DNA-damaging agents, just like a BRCA mutation. A deficiency in the HR pathway alone implies no

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threat to the cell, as other DNA repair mechanism are able to compensate for it. If, however, the cell suffers a deficiency of other DNA repair mechanisms, or if other DNA repair mechanisms were somehow inhibited, the resulting accumulated DNA damage would ultimately lead to cell death [5]. This defines the concept of synthetic lethality, a process by which cancer cells are selectively targeted by the inactivation of two genes or pathways, when inactivation of either gene or pathway alone, is nonlethal [5].

This increasing knowledge regarding the molecular and genetic aspects underlying OC has enabled the possibility to exploit new therapeutic strategies that aim to maximize benefits and limit adverse effects, guided by a patient-tailored principle. One of the most studied groups of novel chemotherapeutic agents is that of the Poly-ADP-Ribose Polymerase (PARP) inhibitors (PARPis), which, along with Vascular Endothelial Growth Factor (VEGF) inhibitors have improved to some extent the maintenance-therapy landscape in OC [2].

Poly-ADP-Ribose Polymerase (PARP) is a family of 17 enzymes with proven DNA repair activity, through the Base Excision Repair (BER) mechanism, with PARP1 being responsible for 85% of it. Their physiological activity requires the consumption of NAD+ and the release of nicotinamide, which is exactly the primary target for PARP inhibition, thus PARP inhibitors (PARPis) are defined as b-nicotinamide adenine dinucleotide (NAD+)-competitive inhibitors [6,7]. It has been recently suggested that "PARP trapping", described as a situation where PARP-1, inactivated by the PARPis, remains trapped to the site of DNA damage, forming toxic PARP–DNA complexes, thus preventing further DNA repair [6,8], might be another mechanism through which PARPis mediate their activity. Other proposed mechanisms of action of PARPis include promotion of increased non-homologous end joining and impairment of BRCA1 recruitment to the site of DNA damage [9,10]. However, in a cell incapable of adequately employing HR, PARP inhibition would cause accumulation of unrepaired DNA damage, and subsequent cell death, falling into the category of the aforementioned synthetic lethality. This is why the development of PARPis as potential treatment agents in OC, initially focused only on BRCA-mutated tumours [11]. However, despite the fact that the majority of studies regarding PARPis in OC report higher effectiveness in BRCA mutated women, this class of drugs appears to have some efficacy in BRCA wild type patients as well. Moreover, the prognostic significance of the BRCA-ness phenotype is not fully clear and it is still uncertain whether these patients effectively have better response rates to conventional or novel chemotherapeutic agents. In this scenario, the aim of this meta-analysis is to investigate the effectiveness of PARPis as maintenance treatment in platinum sensitive recurrent ovarian cancer (ROC) by paying particular attention to the population's BRCA status of mutation and stratifying results into five different categories: whole population, germ-line BRCA mutated patients, somatic BRCA mutated patients, patients with HRD and wild type population.

Methods

Eligibility criteria

The inclusion criteria for the *meta*-analysis were: (1) randomized study with patients affected by platinum-sensitive ROC, where PARPis were used in a maintenance setting after a platinum based chemotherapy; (2) study that randomly compared a PARPi to placebo in terms of progression free survival (PFS). Only articles written in English were included. Studies including combinations of PARPis with chemotherapy were excluded [12].

Search strategies

Two independent reviewers searched through PubMed, Medline, Scopus, EMBASE and clinicaltrials.gov in order to identify articles published up to May 2019 using a combination of the following search terms: BRCA mutation, ovarian neoplasm, ovarian cancer, platinum sensitive, olaparib, rucaparib, niraparib, relapsed ovarian cancer, recurrent ovarian carcinoma, Poly (ADP-Ribose) Polymerase Inhibitors, PARP inhibitors, maintenance therapy. After an initial screening of records on a title-abstract basis, a full text article was retrieved for selected records. References were scrutinized to identify further relevant articles. Both reviewers independently read the full text of the pre-selected articles to confirm fulfilment of inclusion criteria, after which, studies were excluded if reporting partial or incomplete data.

