ENDOMETRIAL CARCINOMA

Claudia De Angelis
Oncologia Clinica
AOU Careggi Firenze

MaNGO
Mario Negri Gynecologic Oncology

ADJUVANT SETTING

- ENGOT-EN 11 (CLOSED) → Adj ICI
- TAPER/RAINBO BLUE (NEW) → Observation vs de-esacalation in POLE mut/NSMP
- ENGOT-EN22/ STREAM – 1 (NEW) → Role of Cytoreductive Sx

ADVANCED /RECURRING SETTING

- ATTEND/ENGOT EN-7 (CLOSED) → Chemo + ICI in 1° line
- POD1UM-204/ENGOT-EN12 (ONGOING) → ICI ± other therapies ICI naive or resistant
- DOMENICA/ENGOT-EN13 (ONGOING) → ICI in mono in dMMR
- ENGOT-EN15 (ONGOING) → ICI in mono in dMMR
- ENGOT-EN17 (UNDER ACTIVATION) → 1° Line Endoncrine Therapy
- ENGOT-EN20/XPORT (UNDER ACTIVATION) → Maintanance after 1° line CT in p53 WT
- ENGOT-EN21/NAVTEMADLIN (UNDER ACTIVATION) → Maintanance after 1° line CT in p53 WT

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KEYNOTE-B21 / ENGOT-en11

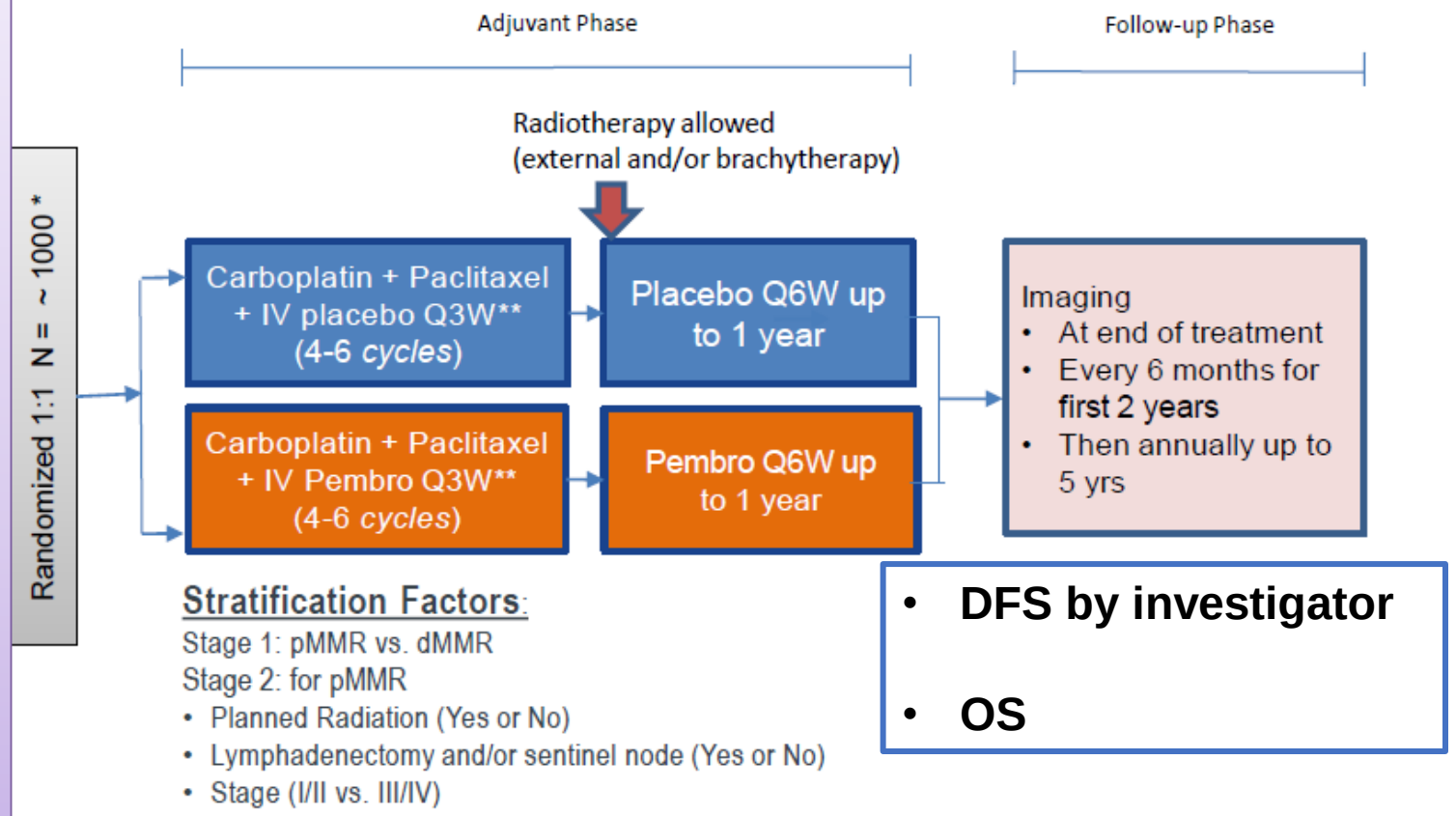
ENGOT model: C
Sponsor: MSD
Lead group: BGOG

Proposed Adjuvant Endometrial Cancer Study

Key Eligibility Criteria:

