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

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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 progressionfree 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 \geq 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 vounger 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 cancerrelated 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 \geq 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.

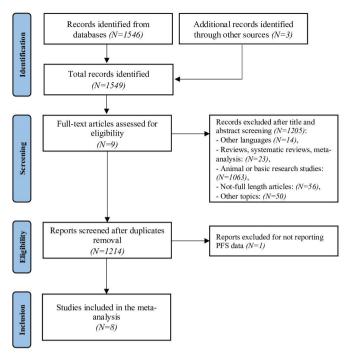


Figure 1 Preferred Reporting Items of Systematic reviews and Meta-Analysis (PRISMA) flow chart of the selection process. PFS, profession-free survival.

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 \geq 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% Cl 0.45 to 0.65; p<0.00001; random effects). The heterogeneity among the studies was not significant (p=0.27; l²=20%). PARP inhibitors, compared with placebo, significantly prolonged progression-free survival also in the younger population (HR=0.43; 95% Cl 0.33 to 0.55; p<0.00001; random effects). Significant heterogeneity was observed between studies in this age subgroup (p<0.0001; l²=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% Cl 0.39 to 0.55; p<0.00001; random effects; p=0.13, l²=56.7% for differences between the subgroups). Significant heterogeneity was retrieved in this analysis (p<0.0001; l²=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; l²=0%, p=0.80), and younger patients (HR=0.37; 95% CI 0.29 to 0.47, p<0.00001; $l^2=70\%$, p=0.006). No differences were detected between the two subgroups (HR=0.40; 95% Cl 0.34 to 0.48; p<0.00001; random effects; p=0.14, l^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; $l^2=58\%$, 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, $l^2=0\%$ for subgroups differences), nor significant heterogeneity (p=0.46; $l^2=0\%$) (Online Supplemental Figures 2 and 3).

The decrease in risk of progression with PARP inhibitors was detected both in the primary advanced and the platinumsensitive 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% Cl 0.48 to 0.74, p<0.00001; l²=26%, p=0.26) and the younger women (HR=0.54; 95% Cl 0.41 to 0.71, p<0.0001; l²=77%, p=0.004), without differences between the two groups (HR=0.56; 95% Cl 0.47 to 0.67, p<0.00001; random effects; p=0.57, l²=0% for subgroup differences). There was heterogeneity between the subgroups (p=0.01; l²=61%). Similarly,

Table 1 Characteri.	Table 1 Characteristics of the included studies	tudies								
Study (registration		Study					Elderly (N)	(N)	Young (N)	(N)
number)	Disease setting	phase	Experimental arm	Control arm	Total N	≥65 years (%)	Exp	Ctrl	Exp	Ctrl
ARIEL3 (NCT01968213)	Platinum-sensitive	≡	Rucaparib 1200 mg/daily	Placebo/daily	564	37.2	138	72	237	117
VELIA/GOG-3005 (NCT02470585)	Primary advanced	≡	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	≡	Niraparib 200 or 300 mg/daily	Placebo/daily	733	39.4	190	66	297	147
SOLO1 (NCT01844986)	Primary advanced	≡	Olaparib 600 mg/daily	Placebo/daily	391	13.8	35	19	225	112
PAOLA-1 (NCT02477644)	Primary advanced	≡	Olaparib 600 mg/daily+bevacizumab 15 mg/kg q3w	Placebo/ daily+bevacizumab 15mg/ kg q3w	806	36.2	205	87	332	182
ENGOT-OV16/NOVA (NCT01847274)	Platinum-sensitive	≡	Niraparib 300 mg/daily	Placebo/daily	553	35.3	132	63	240	118
SOLO2/ENGOT-OV21 Platinum-sensitive (NCT01874353)	Platinum-sensitive	≡	Olaparib 300 mg/twice day	Placebo/twice day	295	21.0	40	22	156	77
NORA (NCT03705156) Platinum-sensitive)) Platinum-sensitive	≡	Niraparib 300 mg/daily	Placebo/daily	265	14.0	25	12	152	76
AUC, area under the curve.	urve.									

			PARPi	PBO		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 Old							
ARIEL3	-0.844	0.387	138	72	3.4%	0.43 [0.20, 0.92]	
NORA	-0.431	0.412	25	12	3.1%	0.65 [0.29, 1.46]	
NOVA	-1.05	0.28	132	63	4.9%	0.35 [0.20, 0.61]	
PAOLA-1	-0.598	0.154	205	87	7.6%	0.55 [0.41, 0.74]	
PRIMA	-0.635	0.17	190	99	7.2%	0.53 [0.38, 0.74]	
SOLO1	-0.799	0.365	35	19	3.7%	0.45 [0.22, 0.92]	
SOLO2	-0.844	0.31	40	22	4.4%	0.43 [0.23, 0.79]	
VELIA	-0.261	0.156	154	142	7.6%	0.77 [0.57, 1.05]	
Subtotal (95% CI)			919	516	41.9%	0.54 [0.45, 0.65]	◆
Heterogeneity: Tau ² =	0.01; Chi ² = 8.79, c	if = 7 (F	P = 0.27	$(); I^2 = 2$	20%		
Test for overall effect:	Z = 6.51 (P < 0.000)	01)					
1.1.2 Young							
ARIEL3	-1.109	0.138	237	117	8.0%	0.33 [0.25, 0.43]	
NORA	-1.204	0.189	152	76	6.8%	0.30 [0.21, 0.43]	
NOVA	-0.942	0.344	240	118	3.9%	0.39 [0.20, 0.77]	
PAOLA-1	-0.494	0.115	332	182	8.5%	0.61 [0.49, 0.76]	
PRIMA	-0.494	0.139	297	147	8.0%	0.61 [0.46, 0.80]	
SOLO1	-1.109	0.16	225	112	7.5%	0.33 [0.24, 0.45]	
SOLO2	-1.171	0.171	156	77	7.2%	0.31 [0.22, 0.43]	
VELIA	-0.431	0.126	228	233	8.2%	0.65 [0.51, 0.83]	
Subtotal (95% CI)			1867	1062	58.1%	0.43 [0.33, 0.55]	◆
Heterogeneity: Tau ² =	0.11; Chi ² = 38.48,	df = 7	(P < 0.0)	0001);	$I^2 = 82\%$		
Test for overall effect:	Z = 6.56 (P < 0.000)	01)					
Total (95% CI)			2786	1578	100.0%	0.47 [0.39, 0.55]	•
Heterogeneity: $Tau^2 =$	0.08: Chi ² = 51.27.	df = 15	(P < 0)	00001	$ ^2 = 71\%$		
Test for overall effect:					,,.		0.1 0.2 0.5 1 2 5 1
Test for subgroup diff		/	(P = 0)	13), I ²	= 56.7%		Favours PARPi Favours PBO

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% Cl 0.34 to 0.55, p<0.00001; l²=0%, p=0.67), as well as the young patients (HR=0.32; 95% Cl 0.27 to 0.38, p<0.00001; l²=0%, p=0.91), without differences between the age-based groups (HR=0.36; 95% Cl 0.31 to 0.41, p<0.00001; random effects; p=0.06, l²=72.3% for subgroups differences) and no significant heterogeneity (p=0.58; l²=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 allgrades anemia and neutropenia in 680 patients, of whom 230 were \geq 65 (33.8%) of age. No differences emerged between elderly and young patients in all-grades anemia (RR=1.22; 95% Cl 0.82 to 1.83; p=0.33) and neutropenia (RR=0.97; 95% Cl 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 \geq 65 (37.6%). Older patients were at a lower risk of severe anemia (RR=0.79; 95% Cl 0.63 to 0.99; p=0.04). There was no increased risk of severe neutropenia (RR=0.97; 95% Cl 0.71 to 1.32; p=0.86). The risk of severe thrombocytopenia was higher among elderly patients (RR=1.27; 95% Cl 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

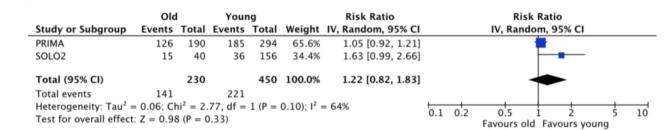
Summary of Findings

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 \geq 65 halves the risk of progression compared with placebo (HR=0.54; 95% Cl 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% Cl 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

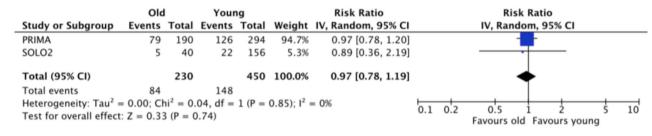
The efficacy of PARP inhibitors in advanced ovarian cancer has been previously demonstrated both for the primary and the recurrent setting.^{18–20,22–24,26} However, the typical patients included in the clinical trials differ from those treated in daily clinical practice. The percentage of patients diagnosed with ovarian cancer at \geq 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



В

А



С

	Old	1	Your	ng		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI		
NOVA	26	132	65	240	33.0%	0.73 [0.49, 1.09]				
PRIMA	52	190	98	294	67.0%	0.82 [0.62, 1.09]				
Total (95% CI)		322		534	100.0%	0.79 [0.63, 0.99]		•		
Total events	78		163							
Heterogeneity: Tau ² = Test for overall effect:				1 (P =	0.63); I ² :	= 0%	0.1 0.2	0.5 1 2	5	10
rescion overall effect.	2 = 2.0	r(r = 0	.04)					Favours old Favours yo	ung	

D

	Old	d	Your	ng		Risk Ratio		Risk Ratio		
Study or Subg	roup Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI		
NOVA	13	132	29	240	24.9%	0.82 [0.44, 1.51]				
PRIMA	40	190	60	294	75.1%	1.03 [0.72, 1.47]				
Total (95% CI))	322		534	100.0%	0.97 [0.71, 1.32]		•		
Total events	53		89							
Heterogeneity:	$Tau^2 = 0.00; C$	$hi^2 = 0.$.42, df =	1 (P =	0.52); I ² :	= 0%	0.1 0.2	0.5 1 2	5 10	1
Test for overal	l effect: $Z = 0.1$	7 (P = 0)	0.86)				0.1 0.2	Favours old Favours you		,

E

	Old	1	Your	ng		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
NOVA	41	132	65	240	31.2%	1.15 [0.83, 1.59]		- + =	
PRIMA	87	190	101	294	68.8%	1.33 [1.07, 1.66]			
Total (95% CI)		322		534	100.0%	1.27 [1.06, 1.53]		◆	
Total events	128		166						
Heterogeneity: Tau ² = Test for overall effect:				1 (P =	0.46); I ² :	= 0%	0.1 0.		10
rescror overall effect.	2 - 2.57	(r = 0)	.01)					Favours old Favours young	

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 asse	ssment			№ of p	atients	E	ifect		
№ of studie s	Study design	Risk of bias	Inconsisten cy	Indirectnes s	Imprecisio n	Other considera tions	PARP inhibitors	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
PFS - O	Dld											
8	randomise d 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)	⊕⊕⊕ ⊕ нісн	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 guality 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 analvsis of eight prospective trials of patients aged \geq 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 \geq 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 \geq 75 years, respectively (p=0.11). Dose interruptions concerned 42.3% of those younger than 75 years and 64.7% of those aged \geq 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 cutoff 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 platinumresistant setting was not considered owing to a lack of agestratified 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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SUPPLEMENTARY MATERIAL

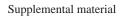
Supplementary Table 1. Terms for the electronic databases search.

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

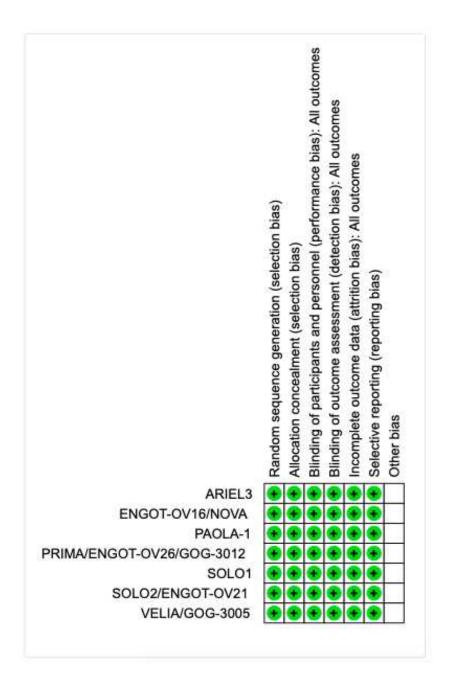
Supplementary Table 2. PICOS structure for the study selection.

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. \geq 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

			PARPi	PBO		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.4.1 Old							
ARIEL3	-0.844	0.387	138	72	4.1%	0.43 [0.20, 0.92]	
NORA	-0.431	0.412	25	12	3.7%	0.65 [0.29, 1.46]	· · · · · · · · · · · · · · · · · · ·
NOVA	-1.05	0.28	132	63	6.6%	0.35 [0.20, 0.61]	
PRIMA	-0.635	0.17	190	99	11.2%	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	5.7%	0.43 [0.23, 0.79]	
Subtotal (95% CI)			560	287	36.0%	0.47 [0.38, 0.59]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 2.37, c	df = 5 (F	P = 0.80	$); ^2 = 0$	0%		
Test for overall effect	: Z = 6.61 (P < 0.000)01)					
1.4.2 Young							
ARIEL3	-1.109	0.138	237	117	13.0%	0.33 [0.25, 0.43]	
NORA	-1.204	0.189	152	76	10.2%	0.30 [0.21, 0.43]	
NOVA	-0.942	0.344	240	118	5.0%	0.39 [0.20, 0.77]	
PRIMA	-0.494	0.139	297	147	13.0%	0.61 [0.46, 0.80]	
SOLO1	-1.109	0.16	225	112	11.7%	0.33 [0.24, 0.45]	
SOLO2	-1.171	0.171	156	77	11.1%	0.31 [0.22, 0.43]	
Subtotal (95% CI)			1307	647	64.0%	0.37 [0.29, 0.47]	•
Heterogeneity: Tau ² =	= 0.07; Chi ² = 16.41,	df = 5	(P = 0.0)	006); I ²	= 70%		
Test for overall effect	Z = 7.75 (P < 0.000)	001)					
Total (95% CI)			1867	934	100.0%	0.40 [0.34, 0.48]	•
Heterogeneity: Tau ² =	= 0.04; Chi ² = 21.72.	df = 11	1 (P = 0)	.03); 12	= 49%		
Test for overall effect							0.1 0.2 0.5 1 2 5
	ferences: $Chi^2 = 2.14$,		S 33 520			Favours PARPi Favours PBO