Data extraction

Two reviewers independently extracted characteristics and outcomes of selected studies (first author, year of publication, trial acronym, number of patients enrolled, patients who received PARPis and those who received placebo, number of patients by BRCA mutational status).

Risk of bias assessment

The methodological quality of the included studies was independently evaluated by two reviewers, using the risk of bias approach proposed by the Cochrane Collaboration, which considers selection bias, performance bias, detection bias, attrition bias and reporting bias [13]. The risk of bias for each category was assessed according to specific criteria and was graded in high, low or unclear risk of bias if data was insufficient. Disagreements were resolved through discussion and consensus among all authors.

Statistical methods

The primary endpointof this meta-analysis was PFS, defined as the time from the date of randomization to last follow-up, death or disease progression, whichever comes first. Hazard Ratios (HR) for PFS, and its 95% confidence intervals (CI) were extracted from each study or calculated, based on data reported in the included articles. Pooled HRs were calculated using the generic inverse of variance method with a fixed-effects model. The result of each study and the pooled analyses were graphically represented through forest plots. A significant two-way p value for comparison was defined as $p < 0.05$.

Statistical heterogeneity was quantified using the I^2 statistic, which indicates the percentage of variability due to heterogeneity rather than to chance alone. Chi-squared tests for homogeneity were also used. The assumption of homogeneity was deemed invalid if the P value was less than 0.10.

In order to detect publication bias (i.e. the bias due to the fact that studies with positive results are more likely to be published than those with negative results) or small-study effect (the tendency for treatment effect estimates to be different in small and larger studies), we visually explored any asymmetry using a funnel plot in which study size was plotted as a function of the measure of interest. All statistical analyses were executed using Review Manager software version 5.3.

Results

This meta-analysis reports results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14].

The electronic search resulted in the pre-selection of 20 full-text articles overall (Fig. 1). Following thorough evaluation of each record, 15 studies were excluded. Four articles were not pertinent to our theme; three studies investigated costs related to PARPis treatment; three records were excluded as PARPis were not investigated against placebo; two records excluded for partial or incomplete data; two because they reported studies that combined a PARP inhibitor with chemotherapy and one study was not written in English. Therefore five

