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Real-World Data on Olaparib in Relapsed BRCA-mutated Ovarian Cancer: A Multicenter GINECO RETROLA Cohort Study

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Abstract. *Background/Aim: Olaparib was approved in 2014 by the European Medicines Agency (EMA) as maintenance treatment for patients with breast cancer gene (BRCA)-mutated platinum-sensitive relapsed high-grade epithelial ovarian cancer (EOC) following the results of the Study 19. We present the results of a national real-world study on the effectiveness of olaparib in relapsed BRCA-mutated EOC patients. Patients and Methods: Patients with EOC, peritoneal, and/or fallopian-tube cancer treated with olaparib in a French Center between May 2014 and March 2017 were included. The primary end-point of the study was progression-free survival. Results: Of the 128 patients analyzed, 89 were treated according to the EMA label. The median progression-free survival was 17.0 months. The most common treatment-related toxicity was fatigue. Treatment-related myelodysplastic syndrome (n=5) and a second cancer (n=1) were diagnosed. Conclusion: In this real-life setting, olaparib confirmed its efficacy and safety profile, as previously shown in clinical trials.*

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Key Words: Ovarian cancer, olaparib, BRCA mutation, routine clinical practice, PARPi, platinum, BRCA, relapsed ovarian cancer.

Ovarian cancer is the fifth leading cause of cancer-related deaths among women (1). The majority (90%) of malignant ovarian cancers are epithelial in origin designated as epithelial ovarian cancer (EOC) (1, 2). Most women are

diagnosed with an advanced International Federation of Obstetrics and Gynaecology (FIGO) stage III and IV EOC and currently the most effective standard treatment is cytoreductive surgery with systemic platinum-taxane chemotherapy. Despite this optimal first-line treatment, more than a half of women will relapse in the first three years (1, 3, 4). Tumor chemosensitivity related to deficiency in repair of DNA damage remains a major factor accounting for this effect. Approximately half of all high-grade serous ovarian cancers are homologous recombination (HR)-deficient and 20% have germline or somatic breast cancer gene (BRCA) mutations (5-7). Inhibitors of poly-ADP-ribose polymerase (PARPi) were shown to be effective in HR-deficient tumors in a synthetically lethal interaction (6-12), leading to major changes in the treatment of tumors with disruptive mutations in BRCA 1/2 or other HR factors. Four PARPi, olaparib, niraparib, rucaparib, and veliparib, have been tested for treatment of EOC in phase III trials (13-20).

In December 2014, the European Medicines Agency (EMA) approved olaparib as maintenance treatment for women with BRCA-mutated (BRCAm) (germline and/or somatic) platinum-sensitive relapsed (with complete or partial response) high-grade serous EOC, fallopian tube, or primary peritoneal cancer (21); this approval was based on the "Study 19" phase II trial results (22, 23). In the BRCAm population, the benefit of olaparib in terms of median progression-free survival (PFS) was greater than in the non-BRACAm population: 11.2 months (95% CI=8.3-not calculable) *versus* 4.3 months (95% CI=3.0-5.4); HR=0.18 (95% CI 0.10-0.31), $p<0.0001$. Adverse events (AEs) were more common in the olaparib arm and included nausea (68.4%), fatigue (48.5%), vomiting (31.6%), and anemia (16.9%). Grade 3 or higher AEs occurred in 35.2% of patients treated with olaparib (*versus* 20.3% on placebo); the most common grade ≥3 AE experienced following olaparib treatment was anemia (7.3%). These promising results led to launching of the pivotal phase III SOLO2 trial including only patients with BRCAm platinum sensitive relapsed ovarian cancer (13). The trial confirmed the efficacy of olaparib with a median PFS of 19.1 months *versus* 5.5 months with placebo (HR=0.30, 95%CI=0.22-0.41, p=0.0001). Importantly, in both Study 19 and SOLO2, olaparib maintenance therapy did not have a negative impact on health-related quality of life compared to placebo. Adverse events observed were generally consistent with the known safety profile of olaparib and were mostly of mild or moderate severity. Dose reduction or interruption for the management of olaparib-associated AEs during the first 3 months did not impact on clinical outcomes (24). At the SOLO2 trial final analysis with longer follow-up, secondary malignancies occurred in 5.1% (5/99) of patients in the placebo group and in 3.6% (7/195) of those following olaparib treatment (34). The separate standalone safety and efficacy findings from the China cohort of SOLO2 (consisting of 32 randomized patients from sites in China) (25) showed similar results.

