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# Carboplatin-paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced or recurrent endometrial cancer: MITO END-2 - A randomized phase II trial

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## HIGHLIGHTS

- Bevacizumab combined with chemotherapy does not increase PFS in comparison to chemotherapy in recurrent endometrial cancer.
- Cardiovascular events were more frequent in the bevacizumab arm.
- Secondary endpoint suggests activity of bevacizumab in endometrial cancer which merits further exploration.

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## ABSTRACT

*Objective:* Increased Vascular Endothelial Growth Factor Receptor (VEGF) expression in endometrial cancer (EC) is associated with a poor prognosis. Preliminary clinical data reported Bevacizumab effectiveness in EC both as single agent and in combination with chemotherapy.
*Methods:* In a phase II trial, patients with advanced (FIGO stage III-IV) or recurrent EC were randomized to receive Carboplatin-Paclitaxel standard dose for 6–8 cycles vs Carboplatin-Paclitaxel and Bevacizumab 15 mg/kg in combination with chemotherapy and maintenance until disease progression or unacceptable toxicity. The primary endpoint was progression free survival (PFS).
*Results:* 108 patients were randomized; PFS (10.5 vs 13.7 months, HR 0.84 p = 0.43), overall response rate (ORR 53.1% vs 74.4%) and overall survival (OS) (29.7 vs 40.0 months, HR 0.71 p = 0.24) resulted in a non-significant increase in Bevacizumab treated patients. The PFS increase became significant when an exploratory analysis with the Breslow test was used. Moreover, patients treated with Bevacizumab experienced a significant increase in 6-month disease control rate (70.4% vs 90.7%). Cardiovascular events were more frequent in the experimental arm ("de novo" grade ≥2 hypertension 21% vs 0% and grade ≥2 thromboembolic events 11% vs 2% in the Bevacizumab vs standard treatment arm, respectively).
*Conclusions:* Bevacizumab combined with chemotherapy in the treatment of advanced/recurrent EC failed to demonstrate a significant increase in PFS in the MITO END-2 trial. Nevertheless, these

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preliminary data suggests some effectiveness of the antiangiogenic agent which merits further exploration in a larger population with a better molecular characterization.



## 1. Introduction

Since 2008, the incidence of endometrial cancer (EC) has increased by 21% and the mortality rate per 100,000 cases doubled over the last two decades [1]. Advanced (FIGO stage III-IV) or recurrent ECs have a dismal prognosis. Carboplatin and Paclitaxel in combination represents the care standard of advanced and recurrent EC, resulting in a median progression free survival (PFS) of 12 months and median overall survival (OS) of 32 months [2].

Vascular Endothelial Growth Factor (VEGF) expression in EC has clinical and biological implications as increased VEGF levels, which are associated with higher histological grade, deeper myometrial invasion, nodal metastasis and poorer outcome [3,4]. Moreover, VEGF expression is associated with elevated tumor vascularization, measured by microvessel density, in EC tissues [5], representing an independent predictive marker for decreased 5-year survival in patients with advanced disease [4,6,7].

Bevacizumab, a humanized anti-VEGF monoclonal antibody showed effectiveness in advanced/recurrent EC, both used as single agent and in combination with chemotherapy [5]. In preclinical studies with orthotopic mouse models, bevacizumab reduced tumor volumes compared to controls [5,8]. Mechanistically, researchers hypothesized that bevacizumab mimics the differentiating effects of progesterone in the endometrium and inhibits EC growth suppressing angiogenic and proliferative signaling pathways [9].

A 13.5% response rate with a median PFS of 4.1 months and a median OS of 10.5 months was reported in a clinical setting, with single agent bevacizumab treatment in a phase II study enrolling 52 recurrent EC patients; of note, more than 40% of patients were progression-free after 6-month of treatment [10]. In a small phase II single arm trial with bevacizumab in combination with Carboplatin-Paclitaxel treating 19 advanced/recurrent EC patients a response rate of 73% with a median PFS of 18 months and a median OS of 58 months were reported; moreover, 93% of patients were progression free 6 months after treatment initiation [11].

The aim of this prospective, randomized phase II trial was to compare Carboplatin-Paclitaxel (CP) chemotherapy in combination with Carboplatin-Paclitaxel-Bevacizumab (CP—B) in advanced or recurrent EC patients.

## 2. Material and methods

MITO END-2 was a multicenter, open label, randomized phase II trial. Histologically confirmed advanced (FIGO stage III-IV) or recurrent EC patients, included endometrioid and serous or clear cell cancer and measurable or evaluable disease, according to Recist criteria version 1.1, were enrolled. Carcinosarcomas and patients receiving before trial initiation more than one platinum-based chemotherapy line were excluded (patients may have received one previous platinum-based chemotherapy if a minimum interval of 6 months from the last platinum treatment had passed).

