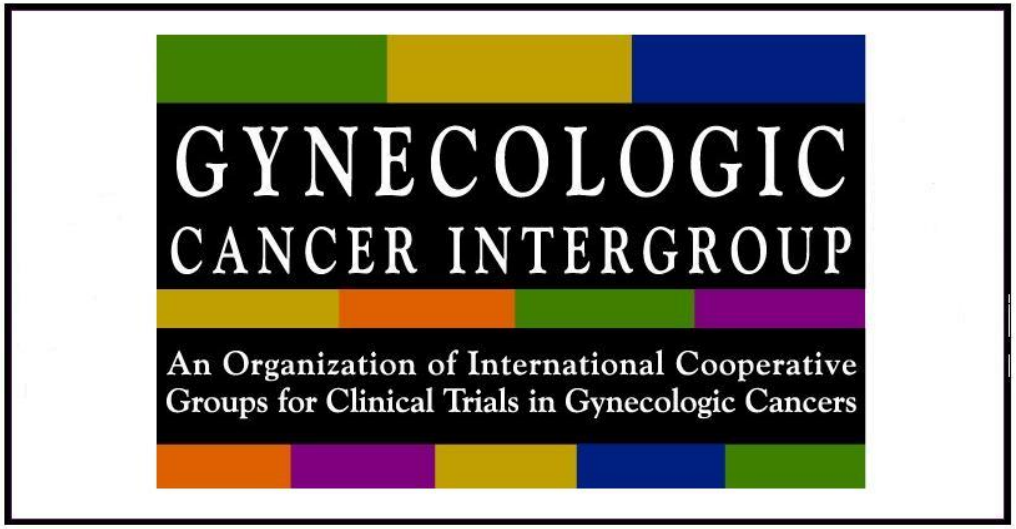


Gynecologic Cancer InterGroup (GCIG)

Ovarian Cancer Committee, Chicago 2016

Chair: P.Harter Co-Chair: A.Gonzalez

Harmonization liaisons:
Carty/Stonebraker (ops); Embleton/Brady (Stats)

Agenda

- Welcome & Introductions (COI disclosures)
- Approval of November 2015 report (posted on GCIG website)
- Closed/ongoing trials (45'): Harter/Gonzalez
- Planned trials:
  - Oreo (10') E Pujade-Lauraine
  - SUNNY (10') RY Zang
  - AGO-OVAR 2.29 (10') P Harter
- Update from already presented trials/proposals
  - WISP (5') K Lu
  - Atalante (5') E Pujade-Lauraine
- 5th OCCC publications update (10') K Ochiai

Closed/Ongoing trials – First line

- AGO-OVAR OP.3 (LION) (c)
- AGO-OVAR OP.7 (TRUST)
- AGO-OVAR 17 (c)
- PAOLA 1
- ICON 8 (c) & ICON 8B
- GOTIC 001/JGOG3019 (iPocc)
- NCIC-CTG OV.21 (c)

AGO – OVAR OP.3 (LION)

Lymphadenectomy In Ovarian Neoplasms

- epithelial invasive ovarian cancer
- FIGO IIB - IV
- ECOG 0/1 and no CI against LNE
- no visible extra- and intra-abdominal tumor residuals
- no bulky lymph nodes

R

n = 640

System. Lymphadenectomy

- pelvic
- para-aortic

no Lymphadenectomy

Endpoints: OS, PFS, QoL *Strata: centre, PS ,age*

LION
AGO-OVAR OP.3

Supported by the Deutsche Forschungsgemeinschaft

LION – Lymphadenectomy in Ovarian Neoplasms

Primary objective:

- Overall survival (after 247 OS events observed)

Secondary objectives:

- Progression-free survival
- Complication rates of surgery
- Qol
- Number of resected lymph nodes

Current Status:

Number of required events for the analysis of the LION study has been reached in April 2016

First Patient in	Dec-2008
Last Patient in	Jan-2012
Enrolment period	36 months
OS analyses	**2016**

AGO OP.7 / TRUST

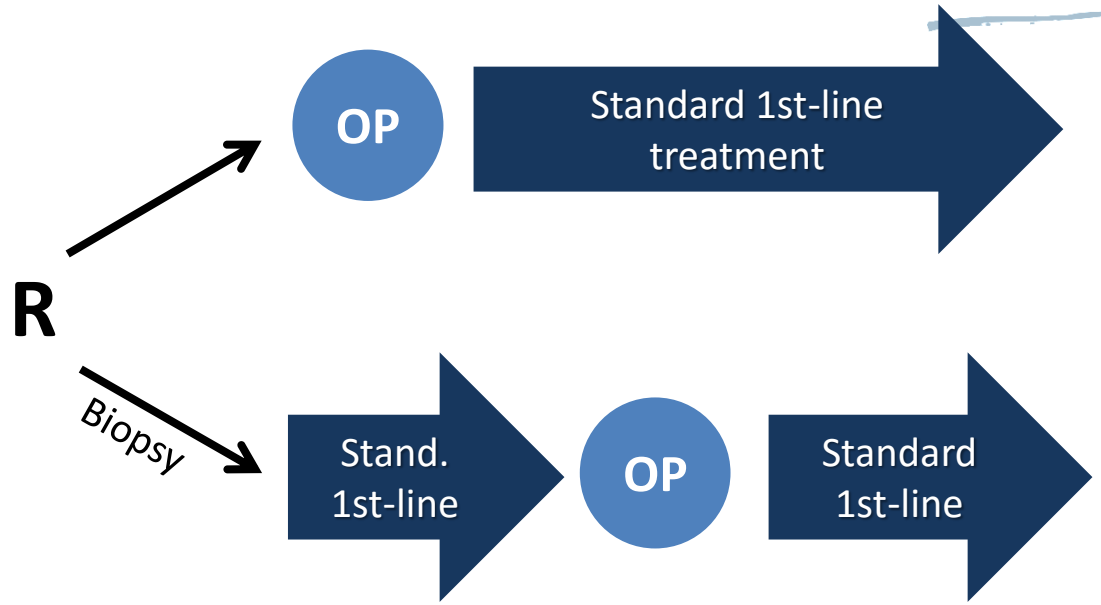
TRUST –
Trial on Radical Upfront Surgical Therapy

A close international cooperation

AGO Studiengruppe

TRUST – Trial on Radical Upfront Surgical Therapy

Pt with ovarian-, tube- or peritoneal carcinoma FIGO Stage IIIB- IV



- *Primary endpoint OS in ITT population*
- *secondary endpoints PFS, complete resection rate, morbidity and mortality within 6 mos, QoL and PRO, „fragility Index“*
- *Strata: FIGO stage (III / IV), country, ECOG 0 vs 1*
- ***Defined selection process for sites with high operative quality***

Recommended treatment: 6x Carboplatin/Paclitaxel + Bev
Also permitted: TC with weekly Paclitaxel (JGOG Regime) or TC without Bev or study participation, if treatment balenced in both arms

Inclusion criteria

- Suspected or histologically confirmed, newly diagnosed **invasive epithelial ovarian cancer FIGO stage III-IV (IV only if potentially resectable metastasis)**
- Age: 18 years or older
- Patients who have given their written informed consent
- **Good performance status (ECOG 0/1)**
- **Good ASA score (1/2)**
- Preoperative CA 125/CEA ratio ≥ 25 (if CA-125 above 2x upper limit of normal (ULN)). An esophago-gastro-duodenoscopy (EGD) and colonoscopy is mandatory to exclude gastrointestinal primary cancer if the ratio is <25 and/or a biopsy has shown with non-serous, non-endometrioid histology
- **Assessment of an experienced surgeon, that based on all available information, the patient can tolerate the procedures necessary to achieve a complete tumor resection**

Endpoints

- **Primary:** overall survival time calculated from the date of randomization until the date of death from any cause or date of last contact (censored observation).
- **Secondary:**
  - Progression-free survival (PFS)
  - PFS2
  - Time to first subsequent anticancer therapy or death (TFST)
  - Time to second subsequent anticancer therapy or death (TSST)
  - Quality of life (QoL) as measured by EORTC QLQ-C30, OV28, EQ-5D

Some of the Site selection/qualification criteria…

- ≥ 50% complete resection rate in upfront surgery for FIGO IIIB, IIIC and IV pts
  („statutory declaration“ by each center)
- A minimum of 36 debulking-surgeries/year
- Upfront review of 24 surgery- and pathology reports
  - Upper abdominal surgery must e established
  - Retroperitoneal surgery must be established
  - M‘n‘M management must be established
- Agreement to be visited and audited by TRUST Quality committee delegates

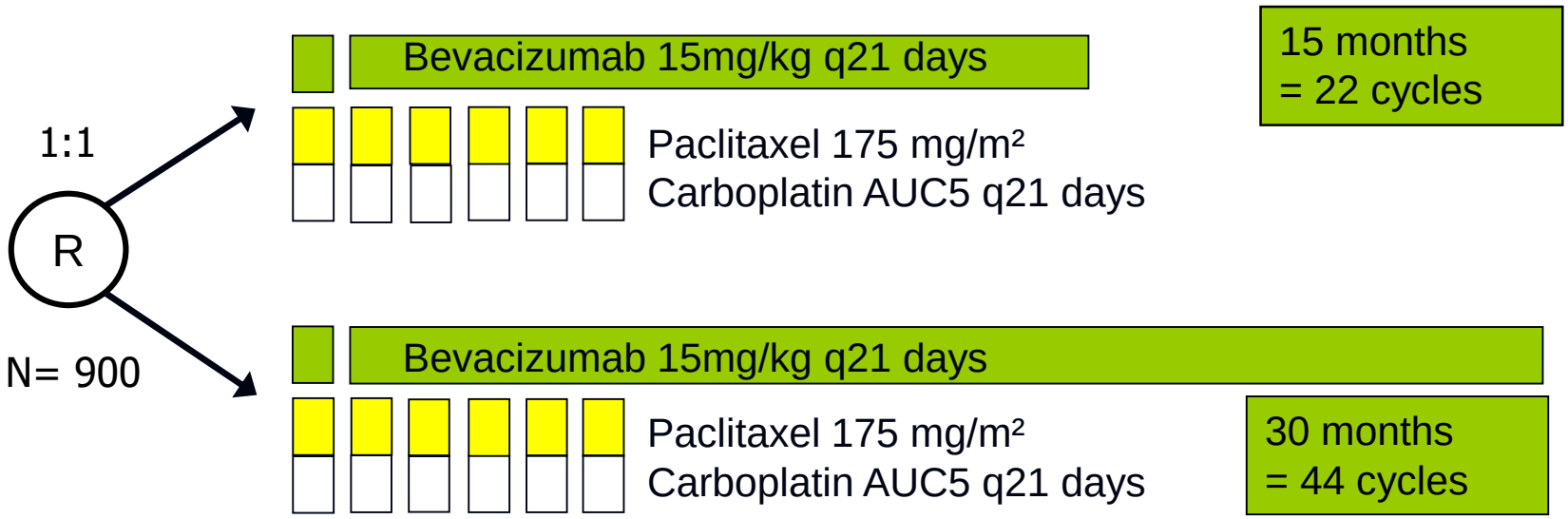
Timelines (1)

- 3. November 2015:
  - Quality Assessment in Germany started
    10 sites under review/ 1 site in UK
- 17. December 2015
  - Protocol finalized
- 12. January 2016
  - Protocol submitted to Ethics committee
  - Queries received in February 2016
- February 2016
  - SOP QA finalized and translated (thanks to Christina Fotopolou)

Timelines (2)

- March 2016: German Patient informed consent was updated according to EC requirements
- **21. March 2016 Approval Ethics Committee**
- March/April 2016
  - Final version of Protocol
  - Distribution of information to interested groups / sites including study presentation slide kit, and SOP QA
- April/May 2016
  - Amendment for Germany to implement AGO-OVAR 19 → Approval EC received on 3 May 2016
- May/June 2016
  - English Patient informed consent, e-CRF access and Monitoring plan to be distributed to groups
- From April on:
  - Groups delegate their representatives (names to AGO)
  - Groups install their QA board/delegates (names to AGO)
  - Groups can start their site selection process (certificate copy to AGO)

ENGOT Ov-15 Trial
AGO-OVAR 17
Study Design



Strata

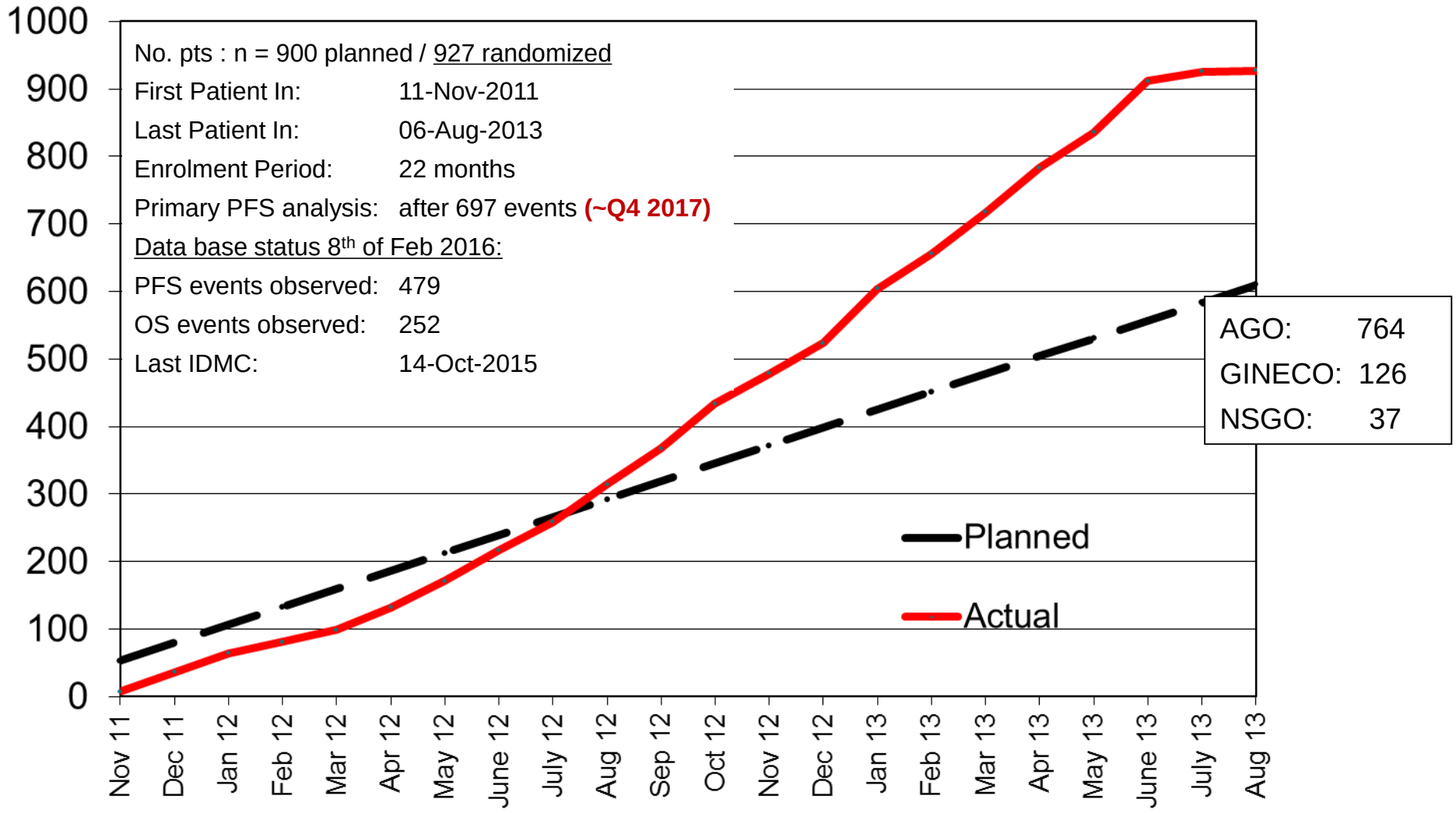
- macroscopic residual tumor (yes vs no)
- FIGO Stage (IIB-IIIC vs IV)
- Study Group

Primary endpoint:

- PFS (non inferiority-> superiority)

Main question: treatment duration Bev

ENGOT Ov-15 Trial
AGO-OVAR 17
Final Recruitment 06-Aug-2013



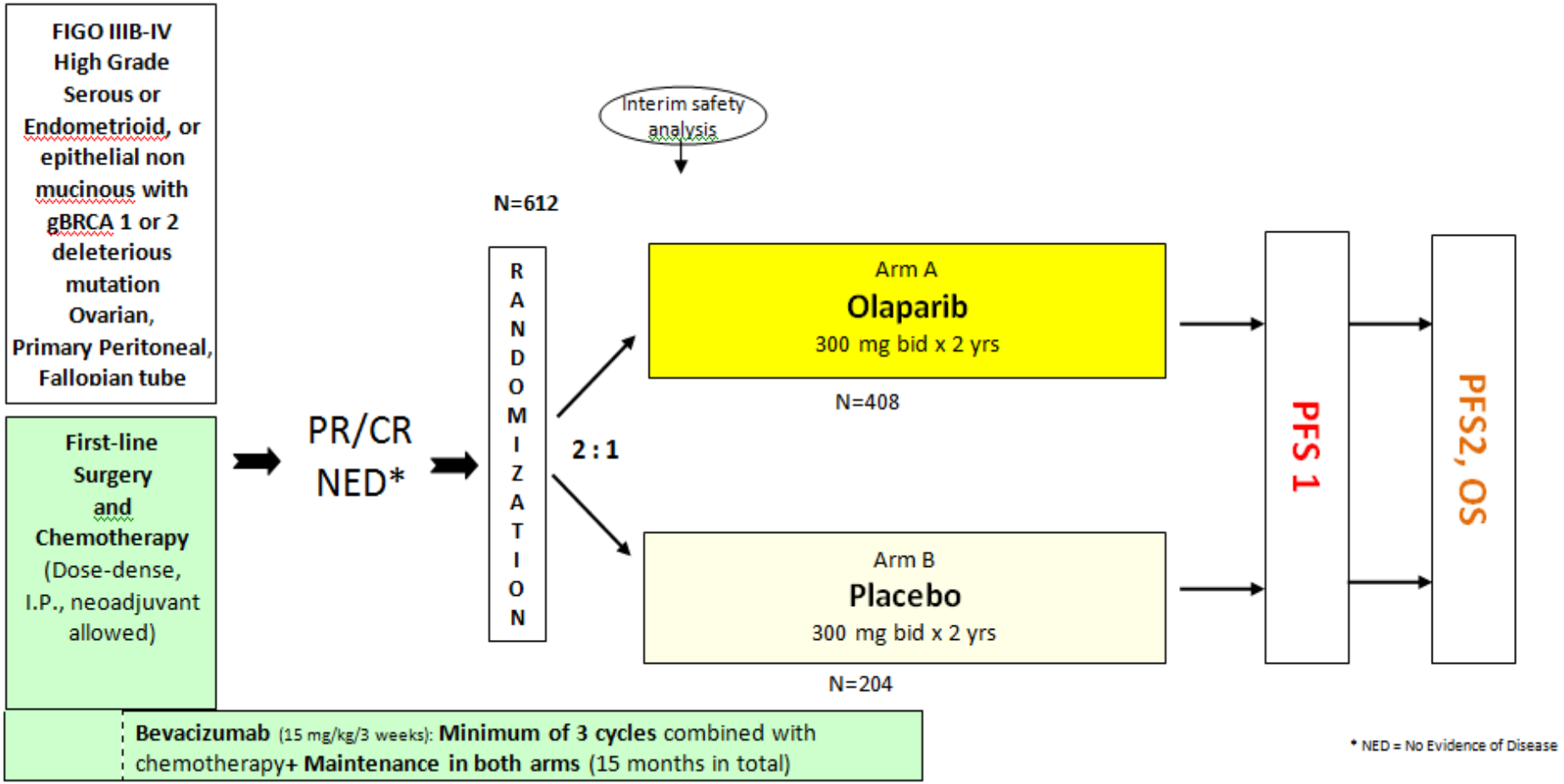
PAOLA-1 STUDY

Platine, Avastin and OLAparib in 1st line of advanced high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB – IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First-Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance.

