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Clinical factors associated with prolonged response and survival under olaparib as maintenance therapy in *BRCA* mutated ovarian cancers

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HIGHLIGHTS

- We report a cohort of 115 ovarian cancer patients treated with olaparib.
- Median PFS was 12.7 months and median OS was 35.4 months, comparable to Study 19.
- PFI ≥ 12 months, CR and normalized CA-125 are associated with prolonged PFS and OS

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ABSTRACT

Objective: To investigate clinical factors associated with prolonged progression-free survival (PFS) and overall survival (OS) in relapsing epithelial ovarian cancer (EOC) patients with *BRCA* mutations and receiving olaparib as maintenance therapy in daily practice.

Methods: Multicenter (8 hospitals) European retrospective study of relapsing EOC patients having germline or somatic mutations of *BRCA1/BRCA2* genes and treated with olaparib as maintenance therapy after platinum-based chemotherapy.

Results: One hundred and fifteen patients were included. Median age was 54 years. There were 90 *BRCA1* carriers, 24 *BRCA2* carriers and one patient had germline mutation of *BRCA1* and *BRCA2*. Six patients had somatic mutations (all *BRCA1*) and 109 had germline mutations. Ninety percent had serous carcinomas and were platinum-sensitive. Following ultimate platinum-based chemotherapy, 69% of the patients had normalization of CA-125 levels and 87% had RECIST objective responses, either partial (53%) or complete (34%). After a median follow-up of 21 months, median PFS was 12.7 months and median OS

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Survival
Prognostic

was 35.4 months. In multivariate analysis, factors associated with prolonged PFS under olaparib were: platinum-free interval (PFI) ≥ 12 months, RECIST complete response (CR) or partial response (PR) and normalization of CA-125 upon ultimate platinum-based chemotherapy. Factors associated with prolonged OS were PFI ≥ 12 months, CR and normalization of CA-125.

Conclusions: Platinum-free interval ≥ 12 months, complete response and normalized CA-125 levels after ultimate platinum-based chemotherapy are associated with prolonged PFS and OS in relapsing *BRCA1/BRCA2* mutated ovarian cancer patients who received olaparib as maintenance therapy.

1. Introduction

Ovarian cancer is the second most lethal gynecological cancer [1]. It is diagnosed at advanced stage in >70% of patients. Standard therapy includes optimal debulking surgery and platinum/taxanes-based chemotherapy. Up to 20% of high-grade serous ovarian carcinomas (HGSOC), the most common histotype of epithelial ovarian cancers (EOC) [2], show germline and/or somatic mutations of *BRCA1/BRCA2* genes [3–5]. *BRCA1* and *BRCA2* are tumor suppressor genes playing a central role in repair of DNA double strand breaks (DSBs) through homologous recombination (HR). Due to their increased sensitivity to DNA damage agents such as platinum, *BRCA1* and *BRCA2* mutated EOC have prolonged survival, with *BRCA2* carriers having the best [6].

Poly(ADP–ribose) polymerase 1 is a key nuclear enzyme involved in single-strand breaks (SSBs) repair through the base excision repair pathway. In the absence of PARP activity, these lesions are thought to be converted into DSBs. HR deficient cells, for instance *BRCA* mutated cells, are profoundly sensitive to PARP inhibition [7,8]. This phenomenon, called “synthetic lethality”, led to the investigation of PARP inhibitors (PARPi) as therapeutic agent in *BRCA1/BRCA2* carriers.

