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Original Research

Efficacy and safety of maintenance olaparib and bevacizumab in ovarian cancer patients aged ≥65 years from the PAOLA-1/ENGOT-ov25 trial

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KEYWORDS
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Abstract ***Background:*** The phase III PAOLA-1/ENGOT-ov25 study (NCT02477644) showed that addition of olaparib to bevacizumab maintenance improved progression-free survival (PFS) in patients with newly diagnosed advanced ovarian cancer. We evaluated maintenance olaparib plus bevacizumab in older patients in PAOLA-1.

Methods: Baseline clinical and molecular data, and PFS, were compared between older (aged ≥65 years) and younger patients (<65 years). Factors associated with olaparib efficacy, and safety in age subgroups, were also assessed.

Results: Of 806 randomised patients, 292 (36.2%) were ≥65 years. A lower proportion of older versus younger patients had an Eastern Cooperative Oncology Group performance status of 0 (61.0% versus 76.2%) and upfront surgery (42.0% versus 55.7%). Older patients were less likely to have a *BRCA1/2* mutation (17.1% versus 36.7%) or homologous recombination deficiency-positive status (34.1% versus 55.7%). After median follow-up of 22.1 months, median PFS was 21.6 months with olaparib versus 16.6 months with placebo in the older population (hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.41–0.75), comparable with the younger population (median 22.9 versus 16.9 months; HR 0.61, 95% CI 0.49–0.77). PFS benefits were observed in patients with a *BRCA* mutation or homologous recombination deficiency-positive tumours. Incidence of olaparib-related grade ≥3 adverse events in older patients was comparable with that of younger patients (36.8% versus 31.7%) although hypertension and anaemia were more common in older patients. No treatment-related deaths occurred in older patients receiving olaparib.

Conclusion: Older patients enrolled in PAOLA-1 achieved similar PFS benefits compared with younger patients, with a similar safety profile.

1. Introduction

Ovarian cancer is the leading cause of mortality among patients with gynaecological malignancies in Western countries [1]. Incidence increases with age, peaking between 75 and 79 years, with mortality peaking between 80 and 84 years [2,3]. Nevertheless, older patients are often under-represented or excluded from large prospective clinical trials [4–6].

Epidemiological studies have highlighted increased age as a negative prognostic factor for survival. This is attributed not only to high-grade and advanced-stage disease but also to the suboptimal implementation of surgical and systemic treatments [7–12].

Recent clinical trials have uncovered treatment options that could be added to the standard carboplatin–paclitaxel regimen. Among these new drugs, bevacizumab and poly (ADP-ribose) polymerase (PARP) inhibitors have been approved for ovarian cancer in the first-line setting. Olaparib was the first PARP inhibitor to receive US Food and Drug Administration and European Medicines Agency approval in advanced ovarian cancer for patients with *BRCA1/2* mutations (*BRCA*m) treated in the upfront maintenance setting [13]. Olaparib is also approved in combination with bevacizumab in patients with homologous recombination deficiency (HRD)-positive tumours based on the results of the PAOLA-1 study [14]. This pivotal phase III trial showed a significant progression-free survival (PFS) improvement in favour of olaparib plus bevacizumab maintenance versus placebo plus bevacizumab for patients with HRD-positive advanced ovarian cancer who had a response after first-line platinum–taxane–bevacizumab triplet. Olaparib can also be used in the same setting as maintenance monotherapy in *BRCA*m tumours [13,15].

Olaparib specificities such as its oral formulation and low rates of high-grade adverse events (AEs) [13] offer an attractive approach for the treatment of ovarian cancer in older patients. Some retrospective studies yield reassuring results, but they are limited due to under-representation of older women in clinical trials [13,16–18].

Here, we present the first analysis of older women receiving the bevacizumab–olaparib combination as first-line treatment for advanced ovarian cancer in a randomised prospective trial. We aimed to describe efficacy of the combination in this population as well as the toxicities related to treatment in these patients.

2. Patients and methods

2.1. Study design and selection criteria

The PAOLA-1/ENGOT-ov25 study (NCT02477644) was a phase III, randomised, double-blind, placebo-controlled, international trial. Patients with newly diagnosed advanced, high-grade ovarian cancer in response after first-line platinum–taxane–bevacizumab triplet were randomised from July 2015 until September 2017. Patients were randomised 2:1 to receive olaparib 300 mg or placebo twice daily for up to 24 months; all patients received bevacizumab for up to 15 months in

total. The primary endpoint was investigator-assessed PFS. All eligibility criteria and study procedures have already been described [14]. PAOLA-1 was performed in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines under the control of an independent data monitoring committee. All patients provided written informed consent.

