Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17

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on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups

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PRESENTED BY: Sandro Pignata

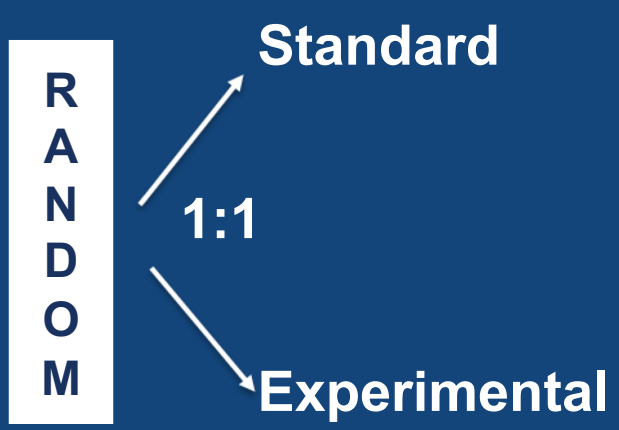
Background

- Bevacizumab added to first line carboplatin and paclitaxel chemotherapy and as maintenance prolongs PFS in patients with stage IIIB-IV ovarian cancer
- In recurrent bevacizumab-naive patients the drug is approved in combination with chemotherapy both for those candidate to receive platinum (OCEANS trial; GOG213 trial) and in those not eligible for platinum (AURELIA trial)
- 70%-80% of recurrent patients are eligible for a rechallenge with platinum-based doublet
- To date, no trials have been specifically designed in ovarian cancer to assess the efficacy of the addition of bevacizumab to chemotherapy in patients recurring after a first line treatment containing bevacizumab

Study Aim

The MITO16B - MaNGO OV2B - ENGOT OV17 trial is an academic randomized, open label, phase III study testing whether the addition of Bevacizumab to a platinum-based chemotherapy prolongs progression-free survival (PFS) for recurrent platinum-sensitive ovarian cancer patients already treated with bevacizumab during first line

Study Design



Platinum-Based Chemotherapy

Platinum-Based Chemotherapy plus Bevacizumab

Platinum-based Chemotherapy:

- Carboplatin + Paclitaxel +/- Beva 15mg/kg q 21
- Carboplatin + Gemcitabine +/- Beva 15mg/kg q 21
- Carboplatin + PLD q 28 +/- Beva 10mg/kg q 14

Stratification:

- center
- relapse during or after 1° line Beva
- performance status
- chemo backbone

Study Population

- FIGO stage IIIB-IV ovarian cancer patients at first relapse, recurring at least 6 months after last dose of platinum
- Patients had received Bevacizumab during first-line treatment
- ECOG PS≤2
- Patients were included if they have a RECIST progression, with either measurable or non-measurable disease
- Normal organ function (bone marrow, heart, liver, renal)
- Availability of tumour samples for molecular analyses from primary surgery (mandatory) and secondary surgery (when available)

Study end-points

- Primary: PFS (Investigator assessed – RECIST 1.1)
- Secondary:
  - Overall survival
  - Safety (CTCAE v4.03)
  - Objective response rate (RECIST 1.1)
  - *PFS centrally reviewed (not yet available)*
  - *Prognostic and predictive molecular factors (not yet available)*

Sample size

- Two-sided alpha error: 0.05
- Power: 90%
- Expected PFS in the standard arm: 8 months
- Projected PFS in the experimental arm: 11.9 months
- Hazard ratio: 0.67
- Events needed for the final analysis: 265
- 400 patients to be randomized
- No interim analyses planned

Study sponsorship and support

- The study is sponsored by the National Cancer Institute of Naples that has the property of the data
- Support from Roche global (funding and drug)
- Translational project also supported by Associazione Italiana per la Ricerca sul Cancro (AIRC) and Associazione Italiana di Oncologia Medica (AIOM)
- Clinicaltrials.gov: NCT01802749
- EUDRACT Number: 2012-004362-17

Study conduction

- Ethical committee approval: December 19th, 2012
- First patient enrolled: December 6th, 2013
- Last patient enrolled: November 11th, 2016
- Database lock: February 28th, 2018
- Median follow-up of alive patients: 20 months

