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Efficacy of chemotherapy according to *BRCA* status in patients with high-grade serous ovarian carcinoma at first platinum-sensitive relapse

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ABSTRACT :

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Objective.

4 Chemotherapy for high-grade serous ovarian cancers in platinum-sensitive relapse include carboplatin/paclitaxel, carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin.

6 According to *in vitro* data, *BRCA* mutated patients are sensitive to replicative stress agents but *BRCA* status is not yet used for the choice of chemotherapy at relapse. Our aim was to assess these doublets according to *BRCA* status in first platinum-sensitive relapse.

10 *Methods.*

ESME ovarian cancer database is a multicenter, retrospective cohort of ovarian cancer patients treated in French cancer centers between January 2011 and December 2017. Patients with high-grade serous ovarian cancers at first platinum-sensitive relapse who received one of these doublets were included. The objective was to compare progression-free survivals of each chemotherapy doublet according to *BRCA* status.

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Results.

18 Among the 10,263 patients of the database, 1,539 patients had a first platinum-sensitive relapse: 825 *BRCA* wild-type (53.6%) and 304 *BRCA* mutated (19.8%) patients (7 patients had an HR mutation and *BRCA* status was unknown for 403 patients). Median progression-free survival was longer in *BRCA* mutated *versus* *BRCA* wild type patients when receiving carboplatin/pegylated liposomal doxorubicin without maintenance treatment (15.8 *versus* 11.8 months; $p < 0.001$). In contrast, we observed no difference in patients treated with carboplatin/paclitaxel (14.6 *versus* 14.3 months; respectively; $p = 0.70$) or with carboplatin/gemcitabine (12.0 *versus* 9.8 months; respectively; $p = 0.18$). In *BRCA* wild type patients without maintenance, we observed a better progression-free survival with carboplatin/paclitaxel (median progression-free survival of 14.3 *versus* 9.8 and 11.8 months with carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin; respectively; $p = 0.017$).

In *BRCA* mutated patients without maintenance, there was no difference between the three doublets (median progression-free survival of 14.6, 12.0 and 15.8 months with carboplatin/paclitaxel, carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin respectively; p=0.40).

Conclusion.

While treatment with carboplatin/paclitaxel, carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin shows comparable efficacy in *BRCA* mutated patients, treatment with carboplatin/paclitaxel appears to be more effective than carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin in *BRCA* wild-type patients with high-grade serous ovarian cancers at first platinum-sensitive relapse.

Key messages

What is already known on this topic

Three main chemotherapy doublets are recommended in first platinum-sensitive relapse of high-grade serous ovarian cancers (carboplatin/paclitaxel, carboplatin/gemcitabine or carboplatin/pegylated liposomal doxorubicin) but there is no data about the relative benefit of these drugs according to *BRCA* status.

What this study adds

According to our results, treatment with carboplatin/paclitaxel, carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin shows comparable efficacy in *BRCA* mutated cases but treatment with carboplatin/paclitaxel appears to be more effective than the others in *BRCA* wild-type patients.

How this study might affect research, practice or policy

BRCA status might affect the efficacy of chemotherapy drugs beyond platinum. These results have to be confirmed in other cohorts and future trials.

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4

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Introduction

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Despite optimal treatment, a majority of high grade serous ovarian carcinomas patients will relapse. At platinum-sensitive relapse, re-treatment with platinum-based chemotherapy is a standard attitude with carboplatin/paclitaxel, carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin, possibly associated with a maintenance treatment with bevacizumab¹⁻³ or a PARP (poly ADP ribose phosphate) inhibitor⁴⁻⁶, improving progression-free survival.

8

BRCA1/2 inactivation is present in one third of high grade serous ovarian carcinomas, with germline mutations in two thirds of these cases^{7 8}. *BRCA1/2* are pivotal factors in the homologous recombination pathway for DNA (deoxyribonucleic acid) repair of double strand breaks. Alkylating agents such as platinum salts generate DNA lesions leading to the accumulation of double-strand breaks and ultimately cell death. *BRCA* mutated ovarian carcinomas present an increased sensitivity to alkylating chemotherapies including platinum salts⁹. Furthermore, an increased sensitivity to other agents has also been reported in *BRCA* mutated tumors beyond ovarian cancers such as pancreas and breast, in particular to cytotoxic agents inducing replicative stress such as gemcitabine¹⁰, topoisomerase I¹¹ and II^{12 13} inhibitors. In contrast, the activity of a spindle poison such as docetaxel was not influenced by the *BRCA* status in the Triple Negative Trial in the metastatic setting while carboplatin strongly increased response rate in *BRCA* mutated tumors¹⁴.

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Actually, the question of an increased sensitivity to topoisomerase II inhibitors in *BRCA* mutated high grade serous ovarian carcinomas was raised in a phase II study comparing olaparib to pegylated liposomal doxorubicin in the platinum-resistant setting¹⁵. In this study, the median progression-free survival with pegylated liposomal doxorubicin was higher than expected at 7.1 compared to 3.5 months in the all-comer, platinum-resistant, high grade serous ovarian carcinomas population from the AURELIA trial¹⁶. Despite these data, *BRCA* status is not currently used for the choice of chemotherapy at relapse. The objective of the present study is to report the efficacy data of these three chemotherapies according to *BRCA* status in a real-life series of high grade serous ovarian carcinomas patients in first platinum-sensitive relapse.