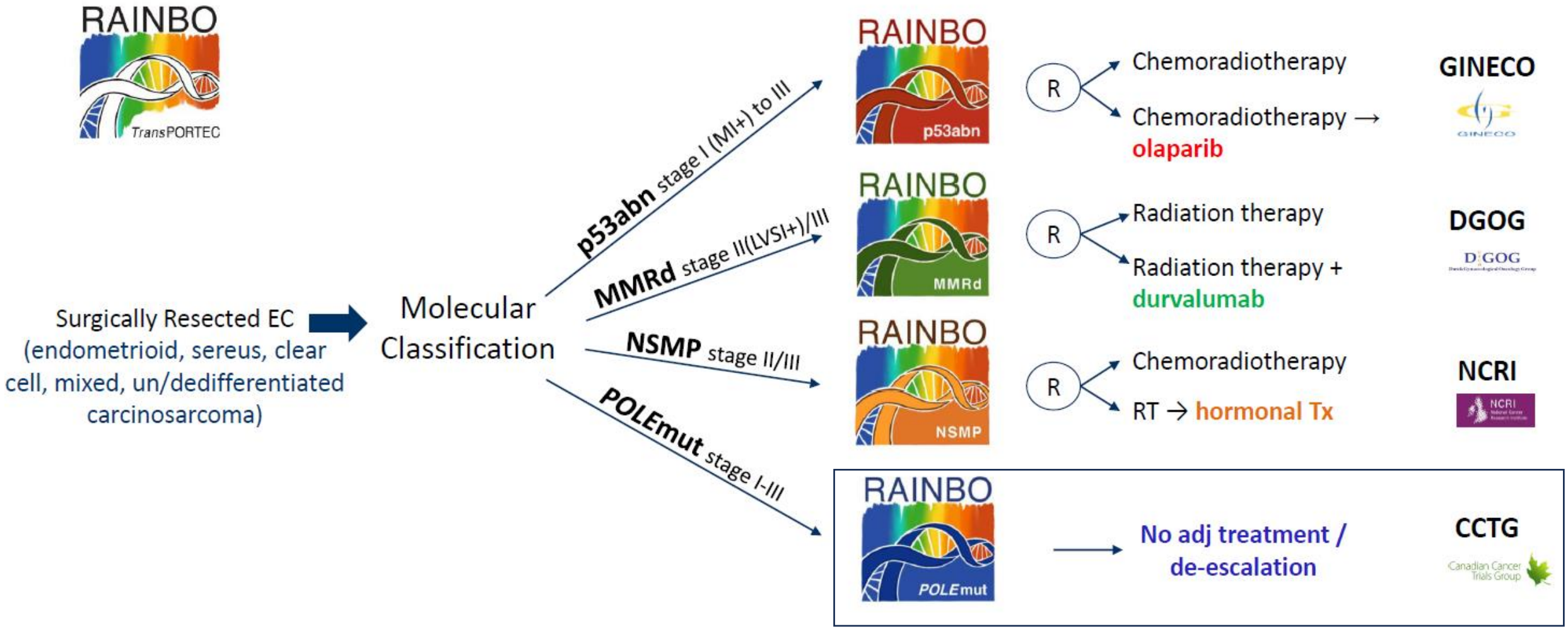
- **Newly diagnosed** Endometrial Carcinoma or Carcinosarcoma
- Undergone **curative intent surgery** with **no residual disease**
- **All-comers** with respect to PD-L1 and MMR status
- **At high risk for recurrence**:
  - FIGO Stage I/II of non-endometrioid histology
  - FIGO Stage I/II of any histology if known to be p53 mutated
  - FIGO Stage III/IVA of any histology
- **No prior radiation or systemic therapy** for EC including neoadjuvant therapy
- ECOG 0-1

Available tumor tissue for determination of histology and MMR status



Partecipano: IEO, IOV, Spedali Civili, INT.
Final DFS analysis expected for June 2025.

TransPORTEC/GCIG/ENGOT-EN14[1-4] - RAINBO



Primary Endpoint: 3-yr RFS

RAINBO blue under activation at MaNGO

TAPER/RAINBO BLUE

This protocol tests de-escalated adjuvant treatment in patients with *POLE*-mutated or p53wt/NSMP (p53 wildtype/no specific molecular profile) early-stage endometrial cancer (EC). Patients may be enrolled to one of two sub-studies (EN10.A/RAINBO BLUE or EN10.B/TAPER) as shown below:

Endometrial carcinoma treated by hysterectomy, bilateral salpingo-oophorectomy, lymph node assessment (pelvic lymph node surgical assessment required for grade 3 and/or stage II):

- Stage IA (not confined to polyp), grade 3, pN0, with or without LVI
- Stage IB, grade 1 or 2, pNx/N0, with or without LVI
- Stage IB, grade 3, pN0, without substantial LVI
- Stage II (microscopic), grade 1 or 2, pN0, without substantial LVI

Higher-risk EC with known pathogenic *POLE* mutation (exploratory cohort):

- Stage IA grade 3 – Stage III not included in above

Intermediate
High-intermediate

Study Enrolment

N = 120 *POLE*-mutated (Sub-study A, Cohort A1)
180 p53 wildtype/NSMP (Sub-study B)
~25 "higher-risk" *POLE*-mutated (Sub-study A, Cohort A2)

Sub-study B (TAPER)

p53 wildtype/NSMP ER+ EC
Observation or de-escalated adjuvant treatment

Sub-study A (RAINBO BLUE)

Cohort A1
***POLE*-mutated EC**
Observation

Cohort A2: Exploratory
Higher-risk *POLE*-mutated EC
Observation or de-escalated adjuvant treatment

Primary Endpoint: pelvic 3-yr RFS

RAINBO-Blue/TAPER MaNGO interested sites

City	Hospital	First Name	Last Name
Milano	Istituto Europeo di Oncologia	Ilaria	Betella
Torino	Ospedale Mauriziano	Annamaria	Ferrero
Brescia	Spedali Civili	Germana	Tognon
Lecco	Ospedale Manzoni	Romerai	D'Amico
Reggio Emilia	Arcispedale S. Maria Nuova	Alessandra	Bologna
Firenze	Policlinico Careggi	Cristina	Petrella
Roma	Ospedale Umberto I	Federica	Tomao
Lucca	Ospedale San Luca	Editta	Baldini
Parma	AOU di Parma	Angelica	Sikokis
Varese	Ospedale Del Ponte	Nicoletta	Donadello
Milano	ASST Ospedale Niguarda	Lorenzo	Ceppi

Update June 2023: The agreement between Sponsor (Canadian group) and Mario Negri Institute (MN) to delegate to MN the submission of the study in Italy and its activation in Italian sites is just finalized.
In collaboration with IEO Milan, MN team is finalizing the submission.

