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ORIGINAL ARTICLE

Quality-of-life analysis of the MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG study comparing platinum-based versus non-platinum-based chemotherapy in patients with partially platinum-sensitive recurrent ovarian cancer

M. C. Piccirillo[1], G. Scambia[2], A. Bologna[3], S. Signoriello[4], I. Vergote[5,6], K. Baumann[7†], D. Lorusso[2,8], V. Murgia[9‡], R. Sorio[10], G. Ferrandina[2,11], C. Sacco[12], G. Cormio[13,14], E. Breda[15], S. Cinieri[16], D. Natale[17], G. Mangili[18], C. Pisano[19], S. C. Cecere[19], M. Di Napoli[19], V. Salutari[2], F. Raspagliesi[9], L. Arenare[1], A. Bergamini[1,18], J. Bryce[1], G. Daniele[1], C. Gallo[4§], S. Pignata[19*§] & F. Perrone[1§]

[1]Clinical Trials Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS – Fondazione G.Pascale, Napoli; [2]Department of Protection of Women's Health, Rising Life, Child and Adolescent, Università Cattolica del Sacro Cuore, Roma; [3]Medical Oncology Unit, Azienda Unità Sanitaria Locale/IRCCS di Reggio Emilia, Reggio Emilia; [4]Medical Statistics, Università degli Studi della Campania "Luigi Vanvitelli", Napoli; [5]University Hospital Leuven, Leuven; [6]Leuven Cancer Institute, Leuven, Belgium; [7]UKGM Gynecology, Frauenklinik, Marburg, Germany; [8]Gynaecologic Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milano; [9]Medical Oncology, Ospedale S. Chiara, Trento; [10]Medical Oncology C, Centro di Riferimento Oncologico, Aviano, PN; [11]Gynaecologic Oncology, Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche, Università Cattolica del Sacro Cuore, Campobasso; [12]Oncology Department, AO S. Maria della Misericordia, Udine; [13]Università di Bari, Bari; [14]Ginecoloy Oncology, Istituto Oncologico "Giovanni Paolo II", Bari; [15]Medical Oncology, Ospedale S.Giovanni Calibita Fatebenefratelli, Roma; [16]Medical Oncology, Ospedale Antonio Perrino, Brindisi; [17]Medical Oncology, Ospedale San Massimo, Penne, PE; [18]Obstertic and Gynaecologic Department, Ospedale San Raffaele, Milano; [19]Uro-Gynaecologic Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS – Fondazione G.Pascale, Napoli, Italy

*Correspondence to: Dr Sandro Pignata, Uro-Gynaecologic Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, IRCCS, Fondazione G.Pascale, via Mariano Semmola, 80131 Napoli, Italy. Tel: +390815903637; Fax: +390815903861; E-mail: s.pignata@istitutotumori.na.it

†Present address: Klinikum der Stadt, Frauenklinik, Ludwigshafen, Germany.
‡Present address: Oncology Department, Medical Oncology Unit, Ospedale S. Maria Annunziata, Bagno a Ripoli, Italy.
§These authors contributed equally as co-last authors.

Background: MITO-8 showed that prolonging platinum-free interval by introducing non-platinum-based chemotherapy (NPBC) does not improve prognosis of patients with partially platinum-sensitive recurrent ovarian cancer. Quality of life (QoL) was a secondary outcome.

Patients and methods: Ovarian cancer patients recurring or progressing 6–12 months after previous platinum-based chemotherapy (PBC) were randomized to receive PBC or NPBC as first treatment. QoL was assessed at baseline, third and sixth cycles, with the EORTC C-30 and OV-28 questionnaires. Mean changes and best response were analysed. Progression-free survival, response rate, and toxicity are also reported for proper interpretation of data. All analyses were based on intention-to-treat.

Results: Out of the 215 patients, 151 (70.2%) completed baseline questionnaire, balanced between the arms; thereafter, missing rate was higher in the NPBC arm. At mean change analysis, C30 scores were prevalently worse in the NPBC than PBC arm, statistical significance being attained for emotional functioning, global health status/QoL, fatigue, and dyspnoea (effect sizes ranging from 0.30 to 0.51). Conversely, as for OV28 scale, the other chemotherapy side-effects item was significantly worse with PBC at three and six cycles, with a larger effect size (0.70 and 0.54, respectively). At best response analysis, improvement of emotional functioning and pain and worsening of peripheral neuropathy and other chemotherapy side-effects were significantly more frequent in the PBC arm. Progression-free survival (median 9 versus 5 months, $P = 0.001$) and objective

response rate (51.6% versus 19.4%, $P = 0.0001$) were significantly better with PBC. Allergy, blood cell count, alopecia, nausea, musculoskeletal, and neurological side-effects were more frequent and severe with PBC; hand–foot skin reaction, rash/desquamation, mucositis, and vascular events were more frequent with NPBC.

