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ORIGINAL REPORT

Carboplatin Plus Paclitaxel Versus Carboplatin Plus Pegylated Liposomal Doxorubicin As First-Line Treatment for Patients With Ovarian Cancer: The MITO-2 Randomized Phase III Trial

Sandro Pignata, Giovanni Scambia, Gabriella Ferrandina, Antonella Savarese, Roberto Sorio, Enrico Breda, Vittorio Gebbia, Pietro Musso, Luigi Frigerio, Pietro Del Medico, Alessandra Vernaglia Lombardi, Antonio Febbraro, Paolo Scollo, Antonella Ferro, Stefano Tamberi, Alba Brandes, Alberto Ravaioli, Maria Rosaria Valerio, Enrico Aitini, Donato Natale, Laura Scaltriti, Stefano Greggi, Carmela Pisano, Domenica Lorusso, Vanda Salutari, Francesco Legge, Massimo Di Maio, Alessandro Morabito, Ciro Gallo, and Francesco Perrone

Author affiliations appear at the end of this article.

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Corresponding author: Sandro Pignata, MD, PhD, Istituto Nazionale Tumori, via Mariano Semmola, 80131 Napoli, Italy; e-mail: sandro.pignata@gmail.com.

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ABSTRACT

Purpose
Carboplatin/paclitaxel is the standard first-line chemotherapy for patients with advanced ovarian cancer. Multicentre Italian Trials in Ovarian Cancer-2 (MITO-2), an academic multicenter phase III trial, tested whether carboplatin/pegylated liposomal doxorubicin (PLD) was more effective than standard chemotherapy.

Patients and Methods
Chemotherapy-naive patients with stage IC to IV ovarian cancer (age ≤ 75 years; Eastern Cooperative Oncology Group performance status ≤ 2) were randomly assigned to carboplatin area under the curve (AUC) 5 plus paclitaxel 175 mg/m^2 or to carboplatin AUC 5 plus PLD 30 mg/m^2, every 3 weeks for six cycles. Primary end point was progression-free survival (PFS). With 632 events in 820 enrolled patients, the study would have 80% power to detect a 0.80 hazard ratio (HR) of PFS.

Results
Eight hundred twenty patients were randomly assigned. Disease stages III and IV were prevalent. Occurrence of PFS events substantially slowed before obtaining the planned number. Therefore, in concert with the Independent Data Monitoring Committee, final analysis was performed with 556 events, after a median follow-up of 40 months. Median PFS times were 19.0 and 16.8 months with carboplatin/PLD and carboplatin/paclitaxel, respectively (HR, 0.95; 95% CI, 0.81 to 1.13; $P = .58$). Median overall survival times were 61.6 and 53.2 months with carboplatin/PLD and carboplatin/paclitaxel, respectively (HR, 0.89; 95% CI, 0.72 to 1.12; $P = .32$). Carboplatin/PLD produced a similar response rate but different toxicity (less neurotoxicity and alopecia but more hematologic adverse effects). There was no relevant difference in global quality of life after three and six cycles.

Conclusion
Carboplatin/PLD was not superior to carboplatin/paclitaxel, which remains the standard first-line chemotherapy for advanced ovarian cancer. However, given the observed CIs and the different toxicity, carboplatin/PLD could be considered an alternative to standard therapy.

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INTRODUCTION

Ovarian cancer is the fourth leading cause of cancer-related death in women.[1] Intensive surgical staging and cytoreduction, followed by chemotherapy with carboplatin/paclitaxel, represent the standard treatment approach.[2-6] However, even after optimal debulking surgery and response to systemic therapy, the risk of recurrence is high, and long-term survival remains poor. Furthermore, standard medical treatment of ovarian cancer negatively impacts on quality of life (QoL) as a result of frequent toxicity, such as alopecia, neurotoxicity, and fatigue.

Anthracyclines were used in the first-line treatment of advanced ovarian cancer before the introduction of taxanes, with data from meta-analyses

suggesting that their addition to the platinum-based treatment might be advantageous.[7] Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin encapsulated in liposomes that are coated with methoxypolyethylene glycol, promoting the prolongation of circulation of the drug in the blood and its concentration in the tumor. This formulation results in a different pharmacokinetic and toxicity profile, as compared with conventional anthracyclines, with less myelotoxicity, alopecia, nausea, vomiting, and cardiotoxicity, but more skin and mucosal toxicity, namely palmer-plantar erythrodysesthesia and stomatitis.[8] In a randomized phase III trial, compared with standard topotecan in second-line treatment, PLD produced better overall survival (OS) in platinum-sensitive patients and was characterized by a favorable tolerability profile, with less severe hematologic toxicity.[9] On this basis, PLD is considered a treatment of choice for relapsed ovarian cancer. PLD was also compared to paclitaxel in the treatment of relapsed ovarian cancer.[10] No significant efficacy difference was found between the two drugs, but PLD caused significantly less alopecia and neurotoxicity. This evidence encouraged the use of PLD in combination with carboplatin. Several phase I and II studies showed the possibility of easily combining PLD with standard doses and schedules of carboplatin.[11,12] A Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens phase II study[13] in patients with relapsed platinum-sensitive ovarian cancer demonstrated that the combination of carboplatin at area under the curve (AUC) 5 with PLD 30 mg/m^2, given every 4 weeks, was active, with a 63% response rate and median progression-free survival (PFS) and OS times of 9.4 and 32 months, respectively. The combination was well tolerated; although nearly half of the patients experienced severe neutropenia, it was complicated by fever in only 3% of patients, and there was only mild to moderate nonhematologic toxicity, including palmer-plantar erythrodysesthesia (32%) and neuropathy (28%).

