VOLUME 35 · NUMBER 29 · OCTOBER 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Controlled Trial Testing the Efficacy of Platinum-Free Interval Prolongation in Advanced Ovarian Cancer: The MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study

Sandro Pignata, Giovanni Scambia, Alessandra Bologna, Simona Signoriello, Ignace B. Vergote, Uwe Wagner, Domenica Lorusso, Viviana Murgia, Roberto Sorio, Gabriella Ferrandina, Cosimo Sacco, Gennaro Cormio, Enrico Breda, Saverio Cinieri, Donato Natale, Giorgia Mangili, Carmela Pisano, Sabrina Chiara Cecere, Marilena Di Napoli, Vanda Salutari, Francesco Raspagliesi, Laura Arenare, Alice Bergamini, Jane Bryce, Gennaro Daniele, Maria Carmela Piccirillo, Ciro Gallo, and Francesco Perrone

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on August 21, 2017.

Clinical trial information: NCT00657878, EudraCT number 2008-001755-22.

Corresponding author: Sandro Pignata, MD, Istituto Nazionale per lo Studio e la Cura dei Tumori Fondazione Pascale IRCCS, via Mariano Semmola, 80131 Naples, Italy; e-mail: s.pignata@istitutotumori.na.it.

0732-183X/17/3529w-3347w/$20.00

ABSTRACT

Purpose
Platinum-based chemotherapy (PBC) for patients with progressing ovarian cancer (OC) is more effective with a longer time interval from previous platinum treatment (platinum-free interval [PFI]). In 1999, it was hypothesized that prolonging PFI with single-agent non-PBC (NPBC) may offer a strategy to improve overall outcome. MITO-8 aimed to verify this hypothesis commonly used in clinical practice although it has not been prospectively tested.

Methods
MITO-8 is an open-label, prospective, randomized, superiority trial. Patients with OC who experienced disease progression 6 to 12 months after their last platinum treatment were randomly assigned 1:1 to the experimental sequence of NPBC followed by PBC at subsequent relapse or the standard reverse treatment sequence. Overall survival (OS) was the primary end point.

Results
Two hundred fifteen patients were enrolled (standard arm [n = 108]; experimental arm [n = 107]). The trial ended before planned because of slow enrollment. PFI was prolonged in the experimental arm (median, 7.8 *v* 0.01 months). There was no OS benefit in the experimental arm (median, 21.8 *v* 24.5 months; hazard ratio, 1.38; 95% CI, 0.99 to 1.94; $P = .06$). Progression-free survival after the sequence was significantly shorter in the experimental arm (median, 12.8 *v* 16.4 months; hazard ratio, 1.41; 95% CI, 1.04 to 1.92; $P = .025$). Global quality-of-life change after three cycles was worse in the experimental arm. Slight differences were observed in the incidence of adverse effects.

Conclusion
MITO-8 supports the recommendation that PBC not be delayed in favor of an NPBC in patients with partially platinum-sensitive OC. PBC should be used as a control arm in future trials of new drugs in this setting.

J Clin Oncol 35:3347-3353. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Most patients with ovarian cancer (OC) experience disease progression after primary surgery and first-line platinum-based chemotherapy (PBC) and require subsequent treatment. Retreatment with PBC is possible—the effectiveness of treatment with PBC increases with a longer interval from the initial PBC treatment.[1,2] Therefore, the time from last platinum treatment to recurrence (platinum-free interval [PFI]) drives a treatment strategy that is based on nonplatinum chemotherapy if PFI is < 6 months (platinum resistant), and on platinum-containing doublets if PFI is > 12 months (platinum sensitive). There is uncertainty when the PFI is between 6 and 12 months (partially platinum sensitive) because of unsatisfactory results from treatment with platinum-containing doublets.

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.73.4293

Data Supplement
DOI: https://doi.org/10.1200/JCO.2017.73.4293

DOI: https://doi.org/10.1200/JCO.2017.73.4293

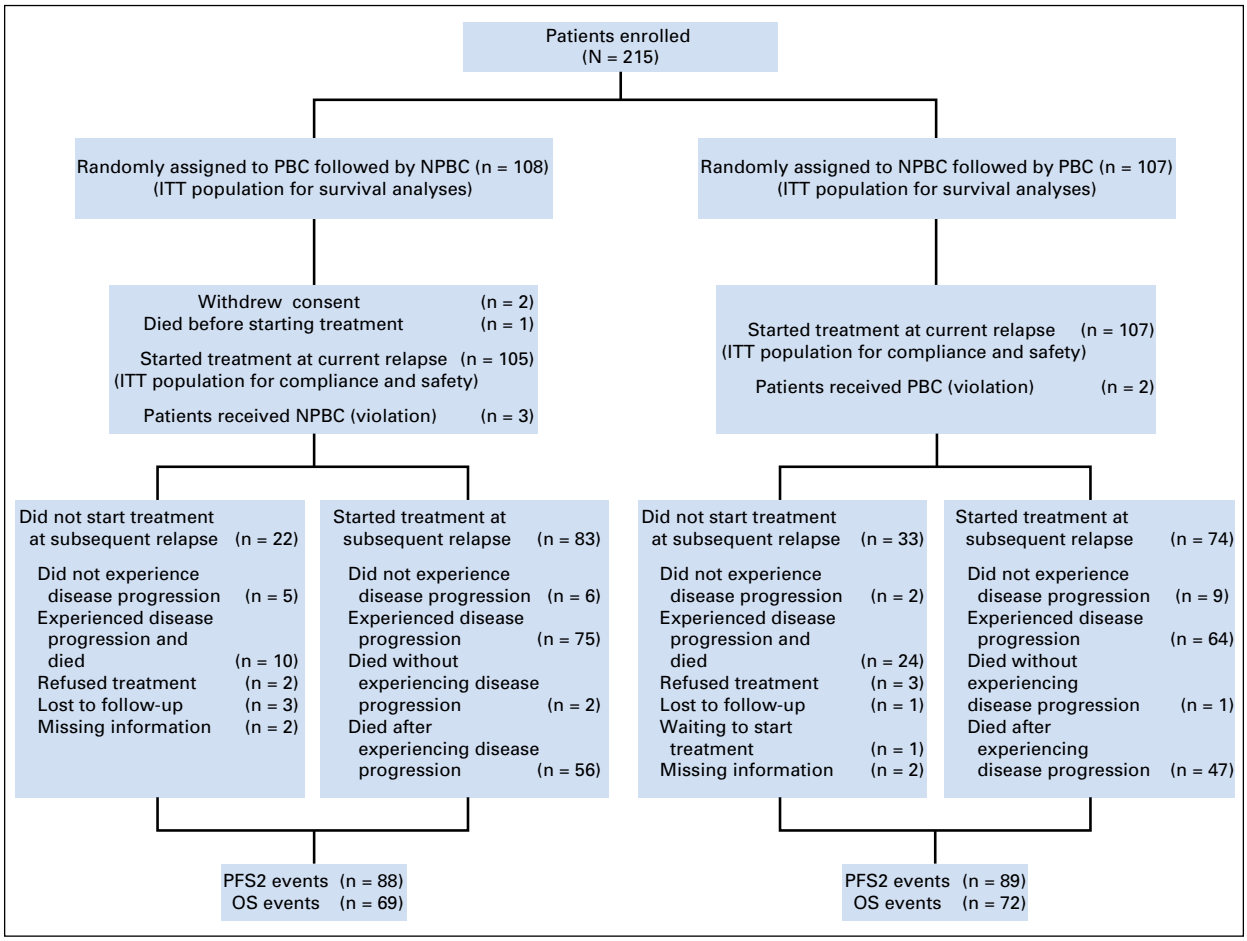

Fig 1. CONSORT diagram. ITT, intention-to-treat; NPBC, non–platinum-based chemotherapy; OS, overall survival; PBC, platinum-based chemotherapy; PFS2, progression-free survival after the two planned treatments.

