OVARIAN CARCINOMA
FIRST LINE TREATMENT

Silvia Derio, IEO Milano

MaNGO
Mario Negri Gynecologic Oncology

- ENGOT OV46 – DUO-O (RESULTS INTERIM AVAILABLE)
- ENGOT OV43 (ACCRUAL CLOSED)
- ENGOT OV33 – TRUST (ACCRUAL CLOSED)
- ENGOT OV63 – NIRVANA-1 (ENROLLING)
- ENGOT OV57 – AGO-OVAR 28 (UNDER ACTIVATION)
- ENGOT OV62 – NPLUS (UNDER ACTIVATION)
- IOLANTHE (UNDER ACTIVATION)

YMaGiNe
Young Mango Gynecologic Network

MaNGO
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ENGOT-ov46 - DUO-O

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

ENGOT model C

Sponsor: AstraZeneca

- **Newly diagnosed advanced high grade epithelial OvC stage III-IV**
- **Primary surgery or interval debulking surgery (IDS)**
- **N~1254**

Stratification:
1) No residual macroscopic disease vs. residual or IDS
2) Region: North America; EU; RoW

BRCAm — **n ~150**

Single arm
CTX 6 cycles q3wk
Optional Bevacizumab 15mg/kg q3wk (15 months)
Durvalumab IV q3wk (24 months)
Olaparib 300mg BD (24 months)

1:1:1 n= 1104

Non-BRCAm

Arm 1 (SOC)
CTX 6 cycles q3wk
Bevacizumab 15mg/kg q3wk (15 months)
Durvalumab Placebo IV q3wk (24 months)
Olaparib placebo BD (24 months)

Arm 2
CTX 6 cycles q3wk
Bevacizumab 15mg/kg q3wk (15 months)
Durvalumab IV q3wk (24 months)
Olaparib Placebo tablets BD (24 months)

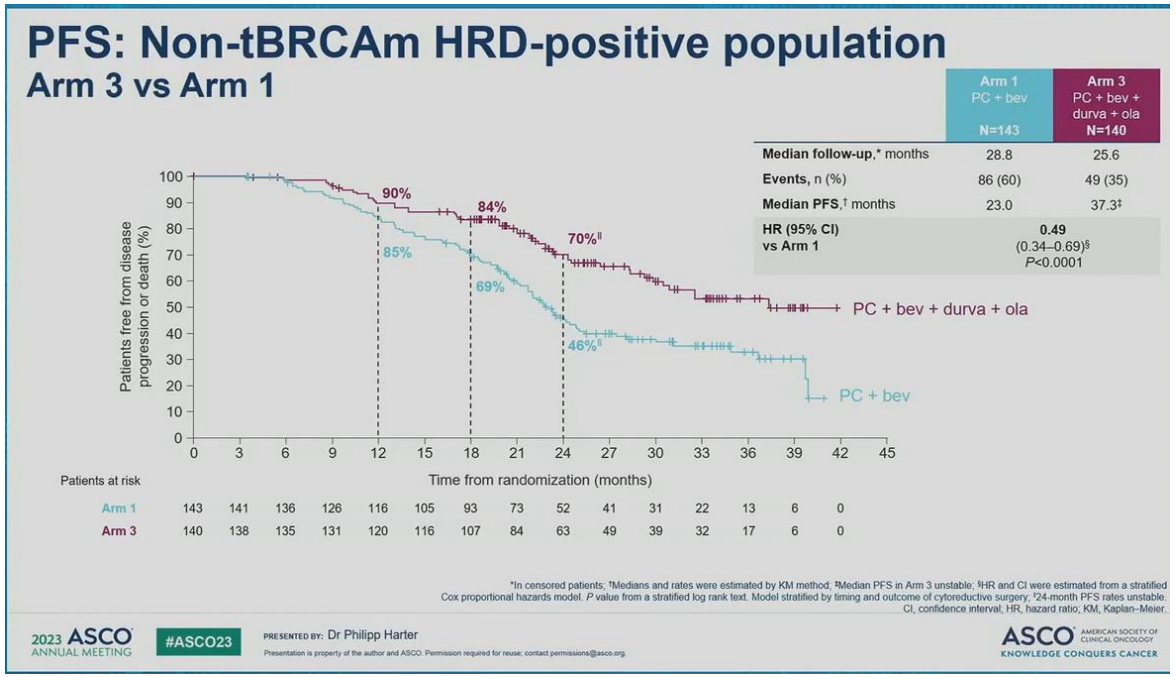
Arm 3
CTX 6 cycles q3wk
Bevacizumab 15mg/kg q3wk (15 months)
Durvalumab IV q3wk (24 months)
Olaparib 300mg BD (24 months)

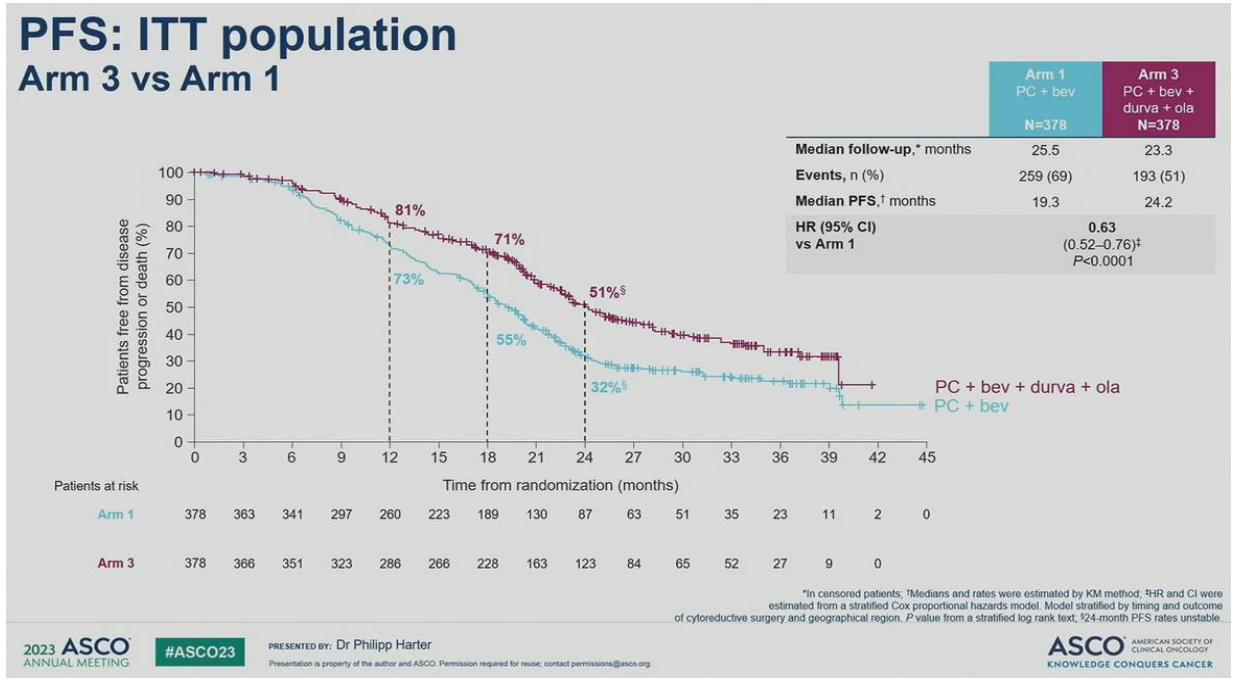
Tumour sample from primary surgery or biopsy to be provided for central BRCA testing