During the early development of the PARPi olaparib, it appeared that platinum sensitivity is associated with higher objective response rate among *BRCA* carriers and non-carriers [9]. This “signal” in the study conducted by Gelmon et al. led to the design of the randomized phase II trial Study 19 that assessed the efficacy of olaparib *versus* placebo as maintenance treatment in platinum-sensitive relapsing patients with serous ovarian cancer who responded to a new line of platinum-based chemotherapy [10]. The olaparib group showed a significantly longer median progression-free survival (PFS) in comparison with the placebo group (8.4 months in the olaparib group *versus* 4.8 months in the placebo group (hazard ratio (HR) = 0.35; [95% CI = 0.25–0.49]; $p < 0.001$). Post-hoc analyses revealed that improvement of PFS in the olaparib group was greater in carriers of *BRCA* germline mutations (*gBRCA*; HR = 0.18; [95% CI = 0.10–0.31]; $p < 0.0001$) [11]. The SOLO2 study, a randomized, controlled, phase III study, further confirmed findings from Study 19 in patients with *gBRCA* mutations (no patients had *BRCA* somatic mutation) [12]. The median PFS, was significantly longer in the olaparib group (19.1 months) than the placebo group (5.5 months; HR = 0.30, [95% CI = 0.22–0.41]; $p < 0.0001$) [12]. Two other phase III trials (NOVA and ARIEL3) [13,14] confirmed the significant benefit from maintenance with PARPi in platinum-sensitive relapsing EOC patients having somatic or germline mutations of *BRCA1/2*. Study 19 and SOLO-2 trials recruited women with recurrent serous ovarian cancer (or fallopian tube or primary peritoneal cancer) who had platinum-sensitive disease defined as platinum-free interval lasting > 6 months. Additionally, patients must present a new response to the ultimate chemotherapy course defined by RECIST and/or CA-125 levels. The criteria varied slightly between Study 19 and SOLO2. In both studies, a key inclusion criteria was baseline CA-125 level prior to randomization that had to be either in the normal range or, if upper, with an increase < 15% in a second assessment made 7 days after. Objective radiological response (partial or complete response) according to RECIST was mandatory in SOLO2, whereas CA-125 response could be sufficient in Study 19, making patient’s selection higher in SOLO2. Similarly, NOVA and ARIEL3 trials requested both radiological and CA-125 response.

Clinical trials have selection bias and do not systematically reflect real-world outcomes. Real-world evidence is part of the regulatory process of approval of new drugs by regulatory agencies and lead to continuous improvement of clinical research [15]. The primary objective of this study is to assess outcome in *BRCA1/BRCA2* mutated ovarian cancer patients treated by olaparib as maintenance therapy in daily practice.

2. Materials and methods

2.1. Patient population

This retrospective study is based on prospectively recorded ovarian cancer patients bearing *BRCA* mutation and treated with olaparib at the time of cancer recurrence. Patients who benefit from early access program or received olaparib after approval were prospectively recorded by the pharmacy of their hospitals in France or their oncologists in Switzerland. Study participants were women with confirmed invasive epithelial ovarian or fallopian tube or primary peritoneal carcinoma, who had been tested positive for germline and/or somatic *BRCA1* or *BRCA2* pathogenic mutations through either blood or tumor tests. All patients were treated with olaparib following the results of Study 19, either on early access program or following EMA/Swissmedic approval of olaparib in ovarian cancers. No patient received olaparib within a clinical trial. Patient and treatment characteristics were collected from the medical records of patients treated at the Hôpitaux Universitaires de Genève (Geneva, Switzerland), Centre Eugène Marquis (Rennes, France), Institut du Cancer Jean Mermoz (Lyon, France), Centre Hospitalier Universitaire Vaudois (Lausanne, Switzerland), Centre Hospitalier Universitaire de Besancon (Besancon, France), Basel University Hospital (Basel, Switzerland), Institut Curie (Paris, France) and Centre Léon Bérard (Lyon, France). Overall, 115 patients who initited treatment with olaparib between March 26th 2014 and December 31st 2017 were included in this study. The database for the current analysis was locked on October 31st 2018, in order to get a minimal follow-up of 10 months for each patient. Most of the patients included in our analysis were platinum sensitive (*i.e.* recurrence of the cancer > 6 months from the last platinum based chemotherapy) and treated with platinum based chemotherapy prior to olaparib maintenance, accordingly to EMA/SwissMedic approval of olaparib.

The study was conducted following ethical guidelines of the declaration of Helsinki. The study was reviewed by the local Institutional Review Board in each hospital. Informed consent was obtained from all living patients in Geneva, Lausanne and Basel

(CCER#15-158). All the French patients consented to the use of their data at the time of genetic analysis. Clinical and pathological data were collected from medical records. These included patient demographics, tumor characteristics, surgical staging, macroscopic residual disease, platinum-sensitivity, recurrence and survival status. Surgical stage was classified according to the Federation internationale de gynécologie et obstétrique (FIGO) at diagnosis. Information regarding residual disease following primary surgery was collected from medical records. Pathology data, including histologic subtypes, tumor stages and grades were obtained from pathology reports. The reasons for discontinuation of olaparib (disease progression, toxicity or other) were recorded.