Conclusion: MITO-8 QoL analysis shows that deterioration of some functioning and symptom scales is lower with PBC, with improvement of emotional functioning and pain, despite worsening of toxicity-related items.

ClinicalTrials.gov: NCT00657878.

Key words: ovarian cancer, quality of life, platinum-based chemotherapy, non-platinum-based chemotherapy, phase III randomised trial, partially platinum-sensitive ovarian cancer

Introduction

Chemotherapy is still the cornerstone of the treatment of patients with recurrent ovarian cancer. Choosing between a platinum-based (PBC) and non-platinum-based chemotherapy (NPBC) is largely driven by the platinum-free interval (PFI), i.e. the time elapsed from the last platinum treatment to recurrence [1, 2]. However, uncertainty still exists for patients with PFI between 6 and 12 months (partially platinum-sensitive); it was claimed indeed that prolongation of the PFI through the intercalation of an NPBC might improve overall prognosis by increasing sensitivity to subsequent retreatment with PBC [3].

We recently published the MITO-8 randomized trial that compared two treatment strategies in partially platinum-sensitive ovarian cancer patients: the experimental approach of NPBC followed at progression by PBC versus the reverse standard sequence of PBC followed at progression by NPBC. Results were negative: PFI indeed was prolonged in the experimental arm (median 7.8 versus 0.01 months), but both progression-free after second treatment (12.8 versus 16.4 months) and overall survival (21.8 versus 24.5 months) were in favour of the standard sequence [4].

In this study, we report the results of quality of life (QoL) analysis that was limited to the first treatment in each sequence, i.e. PBC versus NPBC. Such analysis was prompted by the hypothesis that a possible slightly greater effectiveness of PBC might be counteracted by a higher toxicity, thus negatively affecting QoL.

Patients and methods

MITO-8 (ClinicalTrials.gov NCT00657878) was promoted by the National Cancer Institute (NCI), Napoli, Italy and was conducted in 45 centres, located in Italy, Belgium and Germany, according to the ENGOT rules model A [5].

The detailed description of the trial, the primary analysis (overall survival comparison) and some secondary analyses [progression-free survival (PFS2), response rate and toxicity after the complete treatment sequence] have been reported elsewhere [4]. Assessment of QoL was a pre-planned secondary outcome limited to the first treatment (PBC versus NPBC) in the two sequences. Sample size was calculated based on overall survival hypothesis and no specific QoL hypothesis was prespecified.

Study population

Patients with ovarian cancer recurrence or progression diagnosed 6–12 months after the last platinum injection were eligible if they had received no more than two previous chemotherapy lines, had a life expectancy >3 months, adequate bone marrow, renal and liver function and consented to the trial. ECOG performance status >2, previous treatment with PLD, and residual peripheral neuropathy from the previous treatments (grade >1 in the initial protocol and grade >2 after the April 2012 amendment) were the major exclusion criteria. Participating patients gave written informed consent.

Study procedures

After baseline assessments patients were randomly assigned to receive PBC followed at disease progression by NPBC or the reverse sequence. PBC initially comprised the combination of carboplatin/paclitaxel (carboplatin AUC 5 plus paclitaxel 175 mg/m^2 on day 1 every 21 days), and NPBC initially comprised PLD (40 mg/m^2 on day 1 every 28 days). In August 2011, the international shortage of PLD caused enrolment interruption. In April 2012, an amendment was approved and the study restarted using Topotecan (4 mg/m^2 daily for 5 or 3 consecutive days, every 21 days), gemcitabine (1000 mg/m^2 on days 1, 8, 15 every 28 days), or any other drug approved in this setting as NPBC. Also, the doublet carboplatin/gemcitabine (carboplatin AUC 4 on day 1 plus gemcitabine 1000 mg/m^2 on day 1 and 8 every 21 days) was permitted for patients with grade <3 neurotoxicity at baseline. All the treatments were continued for six cycles, or up to nine cycles in case of partial response or stable disease. Dose modification rules were predefined. Antiemetic therapy was given according to local procedures.