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

			PARPi	PBO		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.5.1 Old							
PAOLA-1	-0.598	0.154	205	87	19.0%	0.55 [0.41, 0.74]	
VELIA	-0.261	0.156	154	142	18.5%	0.77 [0.57, 1.05]	
Subtotal (95% CI)			359	229	37.5%	0.65 [0.47, 0.90]	•
Heterogeneity: Tau ² =	= 0.03; Chi ² = 2.36, c	df = 1 (F	P = 0.12	(); $ ^2 = 1$	58%		6025-04
Test for overall effect							
1.5.2 Young							
PAOLA-1	-0.494	0.115	332	182	34.1%	0.61 [0.49, 0.76]	
VELIA	-0.431	0.126	228	233	28.4%	0.65 [0.51, 0.83]	
Subtotal (95% CI)			560	415	62.5%	0.63 [0.53, 0.74]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.14, o	if = 1 (F	P = 0.71); $ ^2 = 0$	0%		225
Test for overall effect		120 - 12 - 12 - 12 - 12 - 12 - 12 - 12 -					
Total (95% CI)			919	644	100.0%	0.64 [0.56, 0.73]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 2.56, c	df = 3 (F	P = 0.46	5); $ ^2 = 0$	0%		
Test for overall effect		Constant and the second			703.70		0.1 0.2 0.5 1 2 5 10
Test for subgroup dif			(P = 0)	85) 12	= 0%		Favours PARPi Favours PBO

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

			PARPi	PBO		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.2.1 Old							
PAOLA-1	-0.598	0.154	205	87	13.0%	0.55 [0.41, 0.74]	
PRIMA	-0.635	0.17	190	99	12.0%	0.53 [0.38, 0.74]	
SOLO1	-0.799	0.365	35	19	4.6%	0.45 [0.22, 0.92]	
VELIA Subtotal (95% CI)	-0.261	0.156	154 584	142 347	12.9% 42.5%	0.77 [0.57, 1.05] 0.60 [0.48, 0.74]	•
Heterogeneity: Tau ² =	= 0.01; Chi ² = 4.04, o	f = 3 (F)	P = 0.26	5); $ ^2 = 3$	26%		
Test for overall effect							
1.2.2 Young							
PAOLA-1	-0.494	0.115	332	182	15.8%	0.61 [0.49, 0.76]	-
PRIMA	-0.494	0.139	297	147	14.1%	0.61 [0.46, 0.80]	
SOLO1	-1.109	0.16	225	112	12.6%	0.33 [0.24, 0.45]	
VELIA	-0.431	0.126	228	233	15.0%	0.65 [0.51, 0.83]	
Subtotal (95% CI)			1082	674	57.5%	0.54 [0.41, 0.71]	◆
Heterogeneity: Tau ² =	= 0.06; Chi ² = 13.27,	df = 3	(P = 0.0)	004); 1 ²	= 77%		
Test for overall effect	Z = 4.40 (P < 0.000))1)					
Total (95% CI)			1666	1021	100.0%	0.56 [0.47, 0.67]	•
Heterogeneity: Tau ² =	= 0.04: Chi ² = 17.73.	df = 7	(P = 0.0)	(1): $I^2 =$	61%		
Test for overall effect				100			0.1 0.2 0.5 1 2 5 10
Test for subgroup dif			(P = 0)	57), 12	= 0%		Favours PARPi Favours PBO

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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

			PARPi	PBO		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.3.1 Old							
ARIEL3	-0.844	0.387	138	72	3.5%	0.43 [0.20, 0.92]	
NORA	-0.431	0.412	25	12	3.1%	0.65 [0.29, 1.46]	
NOVA	-1.05	0.28	132	63	6.7%	0.35 [0.20, 0.61]	
SOLO2 Subtotal (95% CI)	-0.844	0.156	154 449	142 289	21.7% 35.0%		
Heterogeneity: Tau ² =	= 0.00; Chi ² = 1.55, c	df = 3 (F	= 0.67	$(); 1^2 = ($	0%		
Test for overall effect							
1.3.2 Young							
ARIEL3	-1.109	0.138	237	117	27.7%	0.33 [0.25, 0.43]	
NORA	-1.204	0.189	152	76	14.8%	0.30 [0.21, 0.43]	
NOVA	-0.942	0.344	240	118	4.5%	0.39 [0.20, 0.77]	· · · · · · · · · · · · · · · · · · ·
SOLO2	-1.171	0.171	156	77	18.0%	0.31 [0.22, 0.43]	—
Subtotal (95% CI)			785	388	65.0%	0.32 [0.27, 0.38]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² $= 0.53$, c	if = 3 (F	= 0.91); $ ^2 = ($	0%		
Test for overall effect	Z = 12.61 (P < 0.00)	001)					
Total (95% CI)			1234	677	100.0%	0.36 [0.31, 0.41]	•
Heterogeneity: Tau ² = Test for overall effect Test for subgroup dif	Z = 14.25 (P < 0.00)	001)					0.1 0.2 0.5 1 2 5 10 Favours PARPi Favours PBO

