Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): A randomised, open-label, phase 2 trial

A RANDOMISED MULTICENTER PHASE II TRIAL TESTING THE ADDITION OF PAZOPANIB TO WEEKLY PACLITAXEL IN PLATINUM RESISTANT OR REFRACTORY ADVANCED OVARIAN CANCER. THE MITO 11 TRIAL

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Abstract

Background:

Inhibition of angiogenesis is a valuable treatment strategy for ovarian cancer patients. Pazopanib is an antiangiogenic drug active in ovarian cancer. We performed a randomised phase 2 trial to explore whether the combination of weekly paclitaxel and pazopanib improved progression-free survival (PFS) as compared with weekly paclitaxel alone.

Methods:

Patients with platinum/resistant ovarian cancer pretreated with a maximum of 2 previous lines of chemotherapy, ECOG PS 0-1 and no residual peripheral neurotoxicity were eligible for the MITO 11 trial. These patients were randomised 1:1 to receive weekly paclitaxel 80mg/m^2 with or without pazopanib 800 mg daily. Randomisation was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy) by a computer-driven minimization procedure. The centre, the number of previous chemotherapy lines (1 vs 2), and the platinum free interval status (refractory vs resistant) were considered as stratification variables .The primary endpoint was progression-free survival. All the efficacy analyses have been performed on an intention-to-treat basis. The MITO 11 trial is registered with the clinicaltrials.gov identifier NCT01644825. Data reported represent the final analysis and the trial is completed.

Results:

From 15 December 2010 to 8 February 2013, 74 patients were enrolled. One, in the control arm, withdrew the consent and was excluded. The PFS was significantly longer in the experimental arm with weekly paclitaxel plus pazopanib (median 6·35 months, 95% CI: 5·36-11·02) than in the control arm, with weekly paclitaxel alone, (median 3·49 months, 95% CI: 2·01-5·66); hazard ratio of progression was 0·42 (95% CI: 0·25–0·69, p=0·0002). Neither unexpected toxicities nor toxic deaths were observed. However, adverse events were reported more frequently in the combination arm than in the control arm. The most common

grade 3-4 adverse events observed in the experimental arm include neutropenia (11 [30%] vs1 [3%]), fatigue (4 [11%] vs 2 [5%]), hypertension (3 [8%] vs 0) and ASTL/ALT increase (3 [8%] vs 0), whilst anemia was more frequent in the control arm (5 [14%] vs 2 [5%]). One patient, on the combination arm, experienced ileal perforation.

Interpretation:

A further phase 3 study of the combination of weekly paclitaxel plus pazopanib is worth being conducted in patients with platinum refractory/resistant advanced ovarian cancer, based on the positive findings of the present study.

Funding: The Sponsor of MITO 11 was the National Cancer Institute of Napoli, Italy. GSK provided pazopanib and partial funding.

INTRODUCTION

Worldwide, ovarian cancer is the seventh more frequent tumour and the eighth highest cause of cancer-death among women, whilst in the most developed country ovarian cancer represents the fifth cause of cancer death.[1] For patients with advanced stage ovarian cancer the prognosis is dismal and platinum-based combination therapy is the mainstay of treatment. Albeit the high rate of initial responses to platinum-based combinations, almost all the patients invariantly recur or progress. The prognosis of patients who progress or recur within 6 months (i.e. platinum-resistant) from the last platinum administration is particularly poor and few drugs demonstrated activity in this setting, usually as single agents. Among these, weekly paclitaxel produced responses with a good tolerability profile [2, 3] and represents one of the most used treatment options for these patients. One of the proposed mechanisms of action for weekly paclitaxel is the inhibition of angiogenesis.[4, 5] Pazopanib, is a multitargeted tyrosine-kinase inhibitor of the Vascular-Endothelial Growth Factor (VEGF) receptors family, the Platelet-Derived Growth Factor receptors A and B, and the Fibroblast-Growth Factor Receptors 1 to 3. Recently, pazopanib demonstrated activity in ovarian cancer patients who had initially responded to a platinum-based chemotherapy and who were at high risk of recurrence (as witnessed by raising CA125), with overall response rates, according to modified GCIG criteria, of 18% and 21% among the patients with measurable and non-measurable disease at baseline respectively.[6] More recently a double-blind, phase 3 trial randomised 940 patients with FIGO stage II-IV ovarian cancer having not progressed after first line chemotherapy to receive pazopanib or placebo as a maintenance; a significant advantage was found in term of progression-free survival (PFS) for the patients receiving pazopanib as compared with those receiving placebo (HR = 0·77, 95% CI: 0·64-0·91; p = 0·0021; medians 17·9 vs 12·3 months, respectively), although at the first interim analysis this advantage did not translate into a significant improvement of overall survival (OS). [7]

The MITO 11 trial is an investigator-initiated, non-profit, phase 2 trial aimed at exploring whether the combination of pazopanib to weekly paclitaxel, in platinum resistant/refractory

ovarian cancer patients, is associated with a PFS benefit worth to warrant further evaluations in phase 3.

PATIENTS AND METHODS

Study design

MITO 11 is a multicentre, randomised, open-label phase 2 trial comparing two treatment arms: weekly paclitaxel + pazopanib versus weekly paclitaxel alone in platinum resistant/refractory ovarian cancer.

The progression-free survival (PFS) was the primary endpoint of the trial. The study was designed with so-called relaxed statistical criteria as described by Korn[8] and Rubinstein.[9] Such 'screening' design was chosen to verify whether the experimental treatment was promising enough to warrant a phase III trial for efficacy. Relaxed criteria concern higher type I error, and allow an adequate power, notwithstanding the small study size, thus, preventing an excessive number of patients be acquainted with possibly ineffective treatments. MITO 11 trial was designed to have 80% power of detecting a 0·65 hazard ratio (HR) of progression corresponding to a median PFS prolongation from 3 to 4·6 months with the experimental treatment, with one-tailed alpha=0·2 (EAST 5 software, Cytel Software, Cambridge, MA, U.S.A.). With these parameters, 61 events were necessary for the final analysis and a sample size of 72 patients was planned. Secondary endpoints included overall survival (OS), toxicity and objective response rate (ORR). Randomisation was performed centrally (Clinical Trials Unit, National Cancer Institute, Napoli, Italy) by a computer-driven minimization procedure. The centre, the number of previous chemotherapy lines (1 vs 2), and the platinum free interval status (refractory vs resistant) were considered as stratification variables. Patients could be enrolled either through the web (http:\\www.usc-intnapoli.net) or by phone; in the latter case, personnel at the coordinating centre used the same computer-driven minimization procedure available through the web. Data were collected through the above reported website with dedicated electronic CRF. There was no blinding procedure for patients and physicians.