STREAM-I
(Surgical Treatment in Advanced and Recurrent Endometrial CAncer Management)

AGO-OP.11/ENGOT-en22

Sponsor: AGO
Project Lead:
Prof. F. Trillsch

Evaluation of preoperative clinical and translational selection criteria for cytoreductive surgery in endometrial cancer – A retrospective multicenter trial with an accompanying translational project

Retrospective descriptive, non-interventional, multicenter study
(patients undergoing CRS for EC between 01/2011 and 12/2020)

- Primary diagnosis of advanced EC and peritoneal metastases (FIGO IV)
- Diagnosis of recurrent EC undergoing cytoreductive surgery

Tumor material:

a. Requesting FFPE tumor blocks from Study Centers
b. Evaluation of molecular subgroups according to TCGA
c. Slides für RNA/DNA isolation, establishing TMAs

STREAM-1/ENGOT-en22

Objectives

Primary objective

Identification of clinical selection criteria to predict complete cytoreduction in patients with advanced or recurrent endometrial cancer

Secondary objectives

Clinical part:

- Evaluation of prognostic factors predicting benefit from cytoreductive surgery in advanced or recurrent endometrial cancer
- Identification of prognostic markers for the clinical outcome

Translational part:

- Evaluating the predictive value of the molecular classification according to TCGA for surgical outcome in endometrial cancer
- Identification of biologic and molecular expression profiles to predict complete cytoreduction in patients with endometrial cancer and their prognostic significance

Exploratory objectives

- Description of current treatment practices in participating European countries for advanced or recurrent endometrial cancer

Included pts undergoing cytoreductive surgery for EC between 01/2011 and 12/2020 with:

- **Primary diagnosis of advanced EC and peritoneal metastases (FIGO IV) undergoing cytoreductive sx**

OR

- **Diagnosis of recurrent EC undergoing cytoreductive sx**

Optional but strongly encouraged **for translational part availability of FFPE tumor material from cytoreductive sx**

Excluded pts undergoing sx solely for palliative intent, with secondary malignancies requiring abdominal sx

STREAM-1/ENGOT-en22: Update June 2023

- Protocol and feasibility questionnaire under evaluation of the Mario Negri' DPO to understand how data and samples can be collected and analysed without reconsenting (as stated in the Protocol).

- Feasibility questionnaire will be share soon with MaNGO sites.

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AtTEnd study: Atezolizumab Trial in Endometrial Cancer ENGOT-EN7/MaNGO/AtTEnd

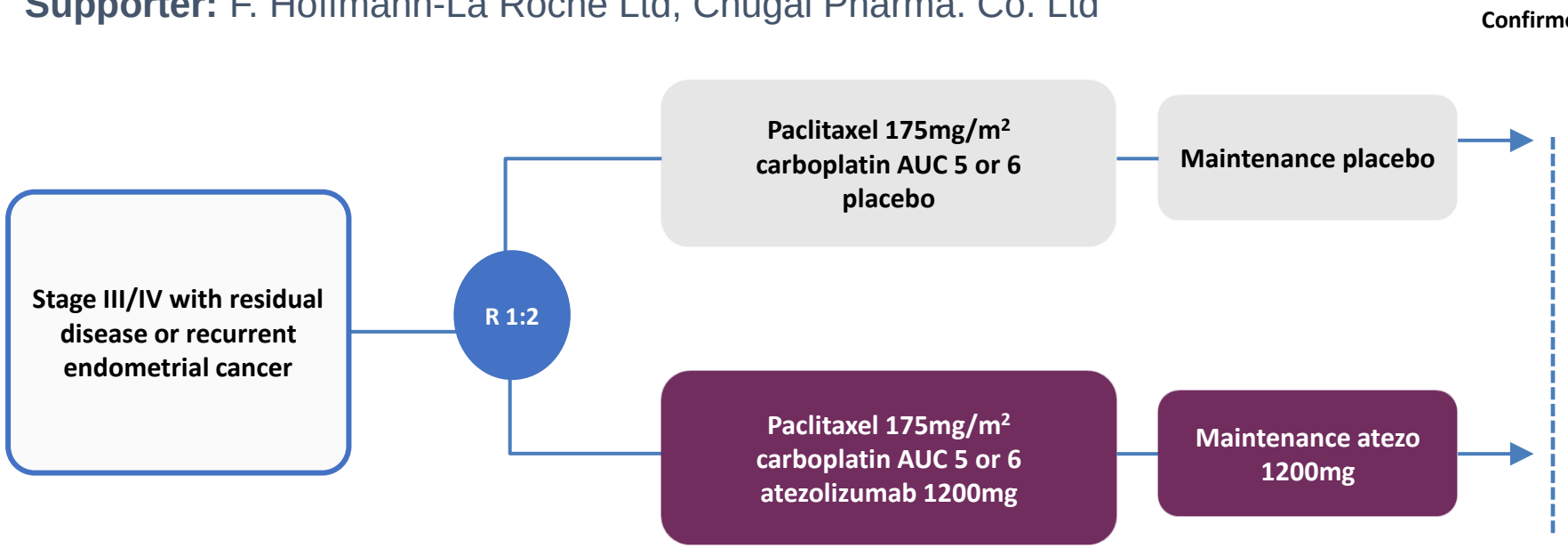
A phase III double-blind randomized placebo-controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer

ENGOT model: A

PI: Nicoletta Colombo, European Institute of Oncology (EIO), Milano

Sponsor: Mario Negri Gynecologic Oncology (MaNGO)