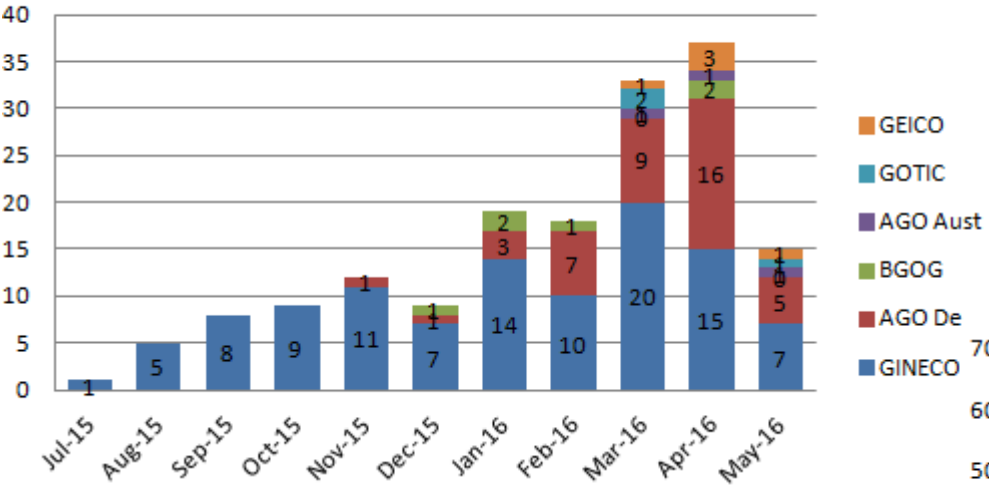
Principal Investigator: Pr Isabelle Ray-Coquard, MD
Centre Léon BERARD, Lyon, France

PAOLA -1 Study design



Recruitment status_13/05/2016

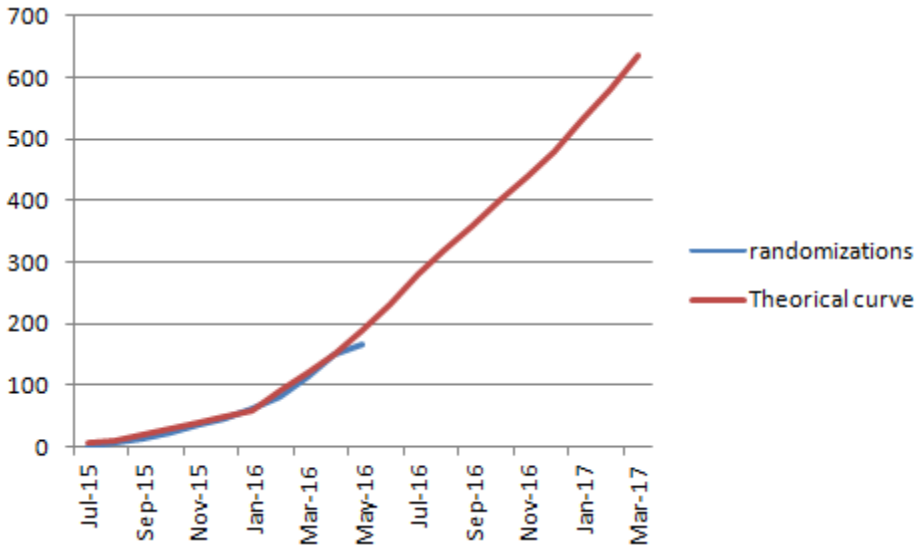
Randomizations per month



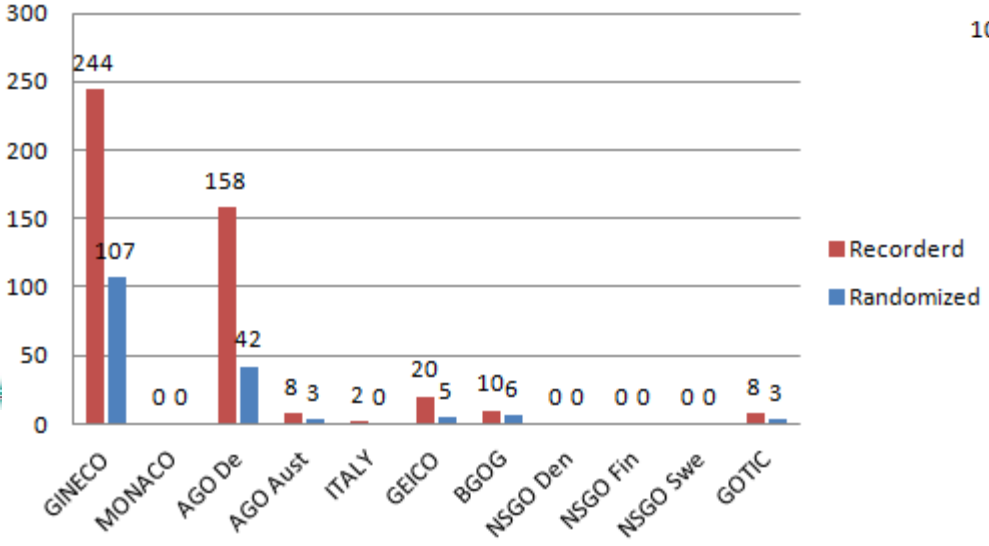
454 registered patients including :

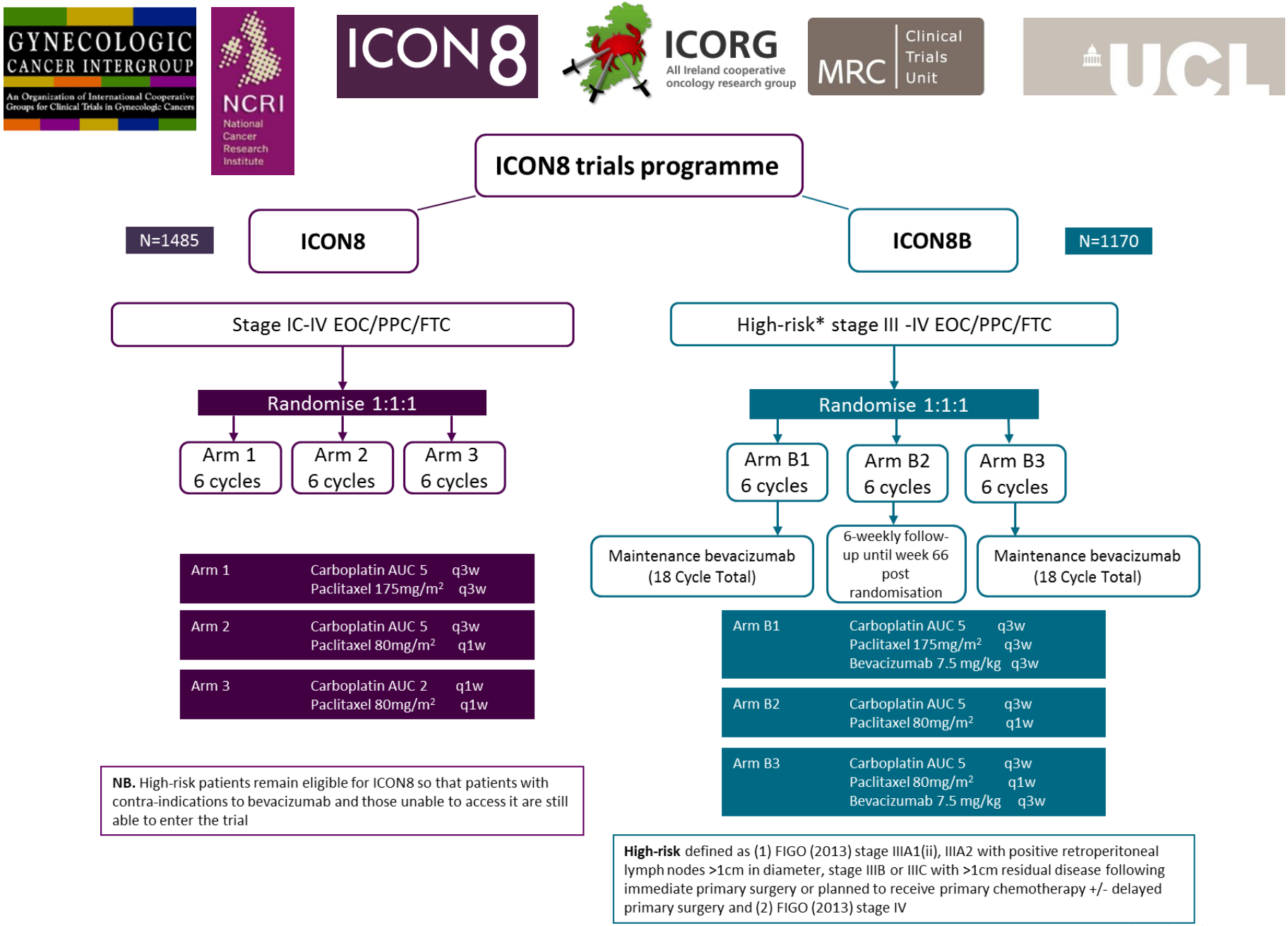
- 166 randomized patients

- 103 screened failure

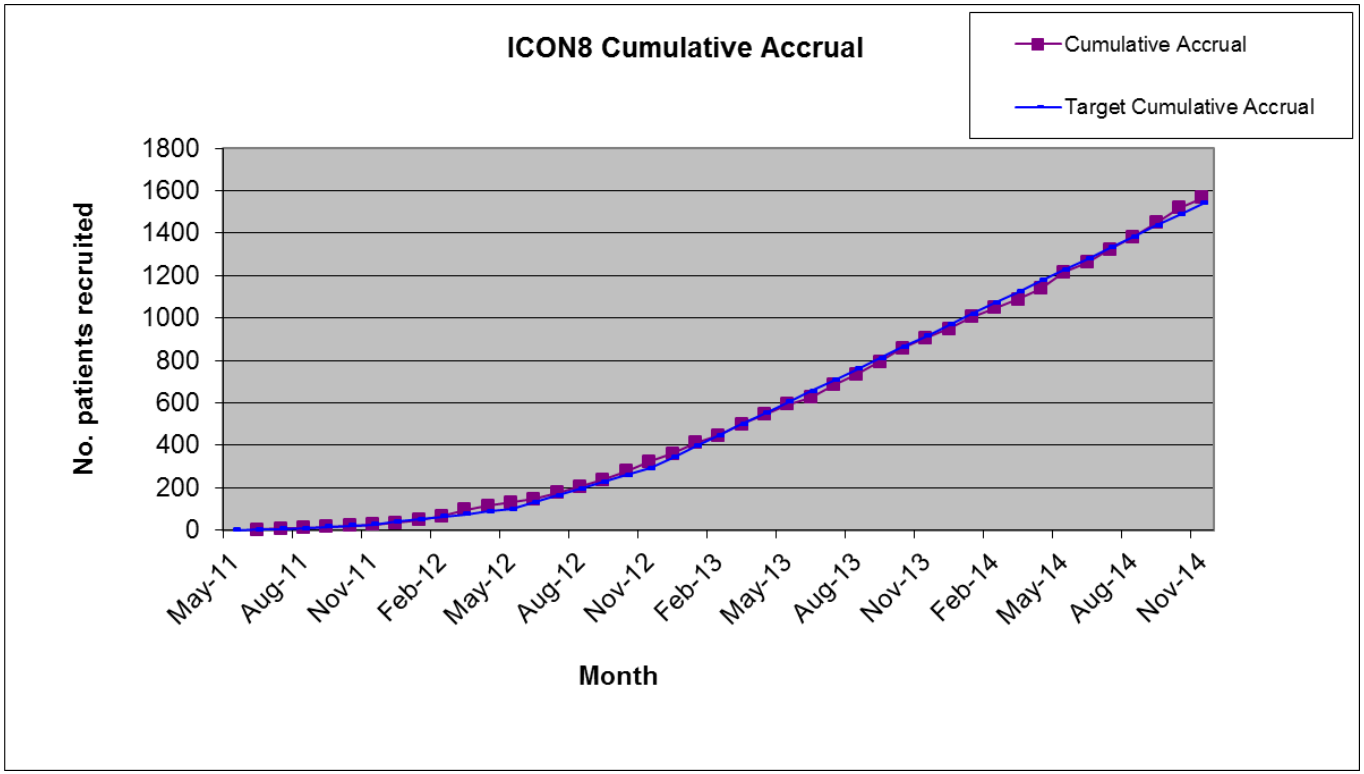


Recruitment per country




ICON8 trials programme
N=1485
ICON8
ICON8B
N=1170
Stage IC-IV EOC/PPC/FTC
Randomise 1:1:1
Arm 1 6 cycles
Arm 2 6 cycles
Arm 3 6 cycles
Arm 1 Carboplatin AUC 5 q3w Paclitaxel 175mg/m² q3w
Arm 2 Carboplatin AUC 5 q3w Paclitaxel 80mg/m² q1w
Arm 3 Carboplatin AUC 2 q1w Paclitaxel 80mg/m² q1w
NB. High-risk patients remain eligible for ICON8 so that patients with contra-indications to bevacizumab and those unable to access it are still able to enter the trial
High-risk* stage III -IV EOC/PPC/FTC
Randomise 1:1:1
Arm B1 6 cycles
Arm B2 6 cycles
Arm B3 6 cycles
Maintenance bevacizumab (18 Cycle Total)
6-weekly follow-up until week 66 post randomisation
Maintenance bevacizumab (18 Cycle Total)
Arm B1 Carboplatin AUC 5 q3w Paclitaxel 175mg/m² q3w Bevacizumab 7.5 mg/kg q3w
Arm B2 Carboplatin AUC 5 q3w Paclitaxel 80mg/m² q1w
Arm B3 Carboplatin AUC 5 q3w Paclitaxel 80mg/m² q1w Bevacizumab 7.5 mg/kg q3w
High-risk defined as (1) FIGO (2013) stage IIIA1(ii), IIIA2 with positive retroperitoneal lymph nodes >1cm in diameter, stage IIIB or IIIC with >1cm residual disease following immediate primary surgery or planned to receive primary chemotherapy +/- delayed primary surgery and (2) FIGO (2013) stage IV

- Accrual began 06/06/2011 and ICON8 pathway closed to recruitment 28/11/2014



- Final recruitment figure = **1566**
- UK= 1397, ANZGOG= 70, GICOM= 43, KGOG= 32, ICORG= 24

ICON8 Outcome measures & analysis

Presentations:
ESGO, October 2013 - oral poster presentation on stage IA analysis
NCRI, November 2013 - poster on stage IA analysis; NCRI award for abstract
ASCO, June 2014 – poster

- **Stage 1A** showed that the weekly regimens were harder to deliver but total doses and dose intensity were increased. Uncomplicated grade 3/4 neutropenia was higher in Arms 2&3 but other toxicities were similar. Earlier use of GCSF was recommended following this analysis.

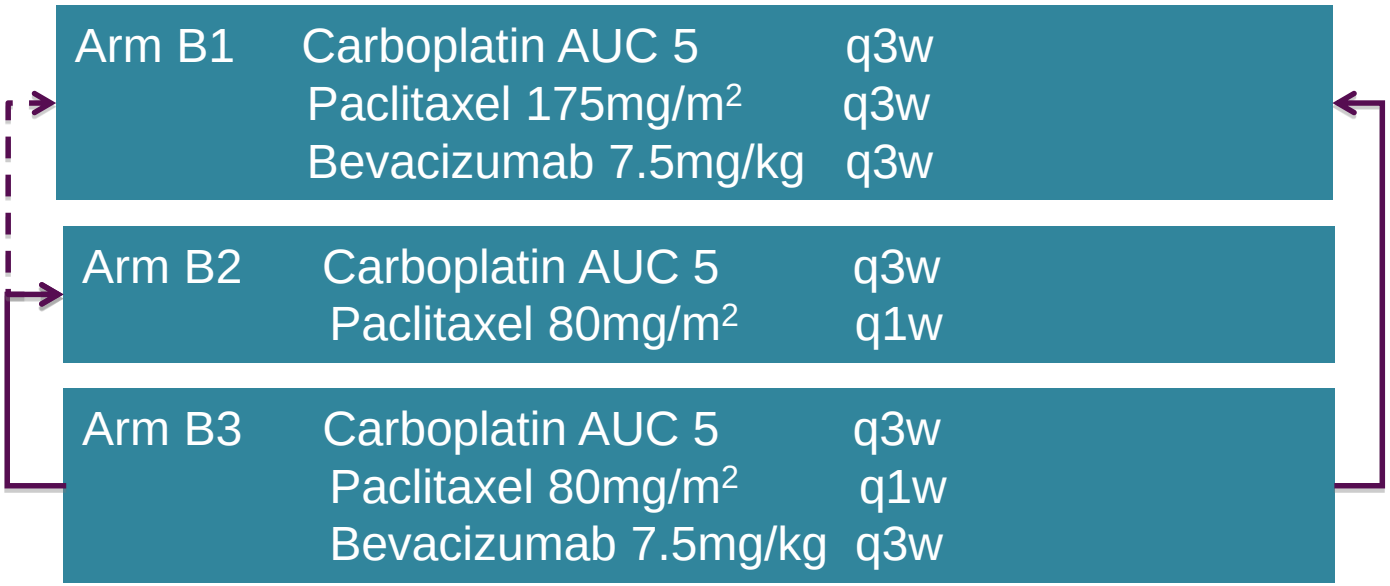
- **Stage 1B** was reviewed by the IDMC in Nov-13. They considered the regimens safe and feasible for neo-adjuvant chemotherapy. DPS was not compromised in the weekly arms.

