



NEW PERSPECTIVES OF CLINICAL RESEARCH IN GYNECOLOGICAL CANCER
30 GIUGNO - 1 LUGLIO 2023 UNIVERSITÀ DEGLI STUDI DI PISA



STUDI SUI TUMORI RARI, PROPOSTA ENGOT/MANGO

1 Luglio 2023

Lorenzo Ceppi,

Grande Ospedale Metropolitano Niguarda Milano





NEW PERSPECTIVES OF CLINICAL RESEARCH IN GYNECOLOGICAL CANCER

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**COI: JOHNSON & JOHNSON, TESARO GSK AND PHARMA MAR
SUPPORT/ADVISORY**



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COSA È RARO?

- 6/100.000 CASI ANNO : 50% TUMORI GINECOLOGICI

(COMPRENDE: CARCINOMA OVARICO NON SIEROSO AD ALTO GRADO, ADENOCARCINOMA ENDOMETRIALE NON ENDOMETRIOIDE E CARCINOMA CERVICE UTERINA NON SQUAMOSO)



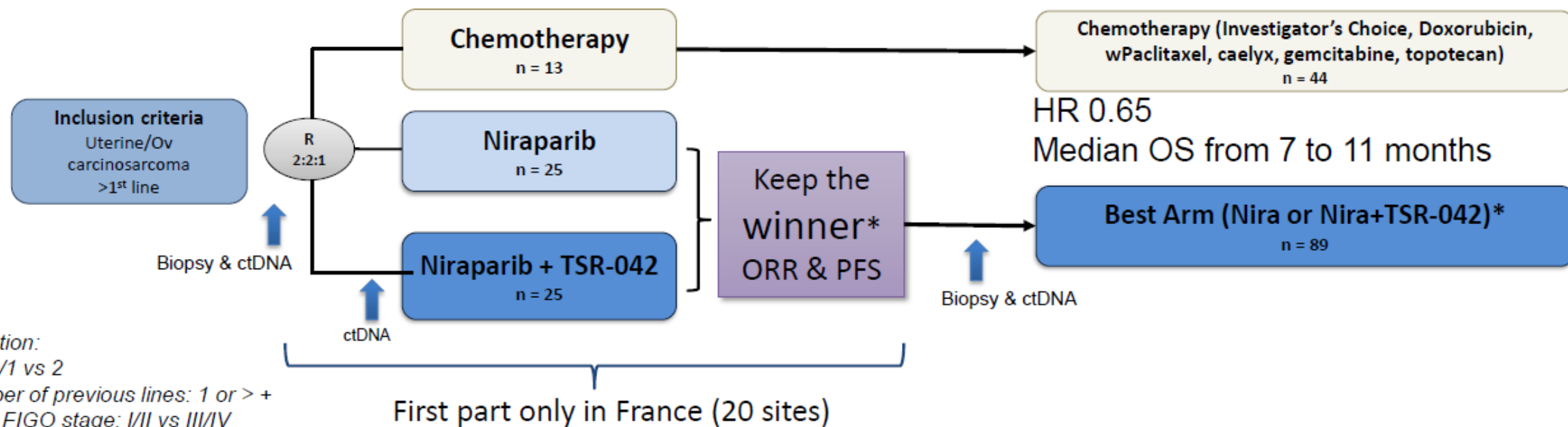
Objectives



- ▶ To develop a network of collaborations among centers and investigators within ENGOT to design clinical trials with strong scientific rationale in rare gynaecological cancer.
- ▶ To develop novel trial designs that allow efficient assessment of new compounds and make it feasible to also investigate rare histological and molecular subtypes.
- ▶ To offer pharmaceutical companies a read-to-go, efficient structure and academic expertise for accelerated clinical development of their compounds in their pipeline.
- ▶ To involve all the groups in this strategic plan that will allow ENGOT to promote a significant gain in the clinical outcomes of many rare tumours.