2.2. Response criteria and outcome measures

The primary objective of our study was to assess outcome with olaparib in real-life patients. The primary end-point was progression-free survival (PFS). Secondary endpoint was overall survival (OS). Date of progression was defined as the first instance of disease progression based on computed tomography imaging by Response Evaluation Criteria In Solid Tumors (RECIST) or clinical progression. Platinum-free interval (PFI) was defined as the interval between the time of completion of first line platinum-based chemotherapy and the date of first relapse or death. Platinum-sensitive patients were defined as those having PFI $\geq$ 6 months. Median observation time corresponded to median time on study for all subjects, *i.e.*, from olaparib initiation to the date of last follow-up. Progression-free survival (PFS) was defined as the time from olaparib initiation to progression or death from any cause. Overall survival (OS) was defined as the time from olaparib initiation to the date of death or last follow-up.

2.3. Statistical methods

Proportions were calculated for categorical data, whereas median and range were calculated for continuous data. Categorical data were compared using a $\chi 2$ test or a Fisher test, as appropriate. PFS and OS were estimated using Kaplan–Meier analysis. To evaluate the relationship between survival and biological and/or clinical factors, all potential prognostic factors were included in univariate Cox proportional hazard regression models. The proportional hazards assumptions were confirmed using log-log plots and Schoenfeld's residuals. Candidate prognostic factors with a 0.05 level of significance in the univariate analysis were then selected for inclusion in the multivariate analysis. Independent prognostic variables of PFS and OS were identified by a Cox regression analysis using a backward selection procedure. Missing data or inapplicable responses were excluded from the analyses. *P* values <0.05 were considered significant. All analyses were performed using STATA software (version 14.0).

3. Results

3.1. Patient characteristics

The clinical files of 120 patients presenting with recurrent ovarian cancer and treated with olaparib as a maintenance therapy were retrieved. A total of 115 women who met the inclusion/exclusion criteria were included in the cohort (Fig. S1): 90 (79%) patients harbored *BRCA1* mutations, 24 (21%) had *BRCA2* mutations and one patient carried both *BRCA1* and *BRCA2* germline mutation (she was analyzed separately from the rest of the cohort). The majority of patients had germline mutations (95%), with only 6 patients having somatic mutations (all were *BRCA1*). Patient demographics and clinical characteristics for 114 patients are summarized in Table 1. Median age was 54 years (33–81). Almost all patients presented with serous carcinoma ($n = 104$; 91.2%) diagnosed at advanced stage (90.2% had FIGO stage III/IV) and 62.8% had no macroscopic residual disease after debulking surgery. The vast majority presented platinum-sensitive recurrence before olaparib initiation (platinum-free survival $\geq$6 months; 90.3%).

There was no difference between *BRCA1* and *BRCA2* carriers regarding histologic subtype ($p = 0.10$), residual disease ($p = 0.64$), initial FIGO staging ($p = 1$), number of previous lines of chemotherapy ($p = 0.82$), PFI ($p = 0.43$), ultimate platinum-based regimen of chemotherapy ($p = 0.15$), CA-125 normalization before olaparib ($p = 0.61$) and response to ultimate platinum-based chemotherapy ($p = 0.81$). The only statistically significant difference was median age at diagnosis with *BRCA1* carriers being younger than *BRCA2* (53 *versus* 60 years old, $p = 0.02$) as expected [6].

3.2. Treatment and toxicity

Regarding platinum-based chemotherapy before initiation of olaparib, carboplatin associated with pegylated liposomal doxorubicin was the preferred regimen (44.7%), 18% received paclitaxel/carboplatin and 11% had gemcitabine/carboplatin. Chemotherapy resulted in objective tumor response according to RECIST criteria in 86.7% of patients and normalization of CA-125 in 68.9%. Virtually all patients (95%) who had normalized CA-125 before initiating olaparib had either partial or complete radiological response ($p < 10^{-3}$; Table 2). Two patients had secondary cytoreduction before starting olaparib.