Supplemental material

Study or Subgroup	log[HR]	SE	PARPi Total	PBO Total	Weight	Hazard ratio IV, Random, 95% Cl	IV, Randor	Iratio n, 95% CI Study or	Subgroup log[HR]	SE	PARPi Total	PBO Total	Weight I	Hazard ratio V, Random, 95% CI	Hazan IV, Rando	
I.1.1 Old								1.1.1 Old								
K ARIEL3	-0.844	0.387	138	72		0.43 [0.20 , 0.92]		✓ ARIEL3		0.387	138	72	3.6%	0.43 [0.20 , 0.92		
NORA	-0.431	0.412	25	12		0.65 [0.29 , 1.46]		# NORA	-0.431	0.412	25	12	0.0%	0.65 [0.29 , 1.46		
NOVA	-1.05	0.28	132	63		0.35 [0.20 , 0.61]		✓ NOVA	-1.05	0.28	132	63	5.4%	0.35 [0.20 , 0.61		
PAOLA-1	-0.598	0.154	205	87		0.55 [0.41, 0.74]		✓ PAOLA		0.154	205	87	8.5%	0.55 [0.41, 0.74		
PRIMA	-0.635	0.17	190	99		0.53 [0.38 , 0.74]		✓ PRIMA	-0.635	0.17	190	99	8.1%	0.53 [0.38 , 0.74		
SOLO1	-0.799	0.365	35	19	4.0%	0.45 [0.22 , 0.92]		✓ SOLO1	-0.799	0.365	35	19	3.9%	0.45 [0.22 , 0.92		
SOLO2	-0.844	0.31	40	22		0.43 [0.23, 0.79]		✓ SOLO2	-0.844	0.31	40	22	4.8%	0.43 [0.23 , 0.79		
VELIA	-0.261	0.156	154	142		0.77 [0.57 , 1.05]	-	✓ VELIA	-0.261	0.156	154	142	8.4%	0.77 [0.57 , 1.05	-	
Subtotal (95% CI)			781	444		0.55 [0.45 , 0.67]	•	Subtotal			894	504	42.8%	0.53 [0.44 , 0.65]	•	
Heterogeneity: Tau ² = Test for overall effect:				.22); P =	28%				eity: Tau ² = 0.02; Chi ² erall effect: Z = 6.09 (F			.19); P = 3	51%			
1.2 Young								1.1.2 You	ng							
ARIEL3	-1.109	0.138	237	117	0.0%	0.33 [0.25 , 0.43]		✓ ARIEL3		0.138	237	117	8.9%	0.33 [0.25 , 0.43		
NORA	-1.204	0.189	152	76	7.7%	0.30 [0.21, 0.43]		× NORA	-1.204	0.189	152	76	0.0%	0.30 [0.21, 0.43		
NOVA	-0.942	0.344	240	118		0.39 [0.20 , 0.77]		✓ NOVA	-0.942	0.344	240	118	4.3%	0.39 [0.20 , 0.77		
PAOLA-1	-0.494	0.115	332	182	9.7%	0.61 [0.49 , 0.76]	-	✓ PAOLA		0.115	332	182	9.5%	0.61 [0.49 , 0.76		
PRIMA	-0.494	0.139	297	147		0.61 [0.46 , 0.80]		✓ PRIMA	-0.494	0.139	297	147	8.9%	0.61 [0.46 , 0.80		
SOLO1	-1.109	0.16	225	112		0.33 [0.24 . 0.45]		✓ SOLO1	-1.109	0.16	225	112	8.3%	0.33 10.24 . 0.45		
SOLO2	-1.171	0.171	156	77		0.31 [0.22 , 0.43]		✓ SOLO2		0.171	156	77	8.0%	0.31 [0.22 , 0.43		
VELIA	-0.431	0.126	228	233		0.65 [0.51, 0.83]		VELIA	-0.431	0.126	228	233	9.3%	0.65 [0.51 , 0.83		
ubtotal (95% CI)	2.401		1630	945		0.44 [0.34 , 0.58]	_	Subtotal		2.1160	1715	986	57.2%	0.45 [0.34 , 0.58]		
eterogeneity: Tau ² = est for overall effect:			= 6 (P <			244 [0.04 ; 0.00]	-	Heterogen	eity: Tau ² = 0.10; Chi ² erall effect: Z = 5.93 (F		f = 6 (P < 0			Ia (a	•	
otal (95% CI) leterogeneity: Tau ² =	0.07: Chi ² =	42.02. df	2411 = 13 (P -		100.0%	0.48 [0.40 , 0.58]	٠	Total (95 Heteroger	6 CI) ieity: Tau ² = 0.07; Chi ² :	= 43.82. c	2609 f = 13 (P <		100.0%	0.48 [0.40 , 0.57]	•	
							alter alter alter	2 5 10 Test for on	erall effect: Z = 8.24 (F	< 0.0000	1)				0.1 0.2 0.5	2
		< 0.00001)													
est for overall effect: est for subgroup diffe				= 0.22), I ^a	= 33.2%		0.1 0.2 0.5 1 Favours PARPi		bgroup differences: Ch	i ² = 1.06,	df = 1 (P =	0.30), l ²	= 5.9%		Favours PARPi	Favou
		¹² = 1.50, c	ff = 1 (P =		= 33.2%	Havard ratio	Favours PARPi	Favours PBO Test for su			PARPI	РВО		Hazard ratio	Haz	ard ratio
est for subgroup diffe		i² = 1.50, c	if = 1 (P =	РВО		Hazard ratio IV, Random, 95% Cl	0.1 0.2 0.5 1 Favours PARPi Hazard IV, Randon	Favours PBO Test for su	ibgroup differences: Ch r Subgroup log[HR]					True or or Totto	Haz	
est for subgroup diffe	rrences: Chi	i² = 1.50, c	if = 1 (P =	РВО			Favours PARPi Hazard	ratio a, 95% CI Study o 1.1.1 Ob	r Subgroup log[HR]	SE	PARPi Total	PBO Total	Weight	IV, Random, 95%	Haz Cl IV, Rand	ard ratio
est for subgroup differences for subgroup differences for subgroup 1.1 Old	rrences: Chi	i² = 1.50, c	if = 1 (P =	РВО			Favours PARPi Hazard	ratio a, 95% CI 1.1.1 Ok ✓ ARIEI	r Subgroup log[HR] d .3 -0.84	SE	PARPi Total	PBO Total	Weight 2 4.3%	IV, Random, 95% 0	Haz 21 IV, Ran 92]	ard ratio
est for subgroup diffe udy or Subgroup 1.1 Old ARIEL3	log[HR]	² = 1.50, c	f = 1 (P = PARPi Total	PBO Total	Weight	IV, Random, 95% Cl	Favours PARPi Hazard	Favours PBO Test for su ratio 1.1.1 00 ✓ ARIEL ✓ NORA	r Subgroup log[HR] 1 .3 -0.84 0.43	SE 4 0.38 1 0.41	PARPi Total 7 138 2 25	PBO Total	Weight 2 4.3% 2 3.9%	U, Random, 95% 0 0.43 (0.20 , 0. 0.65 (0.29 , 1.	Haz 21 IV, Ran 32]	ard ratio
est for subgroup diff udy or Subgroup 1.1 Old ARIEL3 NORA	log[HR]	² = 1.50, c SE 0.387	f = 1 (P = PARPi Total 138	PBO Total	Weight 3.8% 3.5%	0.43 [0.20 , 0.92]	Favours PARPi Hazard	Favours PBO Test for su ratio \$tudy o a, 95% CI 1.1.1 0i / AREI Y NOVA	r Subgroup log[HR] 1 .3 -0.84 0.43 1.0	SE 4 0.38 1 0.41 5 0.2	PARPi Total 7 138 2 25 8 132	PBO Total 3 7: 5 1: 2 6:	Weight 2 4.3% 2 3.9% 3 6.1%	0.43 (0.20 , 0) 0.65 (0.29 , 1) 0.35 (0.20 , 0)	Haz 21 IV, Ran 22] 26] 31]	ard ratio
est for subgroup diff udy or Subgroup 1.1 Old ARIEL3 NORA NOVA	-0.844 -0.431 -1.05	0.387 0.412 0.28	ff = 1 (P = PARPi Total 138 25	PBO Total 72 12 63	Weight 3.8% 3.5% 0.0%	V, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46] 0.35 [0.20 , 0.61]	Favours PARPi Hazard IV, Randon	Favours PBO Test for su ratio \$tudy of 0,95% CI 11.11 Ok / ARIEI Y NOR/ / NOR/ Y NOR/ / NOR/ Y NOR/	r Subgroup log[HR] d .3 -0.84 0.43 1.0 A-1 -0.59	SE 4 0.38 1 0.41 5 0.2 8 0.15	PARPi Total 7 138 2 25 8 133 4 205	PBO Total 3 7: 5 1: 2 6: 5 8:	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0%	IV, Random, 95% (0.43 (0.20, 0.1 0.65 (0.29, 1.4 0.35 (0.20, 0.3 0.55 (0.41, 0.1	Haz 1 IV, Ran 16]	ard ratio
udy or Subgroup diff udy or Subgroup 1.1 Old ARIEL3 NORA NOVA PAOLA-1	-0.844 -0.431	² = 1.50, c SE 0.387 0.412	ff = 1 (P = PARPi Total 138 25 132	PBO Total 72 12	Weight 3.8% 3.5%	0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46]	Favours PARPi Hazard	Favours PBO Test for su ratio \$1,110 b v, 95% CI 1.1.10 b v ARIEI v NOVA v NOVA ¥ PAOL v PRIM v NOVA	r Subgroup log[HR] 1 3 -0.84 -0.43 -1.0 -1.0 -1.0 -1.0 -0.63	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1	PARPi Total 7 138 2 25 8 133 4 205 7 190	PBO Total 3 7: 5 1: 2 6: 5 8: 0 9!	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5%	IV, Random, 95% (0.43 (0.20, 0.5 0.65 (0.29, 1.7 0.35 (0.20, 0.0) 0.55 (0.41, 0. 0.53 (0.38, 0.3)	Haz 21 IV, Rani 22] 46] 31] 74]	ard ratio
tudy or Subgroup diff udy or Subgroup 1.1 Old ARIEL3 NORA NOVA PAOLA-1 PRIMA	-0.844 -0.431 -1.05 -0.598	0.387 0.412 0.28 0.154	rf = 1 (P = PARPi Total 138 25 132 205	PBO Total 72 12 63 87	Weight 3.8% 3.5% 0.0% 8.3%	V, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74]	Favours PARPi Hazard IV, Randon	Favours PBO Test for su ratio Study o 0,95% CI 1.1.1 0 / ARE ARE / NOR NOR / NOR PROL / SOLC Y PRIM	r Subgroup log[HR] 1 3 -0.84 4 -0.43 -1.0 A-1 -0.53 1 -0.79	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36	PARPi Total 7 138 2 25 8 133 4 205 7 190 5 35	PBO Total	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6%	IV, Random, 95% (0.43 (0.20, 0) 0.65 (0.29, 1) 0.35 (0.20, 0) 0.55 (0.41, 0) 0.53 (0.38, 0) 0.45 (0.22, 0)	Haz 1 IV, Rano 16] 11] 14] 12] 14] 14] 14] 14] 14] 14] 14] 14	ard ratio
In the subgroup difference of the subgroup diffe	-0.844 -0.431 -1.05 -0.598 -0.635	0.387 0.412 0.28 0.154 0.17	rf = 1 (P = PARPi Total 138 25 132 205 190	PBO Total 72 12 63 87 99	Weight 3.8% 3.5% 0.0% 8.3% 7.9%	V, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46] 0.35 [0.20 , 0.61] 0.55 [0.41 , 0.74] 0.53 [0.38 , 0.74] 0.45 [0.22 , 0.92]	Favours PARPi Hazard IV, Randon	Favours PBO Test for su ratio \$1.10 study of \$4,875 study of \$4,8	r Subgroup log[HR] 1 3 - 0.84 - 0.43 - 1.0 A-1 - 0.59 A - 0.63 1 - 0.79 2 - 0.84	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3	PARPi Total 7 138 2 25 8 133 4 205 7 190 5 35 1 40	PBO Total	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5%	IV, Random, 95% (0.43 (0.20, 0.1 0.65 (0.29, 1) 0.55 (0.41, 0) 0.55 (0.41, 0) 0.53 (0.38, 0) 0.43 (0.22, 0) 0.43 (0.23, 0)	Haz 1 IV, Rand 10 10 10 11 14 14 14 14 14 14 14 14 14	ard ratio
tudy or Subgroup diff tudy or Subgroup 1.1 Old ARIEL3 NORA NOVA PAOLA-1 PRIMA SOLO1 SOLO2	-0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365	PARPi Total 138 25 132 205 190 35 40	PBO Total 72 12 63 87 99 19 22	Weight 3.8% 3.5% 0.0% 8.3% 7.9% 4.1%	V, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.63 [0.38, 0.74] 0.45 [0.22, 0.92] 0.43 [0.22, 0.79]	Favours PARPi Hazard IV, Randon	Favours PBO Test for su ratio Study o \ 95% CI 1.1.1 00 \ 95% CI NOVR - NOVR - NOVR > SOLC SOLC > SOLC SOLC > SOLC > SOLC	r Subgroup log[HR] 1 3 -0.84 4 -0.43 4 -1.0 4 -1.0.59 A -0.63 11 -0.79 12 -0.84 4 -0.26	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3	PARPi Total 7 138 2 25 8 133 4 200 7 190 5 35 1 40 6 154	PBO Total 3 7: 5 11 2 6: 5 8: 0 9! 5 11 0 2: 4 14	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5% 2 8.9%	IV, Random, 95% (0.43 (0.20, 0.9 0.65 (0.29, 1) 0.35 (0.20, 0) 0.55 (0.41, 0) 0.55 (0.41, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.77 (0.57, 1)	Haz 1 IV, Ran 16] 16] 11] 11] 12] 12] 12] 13] 14] 14] 14] 15] 16] 17] 17] 18] 19] 19] 19] 19] 19] 19] 19] 19	ard ratio
ast for subgroup diff addy or Subgroup 1.1 Old ARIEL3 NOPA PAOLA-1 PRIMA SOL01 SOL02 VELIA	-0.844 -0.431 -1.05 -0.598 -0.635 -0.799	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.31	rf = 1 (P = PARPi Total 138 25 132 205 190 35 40 154	PBO Total 72 12 63 87 99 19 22 142	Weight 3.8% 3.5% 0.0% 8.3% 7.9% 4.1% 4.9% 8.3%	V, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46] 0.55 [0.20 , 0.61] 0.55 [0.41 , 0.74] 0.63 [0.38 , 0.74] 0.45 [0.22 , 0.92] 0.43 [0.23 , 0.79] 0.77 [0.57 , 1.05]	Favours PARPi Hazard IV, Randon	Favours PBO Test for su ratio Study o \ 95% CI 1.1.1 00 \ 95% CI NOVR - NOVR - NOVR > SOLC SOLC > SOLC SOLC > SOLC > SOLC	r Subgroup log[HR] 1 3 - 0.84 - 0.43 - 1.0 A-1 - 0.59 A - 0.63 1 - 0.79 2 - 0.84	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3	PARPi Total 7 138 2 25 8 133 4 205 7 190 5 35 1 40	PBO Total 3 7: 5 11 2 6: 5 8: 0 9! 5 11 0 2: 4 14	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5% 2 8.9%	IV, Random, 95% (0.43 (0.20, 0.9 0.65 (0.29, 1) 0.35 (0.20, 0) 0.55 (0.41, 0) 0.55 (0.41, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.77 (0.57, 1)	Haz 1 IV, Ran 16] 16] 11] 11] 12] 12] 12] 13] 14] 14] 14] 15] 16] 17] 17] 18] 19] 19] 19] 19] 19] 19] 19] 19	ard ratio
est for subgroup diffe	-0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² =	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 5.80, df =	PARPi Total 138 25 132 205 190 35 40 154 787 6 (P = 0.	PBO Total 72 12 63 87 99 19 22 142 453	Weight 3.8% 3.5% 0.0% 8.3% 4.1% 4.9% 8.3% 40.8%	V, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.63 [0.38, 0.74] 0.45 [0.22, 0.92] 0.43 [0.22, 0.79]	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio \$1.00 \$95% CI 1.11 Ol - >NOR - >NOR - >NOR - >SOLC - >SOLC - >SOLC - >SOLC - >SUL - >SOLC - >SUL - >SUL	r Subgroup log[HR] 4 3 -0.84 4 -0.43 4 -1.0 4 -1.0.59 A -0.63 11 -0.79 12 -0.84 4 -0.26	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 * = 8.79, *	PARPi Total 7 138 2 25 8 133 4 200 7 190 5 36 1 40 6 155 3 40 6 155 3 40 7 140 6 156	PBO Total 3 7: 5 11 2 6: 5 8: 0 9! 5 11 0 2: 4 142 4 42!	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5% 2 8.9% 9 41.7%	IV, Random, 95% (0.43 (0.20, 0.9 0.65 (0.29, 1) 0.35 (0.20, 0) 0.55 (0.41, 0) 0.55 (0.41, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.77 (0.57, 1)	Haz 1 IV, Ran 16] 16] 11] 11] 12] 12] 12] 13] 14] 14] 14] 15] 16] 17] 17] 18] 19] 19] 19] 19] 19] 19] 19] 19	ard ratio