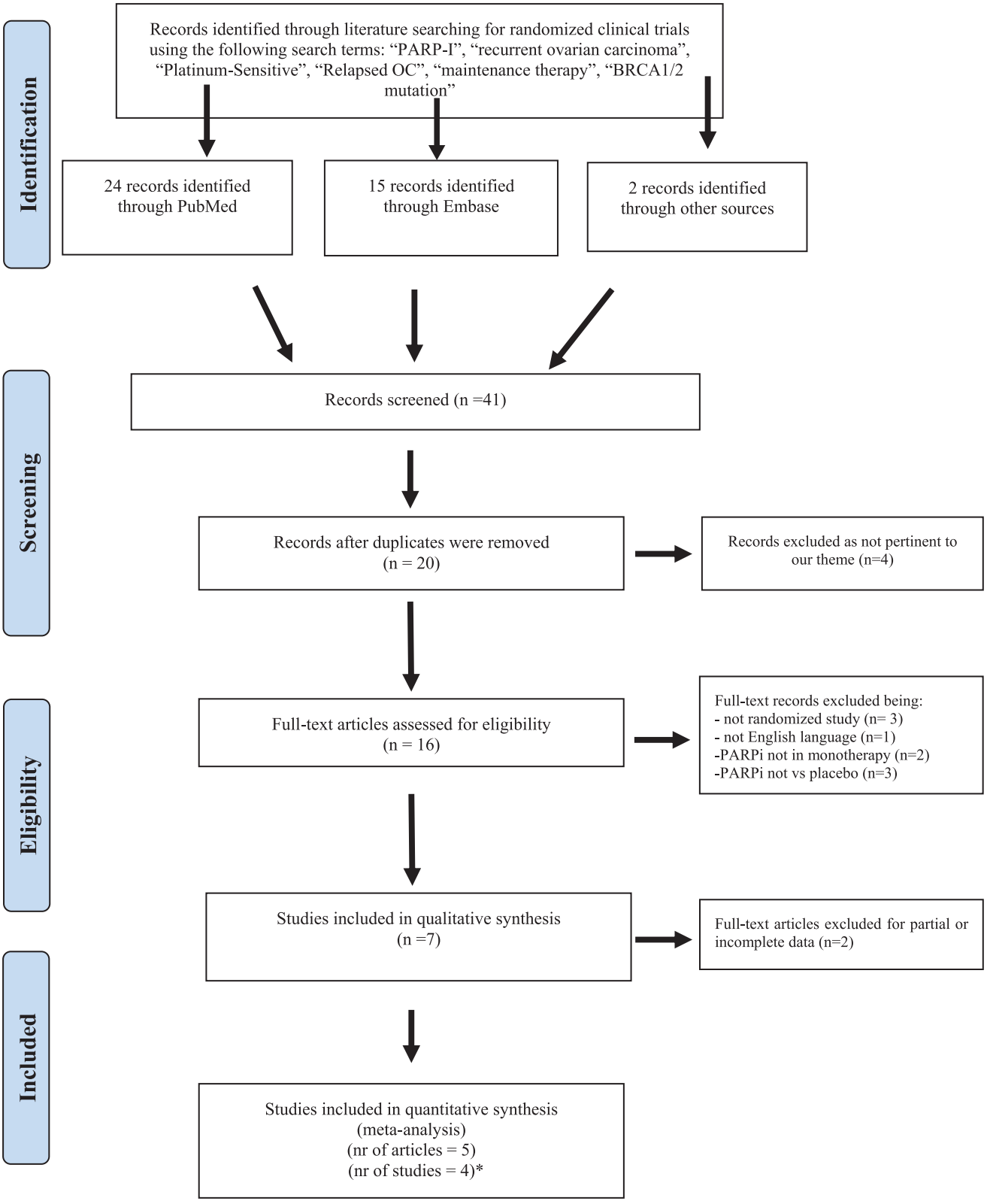

Fig. 1. Trials selection.

papers published between 2012 and 2018, were included in the final analysis [15–19]. However, the paper published by Lederman et al. in 2014 referred to a pre-planned retrospective analysis of efficacy according to BRCA mutational status of Study 19, whose results had been previously published in 2012 by Lederman et al., when data on BRCA mutational status were not yet available. Consequently, four studies were finally analysed: STUDY19 (2012 and 2014), SOLO 2, ARIEL 3 and NOVA. Among these studies, two tested olaparib, one niraparib and one rucaparib as maintenance treatment in platinum sensitive ROC.

Characteristics of the included studies and enrolled patients are reported in Table 1. Median age of patients was similar among all studies. As expected, in the studies that reported age by mutational

Table 1
Randomized studies testing different PARP-Inhibitors as maintenance treatment in platinum sensitive recurrent ovarian cancer.

Author, Year, Study	Total N° of Pts	Median age in years (range)	Testing arm	Comparison arm	N° of BRCAm Pts (%)	N° of BRCAwt Pts (%)	HRD positive patients
Lederman et al, 2012 [15] STUDY 19	265 [97 of whom (37%) with known BRCA mutational status)]	58 (21–89) in Olaparib group 59 (33–84) in Placebo group	Olaparib 800 mg (capsules) 136 Pts	Placebo 129 Pts	59 (22%)	38 (14%)	NA
Lederman et al, 2014 [16]* (a pre-planned restrospective analysis of STUDY 19)	265 [254 of whom (96%) with known BRCA mutational status)]	BRCAm Pts 58 (38–89) in Olaparib group 55 (33–84) in Placebo group BRCAwt Pts 62 (21–80) in Olaparib group 63 (49–79) in Placebo group	Olaparib 800 mg (capsules) 136 Pts	Placebo 129 Pts	136 (51%) both somatic and germline mutations	118 (45%)	NA
Pujade-Lauraine et al, 2017 [17] SOLO 2	295	56 (51–63) in Olaparib group 56 (49–63) in Placebo group	Olaparib 600 mg (tablets) 196 Pts	Placebo 99 Pts	295	0 (Only mutated patiens)	NA
Mirza et al, 2016 [18] NOVA	553	BRCAm Pts 57 (36–83) in Niraparib group 58 (38–73) in Placebo group BRCAwt Pts 63 (33–84) in Niraparib group 61 (34–82) in Placebo group	Niraparib 300 mg (capsules) 372 Pts	Placebo 181 Pts	Germline 203 (37%) Somatic 47 (8%)	350 (63%) The analysis on wild type population included patients with somatic BRCA1-2 mutation	162 (29%)
Coleman et al, 2017 [19] ARIEL 3	564	61 (53–67) in Rucaparib group 62 (53–68) in Placebo group	Rucaparib 1200 mg (tablets) 375 Pts	Placebo 189 Pts	Germline 130 (23%) Somatic 56 (10%) Unknown 10 (2%)	368 (65%) (158 with high LOH, 161 with low LOH and 49 with indeterminate LOH)	354 (63%)