- **Stage 2** Activity Outcome measure: 9-month progression free survival rate in 1st 186 women randomised Completed Jan-14. Analysis reviewed by Independent Data Monitoring Committee, decision to continue all arms

- Anticipate **Progression Free survival analysis Q4 2016** & **overall survival analysis Q4 2018**

ICON8B

A study of bevacizumab and weekly dose-dense paclitaxel in ovarian cancer



Aim to recruit 1170 participants over 4 years in 80+ sites across the UK and Ireland

Will be an international trial with participation interest from Switzerland and Mexico

ICON8B Trial Progress

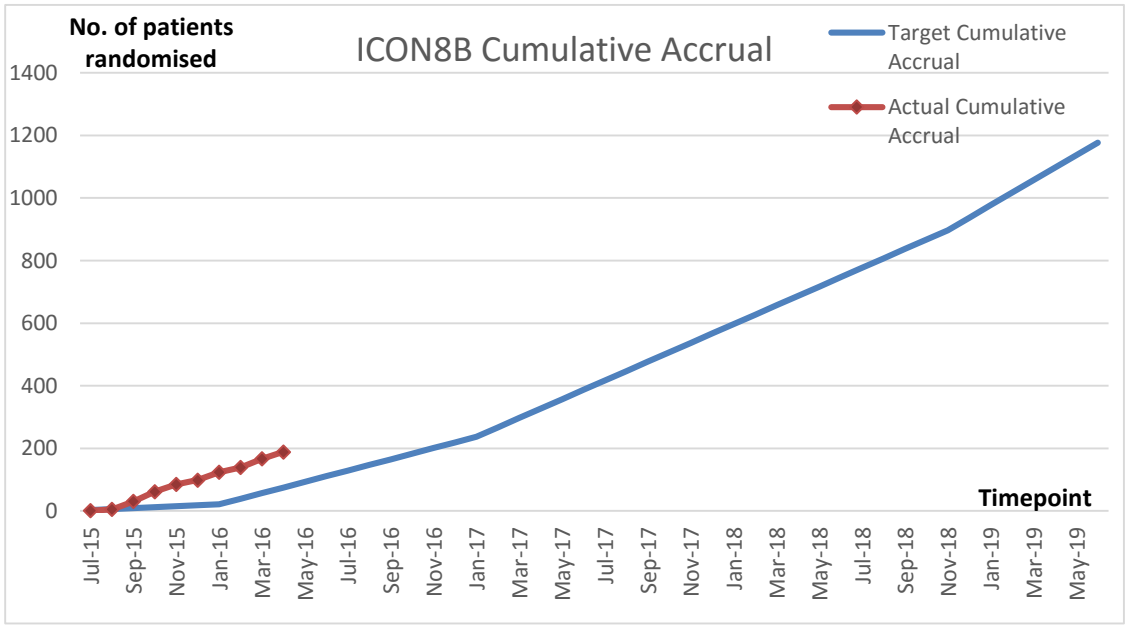
ICON8B submitted as an amendment to the ICON8 trial in January 2015

Overarching trial title changed to the ICON8 Trials Programme encompassing ICON8 and ICON8B

Full UK ethical and MHRA approval gained by February 2015

First site opened to recruitment 21st July 2015

76 sites open to recruitment by May 2016



First patient recruited 24th July 2015

Accrual and site data up until 1st May 2016.

Accrual total to date: 196

iPocc Trial

Stage II to IV varian, primary peritoneal, or fallopian tube cancer Including suboptimal Cases

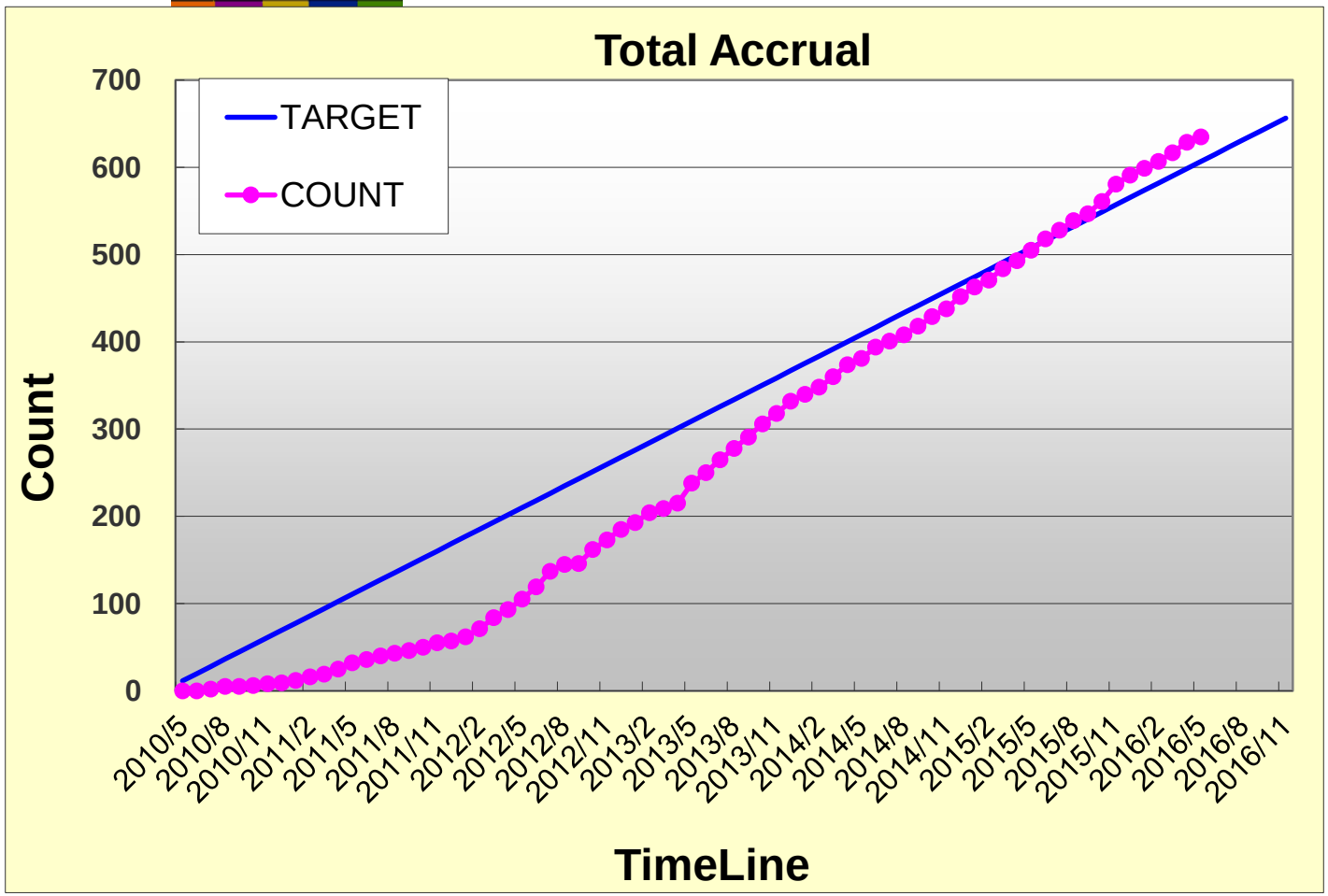
RANDOMIZE

Paclitaxel 80 mg/m^2/1h IV, weekly, Cycles 1-6
Carboplatin AUC 6 IV, Day 1, Cycles 1-6

Paclitaxel 80 mg/m^2/1h IV, weely, Cycles 1-6
Carboplatin AUC 6 IP, Day 1, Cycles 1-6

- **Accrual goal: 654 pts**
- **Primary Endpoint: PFS**
- **Secondary Endpoints: OS, Toxicity, QOL, Cost/Benefit**

iPocc Trial (GOTIC-001/JGOG3019)



Total 636: Singapore 27, KGOG 9, NZ 3, USA 4, Hong Kong 2

OV21/PETROC: A Randomized Gynecologic Cancer Intergroup (GCIG) Phase II Study of Intraperitoneal (IP) vs. Intravenous (IV) Chemotherapy Following Neoadjuvant Chemotherapy and Optimal Debulking Surgery in Epithelial Ovarian Cancer

Co-Chairs Helen J MacKay and Diane Provencher
On behalf of the OV21/PETROC Investigators
CCTG, NCRI (UK), GEICO and SWOG

Cancer Research UK and UCL Cancer Trials Centre
90 Tottenham Court Road, London, W1T 4TJ
Enquiries: +44 (0)20 7679 9898, F: +44 (0)20 7679 9899

OV21/PETROC: Background and Rationale

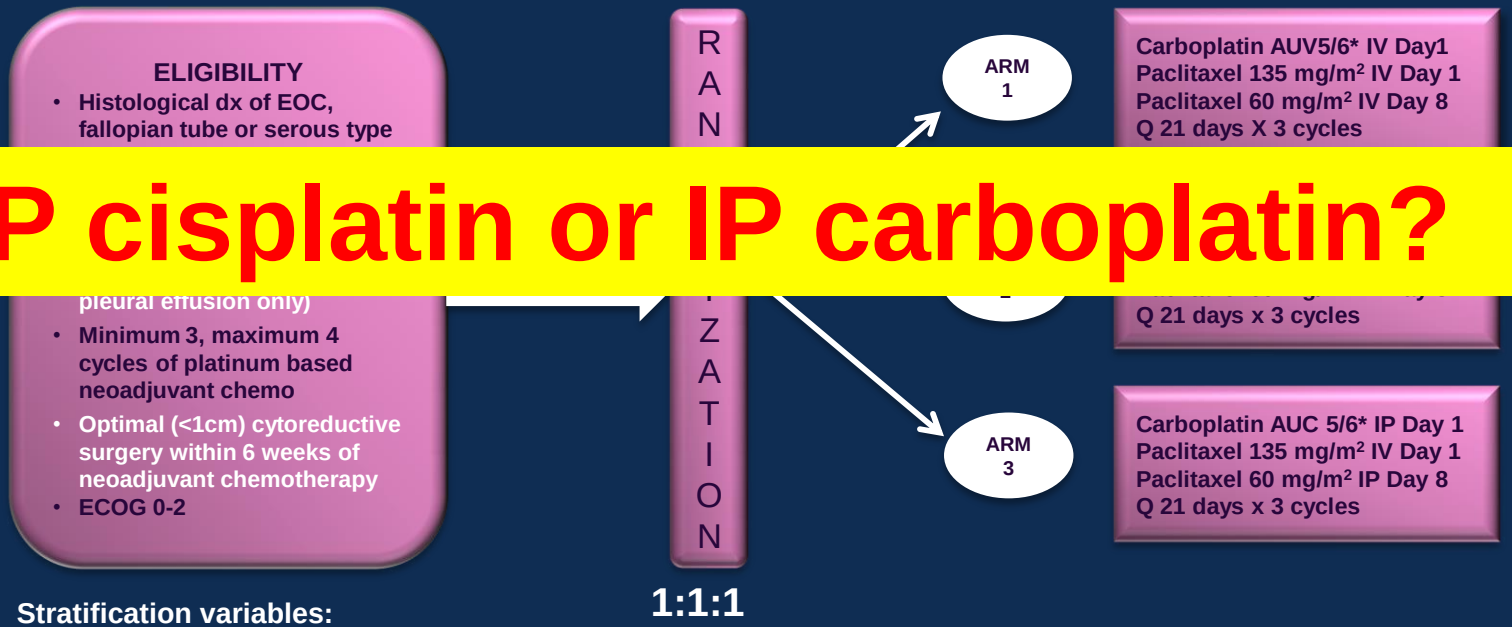
- Epithelial ovarian cancer (EOC) is the 5th most common cancer in women

Do EOC patients who receive neoadjuvant chemotherapy followed by optimal cytoreductive surgery benefit from IP Chemotherapy?

- Increasing rates of neoadjuvant chemotherapy for EOC (approx. 40% in NCCN centres US)

OV21/PETROC: Schema

OV21/PETROC: Schema



IP cisplatin or IP carboplatin?

Stratification variables:
- Cooperative group
- Residual disease: macroscopic vs. microscopic
- Reason for NACT: non-resectable disease vs. other
- Timing of IP catheter insertion: intra-operative vs. postoperative

* AUC 5 (measured GFR)/AUC 6 (calculated GFR)

Canadian Cancer Trials Group

OV21/PETROC: Statistical Plan
First Stage: 3 Arm Phase II

"Pick the winner" design (N=50 each arm)

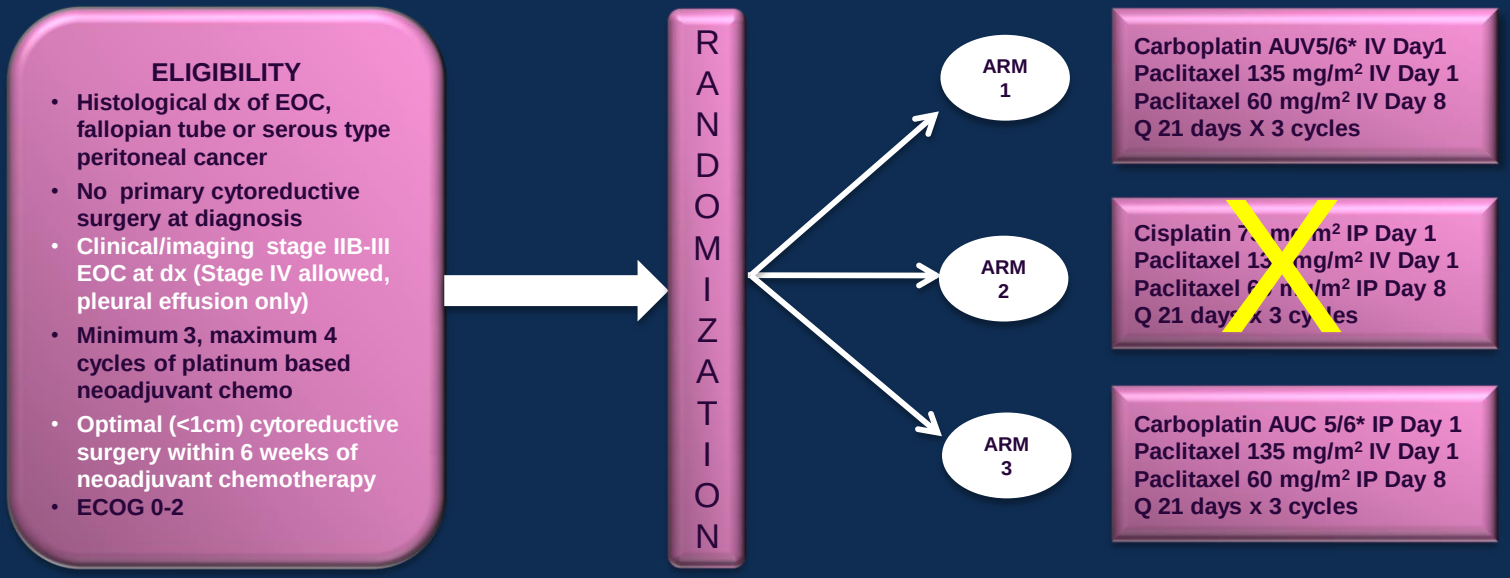
- 9-month progression rate post randomization. Futility/superiority rule

Assume that the 9-month PD rate in IV arm will be 40%. Stop trial if neither arm is at least 5% better. If only 1 arm is 5% better that is the one selected. If both IP arms meet the 5% better rule, select highest

- Completion rate of treatment
- Toxic effects
- Feasibility

OV21/PETROC: Schema

OV21/PETROC: Schema



Stratification variables:
- Cooperative group
- Residual disease: macroscopic vs. microscopic
- Reason for NACT: non-resectable disease vs. other
- Timing of IP catheter insertion: intra-operative vs. postoperative

* AUC 5 (measured GFR)/AUC 6 (calculated GFR)

Canadian Cancer Trials Group

OV21/PETROC: Statistical Plan Second Stage: Two Arm Expanded Randomized Phase II

- Originally planned as phase III study. Trial design modified to Phase II due to low accrual and funding issues
- **Primary endpoint** revised from PFS to **9 month PD rate post randomization** after consultation with DSMC

  Revised sample size 200 patients total (arms 1 and 3). 80% power to detect a 19% difference in progression rate at 9 months 2-sided, $\alpha=0.05$
- **Secondary endpoints:** Progression free survival (PFS), overall survival (OS), toxicity, quality of life, correlative laboratory studies, outcomes related to variation in nursing-related practices

OV21/PETROC: Study Conduct

- Activated September 2009
- Stage I accrual complete March 2013
- Analysis of stage I (n=150) January 2014
- Based on preplanned DSMC recommendation Stage 2 activated February 2014. Arm 2 (IP cisplatin) closed to accrual
- Key protocol amendment October 2014 to randomized phase II study, change in primary endpoint
- Closed to accrual May 2015
- Data cut off, February 28th 2016. Data analysis March 4th 2016

Canadian Cancer Trials Group

Canadian Cancer Trials Group

OV21 ASCO 2016
Final Analysis

Oral Presentation

Sunday June 5th

Gynecologic Session

Oral Presentation

10:45 AM - 10:57 AM

Closed/Ongoing trials – Relapse

- AGO-OVAR OP.4 (DESKTOP III) (c)
- AGO-OVAR 2.21 (c)
- AGO-OVAR 2.20 (PENELOPE) (c)
- SOLO 2 (c)
- NOVA (c)
- INOVATYON
- MITO 16b
- NiCC
- AVANOVA
- NSGO-OV-UMB1
- ICON 9
- AGO-OVAR 2.28

AGO-OVAR OP.4
(AGO-OVAR DESKTOP III)

Prospectively randomized evaluation of cytoreductive surgery as adjunct receding standard platinum-based chemotherapy in platinum-sensitive recurrent cancer of the ovary, fallopian tube, or peritoneum

Shanghai GOG

@CRCTU

AGO Study Group Ovarian Cancer (AGO-OVAR)