Multicentric Randomized Phase II/III Study

ROCSAN (Recurrent Ovarian-Uterus CarcinoSarcoma Anti-PD 1 Niraparib)



Stratification:

- PS: 0/1 vs 2
- Number of previous lines: 1 or > 1
- Initial FIGO stage: I/II vs III/IV
- Ov vs Ut

- Endometrial & Ovarian Carcinosarcoma
- 1st Endpoints RR/PFS for 1st step, then OS, 2nd EP PFS, safety & translational
- Alpha 5%, power 80%, 150 events recruitment 36 months

**ATR inhibitor in combination with olaparib in gynaecological cancer with ARID1A loss or no loss)
A Phase II Proof of Concept Study to assess the ATR inhibitor (AZD6738, ceralasertib) as a Single Agent
and in Combination with Olaparib in ARID1A Stratified Gynaecological Cancers**

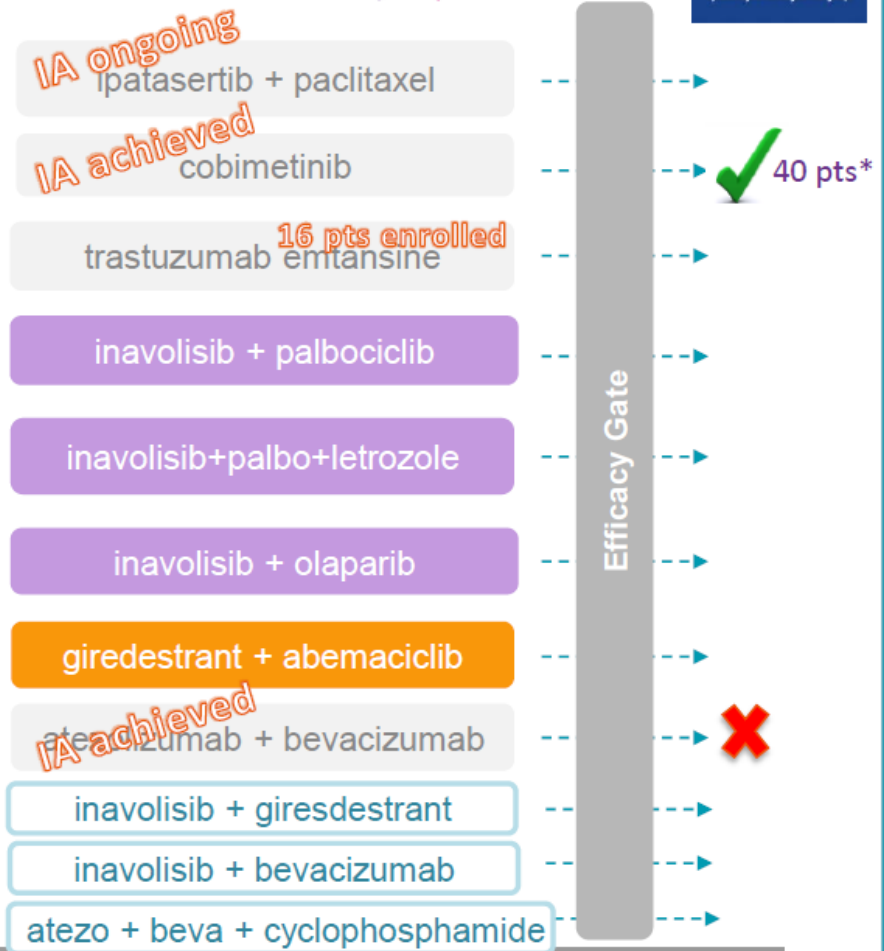
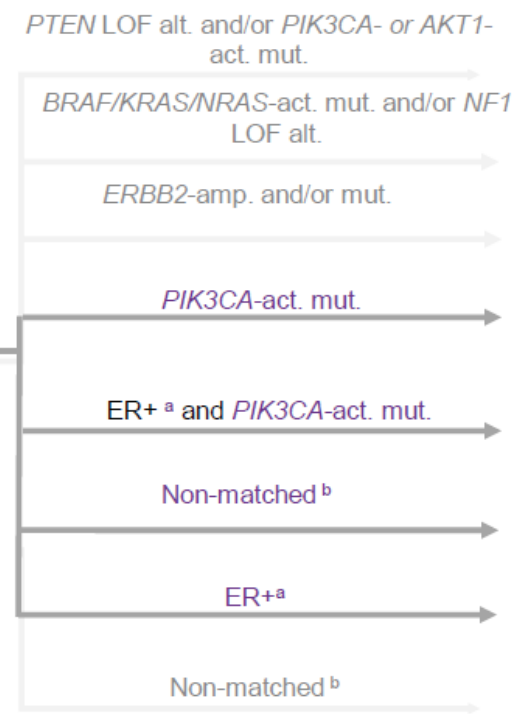
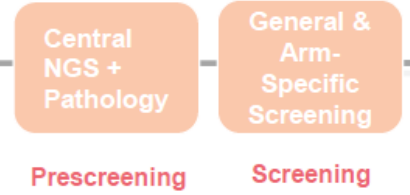
- ENGOT model: A
- Sponsor: The Institute of Cancer Research
- Cooperating groups: NCRI, GINECO, Princess Margaret Consortium
- No. of already recruited patients: 54
- Planned No. of patients: 40-174
- Status: recruitment on hold
- Other important information: Cohort 1A and Cohort 2 (clear cell cohorts) and 3 recruitment closed
Cohort 1-3 presented ESMO Gynaecological Cancers Congress Feb 2023 (oral)
Cohort 4 and 5 (endometrial carcinoma, prior IO) due to open Q22023
Discussion cohort 1B (ARID1A loss CCC) ceralasertib+Olaparib ongoing
ceralasertib+durvalumab cohorts in OCCC according to ARDID1A Status ongoing