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Methods

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Inclusion and exclusion criteria

4 The ESME ovarian cancer database (NCT03275298) is a real-life, French, retrospective, multicentre
database centralizing clinical data of patients treated for an OC at one of the 18 cancer centers in
6 France¹⁷. Patients included were 18 years or older and received at least one therapeutic act for their
ovarian cancer in a cancer center during the selection period (between January 2011 and December
8 2017). To be included, patients had to present an high-grade serous ovarian carcinoma in first
platinum-sensitive relapse (6 months after last platinum) treated with either carboplatin-paclitaxel,
10 carboplatin/pegylated liposomal doxorubicin or carboplatin/gemcitabine after a first line of platinum-
based chemotherapy. Patients were considered *BRCA* mutated if they had a diagnosis of constitutional
12 *BRCA* mutation. Because of the timing of the selection period, *BRCA1/2* were not sequenced in the
tumors.

14

Statistical analyses

16 The objective was to compare the progression-free survival (defined as the time between the start of
the second-line chemotherapy and the date of progression, death or last news) of each chemotherapy
18 according to *BRCA* status in patients presenting an high grade serous ovarian carcinoma in first
platinum-sensitive relapse. Median follow-up was estimated with the reverse Kaplan Meier method.
20 Differences between groups were tested with the Student's t test for the quantitative variables and the
Chi2 or Fisher test for the qualitative variables. Progression-free survival was estimated by the Kaplan
22 Meier method. Survival data were compared according to their characteristics with a log-rank test.
Possible confounding factors were considered with multivariate analyzes using the Cox model. The
24 alpha risk was set at 5%. No adjustment for multiple testing was made because it was an exploratory
analysis.

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2 **Results**

4 **Cohort characteristics according to chemotherapy doublet**

More than 10,000 ovarian cancer patients were included in ESME ovarian cancer database between
6 January 2011 and December 2017 (Figure 1). Among them, 1,069 patients presented a high grade
serous ovarian carcinoma in first platinum-sensitive relapse, with a known *BRCA* status and treated
8 with one of the three most common platinum-based doublets. Approximately one in two patients was
treated with carboplatin/pegylated liposomal doxorubicin, while 22.5% and 23.0% were treated with
10 carboplatin/paclitaxel and carboplatin/gemcitabine respectively. Patient characteristics at baseline are
presented in Table 1. The rate of *BRCA* mutated patients was similar in the three groups ($p=0.029$).

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Progression-free survival according to chemotherapy doublet

14 Median progression-free survival with carboplatin/paclitaxel was 17.8 (95% CI 14.3 to 25.5) in *BRCA*
mutated patients *versus* 14.0 months (95% CI, 12.0 to 17.3) in *BRCA* wild type patients ($p=0.058$);
16 15.6 (95% CI, 13.0 to 27.9) in *BRCA* mutated *versus* 11.0 months (95% CI, 10.2 to 12.6) in *BRCA*
wild type patients with carboplatin/gemcitabine ($p<0.001$) and 18.2 (95% CI, 16.6 to 19.8) in *BRCA*
18 mutated *versus* 11.2 months (95% CI, 10.5 to 12.4) in *BRCA* wild type patients with
carboplatin/pegylated liposomal doxorubicin ($p<0.001$; Figure 2A). Patients receiving a maintenance
20 treatment were subsequently excluded from the next analysis. We observed no difference in terms of
progression-free survival between *BRCA* mutated patients and *BRCA* wild type patients, whether with
22 carboplatin/paclitaxel (median progression-free survival of 14.6 [95% CI, 12.2 to 23.2] in *BRCA*
mutated *versus* 14.3 months [95% CI, 12.0 to 20.3] in *BRCA* wild type; $p=0.70$); or with
24 carboplatin/gemcitabine (12.0 [95% CI, 9.87 to not reached] *versus* 9.8 months [95% CI, 8.06 to
12.9]; $p=0.18$; Figure 2B). However, there was still a difference between *BRCA* mutated and *BRCA*
26 wild type patients with carboplatin/pegylated liposomal doxorubicin (median progression-free survival
of 15.8 [95% CI, 14 to 20.5] in *BRCA* mutated patients *versus* 11.8 months [95% CI, 10.8 to 13.4] in
28 *BRCA* wild type patients; $p=0.001$).

The median number of chemotherapy cycles was 6 in the three treatments groups (interquartile ranges [IQR]: 4-6 with paclitaxel; 5-6 with gemcitabine; 6-6 with pegylated liposomal doxorubicin). The proportion of patients who completed at least 6 cycles was similar in carboplatin/paclitaxel and carboplatin/gemcitabine groups but higher in the carboplatin/pegylated liposomal doxorubicin group (67.3%, 69.4% and 76.6%, respectively; $p=0.004$ and comparison by pairs: carboplatin/paclitaxel versus carboplatin/pegylated liposomal doxorubicin, adjusted $p=0.01$ and carboplatin/gemcitabine versus carboplatin/pegylated liposomal doxorubicin, adjusted $p=0.08$). The median treatment duration was longer in the carboplatin/pegylated liposomal doxorubicin group compared with the two other groups (4.9 *versus* 4.2 and 4.1 months, respectively; $p<0.001$), probably because carboplatin/pegylated liposomal doxorubicin was better tolerated.