Accrual closed with **1284 patients enrolled**

58 pts by 4 MaNGO sites

DUO-O: interim PFS results of non-BRCAm cohort (ASCO 2023)





Harter et a., J Clin Oncol 41, 2023

ENGOT-ov46 - DUO-O

Status MaNGO sites

- Participation with 6 sites planned, 4 of them have enrolled / randomized patients

PI Name	Centre Number	Centre Status	Centre Activation Date	Subjects Enrolled	Subjects Screen Failed	Subjects Randomised
Colombo,Nicoletta	4101	Active	2019-Jul-11	31	7	24
Bologna,Alessandra	4102	Not Activated	-	0	0	0
Katsaros,Dionyssios	4103	Not Activated	-	0	0	0
Ferrero,Annamaria	4104	Active	2020-Sep-17	5	2	3
Tognon,Germana	4105	Active	2019-Aug-27	12	4	8
Ardizzoia,Antonio	4106	Active	2020-Feb-27	10	3	7

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

ENGOT model C

Sponsor: MSD

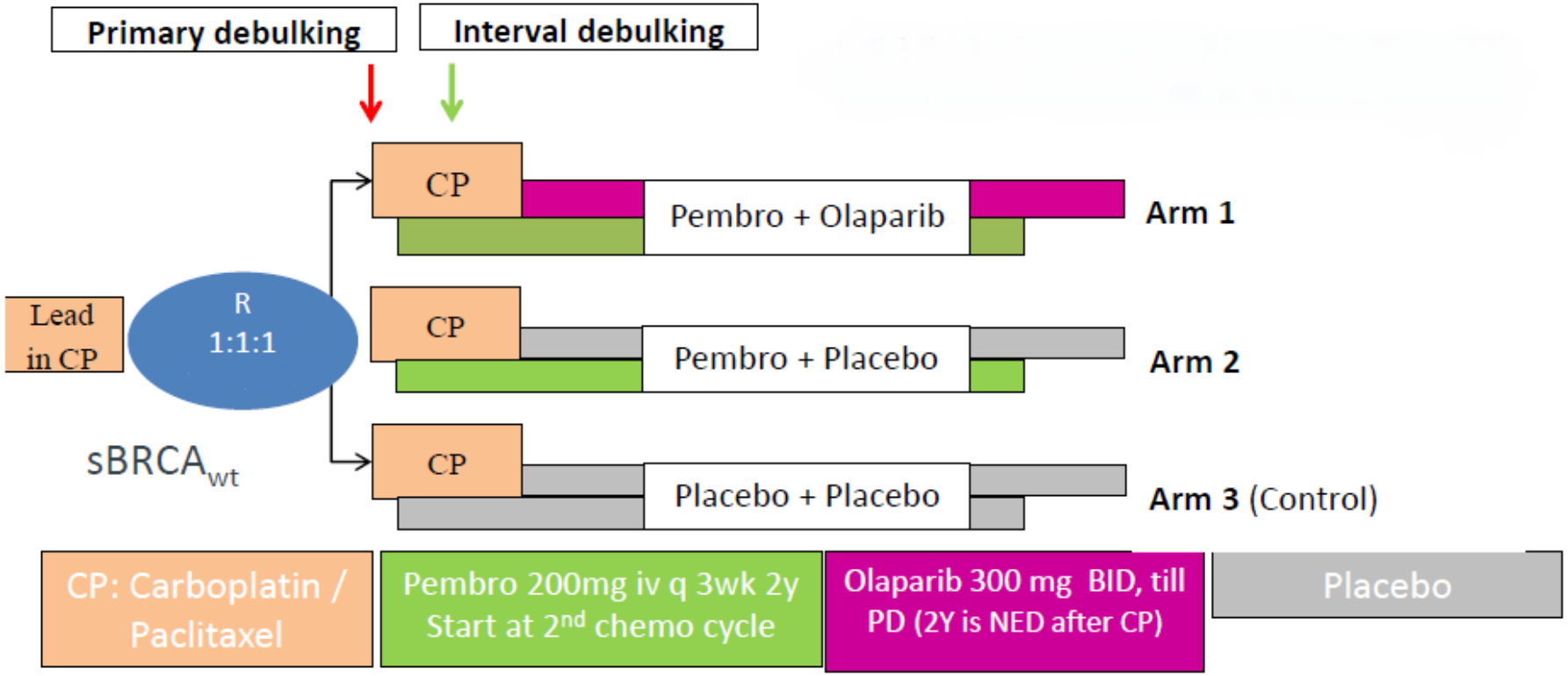
STUDY DESIGN

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)



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

Study Timelines

- Accrual closed with 1314 patients enrolled **114 from Italian sites**
- Safety IA #6 in June 2022 → recommendation to continue the study without modification
- Primary Outcome Measure Q3 2023
- Results expected soon (Sept 2023)