QoL *assessment*

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the ovarian cancer-specific module (EORTC QLQ-OV28) were used to evaluate QoL [6–8]. QoL measurement was planned at baseline (before randomization) and at the third and sixth cycles of chemotherapy. Questionnaires were administered to patients as paper forms and data were reported in web forms by data-managers at participating centres.

The EORTC QLQ-C30 is a 30-item questionnaire composed of five multi-item functional scales (physical, role, emotional, social, and cognitive functioning), three multi-item symptom scales (fatigue, pain, and emesis), a global health status scale, and six single items to assess financial impact and symptoms (dyspnoea, sleep disturbance, appetite, diarrhoea, and constipation) during the previous week [6, 8]. The EORTC QLQ-OV28 is a 28-item questionnaire addressing issues that may be relevant for ovarian cancer patients. In detail, it includes five multi-item symptom/side-effects scales (abdominal/GI, peripheral neuropathy, hormonal, body image, other chemotherapy side-effects), one multi-item scale measuring attitude to disease and treatment, and one multi-item scale measuring sexual functioning. All subscales are referred to the previous week, but for the sexual functioning that refer to the last 4 weeks [7]. Both questionnaires are designed to be completed by the patient. Scores for multi-item scales are calculated by deriving the mean raw scores of single items and transforming them linearly into scales ranging from 0 to 100. For single items, only linear transformation is carried out. For the functional and global health status scales of the QLQ-C30 and for the sexual functioning scale of the QLQ-OV28 higher values represent better

function (i.e. better). For all the other scales, higher values represent greater severity of symptoms (i.e. worse).

QoL *analysis*

QoL missing data patterns were described according to the NCI of Canada Clinical Trials Group QoL framework under three different scenarios: (i) rate of patients completing baseline and subsequent assessments over the total number of patients enrolled into the trial [QoL intention-to-treat (ITT) population]; (ii) rate of patients completing QoL assessments out of those completing the baseline one (QoL efficacy population); and (iii) rate of patients completing QoL assessments out of those expected (QoL expected population), thus excluding patients progressed or dead at a date before the date of planned QoL assessment [9]. No strategy for missing data substitution was applied. Possible selection biases due to missing values were checked by comparing the baseline characteristics of subjects without and with baseline QoL questionnaire and the baseline QoL scores between the two arms.

All analyses were based on intention to treat (ITT). No adjustment was applied for multiple comparisons.

Mean score changes from baseline to the third and sixth cycles were reported to describe behaviour of QoL items. Only patients with available values at baseline and at least one subsequent time point were included in the analysis. A linear regression model adjusted by baseline value, centre (three categories according to tertiles of the number of the enrolled patients), previous lines of chemotherapy (1 versus 2) and previous cytoreduction (optimal versus non-optimal) was applied to test the statistical significance of the differences at each time point. Analysis was stratified according to the enrolment period and the presence of neurotoxicity at baseline as described elsewhere [4]. Clinical relevance of mean changes was assessed by calculating the effect size (mean difference between treatment arms/SD in the PBC arm), where values of 0.2, 0.5 and 0.8 correspond to small, medium and large effects, respectively.

Best QoL response from baseline for each domain or symptom was calculated defining a change score of at least 10 points from baseline as clinically relevant [10]. Patients were considered improved if they reported a score $\geq$10 points better than baseline at any time, and were considered worsened if they reported a score $\geq$10 points worse than baseline without having improved at any time; those with scores changing less than 10 points from baseline were considered stable. Chi-square test was applied to test statistical significance.

Other clinical outcomes

We complemented QoL data with comparison of activity and toxicity data between PBC and NPBC limiting the analysis to the first treatment of each sequence. These data have not been reported in the MITO-8 primary analysis study that detailed the whole effect of the treatment strategies.

PFS was the time between date of randomization and date of first disease progression or death, whichever occurred first. Patients who did not progress were censored on the date of the last follow-up visit. Survival curves were described according to Kaplan–Meier product-limit method. HR was estimated by stratified Cox proportional hazard model adjusted by centre (three categories according to tertiles of the number of the enrolled patients), previous lines of chemotherapy (1 versus 2) and previous cytoreduction (optimal versus non-optimal) and stratified by enrolment period and the presence of neurotoxicity at baseline [4].