Bellier *et al*. reported the first French real-life data through temporary use authorization (ATU) program with olaparib in first-line maintenance treatment of 52 French BRCAm EOC patients (26). In this study, olaparib was well tolerated and no new safety signals were observed in this setting.

Overall, the latter and all above-mentioned findings provide evidence of olaparib efficacy in recurrent, platinum-sensitive, high-grade serous ovarian cancer. The aim of the study was to retrospectively investigate French patients with BRCAm relapsed EOC who received olaparib in real-world clinical practice in order to see whether its clinical efficacy in terms of duration of treatment and survival reflects this observed in the Study 19 and SOLO2 trials.

Patients and Methods

Study design. This retrospective cohort study (ClinicalTrials.gov Identifier: NCT04152941) included BRCAm relapsed EOC patients who received olaparib according to its EMA approved label in a real-life setting between May 2014 and March 2017 in 28 French Centers, each representing different scopes of clinical practice. We used routinely collected data from medical records to investigate duration of treatment, survival, and safety. We described patient, disease, and treatment characteristics in the whole study population, in patients who received olaparib according to the EMA label use (named as "the EMA population" throughout the paper), and in patients given olaparib off-label (named as "the off-label population" throughout the paper).

Patients and treatments. Eligible patients were aged ≥18 years, with histologically confirmed ovarian cancer, primary peritoneal cancer, and/or fallopian-tube cancer treated with olaparib 400 mg monotherapy twice daily (capsule formulation), whatever the line of therapy, in the platinum-sensitive setting. Patients could be either alive or deceased at the time of data collection and must not have any objection to anonymizing obtained data and to automated processing. Patients treated with olaparib in clinical trials were excluded.

Efficacy outcomes. The primary objective was to assess the efficacy of olaparib in terms of progression-free survival (PFS) in the overall population and in association to the following: prior lines of treatment received (two, three or more), type of *BRCA* mutation (germinal, somatic), and dose reduction (yes *versus* no). PFS was defined as the time from the date of treatment start to the date of the first documented progression or death from any cause. Secondary objectives were overall survival (OS), defined as the time from the date of randomization to the date of death from any cause, in the overall population and in association to the following: prior lines of treatment received (two, three or more), type of *BRCA* mutation (germinal, somatic), and dose reduction (yes *versus* no), the incidence of adverse events of special interest (AESIs) (anemia, thrombopenia, nausea and vomiting, fatigue, myelodysplastic syndrome, upper respiratory infections, diarrhea, decreased appetite, dysgeusia, headache, and secondary cancers) related to olaparib treatment and their management in the real-life setting, reasons for treatment modifications (dose discontinuation, interruptions/delay, reduction, and/or increase), the efficacy according to type of BRCA mutation, the number of patients with somatic BRCA treated with olaparib, and the number of long-term responders.

Statistical analysis. At least 112 patients were included in the study in order to insure a precision of at least 10% in the estimation of the 12 months PFS (95% CI).

Consecutive patient data were extracted from medical records. The EMA label population contained all patients who did not have any major protocol violation and received study treatment at least once according to the EMA label use. Patients without progression at the time of the statistical analysis were censored at the date of their last tumor assessment or last contact date, if no tumor assessment was performed. Patients without documentation of death at the time of the statistical analysis were censored at the date they were last known to be alive and randomized patients without any post baseline assessment were censored at a randomized date. Categorical variables were described by frequency and proportion; summary statistics (median, range) were used to report continuous data. Survival curves were obtained using the Kaplan–Meier method and compared with the log-rank test using hazard ratios (HRs) and theirs 95% confidence intervals (CIs). Patient with more than 24 months treatment were defined as long term-responders.