BOUQUET STUDY / ENGOT-GYN2

GINECO STUDY DESIGN



- Persistent or recurrent rare EOC, FTC, PPC
- 1-4 priors
 - ≥1 prior platinum
- ECOG 0 or 1
- Measurable disease
- Submission of tumor specimen



LOF=loss of function.
^a ER-positive, defined as detection of ERα in ≥10% of tumor cells as assessed by central ER IHC (CellCarta; Ventana SP1 IHC assay).
^b The Atezo+Bev and Inavo+Oia arms are for eligible patients who do not have a biomarker profile matching them to an open and enrolling biomarker-driven treatment arm, or do not meet the arm-specific eligibility criteria for an arm they are matched to based on their biomarker profile, or withdraw from another arm.

Preliminary n=20 pts/arm Potential Expansion +30 pts/arm

* Rare EOC other than Clear cell, mucinous carcinoma or carcinosarcoma

BOUQUET STUDY / ENGOT-GYN2

GLOBAL STUDY STATUS

ENGOT GROUP STATUS (35 sites)

Country/Groups	Total Sites	Number of activated sites	Number of patient pre-screened	Number of patient enrolled
Belgium - BGOG	2	2	8	
Czech republic - CEEGOG	2	2	4	1
France - GINECO	10	10	167	23
Germany -AGO	5	4	26	4
Italy - MITO	5	5	49	10
Italy - MaNGO	1	1	10	
Spain - GEICO	4	4	64	12
Switzerland –Swiss GO	1	1	7	3
Turkey -TRSGO	3	3	25	6
UK –NCRI-UK	2	2	32	14
TOTAL	35	34	392	73

Other countries STATUS (29 sites)

Country	Total Sites	Number of activated sites	Number of patient pre-screened	Number of patient enrolled
Australia	2	1	10	3
Canada	3	3	16	3
Korea, Republic of	4	4	74	22
Russia	3	3	9	2
United States	17	17	40	7
TOTAL	29	28	149	37

