MITO-11: A randomized multicenter phase II trial testing the addition of pazopanib to weekly paclitaxel in platinum-resistant or -refractory advanced ovarian cancer (AOC).

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Background

- Ovarian cancer (OC) is the 5th most common cancer in women with a very high mortality rate
- Despite initial high response rate to chemotherapy the majority of the patients recurs and requires second line therapy
- Treatment of platinum resistant/refractory patients is a clear unmet need with poor efficacy of the medical treatments available
- Evidence supports key role for VEGF/PDGF in pathogenesis of OC
- Pazopanib is an orally administered tyrosine kinase inhibitor targeting ATP binding sites of VEGFR, PDGFR and c-Kit receptors
- Single agent pazopanib demonstrated to be active in recurrent OC (Friedlander et al. 2010) and as maintenance after first line chemotherapy in advanced OC (DuBois et al. 2013)

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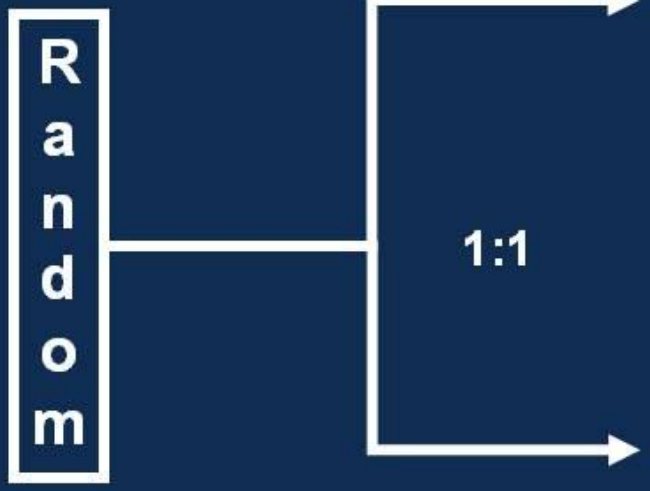
Study Aim

MITO-11 is a randomized, open label, phase II study comparing the combination of pazopanib plus weekly paclitaxel vs single-agent weekly paclitaxel in terms of progression-free survival (PFS) in platinum resistant or refractory OC patients.

Study design



Control arm

- **Paclitaxel** 80 mg/m^2, d1, 8, 15 q28

Treatment continued until progression

Experimental arm

- **Paclitaxel** 80mg/m^2, d1, 8, 15 q28
- **Pazopanib** 800 mg daily

Treatment continued until progression

Strata:
- **Center**
- **Previous chemotherapy lines: I vs II**
- **Platinum Resistant vs Refractory**

ClinicalTrials.gov NCT01644825

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Study population

Main inclusion criteria

- Cyto/histological diagnosis of ovarian, fallopian tube or primary peritoneal cancer
- Recurrent Platinum Resistant/Refractory disease
- Age ≥ 18
- ECOG Performance Status 0-1
- No residual peripheral neurotoxicity from previous chemotherapy treatment

Main exclusion criteria

- More than 2 previous lines of chemotherapy
- ANC < 2000/μL, platelets < 100000/μL
- Creatinine ≥ 1.25 x UNL, SGOT or SGPT ≥ 1.25 x UNL
- Other previous or concomitant malignant neoplasms
- Life expectancy shorter than 3 months

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Study Endpoints

Primary Endpoint

- Progression-free survival (PFS)

Secondary endpoints

- Overall survival
- Toxicity (CTCAE v3.0)
- Objective response rate (RECIST)

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Statistical Design

- Comparative randomized open-label phase 2 trial
  - wPaclitaxel vs wPaclitaxel + Pazopanib
- Primary end-point: PFS
- Relaxed statistical parameter (Rubinstein et al. JCO 2005)
  - 1-tailed alpha= 0.20
  - Power: 80%
  - HR 0.65 (i.e. median PFS from 3 to 4.6 months)
  - 61 events required for final analysis
  - 72 patients were planned

Study Conduction

- The study was sponsored and supported by NCI Naples that has the property of data. GSK provided pazopanib and partial funding
- 11 Italian centers actively recruited the patients
- First patient enrolled: Dec 15, 2010
- Last patient enrolled: Feb 8, 2013
- Final data extraction: May 12, 2014
- Final analysis: May 14, 2014
- Median Follow-up:
  - Weekly paclitaxel 16.1 months
  - Weekly paclitaxel plus pazopanib:16.3 months

