Efficacy and safety of PARP inhibitors in elderly patients with advanced ovarian cancer: a systematic review and meta-analysis

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2022-003614).

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Received 17 April 2022
Accepted 15 September 2022
Published Online First 13 October 2022

To cite: Maiorano BA, Maiorano MFP, Lorusso D, *et al. Int J Gynecol Cancer* 2022;**32**:1410–1418.

ABTRACT

Background Poly-(ADP-ribose)-polymerase (PARP) inhibitors have shown to be effective as maintenance treatment in patients with advanced ovarian cancer. Although most ovarian cancers develop after age 65, older patients are often under-represented in clinical trials.

Objective To assess the efficacy and safety of PARP inhibitors versus placebo as maintenance therapy in older patients with ovarian cancer.

Methods This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA) guidelines. We searched PubMed, Embase, Cochrane databases, and the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), Society of Gynecologic Oncology (SGO) meeting abstracts, for randomized clinical trials using maintenance with PARP inhibitors in patients with advanced ovarian cancer, up to June 30, 2021. The measured outcomes were progression-free survival and safety (number and grade of adverse events), stratified by age (cut-off point: 65 years).

Results A total of eight phase III trials were selected. Among the 4364 patients, 1435 (32.9%) were aged ≥65 (919 receiving PARP inhibitors, 516 receiving placebo). Compared with placebo, maintenance with PARP inhibitors improved progression-free survival in older patients (HR=0.54; 95% CI 0.45 to 0.65; p<0.00001). No differences were found in progression-free survival in comparison with a younger population (HR=0.47; p=0.13). Only hematologic adverse events were available for the age subgroups, and no differences emerged for all-grade hematologic adverse events (risk ratio (RR)=1.22, p=0.33 for anemia; RR=0.97, p=0.74 for neutropenia) and severe neutropenia (RR=0.97, p=0.86); old women were at lower risk of severe anemia (RR=0.79, p=0.04) but had a higher risk of severe thrombocytopenia (RR=1.27, p=0.01).

Conclusions Maintenance with PARP inhibitors prolongs progression-free survival compared with placebo, both as monotherapy and combined with chemotherapy or bevacizumab, in older patients with advanced ovarian cancer (high-quality evidence). Hematologic safety is similar to that seen in younger patients. No overall survival data are available at this time.

PROSPERO registration number CRD42021261039.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although most ovarian cancers develop after age 65, elderly patients are under-represented in clinical trials. PARP inhibitors are effective in advanced ovarian cancer; however, limited data exist regarding older women.

WHAT THIS STUDY ADDS

⇒ Our systematic review and meta-analysis summarizes the current evidence, demonstrating a comparable efficacy and safety of PARP inhibitors in older women compared with younger women with ovarian cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ PARP inhibitors can be used with efficacy in women aged ≥65 with minimal concerns for hematologic toxicity compared with young patients. Prospective trials including a higher number of elderly patients are warranted, and geriatric assessments should be included in the clinical evaluation of these patients.

INTRODUCTION

Ovarian cancer represents the eighth most common cancer among women. The incidence is approximately 8.1 cases/100 000 inhabitants/year worldwide, reaching its peak among white women.[1 2] As aging itself represents a risk factor for ovarian cancer, up to 60% of diagnoses occur in patients aged 65 and over.[1 3–5] With an aging population, the incidence of ovarian cancer among older adults is expected to rise in the next years.[6] In many reports, older age is associated with more advanced disease and seems to play a prognostic role, as 60–66% of ovarian cancer-related deaths occur in patients aged over 65, and the majority of the studies identified a cut-off point of 65 years to divide younger from older patients.[4–7] More inadequate responses to therapies and less aggressive chemotherapies or surgical procedures, limited by the frailty and the comorbidities of older patients, contribute to the worse outcome in older patients.

Nevertheless, older patients are under-represented in clinical trials in advanced ovarian cancer.[3 6 8]

In the metastatic setting, chemotherapy is considered the best treatment option for ovarian cancer; however, a high relapse rate is usually seen.[9–12] The therapeutic landscape for ovarian cancer has been expanding over the last decade, starting with the approval of new agents, such as bevacizumab or poly-(ADP-ribose)-polymerase (PARP) inhibitors, that demonstrated a progression-free survival advantage if combined with chemotherapy.[13 14] The management of ovarian cancer led to the discovery of the so-called 'synthetic lethality' that has represented one of the significant achievements of modern oncology: in the presence of mutations of genes such as BRCA or the homologous recombination, the DNA lesions caused by the pharmacological inhibition of PARP are not repaired, thus resulting in lethality for the cell.[15] Over half of ovarian carcinomas carry germline or somatic mutations of BRCA1/2 or defects of homologous recombination genes, thus making them sensitive to PARP inhibitors.[15 16] Moreover, among older patients, germline BRCA1 and BRCA2 mutations increase the risk of developing ovarian cancer by 49% and 18%, respectively.[17]

In the metastatic setting, maintenance of PARP inhibitors improved disease-free survival in both newly diagnosed and pretreated patients.[18–28] The majority of the studies considered the two age subgroups of <65 and ≥65 years. However, as women aged 65 and more are under-represented in the clinical trials, there is limited prospective evidence of efficacy and safety in this age group. Therefore, the aim of this systematic review and meta-analysis is to determine if PARP inhibitors, compared with placebo, are effective in patients aged ≥65 years. We were also interested in the safety profile of PARP inhibitors in this population.

METHODS

Search Strategy and Data Extraction

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA) guidelines (Online Supplemental Figure 1).[29] The literature search was carried out in July 2021, using the Medline/PubMed, Embase, and Cochrane databases, without restriction on publication year (Online Supplemental Table 1). An additional search for meeting abstracts from the American Association of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and Society of Gynecologic Oncology (SGO) was performed. We registered the review protocol with PROSPERO (CRD42021261039).

Two reviewers independently evaluated full texts and conference abstracts, and screened citations for eligible studies using a predefined information list. In cases of disagreement, a third reviewer was involved. For each eligible study, the following data were independently extracted: study characteristics (authors' names, year of publication, clinical trial name, phase, design, randomization, blinding), population (setting, sample size, patients' demographics), description of interventions (drug class, name, dosage in the experimental and the control groups), outcomes (progression-free survival stratified by age), and safety (number and grade of adverse events). In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

Study Design

Patients diagnosed with ovarian cancer, both as primary advanced and as recurrent disease, aged over 65 years, were included in our analysis. Treatment with PARP inhibitors, given as monotherapy or combined with chemotherapy and/or anti-angiogenic drugs, was considered the experimental therapy. Placebo (alone or plus chemotherapy and/or anti-angiogenic drugs) was considered the control group.

Progression-free survival was the primary outcome. The results were reported comparing PARP inhibitors with placebo in the elderly cohort (age ≥65) and in young patients (age <65). As overall survival was reported by only one trial, it was not considered an endpoint of this analysis. Safety was explored as the number and grade of available adverse events. All original reports in the English language regarding randomized clinical trials were considered. Among them, studies reporting the subgroup analysis based on patients' age were included. Reviews, commentaries, letters, personal opinions, non-randomized clinical trials, single-arm studies, case reports, studies that did not report the outcome data or the outcome subgroup analysis based on patients' age, were excluded.

The Population, Intervention, Comparison, Outcomes and Study (PICOS) structure for study selection is summarized in Online Supplemental Table 2.