Pts = patients; N° = number; BRCAm = BRCA mutated; BRCAwt = BRCA wild type; LOH = loss of heterozygosity *Analysis of outcomes according to BRCA status from study 19, was subsequently described in the paper published by Lederman et al. in 2014 when data on mutational status were complete.

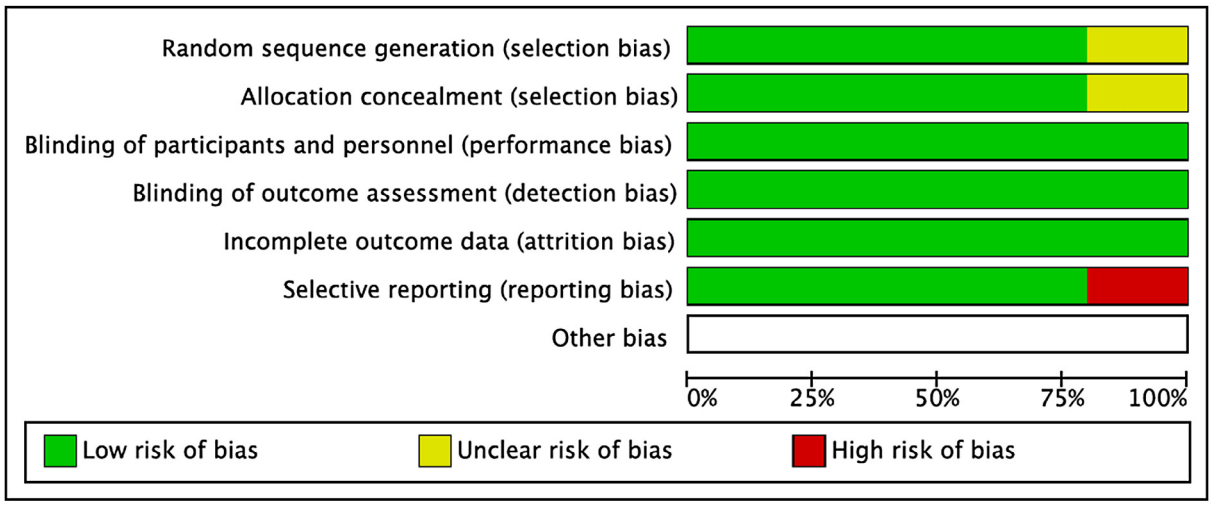

Fig. 2. Risk of bias graph.

status [16,18], BRCA mutated patients seem to be younger than wild-type patients. Most of the studies included both mutated and not mutated patients; only the SOLO 2 trial included exclusively BRCA mutated population [17].

The 'Risk of bias graph' (Fig. 2) illustrates the risk of bias, which was globally low. The NOVA trial was judged at unclear risk for selection bias and reporting bias, since no sufficient information is reported about the random sequence generation, the allocation concealment (for insufficient information within the paper to establish it) and the primary endpoint result regardless of BRCA1-2 mutational status has not been reported. There was no detectable asymmetry in the funnel plots suggesting a low risk of publication bias even if the number of studies for each *meta*-analysis is low. Finally, forest plots were designed.