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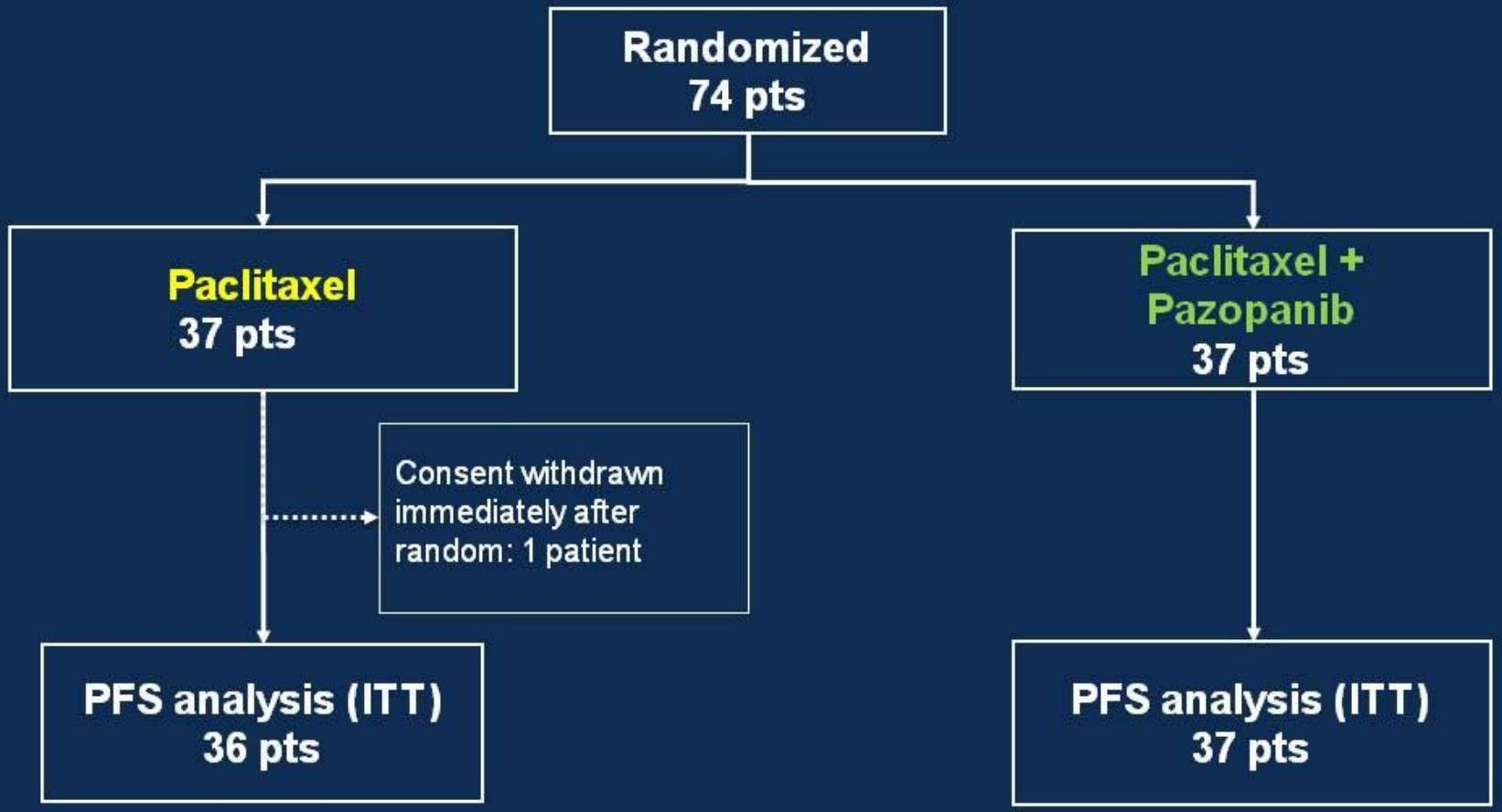
Patients' Flow



ITT: intention to treat

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Characteristics of patients

	Paclitaxel (n = 36)	Paclitaxel + pazopanib (n = 37)	Total (n = 74)
Median age (range)	58 (27-74)	56 (43-74)	57 (27-74)
Platinum-free-interval			
Resistant	27 (76%)	28 (76%)	56 (76%)
Refractory	8 (22%)	9 (24%)	17 (23%)
Sensitive*	1(2%)	0(0%)	1(1%)
Previous chemo lines			
1	15 (41%)	17 (46%)	32 (43%)
2	18 (51%)	17(46%)	36(49%)
3**	3 (8%)	3 (8%)	6 (8%)