Results

Patient characteristics. We identified 130 patients treated with olaparib between May 2014 and March 2017. Two patients were excluded [olaparib given within a clinical trial (n=1), center not available for data entry extraction (n=1)], leaving 128 remaining patients for analysis. A total of 89 patients were treated according to the EMA label use. Of the 39 off-label patients, 20 did not experience a complete or partial response at baseline, 14 received olaparib in off-label prescription, two did not experience a complete or partial response at baseline and received olaparib in off-label prescription, two patients did not experience a complete or partial response at baseline and did not have *BRCA* mutation, and one did not have *BRCA* mutation. Baseline characteristics are shown in Table I.

Table I. *Clinicopathological characteristics of the studied patents at baseline*.

Characteristic	N (%)
Age, (years), median (range)	61.5 (56.0-68.0)
ECOG PS*	
0	40 (31.3)
1	61 (47.7)
2	10 (7.8)
3	1 (0.8)
Missing	16
Histologic finding	
Ovary	117 (91.4)
Peritoneum	9 (7.0)
Fallopian tubes	2 (1.6)
Histopathological subtype	
Serous high grade	97 (75.8)
Endometrioid grade 2/3	4 (3.1)
Serous low grade	3 (2.3)
Endometrioid grade 1	1 (0.8)
Undifferentiated	8 (6.3)
Other	15 (11.7)
FIGO stage	
I	4 (3.1)
II	6 (4.7)
III	89 (69.5)
IV	11 (8.6)
Unknown	18 (14.1)
Number of prior lines of systemic therapy, median (range)	3.0 (1.0-17.0)
Prior lines of systemic therapy	
1	1 (0.8)
2	40 (31.3)
>2	87 (68.0)
Disease status	
Complete response	46 (35.9)
Partial response	44 (34.4)
Non evidence of disease	10 (7.8)
Stable disease	3 (2.3)
Progressive disease	11 (8.6)
Not evaluable	13 (10.2)
Missing	1
BRCA type of mutation	
Germline BRCA 1	64 (64/98; 65.3)
Germline BRCA 2	32 (32/98; 32.7)
Germline BRCA 1 and BRCA 2	2 (2/98; 2.0)
Somatic BRCA 1	13 (13/25; 52.0)
Somatic BRCA 2	12 (12/25; 48.0)
No mutation	3 (2.3)
Missing	2 (1.6)

*If baseline missing, a first variable available. ECOG PS: Eastern Cooperative Oncology Group performance status; FIGO: International Federation of Gynecology and Obstetrics; BRCA 1: breast cancer gene 1; BRCA 2: breast cancer gene 2.

Efficacy. The median treatment duration was 13 months (95%CI=11.0-17.0); 32 patients (26.4%) were long term-responders (more than 24 months of treatment). Treatment dose was reduced or interrupted in 75 patients (58.6%), mainly due to toxicity (35.9%, 46/128). The majority of patients discontinued treatment due to disease progression (75.7%; 78/103) while 14 (13.6%) due to toxicity. At the data cut-off date (February 11, 2019), the median follow-up duration was 41.8 months (95%CI=38.7-45.0); 73 patients (58.9%) died, 47 (37.9%) had completed follow-up as planned, four (3.2%) were lost to follow-up, and four (3.2%) had discontinued treatment because of an unknown reason. The median PFS was 17.0 months (95%CI=14.7-21.3) in the EMA label population and 15.5 months (95% CI=12.6-18.1) in the whole population (Figure 1). Patients who received two or more previous lines of systemic therapy had significantly prolonged PFS; the median PFS in EMA label population and the whole population was 33.8 months (95%CI=21.3-not evaluable) or 14.2 months (95%CI=11.1-16.1), respectively (HR=2.81, 95%CI=1.73-4.55, p=0.001). The median OS in the EMA label population and in the whole population was 34.9 months (95%CI=27.2-46.4) and

