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Chemotherapy and PARP inhibitors in heavily pretreated BRCA1/2 mutation ovarian cancer (BMOC) patients

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HIGHLIGHTS

- Heavily pretreated g/sBMOC patients remain responsive to chemotherapy in the refractory setting.
- Primary platinum-free interval is a strong predictor of the outcome of heavily pretreated g/sBMOC patients.
- Exposure to both platinum-based chemotherapy and PARPi correlates with TTP in heavily pretreated g/sBMOC patients.
- Our data provide benchmarks for design and interpretation of trials in recurrent disease.

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ABSTRACT

Objectives: The hallmarks of germline(g) and/or somatic(s) BRCA1/2 mutation ovarian cancer (BMOC) patients are increased sensitivity to platinum-based chemotherapy (PCT) and PARP inhibitors (PARPi). There is little information on the effectiveness of chemotherapy in heavily pretreated (≥3 CT lines) g/sBMOC patients.

Methods: g/sBMOC patients who received CT from 2006 to 2016 at 4 cancer centers in Spain were selected. Overall survival (OS) and time to progression (TTP) were calculated with Kaplan Meier and Cox models.

Results: 135 g/sBMOC patients were identified (6% s*BRCA1/2* mutations). The median number of chemotherapy lines was 2 (1–7). The 6-years OS rate was 69.4% and 71% in *BRCA1* or *BRCA2* mutation carriers ($p = 0.98$). A total of 57 (42%) patients had ≥3 CT lines (3–7), which encompassed a total of 155 treatments. The median overall TTP across all treatment lines beyond 2nd line was 10.2 months (CI 95% 8.4–11.9 months). In the platinum-sensitive setting, TTP was improved with PCT plus PARPi (17.1 m), PCT (12.6 m) or PARPi (12.4 m) versus non-PCT (4.9 m; $p < 0.001$ all comparisons). In the platinum-resistant setting, these differences in TTP were not statistically significant. A multivariate model confirmed that primary platinum-free interval (PFI) > 12 months and exposure to PCT and PARPi associated with improved outcomes. PARPi exposure did not compromise benefit of subsequent CT beyond 2nd relapse.

Conclusions: Heavily pretreated g/sBMOC demonstrated CT sensitivity, including for non-PCT choices. Primary platinum-free interval (PFI) >12 months and exposure to both platinum-based chemotherapy and PARPi associate with improved prognosis in heavily pretreated g/sBMOC patients.

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1. Introduction

The hallmarks of BRCA1/2 mutation ovarian cancer (BMOC) are a high response rate to platinum-based chemotherapy, increased sensitivity to PARP inhibitors (PARPi) and improved overall survival compared to non-BMOC patients [1,2]. Therefore, establishing the germline(g) and/or somatic(s) *BRCA1/2* mutation status is of paramount importance for the routine care of epithelial ovarian cancer (EOC) patients. Loss of *BRCA1/2* function through germline mutations (15% to 18% irrespective of family history in patients with high-grade serous (HGS) histology); somatic mutations (6%) or epigenetic silencing results in a dependency on alternative error-prone (low-fidelity) DNA double-strand breaks (DSBs) repair pathways and potential genomic instability [3], which ultimately plays a critical role in the increased sensitivity to platinum chemotherapy and PARPi of g/sBMOC patients [4–7]. PARPi have emerged as one of the most exciting new therapies for the treatment of EOC patients. Olaparib, niraparib and rucaparib have been granted regulatory approval in Europe and USA for the maintenance treatment of platinum-sensitive recurrent ovarian cancer patients, who are in complete or partial response to platinum-based chemotherapy, irrespectively of the *BRCA* mutational status [8–12]. In addition, treatment with PARPi (olaparib and rucaparib) is now approved by the FDA for patients with recurrent *BRCA* mutated ovarian cancers. Olaparib has been approved for g*BRCA*m ovarian cancer patients who have received at least three prior lines of therapy [13]; and rucaparib for both g/sBMOC with ≥2 lines prior lines [14,15]. More recently, the EMA has also approved rucaparib as monotherapy for g/sBMOC patients, but only for those with platinum- sensitive relapse who have been treated with ≥2 prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy [16].

Despite our increased understanding of the pathophysiology of *BRCA1/2* mutations, specific chemotherapy recommendations for the subset of g/sBMOC patients have not yet been established and the standard management has not differed from that of non-carriers. Also, limited data are available to address the question of whether chemosensitivity to platinum agents observed in g/sBMOC can be extended to other non-platinum agents. After regulatory approval of PARPi in heavily pretreated population it is pertinent to investigate whether chemotherapy should still be the backbone of treatment in light of the known efficacy of PARPi, but also to address the effect that PARPi resistance might have on the efficacy of subsequent chemotherapy.