Therefore, we planned a randomized phase III clinical trial, Multicentre Italian Trials in Ovarian Cancer-2 (MITO-2), to evaluate whether carboplatin/PLD is superior in terms of PFS to the standard carboplatin/paclitaxel as first-line therapy of patients with advanced ovarian cancer. To plan the same dose-intensity of carboplatin in both arms, we chose an every-3-week schedule of carboplatin and PLD.

PATIENTS AND METHODS

Study Design

MITO-2 was an open-label, randomized, phase III study (Clinicaltrials.gov identifier: NCT00326456). The primary end point was PFS. Secondary end points included OS, treatment activity, toxicity, and QoL.

Overall, 820 patients were planned to be enrolled, and 632 events were needed to have 80% power of detecting a 0.80 hazard ratio (HR) of progression, with two-tailed $\alpha = .05$ (East Software; Cytel, Cambridge, MA). This would represent an increase in median PFS from 18 to 22.5 months. No interim analyses were planned.

Patients were randomly assigned 1:1 to the standard or experimental arm. Telephone random assignment was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy) by a computer-driven minimization procedure. Stratification variables were center, residual disease after surgery (absent, ≤ 1 cm, > 1 cm, or no primary surgery), stage (IC, II, III, or IV), Eastern Cooperative Oncology Group performance status (0 to 1 or 2).

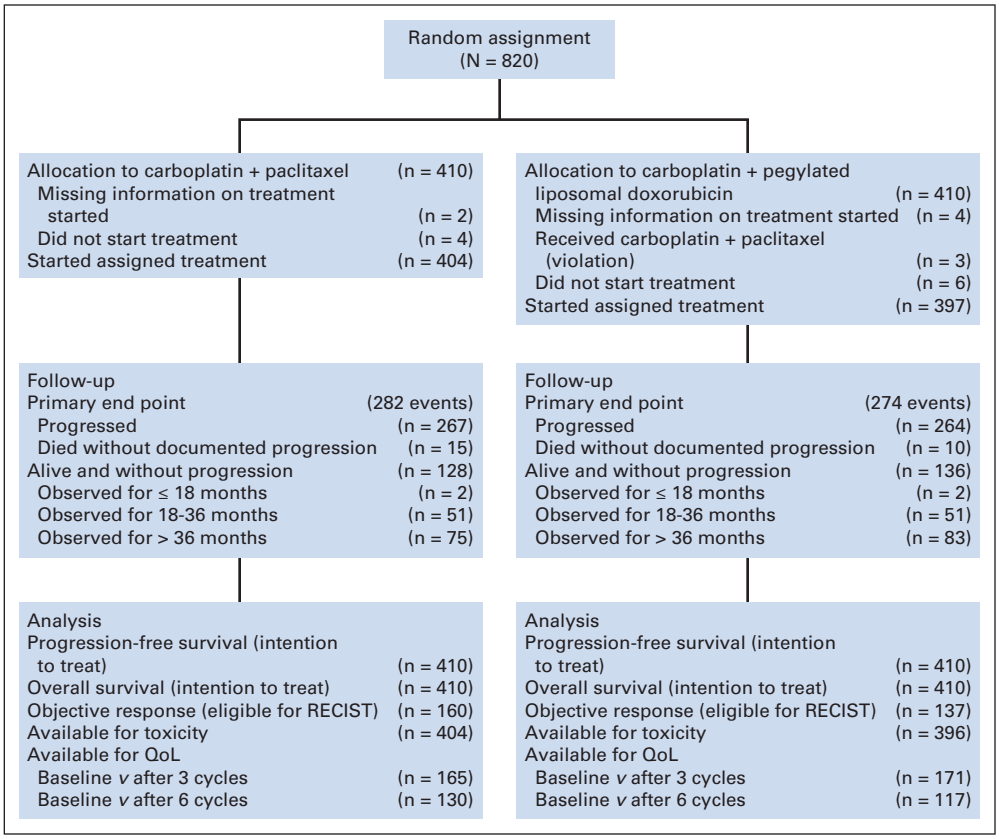

Fig 1. Flow of study procedures and data collection according to CONSORT diagram. QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

Study Population

Women younger than age 75 years, with a cytologic or histologic diagnosis of epithelial ovarian cancer (stage IC to IV according to International Federation of Gynecology and Obstetrics staging system), an Eastern Cooperative Oncology Group performance status ≤ 2, and a life expectancy of ≥ 3 months were eligible. Patients were excluded if they had received previous chemotherapy. Patients with a history of clinically relevant heart disease, with other concomitant diseases representing contraindication to treatment drugs, or with previous or concomitant other malignancy (except nonmelanoma skin cancer or carcinoma in situ of the uterine cervix) were not eligible. Adequate bone marrow, kidney, and liver functions were required. The study was approved by local ethics committees of each participating institution, and all patients gave written informed consent.