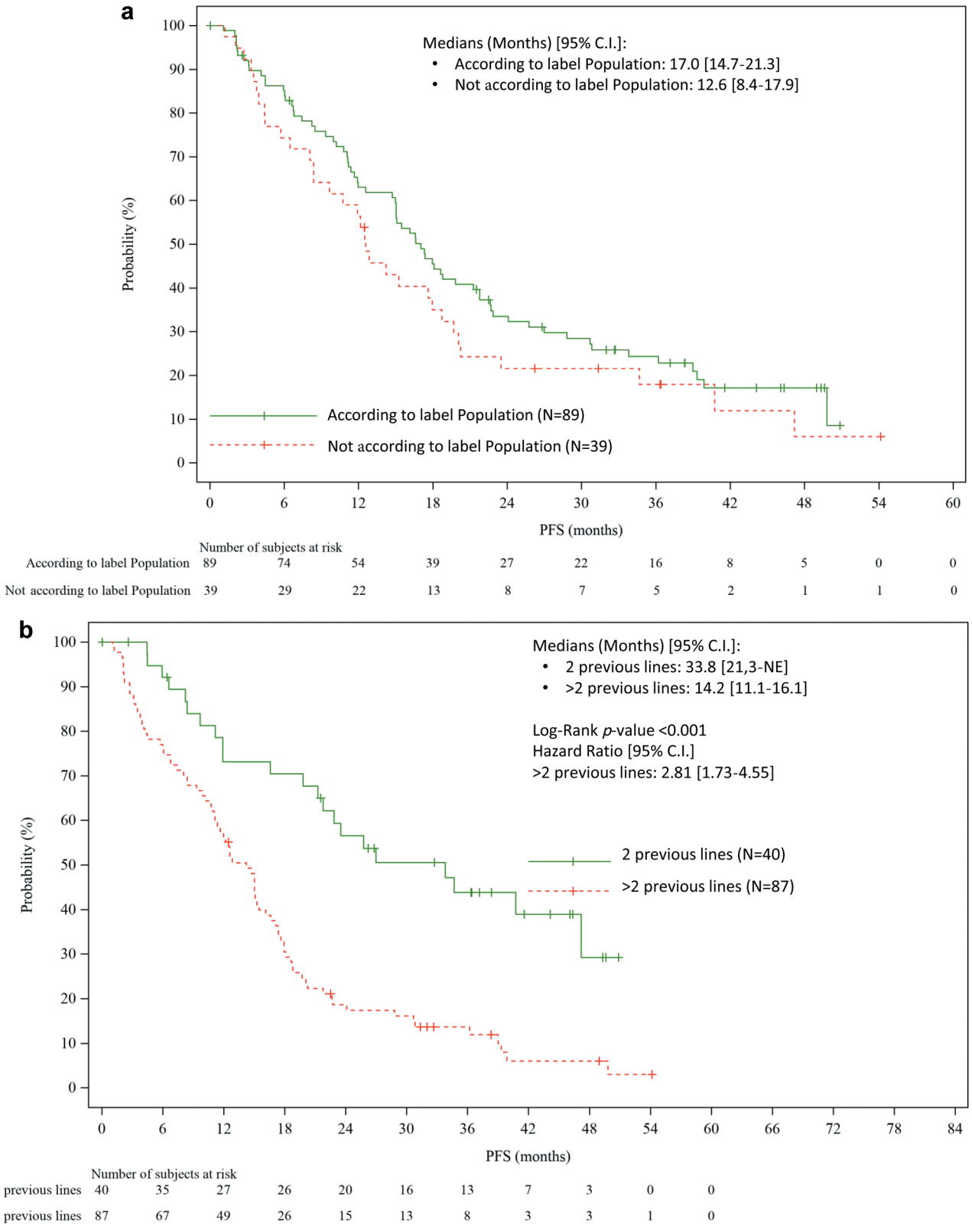

Figure 1. *PFS of studied patients. (a) PFS of patients treated with olaparib according to the EMA label use (green curve) and given olaparib off-label (red curve). (b) PFS of patients who received 2 prior lines of therapy (green curve) and of those who had more than two prior lines of therapy. PFS: Progression-free survival, EMA: European medicines agency.*