12 **Cohort characteristics according to *BRCA* status**

Then, we analyzed our data according to *BRCA* status (Figure 3). Approximately one fourth of the patients were *BRCA* mutated (Table 2). As expected, *BRCA* mutated patients were younger than *BRCA* wild type patients (55 *versus* 62 years old, respectively; $p<0.001$). The proportion of patients treated with carboplatin/pegylated liposomal doxorubicin was similar between the two arms (56.8% in *BRCA* wild type patients *versus* 56.5% in *BRCA* mutated, $p=0.94$), while *BRCA* wild type patients were more often treated with carboplatin/gemcitabine (24.7% *versus* 18.8% in *BRCA* mutated, $p=0.042$) and inversely *BRCA* mutated patients were more often treated with carboplatin/paclitaxel (24.7% *versus* 18.5% in *BRCA* wild type, $p=0.026$).

22 **Carboplatin/paclitaxel and progression-free survival in *BRCA* wild-type patients**

In *BRCA* wild type, carboplatin/paclitaxel was associated with a longer progression-free survival compared with the two other doublets (median progression-free survival of 14.0 months [95% CI, 12.0 to 17.3] with carboplatin/paclitaxel *versus* 11.0 [95% CI, 10.2 to 12.6] and 11.2 [95% CI, 10.5 to 12.4] with carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin, respectively; $p=0.002$; Figure 4A).

As a substantial proportion of patients received a maintenance treatment, we excluded them and observed that carboplatin/paclitaxel was still associated with longer progression-free survival (median progression-free survival of 14.3 months [95% CI, 12.0 to 20.3] with carboplatin/paclitaxel *versus* 9.8 [95% CI, 8.1 to 12.9] and 11.8 [95% CI, 10.8 to 13.4] with carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin, respectively; $p=0.017$; Figure 4B). We searched for confounding factors that could explain this difference. We know that patients with a partially sensitive platinum relapse were less often treated with carboplatin/paclitaxel, which had been administered at first-line. Indeed, we observed an underuse of carboplatin/paclitaxel in case of partially sensitive platinum relapse in our cohort with only 21% treated with carboplatin/paclitaxel compared to 32% with carboplatin/gemcitabine and 35% with carboplatin/pegylated liposomal doxorubicin. Then, we searched if the year of initial diagnosis could have influenced our data.

While carboplatin/paclitaxel is used since the 90's, carboplatin/pegylated liposomal doxorubicin gained popularity after the results of the CALYPSO trial in 2010¹⁸. In our database, the year of initial diagnosis was different according to chemotherapy doublet, with a predominance of carboplatin/paclitaxel before 2007 and a predominance of carboplatin/pegylated liposomal doxorubicin after 2008 and especially after 2013. Indeed, before 2007, 56.2% of patients were treated with carboplatin/paclitaxel *versus* 3.4% and 40.4% with carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin respectively. Between 2008 and 2012, 30.4% were treated with carboplatin/paclitaxel *versus* 23.1% and 46.5% with carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin respectively. In contrast, after 2013, 13.5% were treated with carboplatin/paclitaxel *versus* 25.1% and 61.4% with carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin respectively.

To explore these confounding factors, we performed a multivariate analysis and found three factors independently influencing progression-free survival: time to first relapse (Hazard Ratio [HR]=0.40 for a time to first relapse of 24 months or more, $p<0.001$), use of carboplatin/paclitaxel (HR=0.77, $p=0.013$) and concomitant use of bevacizumab (HR=0.70, $p<0.001$; Supplementary Tables 1 and 2).

Progression-free survival between the three regimens in *BRCA* mutated patients

2 On the contrary no difference in progression-free survival was observed between the three doublets in
4 *BRCA* mutated patients (median progression-free survival of 17.8 [95% CI, 14.3 to 25.5], 15.6 [95%
6 CI, 13.0 to 27.9] and 18.2 months [95% CI, 16.6 to 19.8] with carboplatin/paclitaxel,
8 carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin respectively; p=0.78; Figure
10 4C) even after exclusion of patients treated with a maintenance treatment at relapse (median
12 progression-free survival of 14.6 [95% CI, 12.2 to 23.2], 12.0 [95% CI, 9.8 to not reached] and 15.8
14 months [95% CI, 14.0 to 20.5] with carboplatin/paclitaxel, carboplatin/gemcitabine and
16 carboplatin/pegylated liposomal doxorubicin respectively; p=0.40; Figure 4D). Similarly, there was no
18 difference between the three doublets in patients who received a maintenance treatment with a PARP
inhibitor (median progression-free survival not reached [95% CI, 28.2 to not reached], 32.4 [95% CI,
14.3 to not reached] and 19.6 months [95% CI, 18.1 to 25.5] with carboplatin/paclitaxel,
carboplatin/gemcitabine and carboplatin/pegylated liposomal doxorubicin respectively; p=0.06; Figure
4E). The median number of chemotherapy cycles was 6 in the two treatments groups (interquartile
ranges [IQR]: 5-6 *BRCA* wild type; 5-6 *BRCA* mutated patients). The proportion of patients who
completed at least 6 cycles of therapy was similar in *BRCA* wild type and *BRCA* mutated patients
(73.7% versus 71.1% respectively; p=0.4). The median treatment duration was similar in *BRCA* wild
type and *BRCA* mutated patients (4.6 vs 4.7 months, respectively; p=0.2).