Median delay between the end of ultimate platinum regimen and olaparib initiation was 39 days [7–140]. Half of the patients received olaparib as maintenance therapy at first relapse. At data-cutoff, 32 patients were still receiving olaparib. Five patients stopped olaparib due to toxicity: two for severe nausea/vomiting, one for pulmonary pneumocystosis and two for serious hematologic toxicity (they developed myelodysplasic syndrome while under olaparib). A third patient developed acute myeloid leukemia one year after stopping olaparib.

3.3. Survival

The median follow-up for the 114 women was 21.1 months [1.6–47]. Median PFS since initiation of olaparib was 12.7 months (Fig. 1A). There was no impact of the line of chemotherapy, chemotherapy regimen or type of mutation (germline *versus* somatic) on PFS. In multivariate analysis, factors associated with prolonged PFS were PFI $\geq$ 12 months ($p < 0.01$), partial ($p = 0.04$) or complete response to ultimate platinum ($p < 0.01$) and normalization of CA-125 ($p < 0.01$)(Table 3 and Fig. 2).

Median OS was 35.4 months (Fig. 1B). In multivariate analysis, factors associated with prolonged OS were PFI $\geq$ 12 months ($p = 0.03$), complete response to ultimate platinum ($p = 0.03$) and normalization of CA-125 ($p < 0.01$) (Table 4 and Fig. 2). The patient who carried *BRCA1* and *BRCA2* germline mutations progressed after 7 months of treatment with olaparib. She died 3 months later.

4. Discussion

This retrospective, European, multicenter study is the largest cohort assessing the benefit from olaparib as maintenance therapy in EOC patients with germline or somatic mutations of *BRCA1/BRCA2* genes in daily practice setting. We identified 3 independent factors associated with prolonged response to olaparib: platinum-free interval longer than 12 months, radiological partial or complete response and normalization of CA-125 levels before initiation of olaparib.

Normalization of CA-125 is a strong prognostic factor in relapsing EOC [16]. However, none of the three phase III trials (NOVA,

Table 1
Patients' characteristics. PLD: pegylated liposomal doxorubicin. FIGO: Fédération internationale de gynécologie et obstétrique.

	Entire cohort N = 114	*BRCA1* N = 90	*BRCA2* N = 24	*p*
Age median (min-max)	54.2 (32.10–81.4)	52.9 (32.1–81.4)	59.8 (37.2–81.0)	0.02
<55	59 (51.8)	52 (57.8)	7 (29.2)	
≥55	55 (48.3)	38 (42.2)	17 (70.8)	0.02
Histology				
Serous	104 (91.2)	84 (93.3)	20 (83.3)	
Endometrioid	2 (1.8)	2 (2.2)	0 (0)	
Others	8 (7.0)	4 (4.4)	4 (16.7)	0.10
***BRCA* mutation**				
Germline	107 (94.7)	84 (93.3)	23 (100)	
Somatic	6 (5.3)	6 (6.7)	0 (0)	0.34
Macroscopic residual disease				
Absent	71 (62.8)	57 (64.0)	14 (58.3)	
Present	42 (37.2)	32 (36.0)	10 (41.7)	0.64
FIGO staging				
I–II	11 (9.8)	9 (10.1)	2 (8.7)	
III–IV	101 (90.2)	80 (89.9)	21 (91.3)	1.00
Number of previous lines of chemotherapy				
2	58 (50.9)	45 (50.0)	13 (54.2)	
≥3	56 (49.1)	45 (50.0)	11 (45.8)	0.82
Platinum-free interval				
<6 months	11 (9.7)	8 (8.9)	3 (12.5)	
6–12 months	29 (25.4)	21 (23.3)	8 (33.3)	
≥12 months	74 (64.9)	61 (67.8)	13 (54.2)	0.43
Chemotherapy regimen before olaparib initiation				
Carboplatin-Paclitaxel	21 (18.4)	20 (22.2)	1 (4.2)	
Carboplatin-PLD	51 (44.7)	40 (44.4)	11 (45.8)	
Carboplatin-Gemcitabine	13 (11.4)	9 (10)	4 (16.7)	
Other platinum regimen	29 (25.4)	21 (23.3)	8 (33.3)	0.15
CA-125 normalization before olaparib				
Yes	73 (68.9)	59 (70.2)	14 (63.6)	
No	33 (31.3)	25 (29.8)	8 (36.4)	0.61
Response to ultimate platinum according to RECIST				
Stable disease	15 (13.3)	13 (14.6)	2 (8.3)	
Partial response	60 (53.1)	46 (51.7)	14 (58.3)	
Complete response	38 (33.6)	30 (33.7)	8 (33.3)	0.81

ARIEL3 and SOLO2) reported its predictive value in the setting of PARP inhibitor maintenance. This could be due to the fact that CA-125 levels were not reported in the case report forms, and/or because it had to be (i) less than the upper limit (ARIEL3), or (ii) reduced by >90% before PARP inhibitor administration (NOVA), or (iii) not increasing by >15% within 7 days (SOLO2).