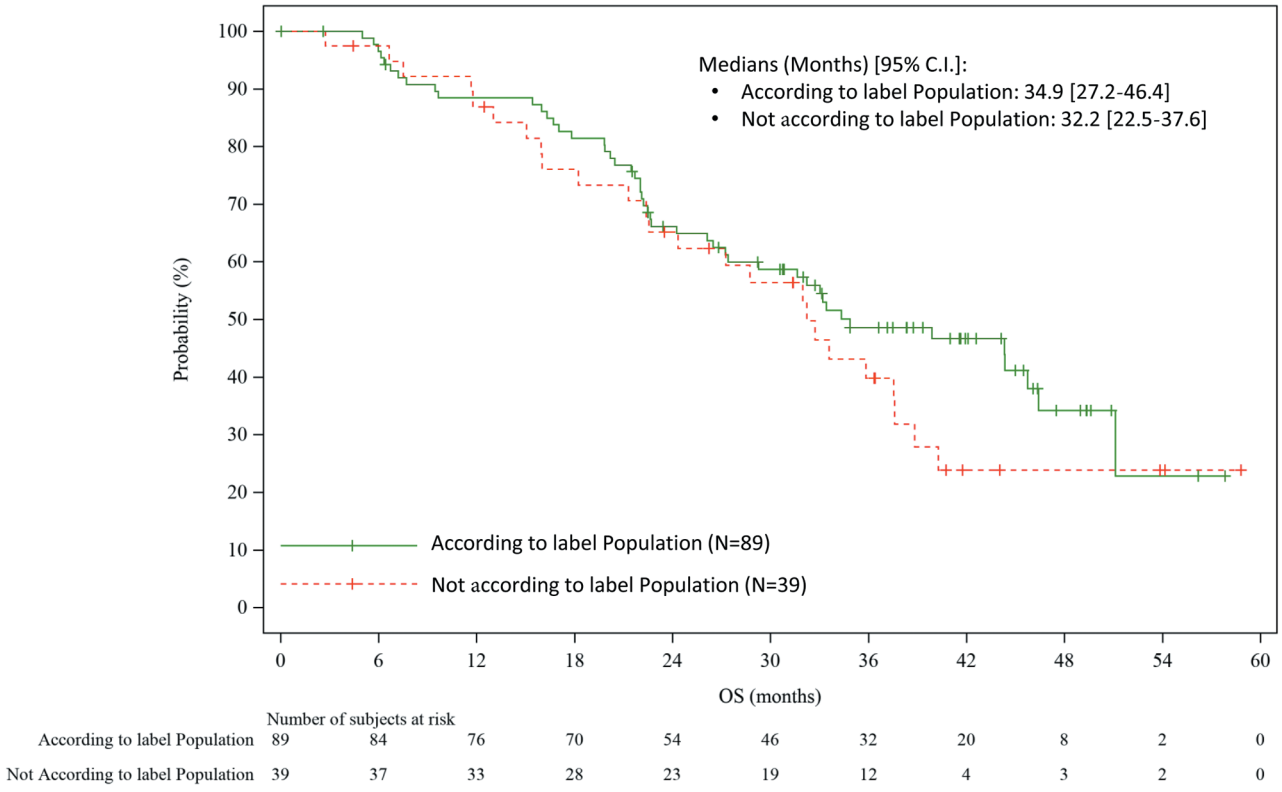

Figure 2. *OS of patients treated according to the EMA label use of olaparib (green curve) and of those treated off-label use (red curve). OS: Overall survival, EMA: European medicines agency.*