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Discussion

2 Summary of Main Results

Progression-free survival was better in *BRCA* mutated patients with a differential of 4 to 7 months in
4 median progression-free survival, confirming the prognostic value of *BRCA* mutations^{19 20}. Our main
question was the chemosensitivity of *BRCA* mutated tumors to topoisomerase II inhibitors as Kaye et
6 al. suggested in their study¹⁵. We did not observe any difference between the three chemotherapies in
BRCA mutated patients. Interestingly, no difference was observed regardless of the use of a PARP
8 inhibitor in maintenance suggesting that the drug associated with carboplatin did not induce cross-
resistance to subsequent PARP inhibitor. Thus, knowing which chemotherapy doublet is most likely to
10 be effective according to *BRCA* status would permit to choose the best option to give the patient the
highest chance to benefit from a PARP inhibitor treatment.

12

Results in the Context of Published Literature

14 In our study, carboplatin/paclitaxel was associated with a better progression-free survival in *BRCA*
wild type patients, even after the exclusion of patients receiving maintenance treatment. This gain was
16 independent of time to relapse. The biological explanation might not be directly linked to an exquisite
sensitivity to paclitaxel but rather to a lower activity of pegylated liposomal doxorubicin and
18 gemcitabine in this context. Pegylated liposomal doxorubicin and gemcitabine are drugs suspected to
be more active in homologous recombination deficient tumors as they target DNA during the S-phase,
20 either blocking chromosome disentanglement through topoisomerase II inhibition or interrupting DNA
polymerization. In contrast, paclitaxel is a spindle inhibitor, acting during the M-phase in cells,
22 regardless of the homologous recombination status. Therefore, it is possible that homologous
recombination proficient are not more “paclitaxel-sensitive” but rather less sensitive to DNA targeting
24 agents than their homologous recombination deficient counterparts. This would explain the observed
difference between *BRCA* wild type and *BRCA* mutated but needs to be validated by further *in vitro*
26 experiments.

2 These observations contradict the CALYPSO study¹⁸ in which the progression-free survival of patients
3 treated with carboplatin/pegylated liposomal doxorubicin was superior compared to
4 carboplatin/paclitaxel (median progression-free survival of 11.3 *versus* 9.4 months; p=0.005).
5 Nevertheless, this population was not the same as patients in second platinum sensitive relapse could
6 be enrolled in CALYPSO, contrary to our study. More importantly, *BRCA* status was not reported in
7 CALYPSO, limiting any conclusion on this question. Our study does not confirm the results of the
8 AGO-OVAR 2.21 randomized controlled trial³ which showed a benefit in progression-free survival of
9 carboplatin/pegylated liposomal doxorubicin with bevacizumab compared to carboplatin/gemcitabine
10 with bevacizumab (median progression-free survival of 13.3 *versus* 11.6 months, respectively;
11 p=0.012) as we only observed a trend toward a benefit when comparing these two regimens.
12 Unfortunately, *BRCA* status was also not known in this study. Multiple factors may explain these
13 discrepancies between randomized controlled trials and real-world data. In both trials, the median
14 progression-free survival difference, albeit statistically significant, was low (approximately two
15 months). Such low difference is difficult to observe in real-world data because of patients'
16 heterogeneity compared to patients enrolled in randomized controlled trials and the unknown factors
17 underlying decision-making reflecting the difference between the concepts of efficacy and
18 effectiveness. Although randomized controlled trials remain the most reliable evidence of the
19 treatment's efficacy, randomized controlled trials do not assess effectiveness in the real-world setting.
20 The question of extrapolation of randomized controlled trials in routine practice is problematic as
21 randomized controlled trials are conducted on highly selected populations which may not represent the
22 whole population given the stringent inclusion criteria. Real-world settings are thus complementary
23 with randomized controlled trials to fill the efficacy–effectiveness gap. Our data also contrast with the
24 observation made by Park and colleagues in a retrospective study in which a sub-analysis between
25 carboplatin/pegylated liposomal doxorubicin and carboplatin/paclitaxel according to *BRCA* status did
26 not show a significant progression-free survival difference²¹. This important observation may be
influenced by other factors than chemotherapy regimens including biology of Eastern Asia population.

Supporting this idea, a discrepancy was observed between the positive results of the JGOG3016 trial, assessing the efficacy of weekly paclitaxel combined with platinum in the Japanese population compared with the results of the ICON8, MITO7 and GOG262 studies which enrolled predominantly Western women.