Our meta-analysis scanned HR from every trial and distinguished in subgroups: germline BRCA mutated patients, somatic BRCA mutated patients, HRD patients, the whole population and wild type population. HRs of all the studies according to BRCA mutational status are reported in Table 2.

Overall, we analysed data from 1677 patients affected by platinum sensitive ROC (1079 had received a PARPi and 598 placebo). Specifically, the analysis on the whole population regardless of the mutational status considered data on PFS of 1382 patients who were randomized to receive PARPi or placebo [15,18,19]. HR in the whole population subgroup was 0.36, 95%, CI 0.32–0.42, $p < 0.00001$ (Fig. 3a). Of note, the HR from NOVA study was calculated from the HR obtained in the mutated and wild type subgroup using the generic inverse of variance method.

Since all studies included in this meta-analysis tested the efficacy of PARPis in BRCA mutated patients, they were all considered for the analysis of PFS in the germline BRCA mutated patients, counting altogether 1677 patients. Of note, since the primary endpoint of Study 19 was PFS regardless of BRCA mutational status in patients treated with olaparib as maintenance treatment in platinum sensitive recurrent disease, efficacy data by mutational status referred to the pre-planned retrospective analysis of BRCA1-2 mutated population published by Lederman et al. in 2014 [16]. Thus, the HR was 0.26, 95% CI 0.21–0.31, $p < 0.00001$ for BRCA1-2 mutated patients (Fig. 3b) [16–19].

Data on efficacy of PARPis in patients with somatic BRCA mutations and HRD positivity were separately analysed only for the NOVA [18] and ARIEL 3 [19] trials with a total amount of 103 and 516 patients respectively. The HR in the group of patients with somatic alterations was 0.24, 95% CI 0.12–0.48, $p < 0.0001$ (Fig. 3c) [18,19].

In Study 19, the group of BRCA mutated patients included without discriminating carriers of germline and somatic mutations, whereas in SOLO 2 trial only patients with germline mutation were included. Of note, in the NOVA trial, although an analysis about somatic population has been separately carried out, these patients were previously included

Table 2
PFS according to the BRCA mutational status.

Author, Year, Study	Whole population Nr. of patients * HR 95% [CI]	BRCA1-2 mutated population Nr. of patients * HR 95% [CI]	BRCA1-2 somatic mutated population Nr. of patients* HR 95% [CI]	HRD positive population Nr. of patients* HR 95% [CI]	Wild-type population Nr. of patients * HR 95% [CI]
Lederman et al, 2012 [15] STUDY 19	136 vs 129 0.35 [0.25, 0.49]				
Lederman et al, 2014 [16] STUDY 19		74 vs 62 0.18 [0.10, 0.32]			57 vs 61 0.54 [0.34, 0.85]
Mirza et al, 2016 [18] NOVA	not reported	138 vs 65 0.27 [0.17, 0.42]	35 vs 12 0.27 [0.08, 0.91]	106 vs 56 0,38 [0.24–0.59]	234 vs 116 0.45 [0.34, 0.60]
Pujade-Lauraine et al, 2017 [17] SOLO 2		196 vs 99 0.30 [0.22, 0.41]			
Coleman et al, 2017 [19] ARIEL 3	375 vs 189 0.36 [0.29, 0.44]	130 vs 66 0.23 [0.16, 0.34]	40 vs 16 0.23 [0.10, 0.53]	236 vs 118 0.32 [0.24–0.42]	High LOH 106 vs 52 0.44[0.29, 0.66] Low LOH 107 vs 54 0·58 [0·40–0·85]

* PARPis vs Placebo; HR = hazard ratio; CI = confidence intervals; LOH = loss of heterozygosity.