Risk of Bias Assessment

Two reviewers independently assessed the risk of bias. The ROB-2 tool for assessing the risk of bias in randomized trials was used, including random sequence generation, allocation concealment, blinding, missing outcome data, and selective reporting of outcomes.[30]

Data Synthesis and Statistical Analysis

Hazard ratios (HRs) for progression-free survival, alongside their 95% confidence intervals (CIs), were extracted from the studies or calculated. The HRs of progression-free survival between the subgroups of old versus young patients were compared.[31] The generic inverse of variance method was used to calculate pooled HRs through the HR logarithm and SE. For the rate of adverse events, risk ratio (RR) with 95% CIs was calculated for each study comparing old and young patients. The presence of heterogeneity between the studies was assessed through the χ^2 test.[32] Due to the inherent clinical heterogeneity of the data, a random-effects model was used. The assumption of homogeneity was considered invalid in the cases of p value <0.05. Subgroup analyses were conducted to detect the underlying source of heterogeneity between the studies in terms of type of therapies (PARP inhibitors monotherapy vs combination) and disease setting (platinum-sensitive recurrent and primary advanced ovarian cancer). A sensitivity analysis was performed to assess the stability of the global estimate by removing one study at a time, whereas we chose not to assess publication bias as the total number of included studies was <10. The statistical significance was considered for p value <0.05 (with reported two-sided p values).

The RevMan software version 5.4 was used for performing the meta-analysis.

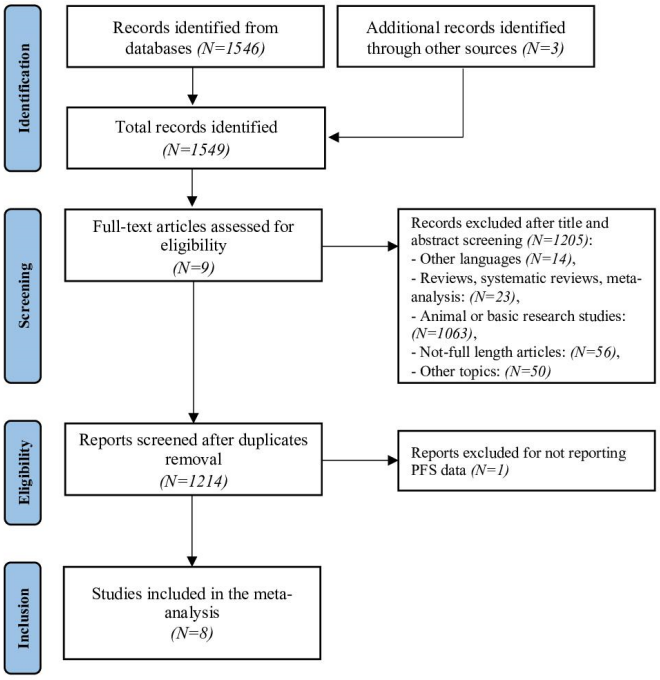

Figure 1 Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA) flow chart of the selection process. PFS, profession-free survival.

Assessment of Evidence Certainty

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used to assess the certainty of the evidence through a non-contextualized approach, including risk of bias, inconsistency of the effect, indirectness, imprecision, and publication bias.[33]

The GRADEpro Guideline Development Tool platform (https://gradepro.org) was used to develop the GRADE summary of findings graphic.

RESULTS

Search Results

The research identified 1549 studies from databases and conference abstracts. After duplicate removal, 1214 manuscripts were screened. Among them, 1205 were excluded for not being English-language, not randomized clinical trials, preclinical papers, or reviews. Another clinical trial was excluded for not reporting the progression-free survival data. At the end of the selection process, eight studies were included in the meta-analysis. The PRISMA flow chart summarizing the selection process is presented in Figure 1.

Study Characteristics

All of the selected studies were phase III, double-blind, randomized clinical trials. In total, four studies were performed in primary advanced ovarian cancer, whereas four other studies were conducted in the platinum-sensitive recurrent setting. All the studies considered the cut-off age of 65 years. A total of 4364 patients were treated in the selected studies, ranging from 265 to 806. Among them, 1435 patients were ≥65 years, representing 32.9% of the population (range 13.8% to 39.4%). All the eligible studies reported progression-free survival stratified by patients' age. For safety, three studies reported partial data in the elderly population regarding only hematologic toxicity.[21 25 27] The main characteristics of the included studies are listed in Table 1. The risk of bias in the selected studies was globally low (Online Supplemental Figure 2).

Efficacy of PARP Inhibitors versus Placebo: Elderly versus Young Patients

The pooled HR showed that, in the elderly population, PARP inhibitors significantly reduced the risk of disease progression compared with placebo (HR=0.54; 95% CI 0.45 to 0.65; p<0.00001; random effects). The heterogeneity among the studies was not significant (p=0.27; I^2=20%). PARP inhibitors, compared with placebo, significantly prolonged progression-free survival also in the younger population (HR=0.43; 95% CI 0.33 to 0.55; p<0.00001; random effects). Significant heterogeneity was observed between studies in this age subgroup (p<0.0001; I^2=82%). When comparing the efficacy of PARP inhibitors between the two subpopulations, no significant difference for progression-free survival was observed (HR=0.47; 95% CI 0.39 to 0.55; p<0.00001; random effects; p=0.13, I^2=56.7% for differences between the subgroups). Significant heterogeneity was retrieved in this analysis (p<0.0001; I^2=71%) (Figure 2).

Subgroup Analyses of Efficacy

We conducted subgroup analyses for efficacy stratified by type of treatment and disease setting. In all subgroups, the ratios of the HRs in older women to the HRs in the younger women indicated comparable benefits from PARP inhibitors for progression-free survival, without significant differences.

The benefits of maintenance of PARP inhibitors as monotherapy were found both among elderly patients (HR=0.47; 95% CI 0.38 to 0.59, p<0.00001; I^2=0%, p=0.80), and younger patients (HR=0.37; 95% CI 0.29 to 0.47, p<0.00001; I^2=70%, p=0.006). No differences were detected between the two subgroups (HR=0.40; 95% CI 0.34 to 0.48; p<0.00001; random effects; p=0.14, I^2=53.2% for subgroups differences), with moderate heterogeneity (p=0.03; I^2=49%). Similarly, when PARP inhibitors were combined with chemotherapy or bevacizumab, the progression-free survival benefit was detected both among the elderly (HR=0.65; 95% CI 0.47 to 0.90, p=0.01; I^2=58%, p=0.12), and young women (HR=0.63; 95% CI 0.53 to 0.74, p<0.00001; I^2=0%, p=0.71). No differences existed comparing the two subpopulations (HR=0.64; 95% CI 0.56 to 0.73, p<0.00001; random effects; p=0.85, I^2=0% for subgroups differences), nor significant heterogeneity (p=0.46; I^2=0%) (Online Supplemental Figures 2 and 3).

The decrease in risk of progression with PARP inhibitors was detected both in the primary advanced and the platinum-sensitive setting, independently of age. In the primary advanced setting, progression-free survival was longer with PARP inhibitors than placebo both among the elderly (HR=0.60; 95% CI 0.48 to 0.74, p<0.00001; I^2=26%, p=0.26) and the younger women (HR=0.54; 95% CI 0.41 to 0.71, p<0.0001; I^2=77%, p=0.004), without differences between the two groups (HR=0.56; 95% CI 0.47 to 0.67, p<0.00001; random effects; p=0.57, I^2=0% for subgroup differences). There was heterogeneity between the subgroups (p=0.01; I^2=61%). Similarly,