6 Strengths and Weaknesses

To our knowledge, this is the first study comparing the activity of three chemotherapy doublets according to *BRCA* status in a real-world setting, with more than 1,500 patients with high-grade serous ovarian cancers in first platinum-sensitive relapse. Although our results are based on a large database, retrospective series are exposed to inherent biases including selection, classification and confounding biases. Complete debulking surgery at relapse may positively impacts progression-free survival^{1 22 23}, but this information is lacking in our data. Furthermore, we expect a substantial proportion of *BRCA* wild type tumors to be homologous repair-deficient, including those carrying somatic *BRCA1/2* mutations, which may bias our results. By analogy with our *BRCA* analyses, if homologous repair-proficient tumors are more sensitive to paclitaxel than homologous repair-deficient including somatic *BRCA*-mutated, these latter cases may have cut down the signal. Lastly, this analysis does not consider the recent use of PARP inhibitor in first-line setting. PARP inhibitor pretreatment not only reduces the efficacy of subsequent PARP inhibitor treatment as shown in the OReO/ENGOT Ov-38 trial but possibly also the efficacy of subsequent platinum-based chemotherapies as shown in a *post hoc* analysis of the SOLO-2 trial, likely because of common mechanisms of resistance (reversion of *BRCA* mutation, *MDR1* translocation, restoration of the replication fork stability)²⁴. These results are therefore not directly applicable to current situations of patients suffering recurrence on or after PARP inhibitor treatment. Conversely, there is, to our knowledge, no data supporting that bevacizumab treatment influences the efficacy of subsequent therapies, including bevacizumab itself as shown in the re-challenge MITO-16B trial²⁵.

Implications for Practice and Future Research

2 According to this retrospective study the carboplatin/paclitaxel doublet is more effective than others in
4 *BRCA* wild type patients but we should take our results with caution because of their retrospective
6 nature. In practice, it is justified to use the carboplatin/pegylated liposomal doxorubicin doublet in
8 *BRCA* wild type patients, while awaiting the forthcoming results of the ATALANTE²⁶ and ANITA²⁷
10 trials which both evaluated chemo/atezolizumab combos in platinum sensitive relapse and were
12 stratified by chemotherapy doublet and *BRCA* status. We confirmed the influence of *BRCA* status on
14 high-grade serous ovarian cancers patients because of its prognostic value as a predictor of platinum
16 and PARP inhibitors benefits. In the era of precision medicine, the *BRCA* status in *BRCA* wild type
18 patients is now essential in daily practice for all high-grade serous ovarian cancer patients to provide
20 the best, personalized management to each of these women.

Conclusion

14 While treatment with carboplatin/paclitaxel, carboplatin/gemcitabine and carboplatin/pegylated
16 liposomal doxorubicin shows comparable efficacy in *BRCA* mutated patients, treatment with
18 carboplatin/paclitaxel appears to be more effective than carboplatin/gemcitabine and
20 carboplatin/pegylated liposomal doxorubicin in *BRCA* wild-type patients with high-grade serous
ovarian cancers at first platinum-sensitive relapse in this retrospective series. These results have to be
confirmed in other cohorts and future trials.

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6

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8

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Ethical approval

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In compliance with French regulations, the ESME ovarian cancer database (NCT03275298) was authorized by the French data protection authority (Registration ID 1976564 and authorization N°DE-2017-311). Moreover, in compliance with the applicable European regulations, a complementary authorization was obtained on 14-Oct-2019 regarding the ESME research Data Warehouse. No formal dedicated informed consent was required but participating centers handle process to ensure that patients are informed about the re-use of their electronically recorded data.

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Figures

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4 **Figure 1.** Flow chart according to chemotherapy doublet.

6 **Figure 2.** Progression-free survival according to chemotherapy doublet in *BRCA* wild type (blue curves) and *BRCA* mutated (yellow curves) patients treated with carboplatine/paclitaxel (left panels), carboplatine/gemcitabine (middle panels) and carboplatin/pegylated liposomal doxorubicin (right panels). A. Whole population. B. Same population after exclusion of patients receiving a maintenance therapy (bevacizumab or PARP inhibitors).

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12 **Figure 3.** Progression-free survival according to *BRCA* status in *BRCA* wild type (upper panels) and *BRCA* mutated (lower panels) patients treated with carboplatine/paclitaxel (yellow curves), carboplatine/gemcitabine (red curves) and carboplatin/pegylated liposomal doxorubicin (blue curves). A. Whole *BRCA* wild type population. B. *BRCA* wild type population after exclusion of patients receiving a maintenance therapy (bevacizumab or PARP inhibitors). C. Whole *BRCA* mutated population. D. *BRCA* mutated population after exclusion of patients receiving a maintenance therapy (bevacizumab or PARP inhibitors). E. *BRCA* mutated patients receiving PARP inhibitors as a maintenance therapy.

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Tables

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24 **Table 1.** Patients characteristics according to chemotherapy doublet. L1/L2 = first-line, second-line; PARPinh = PARP inhibitors; yo = years-old.