ENGOT-ov43

MaNGO METRICS

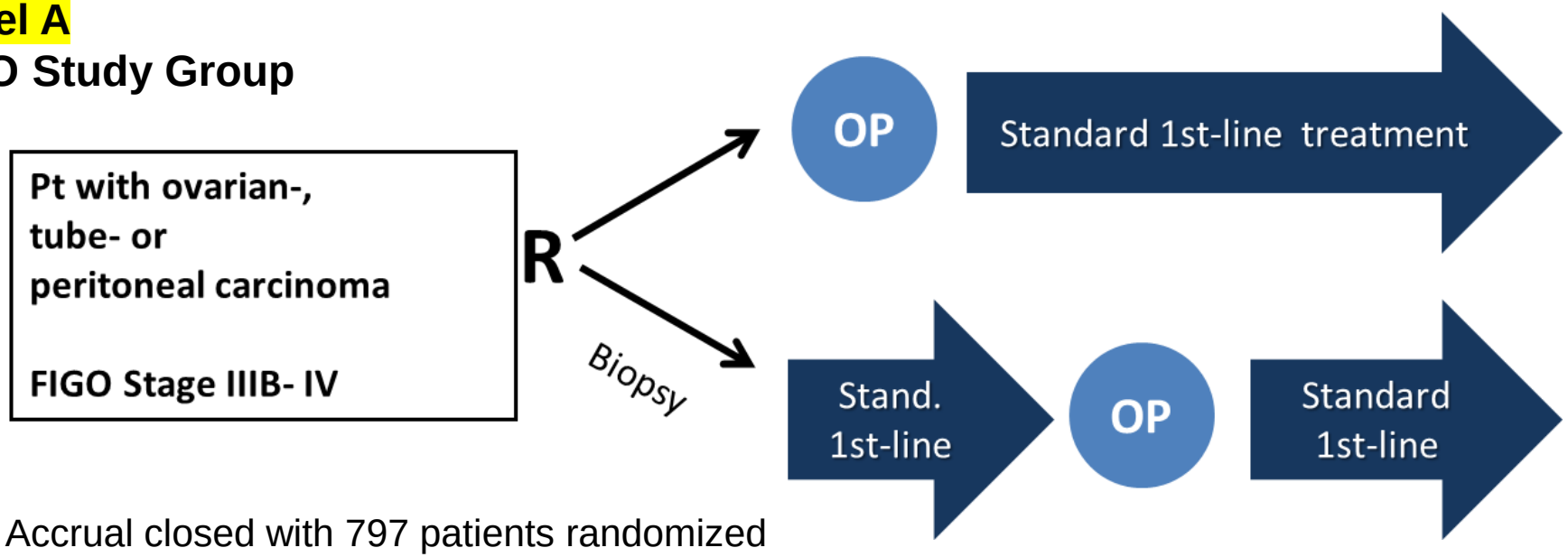
Investigator	Site City	Organization/Institution to which the site belongs to	Total Screened	Screened failed	Total Lead in Fail	Total Randomized
N. COLOMBO	Milano	IEO	46	3	19	24
A. ARDIZZOIA	Lecco	ASST Lecco	8	2	1	5
P. ZOLA	Torino	Città Della Salute e della Scienza	21	1	10	10
P. CONTE	Padova	IOV	15	1	4	10
F. RASPAGLIESI	Milano	Istituto Nazionale Tumori	11	0	1	10

TRUST – Trial on Radical Upfront Surgical Therapy

ENGOT-ov33 – TRUST

ENGOT model A

Sponsor AGO Study Group



Accrual closed with 797 patients randomized

3 sites in Italy with 73 patients randomized (IEO Milano, INT Milano as MaNGO sites)

Primary OS analysis: **after 380 events have been observed in eligible patients (modified ITT analysis ~ 2024)**

THE NIRVANA STUDY

ENGOT study: Model A
Sponsor:GINECO

Newly diagnosed FIGO stage III high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer

- Female patient ≥ 18 years old
- High grade OC
- FIGO stage III A,B,C
- Frontline surgery
- No residual tumor
- PS 0 - 1

CP First cycle

Randomization 1:1

- Carboplatin AUC5-6 + paclitaxel 175 mg/m² q3w → Niraparib 2 years
- Bev 15 mg/kg q3w → Carboplatin AUC5-6 + paclitaxel 175 mg/m² q3w → Niraparib 2 years

N=390

Stratification factors:
- BRCA status
- FIGO stage (IIIA versus IIIB/IIIC)
- Previous HIPEC