Other inclusion criteria were ECOG Performance status (PS) $\leq$2, age $\geq$18 years, adequate bone marrow, renal and hepatic function, controlled hypertension, no clinically significant cardiac disease. Previous radiotherapy was allowed. Patients were ineligible in the following cases: history of concomitant malignancy or prior malignancy other than non-melanoma skin cancer, untreated brain metastasis, bleeding diathesis or coagulopathy, history of abdominal fistula, gastrointestinal perforation or intraabdominal abscess within 6 months prior to study enrollment and signs or symptoms of gastrointestinal obstruction.

Patients were randomized 1:1 to receive Carboplatin AUC 5 + Paclitaxel 175 mg/mq i.v. d 1 q 21 or the same chemotherapy in combination and maintenance with Bevacizumab 15 mg/kg d1 q 21 until disease progression, unacceptable toxicity or patient's refusal. Chemotherapy was given for 6 to 8 cycles based on physician's judgment. The three initial bevacizumab doses were administered first over 90, then over 60 and after over 30 min. The 30-min administration was maintained if well tolerated. In case of uncontrolled hypertension (at least 2 values of systolic pressure > 150 mmHg or diastolic > 90 during a week) or symptomatic hypertension less than CTCAE Grade 4, bevacizumab treatment was suspended until blood pressure was controlled with anti-hypertensive therapy. Bevacizumab was also temporarily interrupted in the event of severe proteinuria defined as a urine protein/creatinine (UPC) ratio > 3.5. Bevacizumab was continued if the UPC ratio recovered to <3.5 within 8 weeks from discontinuation. Bevacizumab treatment was permanently discontinued in case of grade 4 hypertension, reversible posterior leukoencephalopathy syndrome or hypertensive encephalopathy, grade 4 nephrotic syndrome, arterial thrombosis, symptomatic grade 4 or recurrent/worsening venous thromboembolic events after resumption of bevacizumab treatment, grade 3 hemorrhage, bowel perforation or fistula and any complete wound disruption. Chemotherapy cycles were delayed for up to 2 weeks in case of neutrophil count <1500 cells/$mm^3$ or platelet count <100,000/$mm^3$. In case of grade 4 hematological toxicity prophylactic growth factors were used according to local guidelines at the subsequent cycle. Patients who failed to recover adequate blood cell counts within two-weeks and despite growth factor stimulation, were permanently excluded for cytotoxic chemotherapy, but could continue single agent bevacizumab treatment based on physician' judgment.

Stratification criteria were cancer type (endometrioid vs. non endometrioid EC), advanced (stage III-IV) versus recurrent disease and number of previous chemotherapy lines (0 vs 1).

The primary endpoint was PFS, defined as the time between randomization and radiologic or clinical disease progression. Secondary endpoints were OS defined as the time between randomization until death or last patient contact; overall response rate (ORR) defined as the sum of complete (CR) and partial (PR) responses. Responses were evaluated according to Recist criteria version 1.1. in patients with measurable disease. Treatment safety and tolerability was evaluated according to CTCAEs version 4.0 and patient reported outcomes was assessed with EORTC-QLQ-C30 and EN-34.

Patients reporting deterioration of clinical conditions were considered as progressing even in absence of radiologic confirmation.

Radiologic disease evaluation was symmetrically performed every 9 weeks (regardless any cycle delay) during chemotherapy treatment and every 3 months in the maintenance phase. The radiologic assessment schedule was mandatory, given the potential bias in absence of a placebo control arm and PFS as primary endpoint and database evaluation after data lock confirmed

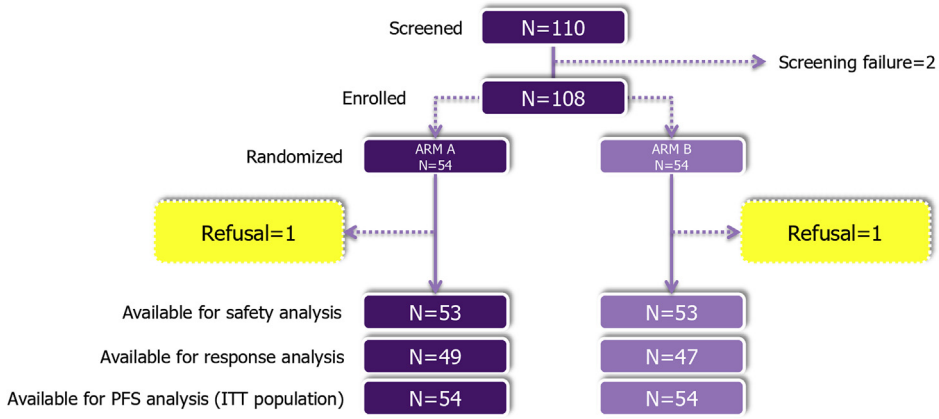



**Fig. 1.** Patient flow.

radiologic evaluation was symmetrical between the two treatment arms.