The primary purpose of this study is to assess the efficacy of chemotherapy for heavily pretreated g/sBMOC patients, with special focus on the effectiveness beyond 2nd line of treatment. Associations between baseline clinical characteristics with efficacy and prognosis, evaluation of PARPi efficacy either as monotherapy or in combination with chemotherapy, and response to chemotherapy following progression on PARPi treatment were also analyzed.

2. Materials and methods

2.1. Study design

This is a retrospective study of consecutive g/sBMOC patients who received chemotherapy in four major cancer centers in Spain from 2006 to 2016. All patients had previously undergone either germline or somatic *BRCA1/2* mutation testing, with documented deleterious or suspected deleterious variant, followed by appropriate genetic counseling. Patients with *BRCA1/2* mutations that are considered to be non-pathogenic were not eligible for the study. Somatic mutational status if available was also recorded.

Demographics and clinicopathologic characteristics, treatment details and antitumor responses were recorded. Patients were classified according to their platinum free interval (PFI) either as platinum-resistant (defined as progression <6 months after the end of the last platinum-based chemotherapy) or as platinum-sensitive (defined as progression ≥6 months after the end of the last platinum-based chemotherapy). In addition, those patients who had completed ≥3 chemotherapy lines were defined as heavily pretreated g/sBMOC patients. For each line of treatment, time to progression (TTP) was calculated. TTP was calculated based off a clinical decision-making (a combination of investigator assessment of response evaluation criteria in solid tumors (RECIST) guidelines and clinical criteria). In our study, patients who had clinical progression or who switched to a different therapy prior to documentation of radiographic RECIST progression were considered as having a progression event. Overall survival (OS) was defined as the interval between histologic diagnosis of ovarian cancer and the date of death as a result of disease, or lost to follow-up.

2.2. Statistical analysis

Descriptive and inferential statistics were applied to baseline clinical and laboratory data. Survival analysis was calculated using the Kaplan–Meier method and statistical comparison between defined groups of patients were assessed using log-rank test. Cox proportional hazard models were used to obtain hazard ratios (HRs) with 95% CIs. For comparison of treatment regimens beyond 2nd line of treatment, univariate TTP Cox models were stratified by treatment line. A p-value of 0.05 in the univariate survival analysis was adopted as the limit for inclusion in the multivariate model. All P values presented were two-sided. The data analyses were carried out using R version 4.1 statistical software package.

3. Results

3.1. Clinical characteristics of g/sBMOC patients

A total of 135 g/sBMOC patients were included and the relationship between carrier status and clinical characteristics is listed in Table 1. One hundred twenty-seven (94%) patients had gBRCA

Table 1
Patient, tumor and treatment characteristics.

Patient characteristics ($N = 135$)		BRCA1 ($N = 85$)	BRCA2 ($N = 50$)
BRCA mutational status	Germline	81 (95%)	46 (94%)
	Somatic	4 (5%)	4 (6%)
FIGO stage at diagnosis	I–II	18 (21%)	3 (6%)
	III–IV	67 (79%)	47 (94%)
Histology	HGS	75 (88%)	46 (94%)
	Endometrioid	5 (6%)	1 (2%)
	Clear cell	2 (2%)	0 (0%)
	Carcinosarcoma	1 (1%)	1 (2%)
	Undifferentiated	2 (2%)	1 (2%)
Neoadjuvant chemotherapy	Yes	31 (36%)	25 (50%)
	No	54 (64%)	25 (50%)
Surgery	Primary debulking	54 (64%)	25 (50%)
	Interval devulking	27 (32%)	24 (48%)
	Unresectable	4 (5%)	1 (2%)
Outcomes of surgery	TR = 0	63 (74%)	43 (86%)
	TR <10 mm	1 (1%)	2 (4%)
	TR ≥10 mm	14 (16%)	3 (6%)
	Unresectable	4 (5%)	1 (2%)
	Not known	3 (4%)	1 (2%)
PFI at 1st relapsed ($n = 88$)	<6 months	7 (14%)	1 (3%)
	≥6 and <12 months	11 (21%)	6 (16%)
	≥12 months	33 (65%)	30 (81%)
		Median (min–max)	
Total number of CT lines	–	2 (1–7)	2 (1–7)

Abbreviations: HGS: high grade serous; TR: residual tumor; PFI: platinum free interval; OS: overall survival: CT: chemotherapy.

mutations (81 (60%) BRCA1 carriers) and 8 (6%) patients had sBRCA mutations. The vast majority of patients had advanced FIGO stages at diagnosis, and 90% had HGS histology. A total of 79 (59%) patients underwent upfront surgery, most of them optimally debulked (tumor residual [TR] = 0). In our series, the median number of chemotherapy lines was 2 (1–7).