This study is registered with ClinicalTrials.gov number NCT01644825 and in EudraCT with the number 2009-016151-21. The protocol is publicly available at https://usc-intnapoli.net/v2-uosc-servizi/studidocs/MITO-11-IT/pubdocs/PROTOCOL%20-%20%20MITO%2011%20%20Emed.%203%20version%202.pdf

Study population

Women aged 18 to 75, with cytological or histological diagnosis of epithelial ovarian, fallopian tube or peritoneal cancer, stage IC-IV according to FIGO staging system, disease evaluable by RECIST 1.1 or CA125 GCIG criteria, an ECOG performance status ≤2, and a life expectancy ≥3 months, whose disease progressed during first line chemotherapy or relapsed within 6 months after the last platinum treatment were eligible. Patients, whose disease progressed or relapsed within 6 months after the last platinum treatment and who received an interval non-platinum regimen were also eligible to the trial. Patients were not eligible if they had previously received weekly paclitaxel or more than 2 chemotherapy lines. Other exclusion criteria were a history of clinically relevant heart disease (heart failure, atrioventricular block of any degree, serious arrhythmia or history of any one or more of the following cardiovascular conditions within the past 6 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina, symptomatic peripheral vascular disease, coronary artery by-pass graft surgery, class II, III or IV congestive heart failure as defined by the New York Heart Association), previous or concomitant malignant neoplasia (except non-melanoma skin cancer or *in situ* carcinoma of the uterine cervix), or with residual peripheral neurotoxicity from previous chemotherapy. Adequate bone marrow (hemoglobin <9 g/dL, neutrophils <1500/mm^3, platelets <100000/mm^3), kidney (creatinine <1.5 times the upper normal limit (UNL); calculated creatinine clearance ≥50 mL/min; urine protein to creatinine ratio <1; in the case of urine protein to creatinine ratio ≥1 the patient had to have a 24-hour urine protein value <1 g to be eligible), and liver function (SGOT or SGPT≤2.5 UNL, alkaline phosphatase ≤2.5 ULN, total bilirubin ≤1.5 times the UNL) were required. Additionally,

patients were also excluded if they had prolonged corrected QT interval (QTc) >480 ms, history of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months, major surgery or trauma within 30 days and hypertension uncontrolled with adequate therapy (i.e. systolic blood pressure ≥140 mmHg, or diastolic ≥90 mmHg). The study was approved by Ethics Committees at each participating Institution, and all the patients signed the informed consent before any study related procedure.

Study treatment

Patients were randomly assigned, with a 1:1 ratio, to either weekly paclitaxel plus pazopanib or weekly paclitaxel. Patients in the control arm received paclitaxel 80 mg/m^2 on days 1, 8 and 15 in a 28 day cycle. Patients in the experimental arm received paclitaxel 80 mg/m^2, on days days 1, 8 and 15 in a 28 day cycle, plus pazopanib 800 mg given daily continuously, fasting at least from 2 hours before and up to 1 hour after the administration. In both the arms, treatment was continued until progressive disease, patient's withdrawal or prolonged/unacceptable toxicity. In both the arms paclitaxel, diluted in 250 mL of 0·9% saline, was infused intravenously over 1 hour. Prophylactic premedication was given according to local procedures to all the patients before paclitaxel administration. Pazopanib had to be discontinued at the first occurrence of ALT/AST elevation >3 x ULN with concomitant elevation in bilirubin (defined as total bilirubin >2 x ULN; with direct bilirubin >35%) or with hypersensitivity symptoms (e.g., fever, rash) or at the recurrence of ALT >8 x ULN without bilirubin elevation (defined as total bilirubin <2 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash).

In both arms, the doses of paclitaxel had to be reduced by 25% in case of neutrophils <500/mm^3 for a period of more than 7 days or platelets <50000/mm^3, and in presence of neuropathy grade 1. In case of neuropathy grade 2 the treatment had to be delayed by two weeks and suspended in case the neuropathy did not recover during that period. Pazopanib

dose had to be reduced stepwise of 200 mg with re-escalation to the previous dose permitted after, at least, 14 days of observation with no new adverse events at the new dose and whether re-escalation was considered safe by the investigator.

Patient evaluation

Baseline staging included clinical examination, chest X-ray, abdomino-pelvic CT scan (or nuclear magnetic resonance), serum CA125. The same radiologic tests performed at baseline were repeated every 8 weeks (2 cycles) of treatment and response evaluation was done in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[10] According to these criteria, disease progression was defined at the first occurrence of an increase >20% in the sum of largest diameters of known lesions or the appearance of a new lesion. Physical examination and blood tests (haematology/biochemistry) were performed weekly.

Statistical analysis

All the efficacy analyses were done on an intention-to-treat basis. PFS was defined as the time between randomization and progression or death (whichever occurred first) or last PFS assessment for patients alive without progression. All the patients who discontinued the treatment due to symptomatic deterioration in absence of radiologic progression were considered as progressive (events) at the date of symptomatic deterioration. Patients lost to follow-up in absence of progression were censored at the date of last follow-up visit in which information was available.

CA 125 serum levels at least twice the upper normal limit, for patients with normal pre-treatment levels or with CA125 levels normalised by treatment, or CA 125 levels at least twice the nadir, for patients whose levels never normalised, were considered as progression also in absence of radiologic or clinical signs of progression.

OS was defined as the time between randomisation and death or date of last follow-up for alive patients. Median follow-up (mFU) was calculated according to the reverse Kaplan-Meier technique. [11] PFS and OS curves were estimated by Kaplan-Meier product limit method [12] and compared by log-rank test.

ORR was defined as the proportion of complete plus partial responses among patients eligible according RECIST1.1 criteria.[10] Patients who died or stopped treatment because of toxicity or refusal before restaging were conservatively defined as non-reponders. Independent review of radiologic tests was not performed and no formal rules regarding blinding of local radiologists were implemented into the protocol. All the radiology reports have been audited by coordinating centre personnel to verify consistency with the data provided by the local investigators. The statistical significance of the difference in ORR between arms was assessed by chi-square test.

Additionally, a non-planned analysis for response according to CA125 criteria[13] was performed. Eligible patients were those with a pre-treatment CA125 level at least twice as the upper limit of normal range of values.