* Ineligible according to protocol, included into ITT analysis.
** Having received 2 platinum-containing regimens, one non-platinum for resistant disease

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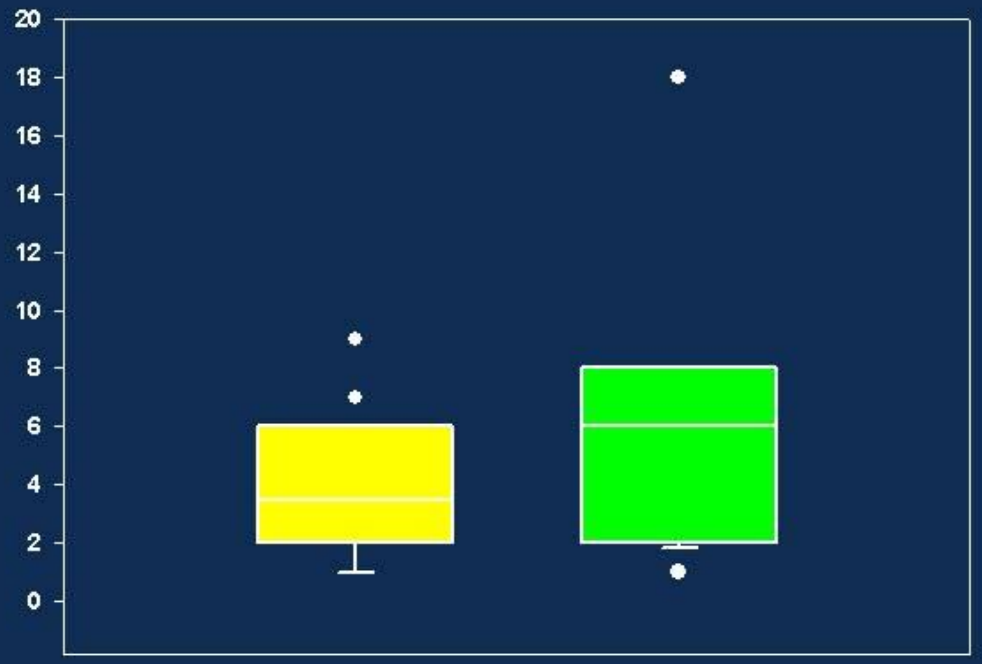
Compliance to paclitaxel

Number of Paclitaxel Cycles administered



	Paclitaxel	Paclitaxel +Pazopanib
Median RDI	4	6
Range	0-9	1-18
Interruption for AEs (%)	1 (3%)	4 (11%)

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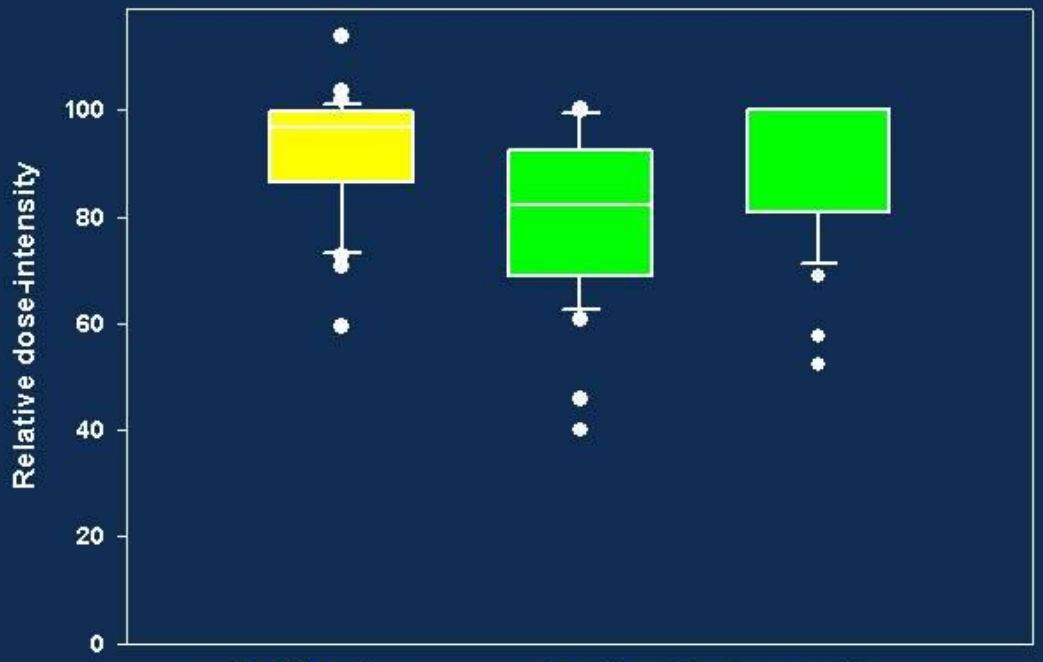
Relative Dose Intensity