3.2. Efficacy of chemotherapy in the overall g/sBMOC patient population

At a median follow-up of 5.8 years (4.7–7.9 years) a total of 88 (65%) patients recurred. Survival analyses were restricted to women with HGS tumors as we had insufficient numbers of patients in other subtypes for analysis. The 6-years OS rate for the entire population was 69.8% (60.4–80.7) with a 6-years OS rate of 69.4% and 71% in BRCA1 or BRCA2 mutation carriers. We did not find significant difference between germline or somatic BMOC patients (71% vs. 54.7% respectively, $p = 0.76$). All the 135 g/sBMOC patients received a platinum-based regimen during the primary treatment, being carboplatin/paclitaxel (121 of 135 patients; 90%) the most common regimen. A total of 88 (65%) patients had disease relapse following primary treatment, being the recurrence rate of 71.9% in stage III–IV patients and 23.8% in stage I–II. The large majority ($n = 87$, 99%) of patients presenting disease recurrence received subsequent treatment. Using a PFI of <6 months as the threshold for platinum-sensitivity, only 8 (9%) patients could be classified as platinum-resistant at first disease relapse (Fig. 1). A total of 34 (25%) patients received PARPi treatment as maintenance following response to platinum chemotherapy at 1st or 2nd line of treatment.

Treatment characteristics and efficacy of chemotherapy in heavily pretreated (≥3 chemotherapy lines) g/sBMOC patients.

A total of 57 (42%) g/sBMOC patients were treated with at least three chemotherapy lines (range 3–7 lines), which encompassed a total of 155 treatments. Platinum-sensitivity status was available for all except from 14 (9%) treatments with missing progression status. A total of 40 (28.4%) and 101 (71.6%) treatments were administered on the platinum-resistant and platinum -sensitive disease setting respectively. The median overall TTP across all treatment lines beyond 2nd line was 10.2 months (CI 95% 8.4–11.9 months).

In total, we investigated 101 treatments in the platinum-sensitive setting beyond 2nd line of treatment. A total of 55 (54%) treatments were platinum-based combos whereas 15 (15%) were non-platinum treatments and 9 (9%) were PARPi as monotherapy. In addition, a total of 22 (22%) platinum-based treatments were followed by PARPi maintenance. Platinum-based combinations followed by maintenance with PARPi treatments were associated with longer TTP compared to either platinum-based combinations alone (HR = 0.49; 95% CI, 0.25–0.94, $p = 0.03$); PARPi monotherapy alone (HR = 0.33; 95% CI, 0.11–0.97, $p = 0.04$) or non-platinum-based treatments (HR = 0.09; 95% CI, 0.03–0.22, $p < 0.001$) (Table 2.A). Activity of PARPi monotherapy in the platinum-sensitive disease setting was also investigated. PARPi