BOUQUET STUDY / ENGOT-GYN2

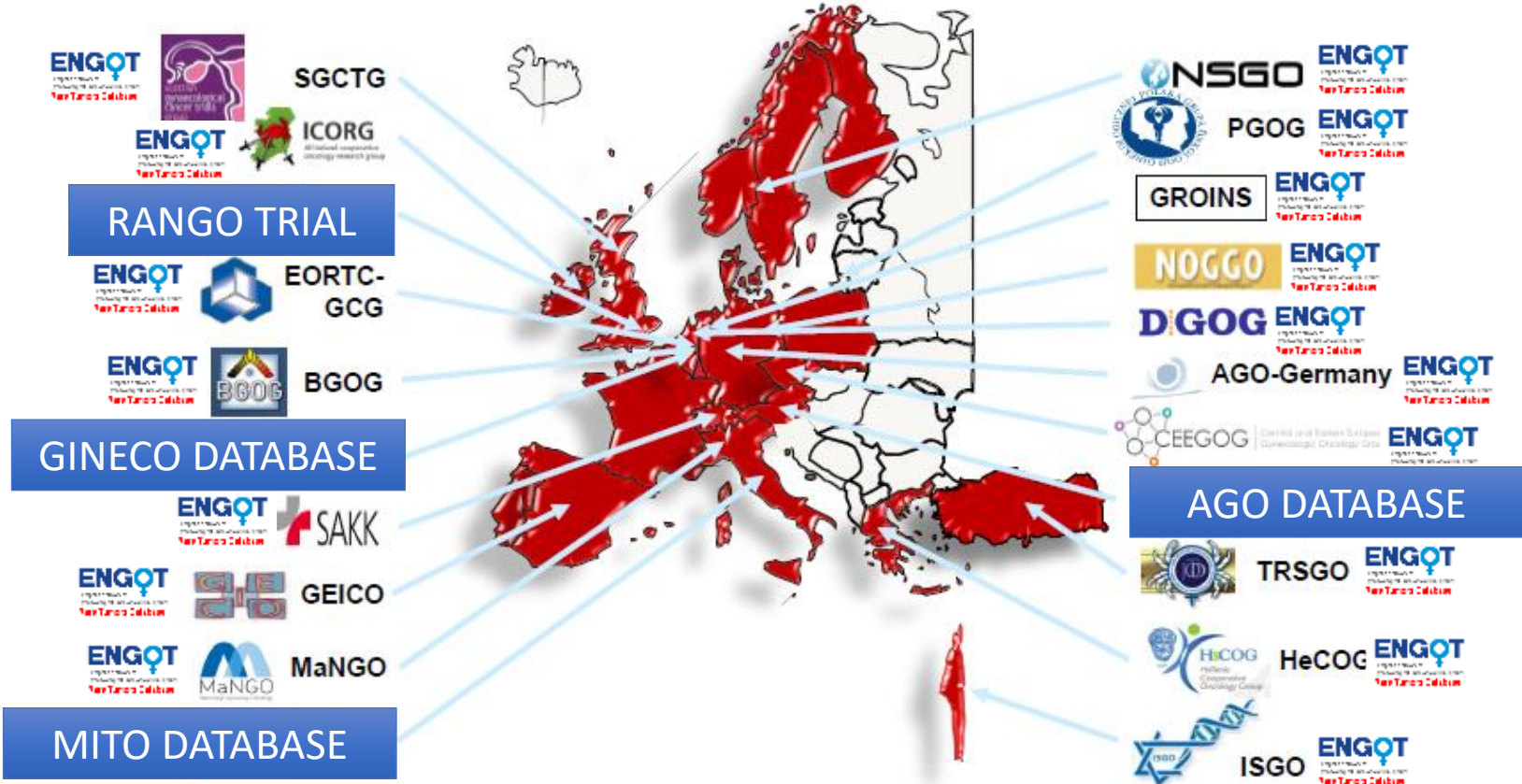
ITALIAN SITES

Site number	Site name	PI	Site status	Total pre-screened	Total screened	Total randomized	
342055	Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale« - Napoli	Dr. Pignata	Activated	9	7	6	1 Screen failed
342057	Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Roma	Dr. Lorusso	Activated	14	3	3	
342058	San Raffaele - Milano	Dr. Mangili	Activated	19	0	0	
342059	Istituto de Candiolo - Candolio	Dr Geuna	Activated	2	0	0	
342100	Ginecologo ospedale consorziale policlinico - Bari	Dr. Cormio	Activated	5	1	1	
TOTAL			5	49	11	10	

Site number	Site name	PI	Site status	Total pre-screened	Total screened	Total randomized	
342056	IRCCS - Istituto Europeo di Oncologia - Milan	Pr. Colombo	Activated	10	0	0	
TOTAL			1	10	0	0	

ENGOT

European Network of
Gynaecological Oncological Trial groups
Rare Tumors Database



RETROSPECTIVE AND PROSPECTIVE RARE TUMOR REGISTRY

Rare Tumors in Gynecologic Oncology, ENGOT initiative for a European Registry



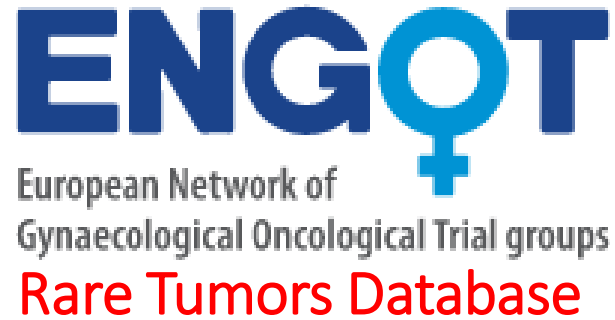
L. CEPPI¹, A. BERGAMINI², E. BIAGIOLI³, O. SELHEIM⁴, A. GONZALEZ-MARTIN⁵, N. OTTEVANGER⁶, E. VAN NIEUWENHUYSEN⁷, A. HASENBURG⁸, K. CADOO⁹, E. BRAICU¹⁰, M. HALL¹¹, D. BAUSERSCHLAG¹², S. AUST¹³, R. GLASSPOOL¹⁴, C. LOK¹⁵, J. KORACH¹⁶, D. CIBULA¹⁷, S. PIGNATA¹⁸, I. RAY-COQUARD¹⁹ on behalf of ENGOT Rare Tumors Group.