In subgroup diff udy or Subgroup I.1 Old ARIEL3 NOVA NOVA NOVA NOVA SOL01 SOL01 SOL02 VELIA biotal (95% CI) terogeneity: Tau ⁹ = st for overail effect:	-0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² =	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 5.80, df =	PARPi Total 138 25 132 205 190 35 40 154 787 6 (P = 0.	PBO Total 72 12 63 87 99 19 22 142 453	Weight 3.8% 3.5% 0.0% 8.3% 4.1% 4.9% 8.3% 40.8%	V, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46] 0.55 [0.20 , 0.61] 0.55 [0.41 , 0.74] 0.63 [0.38 , 0.74] 0.45 [0.22 , 0.92] 0.43 [0.23 , 0.79] 0.77 [0.57 , 1.05]	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio \$85% CI \$85% CI 1.1.1 OI - > NOR - > NOR - > SOL	r Subgroup log[HR] 4 3 - 0.84 4 - 0.43 4 - 0.65 4 - 0.65 4 - 0.65 4 - 0.65 4 - 0.55 4	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 * = 8.79, P < 0.000	PARPi Total 7 138 2 25 8 132 4 200 7 190 5 36 1 44 6 154 714 # = 6 (P = 201)	PBO Total 3 77 5 11 2 63 5 88 0 99 5 11 0 22 4 14 4 429 4 429 4 429 4 0.19); P =	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5% 2 8.9% 9 41.7% = 32%	IV, Random, 95% (0.43 (0.20, 0) 0.65 (0.29, 1) 0.35 (0.41, 0) 0.55 (0.41, 0) 0.45 (0.22, 0)	Haz 1 IV, Ranu 166 11 147 141 141 141 141 141 141	ard ratio
tor subgroup diff addy or Subgroup 1.1 Old ARIEL3 NOVA PRIMA SOLO1 SOLO2 VELIA SOLO2 VELIA SOLO2 VELIA SOLO2 VELIA SOLO2 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO1 SOLO2 VELIA SOLO3	-0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² =	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 5.80, df =	PARPi Total 138 25 132 205 190 35 40 154 787 6 (P = 0.	PBO Total 72 12 63 87 99 19 22 142 453	Weight 3.8% 3.5% 0.0% 8.3% 7.9% 4.1% 4.9% 8.3% 40.8% 0%	V, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46] 0.55 [0.20 , 0.61] 0.55 [0.41 , 0.74] 0.63 [0.38 , 0.74] 0.45 [0.22 , 0.92] 0.43 [0.23 , 0.79] 0.77 [0.57 , 1.05]	Favours PARPi Hazard IV, Randon	Favours PBO Test for at ratio \$55% CI Study o \$55% CI 1.1.1 00 \$700 K PACC \$700 K PACC \$70	r Subgroup log[HR] 4 3 0.44 4 0.43 4 0.43 1 0.58 1 0.78 2 0.68 4 0.28 1 0.78 1 0.78	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 * = 8.79, P < 0.00 9 0.13	PARPi Total 7 138 2 2 25 8 133 4 200 7 199 5 36 1 44 6 154 7 14 6 154 7 14 1 44 6 154 7 199 8 233	PBO Total 3 7: 5 11 2 6: 5 11 5 11 5 11 5 11 0 22 4 142 4 142 4 142 4 142 5 0.19); P =	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5% 2 5.5% 2 8.9% 9 41.7% 32% 7 9.3%	IV, Random, 35% (0.43 (0.20, 0.0 0.66 (0.29, 1. 0.35 (0.20, 0. 0.55 (0.41, 0. 0.55 (0.38, 0. 0.45 (0.22, 0.) 0.45 (0.22, 0. 0.43 (0.22, 0. 0.33 (0.25, 0.)	Haz 1 IV, Rand 12] 14] 14] 15] 15] 16] 17] 17] 13]	ard ratio
In subgroup diff udy or Subgroup I.1 Old ARIEL3 NOVA PACLA-1 PRIMA SOLO1 SOLO1 SOLO2 VELIA bitotal (95% CI) terogeneity: Tau ⁺ = t for overall effect: 1.2 Young ARIEL3	Iog[HR] -0.844 -0.431 -1.05 -0.535 -0.799 -0.844 -0.261 0.00; Chi² = Z Z = 6.64 (P	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.154 0.156 0.31 0.156 5.80, df = < 0.00001	PARPi Total 138 25 132 205 190 35 40 154 787 6 (P = 0.)	PBO Total 72 12 63 87 99 19 22 142 453 45); P =	Weight 3.8% 3.5% 0.0% 8.3% 7.9% 4.1% 4.9% 8.3% 40.8% 0%	V, Random, 95% Cl 0.43 (0.20, 0.92) 0.65 [0.29, 1.46] 0.35 (0.20, 0.61] 0.53 (0.38, 0.74) 0.53 (0.38, 0.74) 0.43 [0.22, 0.92] 0.43 (0.23, 0.79] 0.77 [0.57, 1.05] 0.58 [0.49, 0.68]	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio 1.1.1 O v 95% CI 1.1.1 O V ARE NORV V NORV Y NORV V SOLC SOLC V SOL Y SOL V SOL Y NORV	r Subgroup log[HR] d 30.84 -0.43 -0.44 -0.44 -0.44 -0.44 -0.45 -0.44 -0.45 -0.44 -0.45 -0.44 -0.45 -0.4	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 * = 8.79, • P < 0.00 9 0.13 4 0.18	PARPi Total 7 138 2 25 8 133 4 200 7 199 5 35 1 40 6 154 714 ff = 6 (P = 201) 8 233 9 155	PBO Total 3 7: 5 1: 2 6: 5 8: 0 99 5 1! 0 2: 4 14: 4 42! 0.19); P = 7 11: 2 7!	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 4.6% 2 5.5% 2 8.9% 9 41.7% = 32% 7 9.3% 6 8.1%	IV, Random, 95% (0.43 (0.20, 0) 0.65 (0.29, 1) 0.35 (0.20, 0) 0.55 (0.41, 0) 0.55 (0.41, 0) 0.45 (0.22, 0) 0.45 (0.23, 0) 0.45 (0.23, 0) 0.45 (0.23, 0) 0.53 (0.42, 0) 0.55 (0.41, 0) 0.55 (0.42, 0) 0.55 (0.41,	Haz 1 IV, Ran 12] 14] 14] 15] 17] 15] 16] 17] 16] 17] 16] 17] 16] 17] 16] 17] 17] 18] 19] 19] 19] 19] 19] 19] 19] 19	ard ratio
Int for subgroup diff udy or Subgroup Int Old ARREL3 NOVA NOVA PRIMA SOLO1 SOLO2 VELIA bitotal (95% C) detostal (95% C) detostal (95% C) ARREL3 NOPA ARREL3 NOPA	Iog[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² = Z = 6.64 (P -1.109	0.387 0.412 0.387 0.412 0.154 0.154 0.154 0.17 0.365 0.315 5.80, df = < 0.0001 0.138 0.189	PARPi Total 138 25 132 205 190 35 40 154 787 6 (P = 0.) 237	PBO Total 72 12 63 87 99 19 22 142 453 45); P =	Weight 1 3.8% 3.5% 0.0% 8.3% 4.1% 4.9% 8.3% 40.8% 0%	V, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.53 [0.38, 0.74] 0.43 [0.22, 0.92] 0.77 [0.57, 1.05] 0.58 [0.49, 0.68] 0.33 [0.25, 0.43]	Favours PARPi Hazard IV, Randon	Favours PBO Test for at ratio 55% Cl Study o . 1.1.1 Ok . 26% . 1.1.1 Ok . 26% . 1.1.1 Ok . 26% . 2000 . 200	r Subgroup log[HR] d 30.84 -0.63 -0.44 -0.43 -0.44 -0.43 -0.44 -0.43 -0.44 -0.4	SE 4 0.38 1 0.41 5 0.28 8 0.18 5 0.19 9 0.36 4 0.3 1 0.15 8 = 8.79, (P < 0.00) 9 0.13 4 0.18 2 0.34	PARPi Total 7 138 2 2 22 2 25 3 32 4 200 7 190 5 33 1 40 6 155 7 190 5 35 1 40 6 155 7 190 5 35 1 40 6 155 7 190 5 35 1 40 6 155 7 190 5 35 1 40 6 15 7 190 5 35 1 40 1 40 1 40 1 40 1 40 1 40 1 40 1 40	PBO Total 3 7: 5 12 2 6: 5 8: 0 9: 5 11 2 2: 4 14: 4 42: 0.19); P = 7 11: 2 7? 0 11:	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 8.9% 9 41.7% = 32% 7 9.3% 6 8.1% 8 4.9%	IV, Random, 85% (0.43 (0.20, 0) 0.65 (0.29, 1) 0.35 (0.20, 0) 0.55 (0.41, 0) 0.53 (0.32, 0) 0.43 (0.23, 0) 0.43 (0.23, 0) 0.43 (0.23, 0) 0.53 (0.42, 0) 0.53 (0.42, 0) 0.33 (0.25, 0) 0.33 (0.25, 0) 0.39 (0.20, 0)	Haz 1 IV, Ran 12] 14] 15] 15] 15] 15] 16] 17] 16] 17] 16] 17] 17] 17] 18] 18] 19] 19] 19] 19] 19] 19] 19] 19	ard ratio
In the subgroup difference of the subgroup difference of the subgroup of the s	-0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² = Z = 6.64 (P -1.109 -1.204	P = 1.50, c SE 0.387 0.412 0.28 0.1412 0.28 0.17 0.365 0.31 0.156 5.80, df = < 0.00001 0.138	PARPi Total 138 25 132 205 190 35 40 154 787 6 (P = 0.) 237 152	PBO Total 72 12 63 87 99 19 22 142 453 455): P = 117 76	Weight 1 3.8% 3.5% 0.0% 8.3% 4.1% 4.9% 8.3% 40.8% 0%	V, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74] 0.45 [0.22, 0.92] 0.45 [0.22, 0.92] 0.45 [0.29, 0.710] 0.58 [0.49, 0.68] 0.33 [0.25, 0.43] 0.30 [0.21, 0.43]	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio 1.1.1 Q v 95% CI 1.1.1 Q - > NORU - > NORU - > SOLC - > NORU - > NORU - > NORU - > NORU	r Subgroup log[HR] d 3 − 0.84 4 − 0.43 4 − 0.43 4 − 0.43 1 − 0.55 1	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 ^a = 8.79, 4 P < 0.00 9 0.13 4 0.18 2 0.34 4 0.11	PARPi Total 7 138 2 25 8 133 4 200 7 190 5 33 1 40 6 156 714 ff = 6 (P = 201) 8 231 9 155 4 244 5 335	PBO Total 3 7: 5 1: 2 6: 5 8: 0 99 5 11 0 2: 4 144 4 429 0.19); P = 7 11: 2 7: 0 111 2 7: 0 111 2 18:	Weight 2 4.3% 2 3.9% 3 6.1% 9 8.5% 9 4.6% 2 5.5% 2 8.9% 9 41.7% 9 41.7% 7 9.3% 6 8.1% 8 4.9% 2 0.0%	IV, Random, 95% 4 0.43 (0.20, 0.0 0.65 (0.29, 1, 0.35 (0.20, 0.0 0.45 (0.22, 0.0 0.45 (0.22, 0.0 0.43 (0.22, 0.0 0.43 (0.22, 0.0 0.77 (0.57, 1) 0.53 (0.42, 0.0 0.33 (0.25, 0.0 0.33 (0.25, 0.0 0.38 (0.21, 0.0 0.38 (0.21, 0.0 0.38 (0.21, 0.0 0.38 (0.20, 0.0) 0.61 (0.49, 0.0)	Haz 21 IV, Ran 22] 46] 47] 474 474 474 474 474 474 47	ard ratio
udy or Subgroup diff udy or Subgroup 1.1 Old ARREL3 NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA NOVA	-0.844 -0.431 -1.05 -0.598 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² = Z = 6.64 (P -1.109 -1.204 -0.942 -0.494	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 5.80, df = < 0.00001 0.138 0.189 0.344 0.115	ff = 1 (P = PARPi Total 138 25 132 205 190 35 40 154 787 6 (P = 0.) 237 1520 332	PBO Total 72 12 63 87 99 19 22 142 453; 453; 7 = 117 768 1182	Weight 3.8% 3.5% 0.0% 8.3% 4.9% 8.3% 40.8% 0% 8.7% 7.5% 0.0%	V, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74] 0.45 [0.22, 0.92] 0.45 [0.22, 0.92] 0.45 [0.49, 0.58] 0.33 [0.25, 0.43] 0.30 [0.21, 0.43] 0.30 [0.20, 0.74] 0.46 [0.49, 0.76]	Favours PARPi Hazard IV, Randon	Favours PBO Test for at ratio 55% Cl Study o . 1.1.1 Ok . 26% . 1.1.1 Ok . 26% . 1.1.1 Ok . 26% . 2000 . 200	r Subgroup log[HR] d 3 − 0.84 4 − 0.43 4 − 0.43 4 − 0.43 1 − 0.55 1	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 ^a = 8.79, 4 P < 0.00 9 0.13 4 0.18 2 0.34 4 0.11	PARPi Total 7 138 2 25 8 133 4 200 7 190 5 35 1 44 6 154 714 ff = 6 (P = 201) 8 231 9 152 4 244 5 332 9 29	PBO Total 3 77 5 12 6 6 5 11 5 11 5 11 5 11 5 11 5 11 5 11	Weight 2 4.3% 2 3.9% 3 6.1% 9 8.5% 9 4.6% 2 5.5% 2 8.9% 9 41.7% 9 41.7% 7 9.3% 6 8.1% 8 4.9% 2 0.0%	IV, Random, 95% 4 0.43 (0.20, 0.0 0.65 (0.29, 1, 0.35 (0.20, 0.0 0.45 (0.22, 0.0 0.45 (0.22, 0.0 0.43 (0.22, 0.0 0.43 (0.22, 0.0 0.77 (0.57, 1) 0.53 (0.42, 0.0 0.33 (0.25, 0.0 0.33 (0.25, 0.0 0.38 (0.21, 0.0 0.38 (0.21, 0.0 0.38 (0.21, 0.0 0.38 (0.20, 0.0) 0.61 (0.49, 0.0)	Haz 21 IV, Ran 22] 46] 47] 474 474 474 474 474 474 47	ard ratio
Adv or Subgroup diff idy or Subgroup 1 Old NORA NO	10g[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² = Z = 6.64 (P ⁻¹ -1.109 -1.204 -0.942	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 5.80, df = < 0.00001 0.138 0.189 0.344	F = 1 (P = PARPi Total 138 25 1325 190 355 400 154 787 6 (P = 0.) 237 152 240 332 297	PBO Total 72 12 63 87 99 19 22 142 453 45); P = 117 76 118 182 147	Weight 3.8% 3.5% 0.0% 8.3% 4.1% 4.9% 8.3% 40.8% 0%	V, Random, 95% Cl 0.43 [0 20 , 0.92] 0.65 [0 29 , 1.46] 0.35 [0 20 , 61] 0.55 [0 41 , 0.74] 0.53 [0 38 , 0.74] 0.45 [0 22 , 0.92] 0.45 [0 22 , 0.72] 0.58 [0 49 , 0.68] 0.33 [0 25 , 0.43] 0.33 [0 25 , 0.43] 0.30 [0 21 , 0.43] 0.30 [0 24 , 0.43] 0.30 [0 24 , 0.43] 0.31 [0 49 , 0.76]	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio 1.1.1 Q v 95% CI 1.1.1 Q - > NORU - > NORU - > SOLC - > NORU - > NORU - > NORU - > NORU	r Subgroup log[HR] d 30.84 -0.63 -0.43 -0.43 -0.43 -0.43 -0.43 -0.43 -0.43 -0.43 -0.44 -0.59 -0.26 (0% Cl) -0.26 (0% Cl) -0.26 -0.43 -0.43 -0.43 -0.43 -0.44	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 ³ = 8.79, 4 0.13 4 0.13 4 0.14 2 0.34 4 0.11 4 0.13	PARPi Total 7 138 2 25 8 133 4 200 7 190 5 35 1 44 6 154 714 ff = 6 (P = 201) 8 233 9 152 4 246 5 333 9 29	PBO Total 3 77 5 12 6 6 5 11 5 11 5 11 5 11 5 11 5 11 5 11	Weight 2 4.3% 2 4.3% 2 4.3% 3 6.1% 7 0.0% 9 8.5% 9 8.5% 9 41.7% = 32% 7 9.3% 6 8.1% 8 4.9% 2 0.0% 7 9.3%	IV, Random, 85% (0.43 (0.20, 0) 0.65 (0.29, 1) 0.35 (0.20, 0) 0.55 (0.41, 0) 0.55 (0.41, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.45 (0.22, 0) 0.53 (0.42, 0) 0.53 (0.42, 0) 0.53 (0.42, 0) 0.33 (0.25, 0) 0.33 (0.25, 0) 0.38 (0.49,	Haz IV, Ran 12 14 15 17 131 133 133 133 133 133 133 133 133 133	ard ratio