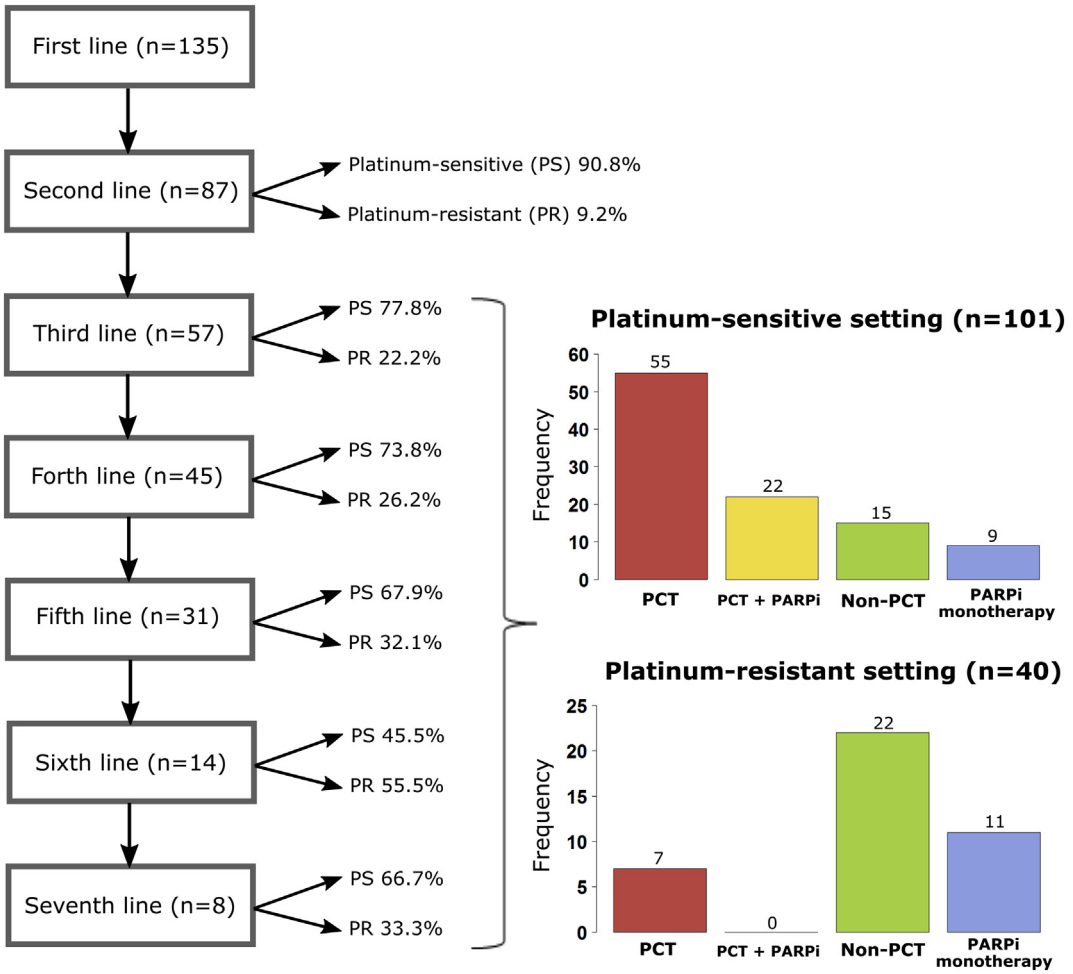

Fig. 1. Response to treatment at first and subsequent treatment lines. Mutation-positive patients are classified into platinum-sensitive and platinum-resistant. Distribution of treatment choices are shown for heavily pretreated (≥3 chemotherapy lines) g/sBMOC patients. Abbreviations: PS: platinum-sensitive; PR: platinum-resistant; PCT: platinum-based treatments; Non-PCT: non-platinum-based treatments; PARPi: PARP inhibitors.

Table 2
Table summarizing the activity of chemotherapy in heavily pretreated (≥3 chemotherapy lines) g/sBMOC patients according to disease setting and chemotherapy regimen. *Cox models were stratified by treatment line.

Setting	Comparison	HR (CI 95%)*	*p*-Value
A) Platinum- sensitive ($n = 101$)	PCT + PARPi (vs. PCT)	0.49 (0.25–0.94)	0.03
	PCT + PARPi (vs. PARPi monotherapy)	0.33 (0.11–0.97)	0.04
	PCT + PARPi (vs. non-PCT)	0.09 (0.03–0.22)	<0.001
	PARPi monotherapy (vs.PCT)	1.5 (0.57–3.94)	0.42
	PARPi monotherapy (vs. non-PCT)	0.26 (0.09–0.82)	0.02
	PCT (vs. non-PCT)	0.18 (0.08–0.4)	<0.001
B) Chemotherapy regimen	Gemcitabine (vs. PLD)	1.4 (0.44–4.49)	0.57
Platinum- sensitive	Paclitaxel (vs. PLD)	0.35 (0.13–0.91)	0.03
($n = 46$)	Paclitaxel (vs. gemcitabine)	0.25 (0.08–0.8)	0.02
	PCT (vs. non-PCT)	0.56 (0.18–1.77)	0.32
C) Platinum- resistant ($n = 40$)	PARPi monotherapy (vs. non-PCT)	0.45 (0.16–1.3)	0.14
	PARPi monotherapy (vs. PCT)	0.81 (0.26–2.48)	0.71

Abbreviations: PCT: platinum-based treatments; Non-PCT: non-platinum-based treatments; PCT + PARPi: platinum-based treatments followed by maintenance with PARP inhibitors; PARPi: PARP inhibitors.

monotherapy showed similar TTP compared to platinum-based chemotherapy (HR = 1.5; CI 95% 0.57–3.94; $p = 0.42$); however, we found improved TTP compared to non-platinum treatments (HR = 0.26; CI 95% 0.09–0.82; $p = 0.02$). In addition, platinum-based combos resulted in longer TTP compared to non-platinum-based treatments (HR = 0.18; CI 95% 0.08–0.4; $p < 0.001$) (Fig. 2.A). Moreover, we analyzed the effectiveness of chemotherapy in the platinum-sensitive setting beyond 2nd line of treatment according to the choice of regimen for platinum-based combinations. A total of 55 treatments were documented, being paclitaxel the most common platinum-based partner selected ($n = 24$; 44%), followed by pegylated liposomal doxorubicin (PLD) ($n = 13$; 24%), Gemcitabine ($n = 9$; 16%) and other treatments ($n = 9$; 16%). Paclitaxel combinations statistically associated with longer TTP compared to gemcitabine (HR, 0.25; CI 95% 0.08–0.8, $p = 0.02$) or PLD combinations (HR, 0.35; CI 95% 0.13–0.91, $p = 0.03$) (Table 2.B).