	Paclitaxel	Paclitaxel	Pazopanib
Median RDI	96%	82%	100%
Range	59-113	40-100	53-100
Pts with dose reductions (%)	5 (14)	20 (54%)	20 (54%)

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Progression-free survival

Arm	N	Events	Median (months)	95% CI
Paclitaxel	36	36	3.5	2.0-5.7
Paclitaxel + Pazopanib	37	37	6.3	5.4-11

1-tailed P=0.0002 HR 0.42 (95% CI 0.25-0.69)

Patients at risk

wP	36	11	2	0	0
WPP	37	22	10	2	2

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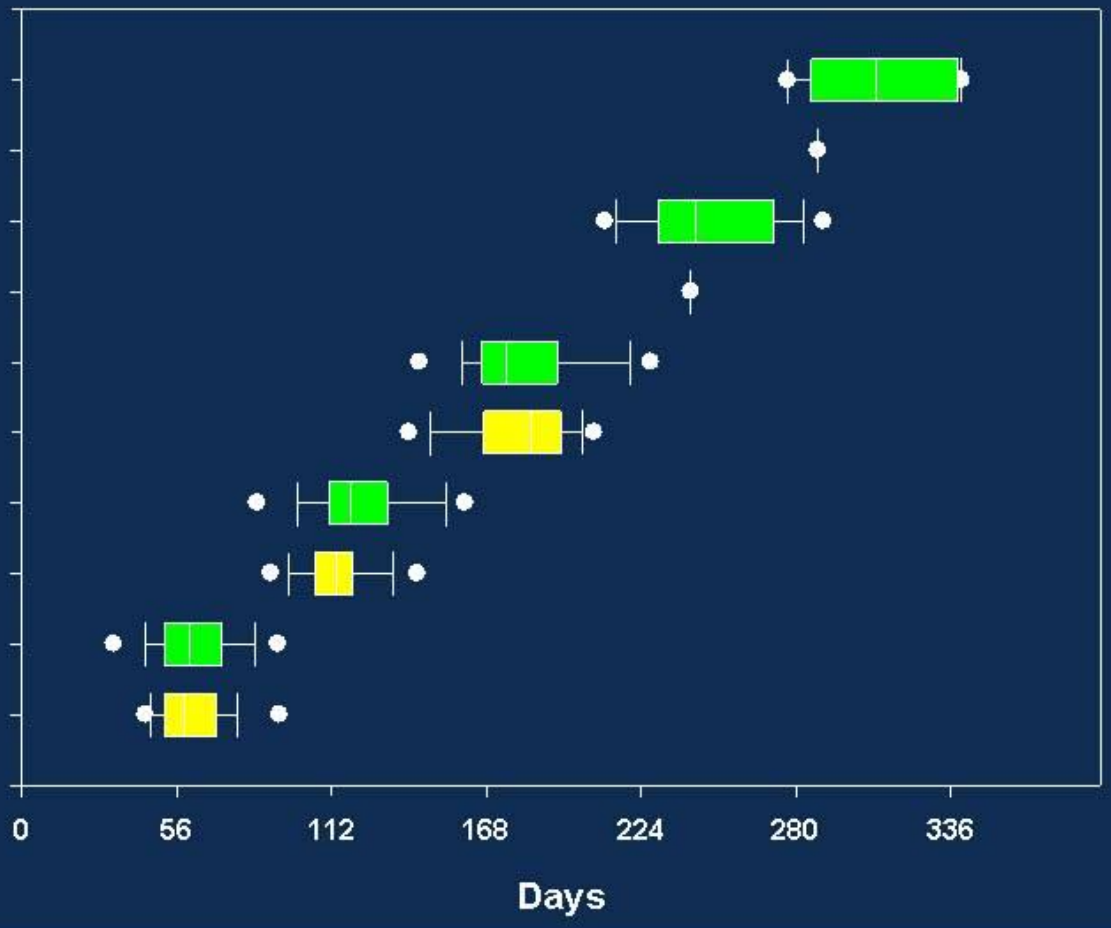
Timing of re-assements between arms



