MaNGO

XVI ASSEMBLEA MANGO

RICERCA BIOLOGICA E FARMACOLOGICA SUL TUMORE DELL'OVAIO: LABORATORIO E CLINICA

REGGIO EMILIA 21-22 GIUGNO 2019

CON IL PATROCINIO DI:

SIOG

SIGO

MaNGO
Mario Negri Gynecologic Oncology

Collaborazioni ENGOT attive

1. Gli studi vengono proposti in sede ENGOT e, solo in alcuni casi, discussi collegialmente.
2. Il gruppo leader chiede quali gruppi collaborativi siano interessati e stima quanti centri possano aggregarsi
3. Le proposte vengono discusse nel CTS di MaNGO
4. I centri afferenti al CTS spesso saturano il numero dei centri partecipanti messi a disposizione dal gruppo leader
5. Le CRO incaricate, in caso di studi ENGOT modello C si fanno carico di tutti gli aspetti operativi
6. In caso di studi ENGOT A e B, l'Istituto Mario Negri si fa carico della gestione del trial in Italia

Come si attuano le collaborazioni?

MaNGO
Mario Negri Gynecologic Oncology

Collaborazioni in corso

- carcinoma ovarico -

Ovaio 1° linea

ENGOT ov39 – ImaGYN 050

ENGOT ov33 - TRUST

ENGOT ov46 - DUO-O

ENGOT ov43

Ovaio recidiva platino sensibile

ENGOT ov38 - OReO

ENGOT ov41 - ANITA

ENGOT ov53

ENGOT ov42 AVATAR

Ovaio recidiva platino resistente

ENGOT ov50

Ovaio 1° linea

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ENGOT Ov-39 Trial
IMaGYN 050
Study Design

ENGOT model C; ENGOT lead group MITO

IMagyn050: Study Design in Primary Surgery Cohort

- Previously untreated ovarian, fallopian tube, or peritoneal cancer
- Stage III w/macroscopic residual disease), Stage IV, or Unresectable advanced stage patients for neo-adjuvant therapy
- ECOG PS 0-2

Stratification variables

- Stage/debulking status
- ECOG PS
- PDL1 IC0 vs IC1+
- Adjuvant/Neo-adjuvant

R 1:1

- Carboplatin AUC 6 q3wk
- Paclitaxel 175 mg/m^2 q3wk
- Bev 15 mg/m^2 q3wk
- Bev* 15 mg/kg X 16 cycles
- Placebo q3w X 22 cycles

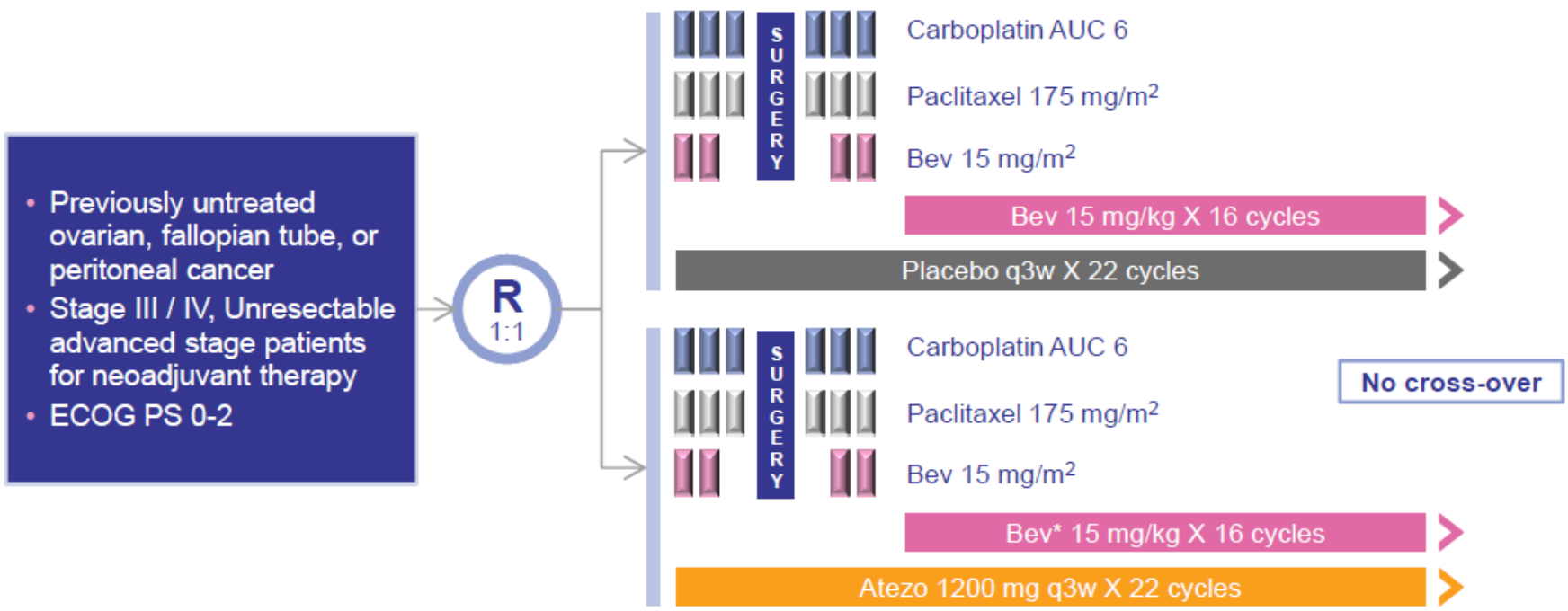
No cross-over

- Carboplatin AUC 6 q3wk
- Paclitaxel 175 mg/m^2 q3wk
- Bev 15 mg/m^2 q3wk
- Bev* 15 mg/kg X 16 cycles
- Atezo 1200 mg q3w X 22 cycles

Co-Primary endpoint: PFS & OS in all comers and Dx+ (IC1+)