All patients who received at least one dose of treatment were eligible for toxicity analysis. The worst grade of toxicity experienced was computed for each patient. For each toxicity, all grades were compared by the exact Kruskal Wallis rank test. Statistical analyses were performed using S-Plus version 6.1 (Insightful Corp., Seattle, WA, U.S.A.). Exact tests were performed using Cytel Studio 10 (Cytel Software, Cambridge, MA, U.S.A.).

Role of the funding source

The MITO 11 trial was an academic non-profit trial. The Sponsor of the trial is the National Cancer Institute of Naples and is the solely responsible for trial performing, data collection and analysis. GSK, only provided the trial with the experimental drug, free of charge, and with

partial funding. GSK had no role in data collection, analysis, interpretation of the results, writing of the report and in the decision to publish the manuscript. S.P., G.D., M.C. P., M.D.M. , C.G. and F.P. had access to the raw data. The corresponding author had the final responsibility to submit for publication.

RESULTS

Patient characteristics

Between 15 December 2010 and 8 February 2013, 74 patients were randomised (Figure 1). One patient was excluded from analysis because she withdrew consent immediately after randomisation. Seven patients were found ineligible after randomisation but were included in the intention-to-treat analysis. Among these, one, in the control arm, was platinum-sensitive and 6 patients, 3 in each arm, had received three previous lines of treatment. In particular, all these patients received two platinum containing regimens and one non-platinum containing regimen for resistant disease. Baseline characteristics of the patients (36 assigned to weekly paclitaxel and 37 to the combination arm) were balanced between the arms (Table 1). The patients who developed platinum resistant/refractory disease during or after only one line of chemotherapy were considered as primary platinum resistant.

Treatment compliance

Seventy-three patients received at least one dose of treatment. The median number of paclitaxel cycles received was 4 (IQR 2-6) and 6 (IQR 2-8) in the control and experimental arm, respectively. Median relative dose intensity (RDI) for paclitaxel was 98% (IQR 85%-100%) and 71% (IQR 62%-82%) in the control and experimental arm, respectively. Median RDI for Pazopanib was 93% (IQR 81%-100%). The paclitaxel dose was reduced in 6 (17%) and 20 (54%) patients in the control and experimental arm, respectively. Pazopanib was reduced in 20 patients (54%). Overall, 4 (11%) and 11 (30%) patients discontinued paclitaxel in the control and experimental arm, respectively; pazopanib was discontinued by 10 patients (27%). In the experimental arm, 6 (16%) patients discontinued both the drugs whilst 9 (24%) patients discontinued either pazopanib or paclitaxel. Most of the dose reductions and discontinuation were due to adverse events (Table 2).

Time-to-event outcomes

The primary analysis was performed in May 2014 with 69 PFS events and a mFU of 16·1 months (IQR:12·5-20·8). Intervals between subsequent tumour assessments were similar between the two study arms (Appendix figure 1A). In particular, 36 PFS events were recorded with a mFU of 16·1 months (IQR: 12·6-19·3) in the control arm and 33 PFS events were recorded, with a mFU of 16·3 months (IQR: 13·7-22·1) in the experimental arm. Estimated median PFS was 3·49 months (95% CI: 2·01-5·66) in the control arm and 6·35 (95% CI: 5·36-11·02) in the experimental arm (HR 0·42, 95% CI: 0·25–0·69, one-tailed log-rank test p=0·0002). PFS curves are shown in figure 2.

For the OS analysis, 40 events (deaths) were recorded, 22 in the control arm and 18 in the experimental arm. Median OS was 13·7 months (95% CI: 9·08 – N/A) in the control arm compared with 19·1 months (95% CI: 11·51 – N/A) in the experimental arm (HR 0·60, 95% CI: 0·32 – 1·13, one-tailed log-rank test p=0·056). OS curves are shown in figure 3.

Objective response rate (ORR)

According to RECIST 1.1 criteria, 72 (98·6%) patients were eligible for response analysis, 36 (100%) in the control arm and 36 (97·3%) in the experimental arm. The ORR was significantly different between the two arms (p=0·008) with 25% (95% CI: 12%-42%) and 56% (95% CI: 38%-72%) of the patients experiencing a response in the control and experimental arm, respectively. One patient (3%) in the control arm and three patients (8%) in the experimental arm experienced a complete response. Among the 52 patients with target lesions the ORR was 21% (95% CI: 9%-41%) in the control arm and 50% (95% CI: 33%-67%) in the experimental arm.

CA125 response analysis

Sixty-one patients, with at least one pre-treatment sample exhibiting CA125 values at least twice the upper normal limit, were eligible. The patients were equally distributed among the

two arms; 30 (49%) in the experimental arm and 31 (51%) in the control arm. Overall, the response rate according CA125 criteria was 77% (95% CI: 59%-88%) in the experimental arm and 35% (95% CI: 21%-53%) in the control arm. The difference in the response rate between the two arms was statistically significant (p= 0·0012). All patients defined as responders in the RECIST analysis were confirmed as responders in the CA125 response analysis.

Toxicity

The worst toxicity, per treatment arm, is summarized in table 3. Neither unexpected toxicities nor toxic deaths were observed. Overall, at least one grade 3 or 4 episode was reported in 11 (30·6%) patients in the control arm and 22 (59·5%) in the experimental one. In the control arm, 6 out of 36 patients required a dose reduction; in the experimental arm, 20 out of 37 patients required at least one dose reduction for paclitaxel and 20 out of 37 for pazopanib. Among these, 3 patients required a second dose reduction for paclitaxel and 9 for pazopanib. Toxicity was the reason for definitive treatment discontinuation in 4 (11·1%) and 3 (8·1%) patients, in the control and experimental arms, respectively (Table 2). However, in the combination arm, further 9 patients suspended either paclitaxel (n=5) or pazopanib (n=4). As expected, the combination of weekly paclitaxel plus pazopanib produced significantly more leukopenia, neutropenia, fatigue, epistaxis, hypertension, diarrhoea, mucositis and sensory neuropathy as compared with paclitaxel alone. Moreover, increase in AST/ALT levels and amylase was also seen more frequently in the experimental than in the control arm. Interestingly, adding pazopanib to paclitaxel did not increase the incidence of thromboembolic events. One patient, in the combination arm, had ileal perforation.

DISCUSSION

The MITO 11 trial met its primary endpoint showing a statistically significant PFS improvement by the addition of pazopanib to weekly paclitaxel as compared with weekly paclitaxel alone.