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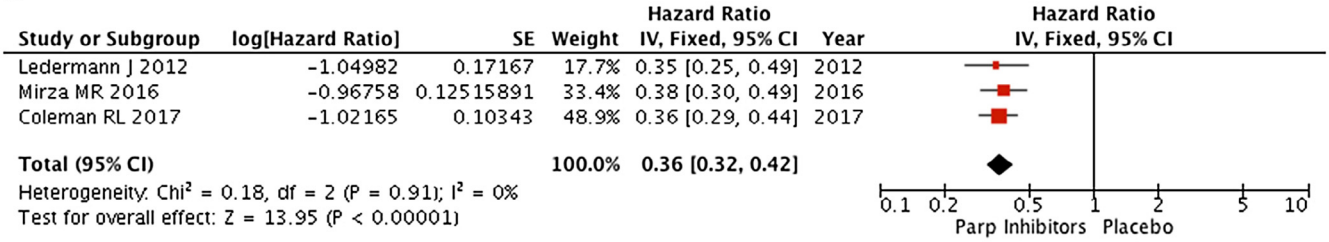

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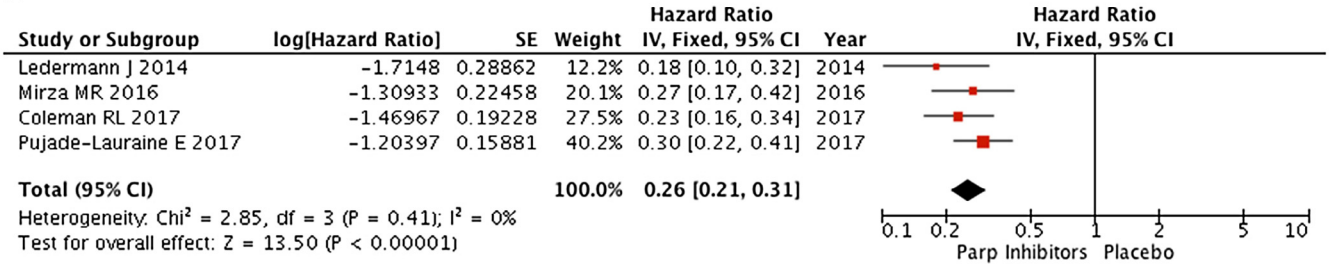

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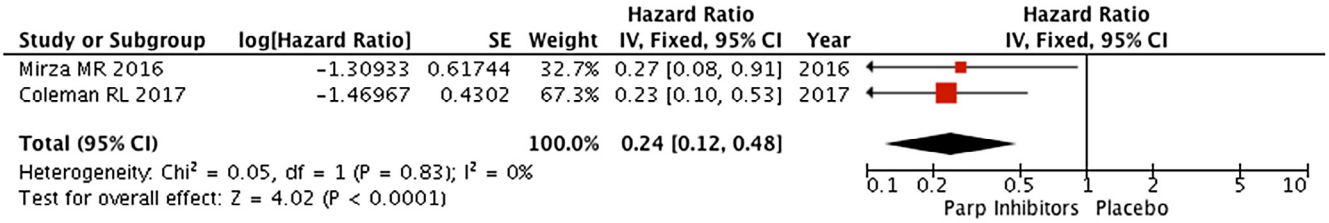

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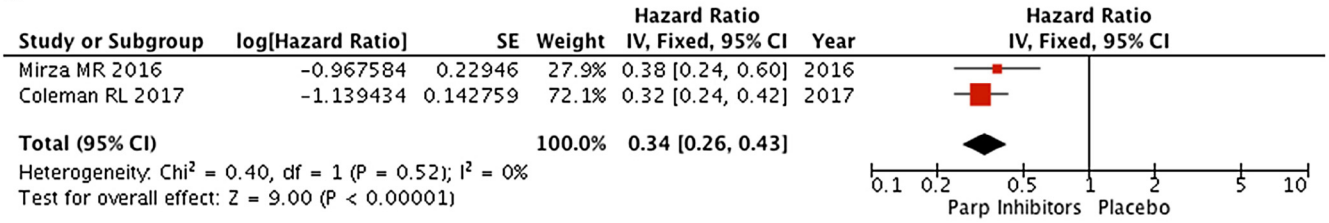