Response was assessed by Investigators according to RECIST version 1.0 and GCIG criteria [11, 12]. No independent radiological review was planned. Response rate (RR) was the number of patients with complete or partial response, divided by the number of patients eligible for response at baseline, in each arm. Patients not evaluated because of death or toxicity or refusal or loss to follow-up before the first restaging were considered non-responders. RRs in the two arms were compared by Mantel–Haenszel χ^2 test stratified as above.

Adverse events were coded according to Common Terminology Criteria for Adverse Events CTCAE version 3.0. The worst grade suffered for each item by each patient during the first treatment in each arm was considered. Any grade ($G > 0$) and severe ($G > 2$) toxicities were compared between study arms by Mantel–Haenszel test stratified as above.

Results

From 26 February 2009 to 16 October 2015, 215 patients were enrolled in the MITO-8 study, 108 assigned to PBC and 107 to NPBC; of these, 75 (69.4%) and 76 (71.0%) completed baseline questionnaires, respectively. Patients with and without baseline QoL questionnaires had similar baseline characteristics (supplementary Table S1, available at *Annals of Oncology* online).

Baseline characteristics of patients included in the QoL efficacy population were well balanced between study arms (supplementary Table S2, available at *Annals of Oncology* online). Median age was 62 years (range 33–84). For all QoL items, baseline values were similar between the two arms (supplementary Table S3, available at *Annals of Oncology* online).

Compliance with QoL questionnaire completion significantly decreased at the third and the sixth cycles. Patterns of missing QoL measurements are reported in supplementary Figure S1, available at *Annals of Oncology* online. The rate of missing QoL measurements after the baseline was consistently higher in the NPBC arm.

Mean change analysis

Mean change analysis, adjusted by baseline value, residual disease, number of previous chemotherapy lines, size of centre, and stratified by enrolment period and presence of baseline neurotoxicity, is reported in supplementary Figures S2–S6, available at *Annals of Oncology* online. The observed QLQ-C30 scores (supplementary Figures S2–S4, available at *Annals of Oncology* online) show that most scales deteriorated with time in both arms, prevalently worse in the NPBC arm; in some cases (emotional functioning, global healthstatus/QoL, fatigue and dyspnoea) differences were statistically significant at the conventional 0.05 level, with effect size ranging from 0.30 to 0.51 in favour of the control arm. Conversely, among OV28 items (supplementary Figure S5, available at *Annals of Oncology* online), other chemotherapy side-effects were significantly worse with PBC after both three and six cycles of treatment, with effect size of 0.70 and 0.54, respectively.

QoL *response analysis*

Consistent results were found when QoL best response was calculated (Table 1). Emotional functioning (41.3% versus 10.4%) and pain (42.2% versus 18.4%) were more frequently improved, while peripheral neuropathy (67.7% versus 46.8%) and other chemotherapy side-effects (74.2% versus 48.9%) were more frequently worsened in the PBC versus the NPBC arm.

Activity analysis

PFS was evaluated with 202 events, 99 in the PBC and 103 in the NPBC arm (Figure 1). HR of the experimental NPBC arm was equal to 3.45 (95% CI: 1.24–2.20, $P = 0.001$). Observed median