The trial was approved by the local Ethical Committees of each participating institution and registered on the European Study Registry with EUDRACT number 003301–16. All patients provided written informed consent.

### 2.1. Statistical analysis

We calculated sample size based on a median PFS in advanced/recurrent EC, which was reported to be approximately 12 months [2]. One hundred and eight patients were randomized in a 1:1 ratio and approximately 89 events (recurrence, progression or death) needed to be observed in order to provide 80% power to detect a 30% improvement in PFS based on a 0.70 proportional hazard ratio (HR). The power projection was based on a one-sided log-rank test at an alpha = 0.20 significance level. The proportion of patients lost to follow up was assumed to be less than 10%.

The Breslow (Generalized Wilcoxon) test assesses homogeneity by comparing odds ratio differences of two datasets analyzed in two different stages [12]: the method gives more weight to early occurring events, and it is considered the most appropriate statistical test when a large fraction of patients are censored at early time points and the curves cross. Given the different velocity with which progression events occurred in the two different observation periods (interim non pre-planned futility analysis and final analysis) and because of the curve crossing, and exploratory analysis with the Breslow test was performed to evaluate differences in PFS between the two treatment arms.

### 2.2. IDMC evaluation

An Independent Data Monitoring Committee (IDMC) was established at the study beginning. The IDMC met on November 2013 to review the safety events during the trial execution and, after careful adverse event (SAEs) evaluation, recommended trial continuation because SAEs retraced the drug's safety profile. Moreover, the IDMC suggested that the Steering Committee would perform a non pre planned interim futility analysis to assess potential impact (if any) of early CP-B patient drop outs, given the higher treatment discontinuation rates due to SAEs in the experimental arm. Interim futility analysis data and final safety data were presented at ASCO 2015 when 75% of progression events had occurred [13]. The present paper reports final efficacy data for PFS and immature OS data.

## 3. Results

Between April 2012 and June 2014, 110 patients were screened, and 108 patients randomized in 12 Italian Institutions; soon after randomization 1 patients in each arm refused treatment. These patients were included in the primary intention to treat analysis but were excluded from the safety analysis involving patients who had received at least one chemotherapy cycle. Forty-nine patients in the standard treatment arm and 47 in the experimental arm represented the population with measurable or non measurable disease, evaluable for response analysis. Final data are presented with a median follow up of 60 months. Fig. 1 reports patient flow.

The two treatment arms were well balanced according to clinical and pathologic characteristics with about 60% recurrent disease patients and approximately 50% grade 3 tumor patients. In 16% of patients serous and clear cell EC were diagnosed, 45% had previously received external radiotherapy and 24% a previous chemotherapy line. At the time of study enrollment, about 48% of patients in both arms had controlled hypertension (with a slight higher prevalence in the standard arm) and 8% of patients had type 2 diabetes. Table 1 reports patient characteristics.

### 3.1. Treatment compliance

A median of 6 chemotherapy cycles were administered in both treatment arms and a median of 12 Bevacizumab courses (range 1–38) were administered in the experimental arm. No difference in chemotherapy dose reductions and toxicity delays were noted in the two treatment arms while more patients treated with

**Table 1**
Patient characteristics.

| Characteristic | | CP (N = 54) | CP-B (N = 54) |
|---|---|---|---|
| Median age, years (range) | | 65 (32–80) | 63 (28–81) |
| **ECOG PS, N** (%) | 0 | 44 (81) | 46 (85) |
| | 1/2 | 10 (19) | 8 (15) |
| **Disease status** | Advanced | 19 (35) | 19 (35) |
| | Recurrent | 33 (61) | 34 (63) |
| **Histology** | Endometrioid | 38 (70) | 37 (72) |
| | Serous/Clear cell | 7 (13) | 11 (20) |
| **Grading** | G1/2 | 19 (35) | 23 (43) |
| | G3 | 28 (52) | 25 (46) |
| **Previous Chemotherapy** | | 15 (28) | 11 (20) |
| **Previous Radiotherapy** | | 26 (48) | 23 (42) |
| **Comorbidities** | Hypertension | 29 (54) | 23 (43) |
| | Renal | 2 (4) | 1 (2) |
| | Diabetes | 4 (7) | 5 (9) |