An open-label prospectively randomized phase III multicenter-trial

AGO-OVAR DESKTOP III
(Protocol AGO - OVAR OP.4)

A randomized trial evaluating cytoreductive surgery
in patients with platinum-sensitive recurrent ovarian cancer

408 Pts with

+ AGO-Score

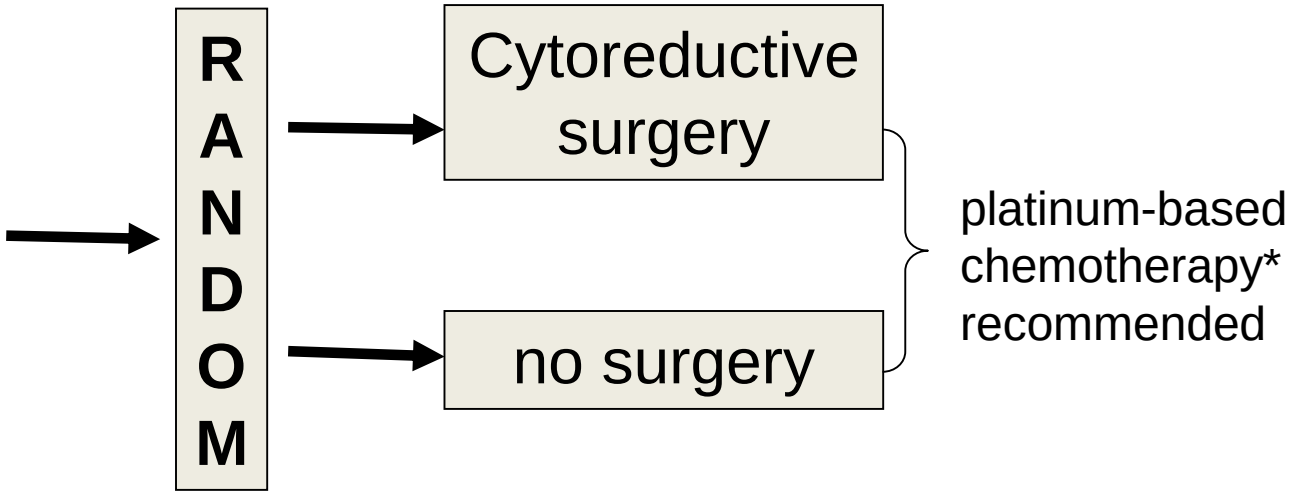
Stratification:

Platinum-free-interval

6-12 vs > 12 months

1st line platinum

based ctx: yes vs no



* Recommended platinum-based chemotherapy regimens:
- carboplatin/paclitaxel
- carboplatin/gemcitabine
- carboplatin/pegliposomal doxorubicin
-or other platinum combinations in prospective trials

AGO-OVAR DESKTOP III
(Protocol AGO - OVAR OP.4)

Primary objective:

- Overall survival (after 244 OS events observed)

Secondary objectives:

- Progression-free survival
- Quality of Life
- Rate of complete resection as prognostic factor
- Complication rates of surgery
- Exploratory analysis of surgical characteristics and chemotherapy, prognostic factors

Status 29JAN2016

82 of 244 OS events observed

First Patient in	14-Jul-2010
Last Patient in	25-Mar-2015
Enrolment period	58 months
Planned period	36 months
OS analyses	final ~ 2019

(planned interim after 122 events)

~ 2016/17

AGO-OVAR DESKTOP III
(Protocol AGO - OVAR OP.4)

Final Recruitment Groups (March 2015)

AGO	121
BGOG	25
GINECO	94
SGOG	12
MITO/MaNGO	26
NSGO	49
KGOG	8
GEICO	28
AGO Austria	8
CRCTU	38
TOTAL	409

AGO-OVAR 2.21
ENGOT ov18

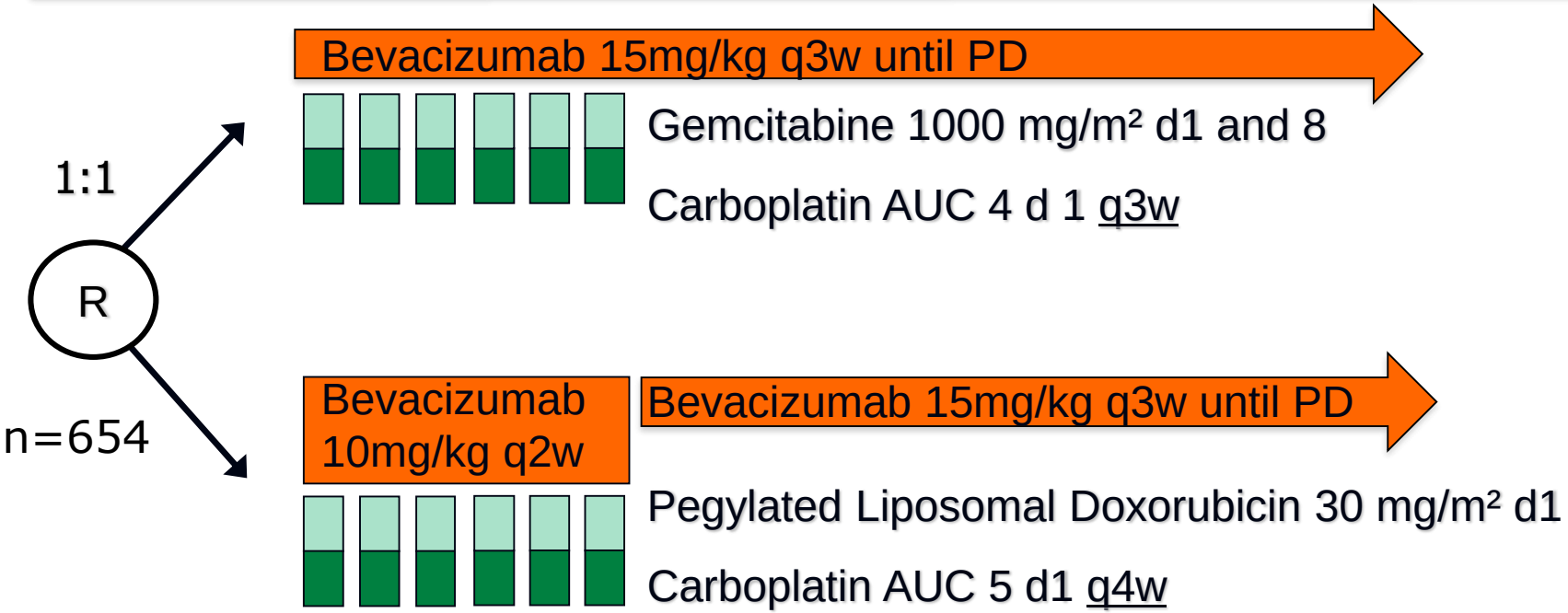
A prospective randomized Phase III trial of Carboplatin / Gemcitabine / Bevacizumab vs. Carboplatin / Pegylated Liposomal Doxorubicin / Bevacizumab in patients with platinum-sensitive recurrent ovarian cancer.

An ENGOT / GCIG Trial.

International Chair: Prof. Dr. med. Jacobus Pfisterer

EudraCT-No. 2012-004125-24

Trial Design



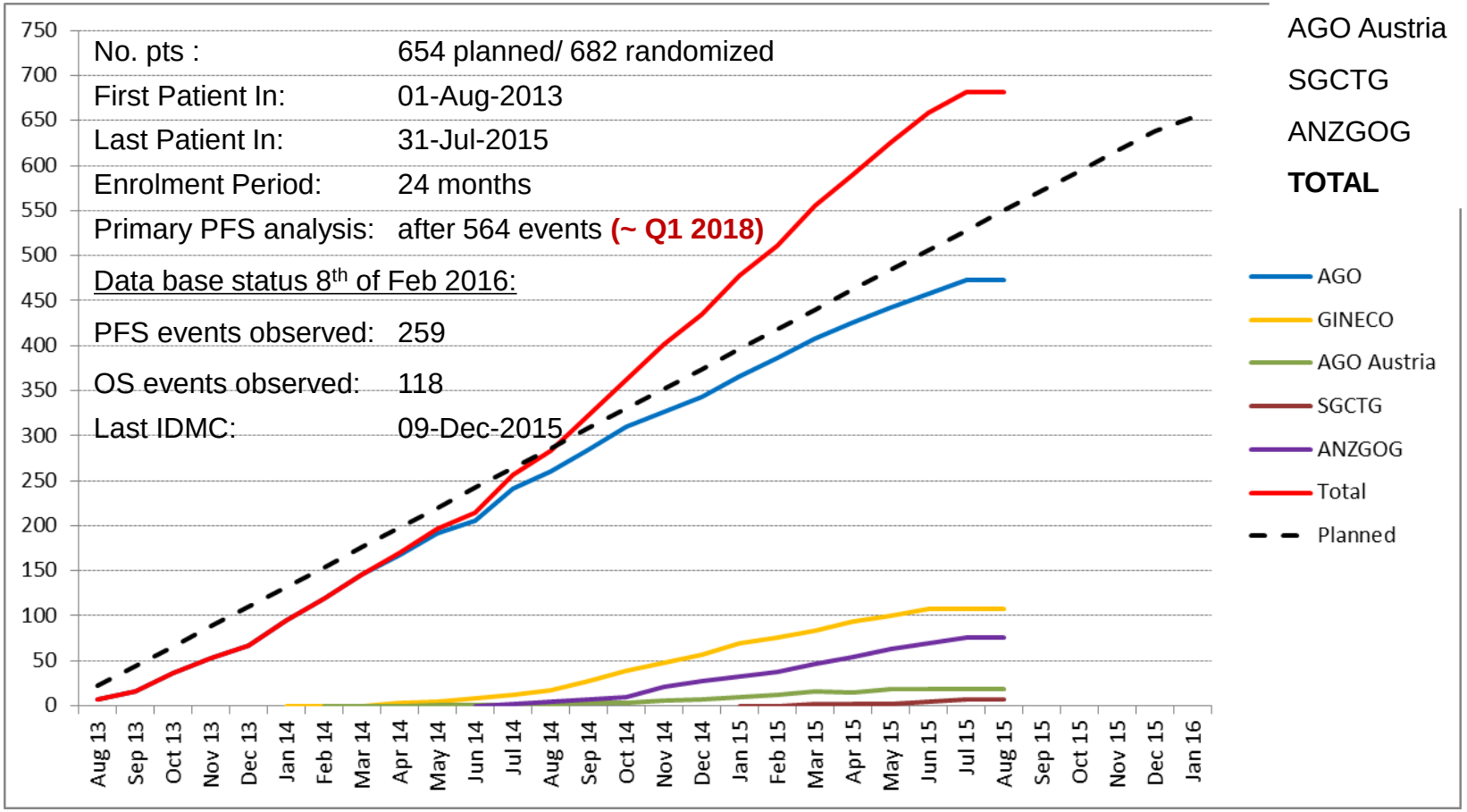
Stratification Factors

- Platinum free interval (6-12 months vs. > 12 months)
- In case of debulking surgery for recurrence: residual tumour (yes vs. no)
  In case of no debulking surgery for recurrence: all pts. categorized to residual tumor = yes
- prior antiangiogenetic treatment (yes vs. no)
- study group

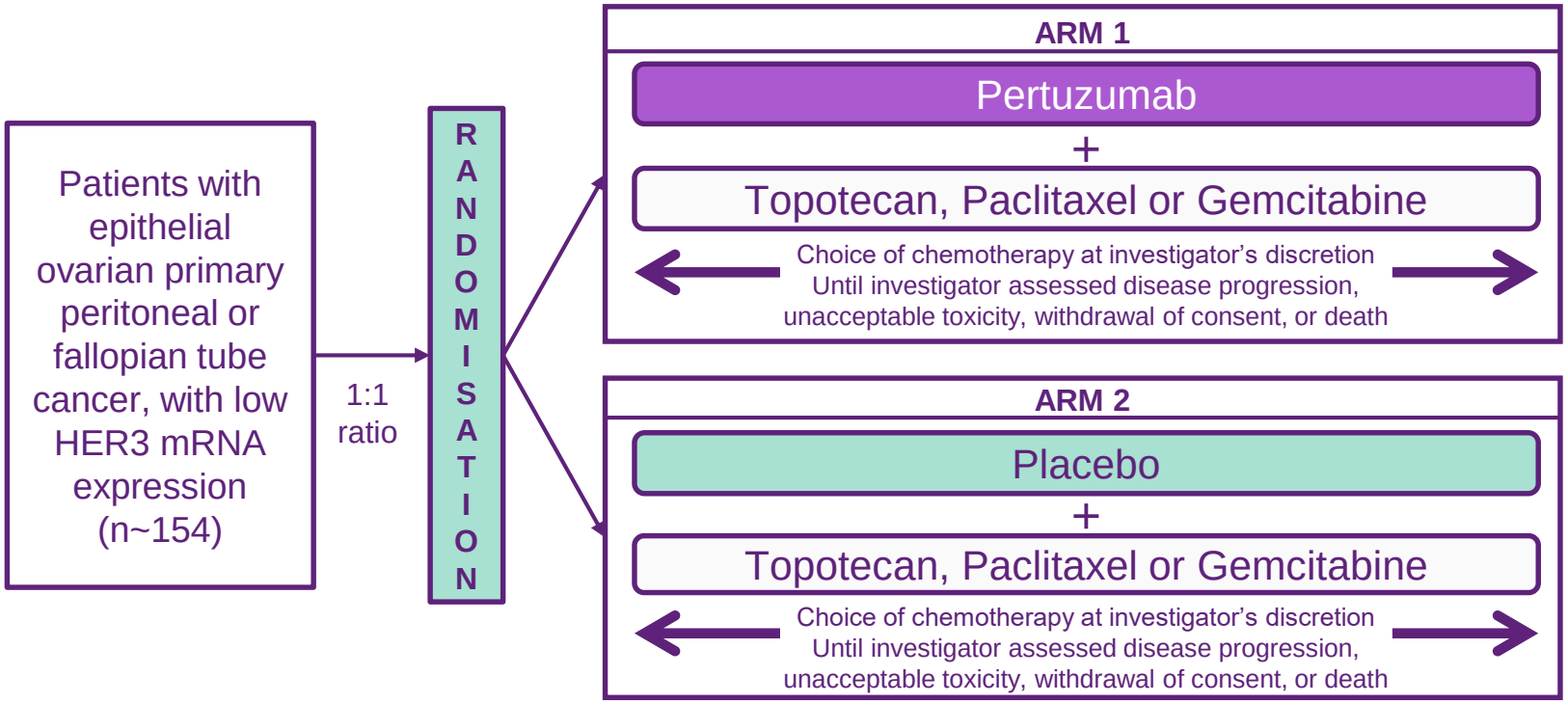
AGO-OVAR 2.21
ENGOT ov18

Final Recruitment Status 31-Jul-2015

AGO	473
GINECO	107
AGO Austria	19
SGCTG	7
ANZGOG	76
TOTAL	**682**



ENGOT Ov-14 Trial
AGO-OVAR 2.20
Study Design Part 2



Stratification factors:

- Selected chemo cohort (topotecan vs. paclitaxel vs. gemcitabine)
- Previous anti-angiogenic therapy (yes vs. no)
- Treatment-free interval from last cycle of platinum to disease progression after platinum therapy (strictly less than 3 months vs. 3 to 6 months inclusive)

ENGOT Ov-14 Trial
AGO-OVAR 2.20
Study Design Part 2

Data primary analysis presented at ASCO 2015

Efficacy and safety of chemotherapy ± pertuzumab for platinum-resistant ovarian cancer: AGO-OVAR 2.20/ENGOT-ov14/PENELOPE double-blind placebo-controlled randomized phase 3 trial

C Kurzeder[1]; I Bover[2]; F Marmé[3]; J Rau[4]; P Pautier[5]; N Colombo[6]; D Lorusso[7]; P Ottevanger[8]; M Bjurberg[9]; C Marth[10]; P Barretina-Ginesta[11]; I Vergote[12]; A Floquet[13]; JM del Campo[14]; S Mahner[15]; L Bastiere-Truchot[16]; L Mitchell[16]; S Polleis[17]; A du Bois[1]; A Gonzalez-Martin[18]

[1]AGO and Kliniken Essen Mitte, Essen, Germany; [2]GEICO and Hospital Son Llàtzer, Palma de Mallorca, Spain; [3]AGO and University Hospital Heidelberg, Heidelberg, Germany; [4]Coordinating Center for Clinical Trials Philipps-University of Marburg, Marburg, Germany; [5]GINECO and Gustave Roussy, Villejuif, France; [6]MaNGO and University of Milan Bicocca – European Institute of Oncology, Milan, Italy; [7]MITO and Fondazione IRCCS National Cancer Institute, Milan, Italy; [8]DGOG and Radboud University Medical Center, Nijmegen, The Netherlands; [9]NSGO and Department of Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden; [10]AGO-A and Department of Obstetrics and Gynecology, Innsbruck Medical University, Innsbruck, Austria; [11]GEICO and Catalan Institute of Oncology, Girona, Spain; [12]AGO and University Hospital Leuven, Leuven, Belgium; [13]GINECO and Institut Bergonié, Bordeaux, France; [14]GEICO and Vall d'Hebron University Hospital, Barcelona, Spain; [15]AGO and University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [16]F Hoffmann-La Roche, Basel, Switzerland; [17]AGO Study Group, Wiesbaden, Germany; [18]GEICO and MD Anderson Cancer Center Spain, Madrid, Spain

PRESENTED AT: ASCO Annual '15 Meeting

Publication Status May 2016

- **Part 1 – Manuscript published online in International Journal of Gynecological Cancer**: June 2016 – Volume 26 – Issue 5 – p 898-905 **(Gonzalez et al.)**
- **Part 2 – Manuscript accepted for publication by JCO (Kurzeder et al.)**

Translational research in progress

Final OS analysis in Q2 2016 (129 OS events observed on April 28, 2016)

ESGO 2015 presentations

GINECO	P. Pautier et al	Subgroup Chemo	abstract #1054	oral presentation
MaNGO	N. Colombo et al	Biomarker results	abstract #1093	Poster
PRO Subc.	F. Hilpert et al	PROs	abstract #1361	Poster