ENGOT Ov-39 Trial
IMaGYN 050
Study Design

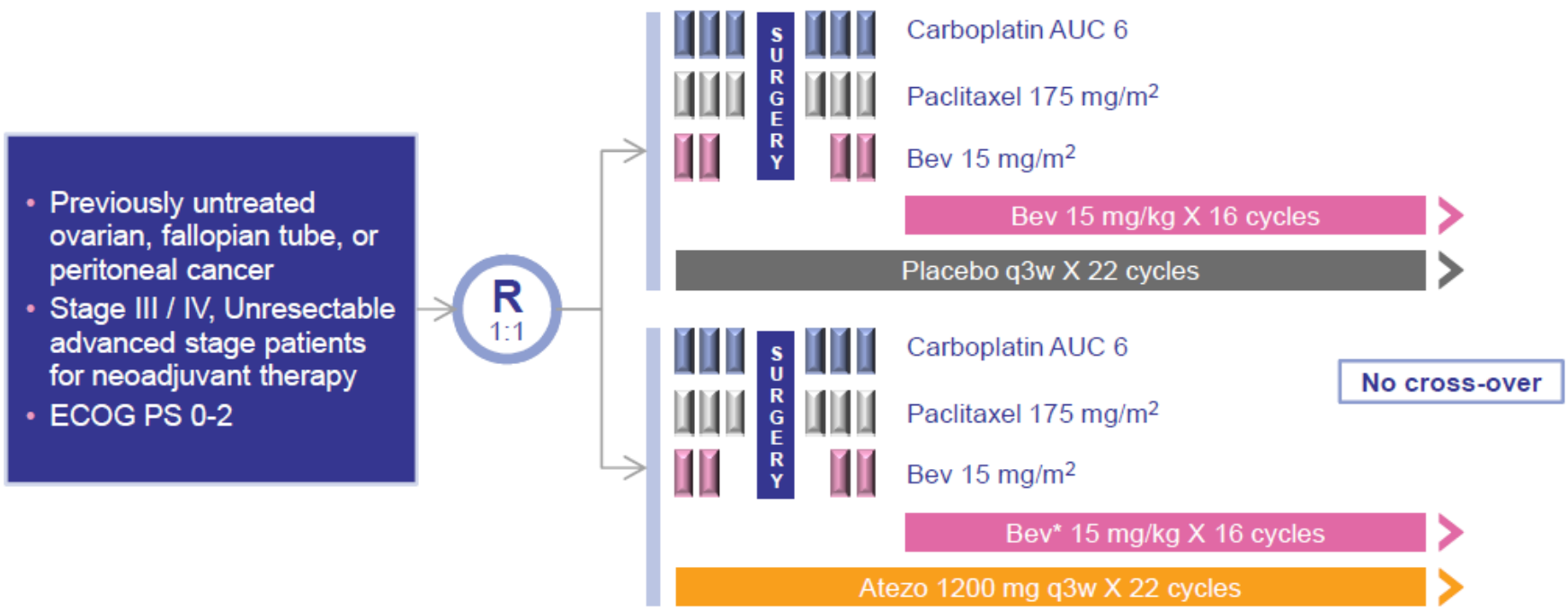
IMagyn050: Study Design in Neoadjuvant Cohort



Planned number of patients:1300; 99% recruited

ENGOT Ov-39 Trial
IMaGYN 050
Study Design

IMagyn050: Study Design in Neoadjuvant Cohort



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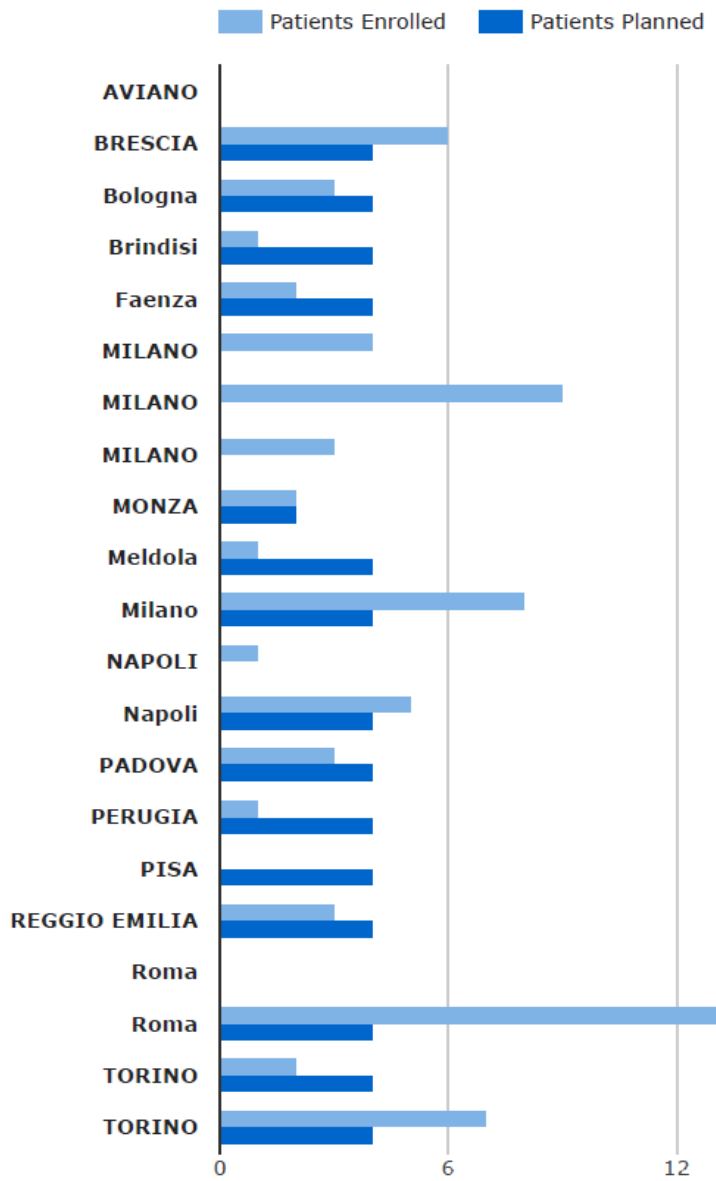
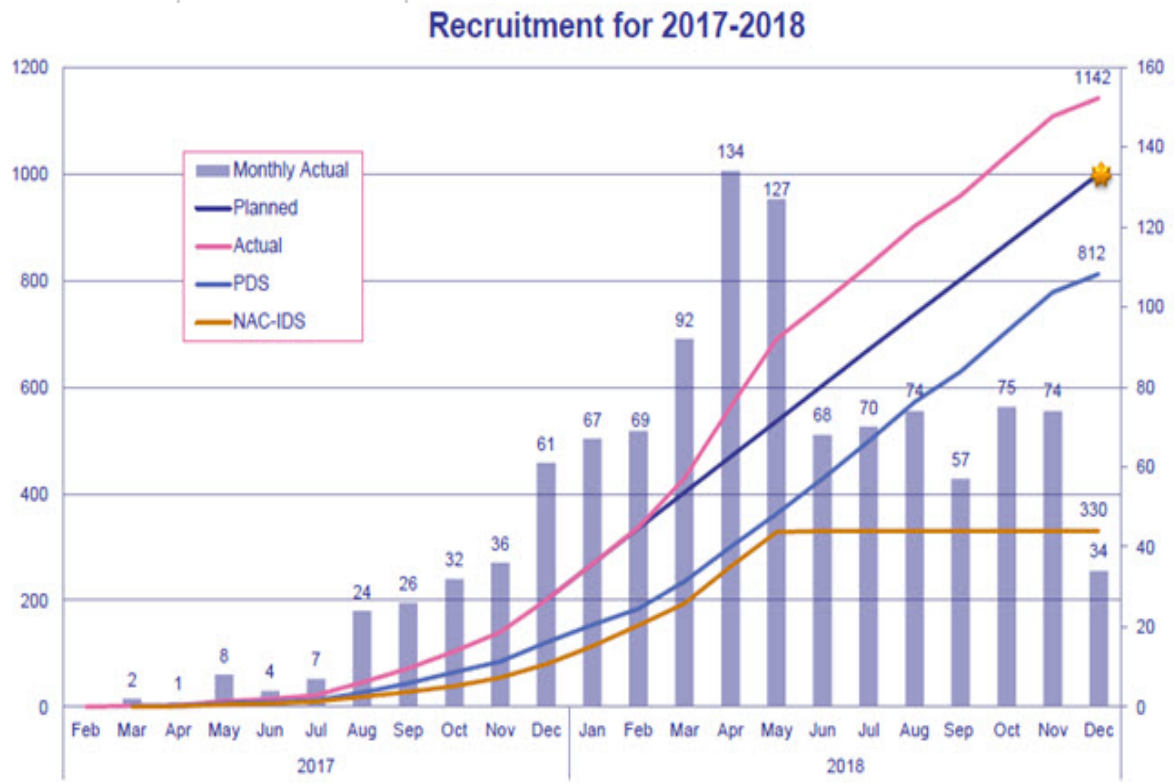
ENGOT Ov-39 Trial
IMaGYN 050