Study Treatment

Patients in the standard arm received carboplatin AUC 5 (dosed according to the Calvert formula, with creatinine clearance estimated according to the Cockcroft formula) and paclitaxel 175 mg/m^2. Patients randomly assigned to the experimental arm received carboplatin AUC 5 and PLD (Caelyx; Schering-Plough, Kenilworth, NJ) 30 mg/m^2. In both arms, chemotherapy was given intravenously on day 1 every 3 weeks. Carboplatin was diluted in 250 mL of glucose 5% and infused over 30 minutes. Paclitaxel was diluted in 250 mL of physiologic saline and infused over 3 hours. PLD was diluted in 250 mL of glucose 5% and infused over 60 minutes, following completion of carboplatin infusion. Treatment was initially administered for three cycles, and patients with stable or responding disease continued treatment for further a three cycles.

Conditions required for re-treatment were leukocytes more than 3,000/μL, neutrophils more than 1,500/μL, platelets ≥ 100,000/μL, and absence of organ toxicity (excluding alopecia) ≥ grade 2. Treatment was discontinued as a result of prolonged toxicity in patients requiring a treatment delay of ≥ 2 weeks.

A 20% dose reduction for all drugs was planned in patients with neutrophils less than 500/μL or platelets less than 50,000/μL for more than 7 days. Carboplatin dose was reduced to AUC 4 in patients with creatinine clearance less than 60 mL. In the event of ≥ grade 2 skin toxicity, PLD was delayed for up to 2 weeks or until toxicity resolved to ≤ grade 1; otherwise, PLD was interrupted. Subsequent doses were reduced by 25% if grade 3 or 4 skin toxicity cleared within 2 weeks. In the standard arm, doses of carboplatin and paclitaxel were reduced by 20% in presence of neuropathy.

Patient Evaluation

Computed tomography scan or nuclear magnetic resonance of the abdomen and pelvis and any other tests that gave positive results during staging were performed after three and six cycles of chemotherapy. Response evaluation was in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.[14] During the follow-up, the first among the following events defined progression: increase of more than 20% in the sum of largest diameters of known lesions; appearance of a new lesion; confirmed increase of more than 25% in CA-125; or death without clinical or instrumental signs of disease progression.

QoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30).[15] Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Statistical Analysis

Efficacy analyses were performed on an intent-to-treat basis. PFS was defined as the time interval between random assignment and progression or death, whichever occurred first, or last follow-up for patients alive without progression. OS was defined as the time interval between random assignment and death or date of last follow-up for patients still alive. Median follow-up was calculated according to the inverted Kaplan-Meier method.[16] PFS and OS curves were estimated using the Kaplan-Meier product-limit method[17] and compared using the log-rank test.[18] For PFS, the Cox proportional hazards model[19] was used to assess treatment effect adjusted by baseline prognostic variables.

A preplanned early activity analysis was performed in 2006, using data from the first 50 patients eligible for response assessment in the experimental arm.[20] For the final analysis, objective response rate (ORR) was defined as the proportion of complete and partial responses among patients with at least one target lesion. Patients who died or stopped treatment because of toxicity or refusal before restaging were conservatively defined as nonresponders. The statistical significance of the difference in ORR between arms was assessed using the χ^2 test. Activity was also described in women with nontarget lesions only and in women without any tumor lesion but with elevated CA-125 levels before starting treatment.

A preplanned toxicity analysis of the experimental combination was performed in 2004, based on the first 50 patients receiving experimental treatment.[21] For the final toxicity analysis, all patients who received chemotherapy at least once were eligible. The worst grade of toxicity experienced was computed for each patient. For each toxicity, two statistical tests were performed to compare study arms; patterns of toxicity (considering all grades) were compared using an exact linear rank test, whereas rates of severe toxicity (grade ≥ 3 ν grade 0 to 2) were compared using χ^2 or Fisher's exact tests as appropriate.

QoL analysis was performed according to the EORTC manual.[22] Multi-item scales were computed by calculating the mean raw scores and transforming them linearly, in scales ranging from 0 to 100. For single items, only linear transformation was performed. Changes from baseline after three and six cycles were calculated for each domain and compared between arms by a linear model, using baseline values as a covariate.

Statistical analyses were performed using S-Plus version 6.1 (Insightful, Seattle, WA). Exact tests were performed using StatXact 7 (Cytel).

