MaNGO
Mario Negri Gynecologic Oncology

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Con il Patrocinio di:

AIOM Associazione Italiana di Oncologia Medica

FICOG | Federation of Italian Cooperative Oncology Groups

SOCIETA' ITALIANA DI CANCEROLOGIA

SIGO SOCIETA' ITALIANA DI GINECOLOGIA E OSTETRICIA

ACTO ALLEANZA CONTRO il TUMORE OVARICO

A phase **I**IIb-IV trial testing **Ol**aparib and Bev**a**cizumab as fro**n**tline maintenance **T**reatment of **H**RD positiv**e** ovarian tumours (IOlanTHe)

SPONSOR: YMaGiNe (Young MaNGO Gynecologic Network)

PI: Federica Tomao

Working group: Federica Tomao (IEO), Elena Biagioli (Istituto Mario Negri), Chiara Battistini (IEO), Lara Paracchini (IRCCS Humanitas Research Hospital), Eliana Rulli (Istituto Mario Negri), Sergio Marchini (IRCCS Humanitas Research Hospital)

A phase **III**b-IV trial testing **Ol**aparib and Bev**a**cizumab as fro**n**tline maintenance **T**reatment of **H**RD positiv**e** ovarian tumours (IOlanTHe)

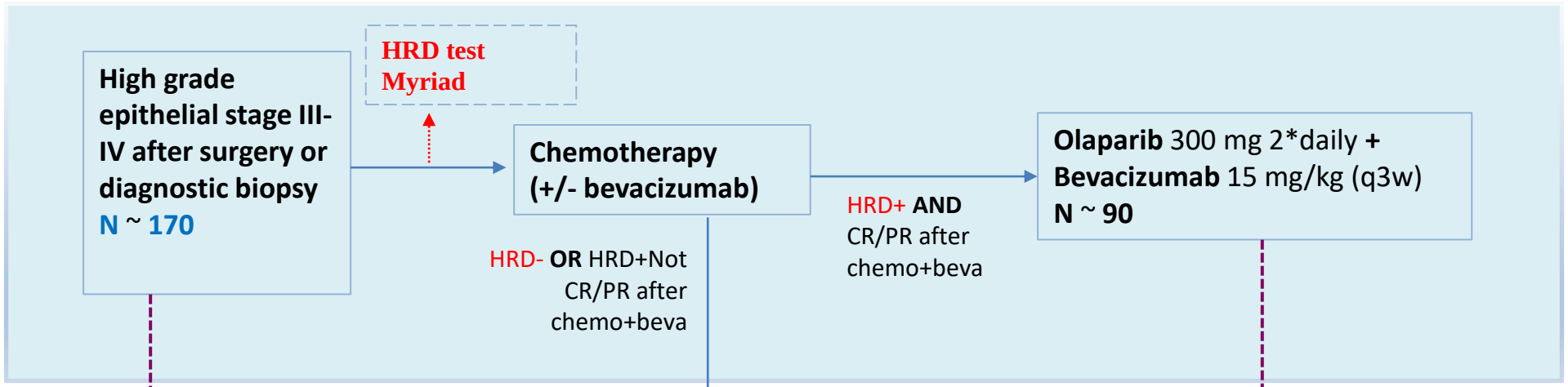
- A clinical study aiming to confirm the efficacy of olaparib and bevacizumab as maintenance therapy in patients with epithelial ovarian cancer, fallopian tube or primary peritoneal cancer

- Two tranlsational sub-projects are included:

  - *Translational study no.1*: liquid biopsy to detect ctDNA conduct and analysed in collaboration with Humanitas (Maurizio D'Incalci group)

  - *Translational study no.2*: organotypic models in collaboration with IEO-Milano (Ugo Cavallaro Unit)

Clinical Study Design



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

Objectives and endpoints clinical study

•to define the proportion of patients with high grade serous or endometroid ovarian cancer who will be treated at first line with Bevacizumab and Olaparib as maintenance and to describe their clinical and demographic characteristics.