In the platinum-resistant setting at 3rd line or beyond, we evaluated 40 treatments in total. The median TTP across all treatment lines beyond 2nd line in the platinum-resistant setting was 6.1 months (CI 95% 4.5–7.7 months). Non-statistically significant differences were observed between platinum-based, non-platinum-based treatments or PARPi monotherapy. Non-platinum-based treatments demonstrated median TTP of 4.6 months (CI 95% 3.7–10.2) compared to 5.6 months (CI 95% 5-NA) for platinum-based treatments and 7.4 months (CI 95% 1.9-NA) for PARPi monotherapy (Fig. 2.C). PARPi monotherapy did not demonstrate longer median TTP compared to platinum-based treatments (HR = 0.81; CI 95% 0.26–2.48; $p = 0.71$) or non-platinum treatments (HR = 0.45; CI 95% 0.16–1.3; $p = 0.14$) (Table 2.C).

A total of 75 patients (55.6%) received PARPi during their disease evolution, with a median of 2 lines before PARPi treatment. The median interval between diagnosis and start of PARPi was 42 months (95% CI, 33.4–49.3). Twenty-one (15.6%) patients received a total of 33 chemotherapy treatments beyond PARPi progression. Of those treatments, 12 (36.4%) and 21 (63.6%) were administered on platinum-resistant and platinum-sensitive disease setting based on the sensitivity to last pre-PARPi platinum-based chemotherapy. In the platinum-sensitive setting, median TTP of the platinum-based chemotherapy was 10.9 months (CI 95% 4.97-NR) while non-platinum-based chemotherapy had median TTP of 3.03 months (CI 95% 2.33-NR). In the platinum-resistant disease setting, non-platinum-based chemotherapy had median TTP of 2.53 months (CI 95% 1.2-NR).

Finally, we investigated clinical factors that might be associated with outcomes in heavily pretreated (≥3 lines) g/sBMOC patients in univariate and multivariable models (Table 3). With regards to TTP, platinum sensitivity, exposure to platinum-based chemotherapy and PARPi associated with improved outcomes in the univariate analyses. However, platinum sensitivity did not associate with improved TTP in the multivariate analysis ($p = 0.22$). Univariate OS analyses demonstrated better survival with early stage at diagnosis, primary debulking surgery and primary PFI >12 months. In multivariate analysis, only primary PFI retained significance (Table 3).

4. Discussion

The current mainstay of therapy of advanced ovarian cancer patients consists of multiple subsequent lines of chemotherapy, where a platinum agent is routinely employed. However, the clinical benefit obtained with chemotherapy is typically transient and a maximum of three lines of subsequent relapse treatment has been suggested as “beneficial” for recurrent ovarian cancer patients [17]. Currently, there is limited evidence supporting the activity of chemotherapy, including non-platinum compounds, in heavily pretreated g/sBMOC population, and the approval of PARPi in this setting reinforces the fact that a better understanding of the magnitude of benefit obtained with chemotherapy is needed.

In this retrospective analysis, we investigated the effectiveness of chemotherapy in the daily practice for g/sBMOC patients focusing on the outcomes of patients who had received at least 2 prior lines of chemotherapy. We were able to show that heavily pretreated g/sBMOC patients retain the potential to respond to further chemotherapy lines. We demonstrated that in addition to primary PFI > 12 months, exposure to platinum-based chemotherapy and PARPi were the most relevant factors associated with outcomes. These results are in line with the results reported by Bookman et al. [18] that revealed that over 750 ovarian cancer patients, those with a primary PFI ≥6 months, and *BRCA1/2* mutation carriers (16%, $N = 42$) had improved outcomes over multiple lines of therapy. In our cohort of heavily pretreated platinum-sensitive g/sBMOC patients, the efficacy results of platinum based chemotherapy followed by PARPi are consistent with results obtained in the pivotal randomized clinical trials that led regulatory approval for PARPi as maintenance, where approximately half of the enrolled patients had received three or more lines of chemotherapy before maintenance with PARPi [8–12,19]. Randomized trials that evaluated the efficacy of chemotherapy in platinum-sensitive recurrences [20–24] have not reported subgroup analyses according to BRCA1/2 mutation status, and therefore the selection of chemotherapy regimens for g/sBMOC patients mirrors that of any patient with platinum-sensitive recurrent EOC. Interestingly, our study suggests that paclitaxel combinations associated with improved median TTP compared to either gemcitabine or PLD combinations. Limited retrospective studies have addressed the chemosensitivity to non-platinum agents in heavily pretreated platinum-resistant g/sBMOC patients [25]. The most convincing evidence of the activity of chemotherapy in platinum-resistant