RESULTS

Patient Characteristics

Between January 2003 and November 2007, 820 patients were randomly assigned, as planned (Fig 1). Baseline characteristics were

Table 1. Baseline Clinical Characteristics of Patients by Treatment Arm

Characteristic	Standard Arm (n = 410) No. of Patients	%	Experimental Arm (n = 410) No. of Patients	%	Total (N = 820) No. of Patients	%
Age, years						
Median	57		57		57	
Range	21-77		25-77		21-77	
FIGO stage						
Ic	37	9.0	37	9.0	74	9.0
II	40	9.8	39	9.5	79	9.6
III	245	59.8	248	60.5	493	60.1
IV	88	21.5	86	21.0	174	21.2
Tumor histology						
Serous	259	63	271	66	530	65
Endometrioid	50	12	48	12	98	12
Clear cell	15	3.7	12	2.9	27	3.3
Mucinous	12	2.9	13	3.2	25	3
Undifferentiated	31	7.6	29	7.1	60	7.3
Mixed or other	27	6.6	17	4.1	44	5.4
Missing information	16	3.9	20	4.9	36	4.4
ECOG performance status						
0-1	398	97.0	397	96.8	795	97.0
2	12	3.0	13	3.2	25	3.0
Residual disease						
None	148	36.1	150	36.6	298	36.3
≤ 1 cm	70	17.1	79	19.3	149	18.2
> 1 cm	116	28.3	111	27.1	227	27.7
No surgery	76	18.5	70	17.1	146	17.8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

balanced between the two arms (Table 1). Median age was 57 years (range, 21 to 77 years), and 97% of the patients had a performance status of 0 to 1. The majority of patients had advanced disease (60% with stage III and 21% with stage IV), and 45% of patients were enrolled after suboptimal surgical debulking.

Treatment Compliance

Information on treatment received was not available in six patients. Of the remaining 814 patients, 10 patients did not start treatment (Table 2).

Eighty-six percent and 81.1% of the patients completed six cycles in the standard and experimental arms, respectively. The proportion of patients delaying treatment because of toxicity, usually hematologic, was higher in the experimental arm at all cycles. Overall, 11.5% and 34.5% of cycles were delayed as a result of toxicity in the standard and experimental arms, respectively. Considering patients receiving six cycles, median times between first and last administration of chemotherapy were 16.3 and 18.1 weeks in the standard and experimental arms, respectively.

Efficacy

All randomly assigned patients were included in the intent-to-treat efficacy analysis. By the end of 2009, the PFS curve of the whole study population (not scattered by arm) showed that event occurrence substantially slowed before the required number of events was attained. More than half of the patients had optimal debulking, and more than one third did not have residual disease at all. This was a result of the significant proportion of patients with early-stage disease. The better prognosis of these subgroups of patients clearly conditioned the overall event rate (Appendix Fig A1, online only) and the time required to attain the planned events. Therefore, in concert with the Independent Data Monitoring Committee, the final analysis was anticipated at 556 events as of December 31, 2009. This number of events still allowed the detection of an HR for PFS of 0.79 with 80% power.

With a median follow-up time of 40 months, 282 events (68.8%) were recorded in the standard arm, and 274 events (66.8%) were recorded in the experimental arm. Median PFS was 16.8 months (95% CI, 15.2 to 19.4 months) in the standard arm and 19.0 months (95% CI, 16.3 to 24.0 months) in the experimental arm (HR, 0.95; 95% CI, 0.81 to 1.13; log-rank test, $P = .58$). PFS curves are shown in Figure 2A. In multivariable analysis adjusted by stage, performance status, residual disease, age, and size of the institution, the difference between treatments remained not significant (HR, 0.97; 95% CI, 0.82 to 1.14;

Table 2. Compliance With Chemotherapy

Treatment	Standard Arm (n = 408/410*)		Experimental Arm (n = 403/410†)	
	No. of Patients	%	No. of Patients	%
No. of cycles administered				
0 (did not start treatment)	4	1.0	6	1.5
Started treatment, but incomplete data on No. of cycles	3	0.7	2	0.5
1	11	2.7	10	2.5
2	12	2.9	19	4.7
3	9	2.2	13	3.2
4	6	1.5	12	3.0
5	10	2.5	14	3.5
6	353	86.5	327	81.1
Cause of treatment interruption				
Missing information	3	0.7	3	0.7
Progression/death	23	5.6	29	7.2
Toxicity/refusal	21	5.1	38	9.4
Violation/other	8	2.0	6	1.5
Cycle delayed because of toxicity				
Second cycle	34/392‡	8.7	120/387	31.0
Third cycle	49/380	12.9	135/368	36.7
Fourth cycle	39/370	10.5	102/354	28.8
Fifth cycle	36/364	9.9	122/341	35.8
Sixth cycle	55/353	15.6	134/327	41.0

*Two patients were excluded because they were missing all information on treatment received.
†Seven patients were excluded (four patients were missing all information on treatment received, and three patients actually received carboplatin/paclitaxel).
‡No. of patients/total No. of patients who received cycle.