•to confirm, in a setting close to clinical practice, the efficacy of the combination of Bevacizumab and Olaparib maintenance after first-line chemotherapy in patients with high grade serous or endometroid ovarian cancer HRD-positive and who have received bevacizumab in combination with chemotherapy.

The efficacy will be evaluated in terms of PFS.
Secondary objectives will be to describe the compliance to the combination of Olaparib and Bevacizumab and its safety profile.

Translational study no. 1- Rationale

HGSOC is characterized by a marked anatomic, molecular, and cellular heterogeneity.
This feature has impaired the identification of reliable predictive biomarkers
Novel and reliable molecular biomarkers are needed to guide therapy and monitor its efficacy.

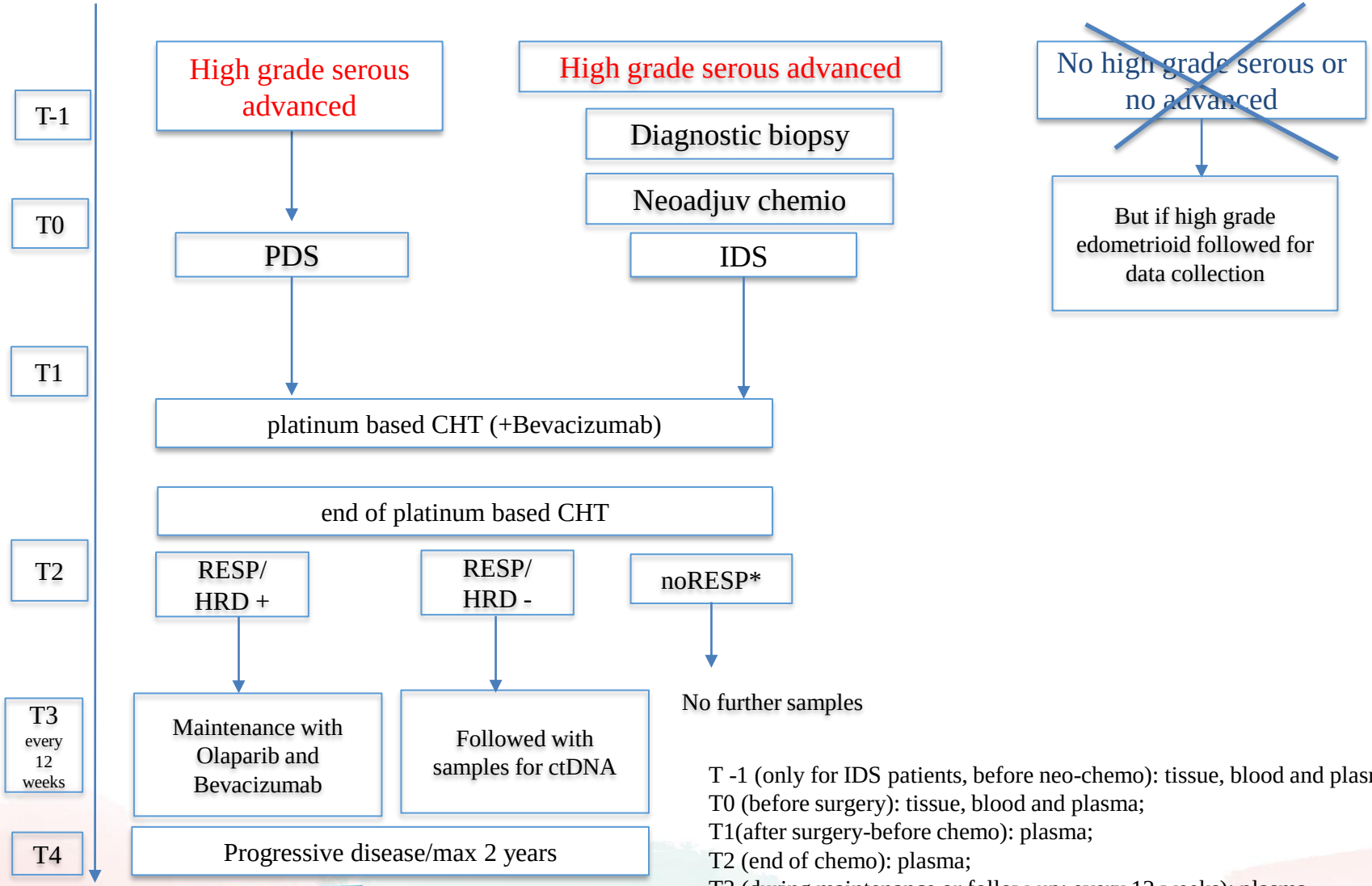
Thanks to high-throughput sequencing and liquid biopsy approach, ctDNA analysis has emerged as a non invasive alternative to profile and monitor tumour evolution over time [1]