Table 1. Best quality of life response by treatment arm

Scale/item	PBC						NPBC						*P*
	Improved		Stable		Worse		Improved		Stable		Worse		
Global health status/QoL	24	(38.71%)	19	(30.65%)	19	(30.65%)	11	(22.92%)	13	(27.08%)	24	(50.00%)	0.09
Physical functioning	12	(18.75%)	34	(53.13%)	18	(28.13%)	6	(12.24%)	23	(46.94%)	20	(40.82%)	0.32
Role functioning	21	(32.81%)	22	(34.38%)	21	(32.81%)	11	(22.45%)	15	(30.61%)	23	(46.94%)	0.27
Emotional functioning	26	(41.27%)	21	(33.33%)	16	(25.40%)	5	(10.42%)	22	(45.83%)	21	(43.75%)	**0.001**
Cognitive functioning	20	(31.75%)	24	(38.10%)	19	(30.16%)	9	(18.37%)	20	(40.82%)	20	(40.82%)	0.24
Social functioning	18	(28.57%)	18	(28.57%)	27	(42.86%)	13	(27.08%)	14	(29.17%)	21	(43.75%)	0.98
Fatigue	20	(31.25%)	12	(18.75%)	32	(50.00%)	13	(26.53%)	6	(12.24%)	30	(61.22%)	0.45
Nausea/vomiting	10	(15.63%)	35	(54.69%)	19	(29.69%)	8	(16.33%)	25	(51.02%)	16	(32.65%)	0.92
Pain	27	(42.19%)	15	(23.44%)	22	(34.38%)	9	(18.37%)	19	(38.78%)	21	(42.86%)	**0.02**
Dyspnoea	15	(23.44%)	35	(54.69%)	14	(21.88%)	6	(12.24%)	25	(51.02%)	18	(36.73%)	0.13
Sleeping disturbance	15	(23.44%)	26	(40.63%)	23	(35.94%)	9	(18.37%)	23	(46.94%)	17	(34.69%)	0.74
Appetite loss	12	(18.75%)	36	(56.25%)	16	(25.00%)	3	(6.12%)	31	(63.27%)	15	(30.61%)	0.14
Constipation	18	(28.57%)	26	(41.27%)	19	(30.16%)	9	(18.37%)	24	(48.98%)	16	(32.65%)	0.45
Diarrhoea	7	(11.11%)	41	(65.08%)	15	(23.81%)	7	(14.29%)	36	(73.47%)	6	(12.24%)	0.29
Financial	12	(19.05%)	38	(60.32%)	13	(20.63%)	6	(12.77%)	31	(65.96%)	10	(21.28%)	0.67
Abdominal/GI	27	(43.55%)	15	(24.19%)	20	(32.26%)	14	(29.79%)	17	(36.17%)	16	(34.04%)	0.26
Peripheral neuropathy	14	(22.58%)	6	(9.68%)	42	(67.74%)	12	(25.53%)	13	(27.66%)	22	(46.81%)	**0.03**
Hormonal	10	(16.13%)	30	(48.39%)	22	(35.48%)	15	(31.91%)	18	(38.30%)	14	(29.79%)	0.15
Body image	17	(27.42%)	17	(27.42%)	28	(45.16%)	11	(23.91%)	17	(36.96%)	18	(39.13%)	0.57
Attitude to disease/treatment	32	(50.79%)	9	(14.29%)	22	(34.92%)	18	(37.50%)	11	(22.92%)	19	(39.58%)	0.31
Other chemotherapy side-effects	7	(11.29%)	9	(14.52%)	46	(74.19%)	9	(19.15%)	15	(31.91%)	23	(48.94%)	**0.02**
Sexual functioning	10	(17.24%)	36	(62.07%)	12	(20.69%)	7	(15.22%)	33	(71.74%)	6	(13.04%)	0.52

P denoting statistically significant difference were highlighted with bold characters.

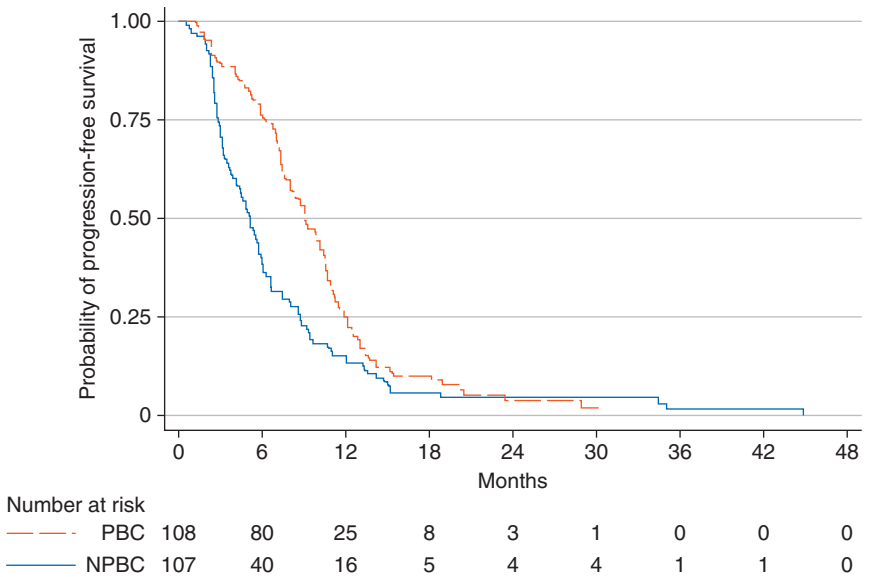

Figure 1. Kaplan–Meier estimated curves of progression-free survival by treatment arms. Continue blue, NPBC; Dashed red, PBC.