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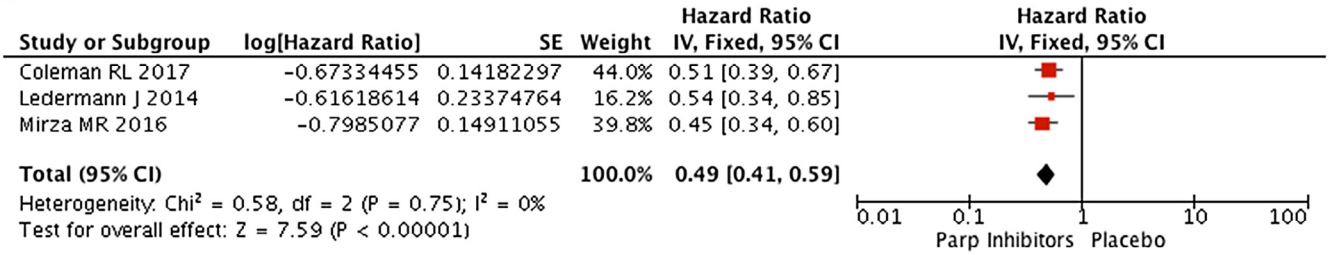

Fig. 3. PFS in: a. whole population b. BRCA1-2 germline mutated population c. BRCA1-2 somatic mutated population d. HRD positive population e. wild type population.

within the wild type cohort, differently by other studies. The analysis on HRD positive population from these two trials showed a PFS improvement with HR 0.34, 95% CI 0.26–0.43, p < 0.00001 (Fig. 3d) [18–19].

Finally, the analysis of wild type patients included Study 19 (2014), NOVA (including patients with somatic mutations) and ARIEL 3 trials [16,18,19]. The cumulative number of wild type patients from these trials was 836 patients. However, ARIEL 3 reported the analysis of PFS distinguishing patients with low genomic loss of heterozygosity (LOH) from those who present high LOH (excluding from the analysis 49 women with indeterminate LOH). Thus, HR from this trial for wild type population was calculated from the HR obtained in both subgroups using the generic inverse of variance method [19]. HR in wild type cancers was 0.49, 95%, CI 0.41–0.59, p < 0.00001 (Fig. 3e) [16,18,19].

Discussion

Around 50% of all HGSOC are estimated to have HRD with about 15% of carcinomas harbouring a germline BRCA mutation, 6% a

somatic BRCA mutation, and 20% a mutation in, or epigenetic silencing of, another homologous recombination gene [20,21]. These tumours are thus subjected to the effect of a series of drugs whose mechanism of action interferes with DNA repair mechanisms, in particular PARPis, that by exploiting the concept of "synthetic lethality" previously described, have greatly changed the landscape of ROC treatment in the last decade. Indeed, PARPis have been extensively tested in ROC, as described in detail elsewhere [15–19].

The results of this meta-analysis confirm the effectiveness of PARPis in improving PFS when administered to germinal or somatic BRCA mutated patients, in a maintenance setting, in platinum sensitive ROC, after a good response to the last platinum-based chemotherapy. These data partially support the concept that it is exactly due to synthetic lethality that PARPis are particularly effective in BRCA mutated patients.

In addition to this, our analysis highlights the measurable effects that PARPis have on HRD tumours and stresses the role that maintenance PARPis have in prolonging PFS in the whole population of patients. Finally, this meta-analysis emphasizes that the use of PARPis in a maintenance setting improves PFS in wild type cancers as well, albeit to a lesser extent than that obtained in other groups of patients. Consequently, despite the difference in terms of PFS obtained with PARPis while comparing BRCA mutated and wild type tumours that is clearly in favour of the first category, our analysis confirms the possibility of expanding the use of these agents to the whole population of OC patients, with measurable benefit.

