MaNGO
Mario Negri Gynecologic Oncology

XVII ASSEMBLEA MaNGO

MILANO

16 OTTOBRE 2020

Con il Patrocinio di:

SIGO SOCIETA' ITALIANA DI GINECOLOGIA E OSTETRICIA

SIOG SOCIETÀ ITALIANA DI ONCOLOGIA GINECOLOGICA

FICOG Federation of Italian Cooperative Oncology Groups

ACTO ALLEANZA CONTRO IL TUMORE OVARICO

STUDIO EXPERT

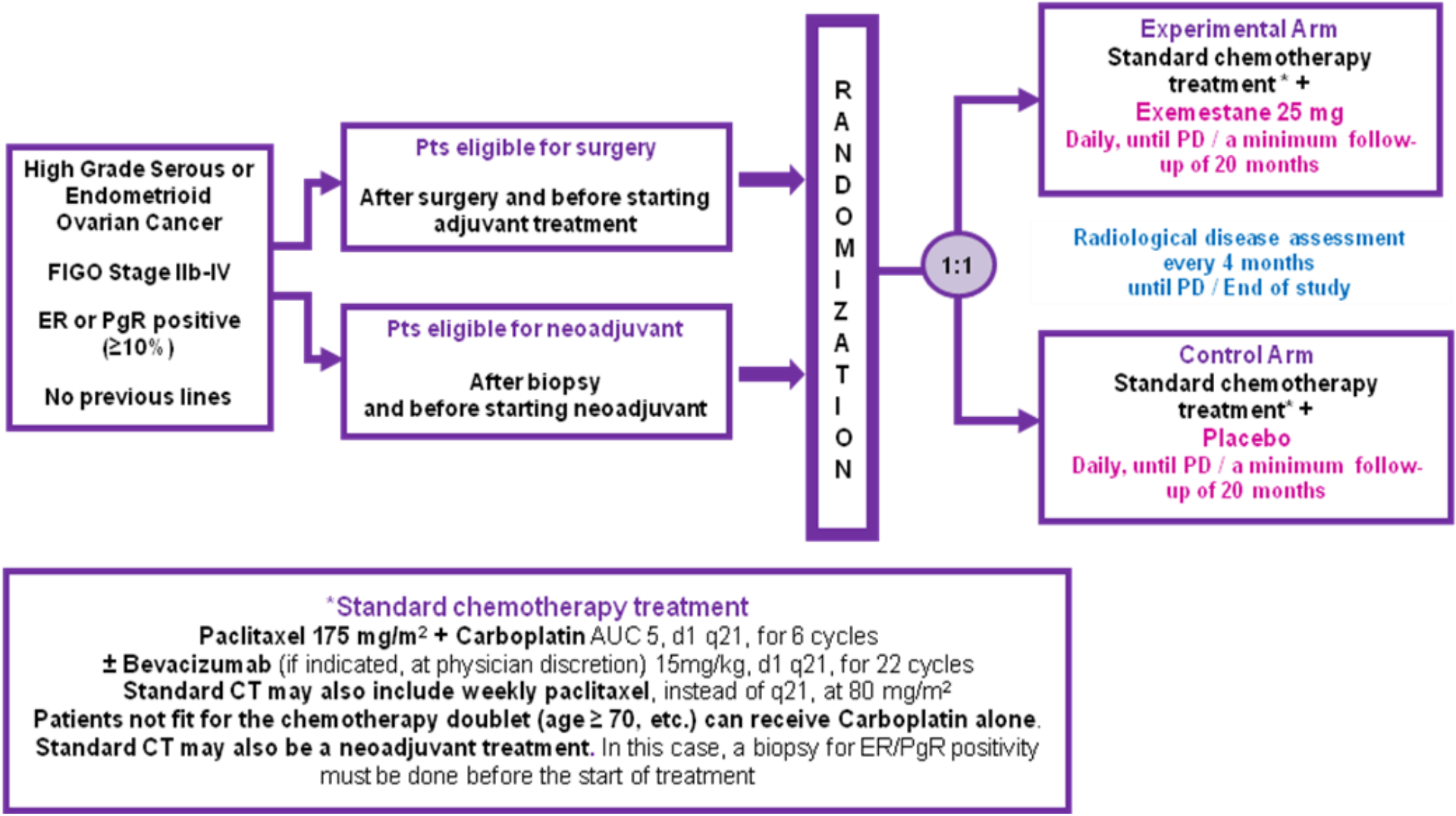
Exemestane in Progesterone and/or Estrogen receptor positive epithelial ovarian cancer. A Randomized phase III Trial.