The extension of PFI, intercalating a nonplatinum treatment, was hypothesized in 1999 as a strategy to increase the sensitivity of the disease to platinum retreatment, thus improving the outcome of patients with partially platinum-sensitive disease.[3] Therefore, in this setting, paclitaxel, topotecan, plus pegylated liposomal doxorubicin (PLD), and PLD plus trabectedin have been tested and entered into clinical practice.[4-7] In addition, single-agent nonplatinum chemotherapy has been the standard arm in phase III studies of a new drug (trebananib).[8,9] In 2006, a retrospective study conducted by the Multicenter Italian Trials in Ovarian Cancer (MITO) group suggested that a nonplatinum single agent as the initial treatment of patients with partially platinum-sensitive recurrent OC may not be the best choice, even though it is used in a third of cases.[10]

In 2008, we launched the Multicenter Italian Trials in Ovarian Cancer (MITO-8), Mario Negri Gynecologic Oncology (MaNGO), Belgian Gynecologic Oncology Group (BGOG) -ov1, Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovar 2.16 trial, European Network of Gynecological Oncological Trial Groups (ENGOT) -ov1, Gynecologic Cancer InterGroup (GCIG), hereafter called MITO-8, to test whether prolonging the PFI by introducing nonplatinum treatment could improve the outcome of patients with partially platinum-sensitive OC.

METHODS

Study Design

MITO-8 is an international, multicenter, randomized, open-label phase III trial in which patients with partially platinum-sensitive OC were randomly assigned (1:1) to the standard arm, (patients received PBC at current relapse followed by NPBC at subsequent relapse) or the experimental arm (patients received the reverse sequence: NPBC at current relapse followed by PBC at subsequent relapse).

The study was sponsored by the National Cancer Institute of Naples, Italy. The sponsor was responsible for the study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the article. The study was conducted in 45 centers located in Italy, Belgium, and Germany. Ethics committees at each participating institution approved the study. The study was performed according to the European Network of Gynecological Oncological Trial Groups rules (model A).[11]

Patients

Patients with OC who experienced disease recurrence or disease progression 6 to 12 months after the last PBC, who had received no more than two previous chemotherapy lines, and who had a life expectancy > 3 months were eligible if they had adequate bone marrow, renal, and liver function. Major exclusion criteria were Eastern Cooperative Oncology Group performance status > 2, previous treatment with PLD, and residual

Table 1. Distribution of Patients' Baseline Characteristics by Study Arm

Characteristic	Standard Arm PBC Followed by NPBC (n = 108)	Experimental Arm NPBC Followed by PBC (n = 107)
Age, years		
Median (IQR)	62 (52-70)	63 (53-69)
Primary tumor site		
Ovary	104 (96.3)	103 (96.3)
Tube	2 (1.9)	3 (2.8)
Peritoneum	2 (1.9)	1 (0.9)
Histology		
Serous	71 (65.7)	90 (84.1)
Mucinous	1 (0.9)	2 (1.9)
Endometrioid	11 (10.2)	8 (7.5)
Undifferentiated	8 (7.4)	0 (0)
Clear cell	7 (6.5)	2 (1.9)
Mixed	2 (1.9)	1 (0.9)
Other	8 (7.4)	4 (3.7)
FIGO stage		
Ic	4 (3.7)	4 (3.7)
II	1 (0.9)	3 (2.8)
III	85 (78.7)	87 (81.3)
IV	18 (16.7)	13 (12.1)
Grading		
I	2 (1.9)	3 (2.8)
II	5 (4.6)	8 (7.5)
III	93 (86.1)	85 (79.4)
Unknown	8 (7.4)	11 (10.3)
Previous surgery		
At least one intervention	102 (94.4)	102 (95.3)
Residual disease		
No residual disease	54 (50.0)	51 (47.7)
≤ 1cm; > 1cm; not operated	54 (50.0)	56 (52.3)
Previous chemotherapy lines		
1	102 (94.4)	100 (93.5)
2	6 (5.6)	7 (6.5)
Enrollment period		
Period 1	62 (57.4)	62 (57.9)
Period 2 without neurotoxicity	28 (25.9)	26 (24.3)
Period 2 with neurotoxicity	18 (16.7)	19 (17.8)

NOTE. Data are presented as No. (%) unless otherwise specified.
Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; NPBC, non–platinum-based chemotherapy; PBC, platinum-based chemotherapy.

peripheral neuropathy from previous treatments (grade > 1 in the initial protocol and grade > 2 after the April 2012 amendment). Participating patients gave written informed consent.

Random Assignment and Masking

Random assignment was performed at the clinical trial unit of the National Cancer Institute of Naples using a computerized minimization procedure with the following stratification variables: previous lines of chemotherapy (one *v* two), previous cytoreduction (optimal *v* nonoptimal or no cytoreduction), and the presence of clinically significant neuropathy (after the April 2012 amendment). No blinding procedure was planned.

Procedures

PBC initially comprised the combination of carboplatin and paclitaxel (carboplatin area under the curve 5 plus paclitaxel 175 mg/m^2 on day 1, every 21 days). NPBC initially comprised PLD (40 mg/m^2 on day 1, every 28 days). In August 2011, the international shortage of PLD caused enrollment interruption. In April 2012, an amendment was approved, and the study restarted. Topotecan (4 mg/m^2 once daily for 5 or 3 consecutive days, every 21 days), gemcitabine (1,000 mg/m^2 on days 1, 8, and 15, every 28 days), or any other drug approved in this setting were permitted as NPBC. In addition, carboplatin and gemcitabine (carboplatin area under the curve 4 on day 1 plus gemcitabine 1,000 mg/m^2 on days 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 for up to nine cycles in the case of partial response or stable disease. Dose modification rules were predefined. Antiemetic therapy was given according to local procedures.

Disease assessment, which included clinical examination, chest radiography, abdominopelvic computed tomography scan or magnetic resonance imaging, and serum CA125 measurement, was performed at baseline, every three cycles, and every 3 months after the end of treatment. Safety assessment, which included physical examination, blood tests (hematology and biochemistry), and collection of adverse events history, was performed at baseline, before each cycle, and 3 weeks after the end of treatment. Hematology was assessed weekly. Electrocardiogram and echocardiography were planned at baseline and every three cycles.

Outcomes

Overall survival (OS) was the primary end point; it was defined as the time that elapsed from the date of random assignment to the date of death, or of the last follow-up visit for living patients.