Ovaio 1° linea

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ENGOT ov46 - DUO-O

ENGOT ov43

Ovaio recidiva platino sensibile

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ENGOT ov42 AVATAR

Ovaio recidiva platino resistente

ENGOT ov50

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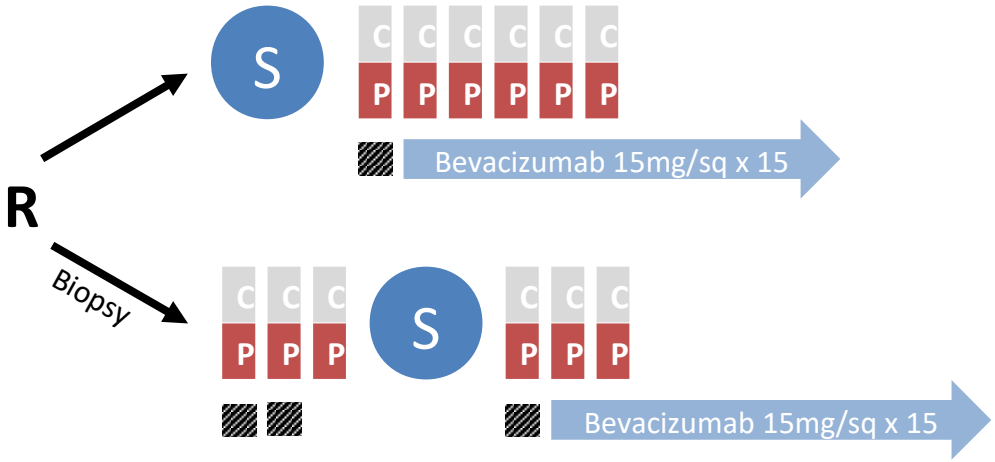
ENGOT-ov33/TRUST

Trial on Radical Upfront Surgical Therapy

ENGOT Model A; ENGOT Lead Group AGO

Pts. with ovarian-, fallopian-tube or peritoneal-cancer FIGO stage IIIB, IIIC and resectable stage IVA/IVB

Total sample size 686



- *Primary Endpoint OS ITT population.*
- *Secondary Endpoints PFS, resection rates, M'nM after 6 months, QoL, „fragility Index"*
- *Strata: Site, age-ECOG combination (EGOG 0 + age up to 65 y vs. ECOG >0 + 66y and older)*
- ***Qualification process for participating centers to ensure high surgical quality***

S surgery C Carboplatin AUC5 P Paclitaxel 175 mg/sq → Bev. 15mg 15 mon

suggested therapy, also weekly paclitaxel possible / or omission of Bev

Standard of Care Treatment

TRUST

Trial on Radical Upfront Surgical Therapy

Amendment n 1

Increase of sample size to account for a higher drop-out rate
New sample size: 772 patients to be randomized

Addition of **translational research part:**
Prospective collection of blood samples and prospective/retrospective collection of tumor tissue for molecular-pathological, molecular-genetic, and pharmacogenetic examinations

Main scientific goals

- Prospective evaluation of a **"debulking signature"** in primary advance epithelial ovarian cancer.
- Prospective evaluation of a **"chemotherapy response score"** of patients undergoing neoadjuvant chemotherapy in primary advance epithelial ovarian cancer
- Prospective evaluation of a **mini-epigenetic signature to predict survival** in primary advanced epithelial ovarian cancer.
- Evaluation of **cell-free (cf) DNA** in the management of primary advanced epithelial ovarian cancer

ENGOT
European Network of Gynaecological Oncological Trial groups

GYNECOLOGIC CANCER INTERGROUP

T*R*U*S*T

Recruitment status 24.05.2019

779/772 patients randomized (= 99.7 %)

MaNGO

GINECO ARCAGY

NSGO-CTU

Country	Sites (20 SIVs / 20 active)	Group	PI	# pts screened	# pts randomized	# pts eligible*
	Essen KEM	AGO	Heitz, F., Harter P., du Bois A.	357	117	**117**
	Berlin Charité	AGO	Sehouli, J., Muallem M., Chekerov R.	152	120	**116**
	Tübingen UFK	AGO	Krämer, B., Brucker S., Kommoss S., Taran F-A.	252	104	**97**
	Düsseldorf, KWD	AGO	Lampe, B.	131	95	**93**
	München LMU	AGO	Burges, A., Trillsch F.; Mahner S.	161	51	**46**
	London, Imperial Hospital	single site / AGO	Fotopoulou, C.	91	44	**44**
	Milan, IEO	MaNGO	Aletti, G.	45ǂ	44	**44**
	Hamburg UKE	AGO	Schmalfeldt, B.	94	38	**36**
	Dresden UFK	AGO	Wimberger, P.	57	32	**30**
	München r.d.I.	AGO	Bronger, H.	36	23	**23**
	Stockholm, Karolinska	NSGO	Falconer, H.	44	18	**18**
	Paris, HEGP	GINECO	Lecuru, F.	19	18	**17**
	Milan, INT	single site / MaNGO	Raspagliesi, F.	92	15	**15**
	Copenhagen, Rigshospital	NSGO	Mosgaard, B.J.	69	13	**13**
	Naples, INT	single site / MaNGO	Greggi, S.	47	12	**11**
	Bordeaux, Institut Bergonié	GINECO	Guyon, F.	11	11	**11**
	Lund, Skane University	NSGO	Kannisto, P.	33	9	**9**
	New York, MSKCC	single site / AGO	Chi, D.	52	8	**8**
	Wien, UFK	Single site / AGO	Reinthaller, A.; Grimm, C.	5	5	**5**
	Villejuif, Inst Gustave Roussy	GINECO	Gouy, S.	2	2	**2**
			TOTAL	**1750**	**779**	**755**