Table 1 Characteristics of the included studies

Study (registration number)	Disease setting	Study phase	Experimental arm	Control arm	Total N	≥65 years (%)	Elderly (N)		Young (N)	
							Exp	Ctrl	Exp	Ctrl
ARIEL3 (NCT01968213)	Platinum-sensitive	III	Rucaparib 1200 mg/daily	Placebo/daily	564	37.2	138	72	237	117
VELIA/GOG-3005 (NCT02470585)	Primary advanced	III	Carboplatin AUC 6+paclitaxel 175 mg/mq q3w+veliparib 300 mg/daily or carboplatin AUC 6+paclitaxel 175 mg/mq+veliparib 300 mg → Veliparib 600–800 mg/ daily maintenance	Carboplatin AUC 6+paclitaxel 175 mg/mq q3w+placebo/daily → Placebo/daily maintenance	757	39.1	154	142	228	233
PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016)	Primary advanced	III	Niraparib 200 or 300 mg/daily	Placebo/daily	733	39.4	190	99	297	147
SOLO1 (NCT01844986)	Primary advanced	III	Olaparib 600 mg/daily	Placebo/daily	391	13.8	35	19	225	112
PAOLA-1 (NCT02477644)	Primary advanced	III	Olaparib 600 mg/daily+bevacizumab 15 mg/kg q3w	Placebo/ daily+bevacizumab 15 mg/ kg q3w	806	36.2	205	87	332	182
ENGOT-OV16/NOVA (NCT01847274)	Platinum-sensitive	III	Niraparib 300 mg/daily	Placebo/daily	553	35.3	132	63	240	118
SOLO2/ENGOT-OV21 (NCT01874353)	Platinum-sensitive	III	Olaparib 300 mg/twice day	Placebo/twice day	295	21.0	40	22	156	77
NORA (NCT03705156)	Platinum-sensitive	III	Niraparib 300 mg/daily	Placebo/daily	265	14.0	25	12	152	76

AUC, area under the curve.

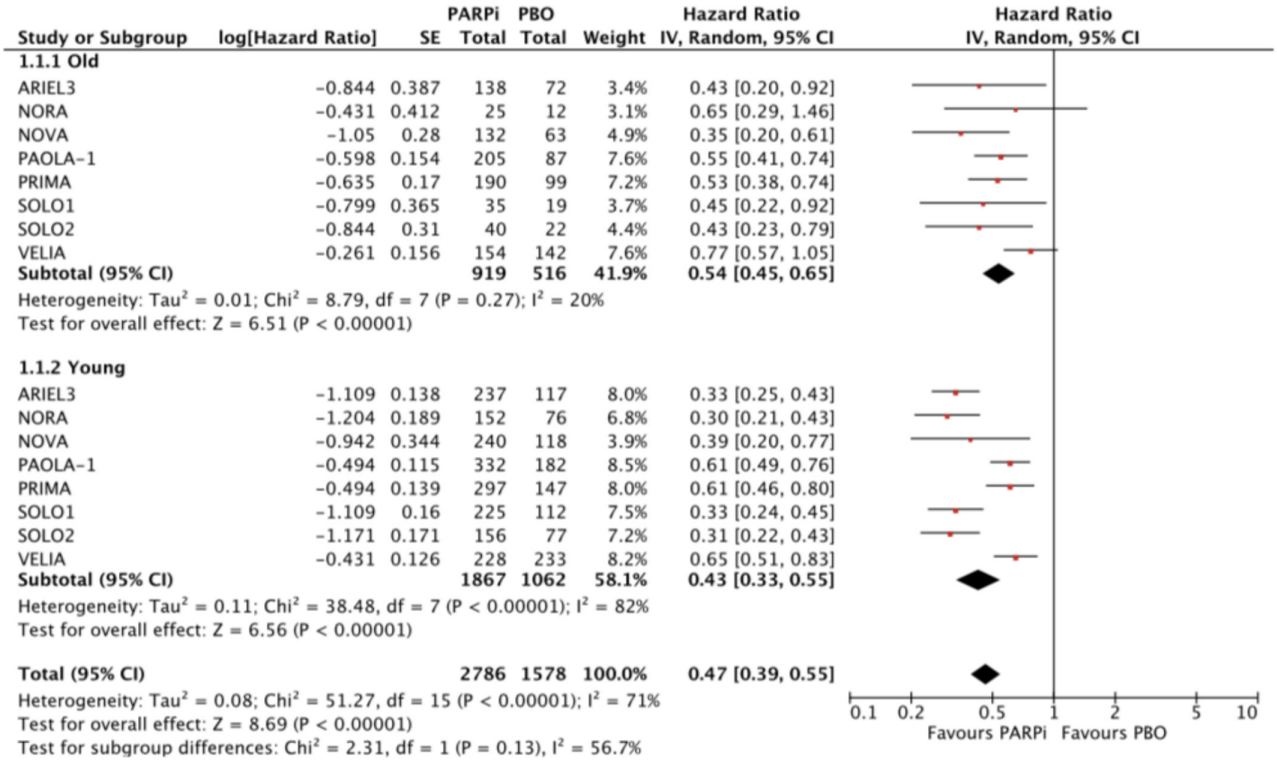

Figure 2 PARP inhibitors versus placebo in old and young patients: progression-free survival. PBO, placebo; PFS, progression-free survival.

the elderly platinum-sensitive patients had progression-free survival benefits with PARP inhibitors (HR=0.43; 95% CI 0.34 to 0.55, p<0.00001; I^2=0%, p=0.67), as well as the young patients (HR=0.32; 95% CI 0.27 to 0.38, p<0.00001; I^2=0%, p=0.91), without differences between the age-based groups (HR=0.36; 95% CI 0.31 to 0.41, p<0.00001; random effects; p=0.06, I^2=72.3% for subgroups differences) and no significant heterogeneity (p=0.58; I^2=0%) (Online Supplemental Figures 4 and 5).

Safety of PARP inhibitors in elderly versus young patients

Hematologic effects were available in only three studies as all-grades anemia and neutropenia in 680 patients, of whom 230 were ≥65 (33.8%) of age. No differences emerged between elderly and young patients in all-grades anemia (RR=1.22; 95% CI 0.82 to 1.83; p=0.33) and neutropenia (RR=0.97; 95% CI 0.78 to 1.19; p=0.74) (Figure 3A and B). Two studies reported the incidence of severe anemia, neutropenia, and thrombocytopenia for 856 patients, of whom 322 were aged ≥65 (37.6%). Older patients were at a lower risk of severe anemia (RR=0.79; 95% CI 0.63 to 0.99; p=0.04). There was no increased risk of severe neutropenia (RR=0.97; 95% CI 0.71 to 1.32; p=0.86). The risk of severe thrombocytopenia was higher among elderly patients (RR=1.27; 95% CI 1.06 to 1.53; p=0.01) (Figure 3C, D and E).

Sensitivity Analysis

We performed a sensitivity analysis to test the single studies' influence on the overall results. The global estimates were not changed after removing every single study at a time (Online Supplemental Figure 6).

DISCUSSION

Summary of Findings

The results of our meta-analysis highlight that PARP inhibitors significantly improve progression-free survival in elderly patients with ovarian cancer. The administration of PARP inhibitors in patients aged ≥65 halves the risk of progression compared with placebo (HR=0.54; 95% CI 0.45 to 0.65, eight studies, 1435 patients), with an absolute effect of disease progressing in 223 fewer people for every 1000 receiving PARP inhibitors (95% CI from 283 to 157 fewer). The quality of the evidence was judged high. Therefore, we are confident that the true effect on progression-free survival lies close to that of the estimated effect on progression-free survival (Figure 4).

Implications for clinical practice and future research

The efficacy of PARP inhibitors in advanced ovarian cancer has been previously demonstrated both for the primary and the recurrent setting.[18–20 22–24 26] However, the typical patients included in the clinical trials differ from those treated in daily clinical practice. The percentage of patients diagnosed with ovarian cancer at ≥65 years of age is high.[1–5] The results of our meta-analysis confirm the efficacy and safety of PARP inhibitors for treating elderly patients, potentially filling the knowledge gap regarding the use of oncologic treatments in the elderly population.