Call for translational projects (TMA, NGS data available) → @ Christian Kurzeder

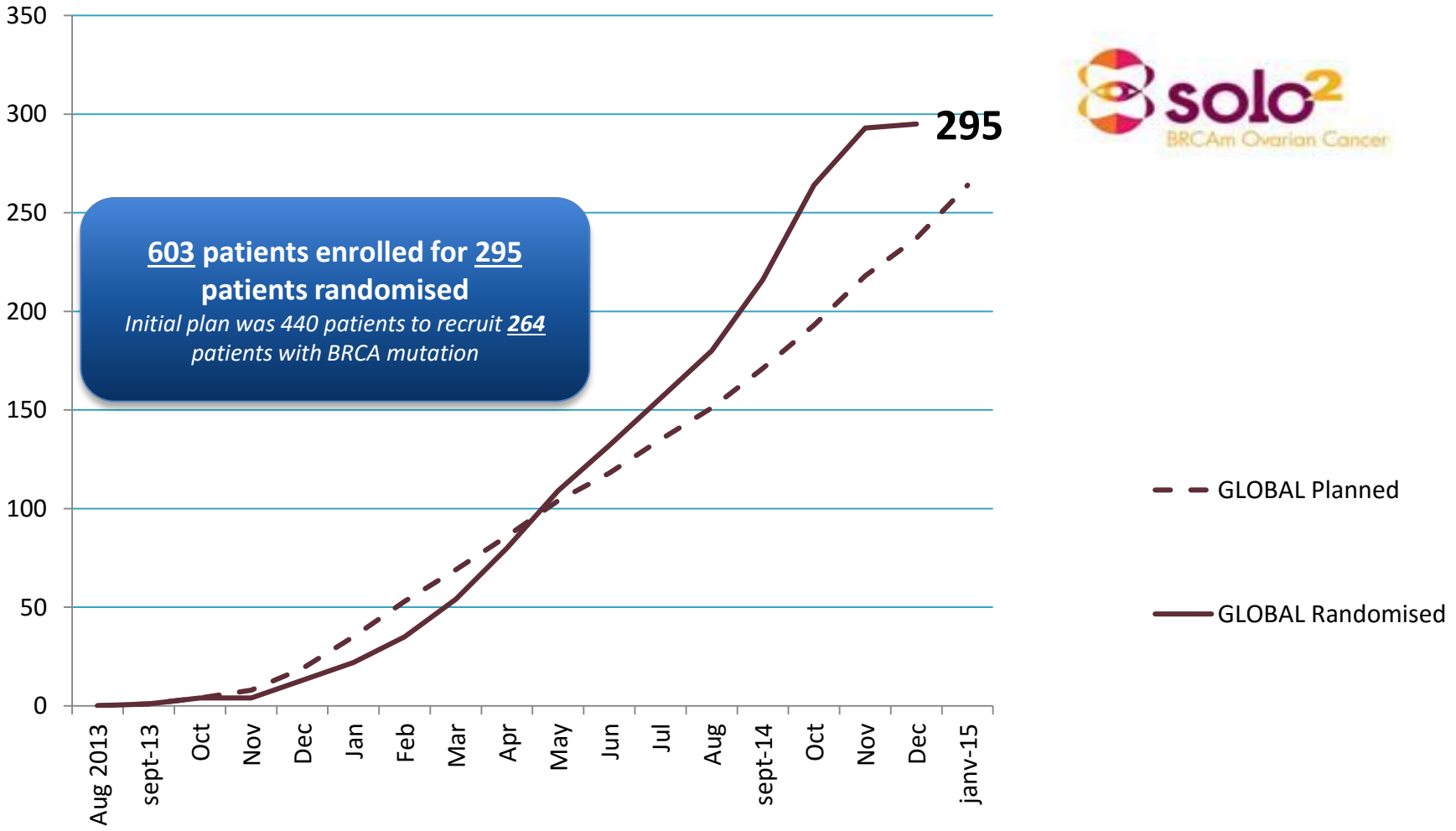
Solo 2

ENGOT-OV21

Study of OLoparib in Ovarian Cancer

A Phase III Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy

Final Global Recruitment



Next Steps

- **Change of the Study Primary Endpoint :** the protocol was modified to use investigator assessment of PFS as the primary endpoint and PFS confirmed by independent panel review as a sensitivity analysis.
- **Protocol amendment in submission**
- **Data cut-off date has been set to 19th Sept 2016**.

ENGOT-OV16 / NOVA

Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

NCT01847274

Sponsor: Tesaro

ENGOT Lead: NSGO

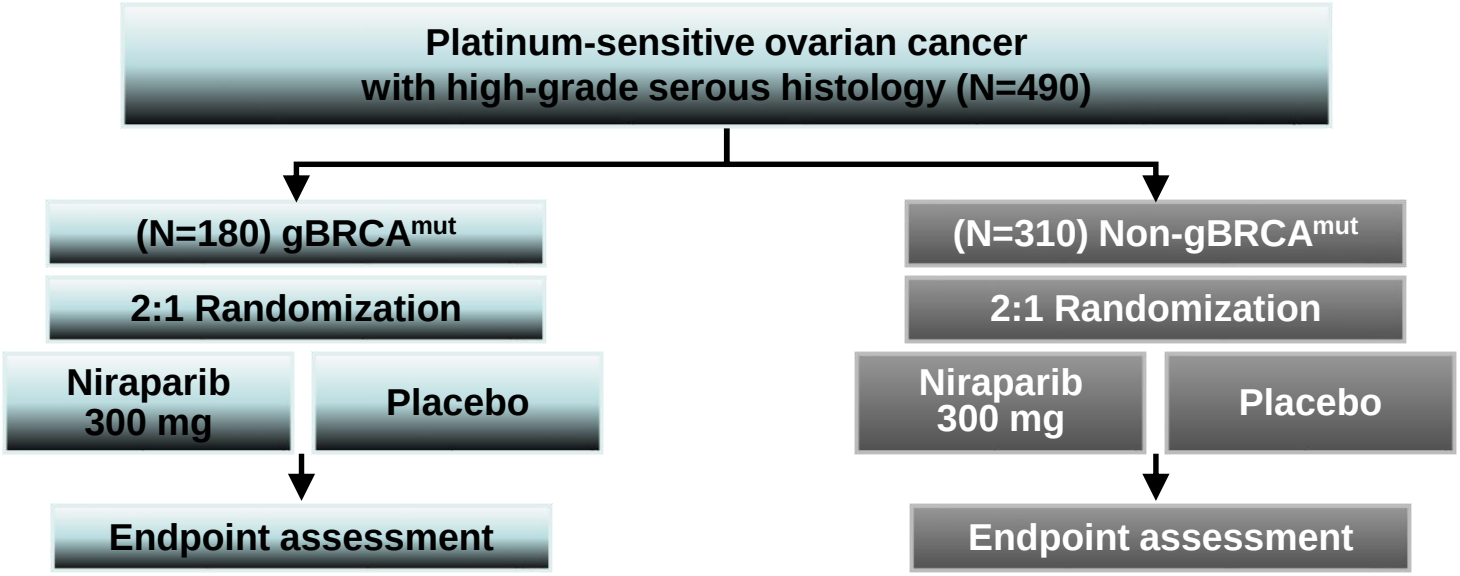
Primary Investigators

Mirza (ENGOT); Matulonis (US)

mansoor@rh.regionh.dk

ENGOT-OV16 / NOVA

Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer



Primary Endpoint	**PFS in gBRCA^{mut} and non-gBRCA^{mut}cohorts (HRD positive subset followed by overall)**
Key Secondary Endpoints	• **Overall survival (OS)** • **Patient-reported outcomes (PRO)** • **Chemotherapy-free interval (CFI)** • **Safety and tolerability** • **PFS2** • **Evaluation of QTc**

NSGO
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PFS=progression-free survival; QTc=corrected QT interval.

http://clinicaltrials.gov/show/NCT01847274. Accessed February 26, 2015.

ENGOT Group	No. of sites	Randomised gBRCA	Randomised non-gBRCA
NSGO (DK, N, SE)	9	22	52
AGO (Germany)	13	22	29
AGO (Austria)	3	3	3
BGOG (Belgium)	5	6	12
GEICO (Spain)	7	13	33
GINECO (France)	7	17	29
MaNGO & MITO (Italy)	8	13	4
NCRI (UK)	9	7	24
ISGO (Israel)	8	8	8
ENGOT TOTAL	**71**	**111 (57%)**	**194 (56%)**
US	39	59	95
Canada	9	21	44
Poland, Hungary	8	3	13
TOTAL	**127**	**194**	**346**

ENGOT-OV16 / NOVA

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INOVATYON

INternational **OVA**rian cancer patients **T**rial with **YON**delis

- **Study title:** Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with relapsed ovarian cancer progressing within 6-12 months of last platinum

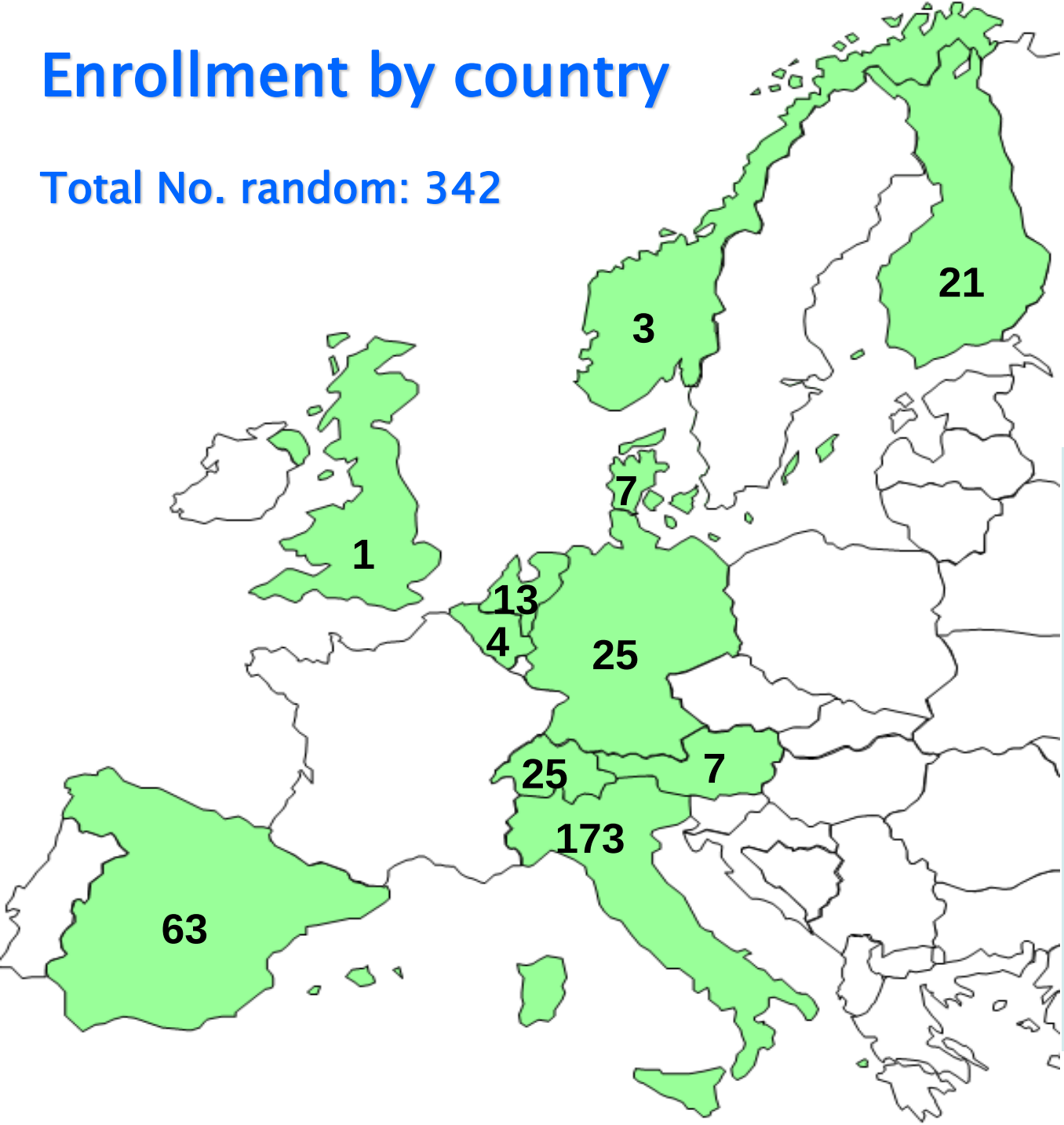
- **Sponsor:** Mario Negri Institute, MaNGO group, Milan, Italy

- **Principal Investigator:** Nicoletta Colombo, European Oncology Institute, Milan, Italy

MaNGO
Mario Negri Gynecologic Oncology

Enrollment by country

Total No. random: 342



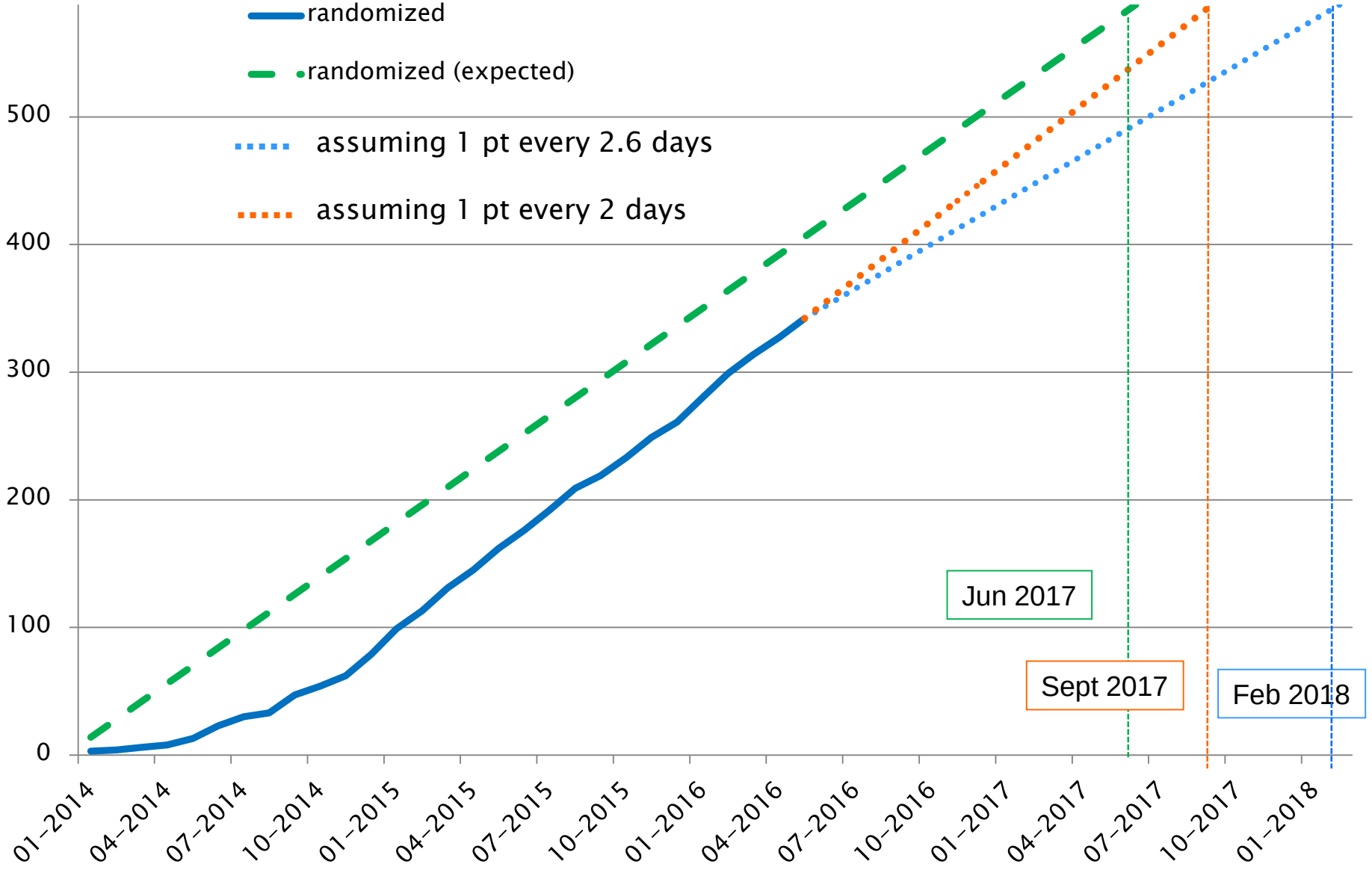
MaNGO
Mario Negri Gynecologic Oncology

1 pt every 2.6 days
about 11 pts per month

Target

1 pt every 2 days
about15 pts per month

Enrollment expected vs. observed



ENGOT Ov-17 Trial
MITO 16b; MANGO-OV2b
Study Design

- Ovarian Ca
- Platinum-sensitive
- Previous Bevacizumab
- ECOG 0-2
- Availability of samples for translational res.
- No Beva contraindications

R

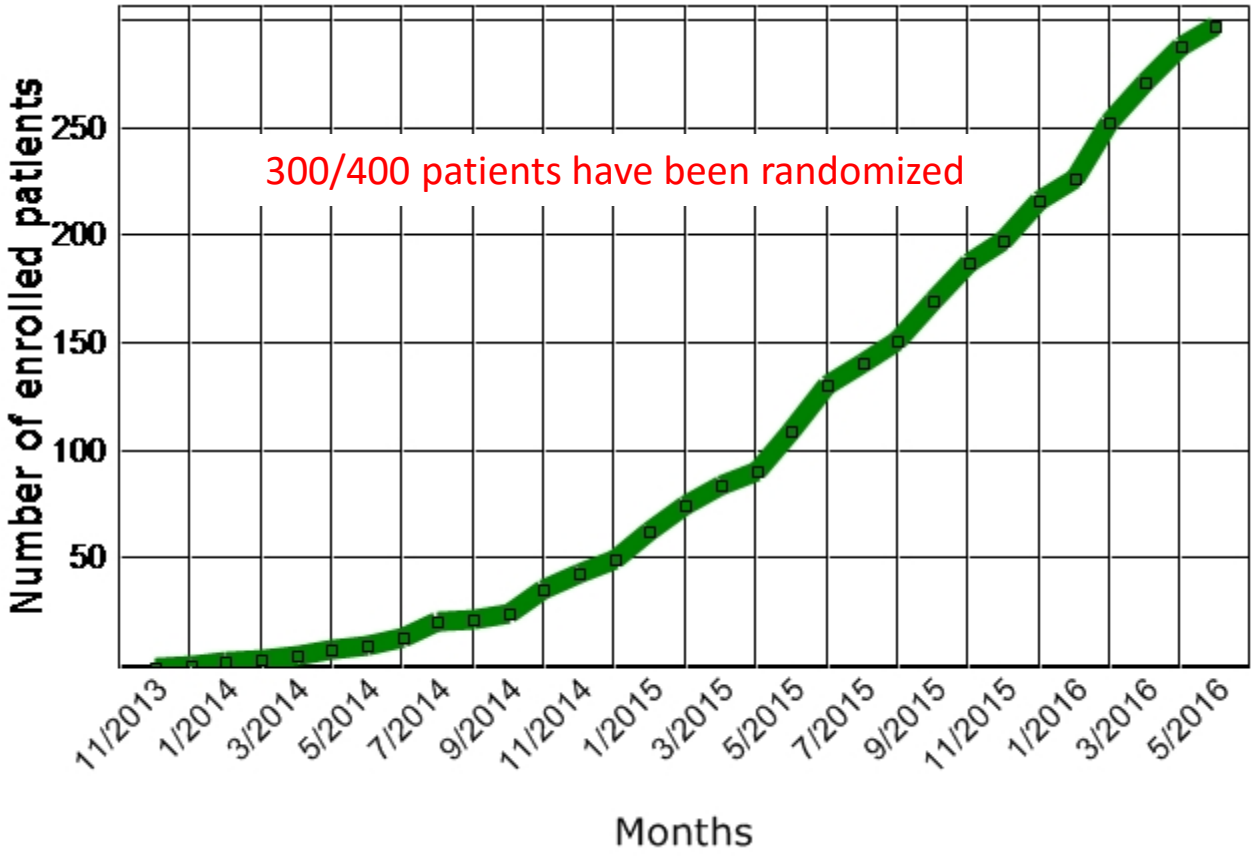
ARM 1: 6 cycles

CBDCA AUC5 + PAC 175 mg/m2 q3w
or
CBDCA AUC4, d1 + GEM 1000mg /m2, d1&8 q3w
or
CBDCA AUC5+PLD 30mg/m2 q4w