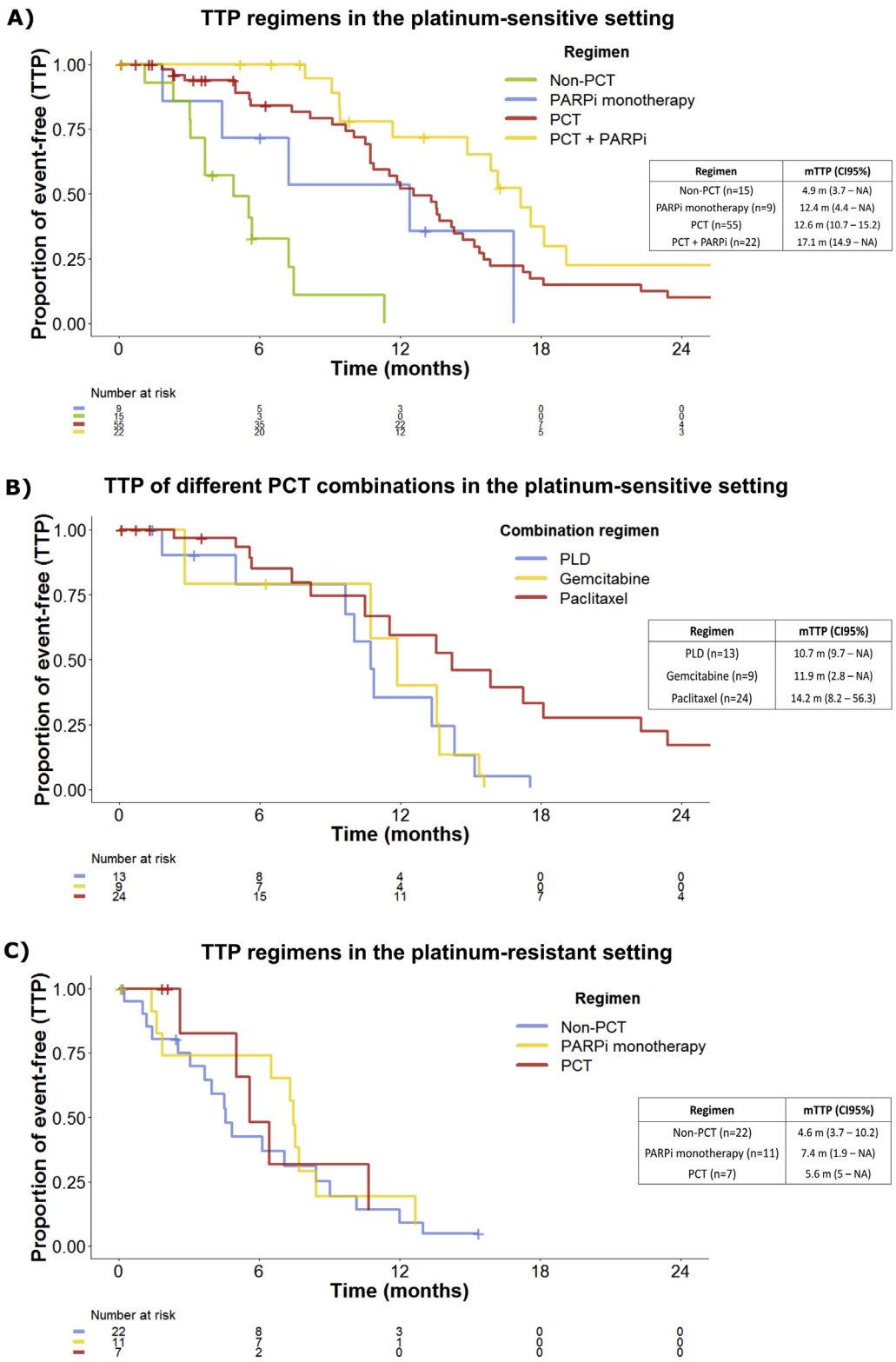

Fig. 2. Efficacy of chemotherapy in heavily pretreated (≥3 chemotherapy lines) g/sBMOC patients. Fig. 2A. Time to progression in platinum-sensitive setting. Fig. 2B. Time to progression in platinum-sensitive setting according to platinum-based regimen of chemotherapy. Fig. 2C. Time to progression in platinum-resistant setting. Abbreviations: PCT: platinum-based treatments; Non-PCT: non-platinum-based treatments; PCT + PARPi: platinum-based treatments followed by maintenance with PARP inhibitors; PARPi: PARP inhibitors.