Safety information is limited to hematologic toxicity. Older people seem to have a lower risk of severe anemia (p=0.04). This was an unexpected finding, especially considering the multiple risk factors for anemia in older patients, such as iron deficiency, the development of myelodysplastic syndromes, the reduced production of

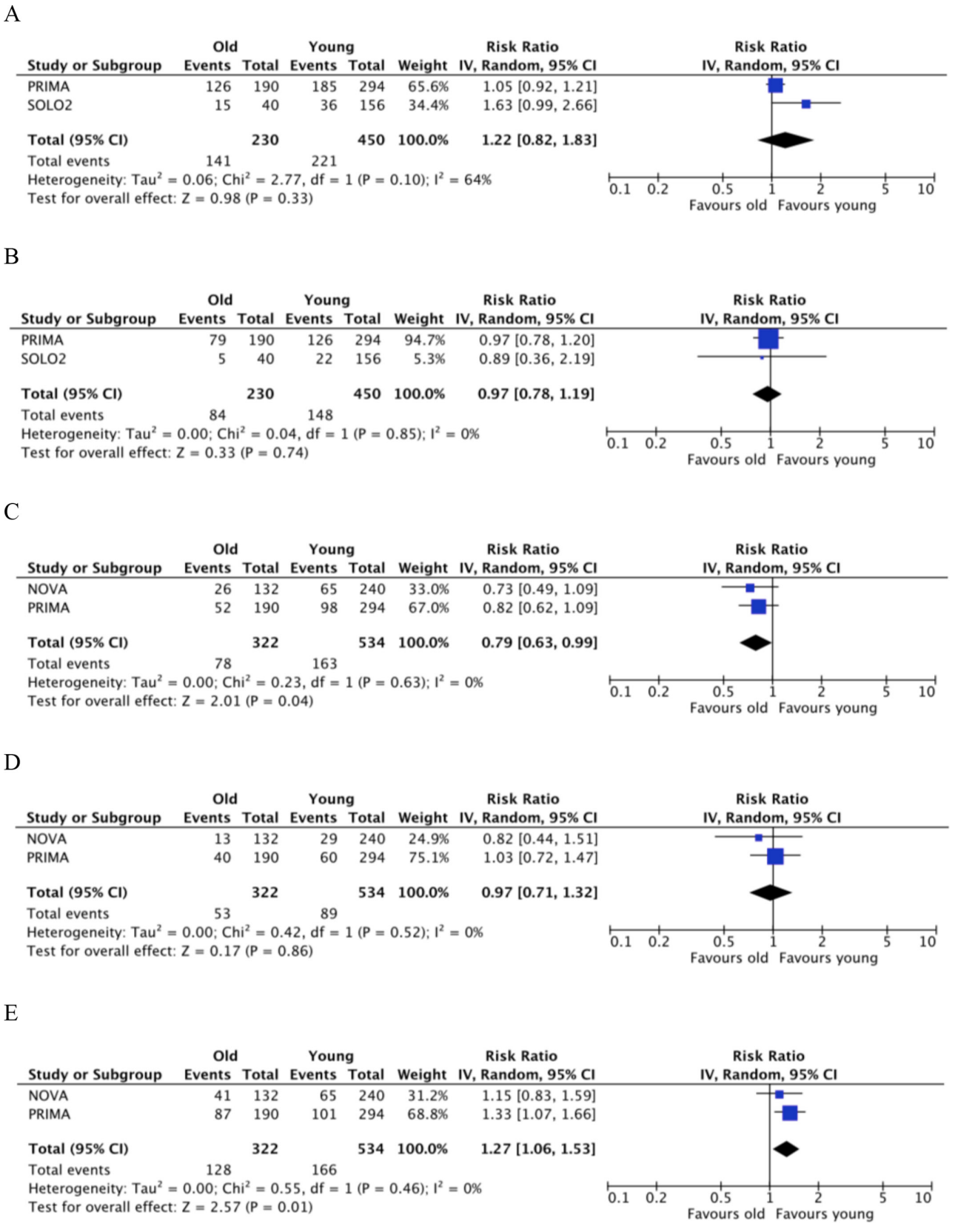

Figure 3 Safety of PARP inhibitors versus placebo in old and young patients: all-grades anemia (A) and neutropenia (B); severe anemia (C), neutropenia (D), thrombocytopenia (E).

erythropoietin, and chronic kidney injury leading to reduced efficacy of erythropoietin.[34] A hypothesis is that these effects could be influenced by age-related chronic inflammation due to the increased levels of circulating levels of pro-inflammatory cytokines, such as interleukin 2/6, interferon-γ, and tumor necrosis factor, that can be reversed by PARP inhibitors.[35]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PARP inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)		
PFS - Old												
8	randomised trials	not serious	not serious	not serious	not serious	none	527/919 (57.3%)	368/516 (71.3%)	**HR 0.54** (0.45 to 0.65)	**223 fewer per 1.000** (from 283 fewer to 157 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL

Figure 4 Summary of findings of the included studies for progression-free survival (PFS) in the old population.

Given the small sample size, further studies are needed to clarify the possible pathogenetic mechanisms. On the other hand, there is an increased risk of severe thrombocytopenia. No substantial differences have emerged between the elderly and the young population regarding non-severe hematologic adverse events and severe neutropenia. These are the first systematic data on this subset of patients. This is a population with multiple comorbidities, complicating treatments and limiting physicians' choices. However, due to an increasingly aging population, developing effective and safe therapies for these patients is crucial. SOLO2 was the only study reporting data about the quality of life and dose modifications during olaparib therapy. There were no significant differences between elderly and young patients regarding dose modification/interruption and quality of life scores.[27] This is in line with retrospective data deriving from an ancillary data analysis of eight prospective trials of patients aged ≥65 years with ovarian cancer treated with olaparib. Among the 398 patients, only 20% were aged ≥65 years. A total of 46.9% of patients younger than 65 required dose reduction compared with 44.7% of patients aged 65–69 years, 47.8% of patients aged 70–74 years, and 64.7% of those aged ≥75 years (p=0.62). Dose interruption occurred in 41.2% of patients younger than 65 years, and 50%, 43.5%, and 64.7% of patients aged 65–69, 70–74, and ≥75 years, respectively (p=0.11). Dose interruptions concerned 42.3% of those younger than 75 years and 64.7% of those aged ≥75 years (p=0.08). Despite the small sample size and not statistically significant differences, we should further investigate the dose attenuation when treating very old patients in prospective studies.[36]

In a sub-analysis of the PAOLA-1 study considering the cut-off age of 70 years, a slight increase of adverse events was reported among patients aged >70 than <70 patients treated with olaparib plus bevacizumab—for example, severe anemia occurred in 21.2% vs 16.5%, severe neutropenia in 9.7% vs 5.1% patients, severe hypertension in 26.9% vs 16.7%, respectively. Quality of life and geriatric assessment data are under evaluation.[37] The age subgroup of patients older than 75 years was explored only by a post hoc exploratory analysis of the ARIEL3 trial. The small subset (n=25) of patients older than 75 years exhibited a non-significant benefit from rucaparib compared with placebo in progression-free survival (9.2 vs 5.5 months; p=0.16), with a similar safety profile in comparison with younger age subgroups. However, in this subgroup of patients, adverse events occurred in 69.9% of cases (vs 54% in the younger group), leading to dose reduction in 70.8% (vs 46.8%) of patients, and treatment discontinuation in 21.2% vs 11.9% of cases.[38]

Strengths and Weaknesses

To the best of our knowledge, this is the first systematic review and meta-analysis examining the efficacy and safety of PARP inhibitors in older patients with ovarian cancer. However, our analysis has several limitations: heterogeneity between the included trials, different PARP inhibitors and schedules in the included studies, lack of overall survival data, limited toxicity evidence, small number of trials with age stratification, and lack of individual patient data. Moreover, the platinum-resistant setting was not considered owing to a lack of age-stratified data at the time of the analysis. Very limited data exist regarding elderly patients; therefore, we could not include them in our meta-analysis. Finally, we have to emphasize that patients included in clinical trials are often selected for good general conditions and performance status 0–1: this could limit the applicability of our results to daily clinical practice, which is characterized by elderly patients with multiple comorbidities and concomitant medications with potential drug interactions. Thus, real-world studies should include a comprehensive geriatric assessment, evaluating functional and nutritional status, comorbidities and concomitant medications, depression and cognition, social activity, and support, to identify frailty risk or geriatric impairments that are not captured during the routine oncologic visit.[39–42]

CONCLUSIONS

Our systematic review and meta-analysis demonstrated that PARP inhibitors effectively treat patients with advanced ovarian cancer older than 65 years. Hematologic toxicity was comparable between elderly and young women. To the best of our knowledge, this is the first meta-analysis performed in this subpopulation, often under-represented in clinical trials but very common in daily practice. A longer follow-up with overall survival data might reaffirm the results of our analysis.