¹Obstetrics and Gynecology, Grande Ospedale Metropolitano Niguarda, MaNGO, Milan, Italy; ²San Raffaele Hospital, MITO, Milan, Italy; ³Mario Negri Institute, MaNGO, Milan, Italy; ⁴Department of gynecological oncology, Norwegian Radiumhospital, Oslo University Hospital, NSGO, Oslo, Norway; ⁵Clinica Universidad de Navarra, GEICO, Madrid, Spain; ⁶EORTC Gynaecological Cancer Group, Netherlands; ⁷Gynaecologic Oncology, BGOG, Leuven, Belgium; ⁸Clinic for Women's Health, Department of Gynecology and Obstetrics, Medical Center Johannes Gutenberg University, AGO, Mainz, Germany; ⁹St. James's Hospital Dublin, Trinity St. James's Cancer Institute, Cancer Trials Ireland, Dublin, Ireland; ¹⁰Charité Universitätsmedizin Berlin, Berlin, NOGGO, Germany; ¹¹East and North Hertfordshire NHS TRUST, NCRI, Northwood, United Kingdom; ¹²University Medical Center Schleswig-Holstein, AGO, Kiel, Germany; ¹³Medical University of Vienna, Department of Obstetrics and Gynecology, Comprehensive Cancer Center, A-AGO, Wien, Austria; ¹⁴Beatson West of Scotland Cancer Centre and Institute of Cancer Sciences, University of Glasgow, SGCTG, Glasgow, United Kingdom; ¹⁵Department of gynecological oncology The Netherlands Cancer Institute, Antoni van Leeuwenhoek hospital, DGOG, Amsterdam, Netherlands; ¹⁶Sheba Medical Center, Sackler School of Medicine, ISGO, Tel Aviv, Israel; ¹⁷Department of Obstetrics and Gynecology, General University Hospital in Prague, First Faculty of Medicine, Charles University, CEEGOG, Prague, Czech Republic; ¹⁸Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione Pascale, MITO, Naples, Italy; ¹⁹Centre Leon Bérard, Laboratoire RESHAPE U1290, Université Claude Bernard, GINECO, Lyon, France

* Survey results (n = 18 groups) **Sept. 2021**

- Many groups have scattered databases on rare tumors both retrospective and prospective, not all active and enrolling patients;
- Lack of manpower in database adoption/organization
- Lack of financial support
- Rules must be defined about data use, data sharing (access and analysis), regulation GDPR and publication, legal issues to be resolved
- **17/18 EUROPEAN GROUPS want to adopt the ENGOT DB, 7/18 in part**

Update July 2023



ENGOT Rare tumors database initiative

Lorenzo Ceppi (MaNGO – Niguarda)

Alice Bergamini (MITO – S. Raffaele)

eCRF design: Elena Biagioli, Giuseppe Funari

Implementation in RedCap: Elda Caccia

Istituto di Ricerche Farmacologiche Mario Negri, Milano

1. Summary of the REDcap program Last steps Jan 2023

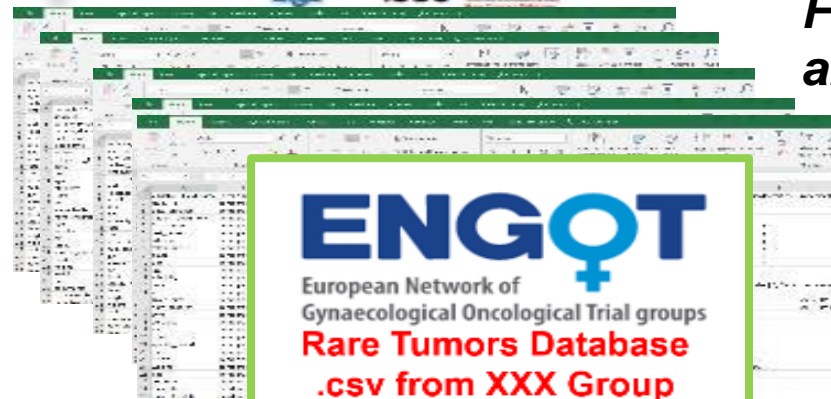
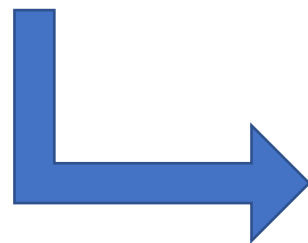
1. Defined **topics**, rules of publication (ESGO document)
2. Discussion regarding the **design of the database** (one single administrative server, many data entries vs. one database structure shared with database server for each country)
3. Creation of the database **REDCap database structure**, Writing of the **protocol** and **informed consent**, drafts to be shared and adapted at national level (2021)
4. Database **Demo version** circulated among «reviewers» (Q4 2021-Q1 2022)
5. Comments and modification sent back (Q2 2022)
6. Database modified and reviewed (Q3-4 2022).
7. Study submission to Ethics Committees at country and site level (Q1 2023), (**EC submission completed and recruiting patients MaNGO group**)
8. **ENGOT harmonization steps ...**