ctDNA during treatment could allow a more objective evaluation of the response than CA-125 levels

From these considerations, the analyses of the circulating-free DNA (cfDNA) derived from plasma samples collected at time of diagnosis, at the end of Pt treatment and during the follow up is planned in *Translational study no.1*

1 Paracchini et al

Flow-chart on tissue and blood/plasma samples for translational study no.1



T -1 (only for IDS patients, before neo-chemo): tissue, blood and plasma;
T0 (before surgery): tissue, blood and plasma;
T1(after surgery-before chemo): plasma;
T2 (end of chemo): plasma;
T3 (during maintenance or follow-up; every 12 weeks): plasma
T4 (PD – or 2 years from last Pt): plasma;

Objectives of the translational sub-study no.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) timing the advent tumor recurrence through longitudinal monitoring of TF plasma levels (16)(17);
3) longitudinal monitor the mutational status of HR-related genes and other genes (Tp53BP1, POLQ, REV7)- known to contribute to resistance to PARP inhibitors- during the treatment.

Translational study no. 2 - Rationale

Predicting patients' response through the use of appropriate experimental models would have a great importance and might guide and support future treatment decisions.

Novel in vitro models able to accurately recapitulate the tumor microenvironment in which ovarian cancer develops is needed. In a selected group of patients treated in this protocol, patient-derived organotypic culture that mimic the omental niche of ovarian cancer will be used to explore the clinical usefulness of such an approach

Our experimental model will be exploited as patients' avatar that will receive the same treatments of the corresponding enrolled patient

Accumulating evidence points to cancer stem cells as main players in ovarian cancer relapse and chemoresistance. Indeed, cancer stem cells are able to elude treatments by means of several mechanisms, either intrinsic or based on the cross-talk with the tumor microenvironment

The organotypic model that includes cancer stem cells will permit to compare the response of the cancer stem cells to that of bulk tumor cells. This approach will hopefully enable to predict ovarian cancer patient therapy response

Translational study no.2 – sample collection

The following samples will be archived at the time of surgery (T0) for the organotypic model generation:

1. Fresh tumor tissue for the isolation of primary tumor cells.
2. Ascitic fluid for the isolation of primary tumour cells.
3. Macroscopically healthy omentum for the isolation of primary mesothelial cells and fibroblasts

Due to the proof-of-concept nature of the translational study 2, the organotypic model will be reconstructed for a subgroup of patients enrolled by the coordinating centre, who has underwent Interval Debulking Surgery (IDS) upon NACT, and treated with combination under study

Objectives of the translational sub-study no.2

The organotypic models are aiming to:

- to compare patients' response to therapy (measured as best response during Olaparib plus Bevacizumab treatment) with response of cancer cells (either stem or bulk), derived from the same patient, and treated with the combination in the matched organotypic model (measured as percentage of dead cells respect to the total number of cells).

Sample size

- Setting a first-type error of 5% one-side and a statistical power of 80%,
- considering a PFS at 24 month (PFS-24mo) of at least 61%,
- a sample size of **87** patients, followed for 24 months, will allow us to reject the null hypothesis (PFS-24mo=51%) in favour of the alternative hypothesis (PFS-24mo=64%) according to PAOLA 1 result.