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	Carboplatin paclitaxel	Carboplatin gemcitabine	Carboplatin doxorubicin	p-value
Number of patients	22.5% (n = 318)	23.0% (n = 324)	54.5 % (n = 768)	
Median (min-max) follow-up	51.7 months (0-2.12.9)	36.1 months (0-96.1)	31.0 months (0-126.7)	<0.001
Median age	59 yo	63 yo	61 yo	<0.001
FIGO at diagnosis	I : 5.3% (n = 12) II : 3.1% (n = 7) III : 64.5% (n = 145) IV : 27.1% (n = 61)	I : 1.3% (n = 3) II : 3.0% (n = 7) III : 67.1% (n = 157) IV : 28.6% (n = 67)	I : 2.1% (n = 12) II : 3.5% (n = 20) III : 66.7% (n = 385) IV : 27.7% (n = 160)	0.17
<i>BRCA</i> mutated	33.3% (n = 72)	22.3% (n = 55)	27.2% (n = 165)	0.029
<i>BRCA</i> wild type	66.7% (n = 144)	77.7% (n = 192)	72.8% (n = 441)	
Bevacizumab L1	20.1% (n= 64)	29.9% (n = 97)	41.9% (n = 322)	<0.001
Bevacizumab L2	14.8% (n= 47)	47.8% (n = 155)	11.5% (n = 88)	<0.001
PARP inhibitor L1	0% (n = 0)	1.5% (n = 5)	0.5% (n = 4)	0.043
PARP inhibitor L2	8.8% (n = 28)	8.3% (n = 27)	13.5% (n = 104)	0.013

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Table 2. Patients characteristics according to *BRCA* status

	<i>BRCA</i> mutated	<i>BRCA</i> wild type	p-value
Number of patients	26.9% (n = 304)	73.1% (n = 825)	
Median (min-max) follow up	42.4 months (0-145.2)	30.8 months (0-212.9)	0.001
Median age	55 yo	62 yo	<0.001
FIGO at diagnosis	I : 2.2% (n = 5) II : 4.3% (n = 10) III : 66.5% (n = 153) IV : 27.0% (n = 62)	I : 1.8% (n = 11) II : 2.8% (n = 17) III : 68.0% (n = 415) IV : 27.4% (n = 167)	0.65
Carboplatin paclitaxel	24.7% (n = 72)	18.5% (n = 144)	0.029
Carboplatin gemcitabine	18.8% (n = 55)	24.7% (n = 192)	
Carboplatin doxorubicin	56.5% (n = 165)	56.8% (n = 441)	
Bevacizumab L1	30.9% (n= 94)	38.7% (n = 319)	0.017
Bevacizumab L2	10.5% (n= 32)	24.0% (n= 198)	<0.001
PARP inhibitor L1	1.3% (n = 4)	0.4% (n = 3)	0.089
PARP inhibitor L2	47.7% (n = 145)	1.2% (n = 10)	<0.001

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Figure 1. Flow chart according to chemotherapy doublet.

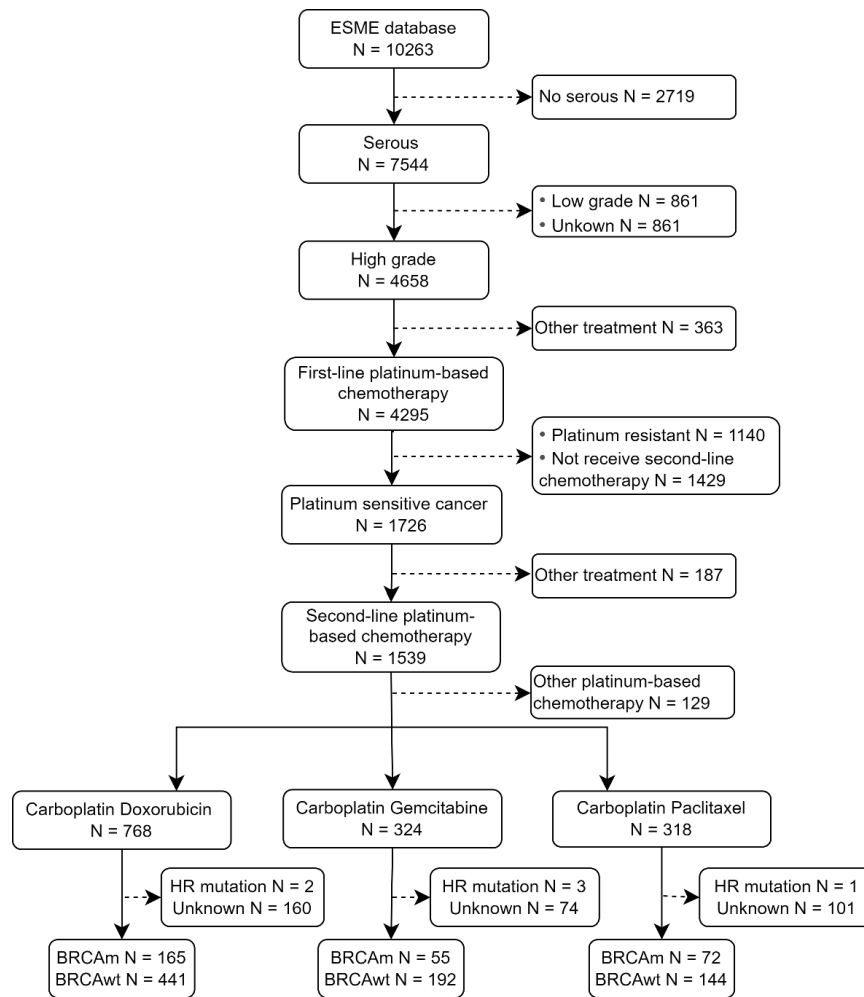


Figure 2. PFS according to chemotherapy doublet in *BRCA* wild type (blue curves) and *BRCA* mutated (yellow curves) patients treated with carboplatine/paclitaxel (left panels), carboplatine/gemcitabine (middle panels) and carboplatin/pegylated liposomal doxorubicin (right panels). A. Whole population. B. Same population after exclusion of patients receiving a maintenance therapy (bevacizumab or PARP inhibitors).