2.2. Objectives of the current study

The primary objective of this prespecified subgroup study was to explore the survival outcomes (PFS) of older patients (aged ≥65 years) receiving olaparib and to compare olaparib benefit in this population with that of younger patients. We also explored clinical or molecular features associated with PFS in both subgroups. Finally, we explored the safety profile of the bevacizumab/olaparib doublet according to age.

2.3. Statistical analysis

The level of statistical significance was set at $\alpha = 0.05$. All tests were two-sided. Statistical analyses were performed with the SAS® 9.4 software. Categorical variables were described using counts and frequencies (computed on the basis of available data for the considered criterion), and quantitative variables were described using medians and ranges. Patients' characteristics and safety data were compared between younger and older patients using chi-squared or Fisher's exact test for qualitative variables.

PFS was defined from the date of randomisation to the date of investigator-assessed disease progression (modified Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) or death. The Kaplan–Meier method was used to estimate PFS. The treatment-effect hazard ratios (HRs) and associated 95% confidence intervals (CIs) were calculated using Cox proportional-hazards models.

Independent prognostic factors for PFS in patients receiving olaparib were explored using multivariate Cox proportional-hazards models. Potential main prognostic features considered were age, Eastern Cooperative Oncology Group performance status (ECOG PS), International Federation of Gynecology and Obstetrics (FIGO) stage, *BRCA*m and HRD status, and complete cytoreductive surgery achievement.

3. Results

3.1. Baseline characteristics

Out of the 806 randomised patients, 292 (36.2%) were aged ≥65 years. In total, 205/292 (70.2%) received olaparib compared with 332 (64.6%) younger patients (Fig. S1).

Median age in the olaparib arm was 70 years in the older group (range 65–87) and 56 years (32–64) in the younger group (Table 1). A lower proportion of older patients had an ECOG PS of 0 (61.0% versus 76.2%). Older patients were less likely to have a *BRCA*m (17.1% versus 36.7%) or HRD-positive status (34.1% versus 55.7%). Concerning surgery, fewer older patients underwent upfront surgery (42.0% versus 55.7%). Complete cytoreduction with no evidence of disease following upfront surgery or interval surgery was achieved in 53.7% of older patients versus 62.0% of younger patients (Table 1). There was less complete cytoreduction at primary debulking surgery in the older population (22.4% versus 33.7%) but similar rates during interval debulking surgery (31.2% versus 28.3%).

These data were similar in patients randomised to the placebo arm (Table S1). Within the older subset, clinical, molecular, and surgical features were well balanced across treatment arms (Table S2). Specifically, there was no difference in FIGO stage, HRD status, and rates of patients without complete cytoreduction after debulking surgery.

3.2. Olaparib efficacy is similar in older and younger patients

In the intention-to-treat population, median follow-up was 22.1 months in older patients (22.1 months in the olaparib arm) and 24.0 months in younger patients (24.0 months in those who received olaparib). In the older subgroup, median PFS was 21.6 months with olaparib and 16.6 months with placebo (HR 0.55, 95% CI 0.41–0.75) (Fig. 1A). This benefit was similar to that observed in the younger population: median of 22.9 versus 16.9 months (HR 0.61, 95% CI 0.49–0.77) (Fig. 1B).

In older patients, analysis of treatment efficacy according to molecular characteristics at inclusion showed that PFS was greater with olaparib in patients with *BRCA*m and/or HRD-positive tumours (Fig. 2). HR for progression was also 0.22 in tumour *BRCA*m and 0.23 in HRD-positive/*BRCA* wild-type patients. As in the younger cohort, PFS in HRD-negative and HRD unknown patients was not improved in the olaparib arm.

3.3. Impact of surgery on olaparib benefit

We then explored the impact of surgical status on olaparib efficacy in the older patients population. Ninety-two (44.9%) older patients in the olaparib arm could not undergo surgery or underwent surgery with gross residual disease. This rate was similar (49.4%) in the placebo arm. Olaparib benefit tended to be higher in patients with complete cytoreduction (HR for PFS 0.43, 95% CI 0.27–0.69) than in patients with macroscopic residual disease after surgery or with no surgery (HR 0.67, 95% CI 0.45–1.01) (Fig. 3).

Table 1
Demographics of patients included in the olaparib arm according to age.