the subgroup difference indy or Subgroup indy or Subgroup indy indy or Subgroup indy	rences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² = Z = 6.64 (P -1.109 -1.204 -0.494 -0.494 -1.109	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.311 0.156 5.80, df = < 0.00001 0.138 0.189 0.344 0.115 0.139 0.344 0.115 0.139 0.364	f = 1 (P = PARPi Total 138 25 132 205 205 205 205 190 154 787 767 6 (P = 0.) 237 152 240 332 297 225	PBO Total 72 12 63 87 99 919 22 142 453; ₽ = 117 76 118 182 147 147 112	Weight 3.8% 3.5% 0.0% 8.3% 4.1% 8.3% 4.9% 8.3% 4.9% 8.3% 40.8% 0%	V, Random, 95% Cl 0.43 [0 20 .0 9.2] 0.65 [0 29 .1.46] 0.33 [0 20 .0 61] 0.55 [0 41 .0.74] 0.43 [0 20 .0 61] 0.55 [0 41 .0.74] 0.43 [0 23 .0.79] 0.77 [0 57 .1.05] 0.58 [0 49 .0.68] 0.33 [0 25 .0.43] 0.30 [0 21 .0.43] 0.33 [0 20 .0.71] 0.61 [0 49 .0.76] 0.61 [0 46 .0.76] 0.51 [0 46 .0.76] 0.53 [0 40 .0.76] 0.51 [0 46 .0.76] 0.53 [0 40 .0.76] 0.53 [0 40 .0.76] 0.53 [0 40 .0.76] 0.54 [0 46 .0.76] 0.53 [0 40 .0.76] 0.54 [0 46 .0.76] 0.53 [0 40 .0.76] 0.53 [0 40 .0.76] 0.53 [0 40 .0.76] 0.54 [0 46 .0.76] 0.53 [0 40 .0.76] 0.53 [0 40 .0.76] 0.54 [0 46 .0.76] 0.55 [0 40 .	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio Study of the st. 0, 95% CI 1.11 Ol - > NOR - > NOR - > SOLC - > NOR - > SOLC	r Subgroup log[HR] 1 3 0084 4 043 4 043 4 043 4 043 4 045 1 0.55 1 0.57 2 0.84 4 0.25 1 0.57 1 0.55 1 0	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.36 4 0.3 1 0.15 ² = 8.79, 4 9 0.13 4 0.18 2 0.34 4 0.11 4 0.11 9 0.13 9 0.14 1 0.15 1 0.25 1 0.15 1 0.15	PARPi Total 7 138 2 228 8 132 4 200 5 39 1 44 6 154 7 14 ff = 6 (P = 201) 8 233 9 155 4 240 5 333 9 299 6 229	PBO Total 3 7: 5 1: 2 6: 5 8: 0 9: 5 1: 0 2: 4 14: 4 42: 0 0.19); P = 7 11: 2 7? 0 11: 1 7 0 11: 1 7 11: 1 7 11: 1 7 11: 1 7 11: 1 7 11: 1 7 11: 1 7 11: 1 7 11: 1 7 111: 1 7 11: 1 7 11: 1 11: 11: 11: 11: 11: 11: 11: 11:	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 4.6% 2 5.5% 2 8.9% 9 41.7% = 32% 7 9.3% 6 8.1% 8 4.9% 2 0.0% 7 9.3% 2 8.8%	IV, Random, 95% 4 0.43 (0.20, 0.0 0.65 (0.29, 1, 1 0.35 (0.20, 0.0 0.45 (0.22, 0, 1 0.45 (0.22, 0, 0 0.45 (0.22, 0, 0 0.45 (0.22, 0, 0 0.45 (0.22, 0, 0 0.33 (0.25, 0, 0 0.33 (0.25, 0, 0 0.30 (0.27, 0, 0 0.46 (0.46, 0, 0 0.46 (0.46, 0, 0 0.31 (0.24, 0, 0 0.31 (0.24, 0, 0 0.31 (0.24, 0, 0 0.31 (0.24, 0)	Haz IV, Rani 10, Rani 10, Rani 11,	ard ratio
udy or Subgroup udy or Subgroup 1.1 Oki AREL3 NORA NORA NORA SGLO1 SGLO2 VELLA VELDA Moral effect 12 Young NORA NORA NORA NORA NORA NORA NORA NORA NORA SOLO1 SOLO2	rences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.739 -0.844 -0.261 0.00; Chi ² = Z = 6.64 (P -1.109 -1.204 -0.494 -0.494 -1.109 -1.109 -1.109	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 5.80, df = < 0.00011 0.138 0.189 0.344 0.113 0.139 0.16 0.171	f = 1 (P = PARPi Total 138 255 205 190 35 40 154 787 76 (P = 0.) 237 152 240 322 240 322 240 325 152 240 325 152 152 152 152 152 152 152 1	PBO Total 72 12 63 387 99 99 19 22 24 53 453; ₽ = 117 76 6 118 182 147 112 77	Weight 3.8% 3.5% 0.0% 8.3% 7.9% 4.1% 4.9% 8.3% 40.8% 0% 8.7% 8.7% 8.7% 8.7% 8.7% 8.7% 8.7%	V, Random, 95% Cl 0.43 [0 20 .0.92] 0.65 [0 29 .1.40] 0.35 [0 28 0.61] 0.55 [0 38 0.74] 0.43 [0 22 0.62] 0.43 [0 22 0.61] 0.43 [0 23 0.74] 0.43 [0 23 0.74] 0.43 [0 23 0.74] 0.45 [0 49 0.68] 0.33 [0 25 0.43] 0.39 [0 20 0.77] 0.61 [0 49 0.76] 0.46 [0 49 0.60] 0.33 [0 24 0.64]	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio \$855,C1 0,855,C1 \$1,11,04 - >NOR// - >SOLC - >SOLC - >ARE - ARE - >NOV//	r Subgroup log[HR] 1 3 0.084 1 0.084 1 0.084 1 0.083 1 0.083 1 0.083 1 0.083 1 0.083 1 0.083 1 0.083 1 0.084 1 0.083 1 0.084 1 0.083 1 0.084 1 0.08	SE 4 0.38 1 0.41 5 0.23 8 0.15 5 0.23 4 0.33 4 0.34 9 0.36 9 0.13 9 0.13 2 0.34 4 0.18 2 0.34 4 0.13 9 0.13 9 0.13	PARPi Total 7 138 2 25 8 133 4 200 7 190 5 33 4 200 7 190 5 33 1 40 6 154 714 4 244 5 33 9 233 9 233 9 233 9 233 9 233 6 222 1 1 55	PBO Total 3 7: 5 1: 2 6: 5 8: 0 99 5 11 0 2: 4 14: 4 42: 0 0.19); P = 7 11: 2 7: 0 111 2 7: 0 111 2 18: 7 14: 5 11: 5 11: 2 6: 5 12: 5 12: 7 12: 5 12: 7 14: 5 11: 5 12: 7 12: 7 11: 5 11: 5 11: 7 14: 5 11: 7 14: 7 14: 5 11: 7 11: 7 11: 7 11: 7 11: 7 11: 7 14: 7 5 11: 7 5	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5% 2 8.9% 9 41.7% = 32% 7 9.3% 6 8.1% 8 4.9% 2 0.0% 7 9.3% 7 8.5% 7 8.5%	IV, Random, 95% 4 . 0.43 (0.20, 0.0 . 0.65 (0.29, 1) . 0.55 (0.41, 0) . 0.55 (0.34, 0) . 0.55 (0.34, 0) . 0.45 (0.22, 0) . 0.43 (0.22, 0) . 0.43 (0.25, 0) . 0.33 (0.	21 Hazz 14, Rani 14, Ran	ard ratio
udy or Subgroup diff udy or Subgroup diff udy or Subgroup diff d	rences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 0.00; Chi ² = Z = 6.64 (P -1.109 -1.204 -0.494 -0.494 -1.109	P = 1.50, c SE 0.387 0.412 0.28 0.154 0.17 0.365 0.311 0.156 5.80, df = < 0.00001 0.138 0.189 0.344 0.115 0.139 0.344 0.115 0.139 0.364	ff = 1 (P = PARPi 138 205 132 205 190 35 40 154 787 6 (P = 0.) 232 297 225 156 2297 2255 1566 228 228	PBO Total 72 12 33 87 99 99 22 142 453 76 76 118 82 147 76 118 82 147 77 72 33	Weight 3.8% 3.5% 0.0% 8.3% 4.9% 8.3% 4.9% 8.3% 40.8% 0% 8.7% 8.7% 8.7% 8.2% 7.9% 8.2% 7.9%	V, Random, 95% Cl 0.43 [0 20 .0 9.2] 0.65 [0 29 .1.46] 0.33 [0 20 .0 61] 0.55 [0 34 .0.74] 0.43 [0 20 .0 61] 0.55 [0 41 .0.74] 0.43 [0 22 .0.79] 0.77 [0 57 .105] 0.58 [0 49 .0.68] 0.33 [0 25 .0.43] 0.30 [0 21 .0.43] 0.30 [0 20 .0.71] 0.61 [0 49 .0.76] 0.61 [0 49 .0.76] 0.61 [0 49 .0.76] 0.33 [0 22 .0.43] 0.33 [0 22 .0.43] 0.34 [0 22 .0.43] 0.35 [0 22 .0	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio Study of the st. (1) 5% CI 1.11 Ol - > NOR - > NOR - > SOLC - > NOR - > SOLC - > SOLC - > SOLC	Subgroup log[fR] j	SE 4 0.38 1 0.41 5 0.23 8 0.15 5 0.23 4 0.33 4 0.34 9 0.36 9 0.13 9 0.13 2 0.34 4 0.18 2 0.34 4 0.13 9 0.13 9 0.13	PARPi Total 7 138 2 22 8 133 4 200 7 199 5 35 1 4 40 6 155 3 35 9 155 4 244 5 335 9 291 6 222 1 156 6 222 1 156	PBO Total 3 7: 5 12 2 6: 5 8: 0 99 5 11 0 22 4 144 4 422 0.19): P = 7 11 2 7: 0 111 2 7: 1 11: 2 7: 1 11: 2 7: 3 7: 5 12: 7 15: 7 11: 7 15: 7 15: 7 15: 7 15: 7 15: 7 15: 7 11: 7 15: 7 15: 7 15: 7 11: 7 15: 7 15:	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 4.6% 9 4.6% 9 4.6% 9 4.6% 9 41.7% 9 32% 7 9.3% 6 8.1% 8 4.9% 2 0.0% 7 9.3% 2 8.8% 7 9.3% 2 8.8% 3 9.5% 3 9.5%	IV, Random, 85% 4 0.43 (0.20, 0.1 0.65 (0.29, 1.1 0.35 (0.20, 0.1 0.55 (0.41, 0.3 0.55 (0.41, 0.3 0.45 (0.22, 0.1 0.45 (0.22, 0.1 0.45 (0.22, 0.1 0.33 (0.25, 0.1 0.33 (0.5, 0.1 0.33 (0.5, 0.1) 0.33 (0.5, 0.1 0.33 (0.5, 0.1) 0.33 (0.5, 0.1 0.33 (0.5, 0.1) 0.33 (0	Haz IV, Ran 121 IV, Ran 123	ard ratio
udy or Subgroup diff udy or Subgroup 1.1 Old NOTA/NEL3 NOTA/NOTA/NOTA/NOTA/NOTA/NOTA/NOTA/NOTA/	rences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.639 -0.844 -0.261 0.00; Chi ^p = Z = 6.64 (P -1.109 -1.204 -0.942 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.494 -0.592 -0.942 -0.942 -0.494 -0.942 -0.494 -0.942 -0.942 -0.494 -0.592 -0.942 -0.944 -0.942 -0.942 -0.944 -0.942 -0.942 -0.942 -0.494 -0.942 -0.944 -0.942 -0.942 -0.944 -0.942 -0.944 -0.942 -0.944 -0.942 -0.944 -0.942 -0.944 -0.944 -0.942 -0.944 -0.944 -0.944 -0.942 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.944 -0.942 -0.944 -0.944 -0.944 -0.944 -0.944 -0.942 -0.494 -0.494 -0.494 -0.743 -0.744 -0.743 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.745 -0.755 -0.	2.5.0, cf SE 0.387 0.412 0.28 0.154 0.154 0.154 0.156 5.80, df = 0.384 0.138 0.138 0.138 0.138 0.139 0.145 0.139 0.145 0.139 0.145 0.139 0.145 0.139 0.145 0.14		PBO Total 72 12 12 12 12 12 12 12 12 12 12 12 12 14 45 142 453; P = 117 76 118 182 187 117 77 233	Weight 3.8% 3.5% 0.0% 8.3% 4.1% 4.9% 8.3% 8.3% 8.3% 8.3% 8.7% 8.7% 8.7% 8.2% 6.7.9% 9.2% 8.7% 59.2%	V, Random, 95% Cl 0.43 [0 20 .0.92] 0.65 [0 29 .1.40] 0.35 [0 28 0.61] 0.55 [0 38 0.74] 0.43 [0 22 0.62] 0.43 [0 22 0.61] 0.43 [0 23 0.74] 0.43 [0 23 0.74] 0.43 [0 23 0.74] 0.45 [0 49 0.68] 0.33 [0 25 0.43] 0.39 [0 20 0.77] 0.61 [0 49 0.76] 0.46 [0 49 0.60] 0.33 [0 24 0.64]	Favours PARPi Hazard IV, Randon	Favours PBO Test for at ratio vass, Cl Study of vass, Cl 1.1.1 Ob AREE - NOVM - NOVM - Solution - NOVM - Solution - Solution - Solution - Solution - Solution - Solution - NOVM - Solution - Solution - Solution -<	r Subgroup log[HR] 1 3 0.084 1 0.084 1 0.084 1 0.083 1 0.083 1 0.083 1 0.083 1 0.083 1 0.083 1 0.083 1 0.084 1 0.083 1 0.084 1 0.083 1 0.084 1 0.08	SE 4 0.38 1 0.41 5 0.2 8 0.15 5 0.1 9 0.38 4 0.3 1 0.15 9 0.38 4 0.3 1 0.15 9 0.38 4 0.3 1 0.15 9 0.38 4 0.3 1 0.41 9 0.38 4 0.3 1 0.41 9 0.38 4 0.3 1 0.41 9 0.38 9 0.39 1 0.17 1 0.12 1 0.12 1 0.58 1	PARPi Total 7 138 2 258 8 132 4 200 7 199 5 36 1 44 200 7 199 5 36 1 44 200 8 231 9 152 4 244 5 332 9 152 4 244 5 332 9 297 6 226 1 156 6 226 1 158 6 6 (P =	PBO Total 3 77 2 63 5 12 63 5 12 63 5 91 5 91 5 91 5 91 5 91 5 91 5 2 4 421 4 421 7 111 2 71 1 163 7 111 5 71 5 73 3 23335 5 888	Weight 2 4.3% 2 3.9% 3 6.1% 7 0.0% 9 8.5% 9 4.6% 2 5.5% 2 8.9% 9 41.7% 5 32% 7 9.3% 6 8.1% 8 4.9% 2 0.0% 7 9.3% 2 8.8% 7 9.3% 2 8.8% 7 9.3% 5 8.5% 0 58.3%	IV, Random, 85% 4 0.43 (0.20, 0.1 0.65 (0.29, 1.1 0.35 (0.20, 0.1 0.55 (0.41, 0.3 0.55 (0.41, 0.3 0.45 (0.22, 0.1 0.45 (0.22, 0.1 0.45 (0.22, 0.1 0.33 (0.25, 0.1 0.33 (0.5, 0.1 0.33 (0.5, 0.1) 0.33 (0.5, 0.1 0.33 (0.5, 0.1) 0.33 (0.5, 0.1 0.33 (0.5, 0.1) 0.33 (0	Haz IV, Ran 121 IV, Ran 123	ard ratio
est for subgroup diff tudy or Subgroup 1.1 Old ARIEL3 NORA PAOLA-1 PAOLA-1 PAOLA-1 PAOLA-1 SOLO1 SOLO2 VELIA SOLO2 VELIA Lubtotal (9K, CI)	rences: Chi log[HR] -0.844 -0.635 -0.700 -0.635 -0.790 -0.644 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.9444 -0.1170 -0.7170 -0.612 -0.71700 -0.71700 -0.71700 -0.71700 -0.71700 -0.717000 -0.7170000000000000000000000000000000000	0.387 0.412 0.387 0.412 0.28 0.154 0.154 0.365 0.31 0.156 0.365 0.31 0.156 0.365 0.31 0.156 0.365 0.31 0.156 0.310 0.138 0.138 0.139 0.141 0.156 0.139 0.139 0.139 0.139 0.139 0.139 0.139 0.139 0.156 0.139 0.149 0.140	ff = 1 (P + ff = 1 (P + Total 138 25 132 205 190 35 40 154 76 240 327 152 240 322 1627 228 1627 0 (P < 0, C)	PBO Total 72 63 87 99 92 24 453; P = 117 76 118 82 147 112 77 73 38 44 94 4 944 944 944 944	Weight 1 3.8% 3.5% 0.0% 3.5% 0.0% 4.9% 8.3% 4.9% 8.3% 4.9% 8.7% 9.2% 8.7% 9.2% 8.7% 59.2% 100.0%	V, Random, 95% Cl 0.43 (0 20 , 0.92) 0.65 (0 29 , 1.46) 0.53 (0 20 , 0.92) 0.53 (0 20 , 0.92) 0.53 (0 20 , 0.91) 0.53 (0 20 , 0.91) 0.58 (0 49 , 0.68) 0.33 (0 25 , 0.43) 0.30 (0 27 , 0.43) 0.30 (0 27 , 0.43) 0.30 (0 20 , 0.74) 0.53 (0 40 , 0.68) 0.33 (0 24 , 0.44) 0.33 (0 24 , 0.44) 0.33 (0 24 , 0.45) 0.43 (0.33 , 0.59) 0.48 (0 40 , 0.57)	Favours PARPi Hazard IV, Randon	Favours PBO Test for st. ratio Study of (\$95% CI) Study of (\$90% CI) 1.1.1 0 • ARBU • ARBU - • NOR/ • NOR/ • SOCI •	Subgroup log[HR] J	SE 4 0.38 1 0.41 5 0.2 8 0.18 4 0.3 4 0.3 4 0.3 4 0.3 9 0.13 4 0.13 9 0.13 9 0.13 9 0.13 9 0.17 1 0.12 1 0.12 1 0.12 1 0.12 1 0.12 1 0.12	PARPi Total 7 138 8 133 4 2000 7 199 5 38 4 2000 7 199 7 199 8 233 4 244 4 244 6 225 2 15 2 21 2 15 2 15 2 15 2 15 2 15	PBO Total 3 7: 5 1: 2 6: 0 9: 10 2: 4 143: 4 143: 7 111: 2 7: 7 111: 2 7: 3 2:3: 5 888 <	Weight 2 4.3% 2 3.9% 3 6.1% 9 8.5% 9 5.5% 2 6.9% 2 5.9% 2 8.9% 9 4.17% 5 8.1% 8 4.9% 2 0.0% 9 8.5% 9 9.3% 9 5.8,3% 9 100.0%	NY Random, 95% 4 0.43 (0 20.0.) 0.65 (0 20.1.) 0.65 (0 20.1.) 0.65 (0 20.1.) 0.65 (0 20.1.) 0.55 (0 20.1.) 0.65 (0 20.1.) 0.55 (0 20.1.) 0.65 (0 20.1.) 0.55 (0 20.1.) 0.65 (0 20.1.) 0.55 (0 20.1.) 0.65 (0 20.1.) 0.55 (0 42.0.) 0.53 (0 25.0.) 0.55 (0 42.0.) 0.53 (0 20.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0.) 0.51 (0 42.0.) 0.55 (0 42.0	Haz Haz 12	ard ratio