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Overall survival

Arm	N	Events	Median (months)	95% CI
Paclitaxel	36	22	13.7	9.8-NA
Paclitaxel + Pazopanib	37	18	19.1	11.5-NA

1-tailed P=0.056 HR 0.6 (95% CI 0.32-1.13)

Patients at risk							
WP	36	26	19	5	0	0	3
WPP	37	32	21	9	3	2	1

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Activty Analysis (RECIST)

52 patients were eligible for analysis as per RECIST criteria

	Paclitaxel N=24	Paclitaxel + Pazopanib N=28	p
Responders - CR+PR	5 (21%)* [95%CI: 9%-41%]	14 (50%)* [95%CI: 33%-67%]	0.03
CR	1 (4%)	2 (7%)*	
PR	4 (17%)	12 (43%)*	

*All the responses were confirmed at CA125 response analysis (not presented here)

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Adverse Events (1)

	Paclitaxel (n=36)				Paclitaxel + Pazopanib (n=37)				
Grade	1	2	3	4	1	2	3	4	p**
Anemia	25%	22%	14%	-	49%	14%	5%	-	0.58
Leukopenia	**17%**	**8%**	**3%**	**-**	**19%**	**35%**	**11%**	**-**	**0.0005**
Neutropenia	**17%**	**11%**	**3%**	**-**	**5%**	**41%**	**22%**	**8%**	**<0.0001**
Febrile Neutropenia			-	-			5%	-	0.5
Infection	3%	3%	3%	-	3%	11%	-	-	0.63
Thrombocytopenia	8%	-	-	-	8%	5%	-	-	0.54

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Adverse Events (2)

	Paclitaxel (n=36)				Paclitaxel + Pazopanib (n=37)				
Grade	1	2	3	4	1	2	3	4	p**
Epistaxis	**3%**	**-**	**-**	**-**	**11%**	**8%**	**-**	**-**	**0.045**
Allergy	-	3%	-	-	-	3%	-	-	1
Hypertension	**-**	**-**	**-**	**-**	**16%**	**19%**	**8%**	**-**	**<0.0001**
Heart, rhythm	3%	-	-	-	5%	-	-	-	1
Heart, other	-	3%	-	-	8%	3%	3%	-	0.18
Thromboembolic event	-	3%	3	-	-	-	3%	-	0.74

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Adverse Events (3)

	Paclitaxel (n=36)				Paclitaxel + Pazopanib (n=37)				
Grade	1	2	3	4	1	2	3	4	p**
Fatigue	**31%**	**11%**	**6%**	**-**	**32%**	**30%**	**11%**	**-**	**0.012**
Skin rash	3%	-	-	-	5%	3%	-	-	0.55
Diarrhoea	**17%**	**3%**	**-**	**-**	**22%**	**30%**	**5%**	**-**	**0.0003**
Mucositis	**8%**	**-**	**-**	**-**	**32%**	**11%**	**-**	**-**	**0.0007**
Ileal perforation	-	-	-	-	-	-	-	3%	1

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Adverse Events (4)

	Paclitaxel (n=36)				Paclitaxel + Pazopanib (n=37)				
Grade	1	2	3	4	1	2	3	4	p**
Nausea	22%	14%	-	-	22%	16%	-	-	0.89
Vomiting	11%	3%	3%	-	22%	5%	-	3%	0.23
ALP	8%	-	-	-	8%	3%	3%	-	0.48
AST/ALT	**14%**	**-**	**-**	**-**	**22%**	**8%**	**5%**	**3%**	**0.011**
Bilirubin	3%	-	-	-	14%	3%	-	-	0.099
Sensory neuropathy	**39%**	**6%**	**-**	**-**	**43%**	**24%**	**-**	**-**	**0.02**

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Conclusions

- The MITO-11 trial met its primary endpoint and found a statistically significant prolongation of PFS adding pazopanib to weekly paclitaxel in platinum-resistant or refractory advanced ovarian cancer patients.
- Promising results are also seen in OS analysis
- No unexpected toxicities were observed adding pazopanib to weekly paclitaxel
- These results warrant further phase 3 evaluation of pazopanib + weekly paclitaxel combination.

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