ARM 2*: 6 cycles

CBDCA AUC5 + PAC 175 mg/m2 q3w
Plus bevacizumab** 15mg/kg q3w
or
CBDCA AUC4, d1 + GEM 1000mg /m2, d1&8 q3w
Plus bevacizumab 15mg/kg q3w
or
CBDCA AUC5+PLD 30mg/m2 q4w
Plus bevacizumab 10mg/kg q2w

ENGOT Ov-17 Trial
MITO 16b; MANGO-OV2b
Enrollment 16/05/2016



Enrollment by Group

GROUP	N. Patients
MITO	154
GINECO	75
MANGO	50
SAKK	14
HeCOG	7
BGOG	-
Total	300

NiCCC
Nintedanib in Clear Cell Carcinoma

A Randomised Phase II Study of BIBF 1120 versus Chemotherapy in Recurrent Clear Cell Carcinoma of the Ovary or Endometrium

SGCTG/NCRI/NSGO

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

NHS Greater Glasgow and Clyde

CANCER RESEARCH UK

scottish gynaecological cancer trials group

NCRI National Cancer Research Institute

NSGO

EORTC European Organisation for Research and Treatment of Cancer

GINECO ARCAGY

European Network of Gynaecological Oncology Trials groups ENGOT

NiCCC Trial Design

90 pts with progressive or relapsed CCC of ovary within 6 months of previous platinum.

Plus up to 30 women with endometrial CCC

RANDOMISE

Chemotherapy

Ovary:

- PLDH (40mg/m^2 day 1q28)
- Weekly Paclitaxel (80mg/m^2 day 1, 8, 15 q28)
- Weekly Topotecan iv (4mg/m^2 day 1, 8, 15 q28)

Endometrium:

- Carboplatin (AUC 5) /Paclitaxel 175 mg/m^2 q21
- Doxorubicin 60mg/m^2 q21

Nintedanib 200mg bd until progression

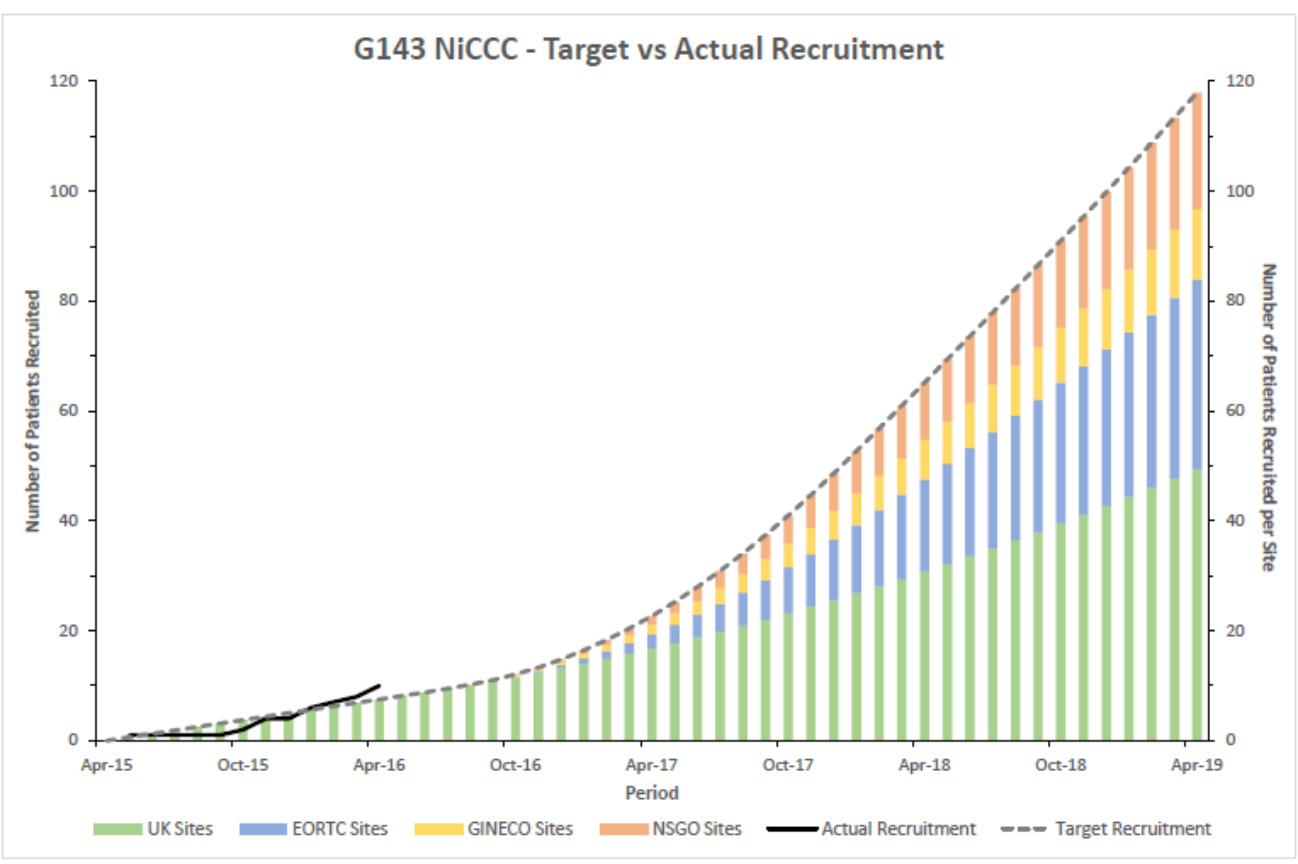
Primary Endpoint: PFS

Secondary Endpoints: OS, Toxicity, RR, QoL, Q-Twist

Trial Status

- Study opened in the UK April 2015
  - 11 centres are open
  - 12 patients randomised
- GINECO due to open June 2016
- EORTC due to open Sept 2016
- NSGO due to open Oct/Nov 2016

Recruitment



Niraparib and niraparib-bevacizumab combination against bevacizumab alone in Women with Homologous Recombination Deficient (HRD) platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer.

ENGOT-OV24 - NSGO / AVANOVA

EudraCT number: 2014-004269-26

ASCO 2016

Gynecologic Cancer

Session Type: Poster Session

Date and Time: 06/06/2016 1:00 PM - 4:30 PM

Abstract Title: *The ENGOT-OV24/AVANOVA1 trial*

Abstract ID: *5555*

Sponsor: NSGO

Project Manager: Louisa Boufercha

Statistitian: DePont Christensen

PI: Mirza

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ENGOT-OV24 - NSGO / AVANOVA

Phase 1 (Completed)

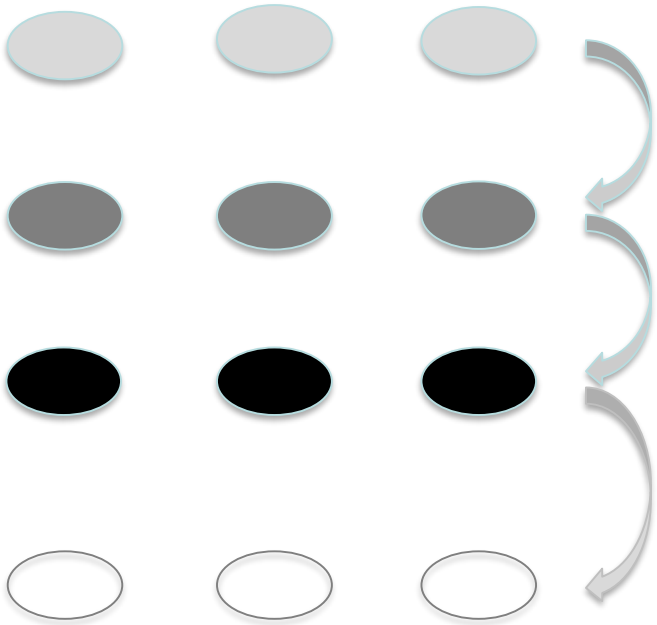
Dose Escalation from cohorts 1 to 2 to 3 to 4

Cohort 1
Niraparib 100mg + Bev 15mg

Cohort 2
Niraparib 200mg + Bev 15mg

Cohort 3
Niraparib 300mg + Bev 15mg

Cohort 4
Niraparib 300mg + Bev 7.5mg



No Dose Limiting Toxicity
Escalate to cohort 2

No Dose Limiting Toxicity
Escalate to cohort 3

Bev related toxicity
Consider cohort 4

Recommended Phase 2 Dose (RP2D) of bevacizumab-niraparib combination

Niraparib 300mg daily + Bevacizumab 15mg/kg q 3 wks

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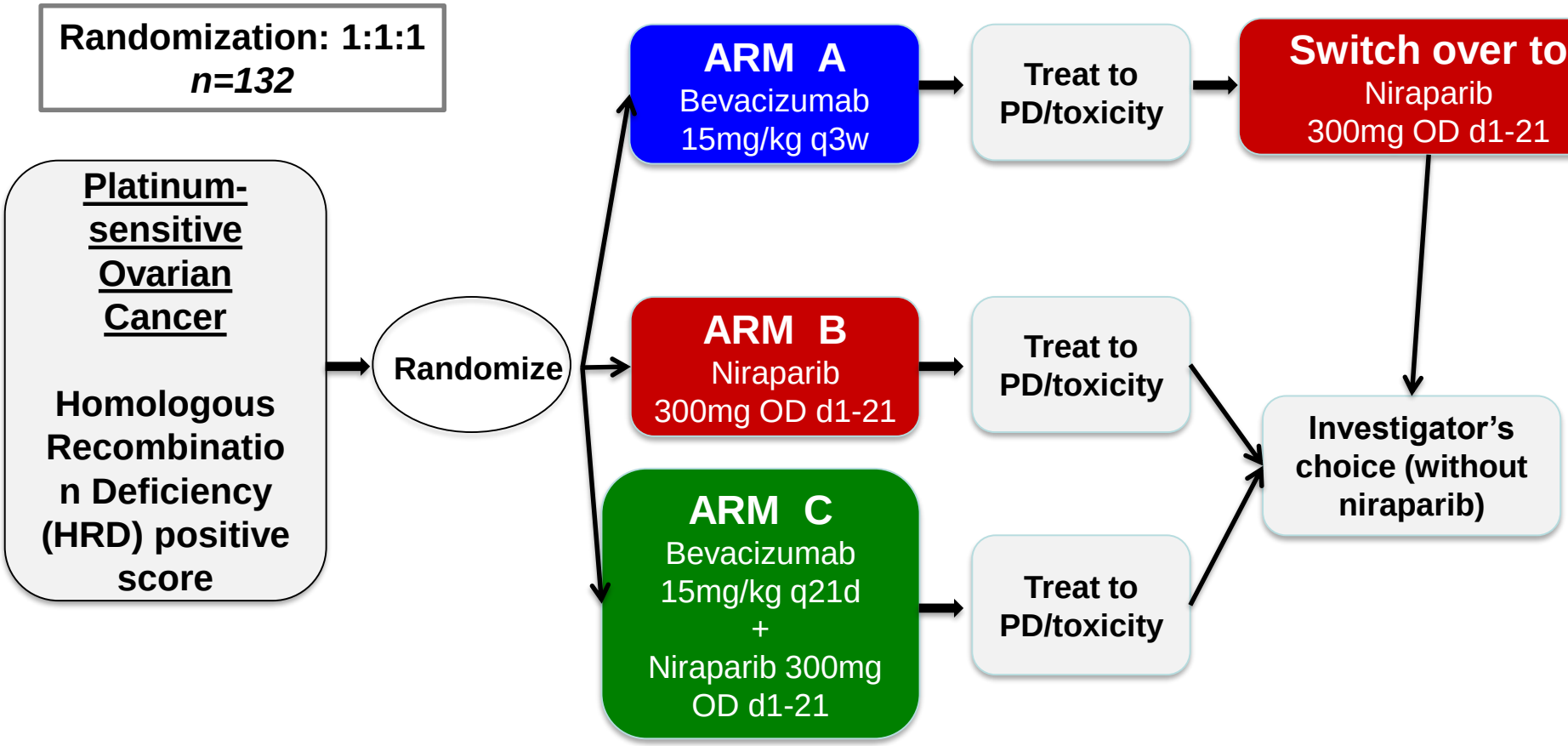
Phase 2 design



Stratifications

- **BRCA status: BRCA mutated vs. non-carrier**
- **Prior receipt of anti-angiogenic therapy (yes/no)**
- **Prior lines of therapy: 1-3 vs > 3 lines**

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Study Status

Part 1	**Completed**
Part 2	**Screening in DK**
	Activations ongoing in SWE
	Submissions completed in (NOR, FIN)
	FDA & IRB submissions in May

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A Phase 2 Randomized Umbrella Trial in Recurrent Ovarian Cancer

NSGO-OV-UMB1

ENGOT-OV30

Sponsor: Nordic Society of Gynaelogical Oncology (NSGO)
Study Chair: MR Mirza

Lead Investigators by participating groups:

MR Mirza:	Nordic Society of Gynaecological Oncology (NSGO)
C Gourley:	The Scottish Gynaecological Cancer Trials Group (SGCTG)
A Oza:	The Princess Margaret Hospital Consortium (PMHC)
I Vergote:	Belgian Gynaelogical Onology Group (BGOG)
M Friedlander:	The Australia New Zealand Gynaecological Oncology Group (ANZGOG)
J Barek:	Cooperative Ovarian Cancer Group for Immunotherapy (COGI)
K Fujiwara:	Gynecologic Oncology Trial and Investigation Consortium (GOTIC)
SY Ryu:	Korean Gynaelogical Onology Group (KGOG)
G Coukos	Ludvig Cancer Research Centre, Switzerland

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Suported by: OVA CURE

NSGO-OV-UMB1

Endpoints

Primary endpoint:
Progression-Free Survival (PFS) by RECIST

Secondary endpoints:
PFS by Immune-RECIST
PFS at 9 months
PFS at 12 months
Median PFS
PFS in each group according to trial stratification factors
Overall survival for each experimental arm
Objective response rate (ORR)
Disease control rate (DCR) (CR+PR+SD)
Duration of (Overall) Response
Patient Related Outcomes (PROs)
Safety and tolerability.