stato di avanzamento e
considerazioni sulla terapia combinata con PARPi

Supported by AIFA

EXPERT Trial

Current Study Design



*Standard chemotherapy treatment

Paclitaxel 175 mg/m² + Carboplatin AUC 5, d1 q21, for 6 cycles
± Bevacizumab (if indicated, at physician discretion) 15mg/kg, d1 q21, for 22 cycles
Standard CT may also include weekly paclitaxel, instead of q21, at 80 mg/m²
Patients not fit for the chemotherapy doublet (age ≥ 70, etc.) can receive Carboplatin alone.
Standard CT may also be a neoadjuvant treatment. In this case, a biopsy for ER/PgR positivity must be done before the start of treatment

Primary objective: **PFS**

	Progression-free survival		Recurrence-free survival*	
	Olaparib (N=260)	Placebo (N=131)	Olaparib (N=189)	Placebo (N=101)
Events, n (%)	118 (45)	100 (76)	79 (42)	74 (73)
Median, m	56.0	13.8	NR	15.3
HR (95%CI)	0.33 (0.25–0.43)		0.37 (0.27–0.52)	
Patients progression or recurrence free at timepoint, % (Kaplan-Meier estimates)				
1y	87.7	51.4	91.0	58.0
2y	73.6	34.6	77.2	39.0
3y	60.1	26.9	64.0	28.9
4y	52.3	21.5	55.2	23.0
5y	48.3	20.5	51.9	21.8

Defined post hoc as time from randomization to disease recurrence or death for patients in complete response to platinum-based chemotherapy at baseline; patients had CR at baseline based on electronic case report form data. CI, confidence interval; HR, hazard ratio; NR, not reached.

OBIEZIONI AIFA

- ***Uso compassionevole di Niraparib; combinazione PARPis e Bevacizumab: non autorizzati***

→Possibile uso di Olaparib in I linea nelle pazienti platino sensibili.
Esclusione di Niraparib fino a quando non otterrà l'indicazione.
Bevacizumab + PARPis sarà concesso quando registrato in indicazione

- ***Studi di combinazione PARPis e Exemestane: assenza di studi di combinazione di olaparib o niraparib ed exemestane***.

→ Safety Exemestane+Olaparib valutata in studio di fase I (Plummer, R et al. Adv Ther. 2018)
Analisi ad interim annuali di safety
Obiettivo primario non cambia nonostante l'aggiunta di Olaparib
Minoranza (5-10%) trattate con Olaparib
Confronto tra Exemestane e placebo aggiustato per terapie standard

- ***Eterogeneità del trattamento:*** **richiesta di dettaglio riguardo all'analisi ad interim**

→ Revisionata sezione analisi statistica del protocollo

EXPERT Trial

New Study Design Proposal

- High Grade Serous Endometrioid Ovarian Cancer (including cancer of fallopian tube and peritoneum)
- FIGO Stage IIb-IV
- ER or PR positive (≥10%)
- No previous lines

PATIENTS ELIGIBLE FOR SURGERY

After surgery and before starting adjuvant treatment

PATIENTS ELIGIBLE FOR NEOADJUVANT

After biopsy and before starting neoadjuvant treatment

RANDOMIZATION

1:1

EXPERIMENTAL ARM

Chemotherapy treatment (carboplatin + paclitaxel)* + Exemestane 25 mg**

CONTROL ARM

Chemotherapy treatment (carboplatin + paclitaxel)* + Placebo**

Radiological disease assessment every 4 months until PD/End of study

***Chemotherapy treatment:**

Paclitaxel 175 mg/m^2 + Carboplatin AUC 5, d1 q21, for 6 cycles

± Bevacizumab (if indicated at physician discretion) 15mg/kg, d1 q21 for 22 cycles

± Olaparib (if indicated) oral administration, patient-tailored dosage

Chemotherapy may also include **weekly Paclitaxel**, instead of q21, at 80 mg/m^2 or weekly Carboplatin AUC2 instead of AUC5 q21

Patients not fit for the chemotherapy doublet (e.g. age ≥ 70) can receive **Carboplatin alone**

Chemotherapy may also be a neoadjuvant treatment. In this case, a biopsy for ER/PR positivity must be done before the start of treatment.