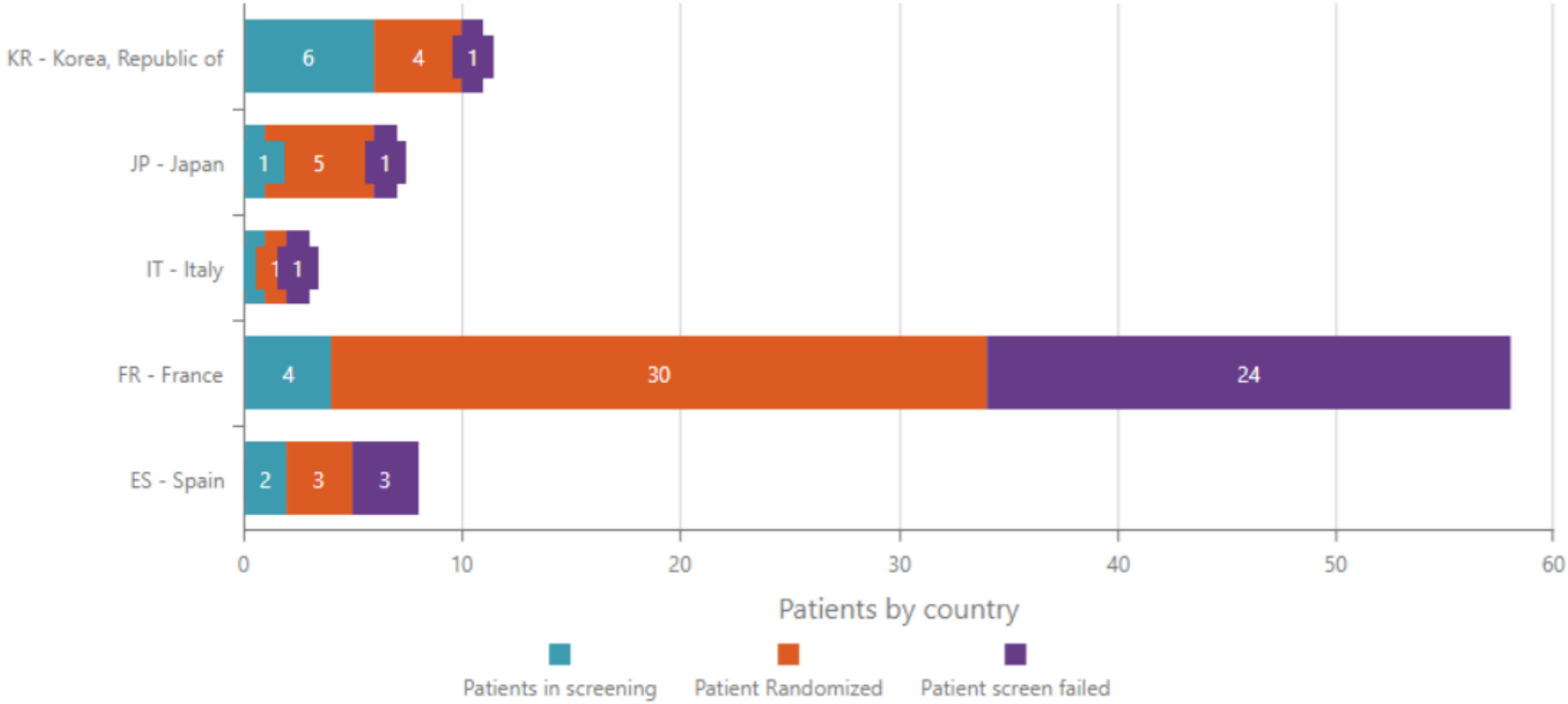
Primary endpoint
Investigator-assessed PFS at 24 months (RECIST v1.1)

Secondary endpoints
PFS
TFST
PFS2, TSST
OS
HRQoL
Safety and tolerability

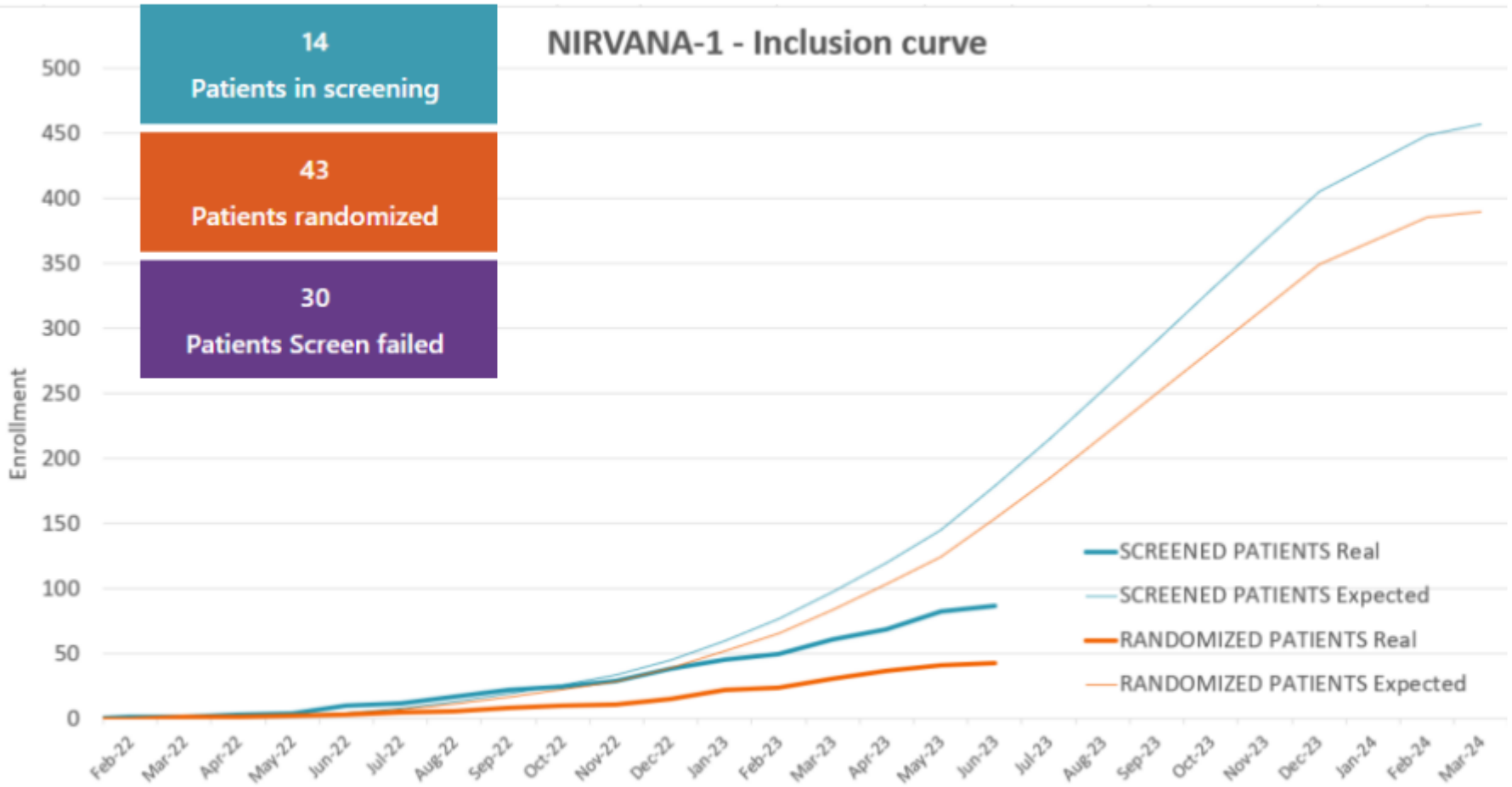
Translational research
- ctDNA
- miRNA
- CHIP