**Table 2**
Haematologic and non haematologic toxicities.

| Grade ≥3 Adverse Events | CP (53 pts) (%) | CP-B (53 pts) (%) |
|---|---|---|
| Anaemia | 6 (11.1) | 6 (11.3) |
| Leukopenia | 15 (27.8) | 15 (28.3) |
| Neutropenia | 25 (46.3) | 30 (56.6) |
| Febrile Neutropenia | 0 | 3 (5.6) |
| Thrombocytopenia | 0 | 3 (5.6) |
| Asthenia | 1 (1.9) | 5 (10)* |
| Nausea | 0 | 1 (1.9) |
| Grade ≥2 Hypertension | 0 | 11 (20.7) |
| Renal toxicity | 0 | 1 (1.8) |
| Thromboembolic events | | |
| Arterial | 1 (1.9) | 2 (3.7) |
| Venous | 0 | 4 (7.4)° |
| Grade ≥2 Cardiac toxicity | | |
| Myocardial Ischemia | 1 (1.9) | 2 (3,7) |
| Arrhythmia | 0 | 1 (1,9) |
| Fistulas | 0 | 2 (3.7) |
| G2 Dyspnea | 2 (3.7) | 1 (1.9) |
| G2 Neurologic Confusional State | 0 | 3 (5.5) |
| G2 Haemorrage | 1 (1.9) | 0 |

*p < 0.09.
°p = 0.005.

Bevacizumab experienced discontinuations due to toxicity (4% vs 18% in standard and experimental arm respectively; p < 0.05) (Table S1).

### 3.2. Toxicity

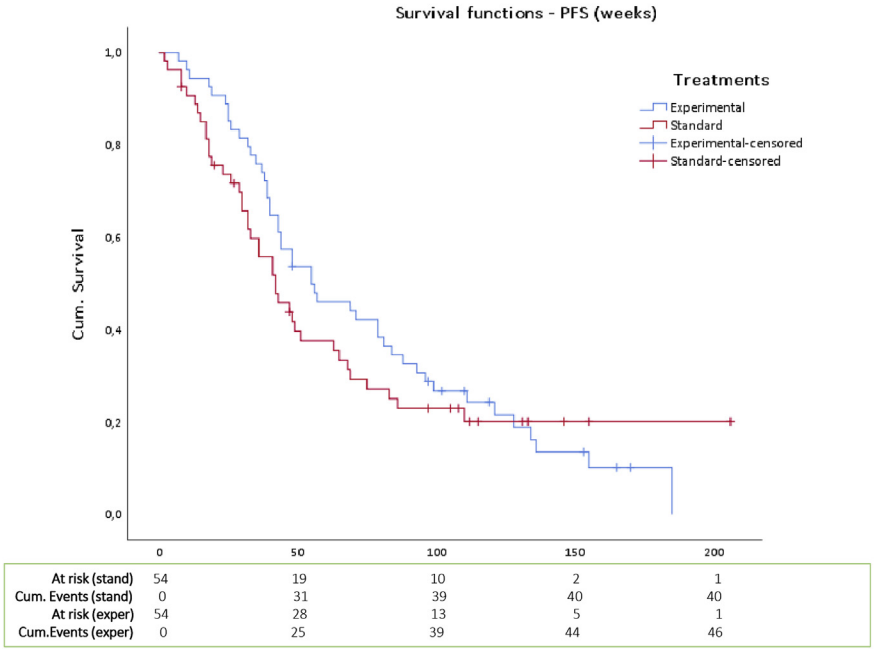
Eight SAEs were reported among 7 patients in the standard treatment arm versus 21 SAEs occurring in 16 patients in the CP-B treatment arm (Table S2). Clinicians reported all SAE as non-treatment related in the standard arm while 14 events were defined as related to the CP-B treatment. In the majority of cases non hematological toxicity was represented by cardiovascular events (grade ≥3 arterial and venous thrombosis 11% vs 2% in the experimental and standard arm respectively) (Table 2). No worsening of preexisting hypertension was registered in enrolled patients while a "de novo" appearance of grade ≥2 hypertension was reported in 21% of patients treated with Bevacizumab. No differences were reported between the two arms in terms of cardiac toxicity: 2 patients in the experimental arm experienced a myocardial ischemia with a clinically significant reduction in left ventricular ejection fraction in one of them (vs 1 patients in the standard arm) and in one patient a G2 arrhythmia was detected. No difference in terms of hematological and others non hematological toxicities were registered between the two treatment arms. In the experimental arm two patients previously received external radiotherapy experiencing gastro-intestinal fistulas and 3 patients reported G2 neurologic disorders (Table 2). One patient in the standard arm reported G2 hemorrhage. No treatment related deaths were registered.