In the current study, median PFS of the entire cohort was shorter than the one reported in the SOLO2 study (12.7 months *versus* 19.1 months) [12]. However, when selecting in our cohort patients who normalized their CA-125 before starting olaparib, median PFS was 20 months, similar to what was observed in *BRCA1/BRCA2*-mutated patients in the three randomized phase III trials suggesting that patients included in these trials were highly selected. For instance, our population included less complete responders than in the SOLO-2 trial (32% *versus* 46%). Similarly, restrictive inclusion criteria in these registration trials limited the possibility to analyze other factors such as radiological response as patients were already in profound biological response. Consequently, there was no substantial difference in PFS in the NOVA and Study 19 trials according to radiological response (CR *versus* PR) or PFI (between 6 and 12 mo or >12 mo).

Table 2
Correlation between normalization of CA-125 and radiological response according to RECIST. RECIST: Response evaluation criteria in solid tumors.

	CA-125 normalization before olaparib	
	No	Yes
RECIST radiological response		
Stable disease	7 (22%)	4 (5%)
Partial response	22 (69%)	35 (48%)
Complete response	3 (9%)	34 (47%)
Total	32 (100%)	73 (100%)

Platinum-free interval is a prognostic and predictive factor of highest value in relapsing EOC, used in daily practice to prioritize subsequent therapies [17,18]. Our results are consistent with the literature, showing that PFI longer than 12 months is an independent factor associated with prolonged response and survival under olaparib.

Our daily practice study has some limitations that are linked to heterogeneity of the population, revealing some degree of liberty in prescribing olaparib. The initial EMA marketing authorization was "monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed *BRCA1/BRCA2* mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy". This authorization was generally respected in our series except a minority of cases presented with platinum-resistant (9.7% of cases) and/or non-serous histology (8.8%) and/or stable RECIST disease (13.3%). There are several potential explanations. Since olaparib is approved in Europe only as a maintenance therapy after platinum-based chemotherapy, oncologists probably tried a new line of platinum-based therapy in some patients, even though the disease was not platinum-sensitive as defined by the 6 months threshold because it was the only way for these young patients to have access to olaparib. This question recently led European ovarian cancer experts to re-define platinum-sensitivity in their recommendations based not on this delay but rather on response to platinum-based therapies [19]. Recent studies showed that ovarian tumors arising in a *BRCA*-deficient context were sensitive to PARP inhibitors,