Participating cooperative groups

Country	Group	Total N
Italy	MITO	206
	MaNGO	72
France	GINECO	100
Switzerland	SAKK	17
Greece	HECOG	10
Total		**405**

Patients' flow

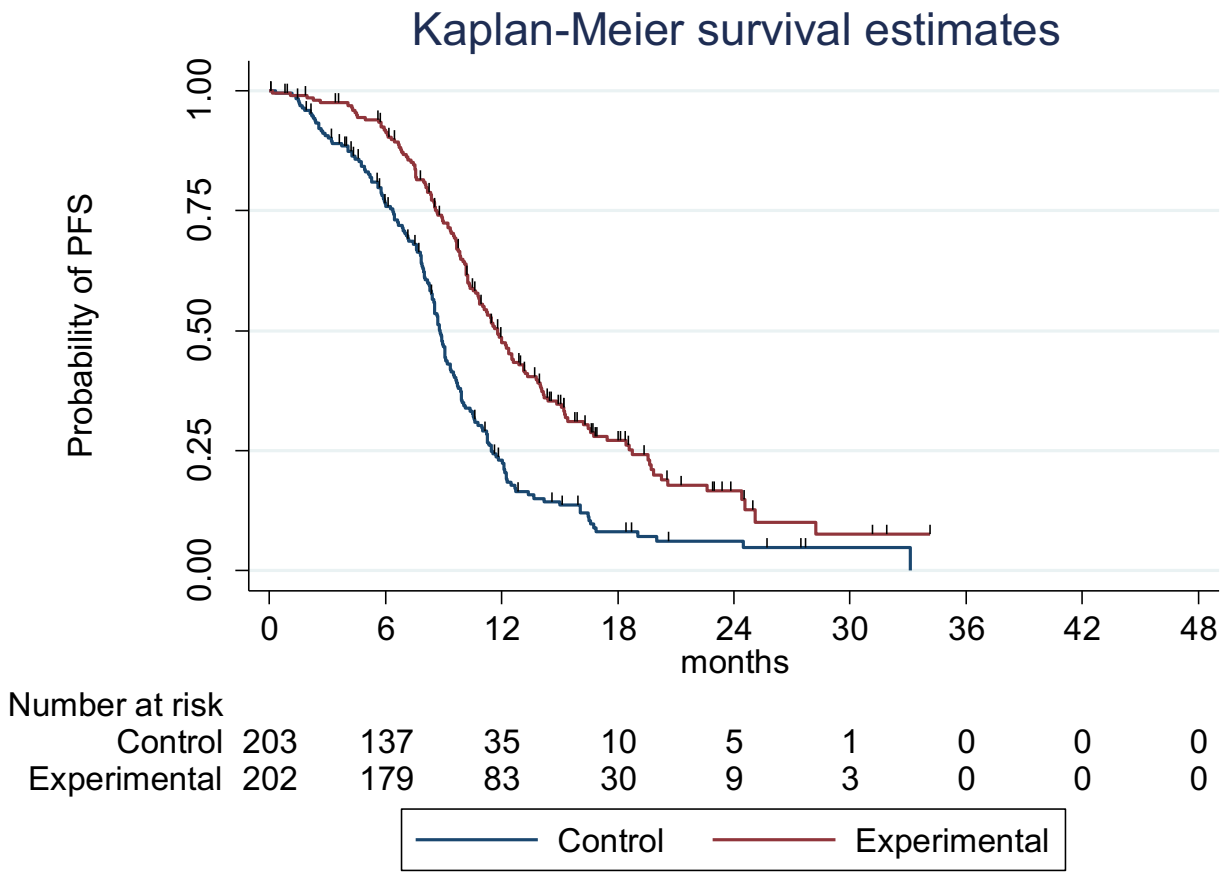
Baseline characteristics of patients (1)