Secondary end points included progression-free survival after the two planned treatments (PFS2), total response rate (TRR), total toxicity, progression-free survival after the first planned treatment (PFS1), and quality of life (QOL).

PFS1 was the time between the date of random assignment and the date of first disease progression or death, whichever occurred first. Patients who did not experience disease progression were censored on the date of the last follow-up visit. PFS2 was the time from random assignment to objective tumor progression after the second treatment or death from any cause, consistent with the definition proposed in the European Medicines Agency guideline on the evaluation of anticancer medicinal products in man.

Response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors (RECIST) and GCIG criteria.[12,13] No independent radiologic review was planned. The TRR was the number of patients with complete or partial response at any time during the trial, divided by the number of patients eligible for response at baseline, in each arm. Patients not evaluated because of death, toxicity, refusal, or loss to follow-up before the first restaging were considered nonresponders.

Adverse events were coded according to Common Terminology Criteria for Adverse Events, version 3.0. Total toxicity was the worst grade suffered for each item by each patient at any time during the trial.

QOL was measured with the European Organisation for Research and Treatment of Cancer (EORTC)-C30 and the EORTC-OV28 questionnaires, at baseline and after the third and the sixth cycle of the initial treatment in each arm. Here, we report data on the global health status and QOL score (items 29 to 30 of EORTC-C30). Additional QOL analyses will be reported elsewhere.

Statistical Analysis

Assuming a median survival in the control arm equal to 18 months and in the experimental arm equal to 27 months, corresponding to a hazard ratio (HR) of death of 0.67, with two-tailed α 5%, 80% power, and no interim analyses, 193 events were required and 250 patients were planned (EAST, version 3.1; Cytel Software, Cambridge, MA).

Efficacy and safety analyses were performed according to intention-to-treat strategy. Survival curves were described according to the Kaplan-Meier product-limit method. According to protocol, HR was estimated previously by a stratified Cox proportional hazard model adjusted by center (divided according to tertiles of the number of enrolled patients), previous lines of chemotherapy (one *v* two), and previous cytoreduction (optimal *v* nonoptimal). Three strata were defined according to the enrollment period and the presence of neurotoxicity at baseline: (1) from

start to August 2011, (2) from restart to the end, without neurotoxicity, and (3) from restart to the end, with neurotoxicity. Heterogeneity of treatment effect among study periods was assessed as in a prospective meta-analysis comparing two nested models, one with period-specific treatment estimates and one with the overall treatment estimate.[14] During the peer review process, a second set of OS and PFS2 analyses was performed, because the proportional hazard assumption was not met for the main treatment effect. Such analyses are explained and detailed in the Appendix (online only).

Patients with at least one target lesion at baseline according to RECIST 1.0 or with baseline CA125 levels at least twice the upper limit of the normal value range were eligible for response assessment. Response rates (complete plus partial) in the two arms were compared by a stratified Mantel-Haenszel χ^2 test.

Statistical significance of the difference in the mean change between the two arms at each point was tested in a linear regression model adjusted by the previous covariates and the baseline global health status and QOL score.

Patients who received at least one study drug dose represented the safety population. All grades and severe (grade $>$ 2) toxicities were compared between study arms by a stratified Mantel-Haenszel test.

Statistical analyses were performed using STATA/MP 14.1 (StataCorp, College Station, TX) and SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

From February 26, 2009 to October 16, 2015, 215 patients were randomly assigned to the standard (n = 108) or the experimental (n = 107) arm (Fig 1). Enrollment was stopped in October 2016 because of slow accrual, following the advice of the independent data monitoring committee.

Baseline patient characteristics were balanced between the arms (Table 1), with the exception of a higher proportion of nonserous histology in the standard arm (34.3% *v* 15.9%). Overall, 124 women were recruited before study interruption, and 91 after trial resumed—37 with neurotoxicity and 54 without.

Details of delivered treatments are listed in Table 2. In the standard arm, protocol violation was reported in three patients who received the opposite sequence. The median number of PBC cycles was six (interquartile range [IQR], six to six), and the median number of NPBC cycles was four (IQR, three to six). Twenty-four patients (22.9%) required a dose reduction of PBC and 18 (21.7%) of NPBC. Six patients stopped chemotherapy because of toxicity, four (3.8%) during PBC, and two (2.4%) during NPBC. In the experimental arm, protocol violation was reported in two patients. The median number of NPBC cycles was five (IQR, three to six), and the median number of PBC cycles was six (IQR, six to six). Ten patients (9.3%) required a dose reduction of NPBC and 18 (33.8%) of PBC. Three patients (2.8%) stopped chemotherapy because of toxicity during NPBC.

The PFI was effectively prolonged in the experimental arm both from random assignment (median, 7.8 *v* 0.01 months) and from the last platinum injection received before study entry (median, 15.8 *v* 8 months). Data were locked on March 1, 2016, after a median follow-up of 38.1 months.

Overall, 141 deaths were recorded (69 in the standard arm and 72 in the experimental arm). Median OS was 24.5 months (95% CI, 22.4 to 33.6 months) in the standard arm and 21.8 months (95% CI, 16.3 to 29.3 months) in the experimental arm (Fig 2A). There was no statistically significant heterogeneity among the three different study periods (P = .83). An unplanned post hoc analysis adding serous histology as a covariate produced similar results.

For PFS2 analysis, 177 events were registered (88 in the standard arm and 89 in the experimental arm). Median PFS2 was 16.4 months (95% CI, 14.8 to 18.9 months) in the standard arm and 12.8 months (95% CI, 10.5 to 15.1 months) in the experimental arm (adjusted HR, 1.41; 95% CI, 1.04 to 1.92; P = .025; Fig 2B). Additional non–protocol-based OS and PFS2 analyses are reported in the Appendix.

With 202 events (99 in the standard arm and 103 in the experimental arm), median PFS1 was 9.0 months (95% CI, 7.6 to 10.4 months) in the standard arm and 5.0 months (95% CI, 4.1 to 5.9 months) in the experimental arm.

According to RECIST, 131 of 215 patients were eligible for total objective response evaluation; 36 (56%) in the standard arm and 29 (43%) in the experimental arm achieved an objective response (P = .59). According to GCIG criteria, 142 patients were eligible for response evaluation; 49 (75%) in the standard arm and 54 (70%) in the experimental arm achieved an objective response (P = .31).

The global health status and QOL score after three cycles of treatment worsened significantly in the experimental arm (P = .003; Fig 3); this effect disappeared after six cycles (P = .46).

There were only minor differences between the two arms in terms of adverse effects, with more any-grade neutropenia, musculoskeletal symptoms, and neuropathy, and more severe nausea in the standard arm (Table 3).