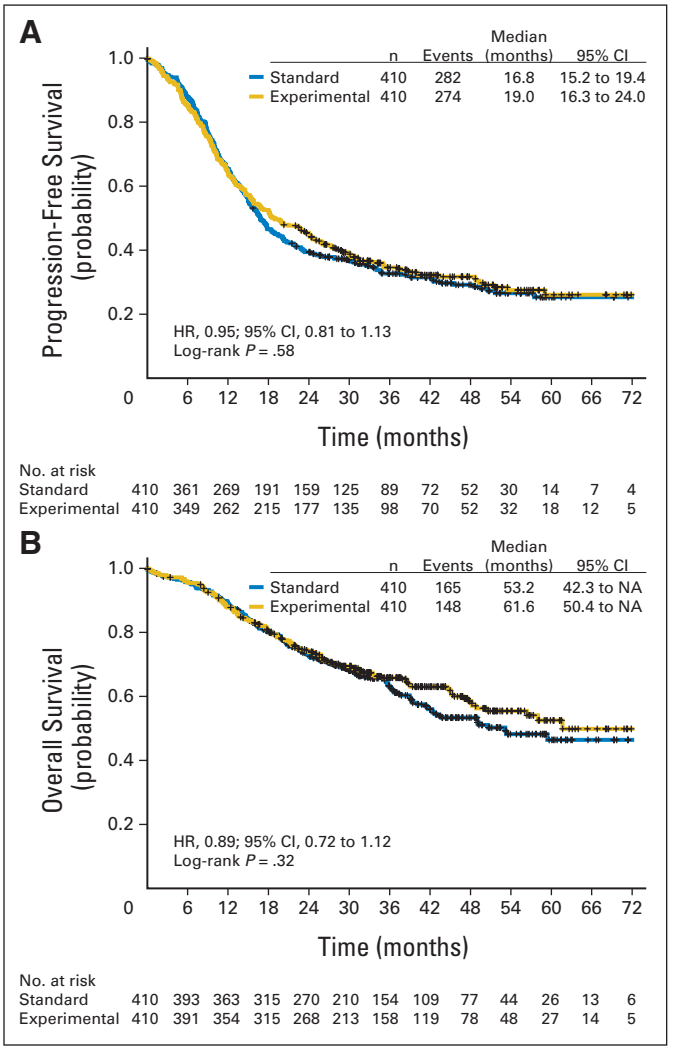

Fig 2. (A) Progression-free survival and (B) overall survival curves by treatment arm. HR, hazard ratio; NA, not available.

Table 3. Cox Proportional Hazard Model for Progression-Free Survival

Factor	Hazard Ratio	95% CI	*P*
Treatment (experimental *v* standard)	0.97	0.82 to 1.14	.70
Stage (III-IV *v* IC-II)	3.11	2.17 to 4.46	< .001
ECOG PS (2 *v* 0-1)	0.92	0.59 to 1.45	.73
Residual disease after surgery			< .001
≤ 1 cm *v* absent	2.00	1.52 to 2.62	
> 1 cm *v* absent	2.74	2.14 to 3.51	
No surgery *v* absent	3.71	2.82 to 4.86	
Age (≥ *v* < 70 years)	1.03	0.81 to 1.32	.79
Size of institution			.38
Intermediate (20-99 patients) *v* large (≥ 100 patients)	0.93	0.74 to 1.15	
Small (< 20 patients) *v* large (≥ 100 patients)	1.01	0.82 to 1.24	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

P = .70), whereas residual disease and stage were independent predictors of PFS (Table 3). Exploratory analysis by subgroups according to International Federation of Gynecology and Obstetrics stage, performance status, age category, residual disease after surgery, and tumor histology showed no heterogeneity of treatment effect (Fig 3). With 313 deaths (38.2%) recorded, the median OS (Fig 2B) was 53.2 months (95% CI, 42.3 months to not available) in the standard arm compared with 61.6 months (95% CI, 50.4 months to not available) in the experimental arm (HR, 0.89; 95% CI, 0.72 to 1.12; log-rank test, *P* = .32).

Two-hundred ninety-seven patients (36.2%) were eligible for response analysis according to RECIST criteria (≥ one target lesion), 160 patients (39.0%) in the standard and 137 patients (33.4%) in the experimental arm. ORR was 59% in the standard arm (24 complete responses and 71 partial responses) and 57% in the experimental arm (23 complete responses and 55 partial responses; *P* = .76). In 184 patients with nontarget lesions only, complete response was 33% and 29% in the standard and experimental arms, respectively (*P* = .69). In 173 patients with elevated CA-125 only, CA-125 normalization was obtained in 82% and 86% of patients in the standard and experimental arms, respectively (*P* = .70; Appendix Table A1, online only).

Toxicity

All patients who received at least one dose were eligible for toxicity analysis (n = 803). Worst toxicities by treatment arm are listed in Table 4. There were six potentially treatment-related deaths—four in the standard arm (allergy during paclitaxel infusion followed by sudden death at home, n = 1; febrile neutropenia, n = 1; nonneutropenic fever, n = 1; intestinal necrosis with septic shock, n = 1) and two in the experimental arm (bleeding, n = 1; disseminated intravascular coagulation, n = 1).