gBMOC patients likely comes from a randomized study that evaluated the activity of PLD compared to the olaparib in gBMOC patients with relapsed disease within 12 months of completing platinum-based therapy [26]. In this study, in which up to 50% of the patients received >3 prior lines and 42% of the randomized patients to PLD were platinum-resistant, PLD yielded an unexpectedly high level response (39% with a combined RECIST/CA125 criteria) and a median PFS of 7.1 months, with similar proportions of patients with platinum-resistant and platinum-sensitive relapsed disease. The meaningful benefit derived from anthracycline-based treatments could be related to defective homologous recombination in gBMOC cells, as doxorubicin, a

Table 3
Table summarizing the association of baseline factors with TTP and OS in heavily pretreated (≥3 lines) g/sBMOC patients.

	Univariate		Multivariate	
	HR (CI 95%)	*p*	HR (CI 95%)	*p*
TTP analysis ($n = 155$)				
BRCA2 (vs. BRCA1)	0.92 (0.63–1.35)	0.66	–	–
Somatic (vs. germinal)	0.75 (0.4–1.41)	0.38	–	–
Line 5+ (vs. line 3–4)	1.33 (0.87–2.04)	0.19	–	–
Platinum-sensitive (vs. platinum-resistant)	0.28 (0.17–0.44)	<0.001	0.68 (0.37–1.26)	0.22
Platinum based-treatment (vs. non-platinum based-treatment)	0.32 (0.21–0.48)	<0.001	0.3 (0.16–0.54)	<0.001
PARPi treatment (vs. non-PARPi treatments)	0.65 (0.42–0.99)	0.04	0.62 (0.38–0.98)	0.04
OS analysis ($n = 135$)				
Age (y)	1.01 (0.97–1.04)	0.8	–	–
BRCA2 (vs. BRCA1)	0.97 (0.49–1.94)	0.93	–	–
Somatic (vs. germinal)	1.2 (0.37–3.94)	0.76	–	–
Stage at diagnosis IV (vs. I–III)	3.8 (1.71–8.47)	0.001	1.51 (0.6–3.8)	0.38
Interval debulking surgery (vs. no)	3.45 (1.72–7.08)	<0.001	1.67 (0.67–4.18)	0.27
Serous histology (vs. no serous histology)	1.5 (0.51–4.17)	0.48	–	–
Residual disease TR1 (vs. TR = 0)	2.78 (1.27–6.11)	0.01	1.95 (0.84–4.56)	0.12
PFI at 1st relapse >12 months (vs. 0–12 months)	0.21 (0.1–0.44)	<0.001	0.32 (0.13–0.8)	0.01

Abbreviations: PFI: platinum-free interval; TR: residual tumor.

topoisomerase II-alpha inhibitor, causes DSBs in DNA by inhibiting the unwinding of DNA for transcription and replication [27] as well as to be related to the amplified immunomodulatory effects of doxorubicin in BMOC tumors [28]. Conflicting evidence regarding the antitumor activity of other common chemotherapeutic agents such as taxanes has been suggested in gBMOC patients [29–32]. Last, correlation between *BRCA1/2*-mutation status and improved efficacy of trabectedin/PLD over PLD alone in the OVA-301 trial was observed and merits further exploration [33].

In our study, heavily pretreated platinum-resistant g/sBMOC patients did obtain clinically remarkable benefit with both non-platinum-based but also platinum-based rechallenge (median TTP 4.57 months and 5.32 months respectively). Our results suggest that platinum resistance status based on the <6-month PFI cut-off should not preclude g/sBMOC patients from receiving platinum-based therapy. This is in line with the consensus statements regarding recurrent ovarian cancer, reached at the 5th Ovarian Cancer Consensus Conference [34], where it was agreed that PFI as integral measure for defining patient populations and predicting outcomes, should be replaced with the broader term of treatment-free interval (TFI) in order to overcome the limitations imposed by the arbitrary division of platinum-sensitive and resistant disease. Also, incorporating TFIs would allow collecting all information regarding prior treatments and it would help to assess the impact of non-platinum and biological agents such as PARPi, angiogenesis inhibitors and immune checkpoint blockade.