### 3.3. Efficacy

At the time of interim, non pre-planned, analysis (May 2015) we noted a significant increase in median PFS in the CP-B arm (13.0 vs 8.7 months) with a HR 0.59 (range 0.35–0.98; Fig. S1) [13]. At that time the OS data were immature, referring to only 35% of events; a not significant increase in median OS was reported in the experimental arm (23.5 vs 18 months) and a HR of 0.65 (0.31–1.36; Fig. S2) [13].

The final analysis is not significant with increased median PFS values of 13.7 vs 10.5 months; p = 0.43 in the CP-B arm and a HR of 0.84 (range 0.5–1.3; Fig. 2; log rank test). Given that in our study, 74% of progression events occurred during the first year after accrual completion and the remaining 26% in the following 3 years of observation, and exploratory analysis with the Breslow (Generalized Wilcoxon) test was performed to evaluate difference in PFS [12]. Analyzing the increased PFS results with the Breslow test the p resulted significant (p = 0.08) according to the level of significance of our statistical plan (p = 0.20) (Fig. 2).

Other clinically interesting parameters were identified among the secondary endpoint which merit further investigations. OS data are still immature: median OS was 40.0 vs 29.7 months in the experimental and standard arm respectively (HR 0.71, range




**FINAL PFS ANALYSIS**

| | CT (N=54) | CT-B (N=54) |
|---|---|---|
| **Events**, n | 40 | 46 |
| **Median PFS**, months **(95% CI)** | 10,5 (7.2-13,5) | 13.7 (7.5-20,0) |
| **HR (stratified) (95% CI) 2-sided log-rank p-value 2-sided Breslow test p value** | 0.846 (0.5–1.3) 0.437 0.08* | |

* p<0.20

**Fig. 2.** Progression free survival.

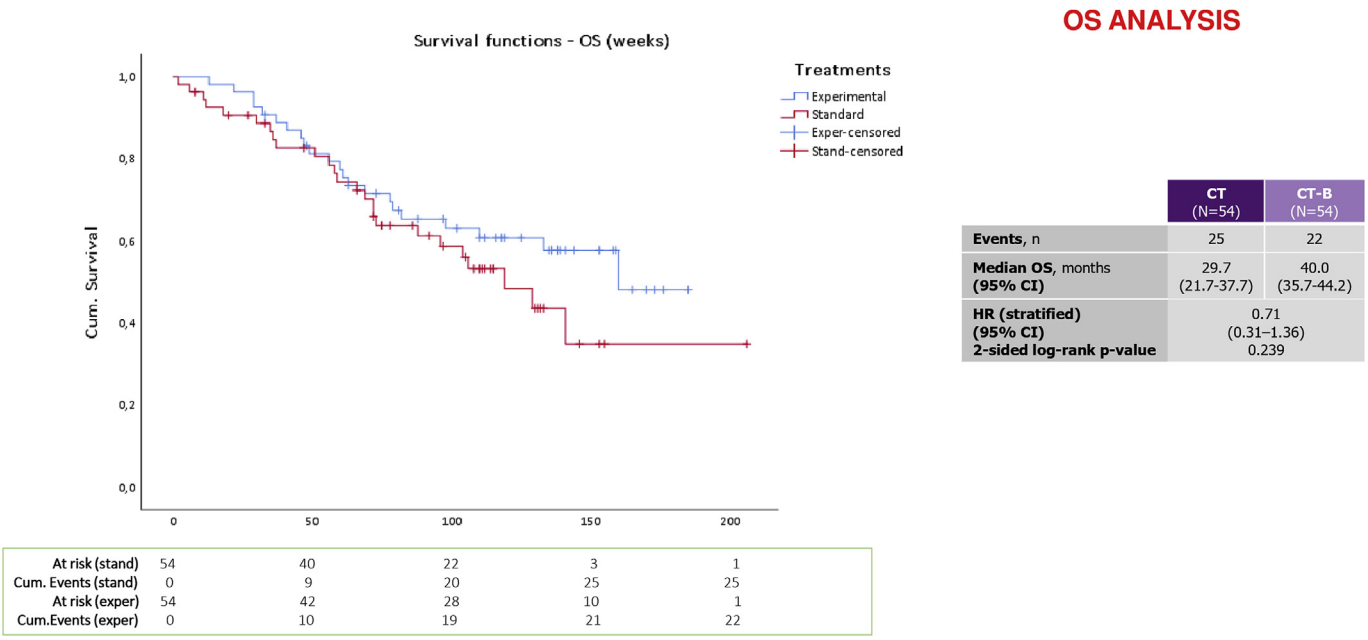



**Fig. 3.** Overall survival.

0.31–1.36, Fig. 3). Forty-nine patients in the standard treatment arm and 47 patients in the CP-B arm, with measurable and not measurable disease were evaluable for response analysis. Objective responses were 74.4% vs 53.1% in the experimental and standard arm, respectively. A significantly higher percentage of 6- and 12-months disease control (90.7% vs 70.4% and 54.7% vs 45.3%) was registered in the CP-B arm (Table 3).