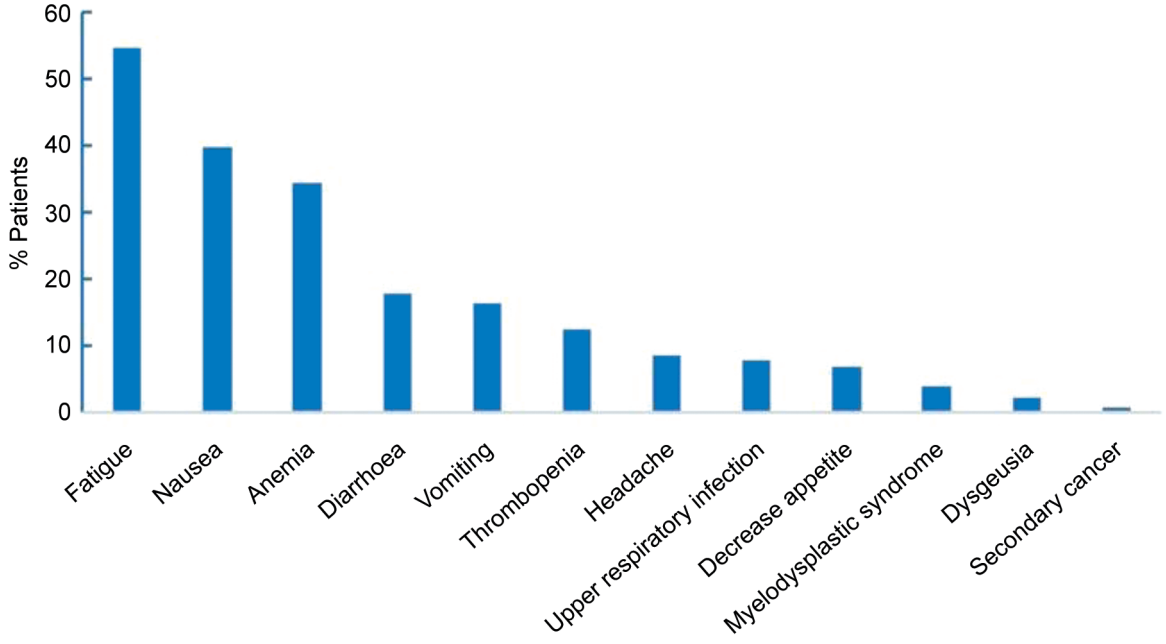

Figure 3. *Percentage of patients experiencing treatment-related toxicities of interest (all grades).*

Table II. *Characteristics of patients who developed treatment-related MDS and secondary AML following olaparib therapy.*

Toxicity	Age (years)	Germline BRCA mutation	Number of prior lines of therapies	Olaparib exposure (days)
MDS	46	BRCA 1	2	326
MDS	65	BRCA 1	3	675
MDS	66	BRCA 2	3	1083
MDS	56	BRCA 2	8	257
MDS	57	BRCA 2	2	427
AML	Unknown	BRCA 2	3	Unknown

MDS: Myelodysplastic syndrome; AML: acute myeloid leukemia; BRCA 1: breast cancer gene 1; BRCA 2: breast cancer gene 2.

33.6 months (95%CI=28.7-40.3), respectively (Figure 2). The 1-year OS rate was 88.4% (95% CI=79.6-93.6) in the EMA label population and 87.9% (95% CI=80.8-92.5) in the whole study cohort; the 2-year OS rate was 66.14% (95% CI=55.1-75.1) and 65.8% (95% CI=56.7-73.5).

Toxicity. The most common treatment-related toxicities (all grades) were fatigue (54.7%; n=70), nausea (39.8%; n=51), anemia (34.4%; n=44), diarrhea (18.0%; n=23), and vomiting (16.4%; n=21) (Figure 3). Five of the patients (3.9%) developed myelodysplastic syndrome (MDS) and one patient (0.8%) acute myeloid leukemia (AML) as a secondary cancer (Table II). Treatment-related toxicities led to permanent treatment discontinuation in nine patients (7.0%) and death in two patients (1.6%).