In this trial, the combination resulted in an absolute PFS gain of approximately 3 months over the single agent. This absolute difference was greater than what planned during the trial design. To exclude that such advantage, in a open-label trial, could be due to a potential bias in the re-evaluation timing in favour of the combination, we evaluated the intervals between tumour assessments and found no appreciable differences capable to affect the PFS advantage achieved with the combined treatment (see Appendix figure 1A). Another issue to consider is a possible event rate in the control arm by chance worse than expected; however, the mPFS in the control arm of 3·5 months is in line to what was recently observed with the same chemotherapy in other trials with platinum resistant/refractory patients.[2, 14, 15] Moreover, the advantage achieved by combining the pazopanib to weekly paclitaxel compares well with the gain in PFS resulting by the addition of bevacizumab, to chemotherapy in the same setting.[14]

Additionally, the combination arm was also associated with an advantage in term of OS and ORR. Regarding the observed OS advantage, we are not able to dissect the role of therapies, including anti-VEGF therapeutics, the patients eventually received after the progression on MITO11, since we did not collect the data on subsequent therapies. However, considering the dismal prognosis of platinum-resistant/refractory advanced ovarian cancer patients and the narrow possibility to receive additional therapies in this setting of disease, it is difficult to imagine a relevant impact of subsequent therapies on the survival of these patients. This is the main reason why we did not collect details of further therapies after disease progression.

As expected, the combination was also associated with an increased frequency of adverse events, although we did not observe any unexpected side effect nor any toxic death. In

particular, in light of previous knowledge and the profile of adverse events reported in the AGO-OVAR 16 trial[7], the increase we found in hypertension, fatigue, diarrhoea, liver toxicity and bleeding can be strictly attributed to pazopanib. On the contrary, the increased neutropenia, mucositis and neurotoxicity might be mostly due to the increased number of paclitaxel cycles received by the patients in the experimental arm, apart from a potential synergistic effect of the combination on the toxicity.

The balance between the positive effect of pazopanib in terms of efficacy and the worse toxicity profile deriving from its addition cannot be reliably assessed in a phase 2 trial and should be a crucial point of a further phase 3 trial. Hopefully, if the benefit in efficacy outcomes were confirmed, this might balance the toxic effects; the use of tools to elicit patients' view on quality of life and subjective perception of side-effects would be important. [16]

A strength of MITO11 is that the PFS advantage observed with the addition of pazopanib is similar with the gain in PFS observed adding bevacizumab, an anti-VEGF monoclonal antibody, to chemotherapy in the randomised phase III trial AURELIA.[14] In this trial, the patients treated with the combination of chemotherapy with bevacizumab experienced a mPFS of 6·7 months (95% CI: 5·7-7·9) against 3·4 months (95% CI: 2·2-3·7) for those treated with chemotherapy alone. Actually, only 115/361 (31·8%) patients in the AURELIA trial received weekly paclitaxel as chemotherapy backbone, alone or in combination with bevacizumab; and even among these patients bevacizumab improved PFS (HR 0·42, 95% CI not available) [17] with a non-significantly prolonged OS (HR 0·65, 95% CI: 0·42-1·02) [17]. Although with all the caveats due to the limitations of indirect comparisons, that in this case are even more important because we are comparing a phase 2 with a phase 3 trial and in the latter only a subgroup of patients received the same chemotherapy backbone, we believe that consistency of MITO11 and AURELIA results strongly support credibility of MITO11 results and push for further phase 3 testing of pazopanib.

However, we acknowledge that MITO11 has an important potential limitation (that however is common with the AURELIA trial) in the fact that the study population had not received an antiangiogenic therapy during the previous lines. The reason for this is that, at the time MITO11 was designed, anti-VEGF therapies were not part of the standard treatment for ovarian cancer in Italy. In fact, several trials recently showed a significant benefit deriving from the addition of bevacizumab to standard chemotherapy.[14, 19-22] Based on these trials, bevacizumab has been approved for the treatment in first line and in second line, for both platinum-sensitive and platinum-resistant ovarian cancer patients. Based on this, most of the future patients in second/third-line will have received antiangiogenics at the time of recurrence. Therefore, the results of MITO 11 should be confirmed in a population of patients previously treated with bevacizumab.

In summary, MITO 11 suggests that the combination of pazopanib with weekly-paclitaxel is feasible and active as treatment for platinum resistant/refractory recurrent ovarian cancer patients. In fact, the prolonged PFS and OS along with the increased proportion of responders warrants the evaluation of the combination in further phase 3 trials.

Declaration of interest

Dr Pignata and Dr Perrone declared research funding from GSK during the study conduct. All the other authors declare no conflicts of interest.

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Panel: **Research in context**

Evidence before this study

To find publications focusing on the treatment of platinum resistant/refractory ovarian cancer patients we searched National Library of Medicine - PubMed with terms including “ovarian cancer”, “platinum-resistant”, “platinum-refractory”, and limiting the results to clinical trials. By carefully assessing the resulting publications emerged that, single agent weekly paclitaxel could be considered as a valid treatment for platinum resistant/refractory ovarian cancer patients and thus a reliable control arm for this study at the time the MITO 11 trial was designed. In particular, the data on which the use of weekly paclitaxel has been consolidated in this setting include those deriving by various phase II [2, 23] and III trials [24], recently reviewed by Kaye et al.[25]

Recently, two large phase III trials have been published with the combination of chemotherapy (including weekly paclitaxel) and antiangiogenic drugs (bevacizumab and trebananib in platinum resistant/refractory ovarian cancer patients. [14, 26] Both the trial yielded positive results in terms of PFS; bevacizumab was also registered by the European Medicine Agency. Finally, the results of a randomised phase IIB trial of weekly paclitaxel with or without pazopanib have been presented at the 2014 IGCS meeting.[27] With 106 randomised patients, there was only a slight PFS prolongation with the combination (7.5 vs 6.2 months at median, HR 0.84, 95% CI: 0.57-1.22; p=0.20). To efficiently discuss the results of this study an extended paper has to be awaited.

Added value of this study

With the limitation of the phase II design, the MITO 11 results add another positive piece of evidence, also with a tyrosine-kinase inhibitor, to the above mentioned data on the activity of an antiangiogenic strategy as treatment for platinum resistant/refractory ovarian cancer patients.

Implications of all the available evidence

The consistency of the MITO 11 trial results with other, phase III, trials with antiangiogenic drugs in the setting of platinum-resistant/refractory ovarian cancer reinforces our results and confirm that the combination of weekly paclitaxel and paclitaxel is deemed for further exploitation in a larger randomised phase III trial.

Authors Contributions

Sandro Pignata, Ciro Gallo and Francesco Perrone designed the study. Sandro Pignata was the Principal Investigator

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Ciro Gallo, Gennaro Daniele and Francesco Perrone performed the analyses.