Taking in to account that:

- approximately a 95-90% of patients with epithelial ovarian cancer, fallopian tube or primary peritoneal cancer will be in response after first line platinum therapy
- out of these, the 60% will be HRD

170 patients with confirmed **epithelial ovarian cancer, fallopian tube or primary peritoneal cancer are needed to be enrolled to have approximately 80-90 patients** that will be probably enrolled in the phase III/IV clinical study to receive the combination with Olaparib and Bevacizumab.

For the translational study 1, samples from all HGSOC will be collected to **have at least 100 patients analysed** (i.e. with most of samples evaluable).

For the translational study 2, according to the patients' accrual capability of the coordinating centre and considering the planned length of the enrolment, **30 patients are expected to be enrolled**

Study organization

- Mario Negri Institute: statistical design and methodological aspects and overall conduction and coordination of the project
- IEO: coordinating centre and translational no. 2 analyses
- Humanitas: sample analysis and elaboration for translational no.1

Study Update

- The study synopsis and the budget have obtained the approval by Astrazeneca May 12, 2021
- The protocol is under preparation and needs to be submitted to Astrazeneca by August 10, 2021

- Approx 10 sites will be involved
- The study activation is planned for Dec 2021

Mutational landscape of women suffering from metastatic ovarian cancer before poly (ADP-ribose) polymerase inhibitorstreatment and during treatment. Incidence of therapy-related hematological neoplasms

SPONSOR: IEO (with fundings from Ricerca Finalizzata)

Working group: Elisabetta Todisco, Corrado Tarella, Federica Gigli, Ramadan Safaa Mahmoud, , Anna Vanazzi, Viviana Amato, Nicoletta Colombo, Parma Gabriella, Federica Tomao, Chiara Ronchini, Myriam Alcalay, Gianleo Tunzi, Pier Giuseppe Pelicci, Chiara Camisaschi, Patrizia Mancuso, Chiara Corsini, Giuliana Gregato, Francesco Bertolini, Vincenzo Bagnardi, Simona Menna

Background and Rationale

Therapy related acute myeloid leukemia and myelodysplasia (t-MN) is a potential late complication of cytotoxic therapy.

-Analyses from trials SOLO1 and SOLO2 showed that the advent of PARPi increases the risk of t-MN with an incidence of 1-2% (vs 0,17% after platinum-based chemotherapy.

-In our single-center experience (IEO), we, recently, reported a higher incidence of t-MN in this population patients: about 6,9% (9/130)

-The inhibition of PARP-mediated repair of DNA lesions created by chemo or radiotherapy can further favor t-MN development.

Todisco E et al. Int J Cancer. 2021

Objectives and endpoints

Primary endpoints: Identification of the following events and determination of their incidence in our patient's population:

-Cell blood count abnormalities

-Morphological alterations allowing a diagnosis of myelodysplastic syndrome or acute myeloid leukemia

-Chromosomal abnormalities

-Clonal hematopoiesis and extent of the expansion and evolution of the CHIP clones induced by PARP inhibitors

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Secondary endpoints

-Overall survival (OS)

-Progression free survival (PFS)

Inclusion and exclusion criteria

Inclusion criteria

-Women with advanced ovarian cancer in complete or partial remission after surgery and eligible to oral PARP inhibitors as first line.

Exclusion criteria

- Presence of blood cell count abnormalities before PARP inhibitor treatment;
- Bone marrow infiltration by EOC cells.

Follow-up

All enrolled patients will be followed from the day of the informed consent signature until development of blood count abnormalities or up to death for any cause or withdrawal of consent. Follow-up will be by medical visit or telephone/email-based contact. Data on survival, disease progression, intervening anti-cancer therapy and toxicities will be collected.