Supporter: F. Hoffmann-La Roche Ltd, Chugai Pharma. Co. Ltd

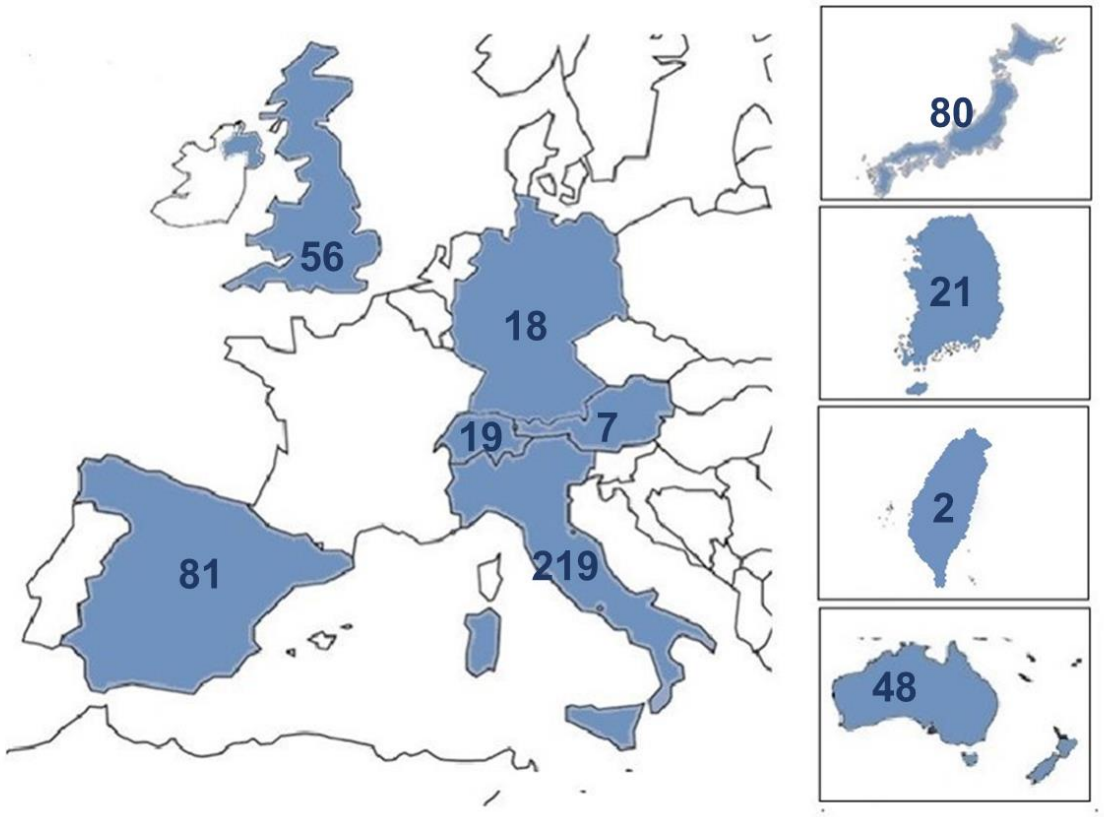


Co-Primary Endpoints:

- **PFS in the MSI population (HR:0.5) and overall (HR:0.7) with a hierarchical approach**
- **OS with HR:0.7**

ENGOT–EN7/AtTEnd Enrollment status

- **First patient in:** October 2018
- **Accrual closure: Jan 2022**
- **Total Number of Randomized: 551**



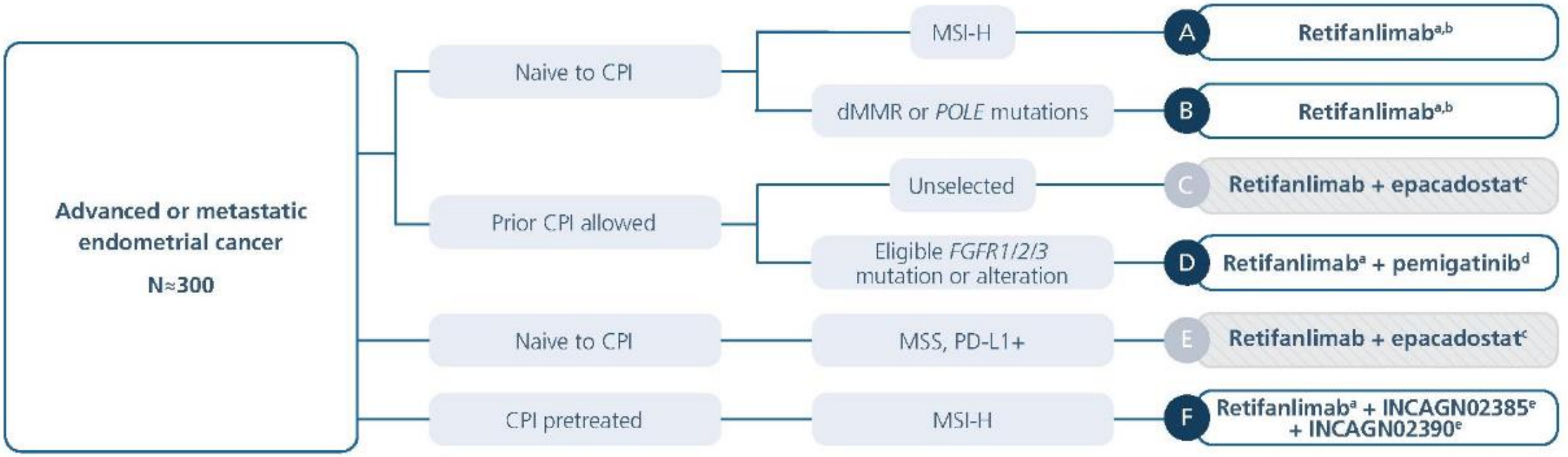
Involved Groups	Activated Sites	Random
ENGOT		
AGO	4	18 (3%)
AGO-A	2	7 (1%)
GEICO	10	81 (15%)
MaNGO	**24**	**219 (40%)**
NCRI	10	56 (10%)
SAKK	8	19 (4%)
Non ENGOT		
ANZGOG	15	48 (9%)
JGOG	10	80 (15%)
KGOG (South Korea)	10	21 (4%)
TGOG (Taiwan)	2	2 (0,4%)

ENGOT-EN7/AtTEnd
Current and Next steps

- Looking at the event projections, showing a flat events rate and at the recently published data (Ruby, GY018) and after IDMC suggestion we decide to anticipate the PFS final analysis (with 73 events in MSI cohort instead of 79 required).
- The data cut-off was May 31st, and we ask all site to report all the information referred to the visits performed until this data in the eCRF.
- Data completion and queries management is crucial in this phase, an intensive program of requests is ongoing.
- **Database lock for the final PFS analysis of the AtTEnd study is planned for July 2023 and we would like to present the study results at ESMO (October 2023).**

ENGOT-EN12/POD1UM-204
Study design*

Safety and Efficacy of Retifanlimab (INCMGA00012) Alone or in Combination With Other Therapies in Participants With Advanced or Metastatic Endometrial Cancer Who Have Progressed on or After Platinum-based Chemotherapy (POD1UM-204)



Pts enrol/tot

83/100

17/40

14/40

4/40

Key inclusion criteria:

- PD on or after treatment with ≥ 1 platinum-containing regimen for advanced or metastatic disease
- ≥ 1 measurable tumour lesion per RECIST v1.1

Key exclusion criteria

- Diagnosis of sarcoma of the uterus

***groups C and E are closed**

Primary EP: Group A: ORR (per RECIST v1.1, by ICR)
Secondary EPs:
Group A and B: DoR, DCR, PFS and OS
Group B-F: ORR
All groups: safety and tollerability