Clinical and pathological features at inclusion		≥65 years (n = 205)	<65 years (n = 332)	P value
Median age at baseline, years (minimum–maximum)		70 (65–87)	56 (32–64)	
ECOG performance status	0	125 (61.0)	253 (76.2)	0.0005
	1	76 (37.1)	77 (23.2)	
	Missing	4 (2.0)	2 (0.6)	
FIGO stage	III	149 (72.7)	229 (69.0)	0.38
	IV	56 (27.3)	103 (31.0)	
BRCA deleterious mutation	All	35 (17.1)	122 (36.7)	<0.0001
	BRCA1	15 (7.3)	96 (28.9)	
	BRCA2	20 (9.8)	25 (7.5)	
	BRCA1 and *BRCA2*	0 (0.0)	1 (0.3)	
HRD status	Positive	70 (34.1)	185 (55.7)	<0.0001
	Negative	101 (49.3)	91 (27.4)	
	Unknown	34 (16.6)	56 (16.9)	
Upfront surgery		86 (42.0)	185 (55.7)	0.0025
	Residual macroscopic disease	39 (45.3)	72 (38.9)	0.35
	No residual macroscopic disease	47 (54.7)	113 (61.1)	
First-line treatment outcomes	NED with complete cytoreduction at primary DS	46 (22.4)	112 (33.7)	0.063
	NED/CR with complete cytoreduction at interval DS	64 (31.2)	94 (28.3)	
	NED/CR with incomplete resection or no DS	29 (14.1)	50 (15.1)	
	PR	62 (30.2)	72 (21.7)	
	Missing	4 (2.0)	4 (1.2)	

Data are n (% of cases with data available) unless otherwise specified.
Abbreviations: CR, complete response; DS, debulking surgery; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; NED, no evidence of disease; PR, partial response.

Cox univariate analysis for PFS including ECOG PS, FIGO stage, HRD status, and surgery results identified HRD status and surgery results as being significantly associated with PFS in the older population. The same variables plus FIGO stage were associated with PFS in younger patients. Multivariate analyses showed that HRD status was the main independent factor associated with PFS within the olaparib arm in both older (HR 0.23, 95% CI 0.14–0.39) and younger patients (HR 0.25, 95% CI 0.18–0.36). Surgery results were also correlated with

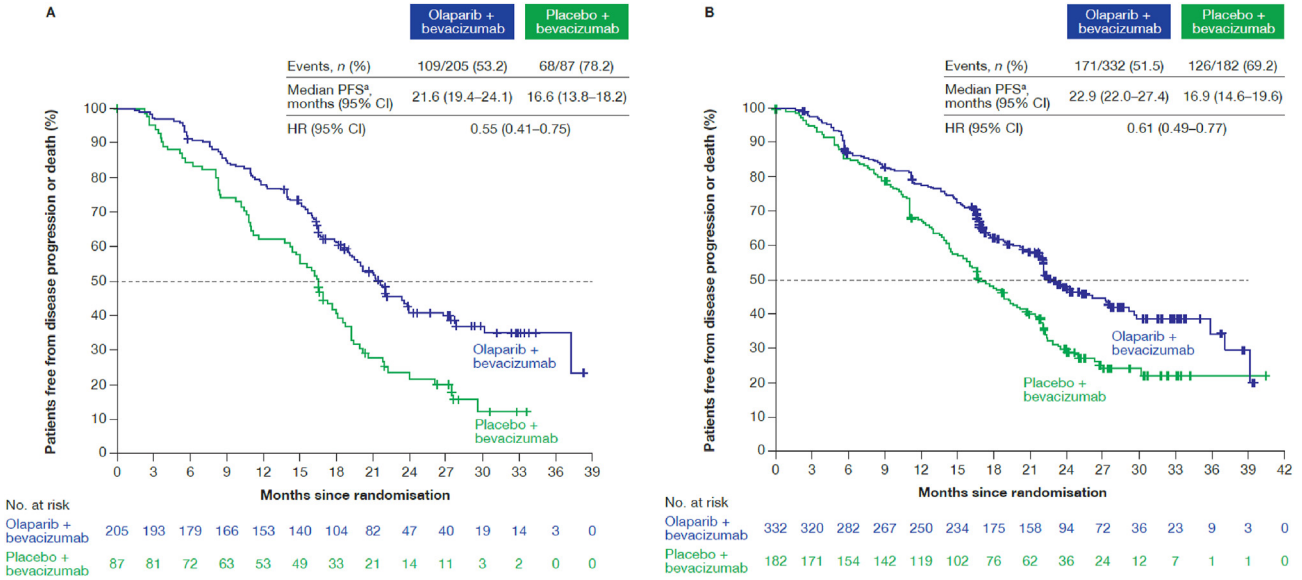

Fig. 1. Kaplan–Meier curves for PFS in the intention-to-treat population. (A) Older patients (aged ≥65 years). (B) Younger patients (aged <65 years). *Abbreviations*: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. [a]Estimated using the Kaplan–Meier method; HRs estimated using a multivariate Cox model.