DISCUSSION

Prolongation of PFI in the MITO-8 trial did not produce any survival advantage for patients with partially platinum-sensitive OC. Rather, both survival (nearly statistically significant) and PFS2 (statistically significant) were worse in the arm in which platinum rechallenge was delayed. Such results are reinforced by a second set of analyses that took into account the nonproportionality of the

Table 2. Drugs Administered by Study Arm

Drug	Standard Arm PBC Followed by NPBC	Experimental Arm NPBC Followed by PBC
First treatment		
Carboplatin + paclitaxel	81 (77.1)	1 (0.9)
Carboplatin + gemcitabine	21 (20.0)	1 (0.9)
PLD	3 (2.9)	97 (90.7)
Gemcitabine	0 (0)	5 (4.7)
Topotecan	0 (0)	2 (1.9)
Trabectedin + PLD	0 (0)	1 (0.9)
Second treatment		
Carboplatin + paclitaxel	2 (2.4)	54 (73.0)
Carboplatin + gemcitabine	1 (1.2)	18 (24.3)
PLD	72 (86.7)	1 (1.4)
Topotecan	4 (4.8)	0 (0)
Other	4 (4.8)	1 (1.4)

NOTE. Data are presented as No. (%).
Abbreviations: NPBC, non–platinum-based chemotherapy; PBC, platinum-based chemotherapy; PLD, pegylated liposomal doxorubicin.

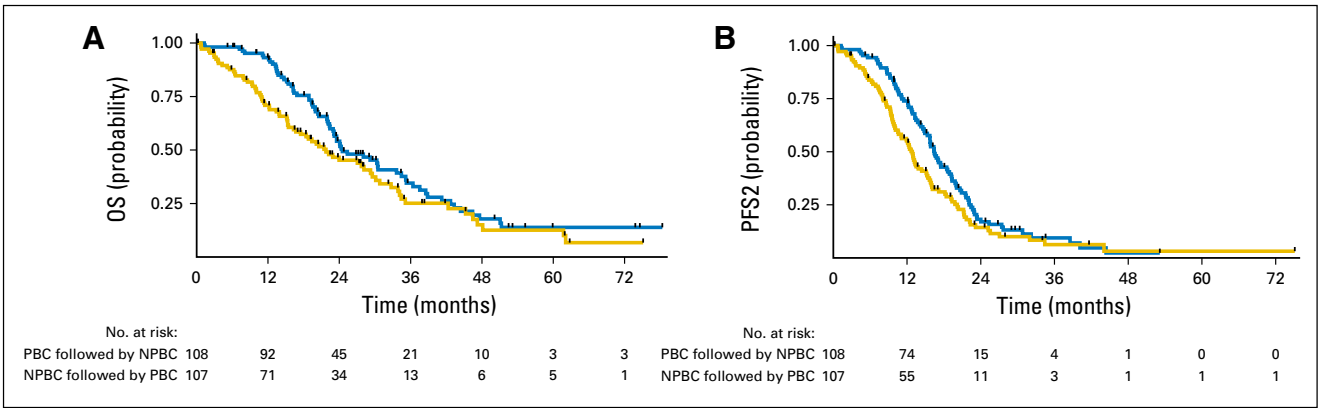

Fig 2. Kaplan-Meier curves of (A) overall survival (OS) and (B) progression-free survival (PFS) after the two planned treatments. The blue line represents the standard arm and gold line represents the experimental arm. Vertical lines represent censoring. NPBC, non–platinum-based chemotherapy; PBC, platinum-based chemotherapy.

hazard functions; indeed, such analyses show a clear advantage in favor of patients starting treatment with PBC, which was reduced progressively over time, possibly because in the experimental arm, patients whose disease progressed after NPBC could benefit from crossover to PBC.

The strength of the rationale behind this trial is a matter of discussion. Twenty years ago, the findings leading to the hypothesis that prolonging PFI may be a therapeutic strategy rather than simply a prognostic observation were extremely weak; they were based on retrospective studies and therefore were potentially biased. Nevertheless, in an Italian retrospective study, we found that a nonplatinum treatment was frequently preferred to platinum rechallenge in clinical practice.[10] Therefore, the actual negative results may well be the consequence of the weak science behind the hypothesis. It is conceivable that the prognostic value of PFI reflects a selection bias or intrinsic biologic properties of the disease and cannot be used as treatment strategy.

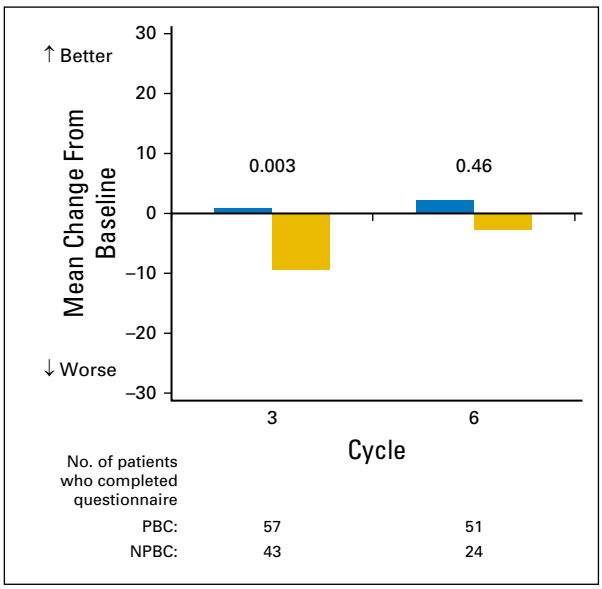

Fig 3. Quality of life analysis. Mean change from baseline of the global health status and quality of life score after three and six cycles of chemotherapy (blue bars represent the standard arm and gold bars represent the experimental arm). NPBC, non–platinum-based chemotherapy; PBC, platinum-based chemotherapy.

MITO-8 has several strengths in terms of internal validity. Risk of bias is low because it was designed primarily as a fully strategy-based randomized trial and was analyzed according to an intention-to-treat approach; compliance was consistent with expectations, and PFI was actually prolonged, thus fulfilling the prerequisite to test the value of the experimental strategy. Furthermore, findings of the different efficacy outcomes (PFS2, OS, and TRR) and global QOL (even if the sample size of this analysis was small) are highly consistent, with no advantage for the experimental strategy.

The main limitation of this study is that it was closed and the data were analyzed before reaching the planned number of events; this was a consequence of an external event (nonavailability of PLD) that mandated an important amendment, prolonged the study, and possibly decreased the interest of participating groups. The different treatment regimens introduced by the April 2012 amendment (ie, carboplatin and gemcitabine instead of carboplatin and paclitaxel for patients with mild baseline neurotoxicity, and topotecan or gemcitabine instead of PLD) may have produced some additional weakness, because they are all reputed to be less active treatments. However, topotecan and gemcitabine were rarely used, and PLD represents > 90% of NPBC. Carboplatin and gemcitabine were administered to approximately 20% of patients, balanced between the two arms, and its use ultimately increases the generalizability of MITO-8 findings, because persistent neuropathy is a relevant clinical problem for a number of patients who experience disease recurrence after first-line treatment. Therefore, notwithstanding limitations, the findings of the MITO-8 trial are highly consistent, and, in our opinion, allow definitive rejection of the study hypothesis that prolonging PFI with a single nonplatinum treatment may improve the outcome of patients with partially platinum-sensitive recurrent OC.