	Standard (n = 203)	Experimental (n = 202)	Total (n = 405)
Median age (range)	60.6 (33.9-91.0)	61.5 (29.5-82.6)	61.2 (29.5-91.0)
Tumor histology			
Serous	158 (77.8%)	165 (81.7%)	323 (79.8%)
Mucinous	2 (1.0%)	1 (0.5%)	3 (0.7%)
Endometrioid	12 (5.9%)	8 (4.0%)	20 (4.9%)
Other	28 (13.8%)	25 (12.4%)	53 (13.1%)
Missing	3 (1.5%)	3 (1.5%)	6 (1.5%)
ECOG performance status			
0	167 (83.5%)	164 (81.6%)	331 (82.6%)
1	33 (16.5%)	35 (17.4%)	68 ((17.0%)
2	0 (0%)	2 (1.0%)	2 (0.5%)
BRCA 1-2 mutational status			
Not available (*Somatic Mutation assay ongoing*)	111 (54.7%)	110 (54.5%)	221 (54.6%)
Wild type	72 (35.5%)	72 (35.6%)	144 (35.6%)
Mutant	20 (9.8%)	20 (9.9%)	40 (9.9%)

Baseline characteristics of patients (2)

	Standard (n = 203)	Experimental (n = 202)	Total (n = 405)
Platinum Free-Interval			
6-12 months	72 (35.5%)	72 (35.6%)	144 (35.6%)
> 12 months	131 (64.5%)	130 (64.4%)	261 (64.4%)
1L Bevacizumab at relapse/PD			
Completed	147 (72.4%)	145 (71.8%)	292 (72.1%)
Ongoing	56 (27.6%)	57 (28.2%)	113 (27.9%)
Chemotherapy backbone			
Carboplatin-Paclitaxel	21(10.3%)	21 (10.4%)	42 (10.4%)
Carboplatin-Gemcitabine	99 (48.8%)	98 (48.5%)	197 (48.6%)
Carboplatin-PLD	83 (40.9%)	83(41.1%)	166 (41%)
Residual Disease after primary surgery			
< 1 cm	116 (57.1%)	96 (47.5%)	212 (52.3%)
≥ 1cm	60 (29.6%)	80 (39.6%)	140 (34.6%)
Missing	27 (13.3%)	26 (12.9%)	53 (13.1%)

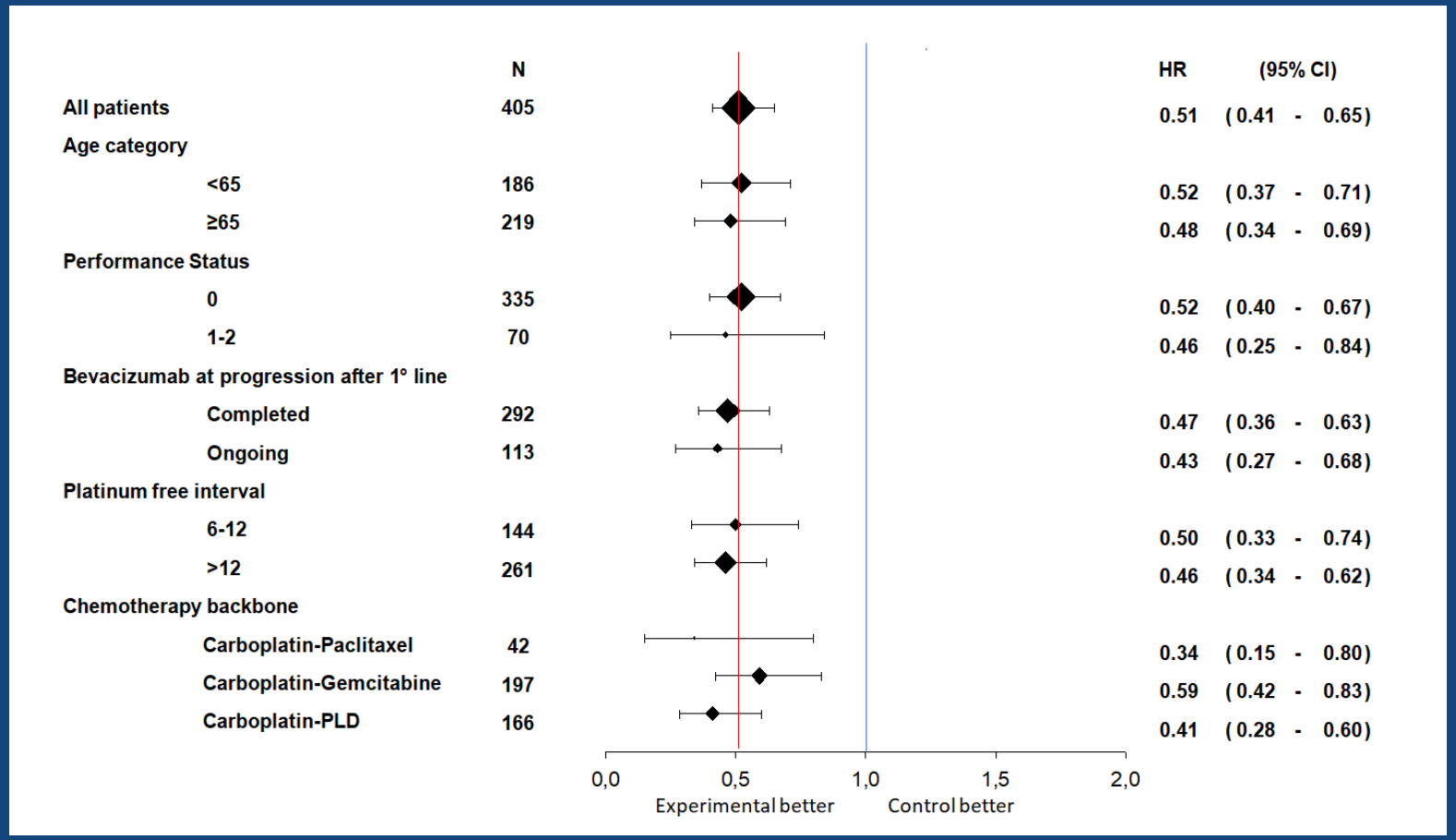
PFS Investigator assessed (primary end-point)