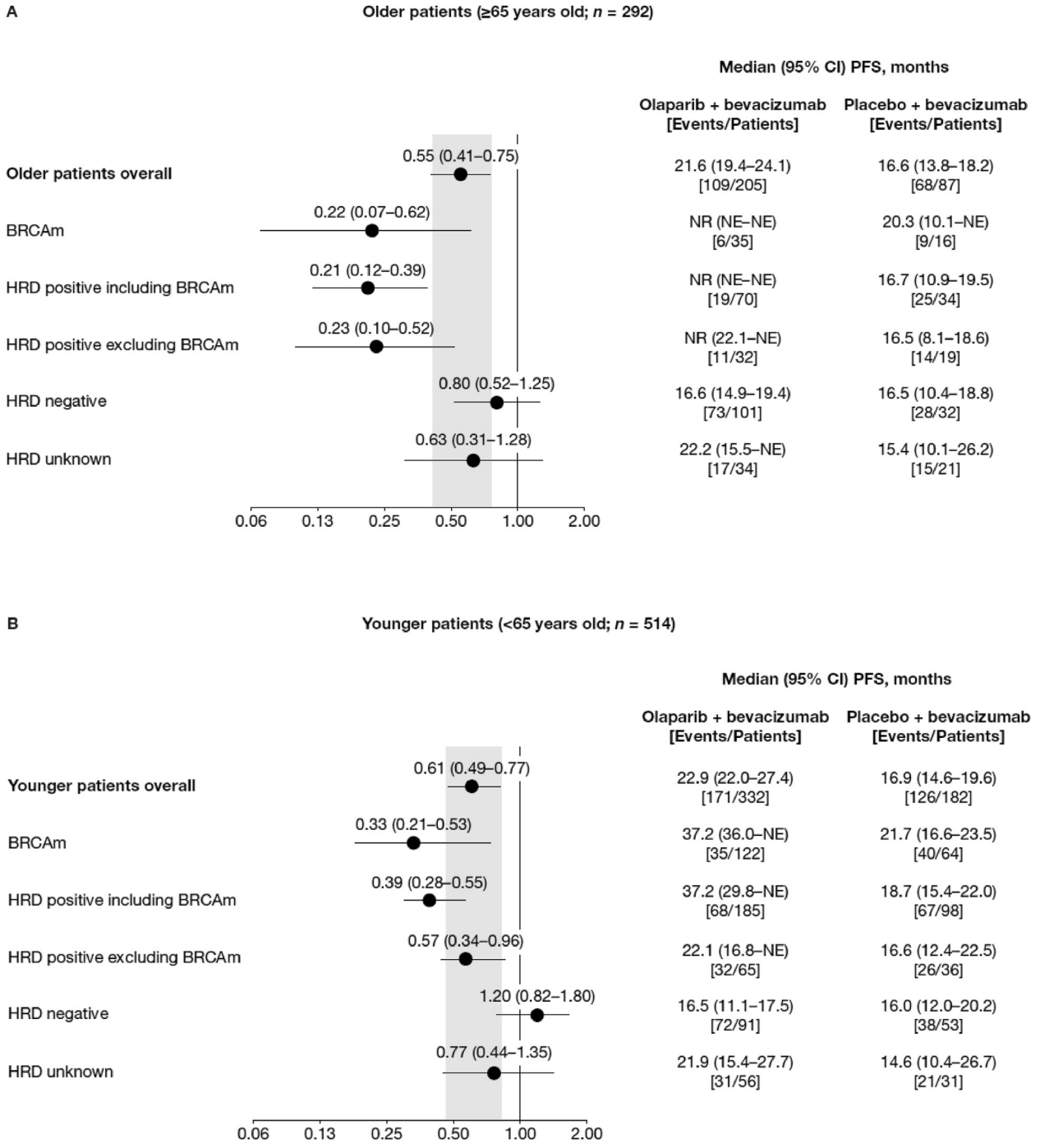

Fig. 2. PFS across treatment arms according to molecular features. (A) Older patients (aged ≥65 years). (B) Younger patients (aged <65 years). *Abbreviations: BRCA*m, *BRCA* mutated; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; NE, not estimable; NR, not reported; PFS, progression-free survival.

PFS in both age groups, and FIGO stage was an independent prognostic feature only in younger patients (Table 2).

3.4. Safety in the older population

We explored safety data according to age in the olaparib arm of PAOLA-1. The safety population included 204 and 331 patients in the older and younger subgroups, respectively. Median duration of treatment was 16.2 months (0.03–33.0) in older patients and 17.9 months (range 0.03–32.1) in younger patients. Rates of treatment interruptions and dose reductions due to treatment-related AEs were similar in older and younger patients (46.6% versus 41.4%, and 37.7% versus 37.8%, respectively). The main AE leading to dose reduction in the older population was anaemia (23.5%) (Table S3). Forty-three older patients (21.1%) discontinued olaparib