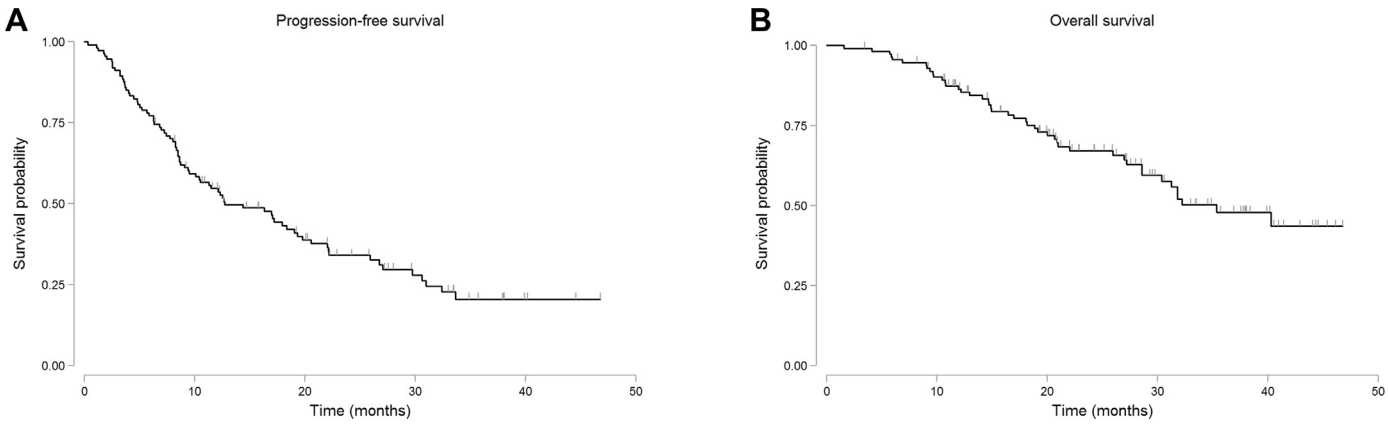

Fig. 1. Progression-free survival and overall survival in the entire cohort. A: progression-free survival. B: overall survival.

Table 3
Univariate and multivariate analysis of progression-free survival. PFS: progression-free survival.

Variable	Univariate analysis			Mutivariate analysis	
	Median PFS (months) (95% CI)	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age					
<55 years	12.6 (8.5–26.8)	R			
≥55 years	14.4 (9.4–22.1)	1.2 (0.7–1.8)	0.53		
BRCA					
BRCA1	12.7 (8.7–19.0)	R			
BRCA2	18.3 (8.2–32.4)	0.8 (0.5–1.4)	0.46		
***BRCA* mutation**					
Germline	16.3 (10.4–19.8)	R			
Somatic	6.8 (5.1-∞)	1.4 (0.5–3.9)	0.52		
Macroscopic residual disease					
Absent	14.4 (8.5–22.1)	R			
Present	12.7 (9.5–22.2)	1.1 (0.7–1.8)	0.59		
Number of previous lines of chemotherapy					
2	12.7 (9.5–19.8)	R			
≥3	17.1 (8.3–26.8)	1.0 (0.6–1.8)	0.98		
Platinum-free interval					
<12 months	10.4 (6.3–17.1)	R		R	
≥12 months	18.0 (10.1–26.8)	0.6 (0.4–0.9)	0.02	**0.5 (0.6–0.8)**	**<0.01**
Chemotherapy regimen before olaparib initiation					
Carboplatin-Paclitaxel	12.7 (3.5-∞)	R			
Carboplatin-PLD	17.0 (10.2–26.8)	0.8 (0.4–1.5)	0.44		
Carboplatin-Gemcitabine	18.0 (4.8-∞)	1.0 (0.4–2.3)	0.98		
Other platinum regimen	12.1 (6.3–22.2)	1.0 (0.5–1.9)	0.98		
Response to last platinum according to RECIST					
Stable disease	4.0 (2.8–8.1)	R		R	R
Partial response	10.4 (8.4–17.0)	0.4 (0.2–0.8)	0.01	**0.5 (0.2–1.0)**	**0.04**
Complete response	33.6 (19.8-∞)	0.1 (0.1–0.3)	<0.01	**0.2 (0.1–0.4)**	**<0.01**
CA-125 normalization after last platinum					
No	7.2 (3.7–10.1)	R		R	
Yes	19.8 (14.4–31.0)	0.3 (0.2–0.5)	<0.01	**0.5 (0.3–0.8)**	**<0.01**

whatever tumor histology, probably explaining the absence of definitive rejection according to this criterion. Finally, the early access program of olaparib was less restrictive than definitive label as response to platinum agents could be estimated either by RECIST criteria or GCIG biological criteria for CA-125. Another important point is that overall survival analysis comparing our data with prospective, interventional phase III trials cannot be validated because their results are still immature.

The median overall survival of our cohort was 35.4 mo, very similar to the 34.9 mo reported in *BRCA* mutated who received olaparib in Study 19 [20]. In a subgroup analysis, we found that PFI ≥ 12 mo, radiological CR and normalization of CA-125 were independently associated with prolonged survival. OS data from the three randomized trials will be presented in the next few years. From Study 19, it appears that long responders to olaparib are enriched in *BRCA2* carriers [21]. In our cohort, *BRCA2* carriers had a trend toward prolonged survival but this was not significant ($p = 0.18$). Our study is limited by the number of *BRCA2* carriers (only 24 cases).