Gennaro Daniele, Sandro Pignata, Ciro Gallo and Francesco Perrone wrote the draft manuscript.

All the authors approved the final version.

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Legend of figures

Figure 1.

Study flow. *wP= weekly paclitaxel; wPP= weekly paclitaxel plus pazopanib*

Figure 2.

Progression-free survival (PFS) curves by treatment arm. *wP= weekly paclitaxel; wPP= weekly paclitaxel plus pazopanib*

Figure 3.

Overall survival (OS) curves by treatment arm. *wP= weekly paclitaxel; wPP= weekly paclitaxel plus pazopanib*

Table 1. Baseline characteristics of the patients

	Paclitaxel (n = 36)	Paclitaxel + pazopanib (n = 37)	Total (n = 73)
Median age (range)	58 (27-74)	56 (43-74)	
Platinum-free-interval			
Resistant	27 (76%)	28 (76%)	56 (76%)
Refractory	8 (22%)	9 (24%)	17 (23%)
Sensitive	1(3%)	0	1(1%)
Median (days)	110	108	
Intequartile range (days)	35·8-150·5	52-138	
Primary resistant/refractory patients	25 (69%)	23 (62%)	
Previous chemotherapy lines			
1	15 (41%)	17 (46%)	32 (43%)
2	18 (51%)	17(46%)	36(49%)
3	3 (8%)	3 (8%)	6 (8%)
Histology			
Serous	24 (67%)	26 (70%)	
Mucinous	0	1 (3%)	
Endometrioid	2 (6%)	4 (11%)	
Undifferentiated	1 (3%)	3 (8%)	
Clear cell	3 (8%)	1 (3%)	
Mixed (serous+endometrioid)	3 (8%)	0	
Transitional cells	2 (6%)	1 (3%)	
Mixed Mullerian	1 (3%)	1 (3%)	

Table 2 Dose reductions and interruptions.

Number of patients with:		Standard Arm (36)	Experimental arm (37)	
		Paclitaxel	Paclitaxel	Pazopanib
dose reductions		6 (17%)§	20 (54%)§§	20 (54%)§§
	once	6 (17%)	17 (46%)	11 (30%)
	twice	-	3 (8%)	9 (24%)
tretament interruption before PD		4 (11%)*	11 (30%)**	10 (27%)***
	only one drug	-	5 (14%)	4 (11%)
	both the drugs	-	6 (16%)****	
Skipped doses		5 (14%)	21 (57%)	-

§ **all the patients were dose-reduced due to neurotoxicity**
§§ **12 patients reduced both the drugs**
***1 patient interrupted the treatment due to AEs, 2 patients refused to continue treatment, 1 patient for medical decision.**
****5 patients due to AEs, 4 patients due to medical decision, 2 interrupted due to refusal.**
*****6 patients due to AEs, 3 patients due to medical decision, 1 patient due to refusal.**
****** all due to AEs; 3 patients interrupted both the drugs simultaneously.**

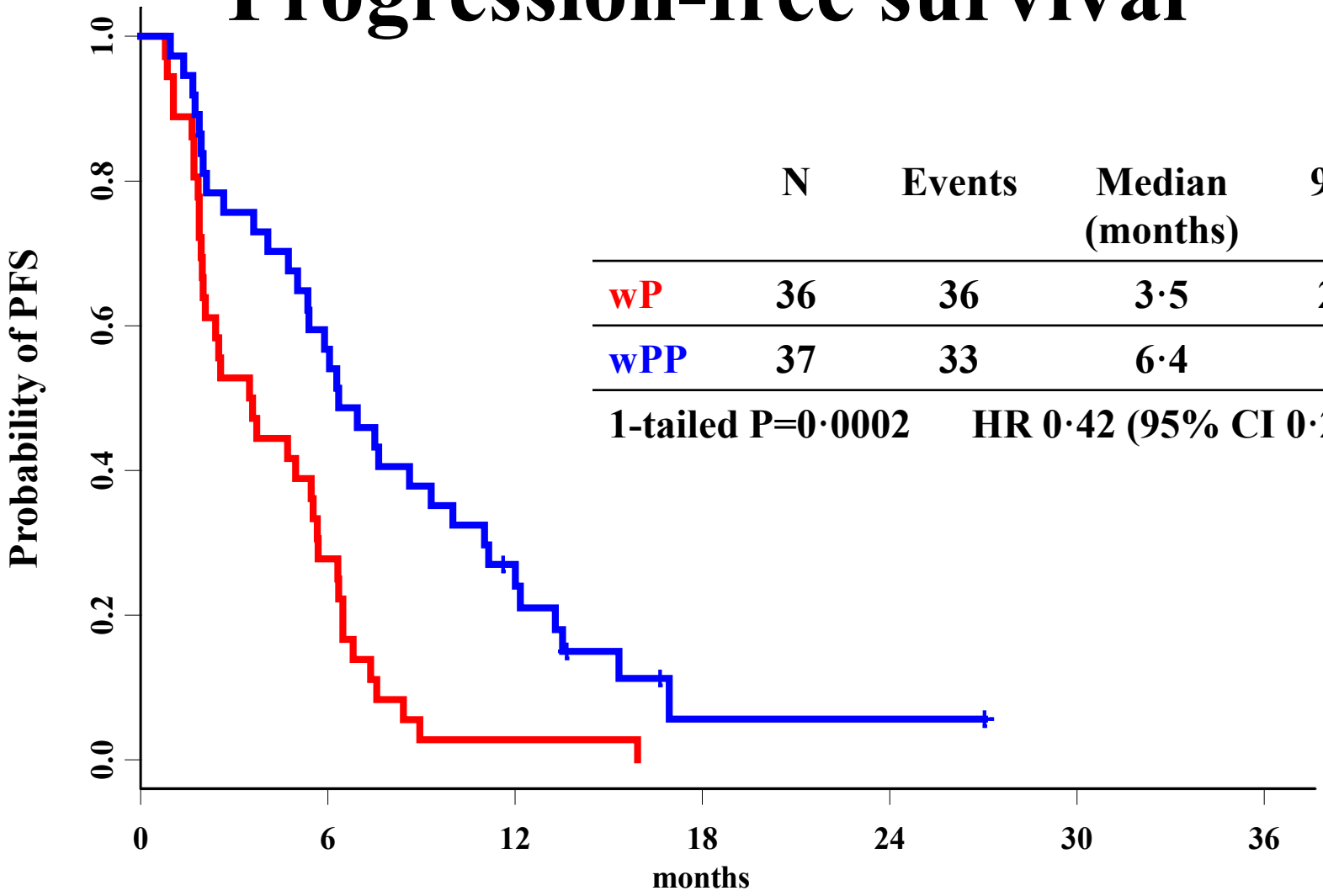
Table 3. Worst Toxicity according to treatment arm*