udy or Subgroup	log[HR]	SE	PARPi Total	PBO Total	Weight	Hazard ratio IV, Random, 95% CI		d ratio m, 95% Cl	Study or Subgroup	log[HR]	SE	Total	Total	Weight	IV, Random, 95% Cl	IV, Rando	om, 95% Cl
									- 1.1.1 Old								
1.1 Old ARIEL3	0.044	0.007	100	72	1.000	0.40.00.00.000			✓ ARIEL3	-0.844	0.387	138	72		0.43 [0.20 , 0.92]		
NORA	-0.844 -0.431	0.387	138 25			0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46]			✓ NORA	-0.431	0.412	25	12		0.65 [0.29 , 1.46]		-
NOVA	-0.431	0.412	132			0.35 [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		0.55 [0.41 , 0.74]			✓ PAOLA-1	-0.598	0.154	205	87	8.6%	0.55 [0.41, 0.74]		
PRIMA	-0.635	0.17	190	99		0.53 [0.38 , 0.74]			✓ PRIMA	-0.635	0.17	190	99	8.1%	0.53 [0.38 , 0.74]		
SOLO1	-0.799	0.365	35			0.45 [0.22 , 0.92]			¥ SOLO1	-0.799	0.365	35	19	0.0%	0.45 [0.22 , 0.92]		
SOLO2	-0.844	0.303	40			0.43 [0.23 , 0.79]			✓ SOLO2	-0.844	0.31	40	22		0.43 [0.23 , 0.79]		
VELIA	-0.261	0.156	154	142		0.77 [0.57 . 1.05]			✓ VELIA	-0.261	0.156	154	142		0.77 [0.57 , 1.05]		+
ubtotal (95% CI)	0.201	0.100	729	417		0.54 [0.43 , 0.68]			Subtotal (95% CI)			884	497		0.55 [0.45 , 0.67]	•	
eterogeneity: Tau ² =	0.03: Chi? =	8.68. df				ered ferred i ereel	•		Heterogeneity: Tau ² =				21); P =	29%			
st for overall effect:				,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,					Test for overall effect:	Z = 5.89 (P	< 0.0000	1)					
1.2 Young									1.1.2 Young								
ARIEL3	-1.109	0.138	237	117	9.2%	0.33 [0.25, 0.43]	-		✓ ARIEL3	-1.109	0.138	237	117	9.0%	0.33 [0.25 , 0.43]		1
NORA	-1.204	0.189	152	76	8.0%	0.30 [0.21, 0.43]			✓ NORA	-1.204	0.189	152	76		0.30 [0.21, 0.43]		
NOVA	-0.942	0.344	240	118	4.9%	0.39 [0.20 , 0.77]	_		✓ NOVA	-0.942	0.344	240	118		0.39 [0.20 , 0.77]		
PAOLA-1	-0.494	0.115	332	182	9.7%	0.61 [0.49 , 0.76]	-		✓ PAOLA-1	-0.494	0.115	332	182		0.61 [0.49 , 0.76]		
PRIMA	-0.494	0.139	297	147		0.61 [0.46 , 0.80]			✓ PRIMA	-0.494	0.139	297	147	9.0%	0.61 [0.46 , 0.80]		
SOLO1	-1.109	0.16	225	112		0.33 [0.24 , 0.45]			¥ SOLO1	-1.109	0.16	225	112		0.33 [0.24 , 0.45]		
SOLO2	-1.171	0.171	156	77	8.4%	0.31 [0.22, 0.43]	_		✓ SOLO2	-1.171	0.171	156	77		0.31 [0.22, 0.43]		
VELIA	-0.431	0.126	228	233		0.65 [0.51, 0.83]	-		✓ VELIA	-0.431	0.126	228	233		0.65 [0.51, 0.83]		1
ubtotal (95% CI)			1570	915	58.3%	0.40 [0.30 , 0.53]	٠		Subtotal (95% CI)			1642	950		0.44 [0.34 , 0.58]	•	
eterogeneity: Tau ² = est for overall effect:				0.00001)	; l ² = 82%		•		Heterogeneity: Tau ² = Test for overall effect:				0.00001)	1 ² = 82%		•	
otal (95% CI)			2299		100.0%	0.45 [0.37 , 0.55]	•		Total (95% CI)			2526		100.0%	0.48 [0.40 , 0.58]	•	
eterogeneity: Tau ² =	0.09; Chi* =	48.03, 0		< 0.00001); $P = 739$	6	Sec. 9	1 1 21	Heterogeneity: Tau ² =				0.0001)	$1^2 = 71\%$			
est for overall effect:			df = 1 (P	,	= 58.7%		0.1 0.2 0.5 Favours PARPi	2 5 10 Favours PBO	Test for overall effect: Test for subgroup diffe				0.22), I ^a PBO	= 32.2%	Hazard ratio	0.1 0.2 0.5 Favours PARPi Hazard	1 2 5 Favours F
est for overall effect: est for subgroup diffe	erences: Chi			,			Favours PARPi Haza			erences: Chi		df = 1 (P =			Hazard ratio IV, Random, 95% Cl	Favours PARPi	Favours F
est for overall effect: est for subgroup diffe Study or Subgroup	erences: Chi	² = 2.42,	df = 1 (P PARPi	РВО		Hazard ratio	Favours PARPi Haza	Favours PBO	Test for subgroup diffe	erences: Chi log[HR]	² = 1.48, SE	df = 1 (P = PARPi Total	PBO Total	Weight	IV, Random, 95% Cl	Favours PARPi Hazard	Favours F
est for overall effect: est for subgroup diffe Study or Subgroup 1.1.1 Old	erences: Chi	² = 2.42, SE	df = 1 (P PARPi Total	PBO Total	Weight	Hazard ratio IV, Random, 95% Cl	Favours PARPi Haza	Favours PBO	Test for subgroup diffe	erences: Chi log[HR] -0.844	² = 1.48, SE 0.387	df = 1 (P = PARPi Total 138	PBO Total	Weight 3.7%	IV, Random, 95% Cl	Favours PARPi Hazard	Favours F
est for overall effect: ast for subgroup diffe Study or Subgroup 1.1.1 Old V ARIEL3	erences: Chi	² = 2.42, SE	df = 1 (P PARPi Total 7 13	PBO Total 8 7:	Weight 2 3.7%	Hazard ratio IV, Random, 95% Cl 0.43 [0.20 , 0.92]	Favours PARPi Haza	Favours PBO	Test for subgroup diffe	erences: Chi log[HR] -0.844 -0.431	se 0.387 0.412	PARPi Total	PBO Total 72 12	Weight 3.7% 3.3%	IV, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46]	Favours PARPi Hazard	Favours F
est for overall effect: est for subgroup diffe Study or Subgroup 1.1.1 Old ✓ ARIEL3 ✓ NORA	-0.844 -0.431	se 0.38 0.41	df = 1 (P PARPi Total 7 13 2 2	PBO Total 8 7: 5 1:	Weight 2 3.7% 2 3.4%	Hazard ratio IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46]	Favours PARPi Haza	Favours PBO	Test for subgroup diffe	-0.844 -0.431 -1.05	se 0.387 0.412 0.28	df = 1 (P = PARPi Total 138 25 132	PBO Total 72 12 63	Weight 3.7% 3.3% 5.6%	IV, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46] 0.35 [0.20 , 0.61]	Favours PARPi Hazaro IV, Randou	Favours F
st for overall effect: est for subgroup diffe Study or Subgroup 1.1.1 Old NORA NORA	-0.844 -0.431 -1.05	se 0.38 0.41 0.2	df = 1 (P PARPi Total 7 13 2 2 8 13	PBO Total 8 7: 5 1: 2 6:	Weight 2 3.7% 2 3.4% 3 5.5%	Hazard ratio IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61]	Favours PARPi Haza	Favours PBO	Test for subgroup diffe	-0.844 -0.431 -1.05 -0.598	se 0.387 0.412 0.28 0.154	df = 1 (P = PARPi Total 138 25 132 205	PBO Total 72 12 63 87	Weight 3.7% 3.3% 5.6% 9.3%	IV, Random, 95% Cl 0.43 [0.20 , 0.92] 0.65 [0.29 , 1.46] 0.35 [0.20 , 0.61] 0.55 [0.41 , 0.74]	Favours PARPi Hazaro IV, Randoi	Favours F
est for overall effect: est for subgroup diffe Study or Subgroup 1.1.1 Old ARIEL3 NORA NOVA PAOLA-1	-0.844 -0.431 -1.05 -0.598	se 0.38 0.41 0.2 0.15	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20	PBO Total 8 7: 5 1: 2 6: 5 8:	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7%	Hazard ratio IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74]	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe	-0.844 -0.431 -1.05 -0.635	se 0.387 0.412 0.28 0.154 0.17	df = 1 (P = PARPi Total 138 25 132 205 190	PBO Total 72 12 63 87 99	Weight 3.7% 3.3% 5.6% 9.3% 8.7%	V, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74]	Favours PARPi Hazaro IV, Randou	Favours F
sst for overall effect: sst for subgroup diffe Study or Subgroup 1.1.1 Old ARIEL3 ARIEL3 NORA NOVA PAOLA-1 PRIMA	-0.844 -0.431 -1.05	se 0.38 0.41 0.2 0.15	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9:	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2%	Hazard ratio IV, Random, 95% CI 0.65 [0.29, 0.43] 0.65 [0.29, 1.46] 0.55 [0.41, 0.74] 0.53 [0.38, 0.74]	Favours PARPi Haza	Favours PBO	Test for subgroup diffe	-0.844 -0.844 -0.431 -1.05 -0.598 -0.635 -0.799	se 0.387 0.412 0.28 0.154 0.17 0.365	df = 1 (P = PARPi Total 138 25 132 205 190 35	PBO Total 72 12 63 87 99 19	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0%	IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.53 [0.38, 0.74] 0.45 [0.22, 0.92]	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: st for subgroup diffe Study or Subgroup 1.1.1 Old × AREL3 × NOVA × NOVA × NOVA × PAOLA-1 × PRIMA × SOLO1	-0.844 -0.8431 -1.05 -0.598 -0.635	se 0.38 0.41 0.2 0.15 0.1	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9: 5 1:	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0%	Hazard ratio IV, Random, 95% CI 0.43 (0.20, 0.92) 0.65 (0.29, 1.46) 0.35 (0.20, 0.61) 0.55 (0.41, 0.74) 0.55 (0.41, 0.74) 0.45 (0.22, 0.92)	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe Study or Subgroup 1.1.1 Old ARIEL3 NORA NOVA PROLA-1 PRIMA SOLO1 SOLO2	log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844	se 0.387 0.412 0.28 0.154 0.17 0.365 0.31	df = 1 (P = PARPi Total 138 25 132 205 190 35 40	PBO Total 72 12 63 87 99 19 22	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.9%	IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.45 [0.22, 0.92] 0.43 [0.22, 0.79]	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: st for subgroup diff Study or Subgroup 1.1.1 Old ~ ARIEL3 ~ NORA ~ NOVA ~ NOVA ~ NOVA ~ NOVA ~ SOL01 ~ SOL01 ~ SOL02	-0.844 -0.844 -0.431 -1.05 -0.598 -0.635 -0.799	SE 0.38 0.41 0.2 0.15 0.1 0.36	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9: 5 1: 0 9: 5 1: 0 2:	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0% 2 0.0%	Hazard ratio IV, Random, 95% Cl 0.65 [0.29, 1.46] 0.55 [0.20, 0.61] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74] 0.55 [0.41, 0.74] 0.45 [0.22, 0.92] 0.43 [0.23, 0.79]	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe Study or Subgroup - 1.1.1 Old ~ AREL3 ~ NORA ~ NORA ~ PACLA-1 ~ PRULA-1 ~ PRULA-1 ~ SOLO1 ~ SOLO2 % VELIA	-0.844 -0.844 -0.431 -1.05 -0.598 -0.635 -0.799	se 0.387 0.412 0.28 0.154 0.17 0.365	H = 1 (P = PARPi Total 138 25 132 205 130 130 40 154	PBO Total 72 12 63 87 99 19 22 142	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.9% 0.0%	IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.53 [0.38, 0.74] 0.43 [0.22, 0.92] 0.43 [0.23, 0.79] 0.77 [0.57, 1.05]	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: st for subgroup diffe study or Subgroup 1.1.1 Old > ARIEL3 > NORA > NOVA > PAOLA-1 > PRIMA > SOLO1 \$ SOLO2 > VELIA	-0.844 -0.431 -1.05 -0.598 -0.799 -0.844	se 0.38 0.41 0.2 0.15 0.1 0.36 0.3	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4	PBO Total 8 7: 5 11: 2 66 5 8 0 99 5 11: 0 2: 4 14:	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 8.2% 9 4.0% 2 0.0%	Hazard ratio IV, Random, 95% CI 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.53 [0.32, 0.20, 0.61] 0.53 [0.34, 0.74] 0.45 [0.22, 0.92] 0.43 [0.23, 0.79] 0.77 [0.57, 1.105]	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe Study or Subgroup 1.1.1 Old ARIEL3 NOVA NOVA PACLA-1 PRIMA Sol.02 X VELIA Subtotal (95% C1)	-0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261	se 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156	PARPi Total 138 25 132 205 130 35 40 154 765	PBO Total 72 12 63 87 99 19 22 142 374	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.9% 0.0% 39.5%	IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.45 [0.22, 0.92] 0.43 [0.22, 0.79]	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: isst for subgroup diffe study or Subgroup 1.1.1 Old ~ AREL3 ~ NOVA ~ NOVA ~ NOVA ~ NOVA ~ NOVA ~ NOVA ~ NOVA ~ NOVA ~ SOL01 ~ SOL01 ~ SOL01 ~ SOL02 ~ VELIA Subtotal (p5%, CI) Heterogeneip(5%, CI)	-0.844 -0.844 -0.431 -1.05 -0.598 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.02; Chi ²	SE 0.38 0.41 0.2 0.15 0.1 0.36 0.35 0.15 = 8.05, 0	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4 6 15 87 ff = 6 (P =	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9: 5 1: 0 9: 5 1: 0 2: 4 14: 9 49-	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 8.2% 9 4.0% 2 0.0% 4 42.2%	Hazard ratio IV, Random, 95% CI 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.53 [0.32, 0.20, 0.61] 0.53 [0.34, 0.74] 0.45 [0.22, 0.92] 0.43 [0.23, 0.79] 0.77 [0.57, 1.105]	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe Study or Subgroup - 1.1.1 Old ~ AREL3 ~ NORA ~ NORA ~ PACLA-1 ~ PRULA-1 ~ PRULA-1 ~ SOLO1 ~ SOLO2 % VELIA	log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; ChP :	se 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 = 3.00, df	df = 1 (P = PARPi Total 138 205 132 205 190 35 40 154 765 = 6 (P = 0	PBO Total 72 12 63 87 99 19 22 142 374	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.9% 0.0% 39.5%	IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.53 [0.38, 0.74] 0.43 [0.22, 0.92] 0.43 [0.23, 0.79] 0.77 [0.57, 1.05]	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: est for subgroup diffe study or Subgroup 1.1.1 Old AREL3 NORA NOVA NOVA NOVA SOLO1 SOLO1 SOLO2 VELIA Subtota (95% CI) Heterogeneily: Tau' Test for overall effect	-0.844 -0.844 -0.431 -1.05 -0.598 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.02; Chi ²	SE 0.38 0.41 0.2 0.15 0.1 0.36 0.35 0.15 = 8.05, 0	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4 6 15 87 ff = 6 (P =	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9: 5 1: 0 9: 5 1: 0 2: 4 14: 9 49-	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 8.2% 9 4.0% 2 0.0% 4 42.2%	Hazard ratio IV, Random, 95% CI 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.53 [0.32, 0.20, 0.61] 0.53 [0.34, 0.74] 0.45 [0.22, 0.92] 0.43 [0.23, 0.79] 0.77 [0.57, 1.105]	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe	log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; ChP :	se 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 = 3.00, df	df = 1 (P = PARPi Total 138 205 132 205 190 35 40 154 765 = 6 (P = 0	PBO Total 72 12 63 87 99 19 22 142 374	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.9% 0.0% 39.5%	IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.53 [0.38, 0.74] 0.43 [0.22, 0.92] 0.43 [0.23, 0.79] 0.77 [0.57, 1.05]	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: est for subgroup diffe Study or Subgroup 11.1 Old ~ AREL3 ~ NORA ~ NOVA ~ NORA ~ NOVA ~ NORA ~ NOVA ~ NORA ~ NOCA ~ SOL01 ~ SOL	-0,844 -0,844 -0,431 -1,05 -0,596 -0,635 -0,799 -0,844 -0,261 = 0,02; Chi ² t; Z = 5,86 (I	SE 0.38 0.41 0.2 0.15 0.1 0.36 0.3 0.15 0.3 0.15 = 8.05, c	df = 1 (P PARPi Total 7 13 2 2 2 3 3 13 4 20 7 19 5 3 1 4 6 15 87 ff = 6 (P = 001)	PBO Total 8 7: 5 11: 2 6: 5 8: 0 9: 5 11: 0 2: 4 14: 9 49: 0.23); P =	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 8.2% 9 4.0% 2 0.0% 2 8.6% 4 42.2% = 25%	Hazard ratio 1V, Random, 95%, Cl 0.43 (0.20, 0.92) 0.55 (0.20, 1.46) 0.55 (0.20, 0.61) 0.55 (0.41, 0.74) 0.53 (0.38, 0.74) 0.53 (0.38, 0.74) 0.53 (0.38, 0.74) 0.53 (0.38, 0.74) 0.53 (0.38, 0.74) 0.55 (0.45, 0.67)	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe	log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; ChP :	se 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 = 3.00, df	df = 1 (P = PARPi Total 138 205 132 205 190 35 40 154 765 = 6 (P = 0	PBO Total 72 12 63 87 99 19 22 142 374	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.9% 0.0% 39.5% 0%	IV, Random, 95% Cl 0.43 [0.20, 0.92] 0.65 [0.29, 1.46] 0.35 [0.20, 0.61] 0.55 [0.41, 0.74] 0.53 [0.38, 0.74] 0.43 [0.22, 0.92] 0.43 [0.23, 0.79] 0.77 [0.57, 1.05]	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: ist for subgroup diffe Study or Subgroup 1.1.1 Old ARIEL3 ARIEL3 NORA NOVA PRUMA VOVA VOLA VOVA VOLA V	-0.844 -0.431 -0.844 -0.431 -1.05 -0.588 -0.635 -0.799 -0.844 -0.261 = 0.02; Chi ² t; Z = 5.86 (f	SE 0.38 0.41 0.2 0.15 0.1 0.36 0.3 0.15 = 8.05, c 0 < 0.000	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4 6 15 87 ff = 6 (P = 001) 8 23	PBO Total 8 7: 5 1: 2 6: 5 8: 9 99 9 49 0.23); P = 7 11	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0% 2 0.0% 2 8.6% 4 42.2% = 25% 7 9.1%	Hazard ratio IX Random, 95% CI 0.43 [0.20, 0.92] 0.65 [0.20, 0.41] 0.55 [0.41, 0.74] 0.45 [0.41, 0.74] 0.45 [0.22, 0.82] 0.43 [0.23, 0.719] 0.55 [0.45, 0.67]	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe	log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; ChP : :: Z = 7.63 (P	se 0.387 0.412 0.28 0.154 0.17 0.365 0.31 0.156 = 3.00, df < 0.0000	df = 1 (P = PARPi Total 138 25 132 205 190 35 190 35 = 6 (P = 0 11)	PBO Total 72 12 63 87 99 19 22 142 374 81); P =	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.0% 39.5% 0%	IV, Random, 95% Cl 0.43 (0.20, 0.92) 0.65 (0.29, 1.46) 0.35 (0.20, 0.61) 0.55 (0.38, 0.74) 0.45 (0.22, 0.92) 0.45 (0.23, 0.79) 0.77 (0.57, 1.05) 0.59 (0.42, 0.60)	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: ist for subgroup diffect: study or Subgroup diffect: v AREL3 v NORA v NOVA v PACLA1 v PACLA1 v PACLA1 v PACLA1 v PACLA1 v PACLA1 v PACLA1 v SOLO2 v VELIA Subtota1 (9% C1) Heterogeneily: Tau ² Test for overall effect 1.1.2 Young v AREL3 v NORA	-0.844 -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.02; Chi ² = 0.02; Chi ² = 1.009 -1.109 -1.204	SE 0.38 0.41 0.2 0.15 0.1 0.36 0.3 0.15 = 8.05, c 0 < 0.000 0.13 0.18	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4 6 15 87 ff = 6 (P = 001) 8 23 9 15	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9: 5 1: 0 2: 4 14: 9 49: 0.23); P = 7 11: 2 7:	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0% 2 8.6% 4 42.2% = 25% 7 9.1% 6 7.7%	Hazard ratio 19, Random, 95%, CI 0.43 [0.20, 0.92] 0.55 [0.29, 1.46] 0.55 [0.41, 0.74] 0.45 [0.20, 0.81] 0.55 [0.41, 0.74] 0.45 [0.23, 0.74] 0.45 [0.23, 0.74] 0.45 [0.23, 0.74] 0.45 [0.23, 0.74] 0.45 [0.24, 0.45] 0.45 [0.45, 0.47] 0.55 [0.45, 0.47]	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe	erences: Chi log[HR] -0.844 -0.431 -1.05 -0.538 -0.635 -0.799 -0.844 -0.261 = 0.00; Ch ² + : Z = 7.63 (F -1.109	² = 1.48, SE 0.387 0.412 0.28 0.154 0.154 0.17 0.365 0.311 0.156 = 3.00, df < 0.0000 0.138	df = 1 (P = PARPi Total 138 25 132 205 190 35 40 154 765 = 6 (P = 0 11) 237	PBO Total 72 12 63 87 99 19 22 142 374 .81); P =	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.9% 0.0% 39.5% 0%	IV, Random, 95% Cl 0.43 (0.20, 0.92) 0.65 (0.29, 1.46) 0.55 (0.41, 0.74) 0.55 (0.41, 0.74) 0.53 (0.38, 0.74) 0.43 (0.22, 0.92) 0.77 (0.57, 1.05) 0.59 (0.42, 0.60) 0.33 (0.25, 0.43)	Favours PARPi Hazaro IV, Randoi	Favours F
st for overall effect: ist for subgroup differences study or Subgroup differences where a sub	-0.844 -0.844 -0.431 -1.05 -0.598 -0.853 -0.799 -0.844 -0.261 = 0.02; Chi ² t; Z = 5.86 (f -1.109 -1.204 -0.942	SE 0.38 0.41 0.42 0.15 0.1 0.15 0.1 0.3 0.15 0.3 0.15 0.3 0.15 0.3 0.13 0.13 0.13 0.13	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4 6 15 87 87 15 87 15 8 23 4 20 15 8 23 4 20 15 8 23 4 20 15 8 15 15 8 15 15 8 15 15 8 15 15 8 15 15 8 15 15 8 15 15 15 15 15 15 15 15 15 15	PBO Total 8 7: 5 1: 2 6: 5 8: 9 9: 5 11: 0 2: 4 14: 9 49: 9 49: 9 49: 9 49: 9 49: 9 49: 7 11: 2 7: 11: 2 7: 11: 11: 2 7: 11: 2 7: 11: 12 7: 11: 12 7: 11: 12 7: 11: 11: 11: 11: 11: 11: 11: 11: 11: 1	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0% 2 0.0% 2 0.0% 2 8.6% 4 42.2% 7 9.1% 6 7.7% 8 4.4%	Hazard ratio IV, Random, 95% Cl 0.43 (0.20, 0.92) 0.55 (0.29, 1.46) 0.53 (0.20, 0.61) 0.53 (0.20, 0.61) 0.53 (0.20, 0.61) 0.53 (0.20, 0.61) 0.53 (0.20, 0.61) 0.53 (0.20, 0.71) 0.55 (0.41, 0.74) 0.55 (0.43, 0.67) 0.55 (0.43, 0.67) 0.33 (0.25, 0.43) 0.39 (0.20, 0.77)	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup, diff.	erences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; Ch ² t; Z = 7.63 (F -1.109 -1.204	² = 1.48, SE 0.387 0.412 0.28 0.154 0.156 = 3.00, df < 0.0000 0.138 0.189	df = 1 (P = PARPi Total 138 25 132 205 190 35 40 154 765 = 6 (P = 0 11) 237 152	PBO Total 72 63 87 99 19 22 142 374 81); P = 117 76	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.0% 39.5% 0.0% 9.8% 8.1% 4.3%	IV, Random, 95% Cl 0.43 (0.20, 0.92) 0.65 (0.29, 1.46) 0.35 (0.41, 0.74) 0.55 (0.41, 0.74) 0.53 (0.20, 0.61) 0.45 (0.22, 0.92) 0.43 (0.23, 0.74) 0.50 (0.42, 0.60) 0.33 (0.25, 0.43) 0.30 (0.21, 0.43)	Favours PARPi Hazaro IV, Randoi	Favours F
sit for overall effect. sit for subgroup diffe Study or Subgroup 1.11 Old 4.11 Old 4.11 Cld 4.11 Cl	Iog[HR] -0.844 -0.8431 -1.05 -0.588 -0.631 -0.632 -0.844 -0.638 -0.638 -0.638 -0.638 -0.638 -0.638 -0.638 -0.638 -0.261 = 0.02; Chi ² -1.109 -1.204 -0.942 -0.942 -0.444	SE 0.388 0.41 0.22 0.155 0.11 0.36 0.35 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.1	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4 6 15 87 1 4 6 15 87 1 5 37 1 5 31 4 20 1 4 5 3 3 1 4 4 20 7 19 5 3 1 4 4 20 7 19 8 13 4 20 7 19 8 13 8 13 4 20 7 19 8 13 8 14 8 15 8 7 10 8 15 8 7 10 8 15 8 15 8 10 8 15 8 10 8 15 8 23 9 15 8 15 8 23 9 15 8 23 9 15 8 24 8 23 9 15 8 3 8 24 8 24 8 3 8 24 8 3 8 24 8 3 8 3 8 24 9 5 3 3 8 24 8 3 8 3 8 3 8 3 8 3 8 3 8 3 8 3	PBO Total 8 7: 5 11: 2 6: 5 8: 0 9: 5 11: 0 2: 4 14: 9 49: 0 0.23); P = 7 11: 2 7: 0 11: 2 18:	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0% 2 0.0% 2 0.0% 2 8.6% 4 42.2% 7 9.1% 6 7.7% 8 4.4% 2 9.7%	Hazard ratio IV, Random, 95%. CI 0.65 (1) 0.0 (0.12) 0.65 (1) 0.0 (0.12) 0.65 (1) 0.0 (0.11) 0.65 (0.11, 0.74) 0.65 (0.11, 0.74) 0.65 (0.11, 0.74) 0.65 (0.12, 0.82) 0.65 (0.12, 0.12) 0.65 (0.12, 0.12) 0.55 (0.45, 0.67) 0.55 (0.45, 0.67) 0.59 (0.11, 0.43) 0.39 (0.21, 0.43) 0.39 (0.21, 0.43) 0.39 (0.21, 0.43)	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe	erences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; Chi ² : t; Z = 7.63 (F -1.109 -1.204 -0.942	se 0.387 0.412 0.28 0.154 0.154 0.156 0.31 0.156 = 3.00, df < 0.0000 0.138 0.189 0.344	ff = 1 (P = PARPi Total 138 25 132 205 190 35 40 154 765 = 6 (P = 0 11) 237 152 240	PBO Total 72 63 87 99 19 22 142 374 81): ₽ = 117 76 118	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.0% 39.5% 0% 9.8% 8.1% 10.6%	IV, Random, 95% Cl 0.43 (0.20, 0.92) 0.65 (0.29, 1.46) 0.55 (0.41, 0.74) 0.55 (0.41, 0.74) 0.55 (0.41, 0.74) 0.45 (0.22, 0.92) 0.45 (0.22, 0.92) 0.56 (0.42, 0.66) 0.33 (0.25, 0.43) 0.30 (0.21, 0.43) 0.30 (0.21, 0.43)	Favours PARPI	Favours F