Discussion

Clinical outcomes of new targeted therapies in the real-life setting are essential to implement safety and efficacy profiles in everyday practice (27). The present study provided the results of a retrospective study evaluating the effectiveness and safety of olaparib in the real-world setting of patients with relapsed BRCA-mutated EOC treated in French clinical centers. The reported treatment outcomes and toxicities in our study are consistent with those published in clinical trials, the Study 19 and SOLO2 studies (13, 22, 23). However, the herein reported 17.0 months (95% CI=14.7-21.3) median PFS is far less in line with those in other real-world studies, mostly including patients treated with olaparib as a third or further-line maintenance treatment (28-33), with median PFS reaching 4.4±1.8 months in third-line therapy (30). Due to the less selective criteria for the EMA authorization, our population is heterogeneous with heavily pre-treated patients. As in SOLO2 trial, where 56.1% of patients received olaparib as a second-line maintenance therapy (13), two-thirds of our patients had received at least three lines of chemotherapy. Patients in the olaparib group in the SOLO2 trial had a significantly prolonged median PFS compared to the placebo group (19.1 months *versus* 5.5 months; HR=0.30, 95% CI=0.22-0.41; p=0.0001) (13). Although most of BRCAm patients with EOC show clinical benefit from olaparib maintenance therapy, the greatest benefit is observed with an early treatment initiation (32). In the phase III SOLO1 trial, first-line maintenance olaparib demonstrated a significant and clinically meaningful improvement in reducing the risk of progression [median PFS was not reached *versus* 13.8 months in placebo group (HR=0.3, 95% CI=0.23-0.41; p=0.0001)] for newly-diagnosed patients with advanced BRCAm EOC following platinum-based chemotherapy (14). Safety data from our study showed that olaparib is a generally well-tolerated therapy by recurrent EOC patients. Our population included unselected patients with less favorable factors than those included in the SOLO2 pivotal trial; they were less fit (at baseline 31.3% of our patients had a ECOG performance status 0 *versus* 82.7%) and older [median age 62.0 years (range=56.0-68.0) *versus* 56 years]. Still, the safety profile and rate of discontinuation for toxicity were similar in both studies (13.6% *versus* 10.8%).

In our retrospective cohort, treatment-related MDS (n=5) and AML (n=1) were diagnosed. To our knowledge, this is the first real-life study presenting such data. This was probably possible due to the prolonged follow-up; with 41.8 months (95% CI=38.7-45.0) compared to follow-up not exceeding 23.8 months in other real-world studies. At the final analysis of the SOLO2 trial, 8% of MDS/AML were reported at a median follow-up of 65.7 months in the olaparib group (34) while only 2% were initially reported at follow-up of 22.1 months. This observation was related to the median time to onset of MDS/AML that was from randomization that was 3 years in the olaparib group. Therefore, MDS appears to be a time dependent late side-effect that should be carefully monitored. It is reassuring that the incidence of MDS/AML in our real-life study with the heavily pre-treated population does not appear to be different from that observed in the SOLO2 trial. The incidence of MDS or secondary malignancies in the olaparib group did

not affect the clinical benefit of olaparib in terms of OS compared to placebo in the SOLO2 trial (51.7 *versus* 38.8 months, HR=0.74; 95%CI=0.54-1.00, *p*=0.0537).

The benefit-risk ratio in our study remains largely in favor of olaparib treatment, with positive efficacy outcomes and good tolerability profiles. However, the SOLO2 study showed a relative risk of 2.03 (95%CI=0.70-5.91) for developing MDS or AML with olaparib (34). A large-scale safety meta-analysis of randomized controlled trials and a retrospective study of the WHO pharmacovigilance database showed that the risk of MDS and AML in patients with PARPi was almost double compared to placebo (35). A pooled analysis of all MDS/AML cases on PARPi therapy should be conducted to clarify the conditions and risk factors predisposing to the occurrence of these toxicities. Clinicians should pay more attention to the risk of these rare, but lethal adverse reactions when using PARPi.

Our study had limitations because of its intentional and retrospective design. Nevertheless, regarding treatment, the short period of inclusion (2014-2017) led to substantially lower risk of such bias. Gathering real-life data remains of importance for health authorities to ensure reproducibility of results found in clinical trial results and moreover, randomized clinical trials and real-world data can complement one another. The real-world evidence on therapies used in ovarian cancer is emerging. For example, the French GINECO group assessed patients with newly diagnosed EOC treated with bevacizumab-containing therapy in a real-life setting (31). They reported the same efficacy and safety profile as the one observed in the pivotal trial (32), except for a higher incidence of hypertension and complications. Therefore, real-world studies can be used in a supplemental manner to create clinical vigilance by oncologists for approval of novel therapies.