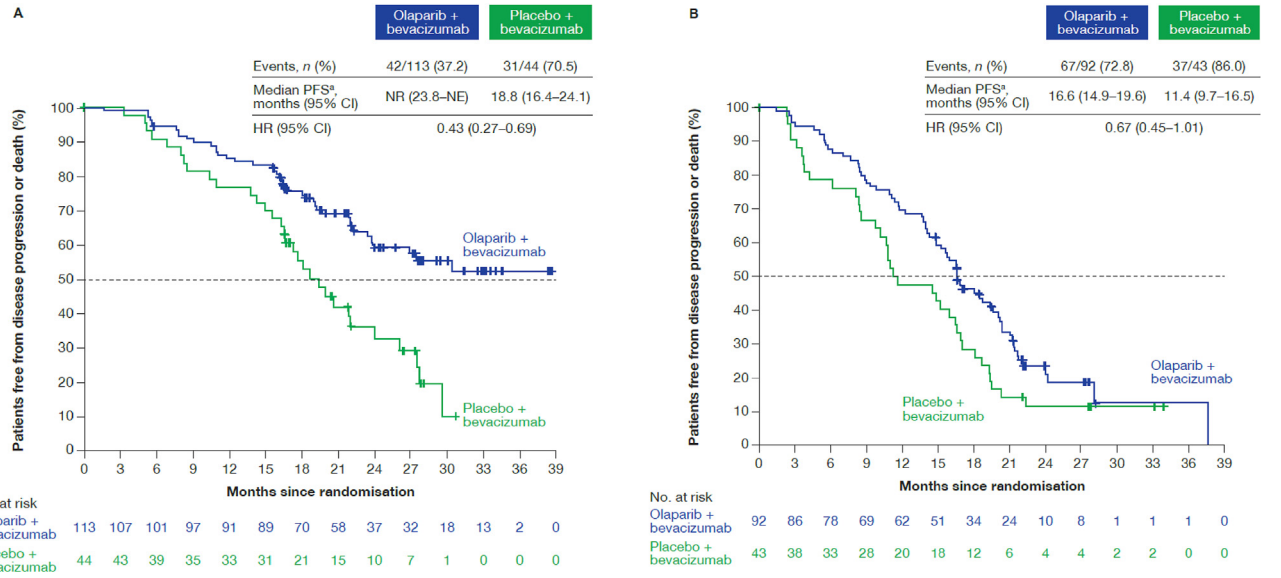

Fig. 3. Kaplan–Meier curves for PFS in the older population (aged ≥65 years). (A) Patients with complete cytoreduction following primary or interval debulking surgery. (B) Patients with macroscopic residual disease after surgery or with no surgery. *Abbreviations*: CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reported; PFS, progression-free survival. Includes patients with both upfront and interval surgery. [a]Estimated using the Kaplan–Meier method.

because of olaparib-related AEs, compared with 52 younger patients (15.7%). The main AEs leading to treatment discontinuation were anaemia (4.9%), nausea (3.4%), and fatigue/asthenia (1.5%).

The most common all-grade AEs with olaparib in the older population were fatigue/asthenia (57.4%), hypertension (52.0%), nausea (48.0%), and anaemia (47.1%) (Fig. 4A). Grade ≥3 AEs were observed in 132 older patients (64.7%) and 171 younger patients (51.7%) who received olaparib ($P = 0.0031$, chi-squared test). In patients randomised to the placebo arm, these rates were 45.9% and 61.6%, respectively (Fig. S2). Rates of olaparib-related grade ≥3 AEs were similar across age subsets: 36.8% in older patients versus 31.7% in younger patients ($P = 0.23$). Grade ≥3 AEs that were more common in the older group than in younger patients were hypertension (26.5% versus 13.9%) and anaemia (20.1% versus 15.7%) (Fig. 4B). During the study, in the olaparib arm, we observed one treatment-related AE with an outcome of death in the younger group and none in older patients. One older patient and two younger patients in the olaparib arm were diagnosed with myelodysplastic syndrome.

To explore AEs specifically related to olaparib, we analysed safety according to treatment arm in the older population (Table S4). As expected, all-grade haematological AEs and fatigue, as well as digestive disorders, were more frequent with olaparib. Among grade ≥3 AEs, anaemia (20.1% versus 0.0%) and lymphopenia (9.3% versus 1.2%) were more frequent in the olaparib arm. Hypertension occurred more often in the placebo arm (73.3% versus 52.0%; grade ≥3, 41.9% versus 26.5%; $P = 0.0097$).

4. Discussion

This pre-planned retrospective analysis explored features and outcomes of the older population included in the practice-changing PAOLA-1 study. Despite more stage IV residual disease after surgery or no surgery, and fewer patients testing HRD positive at inclusion in the older patients group, benefits from olaparib were similar

Table 2
Cox multivariate analyses for progression-free survival in older (aged ≥65 years) and younger patients (aged <65 years) who received olaparib.