Forest Plot of effect treatment by conventional patients' characteristics although limited by the small number of patients suggests a benefit of bevacizumab in higher risk groups (non endometrioid tumour and old age patients) (Supplementary Fig. 3).

## 4. Discussion

VEGF expression in EC is associated with a higher histological grade, myometrial invasion and lymph node metastasis and has been identified as an independent prognostic factor for poor prognosis [3,4]. Our randomized trial investigated bevacizumab effectiveness in combination with carboplatin-paclitaxel compared to standard chemotherapy in advanced and/or recurrent EC, because preliminary clinical data reported bevacizumab effectiveness in advanced EC used as single agent or in combination with chemotherapy [4,10].

Aghajanian et al. [10] administered bevacizumab (15 mg/kg every 3 weeks) to 52 women with persistent or recurrent endometrial cancer after one to two prior chemotherapy regimens.

**Table 3**
Overall response rate.

| Clinical response | CP N = 49 (%) | CP-B N = 47 (%) |
|---|---|---|
| **Complete Responses** | 9 | 21 |
| **Partial Responses** | 17 | 14 |
| **Overall Response rate** | 26 (53.1) | 35 (74.4) |
| **Stabilizations of disease** | 20 (40.1) | 10 (21.2) |
| **Progressions of disease** | 3 (6.1) | 2 (4.2) |
| **6-months non PD**[a] | 38 (70.4) | 49 (90.7) |
| **12-months non PD**[a] | 24 (44.4) | 29 (53.7) |

Notes: PD = progression of disease.
[a] Percentages calculated on ITT basis (54 patients per arm).

Twenty-nine patients (55.8%) additionally received prior radiotherapy. One complete response and 6 partial responses were observed, with an ORR of 13.5%, and a median response duration of 6 months; median PFS and OS were 4.2 months and 10.5 months, respectively [10]. In a single arm phase II trial on 15 patients with persistent or recurrent EC who had received one prior cytotoxic regimen, the combination of CP-B obtained 5 complete responses and 6 partial responses with an ORR of 73.0%, a median PFS of 18 months and a median OS of 58 months [11].

A three-arm randomized phase II GOG 86 P study, comparing CP-B vs paclitaxel + carboplatin + temsirolimus vs ixabepilone + carboplatin + bevacizumab to treat stage III-IV or recurrent EC patients showed a significant 11.3 months increase in OS in the CP-B arm compared with the historical controls of patients treated with carboplatin-paclitaxel alone quite in line with our 10.3 months increase in OS in favor for the CP-B treatment. The same three-armed trial did not show any difference in terms of PFS between the three experimental arms [14].

To the best of our knowledge, this is the first randomized trial addressing the role of bevacizumab in combination with carboplatin-paclitaxel in comparison to standard chemotherapy in advanced and/or recurrent endometrial cancer. Our study did not meet its primary end-point and a not significant 3.2 months increase in PFS and 10.3 months increase in OS were registered with the combination of Carboplatin-Paclitaxel-bevacizumab with respect to chemotherapy alone in advanced disease.

We decided to reanalyze our PFS data with Breslow (Generalized Wilcoxon) test [12], because we noted different event velocity with large patient fraction during early trial stages in the statistical analysis – evaluating the statistical test more appropriate for our trial - even though the study protocol did not foresee the test originally. Notable with Breslow test the median increase in PFS became significant according the alfa level of the study. Secondary end-points (objective response and 6-months disease control rate) were consistent with the findings from the primary endpoint analysis and suggest a possible benefit of Bevacizumab when combined to chemotherapy in advanced/recurrent EC.

Moreover, according to the different velocity of progression events, one could argue that the trial could have potentially