Timing of analysis

Before PARP inhibitor treatment (as first line and as maintenance therapy)

Buccal cells:

- custom myeloid gene panel (Myelo-Panel) to identify germline mutations predisposing to cancer development (Thermo Fisher Scientific)

Bone marrow cells (optional, for comparison, only in a limited number of patients):

- morphological analysis
- immunophenotype
- cytogenetics/FISH
- analysis of CHIP by custom gene panel and high sensitivity NGS

Timing of analysis

Peripheral blood cells:

- analysis of CHIP by custom gene panel and high sensitivity NGS

Bone marrow biopsy (optional, for comparison, only in a limited number of patients):

- histology
- immunohistochemistry

Every 6 months during PARP inhibitor treatment

Peripheral blood cells:

- analysis of CHIP by custom gene panel and high sensitivity NGS

Timing of analysis

- Peripheral blood samples (PBS) and buccal swab before PARPi treatment
- PBS every 6 months during the treatment
- Bone Marrow biopsy only at appearance of blood abnormalities

	Before PARPi treatment	Every 6 months during PARPi treatment	At appearance of blood abnormalities
Informed consent	X		
Registration to the database	X		
Full blood count	X	X	X
Physical exam	X	X	X
Vital signs	X	X	X
Height and weight	X	X	X
Performance status	X	X	X
Morphological analysis of PB			X
Morphological analysis of BM			X
Cytogenetics/FISH			X
Germline variant analysis	X		
Buccal swabs	X		
Myeloid gene mutational analysis			X
CHIP sequencing analysis	X	X	X
Immunephenotyping			X
Histology of BM	X*		X
Immunohistochemistry of BM	X*		X

* **optional,** for comparison, only in a limited number of patients

Appearance of blood count abnormalities and/or haematological neoplasms

During PARP inhibitor maintenance treatment, patients will be monitored monthly with clinical and blood count examination.

In case of appearance of blood count abnormalities (CTCAE grade ≥ 2 and/or platelets<100.000/mmc), involving at least one hematopoietic subpopulation, the drug will be suspended and blood cell counts evaluated every 2 weeks.

In case of recovery the drug will be reintroduced. In case of stability or further deterioration, bone marrow and peripheral blood examinations (analysis detailed below) will be performed after 4-8 weeks from PARP inhibitor interruption at least, unless the worsening of the blood counts is so fast that it requires a bone marrow evaluation before.

Appearance of blood count abnormalities and/or haematological neoplasms

At appearance of blood count abnormalities, the following analysis will be carried out:

Bone marrow cells:

- morphological analysis
- immunophenotype
- cytogenetics/FISH
- analysis of mutations by both Oncomine Myeloid Research Panel and our custom Myelo-Panel (Thermo Fisher Scientific)
- analysis of CHIP by custom gene panel and high sensitivity NGS

Bone marrow biopsy:

- histology
- immunohistochemistry

Sample size and statistical aspects

The study is descriptive in nature and no formal statistical testing is necessary or applicable.

To estimate one of the primary endpoints of the study (i.e. the proportion of patients with stable blood count abnormalities) with adequate precision and, considering as the measure of precision the 90% confidence interval of the estimated proportion, a sample size of **157** patients will be needed.

A patient is defined with stable blood count abnormalities if the status "*CTCAE grade ≥ 2 and/or platelets <100.000/mmc*" persists for at least two weeks.

The sample size calculation is based on the hypothesis that the true prevalence of patients with stable blood count abnormalities **will be 15% and considering as acceptable a margin of error of ± 5%** (i.e. 10% width of the 90% confidence interval). **The 90% confidence interval of the proportion of patients with stable blood count abnormalities will be computed using the exact binomial method.**

The association between the presence of germline mutations and the time of occurrence of the investigated abnormalities and/or alterations will be explored using Cox regression models.

Progression free survival (PFS) will be defined as the time from initiation of PARP-inhibitor treatment to objective disease progression on imaging or death from any cause. Overall survival (OS) will be defined as the time from initiation of PARP-inhibitor treatment to death from any cause.

Both PFS and OS will be estimated using the Kaplan-Meier method.

Study Update

- The study protocol received fundings from Ricerca Finalizzata 2020
- The protocol has been recently emendated in june 2021
- Enrollement ongoing.