Age	*N*	Independent factor	HR (95% CI)	*P* value
≥65 years	205	HRD status (positive versus negative)	0.23 (0.14–0.39)	<0.0001
		CC0 versus residual disease or no surgery	0.36 (0.24–0.54)	<0.0001
<65 years	332	FIGO stage (III versus IV)	0.70 (0.51–0.97)	0.030
		HRD status (positive versus negative)	0.25 (0.18–0.36)	<0.0001
		CC0 versus residual disease or no surgery	0.62 (0.46–0.84)	0.0024

Abbreviations: CC0, without macroscopic residual disease after surgery; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; HRD, homologous recombination deficiency.

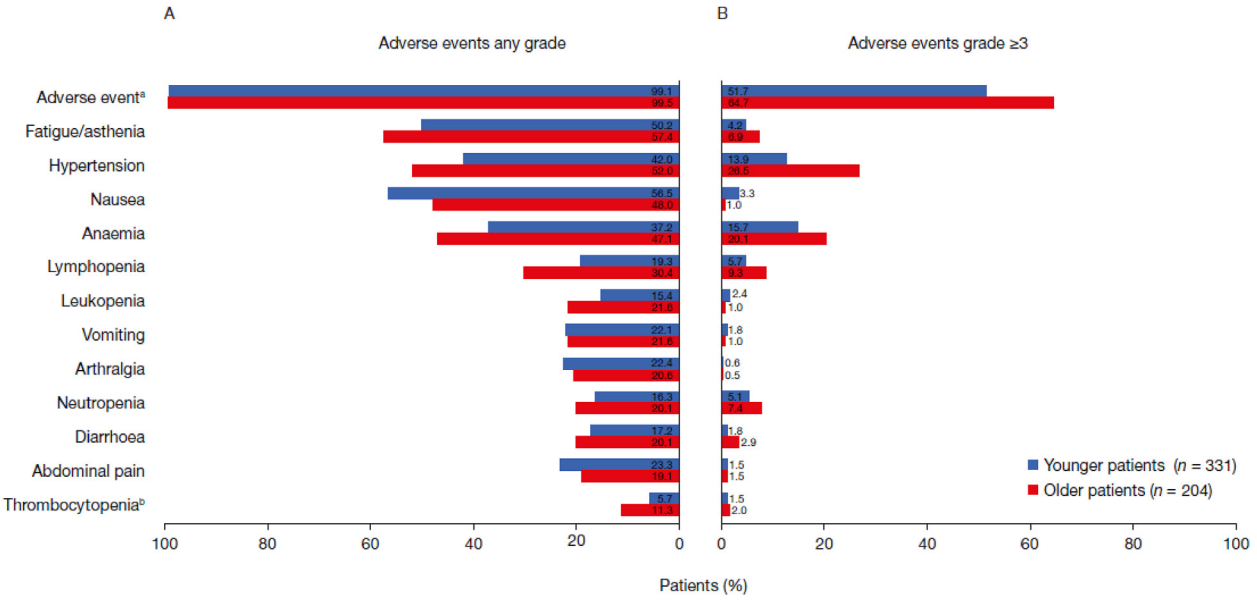

Fig. 4. Most frequent AEs in the olaparib arm by age. (A) All-grade AEs. (B) Grade ≥3 AEs. *Abbreviation*: AE, adverse event. [a]Overall incidence of AEs of any grade (left-hand panel) and grade ≥3 (right-hand panel). [b]Occurred in <20% of patients in either age group, but included to provide more complete information on the haematological safety profile.

between age groups. Even though older patients experienced more grade ≥3 anaemia and hypertension, olaparib discontinuation and dose reduction rates were similar to that of the younger population.

Demographics at baseline are consistent with published data suggesting that older women may be undertreated even without frailty criteria [19]. Only 42.0% of older patients underwent upfront debulking surgery compared with 55.7% of younger women. From a molecular point of view, *BRCA1* mutations are associated with younger age at ovarian cancer diagnosis [20]. Therefore, a lower proportion of those with *BRCA*m in the older versus younger subgroup was expected (17.5% versus 36.7%). Moreover, we observed that a lower proportion in the older population had HRD (34.1% versus 55.7%). Excluding *BRCA*m, HRD alterations, such as *BRCA1* promotor methylation, have been correlated with younger age [21,22]. The lower incidence of HRD in the older population may be suspected to reduce benefits of PARP inhibitors in this population.