enrolled two different populations with different biological characteristics (i.e. POLE or MSI tumors vs high copy number tumors) which have affected the prognosis. Traditionally EC prognosis and treatment have been driven by clinical characteristics such as stage, grade and histology. Cancers of the same stage and histology may present very distinct molecular and genomic profiles that greatly impact clinical behavior. In 2013, the whole genome studies of the Cancer Genome Atlas (TCGA) identified 4 molecular subtypes of EC based on mutational burden and copy number alterations which defines 3 clinical groups of patients with completely different prognosis [15]. 1) A subclass with the highest mutational load (POLE), associated with an excellent prognosis; 2) An unstable microsatellite EC (MSI, driven by mismatch repair deficiency); 3) A low copy number EC with an intermediate outcome; and 4) A subclass characterized by high somatic copy number alterations, mostly driven by TP53 mutation, with unfavorable prognosis [15]. Recently a subgroup analysis of GOG/NRG Study 86P trial reported a greater benefit of bevacizumab in p53 mutant endometrial cancer (PFS 19.6 months vs 12 months in P53 mutated and wild type tumors, respectively) suggesting that patients with more aggressive tumors and earlier progression events, may experience enhanced benefit from suppression of angiogenesis [16]. These results might possible explain why the significant benefit demonstrated with bevacizumab in early progressive patients became inconclusive when less aggressive recurrences were analyzed together with more aggressive, p53 mutated tumors. Future clinical trials will necessary be implemented by the recent knowledge of the molecular heterogeneity of EC, and molecular classification should be used at least as a stratification factor in order to detect a potentially different effect of the drugs in the different subtypes.

Cardiovascular toxicity was a concern in our study: in the experimental arm 11% of patients reported grade $\geq$3 arterial or venous thromboembolic events and 3 patients reported cardiovascular toxicity (one patient experienced a clinically significant reduction in left ventricular ejection fraction, in one patient a silent myocardial injury was detected and in a patient a G2 arrhythmia was reported). Moreover 18% of patients in the experimental arm experienced treatment discontinuations due to toxicity. These figures favorably compare with what reported by previous studies [10,11,14] with bevacizumab in EC patients: all the authors agreed that no new signals of toxicity appeared but our advice is that particular attention should be paid to cardiovascular events when using bevacizumab in patients with preexisting risk factors for cardiovascular events (older age, obesity, and/or concomitant comorbidities such as diabetes and hypertension) like endometrial cancer patients.

A great limitation of our study is represented by the absence of a translational sub-study, evaluating predictive biomarkers for bevacizumab response or a potentially different bevacizumab effect on four EC subtypes. Previous studies demonstrated inconsistent results between VEGF assays, molecular signatures, immunohistochemistry biomarkers and clinical outcomes and, at present, no predictive efficacy biomarker has been validated for bevacizumab in any cancer type [17].

Furthermore, our trial did not evaluate patients reported outcomes (PROs) which would be useful to understand impact of toxicity and prolonged intravenous treatment on patient quality of life and wellbeing. This outcome measure is especially important for elderly women who need a caregiver to manage and support access to treatment in an outpatient setting. Initially, the trial included the evaluation of quality of life. Unfortunately, we achieved a very low responded rate and data could not be analyzed. For future trials, special support, in terms of dedicated research nurses for instance, should be provided to elderly patients.

There is an inadequate number of chemotherapies and biological agents in EC and unfortunately, with the recent exception of FDA label for pembrolizumab in MSI patients, second-line chemotherapy options for recurrent disease are limited in number and efficacy [18]. The optimization of first-line therapy in advanced disease is a logical and evaluable strategy and several signals suggest that the blockade of neovascularization may play a role in EC treatment. In the era of personalized medicine, a careful evaluation of the molecular profile of the disease before treatment initiation would support successful trials and identify the appropriate treatment options.

In conclusion, MITO END-2 trial is the first randomized trial reporting on potential effectiveness of CP-B treatment in advanced/recurrent EC with respect to chemotherapy alone and this combination in our opinion would merit further exploration in a larger population with a deeper molecular characterization. The intrinsic limitations of a randomized phase 2 trial with several methodological and statistical limitations and the small number of enrolled patients preclude to drawn definitive conclusion on the efficacy of bevacizumab in advancer endometrial cancer.

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## Declaration of competing interest

DL reports personal fees from Tesaro, Astra Zeneca, Merck, Clovis, Merrimack; grants from Tesaro, Merck, Clovis. NC reports personal fees from Roche, Pharmamar, Astra Zeneca, Clovis Oncology, Pfizer, MSD. AP worked in AstraZeneca Medical Affair Department until december 2018. GS reports grant from Roche. All remaining authors have declared no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.10.013.