ENGOT model: C, Sponsor: Incyte, Lead group: NOGGO

ENGOT-EN12/POD1UM-204
Study update June 2023

Global Status

Country (# of sites active)	# Total screened	# of in pre/ screening	# enrolled patients	# screen failures
France (6)	**91**	5	33	53
Belgium (5)	**36**	0	12	24
Greece (3)	**28**	1	11	16
Italy (8)	**97**	5	44	48
Germany (0)	**12**	0	0	12
Georgia (6)	**64**	2	22	40
EU total	**328**	**13**	**122**	**193**
US (27)	85	-	44	41

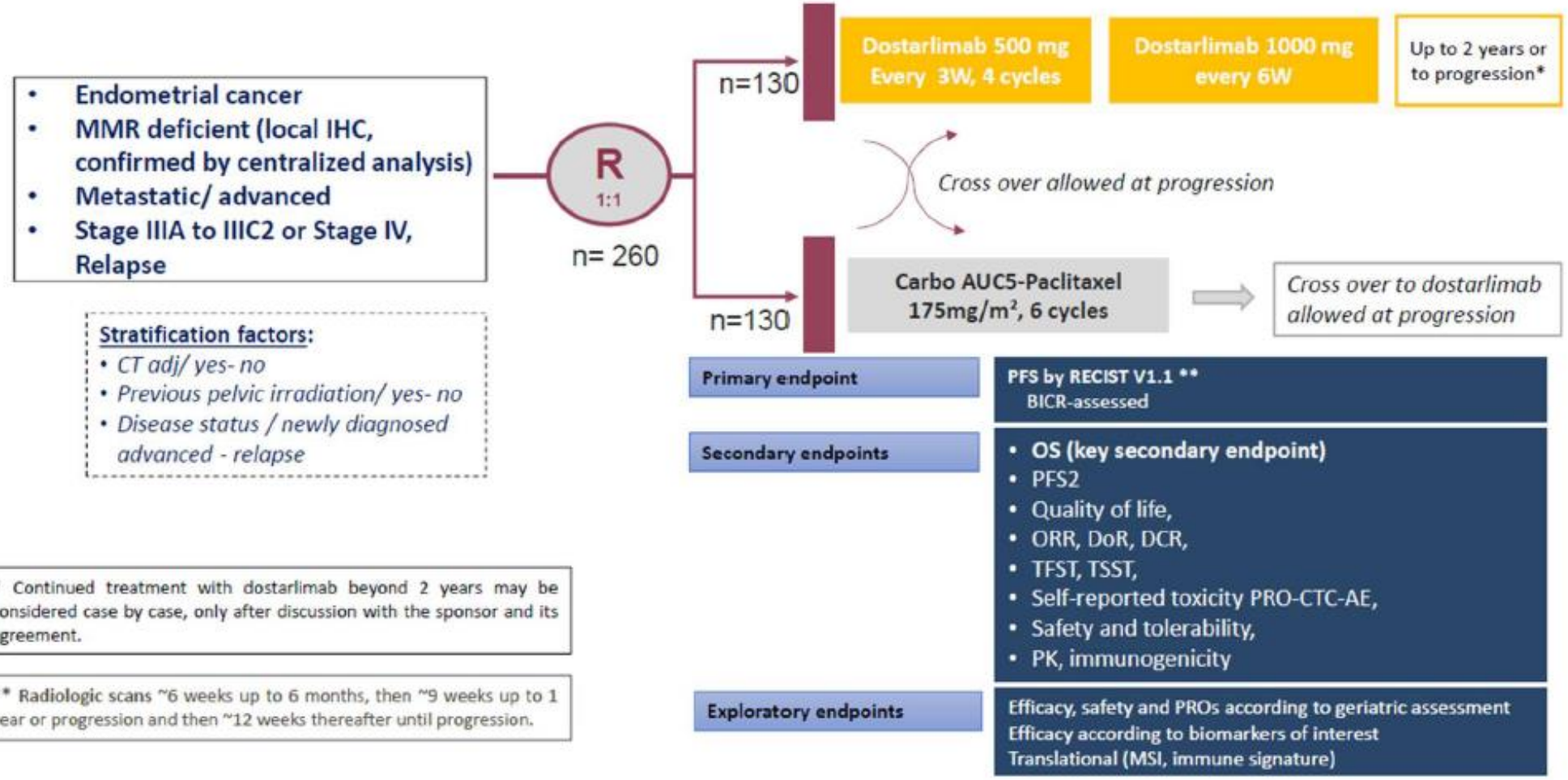
MaNGO enrolled 7 patients from 4 sites:

- **IEO Milano**
- **IOV Padova**
- **S.Orsola Bologna**
- **INT Milano**

Enrolment prolonged until Oct 2023

Domenica/ENGOT-EN13
Current study design*

ENGOT study: Model A
Sponsor: GINECO



*protocol version no. 3 approved only in France

Domenica/ENGOT-EN13: Update June 2023

- Global: 65 patients were randomized from France and recently from Spain;
- Italy will be activated soon;

- In Italy the approval was received in April 2023 by AIFA;
- Agreements with the Italian sites under finalization.

Domenica/ENGOT-EN13
MaNGO sites/activation

City	Hospital	PI	Status of site agreement
Torino	Ospedale Mauriziano	Annamaria Ferrero	Negotiation to be started
Torino	Ospedale Sant'Anna	Dionyssios Katsaros	Negotiation to be started
Brescia	Spedali Civili	Germana Tognon (MaNGO PI)	Under site revision
Lecco	Ospedale Manzoni	Antonio Ardizzoia	Under site revision
Milano	Istituto Europeo di Oncologia	Nicoletta Colombo	Under site revision
Milano	Istituto Nazionale dei Tumori	Francesco Raspagliesi	Under site revision
Monza	Ospedale San Gerardo	Andrea A. Lissoni	Site feasibility to be completed
Pisa	Ospedale Santa Chiara	Angiolo Gadducci	Negotiation to be started
Lucca	Ospedale San Luca	Editta Baldini	Negotiation to be started
Roma	Policlinico Umberto I	Innocenza Palaia (Federica Tomao)	Site feasibility to be completed