* Status of December 4, 2018 (preliminary information; eligibility check via QA Board is ongoing); ǂ patient list was provided, blinded screening log needs to be provided

Ovaio 1° linea

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ENGOT ov46 - DUO-O

ENGOT ov43

Ovaio recidiva platino sensibile

ENGOT ov38 - OReO

ENGOT ov41 - ANITA

ENGOT ov53

ENGOT ov42 AVATAR

Ovaio recidiva platino resistente

ENGOT ov50

ENGOT OV-46/ DUO-O

N = 927

- Newly diagnosed advanced high grade epithelial OvC stage III-IV
- Primary surgery or interval debulking surgery (IDS)

1:1:1

Control arm
- CTX 6 cycles
- Bevacizumab

Tx Intensification
- CTX 6 cycles
- Bevacizumab
- Durvalumab

Tx intensification with olaparib maintenance
- CTX 6 cycles
- Bevacizumab
- Durvalumab

Maintenance for all pts without PD on CTX (CR, PR, SD)

Olaparib till PD for pts with evidence of disease at 24 mo

Olaparib 300mg BD (24 months)

5 months | 15 months | 30 months

Primary:
- PFS

Formal Secondary:
- OS

Stratification:
1) No residual vs. residual or IDS
2) tBRCAwt vs. tBRCAmut
3) Region: US; EU, RoW

ENGOT model C; ENGOT lead group AGO

DUO-O Study / AGO-OVAR 23
ENGOT-ov46

Olaparib and Durvalumab in addition to SoC in newly diagnosed, advanced, ovarian cancer patients

•ENGOT Model C

•Sponsor AstraZeneca

•N° of already recruited patients
227 patient were randomized or allocated to treatment

•Planned N° of patients
•1056 patients

•Status
Recruiting (First patient screened on 04-Jan-2019; First patient randomized On 30-Jan-2019)

•Participating Groups
AGO-A, BGOB, GEICO, GINECO, GOG-F, JGOG, KGOG, MaNGO, MITO, NSGO, PGOG, TRSGO

•Other important information
Countries with EC and RA approval: Austria, Belgium, Canada, Denmark, Finland, France, Germany, Hungary, Italy, Japan, Poland, South Korea, Spain, Turkey, and USA.
First site activation in Italy planned for July 2019

Ovaio 1° linea

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ENGOT ov43

Ovaio recidiva platino sensibile

ENGOT ov38 - OReO

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ENGOT ov53

ENGOT ov42 AVATAR

Ovaio recidiva platino resistente

ENGOT ov50

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ENGOT-ov43:
Pembro and Olaparib in first-line OC

STUDY DESIGN

Trial setting: **Ovary/newly diagnosed**
Sponsor(s): **MSD**
Planned No. of patients: **1086**
FPI: **expected Q4 2018**
Co-primary Endpoints: **PFS (by PI) and OS**

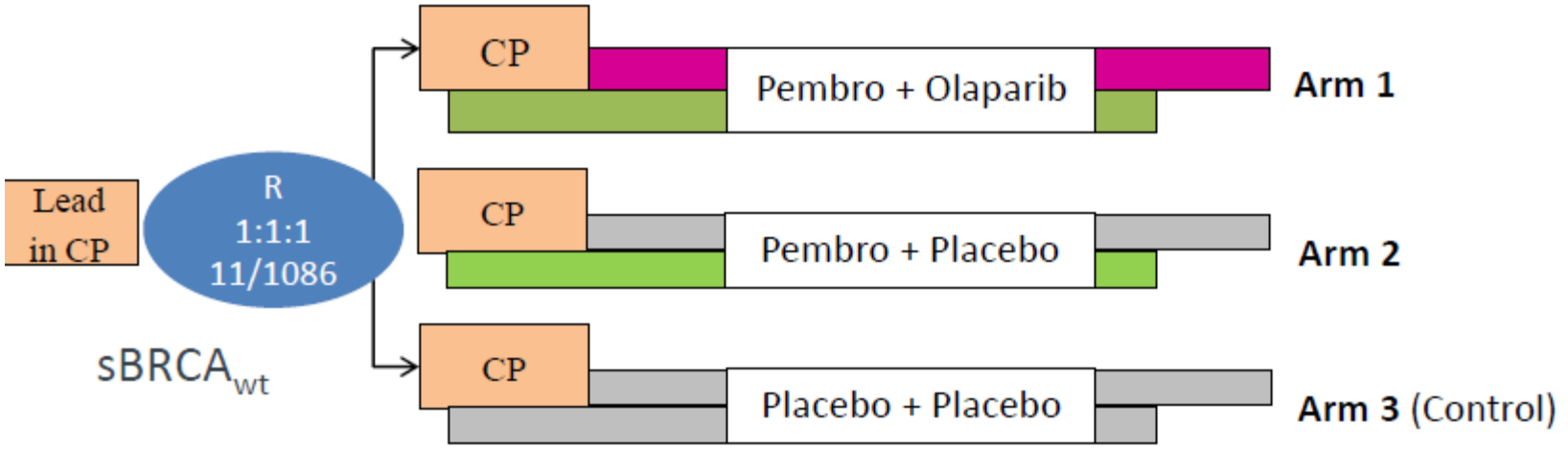
First biopsy for somatic BRCA testing (taken at PDS or laparoscopy or core,…)

Randomization before 2nd chemo cycle if not somatic mutated in BRCA

Stratification: 1. Bev use 2. PDS R0; PDS R>0; NACT->IDS
3. PD-L1 status (CPS < or >= 10)

Primary debulking | **Interval debulking**

Phase II in sBRCAm expected Q2 2019



CP: Carboplatin / Paclitaxel

Pembro 200mg iv q 3wk 2y Start at 2nd chemo cycle

Olaparib 300 mg BID, till PD (2Y is NED after CP)

Placebo

Bevacizumab allowed; to be specified in advance; randomization to be stratified by use of bev or not

ENGOT-ov43: Pembro and Olaparib in first-line OC

STUDY STATUS

FPI: March 2019; 17 patients randomized

ENGOT model C; ENGOT lead group BGOG

ENGOT GROUP	EC/CA approval	N° activated sites	In screening/Lead-in	Enrolled/Expected
BGOG	YES	6/10	2/4	8/83
ISGO	YES	6/11	1/1	2/70
PGOG	YES	4/8	2/0	0/40
GEICO	YES	8/11	2/0	0/66
CEEGOG	Hungary: 22-feb-2019 Czech Republic: Est. April 2019 Ukraine: CA submitted 10-dec-18	Hungary: 0/5 Czech Republic: 0/5 Ukraine: 0/8		Hungary: 0/60 Czech Republic: 0/55 Ukraine: 0/52
GINECO	EC submitted 24-Jan-19; CA Est. March 2019	0/8		0/45
NOGGO/AGO		0/15		0/55
MITO/MaNGO	EC/CA submitted 21-Jan-2019	0/13		0/62
TRSGO	CA: submitted 05-feb-2019	0/8		0/80
Total ENGOT		**24/102**	**7/5**	**10/668**
Non-ENGOT		22/137	10/5	7
Total accrual		**46/239**		**17**