	Standard	Experimental	Log Rank P
# events	161	143	
Median PFS	8.8 mos	11.8 mos	<0.001
HR* (95%CI)	0.51 (0.41-0.65)		

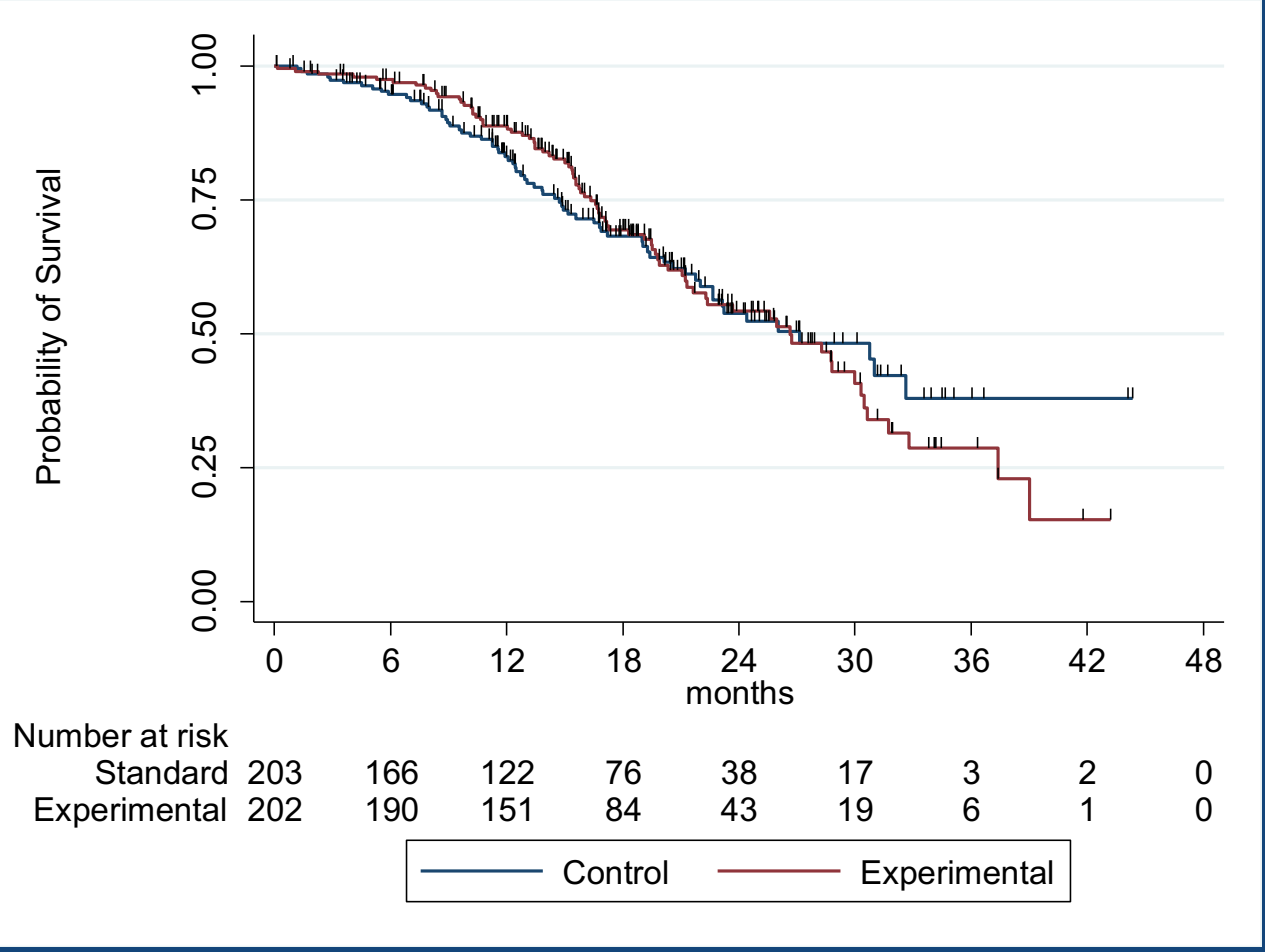
*adjusted by:
age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