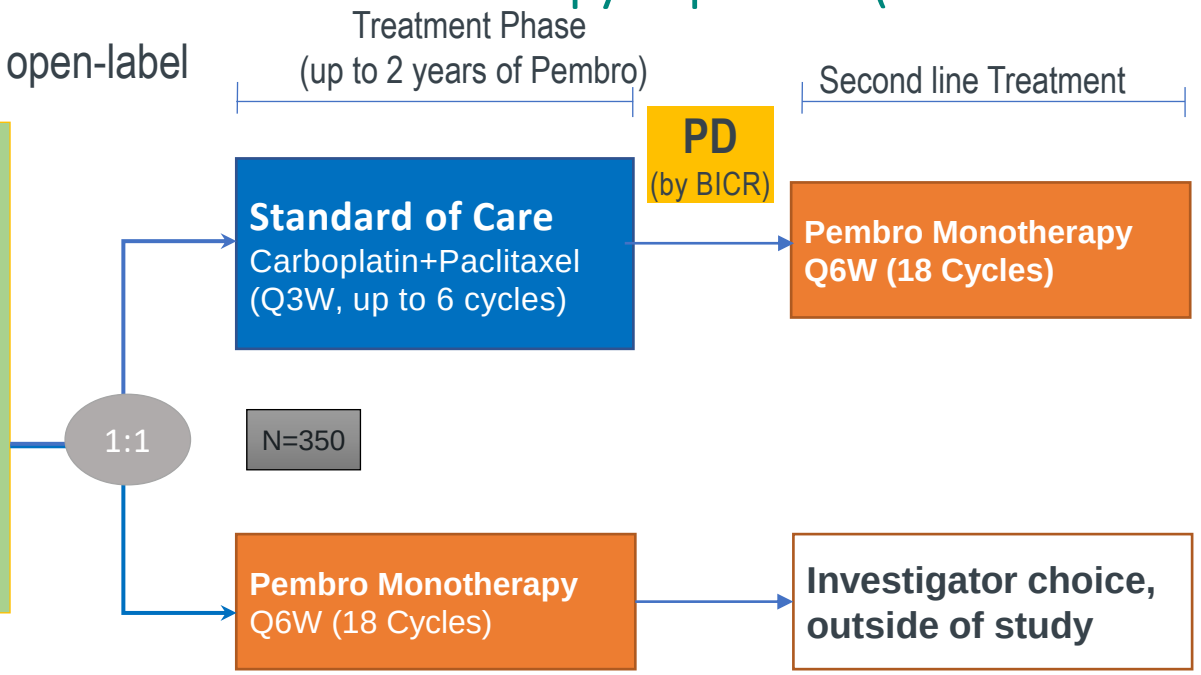
KEYNOTE-C93/ENGOT-EN15

Study Design: 1L dMMR platinum-doublet chemotherapy vs pembro (with formal cross-over)

Phase 3, multi-center, randomized, open-label

Key Eligibility Criteria:

- Stage III or IV, persistent/ recurrent, or metastatic EC
- Measurable/non-measurable disease (radiological apparent)
- dMMR/MSI-H
- No previous chemo for first line except as part of chemoradiation
- No prior adjuvant/neoadjuvant chemotherapy allowed
- ECOG 0-1



ENGOT study:
Model C
Sponsor: MSD
Lead group: MITO

Potential Stratification:

- Disease status (newly diagnosed advanced cancer vs recurrent)
- Histology – endometrioid vs. non-endometrioid

Dual Primary Endpoints

- *PFS (by BICR)*
- *OS*

ENGOT-EN15 Update June 2023

MaNGO randomized 4 pts from 4 sites:

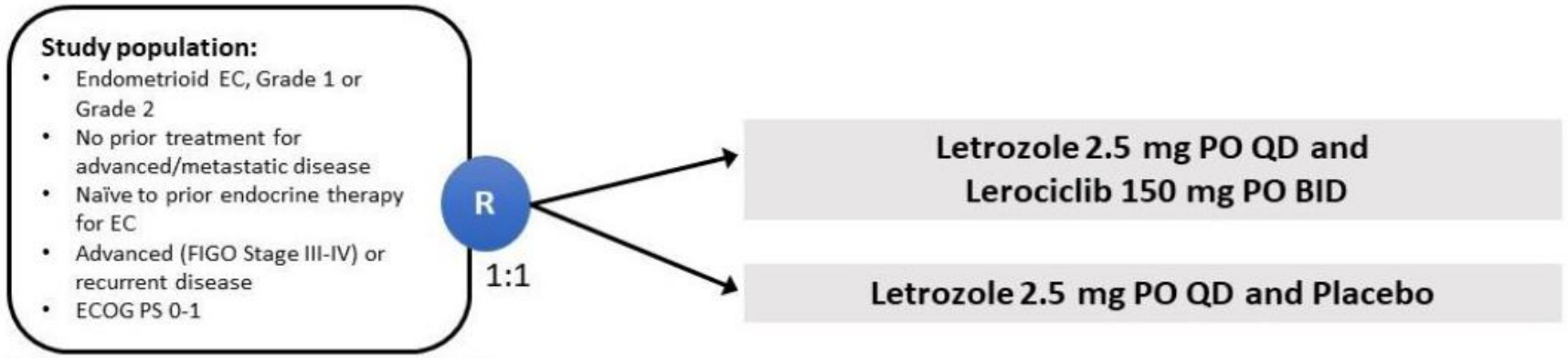
- **IEO Milano**
- **INT Milano**
- **IOV Padova**
- **Careggi Firenze**

MK3475-C93: Recruitment Tracker

Patient Status per Country:

Country	Total Screened	In Screening	Screened Failed	Total Randomized	Total Randomized in Treatment	End of Treatment- Initial Phase
Latin America						
Brazil						
Chile	4	4				
ENGOT						
Belgium (BGOG)	2		1	1	1	
Czech Republic (CEEGOG)	14	1	7	6	4	2
Denmark (NSGO)	2		1	1	1	
FInland (NSGO)	3	1	1	1		1
Germany (NOGGO)	3		2	1		1
Israel (ISGO)	17	4	9	4	2	2
Italy (MITO)	47	2	26	19	16	3
Italy (MANGO)	6		2	4	2	2
Norway (NSGO)	2		2			
Netherlands (DGOG)	11	2	2	7	6	1
Ireland (CTI)	5		1	4	4	
Poland (PGOG)	65	4	41	20	13	7
Spain (GEICO)	11		2	9	5	4
Hungary (CEEGOG)	4		1	3	3	
Sweden (NSGO)	1			1	1	
Turkey (TRSGO)	9		4	5	2	3
UK (NCRI)	6	1	3	2	1	1
Ukraine (On Hold, CEEGOG)						
North America						
USA (GOG)	52	2	17	33	21	12
Canada	30	3	10	17	15	2
APAC						
China	83	5	53	25	21	4
Japan	59	4	47	8	6	2
Russia (On Hold)						
South Korea	25	1	14	10	7	3
Australia	10			9	5	4
New Zealand						
Taiwan	20		10	10	8	2
TOTAL	491	34	256	200	144	56