IM: 8th March in Rome, 200 participants from all participating ENGOT groups and Russia, Canada, South Africa

Ovaio 1° linea

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ENGOT ov46 - DUO-O

ENGOT ov43

Ovaio recidiva platino sensibile

ENGOT ov38 - OReO

ENGOT ov41 - ANITA

ENGOT ov53

ENGOT ov42 AVATAR

Ovaio recidiva platino resistente

ENGOT ov50

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ENGOT Ov38/OReO

OReO design

Total sample size: 416 pts

Eligible patients

- Relapsed non-mucinous EOC
- **Treatment with one course of PARPi maintenance therapy**
- **PR/CR after≥4 cycles of platinum-based chemo**
- Documented *BRCA1/2* status

Cohort 1 *BRCAm*

120 patients
with a germline or somatic mutation in *BCRA1/2*

Exposure for ≥18 months after first-line chemotherapy or ≥12 months after second-/later-line chemotherapy

Cohort 2 non-*BRCAm*

108 patients

Exposure for ≥12 months after first-line chemotherapy or ≥6 months after second-/later-line chemotherapy

PR or CR to most recent course of platinum-based chemotherapy (no bevacizumab)

RANDOMIZATION 2:1

Olaparib tablets

300 mg bid or last tolerable dose

Placebo

PFS
Primary endpoint
(RECIST 1.1)

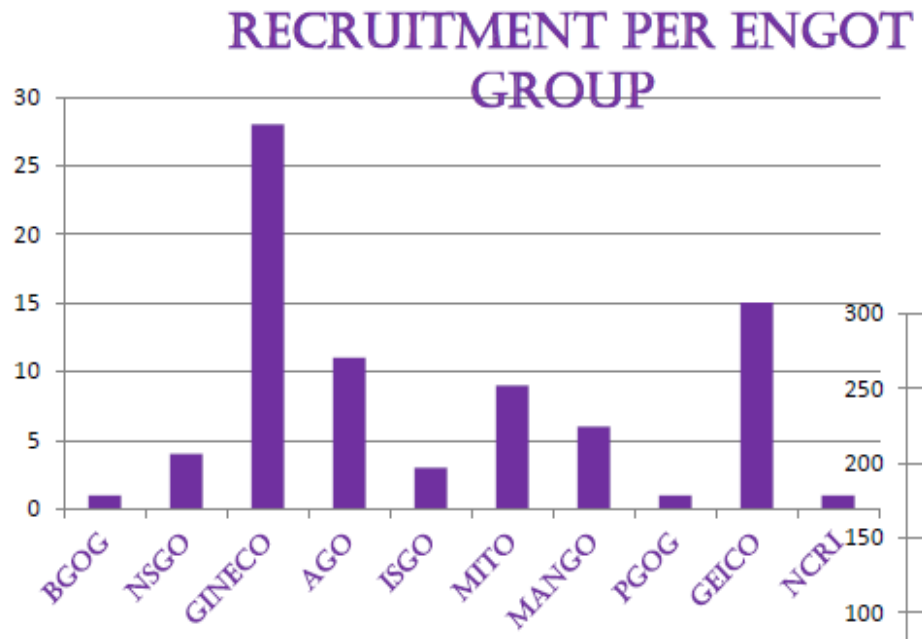
PFS, OS, TTP ‡, TDT, TFST, TSST, HRQoL, Safety

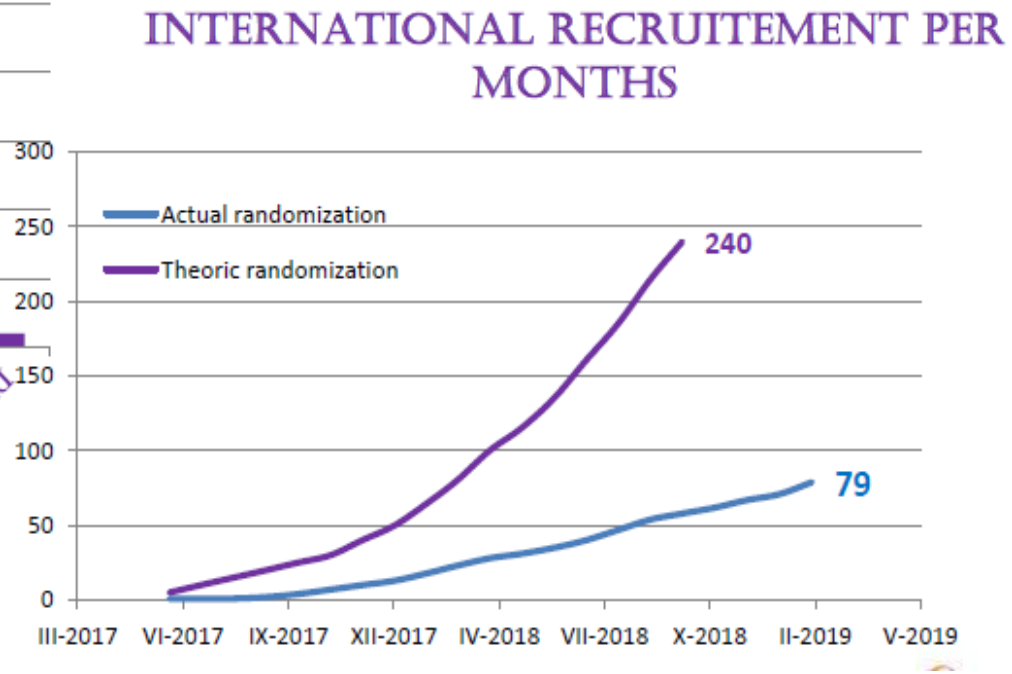
Stratification factors:
- Prior bevacizumab
- ≤3 vs ≥4 prior lines of chemotherapy

ENGOT Model C; Lead Group GINECO

ENGOT Ov38/OReO

ENROLLMENT





ENGOT Ov38/OReO

OReO enrollment – last update May 2019

ENGOT Group	*Country*	*Planned Sites*	*Sites Initiated*	*Sites Active*	*Subjects Enrolled*	*Subjects in Screening*
BGOG	Belgium	3	3	2	2	0
NSGO	Denmark	3	3	2	3	0
	Norway	1	1	1	1	0
GINECO	France	20	19	14	36	1
AGO	Germany	20	19	10	26	0
ISGO	Israel	7	7	2	3	0
MANGO	Italy	7	7	3	7	0
MITO	Italy	11	11	5	11	2
PGOG	Poland	6	5	2	4	1
GEICO	Spain	13	13	9	19	1
NCRI	UK	8	8	3	3	0
	Totals	**99**	**96**	**53**	**115**	**5**