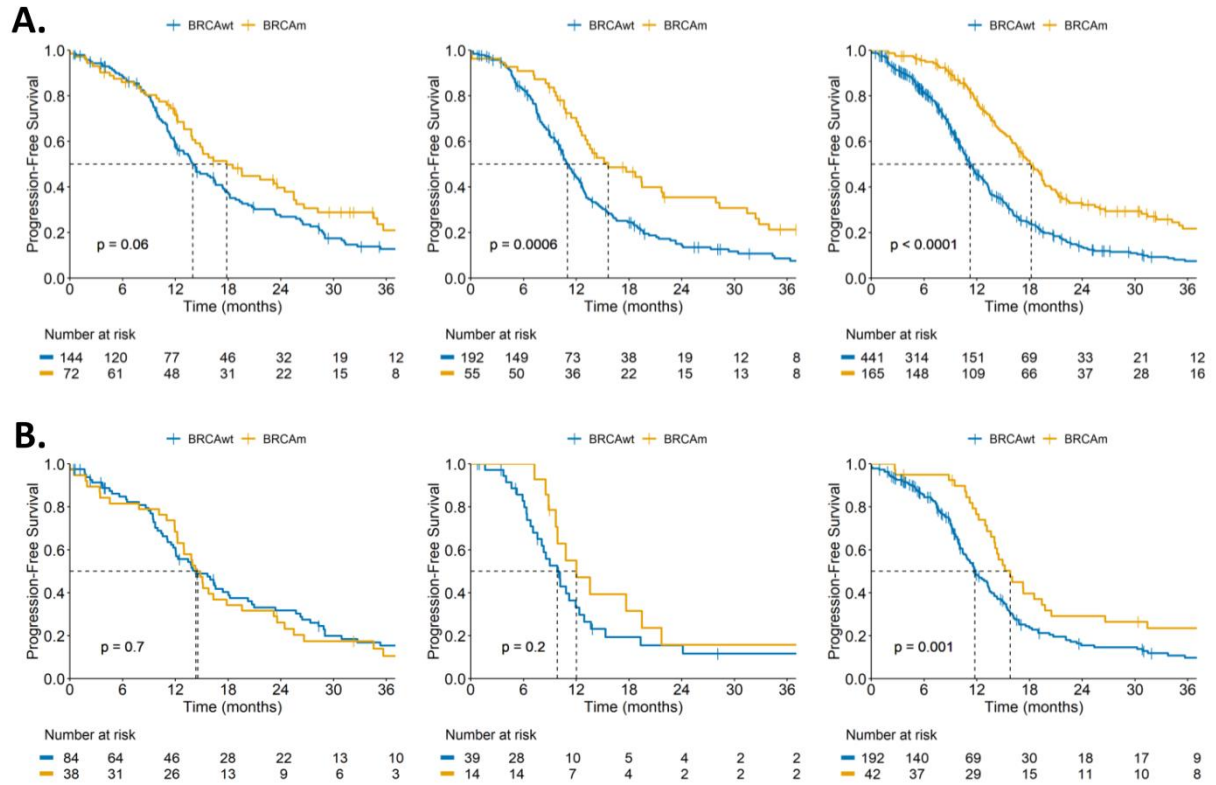
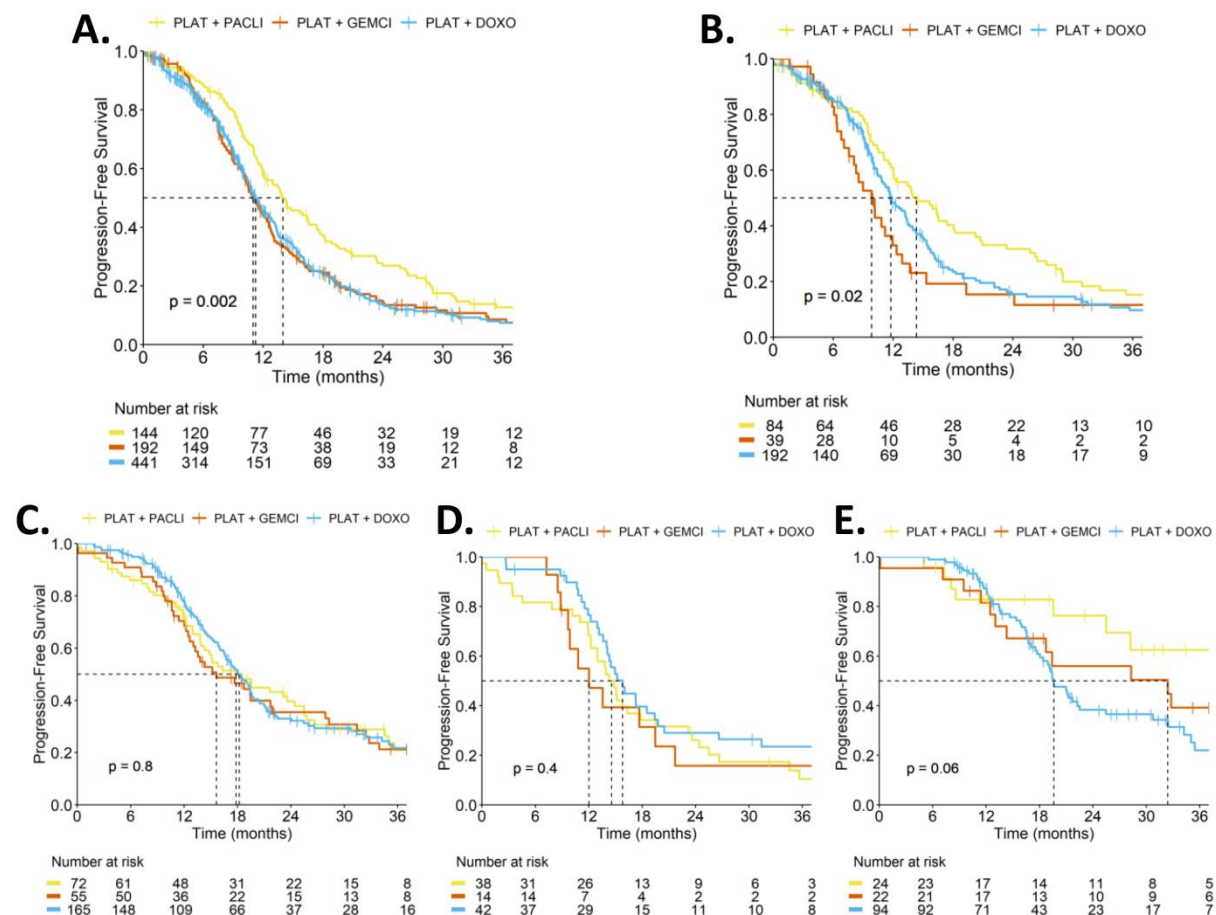