ENGOT-en17/GINECO/EQ132-303/GOG-3075 Study Design



Stratification variables:
- Tumor stage (FIGO III vs IV vs recurrent)
- Tumor grade (Grade 1 vs Grade 2)
- Geographic location

Primary endpoint: PFS by BICR
Key secondary endpoint: OS
Other secondary endpoints: PFS by Investigator, PROs/QoL, safety/tolerability
Exploratory endpoints: ORR, PopPK for lerociclib & letrozole, exposure-response, financial distress, translational analysis of ctDNA

- Hazard ratio for PFS: 0.63
- Significance level: 0.025 (1-sided)
- Randomization ratio: 1:1
- Median PFS in the control arm: 5 months
- Targeted PFS in the experimental arm: 7.94 months

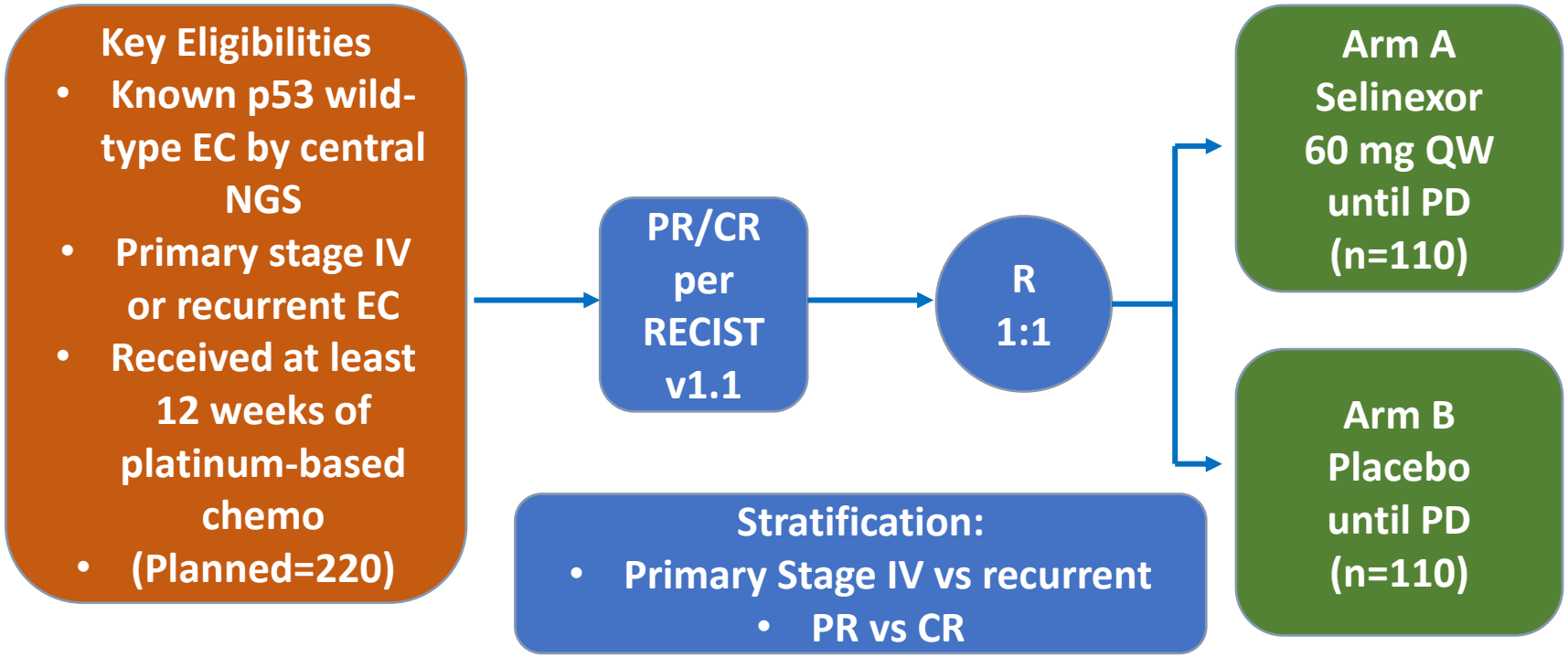
→ **320 patients need to be randomized**

Model C;
Lead Group: GINECO

4 MaNGO sites involved: IEO Milano, INT Milano, IOV Padova, Mauriziano Torino.
Study Submission ongoing

ENGOT–EN20

Background: Pre-specified exploratory subgroup analyses of the ENGOT-EN5/GOG-3055/SIENDO trial identified p53 wild-type as a potential predictor of efficacy of selinexor, with 10-month PFS improvement over placebo; no benefit for selinexor was seen in patients with p53 mutant/aberrant tumors.



Primary Endpoint:
PFS assessed by Investigator

Key Secondary Endpoint:
OS, safety

Other Secondary Endpoint:
PFS assessed by BICR, TFST, PFS2, TSST, DCR, QoL (E6D-5L)

Exploratory Endpoint:
PFS per histology subtypes
PFS per other molecular features
Analysis of tumor molecular biomarkers
CR rate: duration of CR
Potential relationship between PK exposure and efficacy