An important question that needs to be addressed is whether germline and somatic *BRCA*-mutated patients derive the same benefit from olaparib? In our cohort, only 5% of the patients harbored somatic mutation, thus limiting any interpretation. Subgroup analyses of ARIEL3 [14], Study 19 [22] and NOVA suggested no difference between germline and somatic mutations. Now that somatic testing of *BRCA* genes is well implemented in the clinics, this question will be important to address in the future.

We did not investigate the response rate to olaparib in patients who were partial responders to platinum because most of the patients in maintenance setting are monitored by CA-125 with

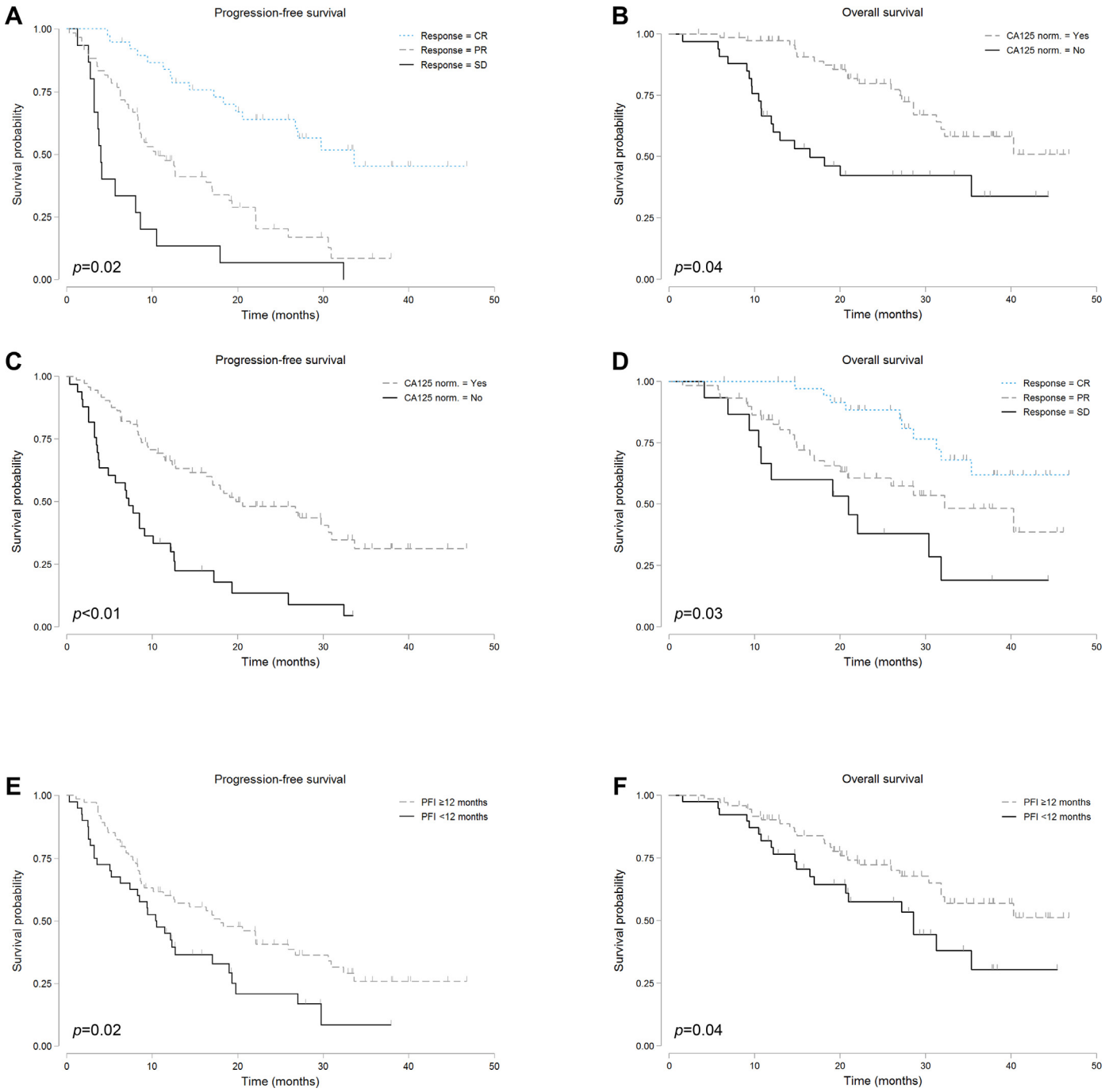

Fig. 2. Factors associated with prolonged PFS and OS under olaparib. A and B. PFS and OS according to CA-125 normalization. C and D. PFS and OS according to RECIST response. E and F. PFS and OS according to Platinum-free interval. Norm: normalization.

radiological assessment only in case of clinical or biological progression. In ARIEL3 study, the response rate to rucaparib in *BRCA* mutant carcinoma with measurable disease was 38%, including conversion to complete response in 18%.