Thrombocytopenia and anemia were significantly more frequent and severe in the experimental arm; RBC transfusions were more frequently required in the experimental arm than the standard arm (6% *v* 2%, respectively; *P* = .001). There were no significant differences in leukopenia, neutropenia, febrile neutropenia, infections, platelet transfusions, and bleeding. The nonhematologic adverse effects profile was significantly different between the arms. Hair loss, diarrhea, and neuropathy were significantly worse in the standard

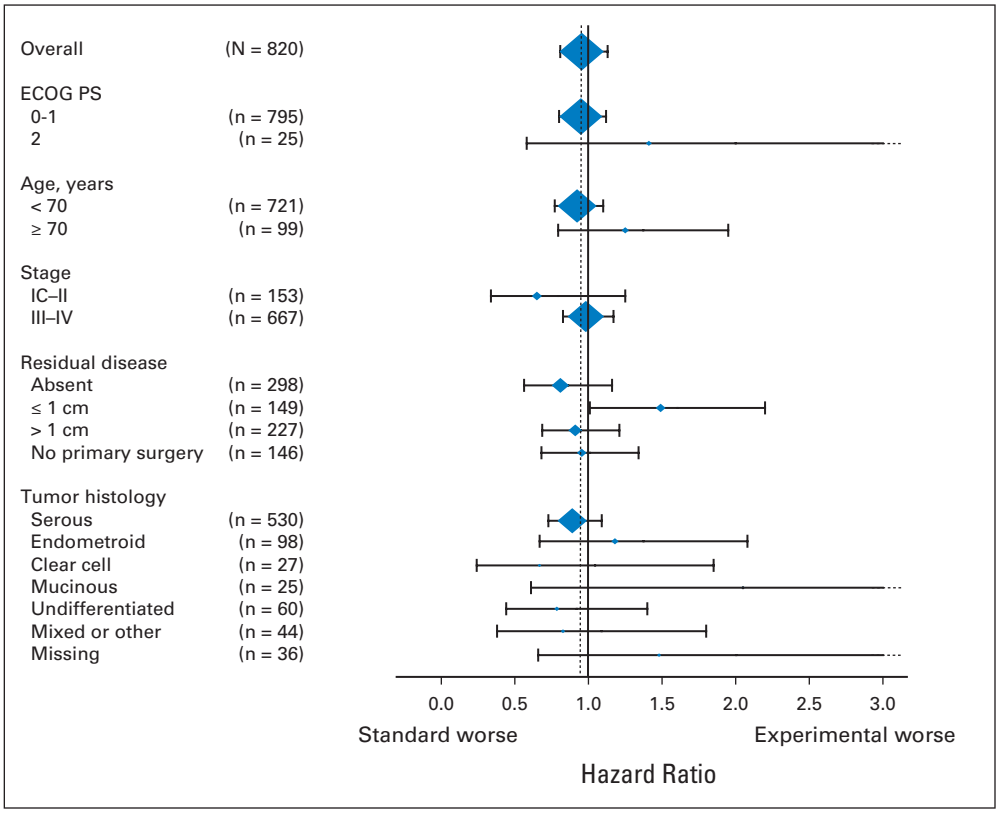

Fig 3. Treatment effect on progression-free survival within major patient subgroups. Vertical dotted line represents hazard ratio (experimental arm *v* standard arm) in the overall study population. ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 4. Worst Grade (according to NCI-CTC) of Toxicity According to Treatment Arm

Toxicity	Carboplatin + Paclitaxel (n = 407*)										Carboplatin + Pegylated Liposomal Doxorubicin (n = 396)											
	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P*†	*P*‡
Anemia	127	31	100	25	13	3	2	< 1			100	25	131	33	36	9	4	1			< .001	< .001
Leukopenia	60	15	133	33	72	18	5	1			62	16	159	40	51	13	6	2			.79	.09
Neutropenia	33	8	64	16	106	26	96	24			31	8	112	28	138	35	33	8			.09	.07
Febrile neutropenia					5	1	4	1	1	< 1					2	< 1	3	1			.27	.21
Neutropenic infection	2	< 1															1	< 1			1.0	.49
Non-neutropenic infection	2	< 1	6	2	1	< 1			1	< 1	4	1	1	< 1	3	1					.69	.68
Thrombocytopenia	49	12	20	5	8	2					89	22	42	11	52	13	11	3			< .001	< .001
Bleeding	1	< 1									1	< 1					1	< 1	1	< 1	.25	.24
Allergy	10	3	4	1	6	1	3	1	1	< 1	8	2	4	1	7	2	2	< 1			.70	.86
Kidney	7	2	3	1	1	< 1					5	15	6	2	1	< 1					.71	1.0
Heart, rhythm	1	< 1									4	1	2	< 1							.051	—
Heart, general	3	1	4	1	1	< 1					1	< 1	2	< 1	4	1	2	< 1			.63	.06
Pulmonary	1	< 1	5	1	1	< 1					5	1									.57	1.0
Fatigue	98	24	68	17	11	3					87	22	73	18	10	3	1	< 1			.89	.95
Fever	8	2	1	< 1							10	3	2	< 1							.46	—
Weight loss	8	2	3	1							8	25	4	1							.76	—
Hair loss	14	3	242	60							34	9	21	5							< .001	—
Skin	15	4	7	2							52	13	24	6	6	2					< .001	.01
Anorexia	18	4	7	2	3	1					15	4	10	3	1	< 1					.85	.62
Constipation	69	17	54	13	5	1					77	19	45	11	2	< 1	1	< 1			.84	.38
Diarrhea	35	9	14	3	3	1					19	5	5	1							< .001	.25
Nausea	120	29	63	15	7	2					120	30	76	19	7	2					.14	.96
Vomiting	53	13	56	14	7	2					55	14	50	13	9	2	1	< 1			.88	.43
Stomatitis	30	7	6	2	1	< 1					41	10	33	8	2	< 1					< .001	.49
Liver	29	7	12	3	5	1					28	7	13	3	2	< 1	1	< 1			.92	.73
Neuropathy	115	28	64	16	12	3					47	12	11	3	1	< 1					< .001	.003
Other	53	13	31	8	7	2			1§	< 1	30	8	15	4	4	1	1‖	< 1	1¶	< 1	< .001	.79