As to how much the MITO-8 results may affect clinical practice, three issues should be considered. First, the initial treatment of OC can now include bevacizumab, which is usually continued after chemotherapy.[15,16] This may reduce the rate of early recurrence, and may modify the biologic properties of the recurring disease. A second reason to support the recommendation that platinum-based treatment be the first treatment option is the fact that in the presence of a *BRCA* mutation, a maintenance treatment with olaparib is indicated after response to PBC.[17] Third, a non–platinum-containing doublet (trabectedin and PLD) was recently introduced in the

Table 3. Toxicity According to CTCAE by Study Arm

CTCAE Category and Subcategory	Any Grade					Grade > 2				
	Standard Arm		Experimental Arm			Standard Arm		Experimental Arm		
	No.	%	No.	%	*P*	No.	%	No.	%	*P*
Allergy	21	20.0	18	16.8	.55	7	6.7	8	7.5	.83
Auditory	2	1.9	0		.16	0		0		—
Blood	88	83.8	79	73.8	.08	60	57.1	46	43.0	.04
Anemia	67	63.8	63	58.9	.47	12	11.4	8	7.5	.33
Leukocyte	58	55.2	52	48.6	.33	11	10.5	14	13.1	.56
Neutropenia	73	69.5	59	55.1	.03	50	47.6	39	36.4	.10
Platelets	31	29.5	34	31.8	.73	10	9.5	10	9.3	.98
Arrhythmia	6	5.7	4	3.7	.51	0		0		—
Cardiac	4	3.8	4	3.7	.99	0		1	0.9	.33
Constitutional	66	62.9	69	64.5	.78	9	8.6	6	5.6	.39
Fatigue	65	61.9	65	60.7	.87	9	8.6	6	5.6	.39
Dermatology	60	57.1	62	57.9	.91	4	3.8	8	7.5	.25
Alopecia	40	38.1	28	26.2	.054					—
Rash and desquamation	15	14.3	20	18.7	.38	1	1.0	2	1.9	.58
HFS reaction	19	18.1	28	26.2	.16	4	3.8	7	6.5	.38
GI	81	77.1	86	80.4	.55	12	11.4	11	10.3	.77
Anorexia	14	13.3	16	15.0	.74	2	1.9	1	0.9	.54
Constipation	41	39.0	41	38.3	.92	3	2.9	3	2.8	.98
Diarrhea	21	20.0	20	18.7	.83	0		0		—
Mucositis	21	20.0	27	25.2	.36	1	1.0	4	3.7	.19
Nausea	64	61.0	56	52.3	.21	4	3.8	0		.04
Vomiting	33	31.4	30	28.0	.60	4	3.8	2	1.9	.40
Hemorrhage	3	2.9	2	1.9	.62	0		0		—
Infection	11	10.5	7	6.5	.29	4	3.8	3	2.8	.66
Lymphatics	2	1.9	3	2.8	.61	0		0		—
Metabolic	21	20.0	19	17.8	.67	5	4.8	3	2.8	.46
ALT	13	12.4	10	9.3	.49	2	1.9	1	0.9	.56
Musculoskeletal	4	3.8	0		.04	1	1.0	0		.33
Neurology	58	55.2	41	38.3	.01	0		2	1.9	.15
Neuropathy sensory	53	50.5	36	33.6	.01	0		1	0.9	.31
Ocular	1	1.0	4	3.7	.19	0		0		—
Pain	47	44.8	40	37.4	.28	3	2.9	3	2.8	.99
Pulmonary	12	11.4	8	7.5	.33	1	1.0	2	1.9	.59
Genitourinary	10	9.5	6	5.6	.29	0		0		—
Syndrome	1	1.0	0		.31	0		0		—
Vascular	2	1.9	6	5.6	.16	2	1.9	3	2.8	.67

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; HFS, hand-foot syndrome.

treatment of patients with intermediate platinum-sensitive recurrent OC on the basis of progression-free survival prolongation in the randomized trial OVA-301 (Efficacy of trabectedin in platinum-sensitive-relapsed ovarian cancer: new data from the randomized OVA-301 study); in this trial, prolongation of OS was subsequently shown in a subgroup analysis in the same setting as that of MITO-8.[7,18,19] The results of MITO-8 suggest that the patients in the control arm in OVA-301 (PLD alone) may have been undertreated, and that confirmatory results should be obtained using PBC as a control arm in a strategy-based design. The ongoing INOVATYON trial (International, Randomized Study in Patients With Ovarian Cancer; ClinicalTrials.gov identifier: NCT01379989) may add useful data, even if a comparison of treatment sequences is not formally planned.

In conclusion, even though we are aware of its limitations, MITO-8 strongly supports the recommendation that platinum rechallenge not be delayed in favor of a nonplatinum treatment in patients with partially platinum-sensitive OC. It is also advisable that PBC be used as the control arm in future trials of new drugs in this setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Sandro Pignata, Ciro Gallo, Francesco Perrone
Financial support: Sandro Pignata, Uwe Wagner, Francesco Perrone
Administrative support: Uwe Wagner
Provision of study materials or patients: Sandro Pignata, Alessandra Bologna, Ignace B. Vergote, Uwe Wagner, Domenica Lorusso, Viviana Murgia, Roberto Sorio, Gabriella Ferrandina, Cosimo Sacco, Gennaro Cormio, Enrico Breda, Saverio Cinieri, Donato Natale, Giorgia Mangili, Carmela Pisano, Sabrina Chiara Cecere, Marilena Di Napoli, Vanda Salutari, Francesco Raspagliesi, Alice Bergamini
Collection and assembly of data: Sandro Pignata, Giovanni Scambia, Alessandra Bologna, Ignace B. Vergote, Uwe Wagner, Domenica Lorusso,

Viviana Murgia, Roberto Sorio, Gabriella Ferrandina, Cosimo Sacco, Gennaro Cormio, Enrico Breda, Saverio Cinieri, Donato Natale, Giorgia Mangili, Carmela Pisano, Sabrina Chiara Cecere, Marilena Di Napoli, Vanda Salutari, Francesco Raspagliesi, Laura Arenare, Alice Bergamini, Jane Bryce, Gennaro Daniele, Maria Carmela Piccirillo

Data analysis and interpretation: Sandro Pignata, Simona Signoriello, Ignace B. Vergote, Francesco Raspagliesi, Laura Arenare, Gennaro Daniele, Maria Carmela Piccirillo, Ciro Gallo, Francesco Perrone
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Gore ME, Fryatt I, Wiltshaw E, et al: Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol 36:207-211, 1990

2. Markman M, Rothman R, Hakes T, et al: Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol 9:389-393, 1991

3. Bookman MA: Extending the platinum-free interval in recurrent ovarian cancer: The role of topotecan in second-line chemotherapy. Oncologist 4: 87-94, 1999

4. Baird RD, Tan DS, Kaye SB: Weekly paclitaxel in the treatment of recurrent ovarian cancer. Nat Rev Clin Oncol 7:575-582, 2010

5. Gordon AN, Fleagle JT, Guthrie D, et al: Recurrent epithelial ovarian carcinoma: A randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 19:3312-3322, 2001

6. McGuire WP, Blessing JA, Bookman MA, et al: Topotecan has substantial antitumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: A Gynecologic Oncology Group study. J Clin Oncol 18:1062-1067, 2000

7. Monk BJ, Herzog TJ, Kaye SB, et al: Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 28:3107-3114, 2010

8. Marth C, Vergote I, Scambia G, et al: ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. Eur J Cancer 70:111-121, 2017

9. Monk BJ, Poveda A, Vergote I, et al: Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): A randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 15:799-808, 2014