Trials including more substantial numbers of old patients or prospective designs explicitly focusing on this age group are warranted.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Terms for the electronic databases search.

Search date	Search string
31 July 2021 - PubMed	("PARP inhibitor" OR "PARP inhibitors" OR olaparib OR niraparib OR veliparib OR rucaparib OR cediranib) AND ("ovarian cancer" OR "ovarian carcinoma" OR ovar*) Filters: English

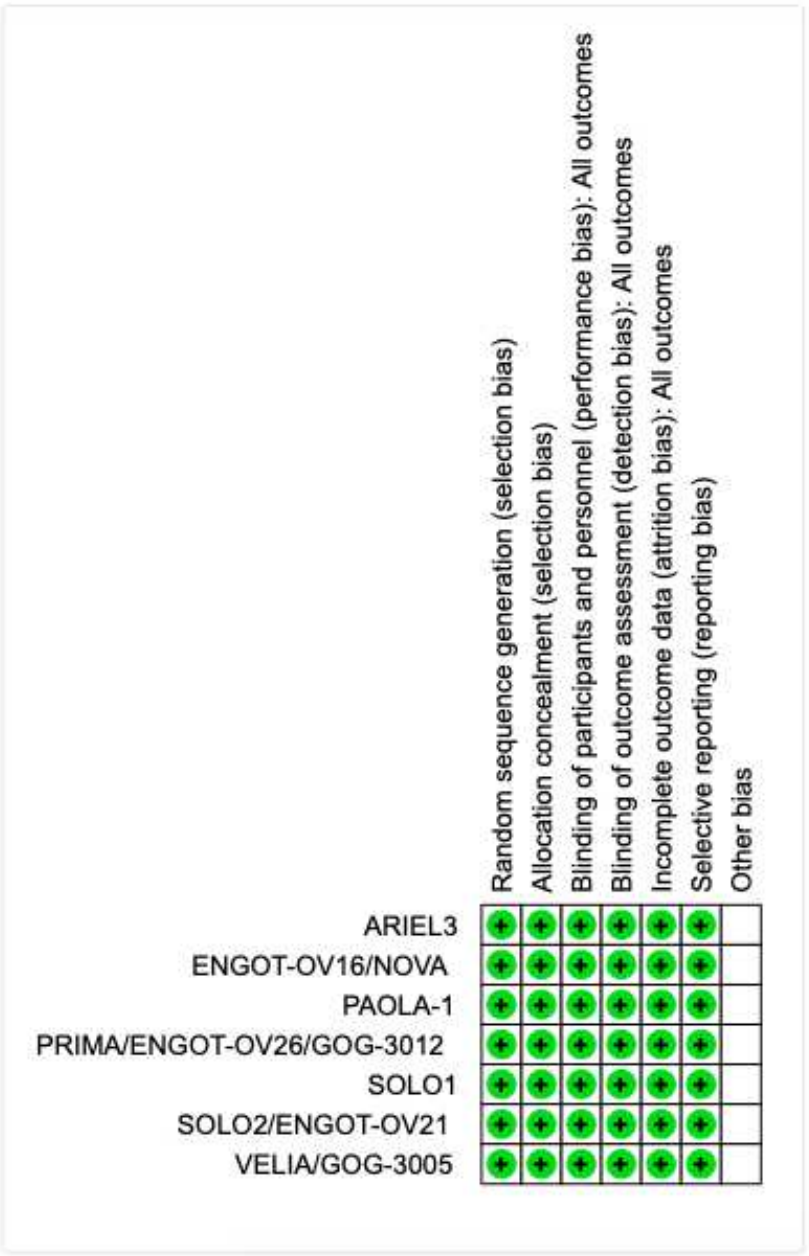
Maiorano BA, *et al. Int J Gynecol Cancer* 2022;0:1–9. doi: 10.1136/ijgc-2022-003614

Supplementary Table 2. PICOS structure for the study selection.

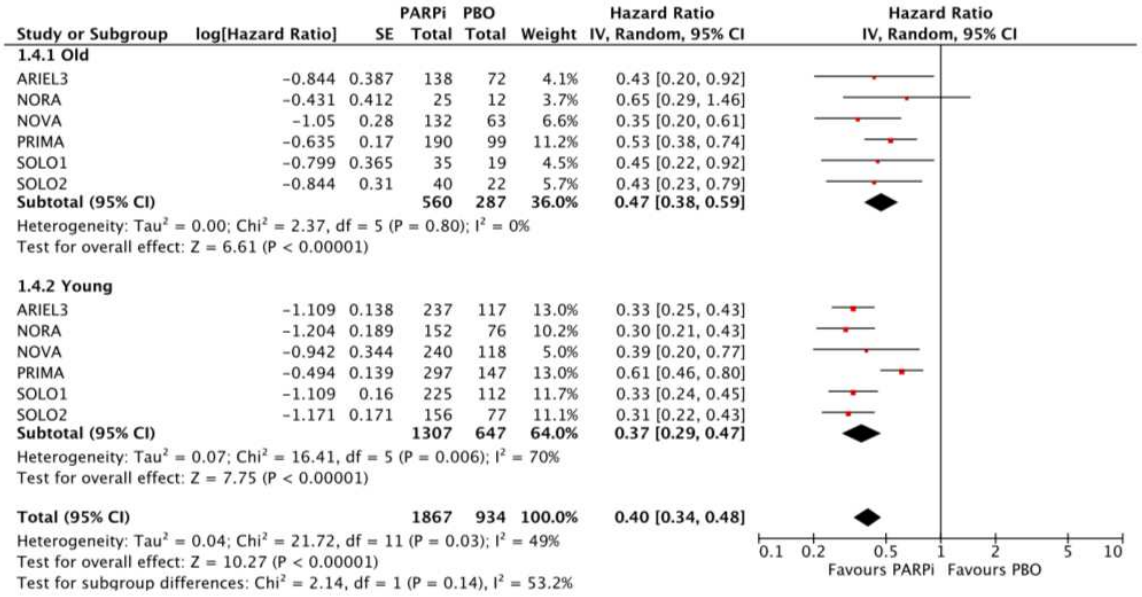
Population	≥65 years-old advanced ovarian cancer patients
Intervention	PARP-inhibitors (monotherapy, plus chemotherapy or bevacizumab)
Control	Non-PARP inhibitors (placebo alone, plus chemotherapy or bevacizumab)
Outcome	HR and 95% CI for progression-free survival, RR for adverse events with information on patients' age (<65 vs. ≥65)
Studies	Randomized clinical trials

CI: confidence interval; HR: hazard ratio; PARP: Poly(ADP-ribose) polymerase-1; RR: risk ratio