PFS was nearly double in the PBC arm (9.0 months) than in the NPBC arm (5.0 months).

In the eligible patients, RR was always markedly higher in the PBC arm, according to both RECIST and GICG criteria (supplementary Table S4, available at *Annals of Oncology* online).

Toxicity analysis

Side-effects were heterogeneously distributed between arms (supplementary Table S5, available at *Annals of Oncology* online). On the whole more side-effects were observed in the PBC arm, mainly allergic reactions, alopecia, haematological and neurological

toxicities; however, they were scarcely severe but for haematological toxicities. On the contrary other dermatological side-effects (including rash/desquamation and hand–foot skin reaction) and mucositis were more frequent and severe with NPBC.

Discussion

MITO-8 compared two strategies of treatment of advanced ovarian cancer patients recurring or progressing 6–12 months after the administration of a platinum-based chemotherapy. The overall survival and PFS analyses showed that the standard sequence with PBC first, followed at progression by an NPBC, was more effective than the reverse sequence [4]. QoL analysis reported in this paper further reinforces the standard treatment showing that there was no consistent trend penalizing PBC, and QoL results seemed profoundly influenced by differences in efficacy of the two compared treatments. In the best QoL response assessment, that relates to change scores of clinical relevance, statistically significant differences were found in only four items. Two favoured PBC, namely emotional functioning and pain. Two, on the contrary, favoured NPBC, namely peripheral neuropathy and other chemotherapy side-effects; the latter includes hair loss, dysgeusia, musculoskeletal pain, hearing disturbance, urinary frequency and skin problems, the first two components being prevalent, consistently with the expected toxicity profile of carboplatin. Quite all other items, possibly related to disease control, were slightly better in the PBC arm. Similar findings were found when score mean changes were evaluated. However, QoL patterns were different between the two treatments and this information might be useful to inform patients regarding the trade-offs between efficacy, toxicity and QoL of possible treatments. Furthermore, analysis of PFS and response after the first treatment of the sequence is also strongly consistent with the main efficacy results.

Therefore, MITO-8 findings overall contradict the hypothesis, proposed several years ago, that artificially prolonging the PFI by intercalating an NPBC might produce a therapeutic advantage.

Among limitations of this study, QoL analysis of MITO-8 trial was planned only during the first treatment, because of the crossover of drugs and the possible selection bias related to timing to progression. It is also worth noting that the time of QoL assessment was slightly delayed in the NPBC arm due to the different duration of the two treatments. Therefore, we did not evaluate time to deterioration of quality of life because potential biases in this type of analysis could not be avoided. We acknowledge a quite high rate of missing questionnaires at baseline, due to the fact that QoL was a secondary end point, and baseline QoL was not checked as mandatory for patients' enrolment. After the baseline, the missing rate was marginally due to the different treatment duration but substantially affected by the different clinical performance of the two treatments. The bias potentially deriving from missing data would favour the experimental arm and is therefore not critical for the final interpretation of data that globally favour the standard arm. Finally, as no correction for multiple testing was applied, data should be interpreted with caution due to the risk of false positive results.

MITO-8 data can be put at glance with two other trials including patients with partially platinum-sensitive recurrent ovarian cancer, and with a study design similar to the first treatment comparison of MITO-8. In the OVA-301 study, trabectedin was added to PLD and compared with PLD alone; QoL analysis showed that the addition of trabectedin to PLD led to little or no decrement in patient-reported functional status [13]. In the TRINOVA-1 study, trebananib was added to weekly paclitaxel and compared with weekly paclitaxel alone; QoL analysis showed that the addition of trebananib did not significantly compromise QoL [14]. As both the OVA-301 and TRINOVA-1 found statistically significant benefits in PFS analyses, the lack of worsening of QoL in the experimental arm was considered as a positive finding. Facing MITO-8 with these two trials and acknowledging the limitations of indirect comparisons, we argue that the lack of QoL worsening versus a standard arm that might be suboptimal in terms of QoL efficacy should not be interpreted as a positive finding.

In conclusion, the QoL analysis of MITO-8 overall supports the primary conclusion of the study in favour of immediate retreatment with PBC of patients with partially platinum-sensitive advanced ovarian. Further platinum-based therapy should still be used as a control arm when assessing new drugs in this particular population [15]. Also, such analysis provides a useful source of information for patients on the short-term trade-offs between efficacy, toxicity and QoL in the initial treatment.

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Disclosure

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