	Weekly Paclitaxel								Weekly Paclitaxel + Pazopanib								
	1		2		3		4		1		2		3		4		p**
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Anemia	9	25%	8	22%	5	14%	-	-	18	49%	5	14%	2	5%	-	-	0·58
Leucopenia	6	17%	3	8%	1	3%	-	-	7	19%	13	35%	4	11%	-	-	**0·0005**
Neutropenia	6	17%	4	11%	1	3%	-	-	2	5%	15	41%	8	22%	3	8%	**<0·0001**
Febrile Neutropenia	-	-	-	-	-	-	-	-	-	-	-	-	2	5%	-	-	0·5
Infection	1	3%	1	3%	1	3%	-	-	1	3%	4	11%	-	-	-	-	0·63
Thrombocytopenia	3	8%	-	-	-	-	-	-	3	8%	2	5%	-	-	-	-	0·54
Epistaxis	1	3%	-	-	-	-	-	-	4	11%	3	8%	-	-	-	-	**0·045**
Allergic reaction	-	-	1	3%	-	-	-	-	-	-	1	3%	-	-	-	-	1
Creatinine	-	-	1	3%	-	-	-	-	1	3%	-	-	-	-	-	-	0·75
Hypertension	-	-	-	-	-	-	-	-	6	16%	7	19%	3	8%	-	-	**<0·0001**
Heart rhythm	1	3%	-	-	-	-	-	-	2	5%	-	-	-	-	-	-	1
Heart general	-	-	1	3%	-	-	-	-	3	8%	1	3%	1	3%	-	-	0·18
Thromboembolic event	-	-	1	3%	1	3%	-	-	-	-	-	-	1	3%	-	-	0·74
Fatigue	11	31%	4	11%	2	6%	-	-	12	32%	11	30%	4	11%	-	-	**0·012**
Hair loss	2	6%	5	14%	-	-	-	-	1	3%	6	16%	-	-	-	-	1
Skin rash	1	3%	-	-	-	-	-	-	2	5%	1	3%	-	-	-	-	0·55
Other Skin	-	-	-	-	-	-	-	-	2	5%	-	-	-	-	-	-	0·49
Lymphedema	-	-	1	3%	-	-	-	-	1	3%	-	-	-	-	-	-	0·75
Weight loss	1	3%	-	-	-	-	-	-	2	5%	-	-	-	-	-	-	1
Anorexia	4	11%	1	3%	-	-	-	-	7	19%	2	5%	-	-	-	-	0·34
Constipation	8	22%	3	8%	1	3%	-	-	7	19%	2	5%	1	3%	1	3%	0·81
Diarrhoea	6	17%	1	3%	-	-	-	-	8	22%	11	30%	2	5%	-	-	**0.0003**
Mucositis	3	8%	-	-	-	-	-	-	12	32%	4	11%	-	-	-	-	**0.0007**
Ileal perforation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	3%	1
Nausea	8	22%	5	14%	-	-	-	-	8	22%	6	16%	-	-	-	-	0·89
Vomiting	4	11%	1	3%	1	3%	-	-	8	22%	2	5%	-	-	1	3%	0·23
ALP	3	8%	-	-	-	-	-	-	3	8%	1	3%	1	3%	-	-	0·48
AST/ALT	5	14%	-	-	-	-	-	-	8	22%	3	8%	2	5%	1	3%	**0·011**
Bilirubin	1	3%	-	-	-	-	-	-	5	14%	1	3%	-	-	-	-	**0·099**
Gamma-GT	-	-	2	6%	-	-	-	-	2	5%	1	3%	1	3%	-	-	0·62
Lipasi	1	3%	-	-	-	-	-	-	-	-	-	-	1	3%	-	-	1
Amylase	-	-	-	-	-	-	-	-	4	11%	-	-	1	3%	-	-	**0·05**
Hyperglycemia	2	6%	2	6%	-	-	-	-	2	5%	1	3%	-	-	-	-	0·87
Hypeuricemia	2	6%	-	-	-	-	-	-	1	3%	-	-	-	-	-	-	0·61
Pain	4	11%	2	6%	-	-	-	-	5	14%	5	14%	-	-	-	-	0·31
Bone pain	3	8%	-	-		-	-	-	1	3%	1	3%	-	-	-	-	0·87
Sensory neuropathy (incl parestehsie)	14	39%	2	6%	-	-	-	-	16	43%	9	24%	-	-	-	-	**0·02**
Hyperthyroidism	-	-	-	-	-	-	-	-	-	-	1	3%	-	-	-	-	1
Hypothyroidism	-	-	-	-	-	-	-	-	2	5%	-	-	-	-	-	-	0·49
Neurology other	-	-	2	6%	-	-	-	-	6	16%	3	8%	-	-	-	-	**0·05**

All the toxic events recorded during thestudy are summarised in this table.any grade comparison (exact Kruskal-Wallis test); NCI-CTC:National Cancer Institute Common Toxicity Criteria version 4.03*