In the current analysis, benefits of olaparib in the older population of PAOLA-1 were greatest in those with HRD-positive tumours, independent of *BRCA*m status. The HR for PFS was 0.22 (95% CI 0.07–0.62) in patients with *BRCA*m and 0.23 (0.10–0.52) in HRD-positive/*BRCA* wild-type cases. As in younger patients, the only subgroup without PFS improvement was the HRD-negative subset. In the first-line setting, whereas olaparib plus bevacizumab failed to improve outcomes in HRD-negative tumours compared with bevacizumab alone [14], niraparib is associated with a better PFS in these patients [23]. However, magnitude of PFS improvement was weaker in this subset than in other patients, and patients with a high platinum sensitivity were selected in the PRIMA-ENGOT-ov26 study, while this was not an inclusion criterion in the PAOLA-ENGOT-ov25 trial. No data have yet been published concerning treatment efficacy in older patients according to HRD status in the PRIMA and NOVA trials (niraparib) or in the ARIEL3 study (rucaparib) [24,25].

Another feature that may predict olaparib efficacy in our population is achievement of macroscopic complete cytoreductive surgery during first-line treatment. As the rate of complete cytoreductive surgery was lower in older patients, and as the PFS improvement associated with olaparib plus bevacizumab combination may be smaller in patients with residual disease after surgery [26], exploration of the impact of surgical status in this population was worthwhile. Although these results must be interpreted with caution due to small sample size, there was a trend, though non-significant, for a higher benefit of olaparib in older patients without macroscopic residual disease after surgery (HR for PFS was 0.43 [95% CI 0.27–0.69]) versus patients with gross residual disease after surgery or no debulking surgery (HR 0.67 [95% CI 0.45–1.01]). These results are consistent with recent data related to the whole HRD-positive population [26]. Therefore, olaparib plus bevacizumab combination is a standard of care in older patients with HRD-positive tumours whether a complete macroscopic resection is achieved or not.

Concerning safety, rates of grade ≥3 treatment-related AEs were comparable between older and younger patients. Also, the age groups had similar rates of dose reduction, treatment interruption, and treatment discontinuation. Moreover, no treatment-related death

was observed in older patients who received olaparib. This is consistent with what was observed with olaparib and niraparib in the recurrent setting. Older and younger patients with platinum-sensitive recurrent ovarian cancer had similar safety profiles [27,28]. The most frequent all-grade toxicities in the current analysis were fatigue, nausea, anaemia, and lymphopenia; all already described with olaparib [16]. The only high-grade AEs more frequent in older patients than younger patients were anaemia and hypertension. Within the older population, grade ≥3 anaemia and lymphopenia, both well-known AEs of PARP inhibitors, were more frequent with olaparib than placebo, whereas the rate of hypertension was higher with placebo plus bevacizumab. This is the first observation of reduced hypertension with a combination of vascular endothelial growth factor receptors (VEGFR) and PARP inhibitors. Although niraparib has been associated with hypertension, olaparib monotherapy has not [13,24,27,29]. VEGFR inhibitors, such as bevacizumab and cediranib, have been shown to increase risk of hypertension development [30,31], with higher rates in older patients [32,33]. Lower rates of hypertension in the olaparib arm compared with placebo may be explained by a protective effect of olaparib on endothelial vessels. Recent data suggest that olaparib may modify expression of long non-coding RNA involved in the regulation of transcription factors associated with angiogenesis-related genes [34]. This information may be useful for hypertension monitoring and management in the older population in which incidence of a history of hypertension is frequent.

Our work has some limitations as it is a subgroup exploratory analysis. Sample size has not been defined to explore olaparib efficacy and toxicity in this specific population. However, this study was one of the exploratory prespecified objectives of the PAOLA-1 trial and is the first work exploring PARP inhibitors administered in the first-line setting with bevacizumab and with a focus on older patients. This will bring important insights to the community and confirm that olaparib–bevacizumab maintenance is effective in older patients, with a good safety profile. Another bias associated with the study is related to the selection of older patients included in the trial. This group had a good performance status even after six cycles of carboplatin–paclitaxel chemotherapy in combination with bevacizumab, and most of them also underwent debulking surgery. Therefore, this population is likely not representative of real-world older patients. Real-world prospective programmes and studies limited to the older population without restriction on frailty [8,35–37] are needed to support our data. The addition of geriatric data such as the geriatric vulnerability score adapted to the ≥70-year-old population could also be of interest for the exploration of the efficacy and safety of PARP inhibitors according to standardised geriatric scales [7]. Another limitation to this work may be the exploration of the impact of surgical status on survival by combining primary and interval complete macroscopic resections. Primary debulking surgery remains a standard of care when feasible [38]. However, prospective data suggest that the prognostic impact of complete macroscopic resection is independent from the time of resection with similar overall survival between primary and interval surgeries [39,40]. To avoid multiple subgroup analyses and to spare statistical power, we chose to explore the impact of complete resection regardless of the timing of surgery in the first-line setting.