Ovaio 1° linea

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ENGOT ov43

Ovaio recidiva platino sensibile

ENGOT ov38 - OReO

ENGOT ov41 - ANITA

ENGOT ov53

ENGOT ov42 AVATAR

Ovaio recidiva platino resistente

ENGOT ov50

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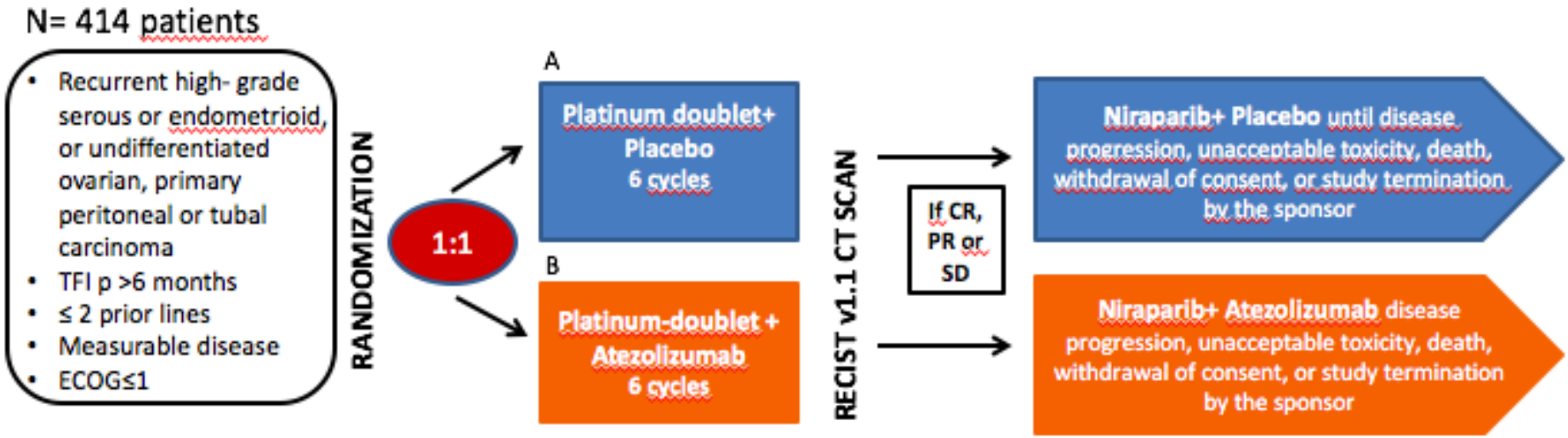
ENGOT Ov41/ANITA

ENGOT Model B; Lead Group GEICO



Stratification factors:

- Platinum based regimen selected
- PFI (6-12 months vs > 12 months)
- BRCA mutation status (mutated vs. non-mutated)

Primary Endpoint:

- PFS by RECIST v.1.1

Secondary endpoints:

- Safety and tolerability
- TFST, TSST,PFS2,OS
- ORR, DOR
- QoL/PRO

Enrollment start: Q4 2018

Randomized patients: 68 pts

Enrollment on hold

JAVELIN Ovarian 200 trial : "Avelumab alone or in combination with **pegylated liposomal doxorubicin** vs **pegylated liposomal doxorubicin** alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase 3"

Prespecified analysis indicate a potential role for **PD-L1 expression as a predictor of clinical benefit**

GEICO and ROCHE decided to **include a PD-L1 stratification factor in the study and submission of the study on hold in Europe until the PD-L1 stratification factor is confirmed and implemented**, which is expected to be approximately 3 months

Current Status Italy :

Submission early July 2019, First SIV September/October 2019

Arruolamento bloccato perchè?

ANITA Centri MaNGO

Site	Principal Investigator	Commitment
Istituto Europeo di Oncologia IEO- Milano	Nicoletta Colombo	40
ASST-Lecco	Antonio Ardizzoia	5
IOV-IRCCS-Padova	Ornella Nicoletto	12
Ospedale Mauriziano-Torino	Annamaria Ferrero	8
Ospedale Sant'Anna-Torino	Paolo Zola	5
IRCCS Arcispedale Santa Maria Nuova-Reggio Emilia	Alessandra Bologna	25
Spedali Civili-Brescia	Germana Tognon	20
Total number of patients		**115**

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ENGOT ov43

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ENGOT ov53

ENGOT ov42 AVATAR

Ovaio recidiva platino resistente

ENGOT ov50

ENGOT-ov50
TTFields in patients with recurrent ovarian cancer not suitable for platinum (ROC-NP)

Trial setting: **Ovary/recurrent (ROC-NP)**
Sponsor(s): **NOVOCURE**
Planned No. of patients: **540**
FPI: **expected Q1 2019**

STUDY DESIGN

Primary endpoint: OS

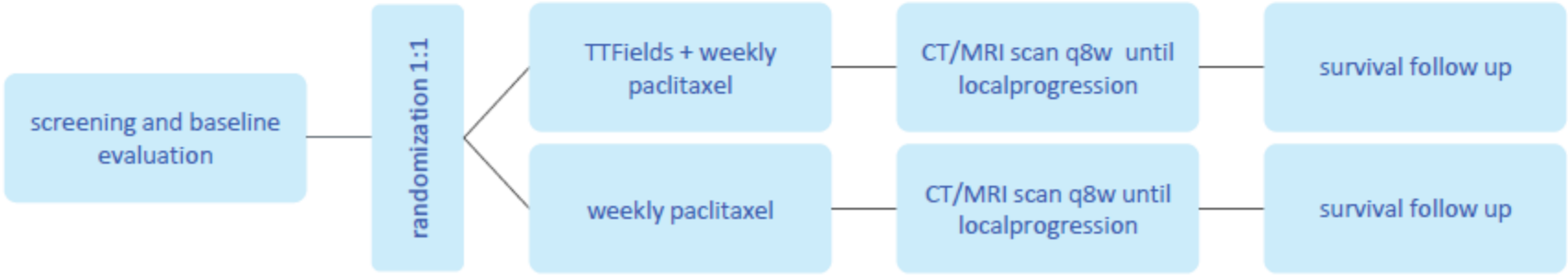
Secondary endpoints: PFS, ORR, severity and frequency of adverse events, QOL, time to undisputable deterioration in health-related QoL / death

Planned sample size: 540

Study population: Ovarian/primary peritoneal or fallopian tube carcinoma, maximum two prior lines of systemic therapy following diagnosis of platinum-resistance, ECOG 0-1

Study duration: 48 months (30 months of patient accrual)

Participant duration: expected 12 months on the trial



ENGOT-ov50
TTFields in patients with recurrent ovarian cancer not suitable for platinum (ROC-NP)