Bev + Niraparib will be provided

NIRVANA-1 Enrollment by country



NIRVANA-1 Enrollment update



Main reason of screen failure:

- Ineligibility (n= 25)
  - IC#4: no CC-0 surgery (n=7)
  - IC#11 and/or 12: biological parameters (n=6)
  - IC#8: no CT-scan at screening (n=3)
  - IC#14: no BRCA result available (n=3)
  - IC#7: time between surgery and C1 >6weeks (n=1)
  - IC#3: diagnostic (n=1)
  - IC#10&13: eligibility beva & controlled hypertension (n=1)
  - EC#30: uncontrolled medical disorder (n=1)
  - Unknown (n=2)
- Consent withdrawn (n= 5)

NIRVANA-1 MaNGO update

Study approval: CA: December 2022; CEC: January 2023

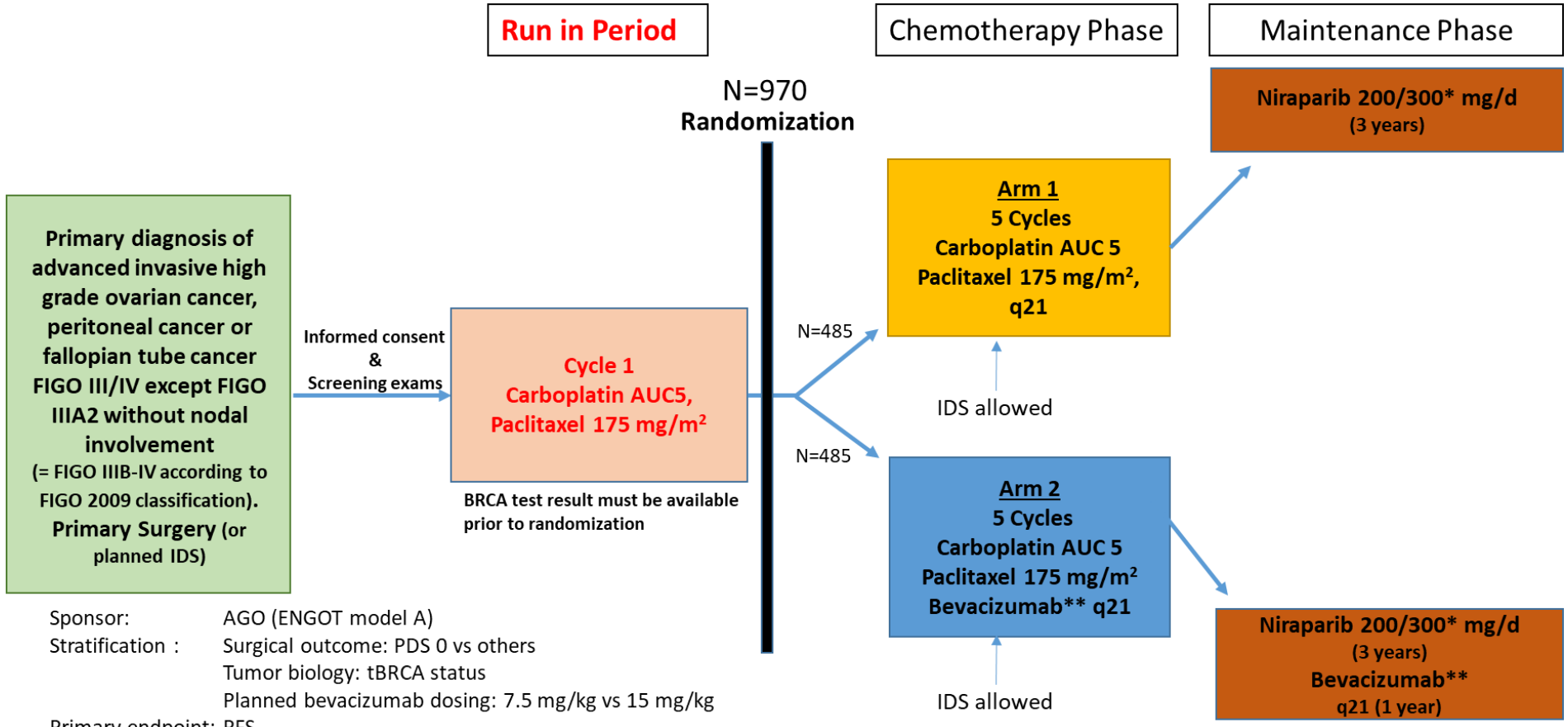
Number of subjects estimated to be contributed by group: 75-85 patients

Site and PI	Status	Patients
Istituto Nazionale dei Tumori (Coordinator) - PI Francesco Raspagliesi	Active since **April 28 2023**	3 enrolled: 2 screen-failed and 1 patient randomized
Istituto Europeo di Oncologia – PI Nicoletta Colombo	Agreement under revision by the site	
Ospedale Croce e Carle - PI Marcella Occelli	Agreement under revision by the site	
AOU Careggi – PI Maria Cristina Petrella	Site specific documents must be completed. Agreement under revision by the site	
Ospedale S. Gerardo - PI Andrea Alberto Lissoni	Agreement under revision by the site	
Ospedale di Sondrio - PI Alessandro Bertolini	Agreement under revision by the site	
Ospedale Sant'Anna – PI Dionyssios Katsaros	The feasibility of the study must be approved by the site in order to finalize the agreement. A dedicated portal must be completed in collaboration with the site. MaNGO is completing its part and will reach the site soon	

AGO-OVAR 28 / ENGOT-ov57

ENGOT study: Model A
Sponsor: AGO-Germany

Study Design



Sponsor: AGO (ENGOT model A)
Stratification : Surgical outcome: PDS 0 vs others
Tumor biology: tBRCA status
Planned bevacizumab dosing: 7.5 mg/kg vs 15 mg/kg
Primary endpoint: PFS

* The recommended starting dose of niraparib is 200 mg, taken once daily. For those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL the recommended starting dose of niraparib is 300 mg, taken once daily.