HR of PFS by major subgroups



Adjusted by: age, performance status, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Overall survival



	Standard	Experimental	Log Rank P
# events	68	79	
Median OS	27.1 mos	26.6mos	0.98
HR* (95%CI)	0.97 (0.70-1.35)		

*adjusted by:
age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Objective Response Rate (RECIST 1.1)

	Standard N= 143	Experimental N= 130	P
Responders (CR+PR)	94 (65.7%) [95%CI: 57.6%-73.0%]	97 (74.6%) [95%CI: 66.5%-81.4%]	0.14
CR	9 (6.3%)	20 (15.4%)	
PR	85 (59.4%)	77 (59.2%)	

Severe Toxicity occurring >4% of patients

	STD (N=200)		EXP (N=201)		P*
	G3	G4	G3	G4	
Hypertension	20 (10%)	0	58 (28.9%)	0	<0.001
Neutrophils	56 (28%)	25 (12.5%)	48 (23.9%)	32 (15.9%)	0.95
Thrombocytopenia	20 (10%)	23 (11.5%)	31 (15.4%)	30 (14.9%)	0.04
Proteinuria	0	0	8 (3.9)	0	0.007
Febrile Neutropenia	6 (3%)	4 (2%)	3 (1.5%)	1(0.5%)	0.17
Allergic Reaction	11 (5.5%)	0	5 (2.48%)	1 (0.5%)	0.22
Anemia	22 (11%)	1(0.5%)	22 (10.9%)	0	0,88

*Chi-square or Fisher's exact test as appropriate (severe vs non-severe)

Translational plan

- 304 baseline hystology samples collected to date
- Blood samples collected before, after chemo, and after bev completion or PD
- 11 research labs involved in Italy

- Analysis ongoing
  - NGS on tissue and blood
  - Cytokines
  - TMA and IHC for 34 proteins
  - Validation of miRNA
  - Circulating endothelial cells
  - Proteomic and lipidomic

Conclusions

- In ovarian cancer patients relapsing ≥6 months after last platinum, previously treated with bevacizumab in first line, rechallenge with bevacizumab in combination with a platinum-based doublet is associated with a significantly prolonged PFS, with no unexpected toxicity

- Rechallenge with platinum based chemotherapy and bevacizumab is a clinical option in recurrent patients already treated with bevacizumab

- Future translational analyses will provide a deeper insight into prognostic and predictive factors

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