start for overall effect. start for subgroup diffe Starty or Subgroup. 1.1.1 Obt v. AREL3 v. NORA v. PRIMA v. SOLO1 v. Ella Subtotal (95% Ct) + AREL3 v. NORA v. NORA v. NORA v. NORA v. PRUAL-1 v. PREMA	-0.844 -0.844 -0.431 -1.05 -0.635 -0.799 -0.844 -0.261 = 0.02; Chi ² t; Z = 5.86 (f -1.109 -1.204 -0.942 -0.494 -0.494	SE 0.38 0.41 0.2 0.15 0.1 0.36 0.3 0.3 0.15 0.3 0.3 0.3 0.15 0.3 0.3 0.15 0.3 0.3 0.3 0.3 0.3 0.3 0.3 0.3 0.3 0.3	df = 1 (P PARPi Total 7 13 2 2 8 13 4 20 7 19 5 3 1 4 6 15 87 ff = 6 (P = 1001) 8 23 9 15 4 33 9 29 9 29	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9: 5 11: 0 2: 4 14: 9 49: 0.23): P = 7 11: 2 7: 0 11: 2 7: 11: 2 7: 11: 12 7: 11: 11: 11: 11: 11: 11: 11: 11: 11: 1	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 4.0% 2 0.0% 2 8.6% 4 42.2% 5 25% 7 9.1% 6 7.7% 8 4.4% 7 9.1% 7 9.1%	Hazard ratio IV, Random, 95%, CI 0.451 (02, 0.52) 0.451 (02, 0.52) 0.551 (02, 0.51) 0.551 (02, 0.51) 0.551 (02, 0.51) 0.551 (02, 0.51) 0.551 (02, 0.52) 0.51 (04, 0.52) 0.51 (04, 0.52)	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup, diffe	erences: Chi log(HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.844 =0.00; Chi ^p : Z = 7.63 (F -1.109 -1.204 -0.942 -0.942 -0.942	0.387 0.412 0.28 0.154 0.154 0.156 = 3.00, df 0.138 0.138 0.138 0.138 0.138 0.138	df = 1 (P = PARPi Total 138 265 132 205 190 355 40 154 765 = 6 (P = 0 11) 237 152 240 332	PBO Total 72 63 87 99 12 22 142 374 81); P = 117 76 118 182	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.9% 0.0% 39.5% 0% 9.8% 8.1% 4.3% 10.6% 9.8%	IV, Random, 95% Cl 0.43 (0.20, 0.92) 0.66 (0.29, 1.46) 0.56 (0.41, 0.74) 0.55 (0.41, 0.74) 0.53 (0.38, 0.74) 0.45 (0.22, 0.92) 0.45 (0.22, 0.92) 0.77 (0.57, 109) 0.50 (0.42, 0.60) 0.33 (0.25, 0.43) 0.30 (0.21, 0.43) 0.39 (0.20, 0.77) 0.61 (0.49, 0.76)	Favours PARPI	Favours F
Int for outgroup different for subgroup	- log[HR] - 0.844 -0.431 -1.05 -0.586 -0.599 -0.844 -0.261 = 0.02; ChP = 0.02; ChP -1.109 -1.204 -0.942 -0.494 -0.494 -0.494 -0.494 -1.109	SE 0.388 0.380 0.41 0.41 0.42 0.15 0.1 0.15 0.1 0.15 0.38 0.33 0.15 0.30 0.000 0.33 0.13 0.13 0.13 0.13 0.1	df = 1 (P PARPi Total 7 13 2 2 2 8 13 4 20 7 19 5 33 1 4 6 15 87 ff = 6 (P = 001) 8 23 9 15 4 24 9 29 6 22	PBO Total 8 7: 5 1: 2 6: 5 8: 0 9 19 5 1! 0 2: 4 14: 9 49 9 49 9 49 9 49 0.23); P = 7 11' 2 7: 11' 2 7: 11' 2 7: 11' 2 7: 11' 2 7: 11' 2 7: 11' 2 7: 5 11' 5 11'	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 4.0% 2 0.0% 2 8.6% 4 42.2% 7 9.1% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 4.4% 2 9.7% 8 5.5%	Hazard ratio IV, Randem, 95%. Cl 0.43 (0.20, 0.92) 0.65 (0.20, 1.46) 0.55 (0.41, 0.74) 0.55 (0.41, 0.74) 0.55 (0.45, 1.054) 0.45 (0.22, 0.82) 0.43 (0.23, 0.75, 1.054) 0.45 (0.25, 0.43) 0.55 (0.45, 0.47) 0.30 (0.21, 0.43) 0.30 (0.24, 0.45) 0.51 (0.46, 0.76) 0.51 (0.46, 0.76) 0.51 (0.46, 0.76) 0.51 (0.46, 0.76) 0.51 (0.46, 0.76) 0.51 (0.46, 0.76)	Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup, diffe	erences: Chi log(HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; ChP -1. -1.109 -1.204 -0.942 -0.942 -0.942 -0.942	se 0.387 0.412 0.28 0.154 0.154 0.156 0.311 0.156 = 3.00, df 0.458 0.138 0.189 0.344 0.1139	ff = 1 (P = PARPi Total 138 25 132 205 190 35 40 154 765 = 6 (P = 0 11) 237 152 240 332 297	PBO Total 72 12 63 87 99 19 22 274 87 87 87 87 87 87 87 87 87 87 87 87 87	Weight 3.7% 3.3% 5.6% 9.3% 4.0% 4.9% 0.0% 39.5% 0% 9.8% 8.1% 4.3% 10.6% 9.8% 9.8%	IV, Random, 95% Cl 0.43 (0.20, 0.52) 0.65 (0.29, 1.46) 0.35 (0.20, 0.61) 0.55 (0.41, 0.74) 0.53 (0.36, 0.74) 0.45 (0.22, 0.92) 0.45 (0.22, 0.92) 0.45 (0.22, 0.77) 0.50 (0.42, 0.60) 0.33 (0.25, 0.43) 0.30 (0.21, 0.43) 0.30 (0.21, 0.43) 0.30 (0.20, 0.77) 0.61 (0.44, 0.80)	Favours PARPI	Favours F
st for overall effect: st for subgroup diffe Study or Subgroup 1.1.1 Old V AREA3 V ROVA V SOLO V PENA V SOLO V VELA V ROVA V SOLO V SOL	-0,844 -0,844 -0,431 -0,884 -0,635 -0,598 -0,635 -0,799 -0,844 -0,261 = 0.02; ChP t; Z = 5.86 (f -1,109 -1,204 -0,942 -0,942 -0,494 -0,494 -1,107	SE 0.38 0.41 0.2 0.15 0.1 0.36 0.3 0.15 0.1 0.36 0.3 0.15 0.4 0.000 0.13 0.13 0.14 0.34 0.11 0.36 0.34 0.34 0.35 0.36 0.38 0.38 0.38 0.41 0.36 0.38 0.41 0.38 0.41 0.36 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.36 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.41 0.38 0.38 0.38 0.41 0.38 0.38 0.38 0.38 0.38 0.38 0.38 0.38	df = 1 (P PARPi Total 7 133 2 2 2 2 32 4 20 7 19 5 33 4 20 7 19 5 33 4 20 5 33 9 15 5 33 9 29 5 33 9 29 1 5 3 4 20 4 20 4 20 5 33 9 10 1 4 20 5 33 9 10 1 4 20 5 33 1 4 20 1 5 33 1 4 20 1 5 33 1 6 (P = 1) 1 6 (P = 1) 1 7 10 1 7 10 1 7 10 1 8 20 1 9 1 1 8 20 1 8 20 1 8 20 1 9 1 1 8 20 1 9 1 1 8 20 1 8 20 1 9 1 1 9 1	PBO Total 8 7: 5 1: 2 6: 5 8: 9 99 5 11: 0 2: 4 14: 9 499 0.23); P = 7 11: 2 7: 0 11: 2 7: 0 11: 2 18: 7 14: 5 11: 2 6: 5 12: 9 499 0.23); P =	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0% 2 8.6% 4 42.2% = 25% 7 9.1% 6 7.7% 8 4.4% 2 9.7% 7 9.1% 2 8.5% 7 9.1% 7 9.1% 2 8.5% 7 0.0%	Hazard ratio IV, Random, 95%, CI 0.45 (102, 002), 146 0.55 (104, 002), 146 0.55 (104, 002), 146 0.55 (104, 002), 146 0.55 (104, 002), 105 0.55 (104, 002), 1	Farours PARPI	Favours PBO	Test for subgroup diffe Study or Subgroup diffe II.1 Obt V AREL3 V NOVA V NOVA V ROLA-1 V RIMA V SOLO2 X VELA Subtotal (9% C) Hereopenet, Tav' Test for overall effect II.2 Young V NOVA V NOVA	erences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; Chi ² : Z = 7.63 (F -1.109 -1.204 -0.942 -0.494 -0.494 -0.494 -1.109	SE 0.387 0.412 0.282 0.154 0.154 0.156 0.31 0.156 0.31 0.156 0.31 0.158 0.344 0.115 0.138 0.344 0.115 0.138 0.344	ff = 1 (P = PARPi Total 138 25 132 2055 190 35 400 154 765 = 6 (P = 0 11) 237 152 2400 332 297 225	РВО Тоtal 72 12 63 87 99 92 22 142 374 374 811; Р = 1177 766 118 182 147 117	Weight 3.7% 3.3% 5.6% 9.3% 4.0% 4.9% 0.0% 39.5% 0% 9.8% 8.1% 4.3% 10.6% 9.8% 9.1% 8.7%	IV, Random, 95% Cl 043 (0 20, 0 92) 065 (0 29, 146) 035 (0 20, 0 61) 055 (0 41, 0.74) 045 (0 22, 0 32) 043 (0 23, 0.79) 0.77 (0 57, 105) 0.59 (0 42, 0.60) 0.33 (0 25, 0 43) 0.39 (0 20, 0.77) 0.61 (0 44, 0.76) 0.61 (0 44, 0.76) 0.61 (0 44, 0.76) 0.61 (0 44, 0.76)	Favours PARPI	Favours F
In the overall effect. Study or Subgroup diffe Study or Subgroup diffe V AREL3 V NORA V V NORA V NORA V NORA V V V NORA V V NORA V V NORA V V V NORA V V V NORA V V V NORA V V V V V NORA V V V V V V V V V V V V V V V V V V V	- log[HR] - 0.844 -0.431 -1.05 -0.586 -0.599 -0.844 -0.261 = 0.02; ChP = 0.02; ChP -1.109 -1.204 -0.942 -0.494 -0.494 -0.494 -0.494 -1.109	SE 0.388 0.380 0.41 0.41 0.42 0.15 0.1 0.15 0.1 0.15 0.38 0.33 0.15 0.30 0.000 0.33 0.13 0.13 0.13 0.13 0.1	df = 1 (P PARPi Total 7 13, 2 2 2 2 3 2 3 4 200 7 19 8 13, 4 200 7 19 8 13, 4 200 7 19 8 13, 4 200 7 19 8 13, 8 13, 8 13, 4 200 7 19 8 13, 8 13, 8 13, 8 13, 8 13, 8 13, 8 13, 8 13, 8 13, 8 14, 8 13, 8 14, 8 13, 8 14, 8 13, 8 14, 8 13, 8 14, 8 13, 8 14, 8 14, 8 14, 8 14, 8 15, 8 14, 8 15, 8 14, 8 14, 8 14, 8 14, 8 14, 8 14, 8 15, 8 14, 8 15, 8 14, 8 14,	PBO Total 8 7; 5 1: 2 6 6 5 1: 2 6 6 9 9 9 9 9 9 9 49 9 49 9 49 9 49 9 4	Weight 2 3.7% 2 3.4% 3 5.5% 7 8.7% 9 8.2% 9 4.0% 2 0.0% 2 8.6% 4 42.2% = 25% 7 9.1% 8 4.4% 2 9.7% 7 9.1% 8 4.4% 2 9.7% 7 9.1% 2 8.5% 7 9.1% 3 9.4%	Hazard ratio IX, Random, 95%. Cl 0.45 (02, 05%, Cl 0.55 (02, 0, 61) 0.55 (Favours PARPi Haza IV, Rando	Favours PBO	Test for subgroup diffe	erences: Chi log[HR] -0.844 -0.431 -1.05 -0.598 -0.635 -0.799 -0.844 -0.261 = 0.00; Chi ² + = 2 - 7.63 (F -1.109 -1.204 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -0.942 -1.109 -1.204 -0.942 -0.942 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.204 -1.109 -1.109 -1.204 -1.109 -1.204 -1.109	se 0.3877 0.412 0.28 0.154 0.154 0.315 0.315 0.315 0.316 0.316 0.317 0.365 0.31 0.355 0.31 0.315 0.317 0.365 0.317 0.365 0.317 0.315 0.317 0.355 0.317 0.345 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.344 0.317 0.357 0.344 0.344 0.344 0.317 0.357 0.344 0.344 0.344 0.317 0.375	tf = 1 (P = PARPi Total 138 25 132 205 132 205 190 35 400 154 765 = 6 (P = 0 11) 237 152 240 332 297 225 156	PBO Total 72 12 12 12 12 12 12 12 12 12 12 12 142 14	Weight 3.7% 3.3% 5.6% 9.3% 8.7% 4.0% 4.9% 0.0% 39.5% 0% 9.8% 8.1% 4.3% 10.6% 9.8% 9.1% 8.7% 0.0%	IV, Random, 95% Cl 0.43 (0.20, 0.92) 0.65 (0.29, 1.46) 0.35 (0.20, 0.61) 0.55 (0.38, 0.74) 0.45 (0.22, 0.92) 0.45 (0.22, 0.72) 0.57 (0.57, 1.02) 0.50 (0.42, 0.60) 0.50 (0.42, 0.60) 0.33 (0.25, 0.43) 0.30 (0.21, 0.43) 0.30 (0.21, 0.43) 0.30 (0.21, 0.43) 0.30 (0.21, 0.43) 0.31 (0.22, 0.43)	Favours PARPI	Favours F
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est for overall effect: est of or subgroup diffe 1.1.1 Ok 1.1.1 Ok 1.1.2	- log[HR] - log[HR] - 0.844 -0.431 -1.05 -0.598 -0.598 -0.635 -0.799 -0.844 -0.431 = 0.02; Chi ² -1.206 -1.206 -1.206 -0.942 -0.494 -0.942 -0.494 -0.431 = 0.10; Chi ² t; Z = 5.90 (f)	SE 0.388 0.41 0.22 0.155 0.36 0.36 0.36 0.36 0.35 0.15 0.36 0.36 0.36 0.36 0.36 0.36 0.36 0.36	af = 1 (P PARPi Total 7 13 2 2 8 13 4 6 15 87 9 16 8 9 16 9 8 9 16 9 9 16 9 29 29 29 29 29 29 29 29 29 29 29 29 29 29 29 21 16 70 259	PBO Total 8 77: 2 66 5 8 8 5 11: 2 66 5 8 8 5 11: 0 2: 1 9 9 49- 9 49- 9 49- 9 49- 9 49- 9 49- 9 49- 9 11: 2 16: 5 11: 1 0 2: 7 11: 2 16: 5 8 8 7 11: 1 0 2: 7 11: 2 16: 5 8 8 9 99 9 9 99 9 9 99 9 9 99 9 9 9 99 9 9 0 99 9 7 11: 1 0 2: 5 11: 1 0 2: 5 8 8 49- 9 49- 9 49- 9 49- 9 49- 9 49- 9 11: 1 0 2: 5 11: 1 0 2: 7 11: 2 16: 5 8 8 9 7 11: 5 11: 5 8 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 11: 1 0 2: 5 11: 1 0 2: 5 11: 5 11: 5 8 8 9 7 11: 5 11: 5 8 8 8 9 7 11: 5 11: 5 8 8 9 7 11: 5 11: 5 11: 5 8 8 9 8 9 8 9 8 9 8 9 9 9 9 9 9 9 9 11: 1 2 18: 5 11: 1 19 8 8 23 1 1 19 8 8 23 1 1 1 19 1 10 1 10 1 10 1 10 1 10 1 10 1	Weight 2 3,77% 3 5,5% 3 5,5% 9 4,0% 2 0,0% 9 8,2% 9 4,2% 9 2,0% 7 9,1% 4 42,2% 7 9,1% 2 8,5% 7 9,1% 2 8,5% 7 9,1% 2 8,5% 7 9,1% 2 8,5% 7 9,1% 2 8,5% 7 9,4% 5 5,7,8% 9 100,0%	Hazard ratio IV, Random, 95%, Cl . 0.43 (0.20, 0.82) 0.55 (0.20, 147) 0.55 (0.20, 147) 0.55 (0.20, 147) 0.55 (0.20, 147) 0.55 (0.20, 0.43) 0.55 (0.45, 0.67) 0.55 (0.45, 0.67) 0.55 (0.45, 0.67) 0.51 (0.46, 0.68) 0.33 (0.25, 0.43) 0.39 (0.21, 0.43) 0.39 (0.21, 0.43) 0.51 (0.46, 0.56) 0.51 (0.24, 0.45) 0.51 (0.24, 0.45) 0.51 (0.24, 0.45) 0.54 (0.24, 0.55)	Farours PARPI	Favours PBO	Test for subgroup, diffe	Iog[HR] -0.844 -0.844 -0.35 -0.598 -0.355 -0.598 -0.356 -0.844 -0.261 =0.00; Chi ² :: Z = 7.63 (F -1.109 -1.204 -0.444 -0.441 -0.942 -0.444 -0.444 -0.494 -0.494 -1.109 -1.111 -0.431 =0.10; Chi ² :: Z = 6.75 (F = 0.06; Chi ²	a = 1.48, SE 0.387 0.412 0.28 0.154 0.365 0.313 0.156 0.313 0.156 0.313 0.156 0.314 0.155 0.310 0.44 0.155 0.313 0.156 0.314 0.156 0.314 0.156 0.315 0.344 0.155 0.334 0.344 0.155 0.344 0.155 0.344 0.155 0.325 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.155 0.344 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3444 0.455 0.3445 0.455 0.345 0.3	$\begin{array}{c} & {}_{\rm s} {\rm df} = 1 \; ({\rm P} = {\rm P} {\rm ARP} {\rm i} \\ & {}_{\rm s} {\rm df} = {\rm Total} \\ \\ & {}_{\rm s} {\rm 1388} \\ {\rm 255} \\ {\rm 1322} \\ {\rm 2055} \\ {\rm 1322} \\ {\rm 205} \\ {\rm 100} \\ {\rm 134} \\ {\rm 100} \\ {\rm 154} \\ {\rm 100} \\ {\rm 154} \\ {\rm 100} \\ {\rm$	PBO Total 72 22 33 74 374 374 881); P = 117 76 76 118 8182 142 147 112 23 39 0.0001); 1203	Weight 3.7% 3.3% 5.6% 4.0% 4.0% 4.0% 3.9.3% 3.9.5% 3.	IV, Random, 95% Cl 043 (0 20, 0 52) 065 (0 29, 146) 035 (0 20, 0 61) 055 (0 41, 0.74) 045 (0 28, 0 24) 043 (0 22, 0.79) 0.77 (0 57, 105) 0.59 (0 42, 0.66) 0.33 (0 25, 0 43) 0.39 (0 2, 1, 0 43) 0.39 (0 2, 1, 0 43) 0.39 (0 2, 1, 0 43) 0.39 (0 2, 0, 0 42) 0.51 (0 44, 0, 0 64) 0.31 (0 24, 0.45) 0.31 (0	Favours PARPI	Favours F