ENGOT-EN20 Update June 2023

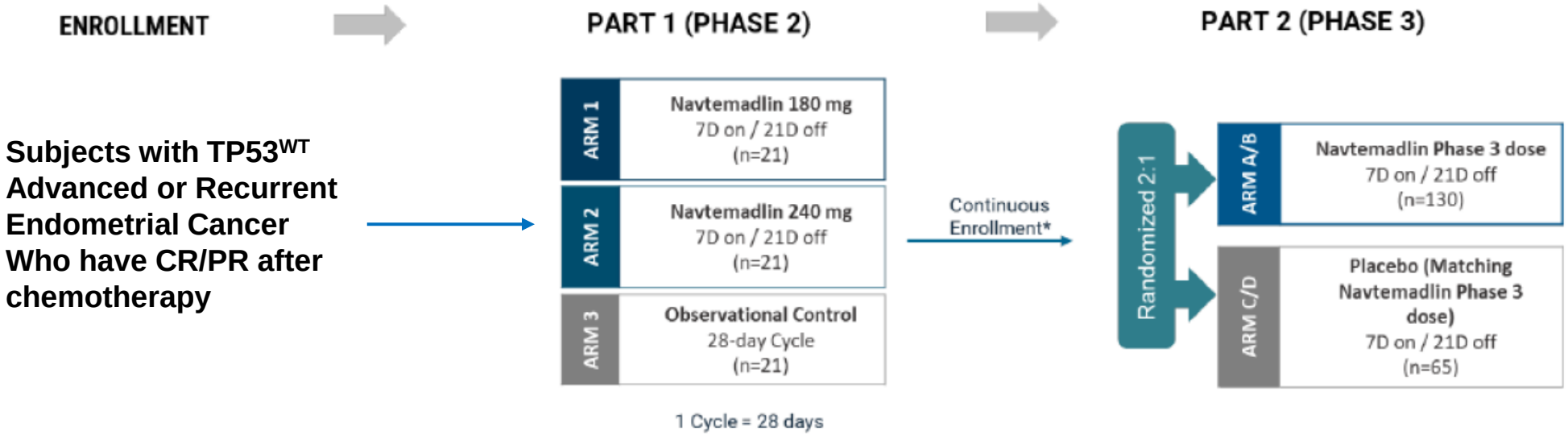
- Global update: 2 patients were randomized out of 18 screened;
- In Italy, AIFA and the central EC approved the study;
- The site agreement is under negotiation in all the MaNGO sites.

MaNGO sites involved

City	Hospital	PI Name
Milano	Istituto Europeo di Oncologia	Nicoletta Colombo (MaNGO PI)
Torino	Ospedale Sant'Anna	Dionyssios Katsaros
Brescia	Spedali Civili	Valentina Zilioli
Milano	Istituto Nazionale dei Tumori	Francesco Raspagliesi
Monza	Ospedale San Gerardo	Andrea A. Lissoni
Padova	Istituto Oncologico Veneto	Valentina Guarnieri
Pisa	Università di Pisa	Angiolo Gadducci

ENGOT-EN21/Navtemadlin

Model C;
Lead Group: AGO-A



Abbreviations: CR = complete response; D = Day; PR = partial response; WT = wild type.
* After enrollment completes for Part 1, subjects will continue to be enrolled for Part 2 and randomized 2:2:1:1 to one of the 4 treatment arms: navtemadlin 180 mg, navtemadlin 240 mg, placebo 180 mg or placebo 240 mg. Once the SRC determines the navtemadlin Phase 3 dose, enrollment will continue with 2:1 randomization to the navtemadlin Phase 3 dose and matching placebo dose for Part 2.

Part 1	To determine the navtemadlin Phase 3 Dose	• To evaluate the ORR, DCR, PFS and OS for each arm • To determine the PK profile of navtemadlin for each arm	Part 1 and 2: • To evaluate efficacy and safety of navtemadlin relative to select PD markers • To monitor the PK of navtemadlin (**Part 2 only**)
Part 2	To compare the PFS by independent review committee between navtemadlin and placebo	• To compare the ORR, DCR, PFS (Inv), TFST and OS between navtemadlin and placebo	

ENGOT-EN21 and competitive studies

Part I (=Phase II) of Navtemadlin trial (approximately 70 patients) will strictly use NON-OVERLAPPING sites with the ENGOT-en20 trial (while ENGOT-en20 trial is going full force with its selected sites).

Part II (=Phase III) of Navtemadlin trial (appoximately 188 patients) will start enrollment later and sites involved in the ENGOT-en20 trial will only be opened for the Navtemadlin trial after completion of enrollment in ENGOT-en20, in this way avoiding competition between both trials.

For the phase III, the Navtemadlin trial will open more sites and countries. Prior Selexinor-sites are welcome and encouraged to participate in Navtemadlin trial once the ENGOT-en20 has closed accrual, as they will be able to enroll the same patient population into the new Navtemadlin trial.

MaNGO sites involved in Part I

Site # and PI	Site	Country	Submitted to CTIS	CTIS approval	Participating in part 2 only	Site Initiation Visit (SIV)	Contact
118-3119 Ilaria Schiavetto	Big Metropolitan Hospital Niguarda Regional Health Authority	Italy	Yes		no		ilaria.schiavetto@ospedaleniguarda.it
118-3142 Rosa Porzio	Osp. Guglielmo da Saliceto	Italy	Yes		no		R.Porzio@ausl.pc.it
118-3143 Nicoletta Donadello	ASST Sette Laghi, Filippo Del Ponte Hospital	Italy	Yes		no		nicoletta.donadello@asst-settelaghi.it
118-3144 Editta Baldini	San Luca Hospital	Italy	Yes		no		editta.baldini@uslnordovest.toscana.it
118-3138 Elena Zafarana	Santo Stefano Hospital of Prato - USL Company Toscana Center	Italy	Yes		no		elena.zafarana@uslcentro.toscana.it
118-3139 Angelica Sikokis	University Hospital of Parma	Italy	Yes		no		asikokis@ao.pr.it
Antonio Ardizzoia	Osp. Manzoni	Italy	No		no		a.ardizzoia@asst-lecco.it
Alessandra Bologna	Arcispedale S. Maria Nuova	Italy	No		no		Alessandra.Bologna@ausl.re.it
Federica Tomao	Policlinico Umberto 1^	Italy	No		no		federica.tomao@uniroma1.it

MaNGO sites interested to Part II

City	Hospital	PI name
Bologna	Policlinico Sant'Orsola	Claudio Zamagni
Brescia	Sedali Civili	Germana Tognon
Padova	Ist. Oncologico Veneto	Valentina Guarneri
Torino	Osp. Mauriziano	Annamaria Ferrero

ENGOT-EN21: Update June 2023

AOB

Site Initiation Visits (SIVs)

- First SIV is planned in mid-July.
- Anticipated is that the first initiated site will be from Georgia (CEEGOG)
- Further initiation visits - expected to take place between mid and end of July.

Potential protocol amendment

- Part I of the trial will continue as planned.
- With the global availability of Dostarlimab, a protocol amendment is being discussed.

Thanks to @Elena Biagioli for support, studies material and updates!

MaNGO
Mario Negri Gynecologic Oncology