Conclusion

In summary, this article presents the real-world results on the effectiveness and safety of olaparib for patients with relapsed BRCA-mutated EOC treated in several French Centers. These observations are consistent with those already shown in previous clinical trials, the Study 19 and SOLO-2. The treatment appeared to be well tolerated; myelodysplastic syndromes is a late side-effect that should be carefully monitored. The benefit-risk ratio remains largely in favor of olaparib treatment. Our data provide information regarding the treatment and outcomes patterns in real clinical practice.

Conflicts of Interest

LBL reports advisory/consultancy roles for AstraZeneca, GSK, and Clovis; speaker bureau/expert testimony for Servier; and travel/accommodation/expenses from Servier. MM- R reports advisory/consultancy roles for AstraZeneca, GSK, Pfizer, Lilly, MSD, Roche, Novartis, and Eisai; and research grant/funding to her institution from AstraZeneca, GSK, Pfizer, Lilly, MSD, Roche, Novartis, and Eisai. BA reports honoraria from BMS, AstraZeneca, Pierre Fabre, Servier, Daiichi and Roche. CG reports speaker bureau/expert testimony for AstraZeneca and GSK; and travel/accommodation/expenses from Pfizer, AstraZeneca, GSK, Roche, and Amgen. EC reports honoraria from Ipsen, BMS, TESARO, MSD, Eisai, and Pfizer; honoraria (paid to her institution) from MSD, Eisai and Ipsen; advisory/consultancy roles for Pfizer, BMS and Eisai; speaker bureau/expert testimony for Clovis and GSK; leadership role for MSD; and travel/accommodation/expenses from Ipsen, Pfizer, MSD, and Eisai. AP reports consulting fees (*e.g.*, advisory boards) and speaker role (both compensated to the hospital) for Pfizer, Lilly, Seagen, and Pierre Fabre; and travel fees from Roche, Eisai, Amgen and Pfizer. MF reports honoraria (paid to his institution) from AstraZeneca, GSK and Clovis. PT reports honoraria from Lilly, BMS, Pfizer and GSK; and advisory/consultancy roles for Lilly, Pfizer, GSK and BMS; and travel/accommodation/expenses from MSD, Novartis, and Pfizer. HS reports honoraria from Daiichi Sankyo, Pfizer, Viatris, Novartis, Lilly, and GSK; and advisory/consultancy roles for Lilly, Viatris, Vifor and Roche; and travel/accommodation/expenses from Lilly, Roche, Accord, Pfizer, Novartis, AstraZeneca, and Chugai. CGT reports honoraria from Pfizer; honoraria (paid to her institution) from MSD; advisory/consultancy roles for Pfizer, speaker bureau/expert testimony for AstraZeneca. research grant/funding to her institution from Roche; and travel/accommodation/expenses from Lilly, MSD, Mylan, and Pfizer. DC reports honoraria from Roche, Astellas, GSK, Pfizer, and Novartis. TDLMR reports honoraria from AstraZeneca, TESARO, Roche/Genetech, Pfizer and Mylan; advisory/consultancy roles for AstraZeneca, TESARO, Pfizer, Roche, Mylan, GSK, Eisai, MSD Oncology; research funding to his institution from Pfizer, Novartis, AstraZeneca and Seagen; and travel/accommodation/expenses from Roche, Pfizer, and AstraZeneca.

Authors' Contributions

Conceptualization and methodology: TDLMR, BA; Statistical analysis: BA; Patient enrollment: TDLMR, LBL, MM-R, BL, CG, CC, LG, EC, AP, MF, CC, PT, HS, DB, DG, CGT, DC, OC; Manuscript draft writing: HB, TDLMR, AM; Manuscript draft review and validation and final approval of manuscript: All Authors.

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