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NSGO-OV-UMB1
Key Inclusion Criteria

- **Relapsed ovarian cancer with TFIchemo either < 6months or ≥ 6months. Patients with TFIchemo of ≥ 6months must have received 3 courses of chemotherapy.**

- **High-grade serious, endometriod, undifferentiated. Apart from these types a limited number of low grade serious carcinoma, clear-cell carcinoma and mucinous carcinoma can be enrolled in this study - maximum of 5 patients per study cohort.**

- **Patient agrees to undergo all analysis (blood, serum, tissue) including tumor biopsy.**

- **ECOG performance status 0-1**
- **Serum albumin >30g/l.**

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NSGO-OV-UMB1

3:1 randomization
In each cohort
Cross-over in Standard arm permitted

Relapsed ovarian cancer

Tumor biopsy

Cohort A — Coordinating Lead Group SGCTG
Durvalumab

Standard of care

Cohort B — Coordinating Lead Group PMHC
Durva + AZD5069

Standard of care

Cohort C — Coordinating Lead Group NSGO
Durva + AZD9150

Standard of care

PET-CT, tumor, blood, plasma and serum samples

Tumor biopsy At progression

Next-Generation Sequencing if required

PET-CT, tumor, blood, plasma and serum samples

Treatment until disease progression

Continous blood, plasma and serum samples

mansoor@rh.regionh.dk

Suported by:

NSGO-OV-UMB1
Study Status

Initial grant from AZ received

Kickoff meeting of Steering Committee Meeting (Feb 20, 2016, London)

Major grant application for study cohorts A-C submitted (March 1, 2016)

Distribution of responsibilities being agreed between the lead groups & sponsor (NSGO)

Planned submissions June 2016

Next wave of molecules/combinations under discussion

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ICON9:
An international phase III randomised double-blind study to evaluate the safety, tolerability and efficacy of 2 regimens of cediranib in combination with platinum-based chemotherapy and placebo controlled olaparib and cediranib maintenance therapy
(in patients with relapsed platinum sensitive ovarian cancer)

NCRI National Cancer Research Institute

CANCER RESEARCH UK

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Trial Schema

Relapsed platinum sensitive ovarian, fallopian tube, primary peritoneal cancer

Arm 1
Chemotherapy + cediranib daily x6 cycles
followed by maintenance cediranib (daily) plus olaparib

Arm 2:
Chemotherapy + cediranib (5:2) x6 cycles
followed by maintenance cediranib (5:2) plus placebo

Stratified by 6-12 vs >12 month progression free interval; BRCA status; surgery vs no surgery at relapse prior to chemotherapy; prior bevacizumab

Cediranib: 20 mg OD
(daily vs 5 days on/ 2 days off-5:2)
Olaparib: 300 mg BD

NCRI National Cancer Research Institute
CANCER RESEARCH UK
GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Study Objectives

- **ICON 9 will assess the efficacy, safety and tolerability of 2 dosing regimens of maintenance cediranib in combination with olaparib compared to maintenance of cediranib and placebo following platinum-based chemotherapy with cediranib**

- Changes in design due to amalgamation of trial protocols for original ICON9 and CATALYST trial
- Main change is use of blinded placebo controlled blister packs to assess toxicity/efficacy of dosing regimen for cediranib with chemotherapy and in maintenance setting with/without olaparib

NCRI National Cancer Research Institute

CANCER RESEARCH UK

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Study Endpoints

	End points
Primary Objective	• PFS (RECIST v1.1) • OS
Secondary objectives	• Toxicity • Adherence • PFS2 • TFST • Quality of Life (FACT-O/TOI) and Patient Reported Outcomes and EQ-5D-5L (health economic analysis) • Progression free survival by CA125 – GCIG criteria • Response rates by RECIST/CA125 at 12 weeks of maintenance therapy in patients with measureable disease or elevated CA125 at randomisation to maintenance therapy

NCRI National Cancer Research Institute

CANCER RESEARCH UK

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Details

- AZ remain supportive of trial
- 30-40 sites UK
- 20 international sites from 2-4 countries
- September 2015: Full CRUK application approved in UK
- Funding approved in Australia and Canada
- Q1 2017 (open trial)

- **GCIG Satellite meeting Friday at 10 am**

AGO-OVAR 2.28
ENGOT-ov28

Cediranib and Olaparib versus Platinum-based Chemotherapy in *Platinum-eligible* Recurrent Ovarian Cancer

Satellite Meeting
June 3rd, 2016
4:30 pm; LaSalle I Room

New Proposals

- Oreo (10’) E Pujade-Lauraine
- SUNNY (10’) RY Zang
- AGO-OVAR 2.29 (10’) P Harter

OReO study

Olaparib Re-treatment in platinum sensitive recurrent Ovarian cancer

ENGOT model C (AZ)
Lead group: GINECO
Co-lead group : ISGO (Pr J Korach)

GINECO

The Israeli Society of Gynecologic Oncology
החברה הישראלית לגינקולוגיה אונקולוגית

ENGOT
European Network of Gynaecological Oncology Trials groups

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

SHANGHAI GYNECOLOGIC ONCOLOGY GROUP
上海妇科肿瘤协作组

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

The Asia SUNNY Study (SGOG OV 4B)

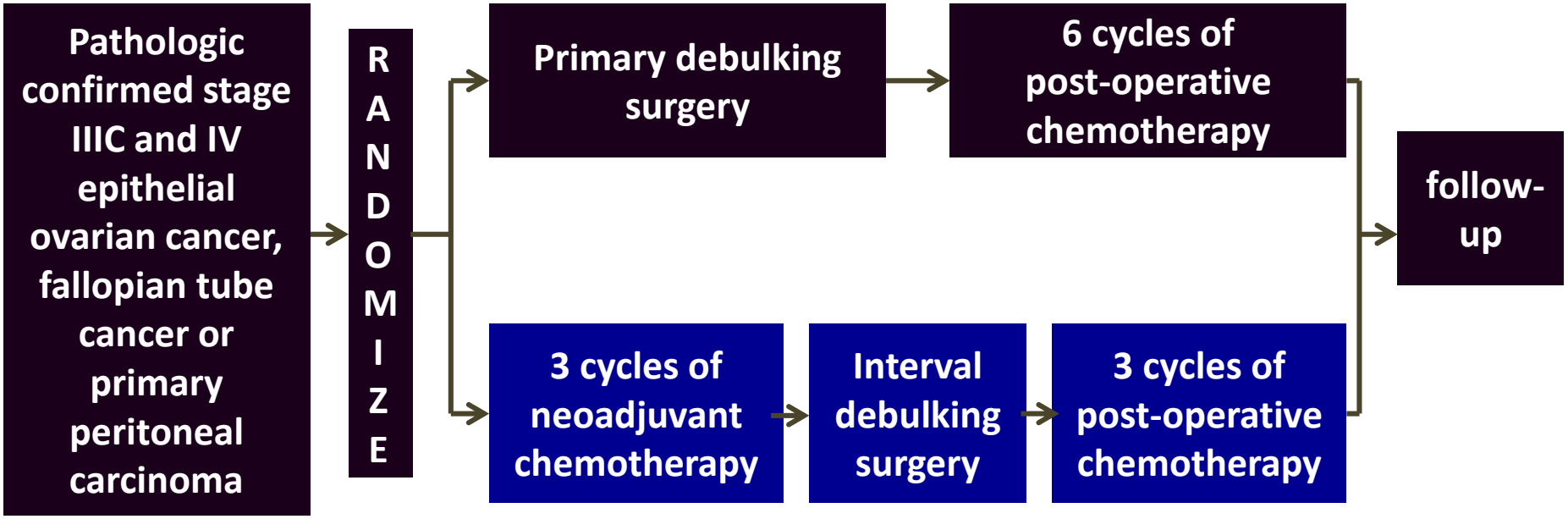
Study of Upfront Surgery versus Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery for Patients with Stage IIIC and IV Ovarian Cancer

Rongyu Zang, MD,PhD
www.ShanghaiGOG.org

SHANGHAI GYNECOLOGIC ONCOLOGY GROUP
上海妇科肿瘤协作组

The Asia SUNNY Study

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers



Primary endpoint

- OS

Secondary endpoints

- PFS
- 30-day post-operative complications
- QOL (surgical times, non-treatment intervals…)

Open: Nov. 2015
Closed: Nov. 2020
Target accrual: 456

Inclusion criteria

- Women aged ≥ 18 years.
- Pathologic confirmed stage IIIC and IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma (diagnosed by biopsy or fine needle aspiration*).

  Laparoscopic biopsy with pictures is recommended.

  – * If fine needle aspiration showing an adenocarcinoma, patients should satisfy the following conditions:

    a. *the patient has a pelvic mass, and*

    b. omental cake or other metastasis larger than 2 cm in the upper abdomen, or pathologic confirmed extra-abdominal metastasis, and

    c. serum CA125/CEA ratio>25. And serum CA199 is recommeded.

    d. If serum CA125/CEA ratio<25 or malignancies of other origins, such as breasts and digestive tract, are suspected from symptoms, physical examinations or imaging diagnosis, endoscopy or ultrasonography should be done to exclusive metastasis ovarian cancer.

Inclusion criteria

- ECOG performance status of 0 to 2.
- ASA score of 1 to 2.
- Adequate bone marrow, liver and renal function to receive chemotherapy and subsequently to undergo surgery:
  - white blood cells >3,000/µL, absolute neutrophil count ≥1,500/µL, platelets ≥100,000/µL, hemoglobin ≥9 g/dL
  - serum creatinine <1.25 x upper normal limit (UNL) or creatinine clearance ≥60 mL/min according to Cockroft-Gault formula or to local lab measurement
  - serum bilirubin <1.25 x UNL, AST(SGOT) and ALT(SGPT) <2.5 x UNL.
- Comply with the study protocol and follow-up.
- Written informed consent.

Exclusion criteria

- Patients with non-epithelial tumors as well as borderline tumors.
- Mucinous ovarian cancer.
- Synchronous or metachronous malignancy within 5 years other than carcinoma in situ.
- Any other concurrent medical conditions contraindicating surgery or chemotherapy that could compromise the adherence to the protocol.
- Other conditions, such as religious, psychological and other factors, that could interfere with provision of informed consent, compliance to study procedures, or follow-up.

Stratification (1)

• Institution	8601, 8602,… 8201,8202,…
• Method of biopsy	☐laparoscopy ☐FNA
• FIGO Stage	☐IIIC ☐IV
• Age	☐≥70 years ☐<70 years
• Extensive metastasis diseases* in the upper abdomen	☐Yes ☐No

* defined as carcinomatosis or the number of lesions ≥ 3 in the upper abdomen

Stratification (2)

IP chemotherapy

- The primary results of the SGOG OV1 IP trial (NCT01669226): an additional intraperitoneal cisplatin and etoposide was the winner when compared to standard chemo

Surgery (1)

- Aim: Maximal cytoreduction in each group.
- 50% R0
- UAD documented, as well as the procedures performed in cytoreduction.
- It is recommended to take pictures by Laparoscopic diagnosis

Surgery (2)

- (NACT+) ICR is performed,
  - 1) if there is no visible lesion in the peritoneum of the pelvic, paracolic sulcus or diaphragm, there is no need to resect the peritoneum; however, if there are any suspected visible lesions after NACT, the involved peritoneum before NACT based on the findinds by laparoscopy should be resected;
  - 2) **Intestine mesenterium**: resection or coagulation is recommended if there is any visible lesion;
  - 3) bowel resection or splenectomy is not **compulsory** except when complete resection is possibly obtained by these procedures.

Endpoints

- **Primary endpoint**
  - Overall survival
- **Secondary endpoints**
  - Progression-free survival
  - 30-day post-operative complications
  - Quality of life assessments (QLQ-C30, FACT-O): baseline; 3th cycle of intravenous chemotherapy; 1 and 6 months after first-line chemotherapy.

Sample size

- **Hypothesis： Upfront radical surgery enhance the survivorship when compared with upfront chemo**

- Accrual target: **456** subjects
  - at a 1:1 ratio
  - accrual time of 5 years
  - a minimum follow-up of 2 years
  - assuming a hazard ratio of **0.6803**
  - α 0.05, power 90%

Randomization

Website Address： http://iwrs.fudan.edu.cn/shmc-1.0.0/login.html

- Username and password is necessary
- Different accounts in different institutions
- Change the default password after login

Study timelines

Study stage	Milestone	Date(act/plan)
Set-up	Protocol approved	**Nov.30 2015**
	First center initiated -**Zhongshan Hospital, Fudan University**	Dec. 2015
	Last center initiated -**KGOG**	Aug. 2016
Recruitment	First subject first visit	Dec.9 2015
	Last subject first visit	Dec.10 2020
Data management	Last subject last visit -Overall survival	**Dec.10 2022**
Analysis	Statistical analysis complete	Mar.10 2023
Report	Approval of study report	Feb.10 2024

Expected accrual: 8 pts. per mos. (7-9)

Grants

Local grant for Dr Rongyu Zang, 2015-2018

Another grant for Dr Jianqing Zhu estimates approved on July 2016

THANK YOU!

GYNECOLOGIC CANCER INTERGROUP

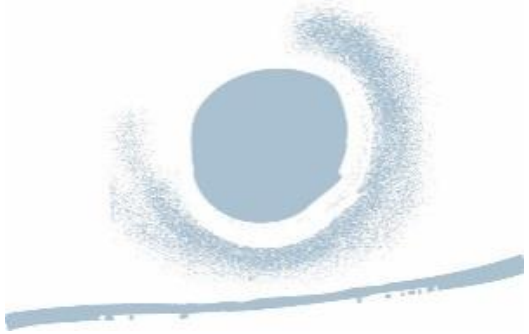
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

AGO-OVAR 2.29

European Network of Gynaecological Oncology Trials groups

ENGOT

Atezolizumab in combination with Bevacizumab +/- Chemotherapy versus Chemo-BEV standard in recurrent ovarian cancer – a randomised trial



ENGOT-ov34

Updates from recently presented trials

- WISP (5’) K Lu
- Atalante (5’) E Pujade-Lauraine

WISP

(**W**omen Choos**I**ng **S**urgical **P**revention)

Pathogenesis of BRCA-associated ovarian cancer

Published OnlineFirst January 28, 2011; DOI: 10.1158/1940-6207.CAPR-10-0266

Cancer Prevention Research

Research Article

Microscopic and Early-Stage Ovarian Cancers in *BRCA1/2* Mutation Carriers: Building a Model for Early BRCA-Associated Tumorigenesis

Melinda S. Yates[1], Larissa A. Meyer[1], Michael T. Deavers[2], Molly S. Daniels[1], Elizabeth R. Keeler[1], Samuel C. Mok[1], David M. Gershenson[1], and Karen H. Lu[1]

Abstract

Risk-reducing salpingo-oophorectomy (RRSO) is the cornerstone of ovarian cancer prevention in *BRCA1/2* mutation carriers. Occult fallopian tube and ovarian cancers have been reported in a small percentage of *BRCA1/2* mutation carriers undergoing RRSO. Here, we review our single-institution experience with RRSO in *BRCA1/2* mutation carriers to characterize cases of microscopic cancers in these patients. At the time of RRSO, 7.9% of *BRCA1* mutation carriers were diagnosed with microscopic fallopian tube or ovarian cancers and no cases were diagnosed in *BRCA2* mutation carriers. The majority of the microscopic cancers include cases that were confined to the fallopian tubes, although there were also cases involving ovaries only or peritoneal washings only. This suggests that the site of origin may be in the ovary, fallopian tube, or peritoneum for BRCA-associated serous cancers. However, an analysis of early-stage (stages I and II) ovarian and fallopian tube cancers diagnosed in *BRCA1/2* mutation carriers confirms that the ovary is a preferred site for tumor growth with 11 of 14 early-stage cancers having a dominant ovarian mass. Overall, these data suggest that cancer initiation may occur in the ovary, fallopian tube, or peritoneum, but tumor growth and progression are favored in the ovary. We present an updated model for *BRCA1/2* mutation–associated ovarian and fallopian tube carcinogenesis, which may aid in identifying improved prevention strategies for high-risk women who delay or decline RRSO. *Cancer Prev Res; 4(3); 463–70. ©2011 AACR.*

Introduction

Women with germline mutations of the tumor suppressor genes *BRCA1* or *BRCA2* have a high lifetime risk of developing ovarian cancer (~39% and 22%, respectively; ref. 1). Currently, there are no effective screening strategies for ovarian cancer (2, 3); therefore, prevention for this population focuses on prophylactic removal of the fallopian tubes and ovaries. Risk-reducing salpingo-oophorectomy (RRSO) reduces the risk of ovarian, fallopian tube, and peritoneal cancer by 85% to 90% for *BRCA1/2* mutation carriers (4–6). Recent reports have shown that occult cancers in the fallopian tubes and ovary are diagnosed in approximately 3% to 10% of RRSO surgical specimens (5, 7–15). Given this risk, consensus groups have recommended that a complete pathology review, including serial sectioning of the ovaries and fallopian tubes, is necessary for identification of occult cancers (16).

Studying occult microscopic cancers can provide insight into the natural history of BRCA-associated ovarian cancers. Significant debate is ongoing related to the tissue site of origin (ovarian, fallopian tube, or peritoneal surfaces) and also the cell type of origin (ovarian surface epithelial cells, ciliated cells in the fallopian tube, or tubal secretory cells). Furthermore, it is not clear how the ovarian, tubal, or peritoneal microenvironments may differentially impact tumor initiation or progression.

This study reports our single-institution experience with microscopic and early-stage cancers diagnosed in *BRCA1* and *BRCA2* mutation carriers. Observations from these cases are combined with a review of the literature to build an updated model of the early steps of BRCA-associated ovarian and fallopian tube carcinogenesis. By generating a data-driven model of ovarian/fallopian tube carcinogenesis, we can begin to address the many remaining questions that hinder the field of ovarian cancer prevention research.

Materials and Methods

Case selection and review

From August 2000 to July 2010, 136 patients with known *BRCA* mutations underwent RRSO at The University

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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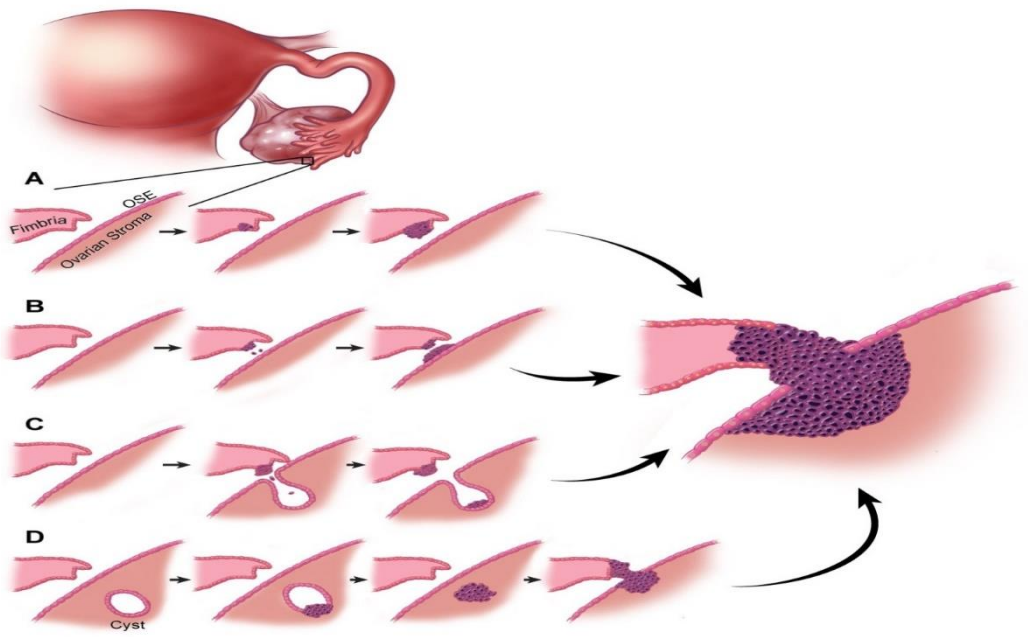