** Bevacizumab dosing according to national standard (either 7.5 mg/kg or 15 mg/kg). In Germany, bevacizumab must be given at a dose of 15 mg/kg body weight at all participating study centers.
In patients with planned IDS, bevacizumab could be given before IDS according to local guidelines, but has to be omitted at the last cycle before IDS AND first cycle after IDS. Irrespective of the application of bevacizumab before IDS, bevacizumab should to be started 2 cycles after IDS. E.g. if IDS is planned after 3 cycles, bevacizumab should be omitted at cycle 3 and cycle 4 and could be started at cycle 5

Primary endpoint:
Progression Free Survival

Stratification:

- Surgical outcome:
  Complete resection of all macroscopic tumor at primary debulking surgery (PDS 0) versus others
- Tumor biology - tBRCA status:
  Presence or absence of a deleterious/suspected deleterious tBRCA mutation
- Planned bevacizumab dosing:
  7.5 mg/kg or 15 mg/kg
  Of note, bevacizumab must be given at a dose of 15 mg/kg body weight at all participating study centers in Germany.

AGO-OVAR 28 / ENGOT-ov57

Study Status

- Niraparib is provided as study drug.
- Bevacizumab, Carboplatin and Paclitaxel are standard of care and **must be provided by site from commercial stock. There will be no reimbursement for these drugs**.

- First Patient First Visit (Signature Informed Consent Form): September 13th 2022
- First Patient randomized: October 18th 2022
- Only Germany is open. In the other ENGOT countries, the study start is currently estimated at the end of 2023 / beginning of 2024. Before this, the study should be migrated in the new EU portal.

AGO-OVAR 28 / ENGOT-ov57

Study Status by country

ENGOT Group	Country	Sites planned	Date of Submission	Date of Approval	Sites activated	Sites active	No. of pts screened	No. of pts randomized
AGO	Germany	80	CA: 6-Oct-2021 EC: 19-Apr-2022	CA: 19-Jan-2022 EC: 1-Aug-2022	50	38	144	81
AGO-Au	Austria	4	Submission through CTIS required					
BGOG	Belgium	5	Submission through CTIS required					
CEEGOG	Czech Republic	3	Submission through CTIS required					
GEICO	Spain	10	Submission through CTIS required					
MaNGO	Italy	10	Submission through CTIS required					

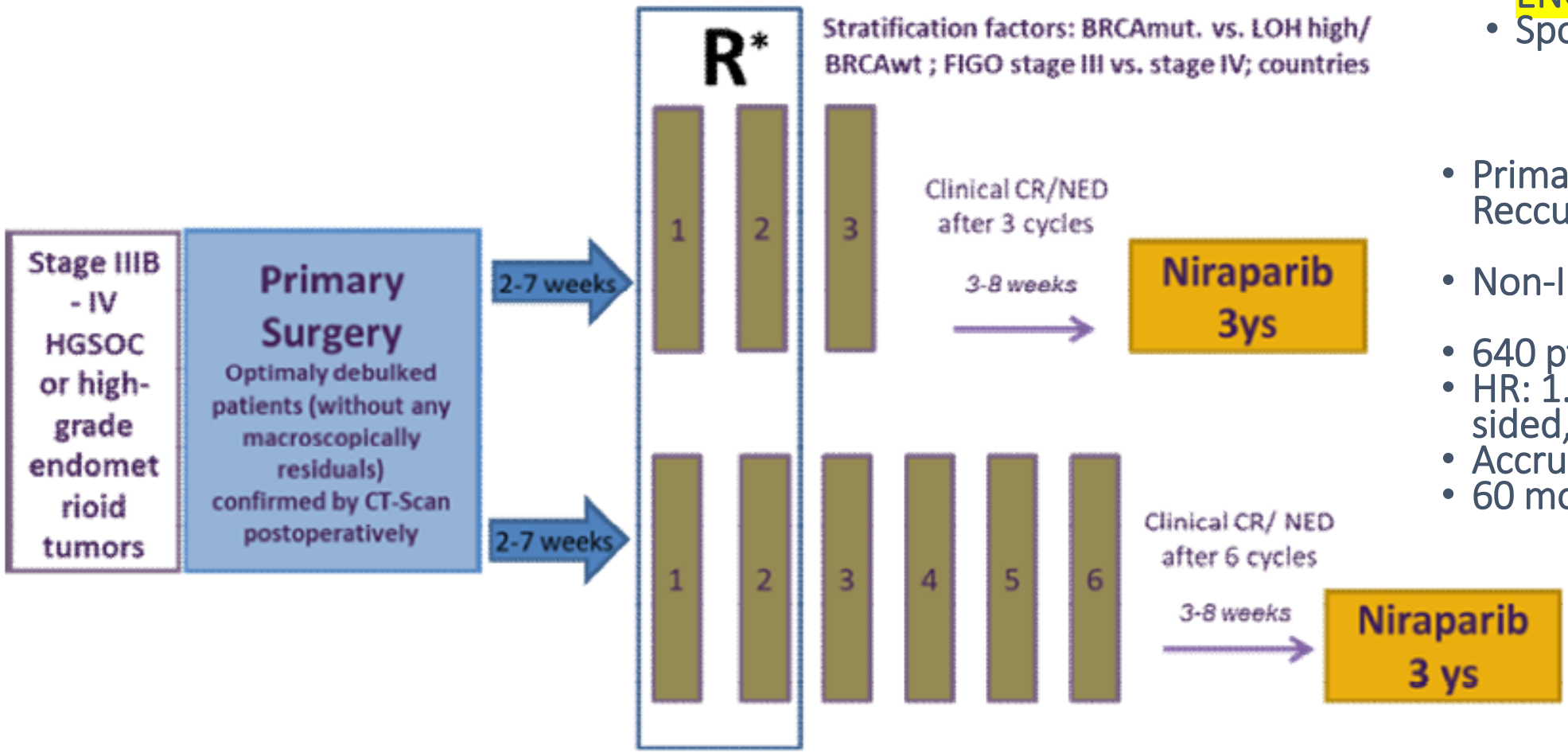
AGO-OVAR 28 / ENGOT-ov57

MaNGO interested sites

City	Hospital	First Name	Last Name
Torino	Ospedale Mauriziano	Annamaria	Ferrero
Brescia	Spedali Civili	Germana	Tognon
Brescia	ASST Garda	Elena	Montani
Lecco	Ospedale Manzoni	Antonio	Ardizzoia
Milano	Istituto Europeo di Oncologia	Nicoletta	Colombo
Padova	Istituto Oncologico Veneto	Valentina	Guarnieri
Reggio E.	Arcispedale S. Maria Nuova	Alessandra	Bologna
Lucca	Ospedale San Luca	Editta	Baldini
Roma	Policlinico Umberto I	Innocenza	Palaia