ENGOT

European Network of
Gynaecological Oncological Trial groups

Rare Tumors Database

CRF scheme



*For data
analysis..*

ENGOT

European Network of
Gynaecological Oncological Trial groups

Rare Tumors Database

.csv from XXX Group

TOPICS OF RESEARCH

1. Low Grade Serous Ovarian Cancer
2. Malignant Germ Cell Tumor of the Ovary
3. Sex Cord Stromal Tumor of the Ovary

Participating groups

AGO, NSGO, GINECO, MANGO, MITO, AGO-A, NSGO, SGCTG, NCRI, TRSGO, NOGGO, SAKK, ISGO,
EORTC, GEICO, CEECOG, BGOG

2, META ANALYSIS ON SCT (MITO AND GINECO INVOLVED OTHER GROUPS COMING SOON)

One project dedicated to surgical question:
-Peritoneal staging as prognostic factor



(MITO/GINECO) working on

- Alice Bergamini working on contract between to share the database from GINECO/CLB with MITO
- 1st merging data set was done IN December, Stat on going !

Next steps

- Publication or presentation of the 1st step: 558 cases adult granulosa cancer
- Several groups have mentioned to be interested to be part (MaNGO, CEEGOG, NSGO, ISGO, SCTGC, BGOG, DGOG)

Issues: Contract and GDPR issues, Necessity to work on site.

- FOR LGSC DATA BASES ACTIVITIES

- 1st project dedicated to surgical questions:
 1. Response rate to first line chemotherapy and impact on survival
 2. Impact on survival and residual disease at primary surgery
 3. Role of secondary cytoreductive surgery
 4. Role of maintenance hormonal treatment in recurrent disease
(GINECO, MANGO, MITO, AGO Austria, BGOG)
- 2nd project dedicated to biology (genomic markers predictive for Tx sensitivity) on going (MITO lead)

ITALIAN SITES INVOLVED

Site	City	Principal Investigator	Site status
Ospedale Niguarda	Milano	Lorenzo Ceppi (coordinating PI)	Activated on 15 May 2023
Ente Ospedaliero "Ospedali Galliera"	Genova	Nicoletta Provinciali	Activated on 18 May 2023
Ospedale Sant'Anna	Como	Monica Giordano	Activated on 26 May 2023
Istituto Europeo di Oncologia	Milano	Nicoletta Colombo	Activated on 19 June 2023
A.O. Ordine Mauriziano	Torino	Annamaria Ferrero	Evaluated by EC
Ospedale Manzoni	Lecco	Antonio Ardizzioia	Submitted on 23 May 2023
Istituto Nazionale dei Tumori	Milano	Francesco Raspagliesi	Activated on 29 June 2023
Ospedale San Gerardo	Monza	Andrea Lissoni	Submitted on 05 June 2023
Istituto Oncologico Veneto	Padova	Giulia Tasca	EC's submission ongoing
Spedali Civili	Brescia	Germana Tognon	EC's submission ongoing
Arcispedale Santa Maria Nuova	R. Emilia	Alessandra Bologna	EC's submission ongoing
Ospedale Santa Chiara	Pisa	Angiolo Gadducci	EC's submission ongoing
ASST Garda	Manerbio	Francesca Chiudinelli	EC's submission ongoing
Ospedale Del Ponte	Varese	Nicoletta Donadello	EC's submission ongoing
Ospedale di Mirano	Mirano	Alessandra Baldoni	EC's submission ongoing
AOU Parma	Parma	Angela Sikokis	EC's submission ongoing
Policlinico Careggi	Firenze	Maria Cristina Petrella	EC's submission ongoing
Ospedale San Luca	Lucca	Giovanna Cirigliano	EC's submission ongoing
AOU Modena	Modena	Cinzia Baldessari	EC's submission ongoing
A.O.U. Citta della Salute e della Scienza	Torino	Dionyssios Katsaros	EC's submission ongoing