- BGOG leading
- 110 sites
- FPI planned Q1 2019

Group/ #sites selected	Submission status (actual/planned)	Planned site initiation
A-AGO – 4	3 LEC approval received CA vote expected 23Mar2019 (1 site) CA submission in Mar2019 (2 sites)	Mar 2019
BGOG – 9	EC /CA vote expected 13Mar2019 (for 3 sites) EC/ CA submission end-Apr2019 (for 6 sites)	First SIV: 4th March (Vergote) Others March 2019
ISGO – 4	3 LEC approval received CA submission mid-Mar2019	Apr/May 2019
DGOG– 4	TBD	TBD
CEEGOG (Czech Republic) – 4	4 LEC approvals received CA queries received	Apr/May 2019
CEEGOG (Hungary) – 2	Planned March 2019	Q2/2019
NOGGO/AGO – 5	Planned March 2019	Q2/2019
PGOG – 9	CEC approval (for 2 sites) CA submission mid-Mar2019 CEC submission (for 7 sites) – Apr/May2019	Jun/Jul2019
MITO - **5** **MaNGO - 3**	LEC Submission planned Mar2019 (for 4 sites) MOH vote expected Apr2019	May/Jun2019
SAKK - 4	CEC/CA queries received (for 3 sites)	May2019
GEICO-8	LEC/CA submission planned in Apr2019	Q3/2019

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Collaborazioni in corso

- carcinoma della cervice -

Cervice - 1° linea

INTERLACE

Cervice - recidiva

ENGOT cx10 - BEAT

ENGOT cx9- EMPOWER

ENGOT cx12

Cervice - 1° linea

INTERLACE

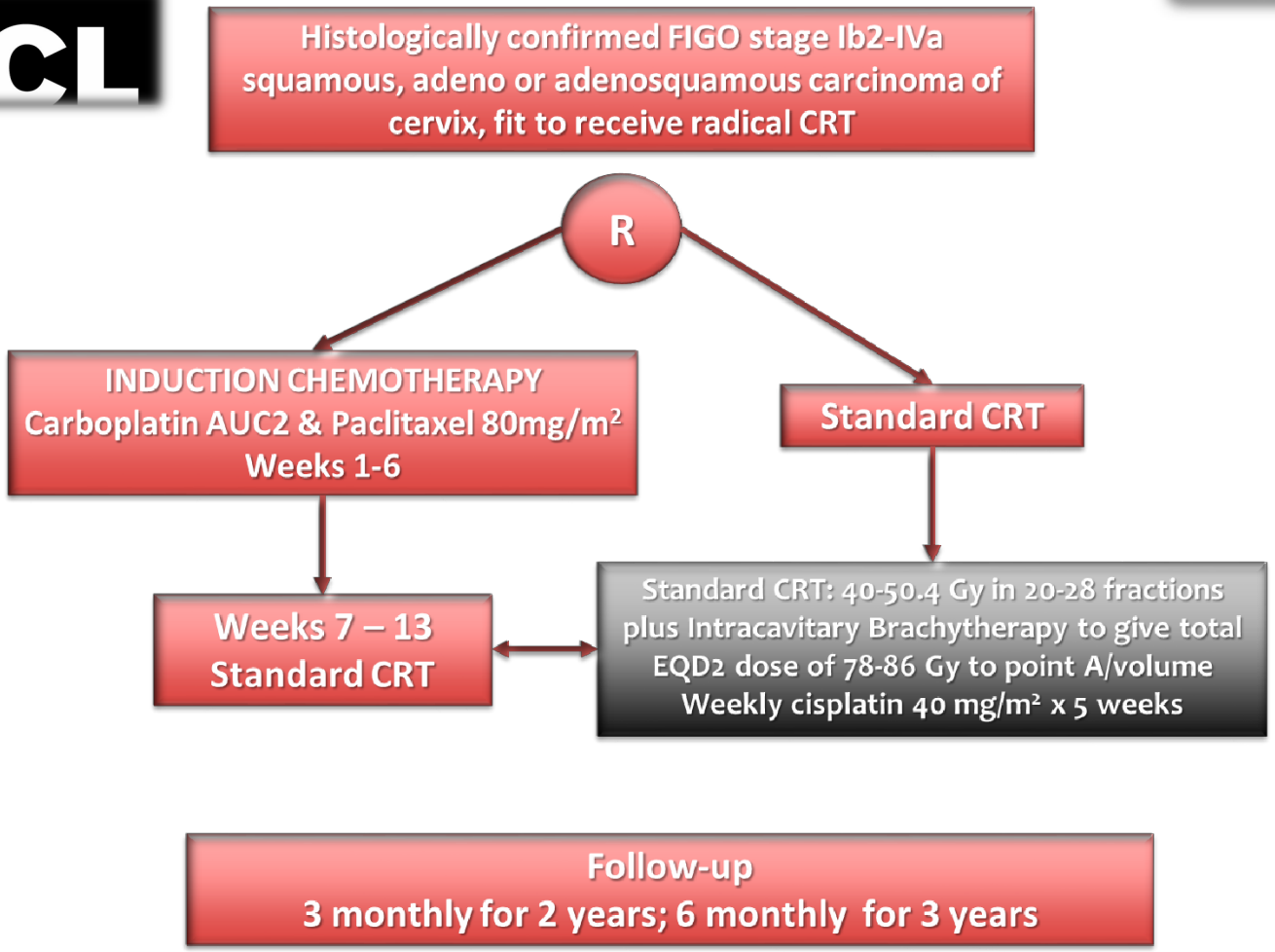
Cervice - recidiva

ENGOT cx10 - BEAT

ENGOT cx9- EMPOWER

ENGOT cx12

INTERLACE



365/500 patients recruited

Recruitment to INTERLACE has been extended to until April 2020 (to recruit the remaining 135 patients)

INTERLACE Italian sites

Italian sites	Principal Investigator	Status	Pending activities
IEO Milano	Nicoletta Colombo	Active 3 pts randomised	
S. Gerardo Monza	Andrea A.Lissoni	SIV performed 25 th February 2019	
AUSL Romagna Ravenna	Claudia Casanova	Site set up completed, queries outstanding	1.Process document 2.EBRT outlingin cases 3.EBRT planning cases 4.Brachytherapy example case
Mauriziano Torino	Annamaria Ferrero	Site set up completed	Brachytherapy cases subordinate to Sant'Anna
A. Manzoni Lecco	Federica Villa	Site set up completed, queries outstanding	All tasks have been submitted , under review
Sant'Anna Torino	Sergio Gribaudo	Site set up ongoing	all RTQA tasks
AOU Pisa	Angiolo Gadducci	Unable to comply with RTQA requirements	Unable to comply with RTQA requirements