## References

[1] J.I. Sorosky, Endometrial cancer, Obstet. Gynecol. 120 (2 Pt 1) (2012 Aug) 383–397, https://doi.org/10.1097/AOG.0b013e3182605bf1.
[2] D.F.V. Miller, G. Fleming, R. Mannel, D. Cohn, T. Matsumoto, K. Tewari, et al., Randomized phase III non inferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a gynecologic oncology group study. [SGO abstract LBA-1], Gynecol. Oncol. 125 (3) (2012) 771–773.
[3] Y. Yokoyama, D.S. Charnock-Jones, D. Licence, A. Yanaihara, J.M. Hastings, C.M. Holland, et al., Expression of vascular endothelial growth factor (VEGF)-D and its receptor, VEGF receptor 3, as a prognostic factor in endometrial carcinoma, Clin Cancer Res Apr 9 (4) (2003) 1361–1369.
[4] F. Sanseverino, R. Santopietro, M. Torricelli, G. D'Andrilli, G. Russo, G. Cevenini, et al., pRb2/p130 and VEGF expression in endometrial carcinoma in relation to angiogenesis and histopathologic tumor grade, Cancer Biol Ther Jan 5 (1) (2006) 84–88.
[5] A.A. Kamat, W.M. Merritt, D. Coffey, Y.G. Lin, P.R. Patel, R. Broaddus, et al., Clinical and biological significance of vascular endothelial growth factor in endometrial cancer, Clin. Cancer Res. 13 (24) (2007) 7487–7495. Dec 15.
[6] D.S. McMeekin, M.W. Sill, D. Benbrook, K.M. Darcy, D.J. Stearns-Kurosawa, L. Eaton, , et al.Gynecologic Oncology Group, A phase II trial of thalidomide in patients with refractory endometrial cancer and correlation with angiogenesis biomarkers: a Gynecologic Oncology Group study, Gynecol Oncol May 105 (2) (2007) 508–516.
[7] M. Hirai, A. Nakagawara, T. Oosaki, Y. Hayashi, M. Hirono, T. Yoshihara, Expression of vascular endothelial growth factors (VEGF-A/VEGF-1 and VEGF-C/VEGF-2) in postmenopausal uterine endometrial carcinoma, Gynecol Oncol Feb 80 (2) (2001) 181–188.
[8] S. Davies, D. Dai, G. Pickett, K.W. Thiel, V.P. Korovkina, K.K. Leslie, Effects of bevacizumab in mouse model of endometrial cancer: defining the molecular basis for resistance, Oncol Rep Mar 25 (3) (2011) 855–862.

[9] L. Cerezo, H. Cárdenes, H. Michael, Molecular alterations in the pathogenesis of endometrial adenocarcinoma. Therapeutic implications, Clin Transl Oncol Apr 8 (4) (2006) 231–241.
[10] C. Aghajanian, M.W. Sill, K.M. Darcy, B. Greer, D.S. McMeekin, P.G. Rose, et al., Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study, J Clin Oncol Jun 1 29 (16) (2011) 2259–2265.
[11] F. Simpkins, R. Drake, P.F. Escobar, B. Nutter, N. Rasool, P.G. Rose, A phase II trial of paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma (EMCA), Gynecol Oncol Feb 136 (2) (2015) 240–245.
[12] N. Breslow, Statistical methods for censored survival data, Environ. Health Perspect. 32 (1979 Oct) 181–192. PubMed PMID: 396152; PubMed Central PMCID: PMC1637936.
[13] Lorusso D, Ferrandina G, Colombo N, S. Pignata, A. Pietragalla, C. Sonetto, et al., Randomized phase II trial of carboplatin-paclitaxel (CP) compared to carboplatin-paclitaxel-bevacizumab (CP-B) in advanced (stage III-IV) or recurrent endometrial cancer: the MITO END-2 trial. J. Clin. Oncol. 33, 2015 (suppl; abstr 5502).
[14] C. Aghajanian, V. Filiaci, D.S. Dizon, J.W. Carlson, M.A. Powell, A.A. Secord, et al., A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer, Gynecol. Oncol. 150 (2) (2018 Aug) 274–281, https://doi.org/10.1016/j.ygyno.2018.05.018. Epub 2018 May 24.
[15] C. Kandoth, N. Schultz, A.D. Cherniack, R. Akbani, Y. Liu, H. Shen, et al., Cancer genome Atlas research network, integrated genomic characterization of endometrial carcinoma, Nature 497 (7447) (2013) 67–73, https://doi.org/10.1038/nature12113. May 2.
[16] A.R. Mallen, V.L. Filiaci, D.A. Levine, K. Thield, C.A. Aghajaniane, X. Mengf, et al., Evidence for synthetic lethality between bevacizumab and chemotherapy in advanced, p53 null endometrial cancers, Oral presentation at: Society of Gynecologic Oncology Annual Meeting on Women's Cancer, New Orleans, LA (2018). March 24-27.
[17] D. Lambrechts, H.J. Lenz, S. de Haas, P. Carmeliet, S.J. Scherer, Markers of response for the antiangiogenic agent bevacizumab, J. Clin. Oncol. 31 (9) (2013) 1219–1230. Mar 20.
[18] FDA, KEYTRUDA® (pembrolizumab) highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125514s034lbl.pdf.