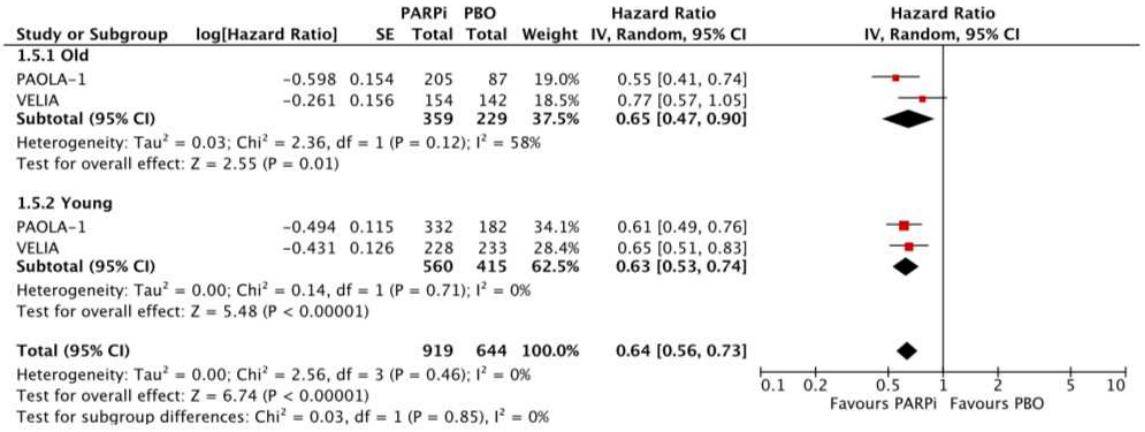
Supplementary Figure 1. Risk of Bias (ROB-2) analysis of the included studies.



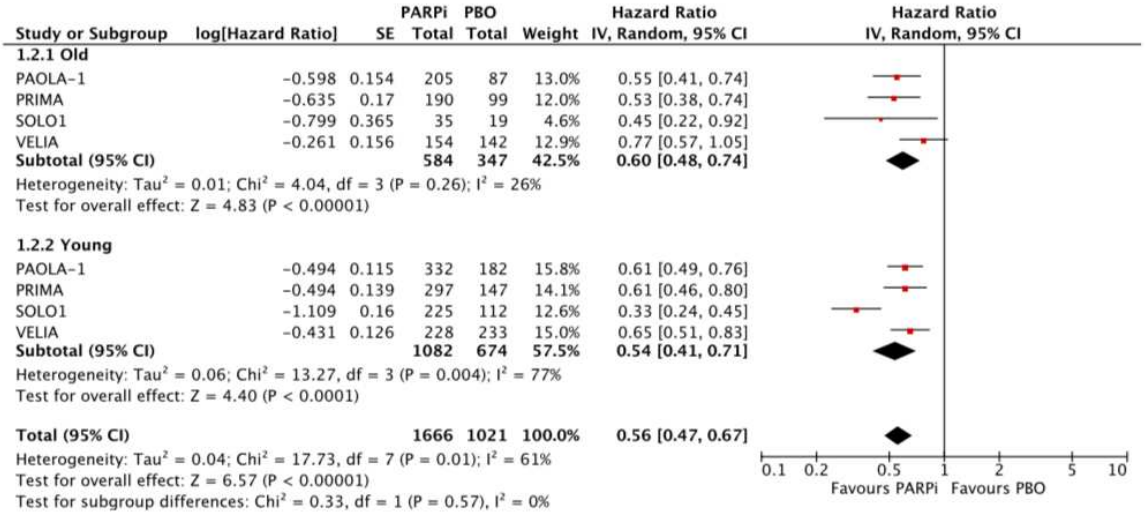
Supplementary Figure 2. Subgroup analysis: Forest plot of HRs in subgroup analysis stratified by type of therapy for progression-free survival in older and younger patients – Monotherapy



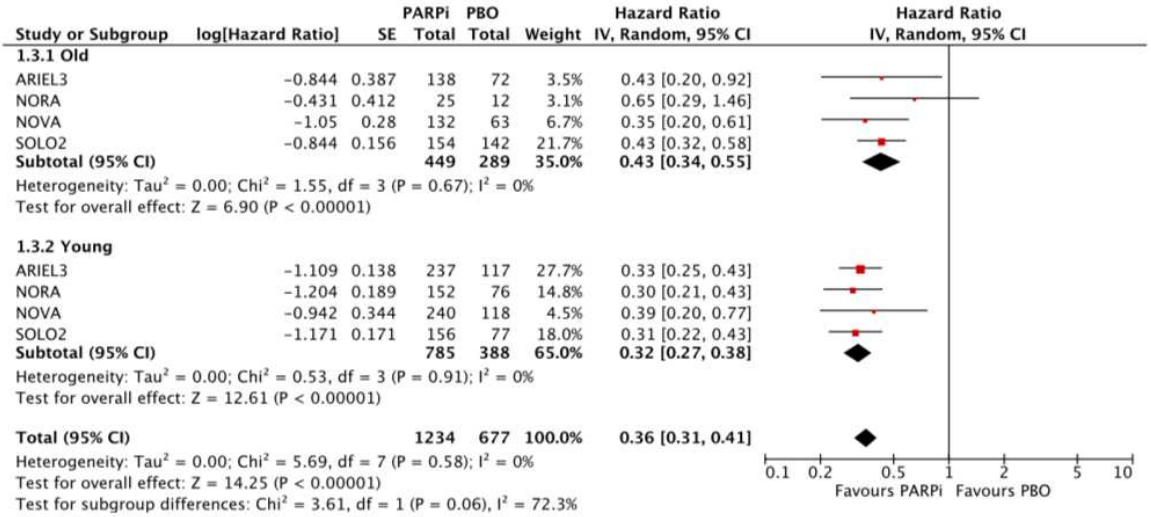
Supplementary Figure 3. Subgroup analysis: Forest plot of HRs in subgroup analysis stratified by type of therapy for progression-free survival in older and younger patients – Combination



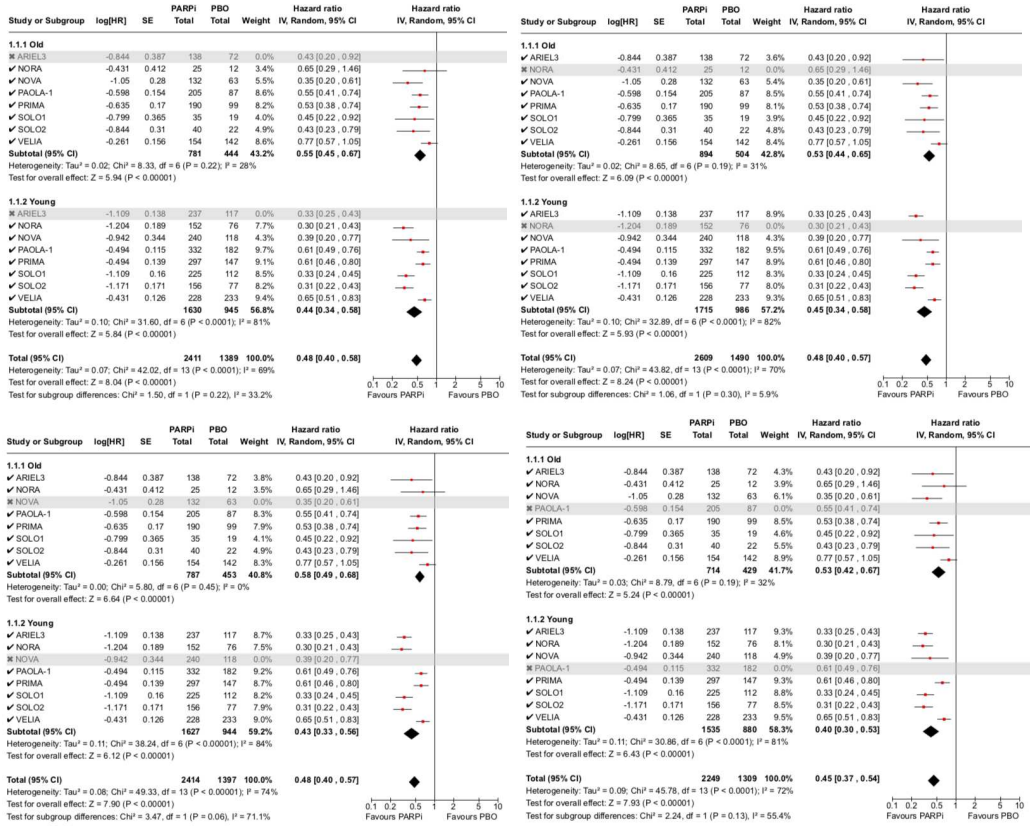
Supplementary Figure 4. Subgroup analysis: Forest plot of HRs in subgroup analysis stratified by disease setting for progression-free survival in older vs. younger – Primary advanced ovarian cancer