Abbreviation: NCI-CTC, National Cancer Institute Common Toxicity Criteria.
*Including three patients assigned to the experimental arm who received carboplatin plus paclitaxel.
†Any grade (test for trend).
‡Severe toxicity (grade ≥ 3).
§Death as a result of intestinal necrosis and septic shock.
‖Grade 4 hypocalcemia.
¶Death as a result of disseminated intravascular coagulation.

arm, whereas skin toxicity and stomatitis were significantly worse in the experimental arm.

QoL

Overall, 620 patients (76%; 309 patients in the standard arm *v* 311 patients in the experimental arm) completed the valid baseline QoL questionnaire. Of these, 336 patients completed the questionnaire after three cycles (165 patients in the standard arm *v* 171 patients in the experimental arm), and 247 patients completed the questionnaire after six cycles (130 patients in the standard arm *v* 117 patients in the experimental arm). Mean difference from baseline in global QoL (EORTC QLQ-C30 items 29 and 30) was 3.70 in the standard arm versus 4.09 in the experimental arm after three cycles, and 8.07 in the standard arm versus 10.56 in the experimental arm after six cycles. Both comparisons were not statistically significant. No relevant differences were observed in all functional domains and in most symptom scales. Statistically significant differences were reported in loss of appetite after three cycles, favoring the standard treatment, and in diarrhea after three cycles, favoring the experimental arm (Appendix Fig A2, online only).

DISCUSSION

The MITO-2 trial compared an experimental regimen of carboplatin/PLD versus standard carboplatin/paclitaxel as first-line treatment of patients with advanced ovarian cancer. The experimental treatment did not significantly prolong PFS, the primary end point of the trial, and no differences were apparent in OS, ORR, and QoL. Nonhematologic toxicity significantly differed between the arms, with hair loss and neurotoxicity being drastically less frequent in the experimental arm, but with this arm having more skin toxicity and stomatitis. Hematologic toxicity was also worse with experimental treatment but within acceptable limits for clinical practice. Overall, given these results and considering that CIs of both PFS and OS completely lie within limits typically considered acceptable for noninferiority, the experimental treatment might be considered as an alternative to the standard treatment. This choice, of course, should take into account patient's will and consider limitations as a result of the lack of regulatory approval of PLD for first-line treatment and its cost.

The dramatic reduction of hair loss and neurotoxicity seen with the experimental treatment is extremely important. Approximately three fourths of patients experience some degree of peripheral neuropathy while on carboplatin/paclitaxel, and 7% have ≥ grade 3 peripheral neuropathy.[5] We previously showed that residual neurotoxicity occurs frequently in patients after completion of carboplatin/paclitaxel, with a long-lasting pattern of recovery and 14% of patients still suffering residual neuropathy 1 year after treatment.[23] In addition, such toxicity may still persist in a significant proportion of patients who experience relapse and, therefore, affects second-line treatment choice. However, in the MITO-2 trial, differences in toxicity pattern did not translate into relevant QoL differences. This might eventually depend on the fact that we limited QoL data collection to the treatment period, therefore missing late neurotoxicity. Furthermore, we only used the EORTC QLQ-C30 general questionnaire and not a more specific QoL questionnaire (eg, EORTC QLQ Ovarian Cancer Module).