A Phase II randomized, open label non-inferiority study of Niraparib maintenance after 3 vs. 6 cycles of platinum-based chemotherapy in completely debulked advanced HRDpositive high-grade ovarian cancer patients in first line therapy (N-Plus)

- ENGOT model: B
- Sponsor: NOGGO



- Primary outcome: Reccurence free survival
- Non-Inferiority trial
- 640 pts
- HR: 1.3 (alpha 5% one-sided, power:80%)
- Accrual 36 months;
- 60 months f-up

N-PLUS: Study update June 2023

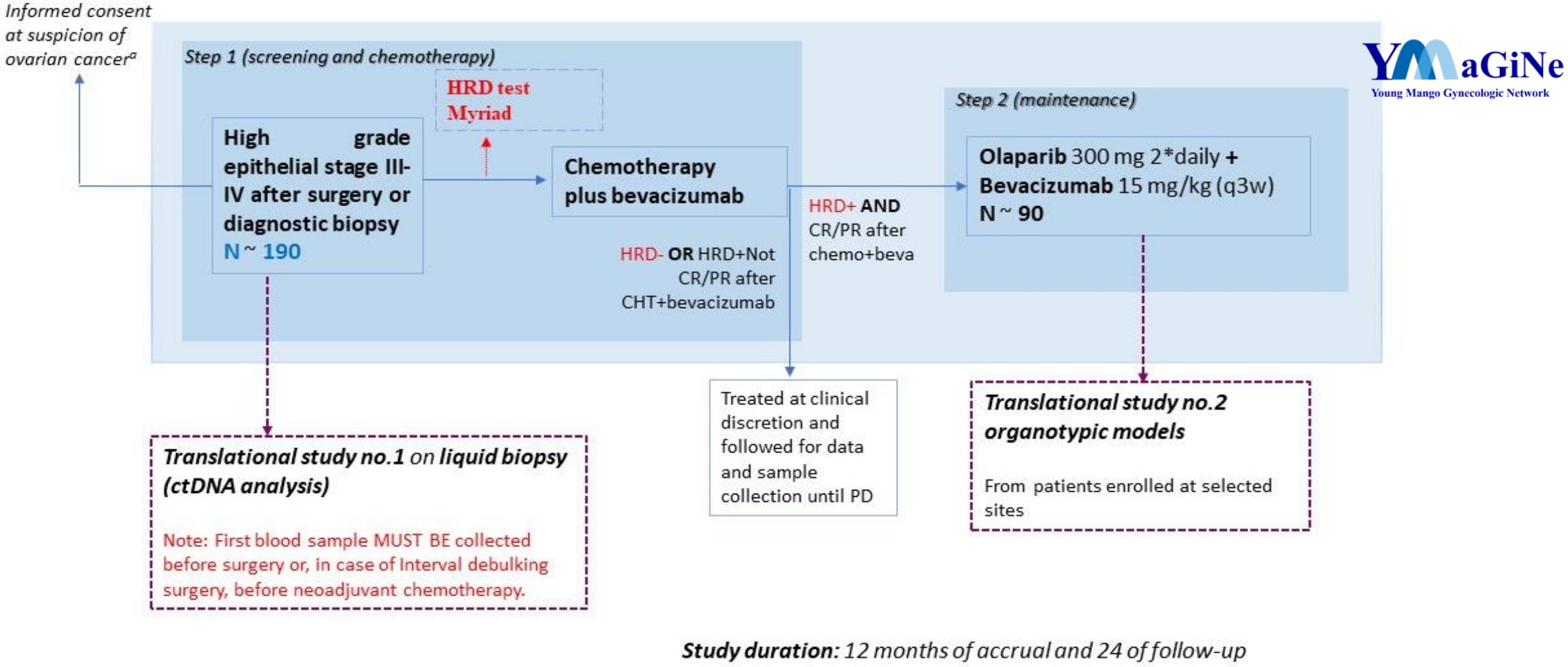
- The study was not yet recruting;
- NOGGO as study Sponsor is coordinating the submission process in the new EU portal. Due to some problems with documents to be provided by the Pharma Company, the first submission is not yet finalized.
- Very soon the interested sites will be contacted by MaNGO team to finalize the site specific documents needed to submit the study to the indipendent EC

N-PLUS: Study update June 2023

MaNGO Sites interested

Nr.	Site	City	Principal Investigator
1	AOU Città della Salute e della Scienza di Torino - Ospedale Sant'Anna – **Coordinating Site**	Torino	Dionyssios Katsaros - **National PI**
2	AOU Cagliari, Policlinico Universitario	Cagliari	Elena Massa
3	Istituto nazionale dei Tumori	Milano	Francesco Raspagliesi
4	Policlinico S. Orsola Malpighi	Bologna	Claudio Zamagni
5	Ospedale Manzoni	Lecco	Antonio Ardizzoia
6	Spedali Civili di Brescia	Brescia	Germana Tognon
7	AOU Pisana	Pisa	Angiolo Gadducci
8	Istituto Oncologico Veneto (IOV)	Padova	Giulia Tasca
9	AO Arcispedale Santa Maria Nuova	Reggio Emilia	Alessandra Bologna
10	Ospedale Mauriziano	Torino	Annamaria Ferrero

A phase IIIb-IV trial testing Olaparib and Bevacizumab as frontline maintenance Treatment of HRD positive ovarian tumours (IOLANTHE)

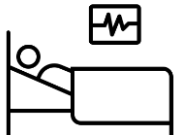


Study duration: *12 months of accrual and 24 of follow-up*

Legend: a: required to start data and sample collection (please remind to collect blood samples before surgery even if the ovarian cancer was not yet confirmed, in case of Interval debulking surgery start the sample collection before neoadjuvant)