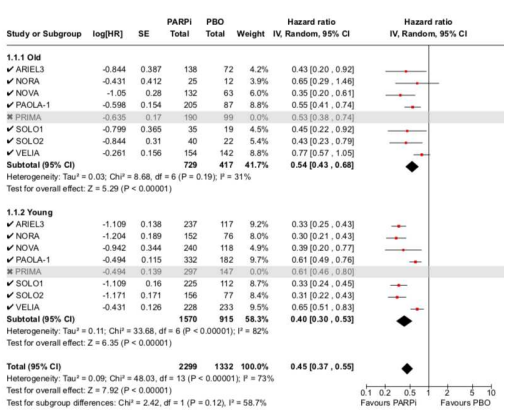


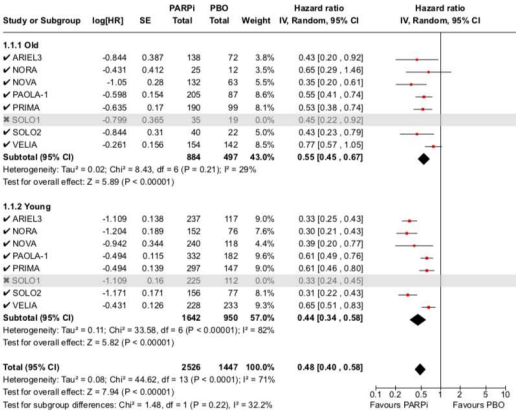
Supplementary Figure 5. Subgroup analysis: Forest plot of HRs in subgroup analysis stratified by disease setting for progression-free survival in older vs. younger – platinum-sensitive recurrent ovarian cancer

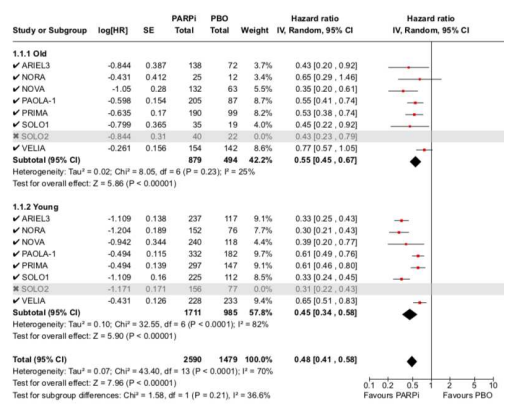


Supplementary Figure 6. Sensitivity analysis for progression-free survival.




Study or Subgroup log[HR] SE PARPi Total PBO Total Weight Hazard ratio IV, Random, 95% CI
1.1.1 Old
✔ ARIEL3 -0.844 0.387 138 72 4.2% 0.43 [0.20 , 0.92]
✔ NORA -0.431 0.412 25 12 3.9% 0.65 [0.29 , 1.46]
✔ NOVA -1.05 0.28 132 63 6.0% 0.35 [0.20 , 0.61]
✔ PAOLA-1 -0.598 0.154 205 87 8.8% 0.55 [0.41 , 0.74]
✖ PRIMA -0.635 0.17 190 99 0.0% 0.53 [0.38 , 0.74]
✔ SOLO1 -0.799 0.365 35 19 4.5% 0.45 [0.22 , 0.92]
✔ SOLO2 -0.844 0.31 40 22 5.4% 0.43 [0.23 , 0.79]
✔ VELIA -0.261 0.156 154 142 8.8% 0.77 [0.57 , 1.05]
Subtotal (95% CI) 729 417 41.7% 0.54 [0.43 , 0.68]
Heterogeneity: Tau² = 0.03; Chi² = 8.68, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 5.29 (P < 0.00001)
1.1.2 Young
✔ ARIEL3 -1.109 0.138 237 117 9.2% 0.33 [0.25 , 0.43]
✔ NORA -1.204 0.189 152 76 8.0% 0.30 [0.21 , 0.43]
✔ NOVA -0.942 0.344 240 118 4.9% 0.39 [0.20 , 0.77]
✔ PAOLA-1 -0.494 0.115 332 182 9.7% 0.61 [0.49 , 0.76]
✖ PRIMA -0.494 0.139 297 147 0.0% 0.61 [0.46 , 0.80]
✔ SOLO1 -1.109 0.16 225 112 8.7% 0.33 [0.24 , 0.45]
✔ SOLO2 -1.171 0.171 156 77 8.4% 0.31 [0.22 , 0.43]
✔ VELIA -0.431 0.126 228 233 9.5% 0.65 [0.51 , 0.83]
Subtotal (95% CI) 1570 915 58.3% 0.40 [0.30 , 0.53]
Heterogeneity: Tau² = 0.11; Chi² = 33.68, df = 6 (P < 0.0001); I² = 82%
Test for overall effect: Z = 6.35 (P < 0.00001)
Total (95% CI) 2299 1332 100.0% 0.45 [0.37 , 0.55]
Heterogeneity: Tau² = 0.09; Chi² = 48.03, df = 13 (P < 0.00001); I² = 73%
Test for overall effect: Z = 7.92 (P < 0.00001)
Test for subgroup differences: Chi² = 2.42, df = 1 (P = 0.12), I² = 58.7%
0.1 0.2 0.5 1 2 5 10
Favours PARPi Favours PBO


Study or Subgroup log[HR] SE PARPi Total PBO Total Weight Hazard ratio IV, Random, 95% CI
1.1.1 Old
✔ ARIEL3 -0.844 0.387 138 72 3.8% 0.43 [0.20 , 0.92]
✔ NORA -0.431 0.412 25 12 3.5% 0.65 [0.29 , 1.46]
✔ NOVA -1.05 0.28 132 63 5.5% 0.35 [0.20 , 0.61]
✔ PAOLA-1 -0.598 0.154 205 87 8.6% 0.55 [0.41 , 0.74]
✔ PRIMA -0.635 0.17 190 99 8.1% 0.53 [0.38 , 0.74]
✖ SOLO1 -0.799 0.365 35 19 0.0% 0.45 [0.22 , 0.92]
✔ SOLO2 -0.844 0.31 40 22 5.0% 0.43 [0.23 , 0.79]
✔ VELIA -0.261 0.156 154 142 8.5% 0.77 [0.57 , 1.05]
Subtotal (95% CI) 884 497 43.0% 0.55 [0.45 , 0.67]
Heterogeneity: Tau² = 0.02; Chi² = 8.43, df = 6 (P = 0.21); I² = 29%
Test for overall effect: Z = 5.89 (P < 0.00001)
1.1.2 Young
✔ ARIEL3 -1.109 0.138 237 117 9.0% 0.33 [0.25 , 0.43]
✔ NORA -1.204 0.189 152 76 7.6% 0.30 [0.21 , 0.43]
✔ NOVA -0.942 0.344 240 118 4.4% 0.39 [0.20 , 0.77]
✔ PAOLA-1 -0.494 0.115 332 182 9.6% 0.61 [0.49 , 0.76]
✔ PRIMA -0.494 0.139 297 147 9.0% 0.61 [0.46 , 0.80]
✖ SOLO1 -1.109 0.16 225 112 0.0% 0.33 [0.24 , 0.45]
✔ SOLO2 -1.171 0.171 156 77 8.1% 0.31 [0.22 , 0.43]
✔ VELIA -0.431 0.126 228 233 9.3% 0.65 [0.51 , 0.83]
Subtotal (95% CI) 1642 950 57.0% 0.44 [0.34 , 0.58]
Heterogeneity: Tau² = 0.11; Chi² = 33.58, df = 6 (P < 0.0001); I² = 82%
Test for overall effect: Z = 5.82 (P < 0.00001)
Total (95% CI) 2526 1447 100.0% 0.48 [0.40 , 0.58]
Heterogeneity: Tau² = 0.08; Chi² = 44.62, df = 13 (P < 0.0001); I² = 71%
Test for overall effect: Z = 7.94 (P < 0.00001)
Test for subgroup differences: Chi² = 1.48, df = 1 (P = 0.22), I² = 32.2%
0.1 0.2 0.5 1 2 5 10
Favours PARPi Favours PBO