****Exemestane/Placebo:** Daily somministration and follow up visits until the End of Study (20 months) or PD.

Statistical considerations

Original sample size

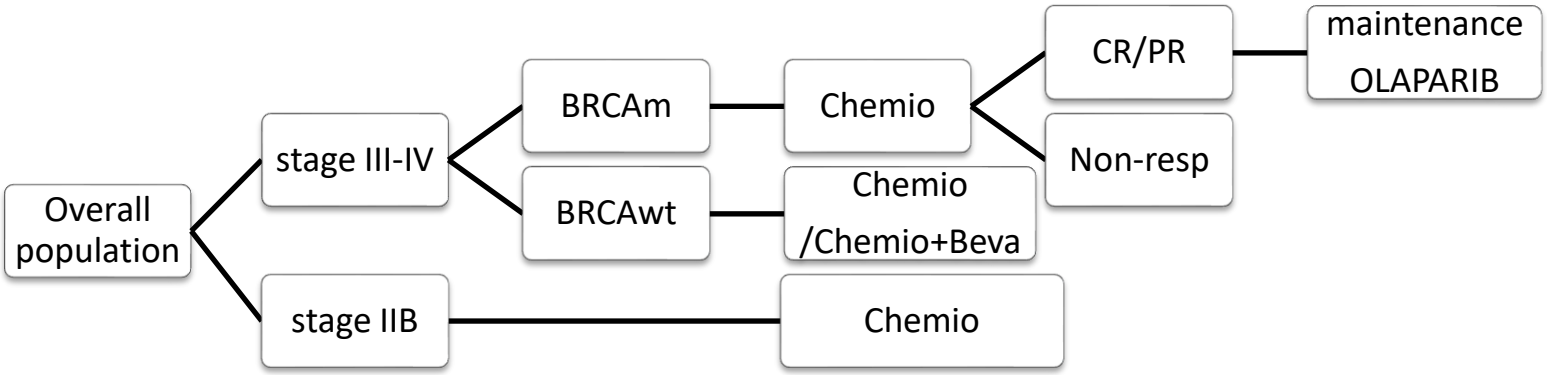
Hypothesis

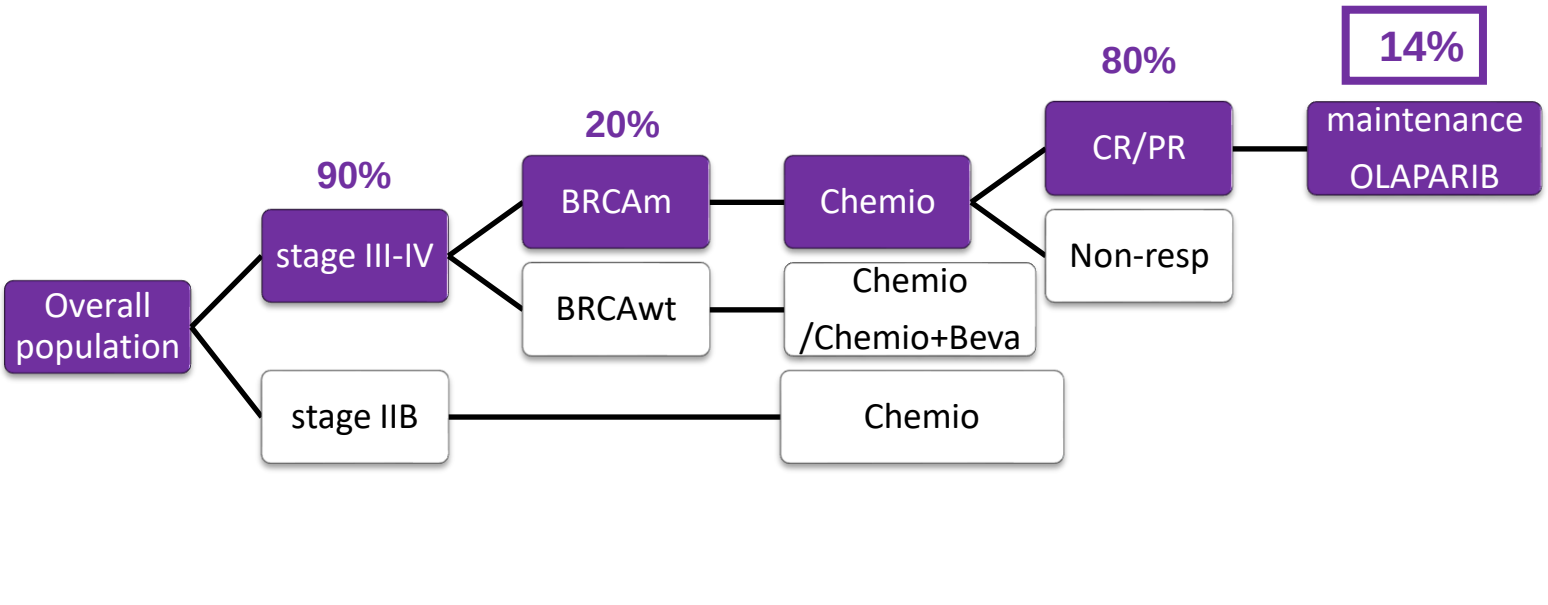
HR=0.70
alpha 5% two sided
power 80%

median PFS in the control arm 18-20 mos
Accrual: 12 months
Follow-up: 20 months

247
events (progressions or deaths)