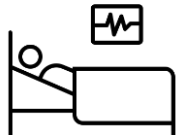
A phase IIIb-IV trial testing Olaparib and Bevacizumab as frontline maintenance Treatment of HRD positive ovarian tumours (IOLANTHE)

- For **translational study no.1** and exploratory objectives, three types of samples are requested: FFPE sample of the primary tumor, blood and plasma samples at different time points.
- FFPE Primary tumor samples are to be collected at the time of PDS, IDS, and, if possible, during laparoscopic investigation in case of NACT+IDS.
- All samples will be sent to the Mario Negri Institute for Pharmacological Research



100 patients

- For the **translational study no.2**, the following samples will be requested:
- Fresh tumor tissue for the isolation of tumor cells
- Ascitic fluid for the isolation of tumor cells
- Macroscopically healthy omentum for the isolation of mesothelial cells and fibroblats
- All samples will be processed and analysed at European Institute of Oncology, Milan.



30 patients

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A phase IIIb-IV trial testing Olaparib and Bevacizumab as frontline maintenance Treatment of HRD positive ovarian tumours (IOLANTHE)

AIM OF TRANSLATIONAL SUB-STUDY N°1

The analysis of cfDNA exploiting low pass whole genome sequencing (sWGS) approaches, will be aimed at:

1) investigating the association between residual tumour and circulating-tumor DNA levels (i.e., % of Tumor Fraction, TF);
2) the diagnostic anticipation of the tumor recurrence through longitudinal monitoring of TF plasma levels;
3) to longitudinal monitor during the maintenance therapy the mutational status of HR-related genes and other genes such as Tp53BP1, POLQ, REV7 known to contribute to PARPi resistance

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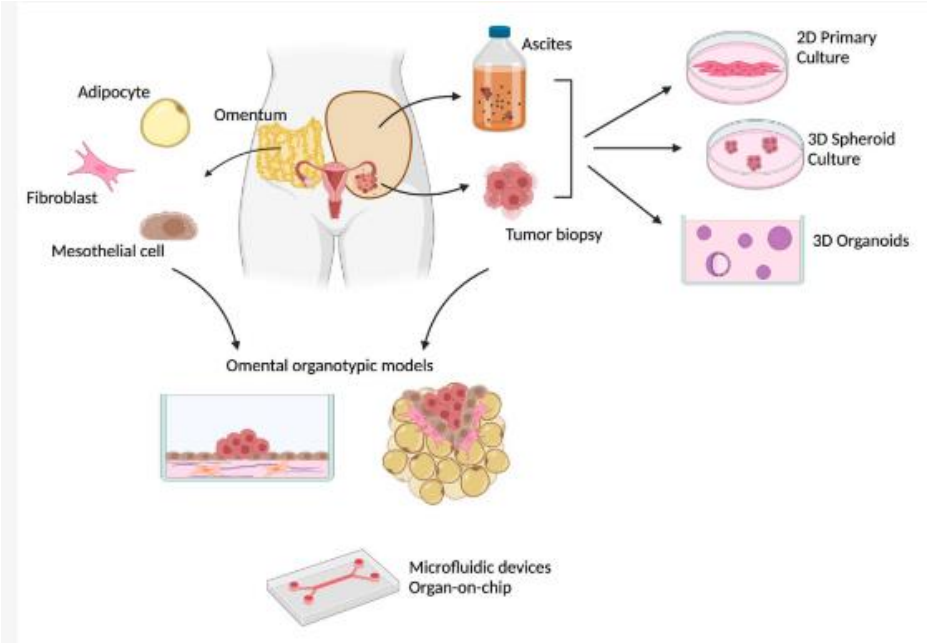
AIM OF TRANSLATIONAL SUB-STUDY N°2

- Compare patients' response to therapy (according to PFS 24-month) with that of cancer cells (either stem or bulk), derived from the same patient, and treated with the combination of olaparib and bevacizumab in the matched organotypic model.

- The patients' response to therapy will be evaluated in terms of PFS 24-mo defined as the patient status at 24 months after the start of olaparib treatment (free from progression/progressed or died).

- The cancer cells' response is defined as the percentage of either bulk or cancer stem cells which died upon 72-hour after exposure to olaparib.



ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

PROJECT UPDATE

MaNGO
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- First trial sponsored by YMaGINe
- Agreement with supporter (Astrazeneca) signed in June 2022 (Note: more than 2 years to obtain approval of the protocol by AZ e contract signature);
- Protocol internal revision (Regulatory, DPO and Quality Assurance) ended in October 2022;
- Trial submitted in December 2022 through CTIS european portal;
- **Final AIFA and EC approval on 19th of June 2023 after 2 requests of clarification by AIFA and 1 by Independent EC;**
- Sites specific agreements under finalization;
- Site Initiation Visits under definition

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

SITES INVOLVED

MaNGO
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Site	City	Principal Investigator	Commitment*	Agreement status
Ospedale Umberto I	Roma	Federica Tomao	15	Site feasibility to be completed
Istituto Naz. dei Tumori	Milano	Mara Mantiero	8	Under site revision
Ist. Europeo di Oncologia	Milano	Silvia Derio	30	Under signature
Ospedale Manzoni	Lecco	Federica Villa	12	Under site revision
AOU Parma	Parma	Angelica Sikokis	10	Site feasibility to be completed
Ospedale Santa Chiara	Pisa	Clara Baroni	10	Site feasibility to be completed
Arcispedale S. Maria Nuova	Reggio Emilia	Elisa Gasparini	30	Under signature
Ospedale Sant'Anna	Torino	Fulvio Borella	10	Under site revision
Ospedale Mauriziano	Torino	Annamaria Ferrero	6	Under signature
Spedali Civili	Brescia	Monica Ragnoli	20	Under site revision
IOV	Padova	Giulia Tasca	20	Under signature
Ospedale Sant'Anna	Como	Monica Giordano	10	Site feasibility to be completed
Policlinico Careggi	Firenze	Mariacristina Petrella	40	Under site revision
Ospedale San Luca	Lucca	Editta Baldini	10	Under site revision

***Estimated patients enrollment with confirmed epithelial ovarian cancer in 12 months**

First SIV planned in July 2023