The MITO-2 study, which studied the substitution of paclitaxel with PLD in combination with carboplatin, adds important evidence about the role of anthracyclines in first-line treatment of ovarian cancer. Meta-analysis of trials performed before the introduction of taxanes showed that the addition of doxorubicin prolonged survival[7]; however, on the contrary, in the taxane era, the addition of epirubicin to carboplatin/paclitaxel did not prolong OS and PFS in two phase III trials.[24,25] In a recent phase III trial[26] comparing carboplatin/PLD with carboplatin/paclitaxel in platinum-sensitive recurrent ovarian cancer, a statistically significant advantage in PFS in favor of carboplatin/PLD was found (HR of PFS, 0.821; $P = .005$; median PFS, 11.3 *v* 9.4 months, respectively). Carboplatin/PLD was associated with less alopecia and neurotoxicity.

To our knowledge, the only study testing PLD in first-line treatment of ovarian cancer is a phase III trial performed by the Gynecology Oncology Group comparing standard carboplatin/paclitaxel with two triplet regimens (standard carboplatin/paclitaxel plus gemcitabine or PLD) and two sequential doublet regimens (carboplatin plus topotecan or gemcitabine, both followed by carboplatin/paclitaxel).[27] Although efficacy was similar across the five arms, hematologic toxicity increased with three-drug combinations. However, the information regarding PLD efficacy in this trial is limited because PLD was given in association with carboplatin/paclitaxel every other cycle, and the overall dose-intensity was 5 mg/m^2/wk, much lower than that considered optimal.

Final MITO-2 analysis was performed with fewer events than planned (556 instead of 632 events), but it is unlikely that this affected the results. The reason was a dramatic decrease in the incidence of PFS events, which was not a result of flaws in follow-up procedures, consistent with plans, but rather a result of the favorable prognostic characteristics of the enrolled patients (significant proportion of patients with early-stage disease and of patients without residual disease after surgery). Therefore, an extremely longer time would have been required to get the planned number of events, and non–ovarian cancer deaths might dilute PFS differences. The Independent Data Monitoring Committee blindly advised to perform final analysis with the available events, considering that statistical power was reduced just to 75% and that there was still 80% power in detecting an HR for PFS of 0.79.

In conclusion, the MITO-2 trial shows that the combination of carboplatin/PLD does not prolong PFS compared with standard carboplatin/paclitaxel. However, given the observed difference in toxicity, it can be considered as a reasonable alternative for first-line treatment of advanced ovarian cancer, particularly in patients at high risk of neurotoxicity or wishing to avoid alopecia.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Sandro Pignata, Giovanni Scambia, Ciro Gallo, Francesco Perrone

Collection and assembly of data: Sandro Pignata, Giovanni Scambia, Gabriella Ferrandina, Antonella Savarese, Roberto Sorio, Enrico Breda, Vittorio Gebbia, Pietro Musso, Luigi Frigerio, Pietro Del Medico, Alessandra Vernaglia Lombardi, Antonio Febbraro, Paolo Scollo, Antonella Ferro, Stefano Tamberi, Alba Brandes, Alberto Ravaioli, Maria Rosaria Valerio, Enrico Aitini, Donato Natale, Laura Scaltriti, Stefano Greggi, Carmela Pisano, Domenica Lorusso, Vanda Salutari, Francesco Legge, Massimo Di Maio, Alessandro Morabito, Francesco Perrone

Data analysis and interpretation: Sandro Pignata, Massimo Di Maio, Alessandro Morabito, Ciro Gallo, Francesco Perrone

Manuscript writing: All authors

Final approval of manuscript: All authors

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Affiliations

Sandro Pignata, Stefano Greggi, Carmela Pisano, Massimo Di Maio, Alessandro Morabito, and Francesco Perrone, Istituto Nazionale Tumori; Ciro Gallo, Seconda Università di Napoli, Napoli; Giovanni Scambia, Domenica Lorusso, and Vanda Salutari, Policlinico Gemelli, Università Cattolica del Sacro Cuore; Antonella Savarese, Istituto Nazionale Tumori Regina Elena; Enrico Breda, Ospedale S. Giovanni Calibita Fatebenefratelli, Roma; Gabriella Ferrandina and Francesco Legge, Università Cattolica del Sacro Cuore, Campobasso; Roberto Sorio, Centro di Riferimento Oncologico, Aviano; Vittorio Gebbia, Casa di Cura La Maddalena; Pietro Musso, Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Civico Di Cristina Benfratelli; Maria Rosaria Valerio, Policlinico Giaccone, Università, Palermo; Luigi Frigerio, Ospedali Riuniti, Bergamo; Pietro Del Medico, Ospedale Bianchi Melacrino Morelli, Reggio Calabria; Alessandra Vernaglia Lombardi, Casa di Cura Malzoni Villa dei Platani, Avellino; Antonio Febbraro, Ospedale Fatebenefratelli, Benevento; Paolo Scollo, Ospedale Cannizzaro, Catania; Antonella Ferro, Ospedale S. Chiara, Trento; Stefano Tamberi, Ospedale Civile, Faenza; Alba Brandes, Ospedale Bellaria, Bologna; Alberto Ravaioli, Ospedale degli Infermi, Rimini; Enrico Aitini, Ospedale Carlo Poma, Mantova; Donato Natale, Ospedale S. Massimo, Penne; and Laura Scaltriti, Ospedale Ramazzini, Carpi, Italy.