10. Pignata S, Ferrandina G, Scarfone G, et al: Extending the platinum-free interval with a non-platinum therapy in platinum-sensitive recurrent ovarian cancer. Results from the SOCRATES retrospective study. Oncology 71:320-326, 2006

11. Vergote I, Pujade-Lauraine E, Pignata S, et al: European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and pharmaceutical companies. Int J Gynecol Cancer 20:476-478, 2010

12. Rustin GJ, Quinn M, Thigpen T, et al: Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). J Natl Cancer Inst 96: 487-488, 2004

13. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000

14. Smith CT, Williamson PR, Marson AG: Investigating heterogeneity in an individual patient data meta-analysis of time to event outcomes. Stat Med 24:1307-1319, 2005

15. Burger RA, Brady MF, Bookman MA, et al: Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 365: 2473-2483, 2011

16. Perren TJ, Swart AM, Pfisterer J, et al: A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 365:2484-2496, 2011

17. Ledermann J, Harter P, Gourley C, et al: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 366: 1382-1392, 2012

18. Monk BJ, Herzog TJ, Kaye SB, et al: Trabectedin plus pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer: Overall survival analysis. Eur J Cancer 48: 2361-2368, 2012

19. Poveda A, Vergote I, Tjulandin S, et al: Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer: Outcomes in the partially platinum-sensitive (platinum-free interval 6-12 months) subpopulation of OVA-301 phase III randomized trial. Ann Oncol 22:39-48, 2011

Affiliations

Sandro Pignata, **Carmela Pisano**, **Sabrina Chiara Cecere**, **Marilena Di Napoli**, **Laura Arenare**, **Alice Bergamini**, **Jane Bryce**, **Gennaro Daniele**, **Maria Carmela Piccirillo**, and **Francesco Perrone**, Istituto Nazionale per lo Studio e la Cura dei Tumori—Fondazione G. Pascale, IRCCS; **Simona Signoriello** and **Ciro Gallo**, Università degli Studi della Campania Luigi Vanvitelli, Naples; **Giovanni Scambia**, **Domenica Lorusso**, **Gabriella Ferrandina**, and **Vanda Salutari**, Università Cattolica del Sacro Cuore; **Enrico Breda**, Ospedale San Giovanni Calibita Fatebenefratelli, Rome; **Alessandra Bologna**, Azienda Ospedaliea Santa Maria Nuova, IRCCS, Reggio Emilia; **Domenica Lorusso** and **Francesco Raspagliesi**, Fondazione IRCCS Istituto Nazionale dei Tumori; **Giorgia Mangili** and **Alice Bergamini**, Ospedale San Raffaele, Milan; **Viviana Murgia**, Ospedale Santa Chiara, Trento; **Roberto Sorio**, Centro di Riferimento Oncologico, Aviano; **Gabriella Ferrandina**, Centro di Ricerca e Formazione Ad Alta Tecnologia nelle Scienze Biomediche, Università Cattolica del Sacro Cuore, Campobasso; **Cosimo Sacco**, Azienda Ospedaliera di Perugia Santa Maria della Misericordia, Udine; **Gennaro Cormio**, Ginecologia Oncologica, Università di Bari e Istituto Oncologico "Giovanni Paolo II" Bari; **Saverio Cinieri**, Ospedale Antonio Perrino, Brindisi; **Donato Natale**, Ospedale San Massimo, Penne, Italy; **Ignace B. Vergote**, University Hospital Leuven and Belgian and Luxembourg Gynaecological Oncology Group, Leuven Cancer Institute, Leuven, Belgium; and **Uwe Wagner**, Uniklinkum Giessen und Marburg Gynäkologie, Marburg, Germany.

Support

Supported by Grant No. 01KG1002 from the German Ministry of Research and Education.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Controlled Trial Testing the Efficacy of Platinum-Free Interval Prolongation in Advanced Ovarian Cancer: The MITO-8, MaNGO, BGOG-Ov1, AGO-Ovar2.16, ENGOT-Ov1, GCIG Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Sandro Pignata
Honoraria: AstraZeneca, Roche, PharmaMar
Consulting or Advisory Role: AstraZeneca, Roche, PharmaMar, Pfizer, TESARO
Research Funding: Roche, Pfizer (Inst), MSD (Inst)

Giovanni Scambia
No relationship to disclose

Alessandra Bologna
No relationship to disclose

Simona Signoriello
No relationship to disclose

Ignace B. Vergote
No relationship to disclose

Uwe Wagner
No relationship to disclose

Domenica Lorusso
Consulting or Advisory Role: Roche, AstraZeneca, Clovis Oncology
Research Funding: PharmaMar (Inst)

Viviana Murgia
No relationship to disclose

Roberto Sorio
No relationship to disclose

Gabriella Ferrandina
Honoraria: Roche, PharmaMar

Cosimo Sacco
No relationship to disclose

Gennaro Cormio
No relationship to disclose

Enrico Breda
No relationship to disclose

Saverio Cinieri
Travel, Accommodations, Expenses: Bayer AG

Donato Natale
No relationship to disclose

Giorgia Mangili
Honoraria: AstraZeneca
Research Funding: Ipsen
Travel, Accommodations, Expenses: Roche, PharmaMar

Carmela Pisano
No relationship to disclose

Sabrina Chiara Cecere
No relationship to disclose

Marilena Di Napoli
No relationship to disclose

Vanda Salutari
Honoraria: Roche, PharmaMar, AstraZeneca
Consulting or Advisory Role: Roche, PharmaMar, AstraZeneca

Francesco Raspagliesi
Consulting or Advisory Role: PharmaMar
Speakers' Bureau: Roche, AstraZeneca

Laura Arenare
No relationship to disclose

Alice Bergamini
Travel, Accommodations, Expenses: Roche

Jane Bryce
Consulting or Advisory Role: AstraZeneca, Novartis, Merck, Bristol-Myers Squibb

Gennaro Daniele
Honoraria: Bayer Schering Pharma

Maria Carmela Piccirillo
Honoraria: Bayer AG
Travel, Accommodations, Expenses: Bayer AG, Roche

Ciro Gallo
No relationship to disclose

Francesco Perrone
Honoraria: Bayer AG, Daiichi Sankyo, Ipsen, AstraZeneca, Bristol-Myers Squibb
Research Funding: Roche (Inst), Bayer AG (Inst)
Travel, Accommodations, Expenses: Bayer AG, Daiichi Sankyo, Bayer AG

Acknowledgment

We thank Enzo Ballatori, Christian Marth, and Eric Pujade-Lauraine, members of the independent data monitoring committee. We also thank Paolo Chiodini for collaboration in performing SAS analyses and an anonymous reviewer for helpful comments that greatly enhanced the quality of the study.

Appendix

Additional Statistical Analyses to Evaluate Dependency of the Effect on Time

During peer review, it was assessed that proportional hazard assumption was not met for the main treatment effect in overall survival (OS) and progression-free survival after the two planned treatments (PFS2) analyses. Therefore, a treatment-by-(log)time interaction covariate was added to the Cox model testing OS and PFS2. As in the presence of a significant interaction, the hazard ratio (HR) estimate of treatment has no meaning in itself. For a better understanding, we reported the main findings in three different ways: (1) we graphically depicted the variation of HR with time; (2) we reported the values of HR (ie, the relative treatment effect) at fixed time points; and (3) we reported the differences in survival estimates at the same fixed time points (ie, the absolute treatment effect).