Figure 2

Progression-free survival



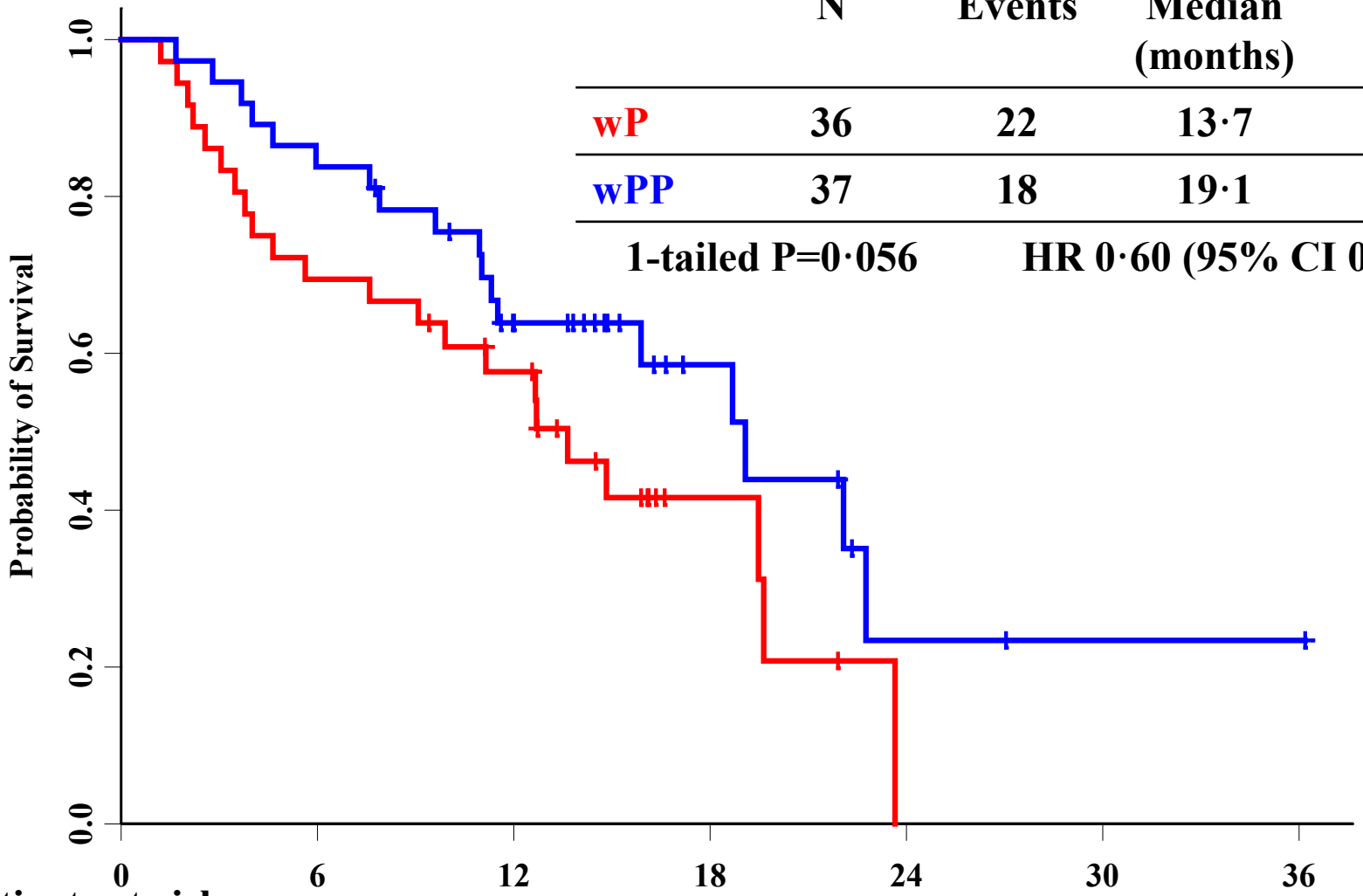
	N	Events	Median (months)	95% CI
wP	36	36	3·5	2·0-5·7
wPP	37	33	6·4	5·4-11

1-tailed P=0·0002 HR 0·42 (95% CI 0·25-0·69)

Patients at risk

wPac	36	11	2	0	0
wPP	37	22	10	2	2

Overall survival



	N	Events	Median (months)	95% CI
wP	36	22	13·7	9·1-NA
wPP	37	18	19·1	11·5-NA

1-tailed P=0·056 HR 0·60 (95% CI 0·32-1·13)

Patients at risk

wP	36	26	19	5	0	0	0
WPP	37	32	21	9	3	2	1

Section/topic	Item number	Checklist item	Reported on page number
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts[21,31])	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	7-8
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	9-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12-15
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% CI)	12-15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-15
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	11,14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[28])	14,15
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-18
Other information			
Registration	23	Registration number and name of trial registry	7
Protocol	24	Where the full trial protocol can be accessed, if available	7
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration[13] for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials,[11] non-inferiority and equivalence trials,[12] non-pharmacological treatments,[32] herbal interventions,[33] and pragmatic trials.[34] Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see http://www.consort-statement.org.

Table: **CONSORT 2010 checklist of information to include when reporting a randomised trial***