Study or Subgroup log[HR] SE PARPi Total PBO Total Weight Hazard ratio IV, Random, 95% CI
1.1.1 Old
✔ ARIEL3 -0.844 0.387 138 72 3.7% 0.43 [0.20 , 0.92]
✔ NORA -0.431 0.412 25 12 3.4% 0.65 [0.29 , 1.46]
✔ NOVA -1.05 0.28 132 63 5.5% 0.35 [0.20 , 0.61]
✔ PAOLA-1 -0.598 0.154 205 87 8.7% 0.55 [0.41 , 0.74]
✔ PRIMA -0.635 0.17 190 99 8.2% 0.53 [0.38 , 0.74]
✔ SOLO1 -0.799 0.365 35 19 4.0% 0.45 [0.22 , 0.92]
✖ SOLO2 -0.844 0.31 40 22 0.0% 0.43 [0.23 , 0.79]
✔ VELIA -0.261 0.156 154 142 8.6% 0.77 [0.57 , 1.05]
Subtotal (95% CI) 879 494 42.2% 0.55 [0.45 , 0.67]
Heterogeneity: Tau² = 0.02; Chi² = 8.05, df = 6 (P = 0.23); I² = 25%
Test for overall effect: Z = 5.86 (P < 0.00001)
1.1.2 Young
✔ ARIEL3 -1.109 0.138 237 117 9.1% 0.33 [0.25 , 0.43]
✔ NORA -1.204 0.189 152 76 7.7% 0.30 [0.21 , 0.43]
✔ NOVA -0.942 0.344 240 118 4.4% 0.39 [0.20 , 0.77]
✔ PAOLA-1 -0.494 0.115 332 182 9.7% 0.61 [0.49 , 0.76]
✔ PRIMA -0.494 0.139 297 147 9.1% 0.61 [0.46 , 0.80]
✔ SOLO1 -1.109 0.16 225 112 8.5% 0.33 [0.24 , 0.45]
✖ SOLO2 -1.171 0.171 156 77 0.0% 0.31 [0.22 , 0.43]
✔ VELIA -0.431 0.126 228 233 9.4% 0.65 [0.51 , 0.83]
Subtotal (95% CI) 1711 985 57.8% 0.45 [0.34 , 0.58]
Heterogeneity: Tau² = 0.10; Chi² = 32.55, df = 6 (P < 0.0001); I² = 82%
Test for overall effect: Z = 5.90 (P < 0.00001)
Total (95% CI) 2590 1479 100.0% 0.48 [0.41 , 0.58]
Heterogeneity: Tau² = 0.07; Chi² = 43.40, df = 13 (P < 0.0001); I² = 70%
Test for overall effect: Z = 7.96 (P < 0.00001)
Test for subgroup differences: Chi² = 1.58, df = 1 (P = 0.21), I² = 36.6%
0.1 0.2 0.5 1 2 5 10
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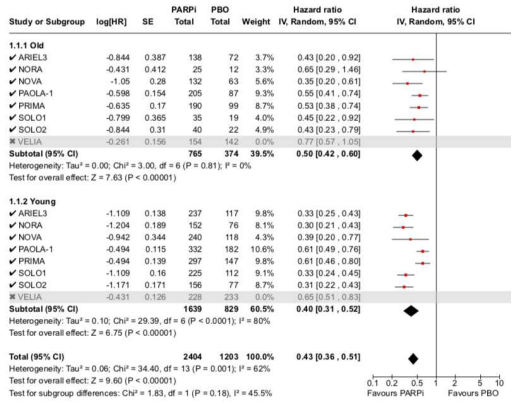
Study or Subgroup log[HR] SE PARPi Total PBO Total Weight Hazard ratio IV, Random, 95% CI
1.1.1 Old
✔ ARIEL3 -0.844 0.387 138 72 3.7% 0.43 [0.20 , 0.92]
✔ NORA -0.431 0.412 25 12 3.3% 0.65 [0.29 , 1.46]
✔ NOVA -1.05 0.28 132 63 5.6% 0.35 [0.20 , 0.61]
✔ PAOLA-1 -0.598 0.154 205 87 9.3% 0.55 [0.41 , 0.74]
✔ PRIMA -0.635 0.17 190 99 8.7% 0.53 [0.38 , 0.74]
✔ SOLO1 -0.799 0.365 35 19 4.0% 0.45 [0.22 , 0.92]
✔ SOLO2 -0.844 0.31 40 22 4.9% 0.43 [0.23 , 0.79]
✖ VELIA -0.261 0.156 154 142 0.0% 0.77 [0.57 , 1.05]
Subtotal (95% CI) 765 374 39.5% 0.50 [0.42 , 0.60]
Heterogeneity: Tau² = 0.00; Chi² = 3.00, df = 6 (P = 0.81); I² = 0%
Test for overall effect: Z = 7.63 (P < 0.00001)
1.1.2 Young
✔ ARIEL3 -1.109 0.138 237 117 9.8% 0.33 [0.25 , 0.43]
✔ NORA -1.204 0.189 152 76 8.1% 0.30 [0.21 , 0.43]
✔ NOVA -0.942 0.344 240 118 4.3% 0.39 [0.20 , 0.77]
✔ PAOLA-1 -0.494 0.115 332 182 10.6% 0.61 [0.49 , 0.76]
✔ PRIMA -0.494 0.139 297 147 9.8% 0.61 [0.46 , 0.80]
✔ SOLO1 -1.109 0.16 225 112 9.1% 0.33 [0.24 , 0.45]
✔ SOLO2 -1.171 0.171 156 77 8.7% 0.31 [0.22 , 0.43]
✖ VELIA -0.431 0.126 228 233 0.0% 0.65 [0.51 , 0.83]
Subtotal (95% CI) 1639 829 60.5% 0.40 [0.31 , 0.52]
Heterogeneity: Tau² = 0.10; Chi² = 29.39, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 6.75 (P < 0.00001)
Total (95% CI) 2404 1203 100.0% 0.43 [0.36 , 0.51]
Heterogeneity: Tau² = 0.06; Chi² = 34.40, df = 13 (P = 0.001); I² = 62%
Test for overall effect: Z = 9.60 (P < 0.00001)
Test for subgroup differences: Chi² = 1.83, df = 1 (P = 0.18), I² = 45.5%
0.1 0.2 0.5 1 2 5 10
Favours PARPi Favours PBO