As of May 2019, PARPis have different approval policies worldwide. Specifically, while niraparib was approved in all patients regardless of the mutation status, olaparib has been approved in BRCA mutated patients in USA as first-line therapy and regardless of BRCA mutational status in recurrent OC. In Europe, olaparib has just recently been approved by the European Medicines Agency (EMA), with significant differences within all countries (i.e. it is not reimbursed in Italy in non-mutated patients). Rucaparib has been approved in USA first as monotherapy, and afterwards in a maintenance setting in BRCA mutant tumours, and lately in Europe with the same indications, although there persist significant inconsistencies among countries (i.e. it is not approved in Italy). In view of our results, we support the tendency to expand the use of this class of drugs as maintenance therapy for platinum-sensitive ROC, regardless of mutational status. In fact, the efficacy of PARPis on wild type tumours is not exceptional; however, in the general population of patients with ROC, this benefit does not differ much from that obtained with other maintenance strategies such as bevacizumab. Indeed, in the OCEANS trial, the gain in PFS in the bevacizumab arm vs placebo (12.4 vs 8.4 months, respectively) is comparable to the gain in PFS obtained in wild type patients using olaparib as maintenance treatment versus placebo (8.4 vs 4.8 months, respectively), as described in Study 19 [15,22].

Furthermore, BRCA mutated tumours, particularly BRCA 2, have better prognosis and have been proven to better respond not only to PARPis, but to chemotherapy in general, be it platinum based, or even liposomal doxorubicin or trabectedin [23–25]. This implies that wild type tumours respond less to conventional chemotherapy and other maintenance strategies when compared to BRCA mutated tumours. In a similar way, wild type tumours can respond to PARPIis, albeit with minor efficacy when compared to BRCA mutated tumours.

To our knowledge, this is the first meta-analysis that incorporates all randomized clinical trials that assessed PARPis as single agents in a maintenance setting in platinum sensitive ROC patients, with particular attention paid to their type of BRCA mutation. When compared to other meta-analyses that address the use of PARPis in OC, this study presents several strength points [26,27]. First, we include the results of ARIEL 3 study, which were not available until the end of 2017 and are thus not included in previous meta-analyses. Additionally, in order to reduce risk of bias, we only included studies where PARPis were administered as an exclusive agent against placebo, at the end of chemotherapy, after patients showed an adequate response to platinum-based treatment. These strict inclusion criteria account for better homogeneity of included studies and powers our results: for instance we excluded studies where the arms of treatment included the combination of a PARPi with chemotherapy [12,26,27].

Finally, this meta-analyses stratified results according to BRCA mutational status; analysing PARPis efficacy while distinguishing in different categories: whole population, BRCA1-2 germline mutated population, BRCA1-2 somatic mutated population, HRD patients and wild type population. This allows to better assess the extent of the efficacy of PARPis throughout different HRD phenotypes.

Inevitably, the major limitation of this meta-analysis relies the difficulty to retrieve all data relating to the risk of bias regarding the NOVA trial, which was considered unclear.

In future investigations, it might be useful to compare the different PARPis in order to distinguish them in terms of efficacy and toxicity, as well as to assess their use as monotherapy. In addition, it might be of particular interest to evaluate the efficacy of PARPis according to HRD status in a maintenance setting, to further explore our findings. Finally, with the introduction of olaparib as a first-line maintenance treatment agent in OC, there is a rising need to consider study designs that anticipate sequential therapeutic strategies with the possible re-use of the same agent, as for instance the OReO trial [28,29].

Author contribution

Federica Tomao and Nicoletta Colombo are responsible for the initial conceptualization of the paper, coordination of the project and resolved disagreement between reviewers. Erlisa Bardhi, Anna Di Pinto and Carolina Maria Sassu are responsible for the search and collection of data. Federica Tomao and Elena Biagioli are responsible for analysis of data. Erlisa Bardhi, Anna Di Pinto, Carolina Maria Sassu, are responsible for writing and editing the manuscript. Maria Cristina Petrella revised the article. Innocenza Palaia, Maria Cristina Petrella, Ludovico Muzii and Pierluigi Benedetti Panici critically reviewed the paper. Pierluigi Benedetti Panici supervised all steps of the preparation of our paper.

Declaration of Competing Interest

None.

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