Analysis of OS Considering Nonproportionality of the Hazard Functions

In OS analysis, the treatment-by-(log)time interaction was statistically significant ($P = .012$), meaning that hazard functions of treatment arms were not proportional and that HR changed with time (Fig A1). Indeed, the HR for death was statistically significant in favor of the platinum-based chemotherapy arm in the first 12 months, decreasing over time from 2.5 at 6 months to approximately 1 at 24 months.

OS differences in favor of the PBC arm were clear in the first 18 months and persisted thereafter, although they were reduced, as expected, because of crossover (Table A1). Results were similar among subgroups of residual disease (interaction $P = .66$), previous lines of chemotherapy ($P = .67$), and center size ($P = .74$).

Analysis of PFS2 Considering Nonproportionality of the Hazard Functions

Also in the PFS2 analysis, there was a statistically significant treatment-by-(log)time interaction ($P = .015$), meaning that the HR changed with time (Fig A2).

The HR for second experience of disease progression or death was statistically significant in favor of the PBC arm in the first 12 months, decreasing over time from 2.17 at 6 months to approximately 1 at 18 months, as expected on the basis of the crossover design (Table A2).

MITO-8 Participating Institutions, Investigators, and Study Coordinators

- Dipartimento di Oncologia Uroginecologica, Istituto Nazionale per lo Studio e la Cura dei Tumori—Fondazione G. Pascale, IRCCS, Naples, Italy: Sandro Pignata, Carmela Pisano, Sabrina Chiara Cecere, Marilena Di Napoli, Stefano Greggi, and Rosa Tambaro. Study coordinators: Angela Maria Trujillo and Margherita Tambaro.
- Dipartimento per la Tutela della Salute della Donna della Vita Nascente del Bambino e dell' Adolescente, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy: Giovanni Scambia, Gabriella Ferrandina, Vanda Salutari, Giulia Amadio, Mariagrazia Distefano, Rosa Pasqualina De Vincenzo, Caterina Ricci, Antonella Pietragalla, and Alessia Di Legge. Study coordinator: Michela Panella.
- Oncologia Medica, Azienda Ospedaliera Santa Maria Nuova, IRCCS, Reggio Emilia, Italy: Alessandra Bologna* and Corrado Boni. Study coordinators: Erika Gervasi and Roberta Gnoni. *Current address: Dipartimento Oncologico, Srutturo Operativa Complessa Oncologia Medica, Ospedale Santa Maria Annunziata, Bagno a Ripoli, Florence, Italy.
- Statistica Medica, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy; Ciro Gallo, Paolo Chiodini, Simona Signoriello, and Giuseppe Signoriello.
- University Hospital Leuven and Belgian and Luxembourg Gynaecological Oncology Group, Leuven Cancer Institute, Leuven, Belgium: Ignace Vergote. Study coordinators: Joke De Roover and Leen Trappeniers.
- Universitätsklinikum Gießen und Marburg GmbH, Klinik für Frauenheilkunde und Geburtshilfe, Marburg, Germany: Uwe Wagner and Klaus Baumann.
- Unità di Ginecologia Oncologica, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy: Domenica Lorusso, Francesco Raspagliesi, Giuseppa Maltese, Stefano Lepori, Antonino Ditto, Giorgio Bogani, Ilaria Sabatucci, Valentina Chiappa, Cono Scaffa, and Mauro Signorelli. Study coordinator: Elisa Grassi.

- Oncologia Medica Ospedale Santa Chiara, Trento, Italy: Viviana Murgia and Enzo Galligioni.
- Oncologia Medica C - Centro di Riferimento Oncologico, Aviano, Italy: Roberto Sorio. Study coordinator: Gianna Tabaro.
- Ginecologia Oncologica, Centro di Ricerca e Formazione Ad Alta Tecnologia nelle Scienze Biomediche, Università Cattolica del Sacro Cuore, Campobasso, Italy: Gabriella Ferrandina and Aida Di Stefano. Study coordinator: Francesca Risi.
- Dipartimento di Oncologia, Azienda Ospedaliera di Perugia Santa Maria della Misericordia, Udine, Italy: Cosimo Sacco.
- Ginecologia Oncologica, Università di Bari e Istituto Oncologico "Giovanni Paolo II," Bari, Italy: Gennaro Cormio and Vera Loizzi
- Oncologia Medica, Ospedale San Giovanni Calibita Fatebenefratelli, Rome, Italy: Enrico Breda.
- Oncologia Medica, Ospedale Antonio Perrino, Brindisi, Italy: Saverio Cinieri and Enrica Mazzoni. Study coordinators: Ermelinda Ferrara and Angelarita Lanzillotti.
- Oncologia Medica, Ospedale San Massimo, Penne, Italy: Donato Natale.
- Clinica Ostetrico-Ginecologica, Ospedale San Raffaele, Milan, Italy: Giorgia Mangili and Alice Bergamini.
- Unità Sperimentazioni Cliniche, Istituto Nazionale per lo Studio e la Cura dei Tumori—Fondazione G. Pascale, IRCCS, Naples, Italy: Francesco Perrone, Maria Carmela Piccirillo, Gennaro Daniele, Jane Bryce, Massimo Di Maio*, Alessandro Morabito†, Laura Arenare, Giuliana Canzanella, Federika Crudele, Antonia Del Giudice, Cristiana De Luca, Giovanni De Matteis, Manuela Florio, Anna Gimigliano, Marilena Martino, Maria Teresa Ribecco, Fiorella Romano, Alfonso Savio, and Lucia Sparavigna. Current address: *Oncologia Medica, AO Mauriziano, Torino, Italy; †Oncologia Toraco-Polmonare, Istituto Nazionale per lo Studio e la Cura dei Tumori—Fondazione G. Pascale, IRCCS, Naples, Italy.
- Clinica Ostetrica e Ginecologica, Università di Bari Policlinico, Bari, Italy: Marco Marinaccio.
- Dipartimento di Oncologia Clinica e Sperimentale, Istituto Oncologico Veneto, Padova, Italy: Maria Ornella Nicoletto. Study coordinator: Miriam Farina.
- Oncology Christian Hospital Center (CHU) -Clinique Saint-Joseph, Liege, Belgium: Marie-Pascale Graas. Study coordinator: Alexandro Maniglia.
- Oncologia Medica, Policlinico Universitario Federico II, Naples, Italy: Rossella Lauria.
- Ginecologia ed Ostetricia, Ospedali Riuniti Villa Sofia e Cervello, Palermo, Italy: Desiderio Gueli Alletti and Nenzi Varsellona.
- Ospedale Del Ponte,Varese, Italy: Nicoletta Donadello.
- Kliniken-Essen-Mitte, Klinik für gynäkologische Onkologie, Essen, Germany: Christian Kurzeder.
- University Hospital Essen, Gynecology and Obstetrics, Essen, Germany: Pauline Wimberger.
- Klinikum rechts der Isar, Frauenklinik und Poliklinik, Munchen, Germany: Barbara Schmalfeldt.
- Oncologia Medica, Ospedale Santa Maria della Misericordia, Perugia, Italy: Anna Maria Mosconi. Data manager: Sara Baglivo.
- Oncologia Medica Senologica, Istituto Nazionale per lo Studio e la Cura dei Tumori—Fondazione G. Pascale, IRCCS, Naples, Italy: Andrea De Matteis. Study coordinator: Gaetano Bonfanti.
- Onco-Ematologia, Ospedale Andrea Tortora, Pagani, Italy: Antonietta Fabbrocini and Linda Ferrara.
- Oncologia, Ospedale Umberto I, Lugo, Italy: Stefano Tamberi. Study coordinator: Alessandra Piancastelli.
- Ostetricia e Ginecologia, Ospedale Cannizzaro, Catania, Italy: Paolo Scollo and Giuseppe Scibilia.
- Oncologia Medica, Ospedale Santa Maria delle Croci, Ravenna, Italy: Giorgio Cruciani. Study coordinator: Federica Zumaglini.
- Oncologia Medica, Istituto Romagnolo per lo Studio e la Cura dei Tumori, IRCCS Meldola, Italy: Ugo De Giorgi. Study coordinator: Sara Testoni.
- Centro Oncologico, Ospedale Don Luigi Di Liegro, Gaeta, Italy: Enzo Veltri.
- Oncologia Medica, Ospedale Alessandro Manzoni, Lecco, Italy: Antonio Ardizzoia and Antonio Pellegrino. Study coordinators: Angelita Lagati and Davide Colombo.
- Azienda Opsedaliera Ordine Mauriziano,Torino, Italy: Annamaria Ferrero.
- Ginecologia, Istituto Europeo di Oncologia, Milan, Italy: Nicoletta Colombo. Study coordinator: Sara Boveri.
- Oncologia Ginecologica, Ospedale San Gerardo, Monza, Italy: Andrea Alberto Lissoni.
- Oncologie AZ (AZ) Groeninge Maria's Voorzienigheid (Kortrijk, Belgium): Philip Debruyne. Study coordinators: Ellen Callens and Delphine Mullebrouck.
- Oncology department, CHU Université catholique de Louvain Namur, site Sainte Elisabeth, Namur, Belgium: Peter Vuylsteke. Study coordinator: Monique Gilsoul.