We also provide important insights in the incorporation of PARPi treatment into the routine care of g/sBMOC patients, addressing the effectiveness of both, maintenance or monotherapy PARPi strategies. Regulatory approvals for PARPi are based on the clinically meaningful benefit provided for PARPi in both maintenance and treatment settings. However, there is no guidance as to when along the treatment timeline to best use PARPi, and to our knowledge there are not planned head-to-head trials assessing both PARPi treatment strategies. Although our study was not design to address which of the PARPi treatment strategies (maintenance or upfront monotherapy) might yield improved outcomes at the time of recurrence, our results suggest a greater range of activity for the platinum-based chemotherapy followed by PARPi maintenance strategy. Regulatory approval by the FDA of olaparib [13] or rucaparib [14] as monotherapy in heavily pretreated g/sBMOC patients is independent of the platinum sensitivity status. However, EMA has been more restrictive in its approval and has limited it to patients with platinum-sensitive relapse [16]. Our data with PARPi in monotherapy for platinum-sensitive patients is in line with the ARIEL2 Part I study results in which rucaparib as monotherapy demonstrated a median PFS of 12.8 months (95% CI 9.0–14.7) in the *BRCA1/2* mutant subgroup [35]. It is important to point it out that in the ARIEL2 Study more than half of the patients had only received one previous line of chemotherapy making our results even more challenging. In the platinum-resistant setting, our study did not demonstrate differences in efficacy with PARPi, platinum or non-platinum strategies. Currently, two randomized clinical trials (SOLO3 trial (NCT02282020); ARIEL4 (NCT02855944) study are investigating the efficacy of PARPi as monotherapy in comparison to standard of care, based on physician's choice of chemotherapy, in heavily pretreated g/sBMOC patients.

Our patient cohort is also unique so far as we were able to provide evidence of the activity of chemotherapy in the context of PARPi treatment resistance. Relatively little is known about how PARPi, either maintenance or treatment, impacts subsequent chemotherapy response and outcomes. As previously reported by Ang et al. [36] we observed that development of PARPi resistance does not compromise benefit to subsequent chemotherapy. In our study, the range of activity of chemotherapy strategies post PARPi, in both platinum-sensitive (mTTP 10.9 months) and resistant (mTTP 2.53 months) disease setting, is in line to what has been reported in previous randomized clinical trials [17,20–24,37]. Hypothetical concerns related to decreased effectiveness of subsequent treatments due to cross-resistance to chemotherapy induced by PARPi have been addressed by the maintenance studies with PARPi. Analysis of secondary endpoints from the randomized pivotal randomized clinical trials of PARPi as maintenance, ENGOT-OV16/NOVA trial [38], SOLO2/ENGOT Ov-21 trial [10] and have shown a significant improvement in time to first subsequent therapy and time to second progression, and time to second subsequent therapy in favour of PARPi over control which suggests that patients reach their second subsequent treatment without the potential occurrence of chemotherapy resistance and speculating that mechanisms of resistance to PARPi and chemotherapy are significantly different and may impact the future design of clinical trials for patients previously treated with PARPi. The ongoing OReO study (NCT03106987) will assess the efficacy of olaparib rechallenge in patients who have had disease progression following maintenance therapy with a PARPi and experience response to subsequent treatment with platinum-based chemotherapy. Certainly, further work is required to address the possible molecular mechanisms underlying the increased sensitivity to platinum and non-platinum compounds, but also to investigate the mechanisms of resistance to chemotherapy and PARPi in g/sBMOC

patients, including but not limited to the presence of secondary BRCA1/2 mutations leading to restoration of gene function [39]. Further work is also needed to better understand the impact of mutations in other HR, non-BRCA genes, such as ATM, CHEK1, CHEK2, NBN, and RAD51D, on the increased sensitivity to DNA-damaging agents and PARPi.

Our study has a number of limitations inherent in a retrospective study and the lack of investigation for possible molecular mechanisms underlying continuing response and resistance development to platinum and PARPi based therapies. However, collectively we show that heavily pretreated g/sBMOC patients retain the benefit obtained with subsequent chemotherapy lines, including with non-platinum strategies. In addition, analysis of predictive factors demonstrated primary PFI as the most relevant clinical characteristic associated with improved outcomes. We also observed that in the platinum-sensitive setting, platinum based combinations, particularly platinum and taxanes, followed by PARPi may represent the treatment strategy associated with the greatest time to progression. Finally, our results confirm that PARPi resistance do not compromise benefit to subsequent chemotherapy.

Conflict of interest statements

The authors have declared no conflicts of interest. A. Oaknin is a consultant/advisory board member of AstraZeneca, Clovis, Tesaro, Roche, PharmaMar. R. Dientsmann reports personal fees from Roche, outside the submitted work.

Author contribution

VRF, LFM, MGM, MPB, MR, BR, HAO, SR, JMP, MCG, AG, ES, SMR, CM, EC, and AO collected, analyzed, and interpreted the data. RD, GV, VRF, and AO involved in data generation and interpretation.

Presentation

Partial results of this study were previously presented at ESMO 2017 congress as a poster communication in the Gynecologic Cancer field. Annals of Oncology (2017) 28 (suppl_5):v330-v354.https://doi.org/10.1093/annonc/mdx372.

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