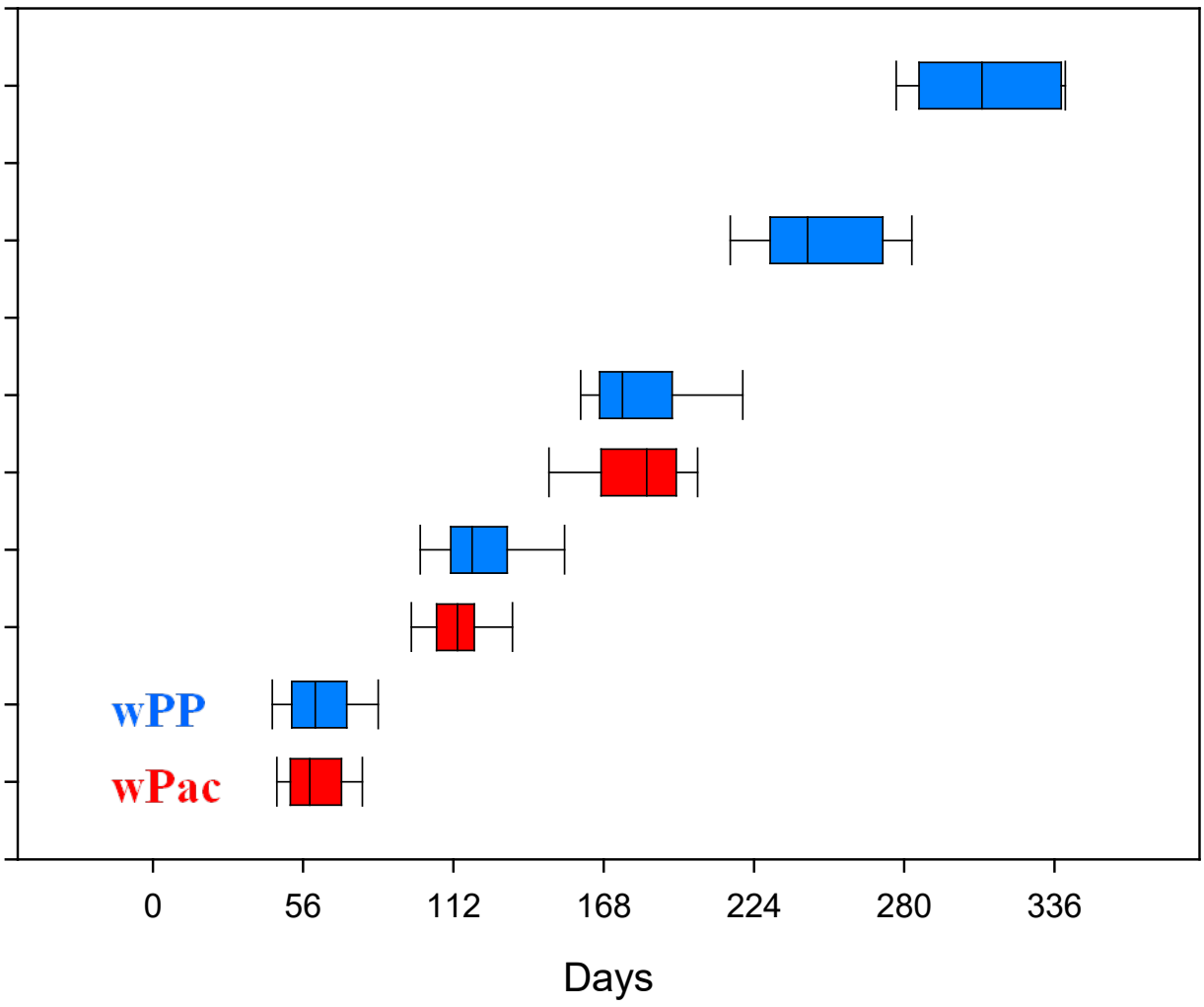
Web appendix

Summary

Figure 1A. 1
List of the Centres participating to the MITO 11 trial with the number of patients randomised and the PI. 2
List of participating Institutions (town), physicians, research nurses and data managers..... 3

Figure 1A.

Distribution of the re-assessment timings between the two study arms. *wP= weekly paclitaxel; wPP= weekly paclitaxel plus pazopanib*



List of the Centres participating to the MITO 11 trial with the number of patients randomised and the PI.

Centre (Town)	# patients enrolled	PI
Dipartimento di Oncologia Uroginecologica, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G.Pascale" IRCCS - Italia (Napoli);	30	Sandro Pignata
Unità di Ginecologia Oncologica, Fondazione IRCCS Istituto Nazionale Tumori – Milan (Milano);	15	Domenica Lorusso
Dipartimento per la Tutela della Salute della Donna della Vita Nascente del Bambino e dell' Adolescente, Università Cattolica del Sacro Cuore (Roma);	15	Giovanni Scambia
Unità di Oncologia Medica, AORN Garibaldi - Nesima (Catania);	5	Roberto Bordonaro
U.O di Oncologia Medica, Presidio Ospedaliero di Faenza (Faenza);	2	Stefano Tamberi
Oncologia Medica & Breast Unit, Ospedale Antonio Perrino (Brindisi) e Istituto Europeo di Oncologia (IRCCS) (Milano);	2	Saverio Cinieri
Oncologia Medica, Ospedale S. Maria della Misericordia, Perugia	1	Anna Maria Mosconi
U.O.C. Oncoematologia, Dipartimento di Medicina Sperimentale e Clinica "F. Magrassi", Seconda Università degli Studi di Napoli (Napoli);	1	Michele Orditura
Dipartimento di Oncologia Medica, Ospedale Bellaria-Maggiore Hospital, Azienda USL - IRCCS Istituto delle Scienze Neurologiche (Bologna);	1	Alba A. Brandes
U.O. Oncologia, Ospedale Infermi, (Rimini);	1	Valentina Arcangeli
Ginecologia Oncologica, Policlinico Umberto I, Università La Sapienza (Roma);	1	Pierluigi Benedetti Panici

List of participating Institutions (town), physicians, research nurses and data managers.

1. Dipartimento di Oncologia Uroginecologica, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G.Pascale" IRCCS - Italia (Napoli): Sandro Pignata, Carmela Pisano, Stefano Greggi, Marilena Di Napoli, Sabrina Chiara Cecere, Rosa Tambaro, Gaetano Facchini, Carla Cavaliere; Carmelina Landolfi, Vincenza Lanza, Adele Tatarella; Balbina Apice, Antonietta Linardi.
2. Unità di Ginecologia Oncologica, Fondazione IRCCS Istituto Nazionale Tumori – Milan (Milano): Francesco Raspagliesi, Domenica Lorusso, Giuseppa Maltese.
3. Dipartimento per la Tutela della Salute della Donna della Vita Nascente del Bambino e dell' Adolescente, Università Cattolica del Sacro Cuore (Roma): Giovanni Scambia, Vanda Salutari, Caterina Ricci, Distefano Maria Grazia, Devincenzo Rosa Pasqualina, Mascilini Floriana, Ludovisi Manuela, Amadio Giulia, Pietragalla Antonella, Conte Carmine, Masciullo Valeria.
4. Unità di Oncologia Medica A.O.R.N. "Garibaldi - Nesima" (Catania): Roberto Bordonaro, Daniela Sambataro.
5. U.O.di Oncologia Medica, Presidio Ospedaliero di Faenza (Faenza): Stefano Tamberi.
6. Oncologia Medica & Breast Unit, Ospedale Antonio Perrino (Brindisi) e Istituto Europeo di Oncologia (IRCCS) (Milano): Saverio Cinieri, Mazzoni Enrica, Maria D'Amico, Eufemia Stefania Lutrino, Laura Orlando, Concetta Chetrì Liana Falcone, Marilù Pinto, Pasqualinda Ferrara, Margherita Cinefra.
7. Oncologia Medica, Ospedale S. Maria della Misericordia, Perugia: Anna Maria Mosconi.
8. Dipartimento di Medicina Sperimentale e Clinica "F. Magrassi", Seconda Università degli Studi di Napoli (Napoli): Michele Orditura, Anna Diana.
9. Dipartimento di Oncologia Medica, Ospedale Bellaria-Maggiore Hospital, Azienda USL - IRCCS Istituto delle Scienze Neurologiche (Bologna) Alba A. Brandes, Stefania Bartolini.
10. U.O. Oncologia, Ospedale Infermi, (Rimini): Valentina Arcangeli.
11. Ginecologia Oncologica, Policlinico Umberto I, Università La Sapienza (Roma): Pierluigi Benedetti Panici, Claudia Marchetti, Innocenza Palaia, Angela Musella, Laura Salerno.
12. Unità Sperimentazioni Cliniche, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G.Pascale" IRCCS - Italia (Napoli): Francesco Perrone, Massimo Di Maio, Maria Carmela Piccirillo, Gennaro Daniele, Jane Bryce, Giuliana Canzanella, Federika Crudele, Manuela Florio, Giovanni De Matteis, Cristiana De Luca, Francesca Laudato, Fiorella Romano, Antonia Del Giudice, Marilena Martino, Maria Teresa Ribecco, Alfonso Savio, Lucia Sparavigna.
13. Cattedra di Statistica Medica, Seconda Università degli Studi (Napoli): Ciro Gallo.