Furthermore, our data suggest that despite unfavourable prognostic and predictive baseline features (lower rates of complete macroscopic resection and HRD), PFS benefit in older patients is similar to the younger population, as was observed in the recurrent setting with olaparib or niraparib [27,28]. As no clear explanation to this observation can be brought to light based on our data, further research is needed to identify additional features predictive of olaparib efficacy in older patients. Ongoing translational research exploring tumour characteristics may be of interest to answer this question.

5. Conclusion

Despite a lower rate of complete upfront surgery, older patients enrolled in PAOLA-1 achieved a similar PFS benefit compared with younger patients, with a comparable safety profile. Rates of grade ≥3 anaemia and hypertension were increased in older patients and special attention should be paid to these events. Our findings support the efficacy of bevacizumab–olaparib maintenance after first-line chemotherapy in patients aged ≥65 years. Additional data are warranted to confirm these results in unselected older patients.

Author contributions

Renaud Sabatier: Study conceptualisation and methodology, data interpretation, writing – original draft, writing – review and editing.
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Claire Cropet: Formal analysis, writing – original draft, writing – review and editing.
Coline Montégut: Investigation and resources, writing – original draft, writing – review and editing.
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Hiroyuki Yoshida: Investigation and resources, writing – original draft, writing – review and editing.
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Nicoletta Colombo: Investigation and resources, writing – original draft, writing – review and editing.
Sakari Hietanen: Investigation and resources, writing – original draft, writing – review and editing.
Rémi Largillier: Investigation and resources, writing – original draft, writing – review and editing.
Ulrich Canzler: Investigation and resources, writing – original draft, writing – review and editing.
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Frederik Marmé: Investigation and resources, writing – original draft, writing – review and editing.
Laure Favier: Investigation and resources, writing – original draft writing – review and editing.
Eric Pujade-Lauraine: Study conceptualisation and methodology, data interpretation, original draft writing, final version approval.
Isabelle Ray-Coquard: Study conceptualisation and methodology, data interpretation, original draft writing, final version approval.

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Data availability

ARCAGY-GINECO has a long history of academic data sharing for research purposes.

The process is similar for every trial sponsored by ARCAGY-GINECO (or ARCAGY Research):

- Researchers are required to submit a request to the sponsor directly or through the principal investigator. The request should be written in a predefined format of a short synopsis indicating the objective of the research, the methodology intended to be used, including the statistical analysis plan, and the variables within the database required for the research
- A scientific board will review and approve the requests on a case-by-case basis.

Only encoded datasets will be used, which enables us to fulfil legal and ethical obligations to protect our patients while at the same time utilising patient data in progressing medical research to its full potential in the best interests of public health.

A specific agreement between the sponsor and the researcher is requested for data transfer. This data transfer agreement details both parties' responsibilities to ensure the required level of data integrity and legal and ethical obligations.

In the case of sharing encoded patient-level data, please note that the full dataset may not be shared in view of the following:

- Clinical consent for some countries prohibits secondary use of the data.
- Patients may withdraw their consent for participation in the trial at any point.

Other aspects might also be taken into consideration to protect patient privacy (e.g., review of rare clinical events where information is aggregated to a higher level before sharing).

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Renaud Sabatier: reports research grants from Eisai and AstraZeneca; advisory board for Roche, GSK, and Novartis; non-financial support (travel, accommodation, and meeting registration fees) from Pfizer, Roche, GSK, BMS College of Engineering, and AstraZeneca.

Frédérique Rousseau: reports advisory boards for Eisai, Novartis, and Viatris-Mylan.

Florence Joly: consulting fees from GSK (consulting EMA); payment/honoraria (advisory board) from AstraZeneca, MSD, and Seagen; payment/honoraria (advisory board, lectures) from GSK and Clovis; support for attending meetings and/or travel (symposium) from GSK, AstraZeneca, and MSD.

Claire Cropet: reports no conflict of interest.

Coline Montégut: reports no conflict of interest.

Johanna Frindte: reports no conflict of interest.

Saverio Cinieri: reports no conflict of interest.

Eva María Guerra Alía: reports consulting fees from AstraZeneca-MSD, Clovis Oncology, GSK-Tesaro, PharmaMar, and Roche; speaker bureau/expert testimony honoraria from AstraZeneca-MSD, PharmaMar, Roche, GSK-Tesaro, and Clovis Oncology; travel support from Roche, GSK-Tesaro, and Baxter.

Stephan Polterauer: reports advisory board for AstraZeneca, Eisai, MSD, Roche, GSK/Tesaro, Clovis; non-financial support (travel, accommodation, and meeting registration fees) from Roche, GSK/Tesaro, and AstraZeneca.

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Ulrich Canzler: reports advisory fees from Astra Zeneca; speakers' bureau fees from Lilly and AstraZeneca.

Alain Gratet: reports no conflict of interest.

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Appendix A. Supplementary data

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