Figure 3. PFS according to *BRCA* status in *BRCA* wild type (upper panels) and *BRCA* mutated (lower panels) patients treated with carboplatine/paclitaxel (yellow curves), carboplatine/gemcitabine (red curves) and carboplatin/pegylated liposomal doxorubicin (blue curves). A. Whole *BRCA* wild type population. B. *BRCA* wild type population after exclusion of patients receiving a maintenance therapy (bevacizumab or PARP inhibitors). C. Whole *BRCA* mutated population. D. *BRCA* mutated population after exclusion of patients receiving a maintenance therapy (bevacizumab or PARP inhibitors). E. *BRCA* mutated patients receiving PARP inhibitors as a maintenance therapy.



Supplementary Table 1 : Univariate analysis of risk factors for PFS in *BRCA* wild type patients.

Factors	n	HR	IC	P.value
Age at diagnosis	825	1.01	[1 ; 1.02]	0.04
Chemotherapy				
1 - PLAT + DOXO	441	1		0.002
2 - PLAT + GEMCI	192	1.01	[0.83 ; 1.22]	
3 - PLAT + PACLI	144	0.69	[0.56 ; 0.85]	
Bevacizumab L2				
0 - No	627	1		0.004
1 - Yes	198	0.76	[0.64 ; 0.92]	
PARP inhibitor L1				
0 - No	822	1		0.025
1 - Yes	3	3.4	[1.09 ; 10.61]	
PARP inhibitor L2				
0 - No	815	1		0.214
1 - Yes	10	0.63	[0.3 ; 1.32]	
Time to relapse (1st line)				
1 - 6-12 months	277	1		<0.001
2 - 12-24 months	348	0.6	[0.5 ; 0.71]	
3 - >24 months	200	0.39	[0.32 ; 0.49]	

Supplementary Table 2 : Multivariate analysis of risk factors for PFS in *BRCA* wild type patients.

Factors	categories	N	HR	IC	P.value
Age at diagnosis		777	1	[1.00 ; 1.01]	0.35
Chemotherapy	1 - PLAT + DOXO	441	1		0.013
	2 - PLAT + GEMCI	192	1.12	[0.90 ; 1.38]	
	3 - PLAT + PACLI	144	0.77	[0.62 ; 0.96]	
Bevacizumab L2	0 - No	583	1		<0.001
	1 - Yes	194	0.70	[0.57 ; 0.85]	
PARP inhibitor L1	0 - No	774	1		0.25
	1 - Yes	3	2.14	[0.67 ; 6.78]	
Time to relapse (1st line)	1 - 6-12 months	253	1		<0.001
	2 - 12-24 months	336	0.58	[0.48 ; 0.70]	
	3 - >24 months	188	0.40	[0.32 ; 0.50]	