- Department of Oncology AZ Nikolaas, Sint-Niklaas, Belgium: Willem Lybaert. Study coordinator: Goele Wallays.
- Oncologia Medica, Ospedale Boldrini, Thiene, Italy: Alessandra Perin.
- University Hospital Freiburg, Gynecology, Freiburg, Germany: Annette Hasenburg.
- Universitätsklinikum Schleswig-Holstein, Gynecology and Obstetrics, Campus Kiel, Germany: Felix Hilpert.
- Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum, Gynecology, Berlin, Germany: Jalid Sehouli.
- Albertinen Krankenhaus, Gynecology, Hamburg,Germany: Uwe Herwig.
- Oncologia Medica, Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria, Italy: Pietro Del Medico. Data manager: Antonia Falzea.
- Coordinating Centre Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group: Gabriele Elser.
- Koordinierungszentrum für Klinische Studien (KKS) Marburg - Center for Clinical Trials: Erdmute Ronicke.

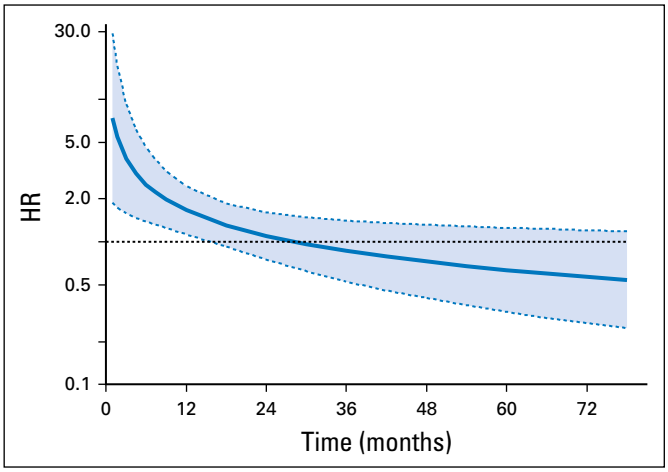

Fig A1. Estimated hazard ratio (HR) for death in the experimental versus standard arm according to time.

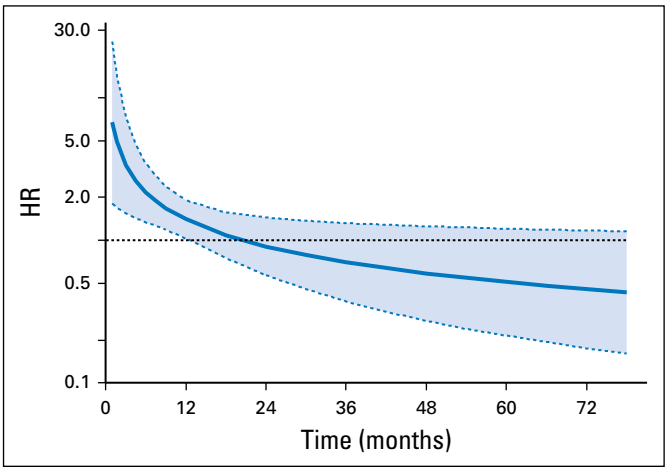

Fig A2. Estimated hazard ratio (HR) for progression-free survival after the two planned treatments for experimental versus standard arm according to time.

Table A1. Relative (HR) and Absolute Effect (difference) on OS at Fixed Time Points

OS	Standard Arm	Experimental Arm	HR (95% CI)	Difference (95% CI)
At 6 months	0.98	0.88	2.52 (1.39 to 4.60)	−0.10 (−0.17 to −0.04)
At 12 months	0.93	0.71	1.67 (1.13 to 2.45)	−0.22 (−0.32 to −0.12)
At 18 months	0.76	0.57	1.31 (0.92 to 1.85)	−0.18 (−0.31 to −0.05)
At 24 months	0.54	0.45	1.10 (0.75 to 1.61)	−0.09 (−0.23 to 0.06)
At 30 months	0.45	0.37	0.96 (0.62 to 1.49)	−0.08 (−0.23 to 0.07)

Abbreviations: HR, hazard ratio; OS, overall survival.

Table A2. Relative (HR) and Absolute Effect (difference) on PFS2 at Fixed Time Points

PFS2	Standard Arm	Experimental Arm	HR (95% CI)	Difference (95% CI)
At 6 months	0.94	0.84	2.17 (1.35 to 3.50)	−0.10 (−0.19 to −0.02)
At 12 months	0.74	0.55	1.40 (1.03 to 1.92)	−0.19 (−0.31 to −0.06)
At 18 months	0.43	0.31	1.09 (0.75 to 1.57)	−0.12 (−0.25 to 0.02)
At 24 months	0.17	0.14	0.91 (0.57 to 1.44)	−0.03 (−0.13 to 0.08)
At 30 months	0.13	0.10	0.79 (0.45 to 1.37)	−0.03 (−0.13 to 0.07)

Abbreviations: HR, hazard ratio; PFS2, progression-free survival after the two planned treatments.