From this large daily practice cohort it appears that a subset of relapsing *BRCA* carriers had limited benefit from olaparib monotherapy as maintenance therapy. Combining olaparib with oral anti-angiogenic cediranib does not seem to bring additional benefit (compared to olaparib monotherapy) in *gBRCA1/BRCA2* platinum-sensitive women [23]. *BRCA* mutated EOC are highly infiltrated by tumor-infiltrating lymphocytes [24,25] that express PD1/PD-L1 [26]. According to preclinical studies in a mouse model of EOC they are very likely to benefit from combining olaparib and anti-PD1, through activation of the STING pathway [27]. Several trials investigating a combination of PARPi and anti-PD1/PD-L1 are ongoing to test this hypothesis (NCT02734004, NCT02657889).

5. Conclusion

In this daily practice retrospective study, we found that olaparib in the maintenance setting in *BRCA*-mutated patients resulted in long median PFS and OS, similar to what has been observed in Study 19. We identified three baseline clinical factors predictive for prolonged response and survival under olaparib that are easily

Table 4
Univariate and multivariate analysis of overall survival. OS: overall survival.

Variable	Univariate analysis			Mutivariate analysis	
	Median OS (months) (95%CI)	Hazard Ratio (95%CI)	*P* value	Hazard Ratio (95%CI)	*P* value
Age					
<55 years	40.3 (30.4-∞)	R			
≥55 years	31.8 (20.9-∞)	1.2 (0.7–2.2)	0.56		
BRCA					
BRCA1	31.8 (27.0-∞)	R			
BRCA2	∞ (27.2-∞)	0.6 (0.2–1.3)	0.18		
***BRCA* mutation**					
Germline	35.4 (28.6-∞)	R			
Somatic	20.7 (9.0-∞)	2.5 (0.8–8.2)	0.13		
Macroscopic residual disease					
Absent	40.3 (27.0-∞)	R			
Present	31.8 (20.0-∞)	1.2 (0.7–2.2)	0.56		
Number of previous lines of chemotherapy					
2	∞ (27.1-∞)	R			
≥3	31.8 (20.0-∞)	1.4 (0.8–2.5)	0.30		
Platinum-free interval					
<12 months	28.6 (16.5-∞)	R		R	
≥12 months	∞ (31.8-∞)	0.53 (0.3–1.0)	0.04	**0.5 (0.3–0.9)**	**0.03**
Chemotherapy regimen before olaparib initiation					
Carboplatin-Paclitaxel	∞ (18.2-∞)	R			
Carboplatin-PLD	40.3 (31.3-∞)	0.9 (0.4–2.2)	0.82		
Carboplatin-Gemcitabine	25.9 (9.6-∞)	2.0 (0.7–5.8)	0.19		
Other platinum regimen	28.6 (18.1-∞)	1.3 (0.5–3.4)	0.54		
Response to last platinum according to RECIST					
Stable disease	21.0 (9.4–31.8)	R		R	
Partial response	32.2 (20.0-∞)	0.6 (0.3–1.1)	0.11	0.7 (0.3–1.7)	0.47
Complete response	∞ (31.8-∞)	0.2 (0.1–0.5)	<0.01	**0.3 (0.1–0.9)**	**0.03**
CA-125 normalization after last platinum					
No	16.5 (10.8-∞)	R		R	
Yes	∞ (31.3-∞)	0.3 (0.2–0.6)	<0.01	**0.4 (0.2–0.8)**	**<0.01**

accessible in the routine. In the era of precision medicine, identifying further biomarkers such as a correlation between *BRCA1/BRCA2* genotype [21,28–30] and response to olaparib will help in better tailoring therapies.

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