438-468
patients


Overall population
stage III-IV
stage IIB
BRCAm
BRCAwt
Chemio
Chemio /Chemio+Beva
Chemio
CR/PR
Non-resp
maintenance OLAPARIB



Original hypothesis: Median 20 mos → **468 patients** → **pts receiving OLAPARIB ≤5%**

Alternative scenario: **pts receiving OLAPARIB ~14%** → **Median 24 mos** → **+60 patients**

PRO

no selection of patients to be enrolled

the BRCA testing will be not necessary at study entry

all BRCA mut patients will be included in the study without hesitation

Olaparib treatment will have no negative impact on accrual

CONTRA

in case of a >5% prevalence of pts receiving OLAPARIB

- increase in the sample size

- possible negative impact on efficacy

HR: 0.7

Median PFS 18 mos → +7.7 mos

Median PFS 60 mos → +25.7 mos

HR: 0.7

Median PFS 18 mos → +7.7 mos

Median PFS 60 mos → +25.7 mos

No Olaparib → minimum 86% → HR 0.7

Olaparib → maximum 14% → HR 1

Maximum HR

0.78

HR overall population

0.74

Enrolling Sites: updates

50 sites in Italy thanks to the collaboration between MaNGO and MITO

Approvazione AIFA: **15/10/2019**

ACTIVE

7 sites

1-De Censi, Genova 18/12/2019
33-Scambia, Roma 07/05/2020
25-Cassani, Pavia 14/05/2020
23-Pignata, Napoli 14/09/2020
40-Massa, Cagliari 22/09/2020
43-Scandurra Catania 07 Ottobre 2020
14-Mencoboni Genova 08 Ottobre 2020

4 patients enrolled at E.O. Galliera
2 patients enrolled at Policlinico Gemelli

Sites Activation Update

ETHICAL APPROVALS
24 sites

- **01-**De Censi , Genova: 25/11/2019
- **14-**Mencoboni , Genova: 25/11/2019
- **39-**Mammoliti, Genova: 25/11/2019
- **25-**Cassani, Pavia: 15/01/2020
- **15-**Ronzino, Lecce: 21/01/2020
- **28-**Bilancia, Potenza: 21/01/2020
- **33-**Scambia, Roma: 23/01/2020
- **18-**Colombo, Milano: 22/01/2020
- **23-**Pignata, Napoli: 26/02/2020
- **02-**Fusco, Alessandria: 21/05/2020
- **13-**Occelli ,Cuneo: 24/06/2020
- **30-**Bologna Reggio Emilia: 28/07/2020
- **24-**Gennari, Novara: 12/06/2020
- **42-**Dessole, Sassari: 22/07/2020
- **40-**Massa, Cagliari: 26/02/2020
- **48-**Segati, Feltre: 25/06/2020
- **43-**Scandurra, Catania: 2/03/2020
- **7-**Tognon, Brescia: 10/03/2020
- **8-**Abeni, Brescia: 31/03/2020
- **35-**Ferrero, Torino: 6/04/2020
- **32-**Maiello, Foggia :22/04/2020
- **9-**Aglietta, Candiolo: 21/05/2020
- **6-**Zamagni, Bologna: 21/05/2020
- **37**-Gasparre, Vercelli:21/05/2020

Sites Activation Update

PENDING ETHICAL APPROVAL / CONTRACT NEGOTIATION 23 sites

- **3-**Sorio, Aviano
- **4-**Lo Russo, Bari
- **5-**Zavallone, Biella
- **10-**Sambataro, Catania
- **11-**Natoli, Chieti
- **12-**Giordano, Como
- **16-**Ardizzoia, Lecco
- **17-**De Giorgi, Forlì Cesena
- **19-**Battelli, Macerata
- **20-**Cortesi, Modena
- **21-**Puppo, Cuneo
- **22-**Lissoni, Monza
- **26-**Cavanna, Piacenza
- **27-**Gadducci, Pisa
- **29-**Casanova, Ravenna
- **31-**Benedetti Panici, Roma
- **34-**Bertolini, Sondrio
- **36-**Katsaros, Torino
- **41-**Casanova, Lugo
- **44-**Montani, Manerbio
- **45-**Ardizzoia, Alba
- **46-**Casanova, Faenza
- **47-**Blasi, Palermo

What's next?

- A second draft of the amendment was sent back to AIFA for their evaluation as study funder

- Activation of all 50 enrolling sites

- Inclusion of further sites