Local ECs requested the coordinating EC favorable opinion (18 Apr 2023) to evaluate the study

ENGOT'S GROUPS ANSWERS

ENGOT Group	Principal Investigator	Group's feedback	MaNGO feedback
UK	Marcia Hall	Possibility to integrate RaNGO study, very similar to ENGOT rare tumours database	Protocol and blank eCRF shared with the group. Group's participation under discussion
ISGO (Israel)	Jacob Korach	Asked to receive the database structure for the sites with RedCap experience and to delegate MaNGO to database set-up and maintenance for the sites without RedCap experience	Explained that each country should have one RedCap in a coordination site and the other sites will enter data into that RedCap. Alternately, the group could join to MaNGO RedCap system with a specific agreement. Group's participation under discussion
CEECOG (Central and Eastern European countries)	Prof. David Cibula	Decided to initiate the participation in one site in Prague and subsequently to extend it to other CEEGOG countries	Under definition the steps necessary for study initiation.
GEICO (Spain)	Pilar Barretina Ginesta	Possibility to integrate local GEICO registry into the ENGOT rare tumours database	Protocol and blank eCRF shared with the group. Group's participation under discussion

Waiting for feasibility questionnaire from A-AGO (Austria), NSGO (Nordic countries), DGOG (Netherlands) and AGO (Germany) and CTI (Ireland)

MANGO LOW GRADE SEROUS OC DATASET

Subtype	Monza	IEO	Pisa	Torino	Reggio Emilia*	Brescia	Niguarda	TOT
Low Grade Serous Tumors of the Ovary	60	79	10	25	10	19	20	197
*: stima per 5 anni sulla base di 2 casi/anno								

ENGOT LOW GRADE SEROUS OC DATASET

Subtype	GINECO	AGO	MITO	TOT
Low Grade Serous Tumors of the Ovary	200	100	150	450
*: stima per 5 anni sulla base di 2 casi/anno				

CALL FOR ACTION!

1 - INSERT CASES IN THE DATABASE
REPORT THE 'DATA ENTRY ACTIVITY' FOR ALL SUBTYPES (MOGCT, SCST, LGSOC)

2- PARTICIPATE IN LOW GRADE SEROUS OVARIAN CANCER DATA SET
* HISTOLOGICALLY CONFIRMED LGSOC
* EARLY AND ADVANCED STAGE, FULL CLINICAL ANNOTATION
* CONSENT NECESSARY WHEN AVAILABLE

**DEADLINE FOR FIRST DATA CUT-OFF AND ANALYSIS:
30 SEPTEMBER 2023**

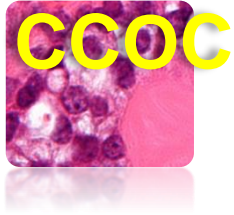
ESGO 2024 Congress

ESGO 2024 Congress
Barcelona, Spain

March 7-10, 2024

NEW PROPOSAL FOR RARE TUMOR DATABASE

Clear cell tumor registry



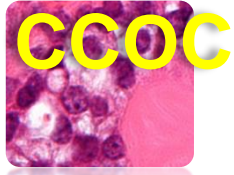
PROPOSAL FOR RARE HISTOTYPES: CLEAR CELL OVARIAN CANCER (CCOC) MULTI INSTITUTIONAL CLINICAL ANNOTATION AND GENOMIC PROFILING

1. What is the proper adjuvant treatment for EARLY STAGE CCOC?

- 1.A proper adj. treatment of 'surgically staged early stage IA-IC1 ovarian cancer'
- 1.B proper adj. treatment of 'high risk early stage CC OC'

1. How to identify **advanced/relapsing patients** that may need tailored therapy due to their intrinsic chemoresistance to standard treatment?

- 2.A Genomic profiling molecular subtypes for prognosis,
- 2.B Mutation profiling to identify available targeted treatments
- 2.C Prediction to immune checkpoint blockade (ICB)



PROPOSAL FOR RARE HISTOTYPES: CLEAR CELL OVARIAN CANCER (CCOC) MULTI INSTITUTIONAL CLINICAL ANNOTATION AND GENOMIC PROFILING