Cervice - 1° linea

INTERLACE

Cervice - recidiva

ENGOT cx10 - BEATcc

ENGOT cx9- EMPOWER

ENGOT cx12

ENGOT Cx10/ BEATcc Trial STUDY DESIGN

N=404 Pts

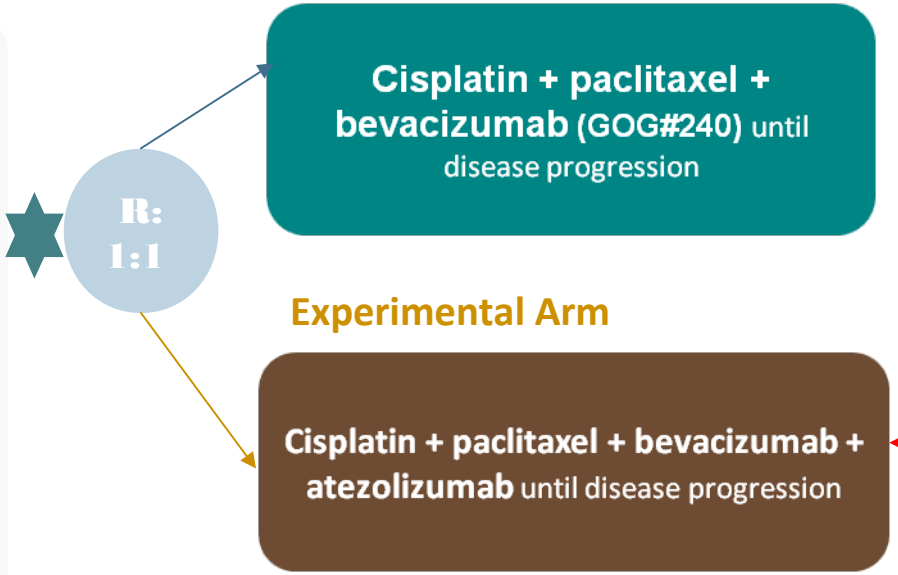
Primary Stage IVB, persistent or recurrent carcinoma of the cervix

Measurable disease by RECIST v1.1

ECOG-PS: 0-1

No previous systemic chemotherapy for advanced or recurrent disease

Available archival tumour for PD-L1 expression



Primary Endpoints:
- Overall survival (OS)

Safety run-in cohort: 12 pts after 2 cycles of treatment

ENGOT model: B

Sponsor(s): GEICO

No. of already recruited patients: 32 randomized / 1 in screening

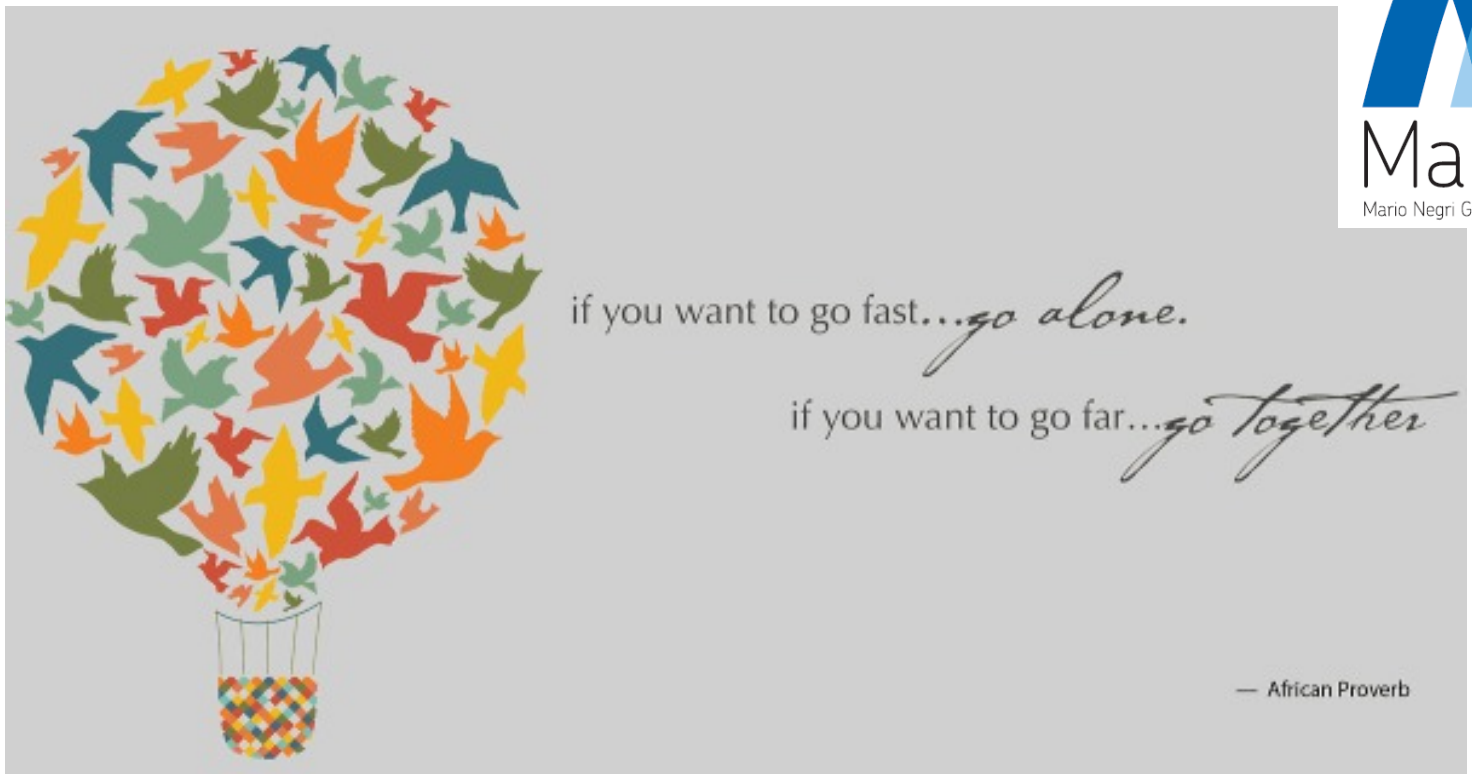
Planned No. of patients: 404

Status: recruiting

BEATcc Centri MaNGO

Site	Principal Investigator	Commitment
Istituto Europeo di Oncologia IEO- Milano	Nicoletta Colombo	15
ASST-Lecco	Antonio Ardizzoia	5
IOV-IRCCS- Padova	Ornella Nicoletto	5
Ospedale Mauriziano-Torino	Annamaria Ferrero	6
AOU Pisana	Angiolo Gadducci	10
Ospedale Sant'Anna-Torino	Dyonissios Katsaros	5
IRCCS Arcispedale Santa Maria Nuova-Reggio Emilia	Alessandra Bologna	6
Ospedale San Gerardo-Monza	Andrea Lissoni	6
Total number of patients	**58**	

Submission performed on March 30th 2019
AIFA objections to be answered by 27th June
Investigators meeting 12th July
First Site Initiation Visit: end July 2019



MaNGO
Mario Negri Gynecologic Oncology

Grazie per l'attenzione