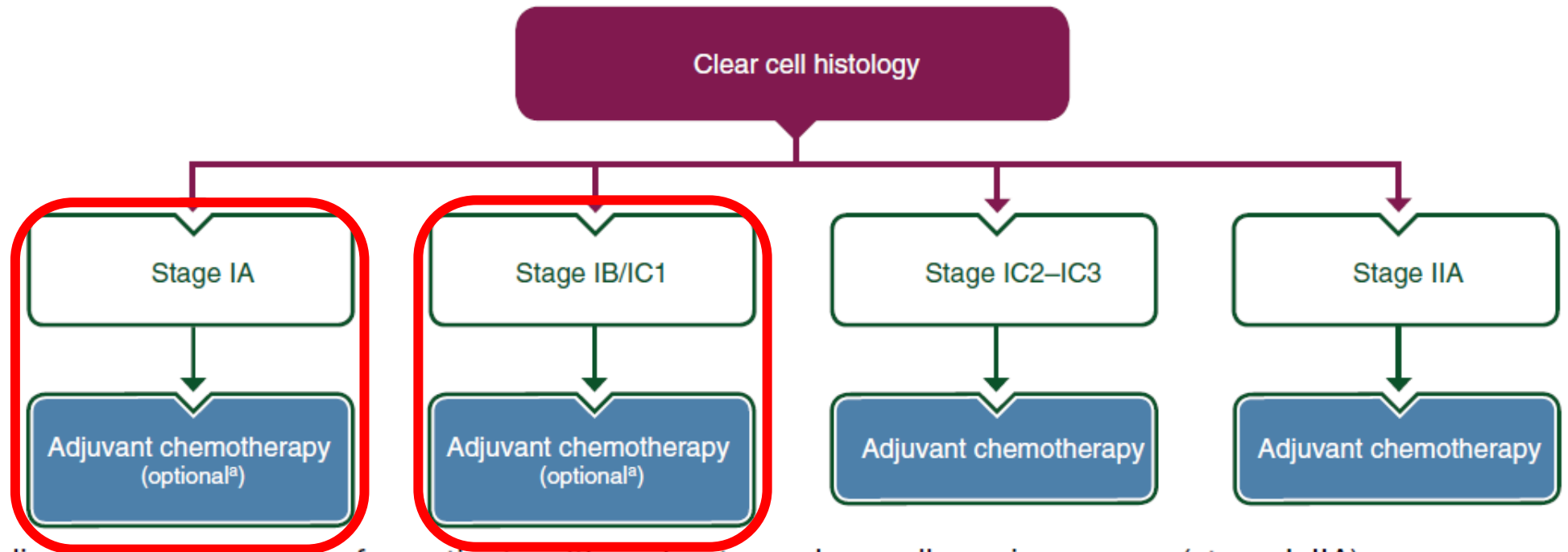
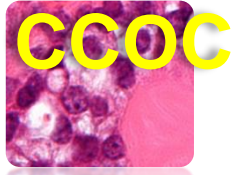


Figure 3 Adjuvant chemotherapy for patients with early-stage clear cell ovarian cancer (stage I–IIA).

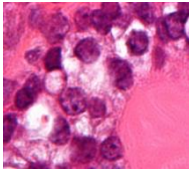
^aConsidered no adjuvant chemotherapy only for patients with complete surgical staging.



PROPOSAL FOR RARE HISTOTYPES: CLEAR CELL OVARIAN CANCER (CCOC) MULTI INSTITUTIONAL CLINICAL ANNOTATION AND GENOMIC PROFILING

Strategic plan:

1. Amendment to expand RARE TUMOR REGISTRY FOR CLEAR CELL OVARIAN CANCER (or not common OVARIAN CANCER EPITHELIAL HISTOTYPES?), reconsenting necessary if patient available
 2. Protocol amendment draft ongoing
 3. Inclusion criteria
 - histologically confirmed non-mixed-clear cell ov cancer, if possible an expert gyn-pathologist confirmation
 - early and late stages included (clinical question 1 and 2)
 - time range 2010-2020 at diagnosis
 - complete clinical annotation and follow up including surgical staging, residual tumor, chemotherapy regimen and response, relapse and last follow up
 - genomic characterization by clinically available gene panels



MARIO NEGRI GYNECOLOGIC ONCOLOGY GROUP (MANGO) DATASET

Groups	Resources
Retrospective databases	To be proposed among Ymagine collaborators (Niguarda, Torino, IEO, others..)
Regional registries	Regione Piemonte
Clinical trials	...

1. Contact at mango@marionegri.it
2. Database protocol, informed consent and CRF will be provided for EC approval by MaNGO office
3. Activation of the center with IT assistance where needed
4. Data entry!



WE SUPPORT
RARE DISEASE DAY
28 FEBRUARY 2023
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POINTS



RARE CANCERS