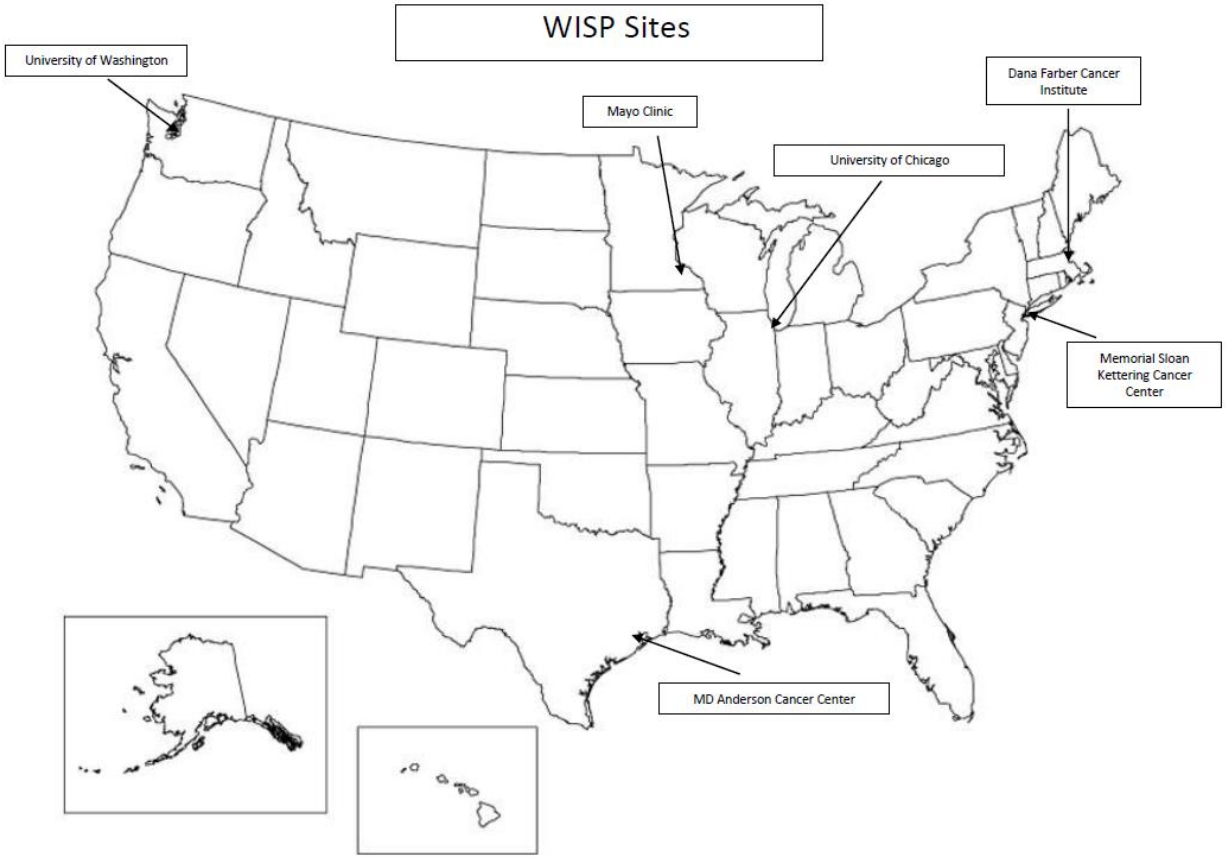
(*Yates, CaPrevRes 2011*)

Rationale for salpingectomy/delayed oophorectomy

- Clinical
  - Improve side effects associated with BSO, while maintaining long term cancer preventive benefits
  - Community of BRCA previvors very interested in salpingectomy as prevention option. Of 204 women survey, 34% found risk of cancer acceptable and were “definitely interested”

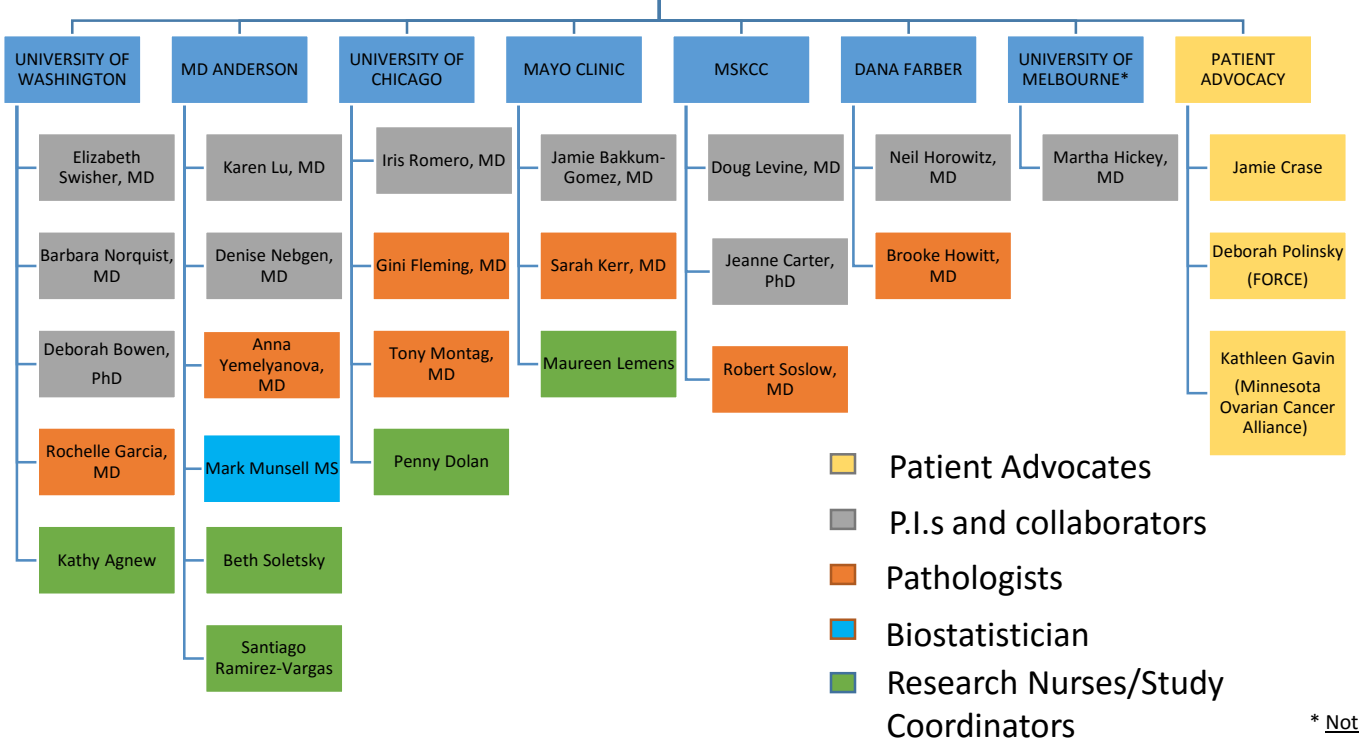
- Pilot feasibility study (n=40, 2 centers) ASCO oral presentation 2016 (Nebgen et al)

Holman et al, Gyn Onc 2014
Daly et al, Canc Prev Res, 2015 *in press*


WISP Sites
University of Washington
Mayo Clinic
University of Chicago
Dana Farber Cancer Institute
Memorial Sloan Kettering Cancer Center
MD Anderson Cancer Center

SU2C: WISP

(Women ChoosIng Surgical Prevention)



* Not an enrolling site

Surgical Prevention trial

- Eligibility:
  - age 30-50
  - BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2
  - RAD51C, RAD51D, BRIP1, BARD1, PALB2

- Pre-menopausal
- Desires permanent sterilization
- Presence of at least 1 fallopian tube and ovary
- Exclude women on tamoxifen or aromatase inhibitor

Study Design

- 270 evaluable patients recruited into one of two arms
  - Arm 1: interval salpingectomy with delayed oophorectomy (ISDO) with approximately 135 patients
  - Arm 2: risk-reducing salpingo-oophorectomy (RRSO) with approximately 135 patients.

Questionnaires

OUTCOME	INSTRUMENT	NUMBER OF QUESTIONS
Sexual function	1. Sexual Activity Questionnaire (SAQ) [40] 2. Female Sexual Function Index (FSFI) [41, 42] 3. PROMIS [43] 4. Female Sexual Distress Scale-Revised (FSDS-R) [44]	4 19 2 13
Menopausal symptoms	1. Menopausal Symptoms Checklist [45]	28
Mood	1. PHQ-9 [46]	9
Anxiety	1. Generalized Anxiety Disorder (GAD-7) [47]	9
Cancer worry	1. Impact of Events Scale [48]	15
Decision	1. Decisional Regret Scale (DRS) [49]	5
QOL	1. Veterans RAND 12-Item Health Survey (VR-12) [50]	12
Sleep	1. The Sleep Condition Indicator (SCI) [51]	8
Coping Style	1. Monitor-Blunter Style Scale (MBSS) [52, 53]	8
Total		**132**

Surgical Prevention trial: Endpoint

- Primary endpoint: percent of women with a clinically meaningful worsening in sexual function, as measured by the Female Sexual Function Index (FSFI) (Wiegel 2005).
- A worsening of the FSFI score from baseline to 6 months after surgery of 4 points or more will be considered clinically meaningful.
- Safety stopping rule

Opportunity for international collaboration

- Currently working with Doug Levine and NIH DCP to consider harmonization with NRG concept
- Opportunity for multiple groups to collaborate for efficacy endpoint
- Opportunity for translational research on specimens

GOG199 Risk-Reducing Salpingo-Oophorectomy (RRSO) Arm: Pathology results 966 high risk women

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Pathologic Findings at Risk-Reducing Salpingo-Oophorectomy: Primary Results From Gynecologic Oncology Group Trial GOG-0199

Mark E. Sherman, Marion Piedmonte, Phuong L. Mai, Olga B. Ioffe, Brigitte M. Ronnett, Linda Van Le, Iouri Ivanov, Maria C. Bell, Stephanie V. Blank, Paul DiSilvestro, Chad A. Hamilton, Krishnansu S. Tewari, Katie Wakeley, Noah D. Kauff, S. Diane Yamada, Gustavo Rodriguez, Steven J. Skates, David S. Alberts, Joan L. Walker, Lori Minasian, Karen Lu, and Mark H. Greene

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M.E.S., M.P., and P.L.M. are co-first authors of this work.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00489049.

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0732-183X/14/3229w-3275w/$20.00

DOI: 10.1200/JCO.2013.54.1987

ABSTRACT

Purpose
Risk-reducing salpingo-oophorectomy (RRSO) lowers mortality from ovarian/tubal and breast cancers among *BRCA1/2* mutation carriers. Uncertainties persist regarding potential benefits of RRSO among high-risk noncarriers, optimal surgical age, and anatomic origin of clinically occult cancers detected at surgery. To address these topics, we analyzed surgical treatment arm results from Gynecologic Oncology Group Protocol-0199 (GOG-0199), the National Ovarian Cancer Prevention and Early Detection Study.

Participants and Methods
This analysis included asymptomatic high-risk women age ≥ 30 years who elected RRSO at enrollment. Women provided risk factor data and underwent preoperative cancer antigen 125 (CA-125) serum testing and transvaginal ultrasound (TVU). RRSO specimens were processed according to a standardized tissue processing protocol and underwent central pathology panel review. Research-based *BRCA1/2* mutation testing was performed when a participant's mutation status was unknown at enrollment. Relationships between participant characteristics and diagnostic findings were assessed using univariable statistics and multivariable logistic regression.

Results
Invasive or intraepithelial ovarian/tubal/peritoneal neoplasms were detected in 25 (2.6%) of 966 RRSOs (*BRCA1* mutation carriers, 4.6%; *BRCA2* carriers, 3.5%; and noncarriers, 0.5%; $P < .001$). In multivariable models, positive *BRCA1/2* mutation status ($P = .0056$), postmenopausal status ($P = .0023$), and abnormal CA-125 levels and/or TVU examinations ($P < .001$) were associated with detection of clinically occult neoplasms at RRSO. For 387 women with negative *BRCA1/2* mutation testing and normal CA-125 levels, findings at RRSO were benign.

Conclusion
Clinically occult cancer was detected among 2.6% of high-risk women undergoing RRSO. *BRCA1/2* mutation, postmenopausal status, and abnormal preoperative CA-125 and/or TVU were associated with cancer detection at RRSO. These data can inform management decisions among women at high risk of ovarian/tubal cancer.

J Clin Oncol 32:3275-3283. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Risk-reducing salpingo-oophorectomy (RRSO) reduces number of deaths resulting from ovarian/tubal and breast cancers among carriers of deleterious *BRCA1/2* mutations and thus has become a preferred management strategy for these women.[1-3] Although oral contraceptive use and tubal ligation reduce the risk of ovarian/tubal neoplasms, level of protection is lower than that achieved with RRSO, and breast cancer risk is not reduced.[4-7] The effectiveness of screening in reducing mortality attributable to these cancers remains unproven. Annual concurrent cancer antigen 125 (CA-125) serum testing and transvaginal ultrasound (TVU) in the Prostate, Lung, Colorectal and Ovarian trial did not reduce ovarian/tubal cancer mortality.[8] Preliminary results from the UK Collaborative Trial of Ovarian Cancer Screening, which targeted similar women, reported potentially better results using algorithm-based CA-125 testing with secondary TVU examination[9]; final results are pending, and data from high-risk women are just emerging.[10] Thus, determining which women

- BRCA1: no cancers under age 42
- BRCA2: no cancers under age 51

- Primary site of 11 small volume cancers/STIC
  - 4 STIC
  - 4 fallopian tube
  - 1 ovary
  - 1 fallopian tube and ovary

ATALANTE
Atezolizumab and Avastin in late recurrent disease

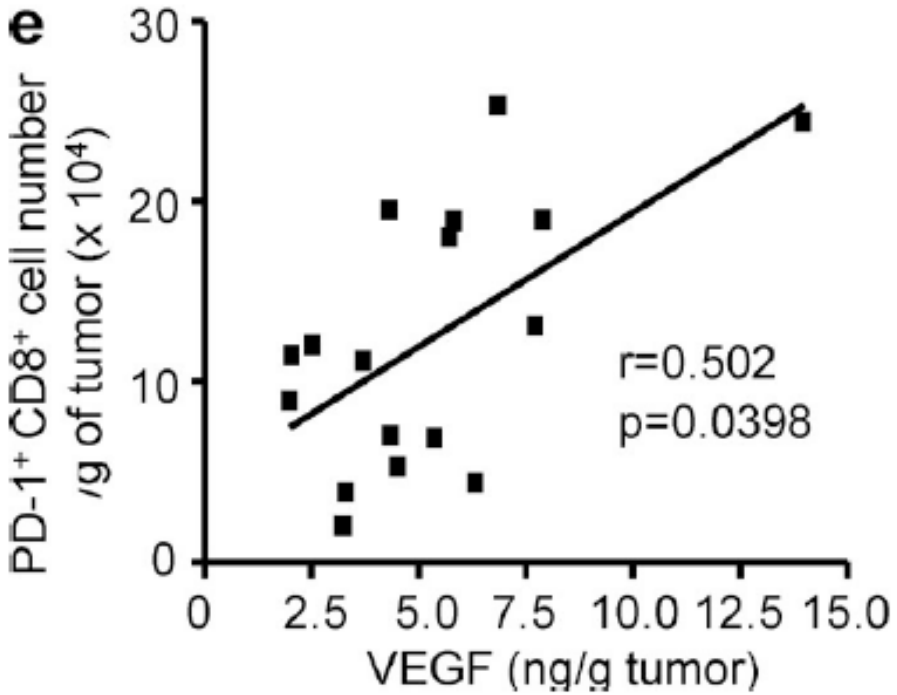
ATezolizumab and Avastin in LAte recurreNT diseasE
ENGOT-ov29-GCIG

A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab

Sponsor: ARCAGY-GINECO
Lead group: GINECO (Pr JE Kurtz)

Rationale for combining anti-PDL-1 with anti-VEGF therapy

VEGF expression is correlated with expression of PD1 on CD8+ cells



Voron T, et al. J Exp Med 2015 212: 139

Rationale for combining anti-PDL-1 with anti-VEGF therapy

VEGF exerts an immunosuppressive effect in cancer

- **Inverse correlation between VEGF levels and presence of TILs**

  Zhang L et al N Engl J Med 2003;348:203-13.

- VEGFR2 is selectively expressed in Treg CD4+FoxP3 + cells and VEGF directly **suppresses activation of T Cells**

  H. Suzuki Eur J of Immunology, vol. 40, no. 1,2010; Gavalas NG et al British Journal of Cancer (2012) 107, 1869

- **In response to VEGF**, **immature DCs** acquire a pro-angiogenic phenotype and contribute to ovarian cancer progression

  Coukos G Br J Cancer. 2005;92:1182–1187.

GINECO

ENGOT

GYNECOLOGIC CANCER INTERGROUP

GINECO

ATALANTE

Atezolizumab and Avastin in late recurrent disease

ENGOT

GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Recurrent late relapse

N=405

- Non-mucinous histology
- TFI p (platinum-free interval)>6 months
- One or 2 prior lines of Cx
- ECOG ≤ I

BIOPSY

R
1:2

Carboplatin-based chemotherapy

Bevacizumab+Placebo

b 12 24 48 72 96

PD

Confirmatory CT-Scan

Bevacizumab + ATEZOLIZUMAB

PD

Confirmatory CT-Scan

Interim safety analyses

Stratification factors

- PDL-I expression
- TFI p (6-12, >12 mos)
- Chemotherapy cohort

Chemotherapy-based schedule options (investigator's choice): carboplatin AUC5 + paclitaxel (175mg/m² q3wks) or gemcitabine (1000 mg/m² D1&D8 q3wks) or PLD* (30mg/m² q 4wks). BEV 15mg/kg q3 wks or 10mg/kg q2 wks. ATEZO/PLACEBO: 1200mg, I.V q3wks or 800mg q2wks.*

objectives

- **Primary: efficacity**

  - RECISTv1.1 **PFS1** from median of 13 to 18.6 months (HR: 0.70) alpha:0.05, beta:0.8, two-sided with landmark CT-scans/MRI at 12, 24, 48, 72 and 96 weeks

  - and **supported by secondary endpoints**: TSST and QoL + PROs (EORTC QLQ-30 and OV28); OS

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Others secondary objectives

1- **Additional efficacy assessments in the ITT population**

- ORR
- PFS1 as assessed per irRECIST
- Time from randomization to first subsequent therapy or death (TFST)
- PFS2

2- **Efficacy between arms in the PD-L1-ve and PD-L1 +ve** subgroups

3- **Safety and tolerability** of atezolizumab compared to placebo

4- Impact of treatment and disease on **resource use** (EQ-5D)

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timelines

- **FPI:** Q3 2016
- **Accrual period:** 24 months
- **LPI:** Q2 2018
- **Follow-up period:** 20 months

5th OCCC publication update

- K. Ochiai

5th Ovarian Cancer Consensus Conference

Host: JGOG

Chair	**Ochiai,**	**Kazunori**	**JGOG**
Co-Chairs	**Okamoto,**	**Aikou**	**JGOG**
	Stuart,	**Gavin**	**NCIC**
Scientific Committee	**Harter,**	**Phillipe**	**AGO**
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	Bookman,	**Michael**	**GOG**
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	Quinn,	**Michael**	**ANZGOG**
	Aoki,	**Daisuke**	**JGOG**
	Fujiwara,	**Keiichi**	**GOTIC**
	Kim,	**JW**	**KGOG**

Publication

- Annals of Oncology
- Review article
- Authorship
  - Summary Paper
    - Scientific Committee(9), Supporter(2)
  - Group Paper
    - Lead Author: Rapporteur
      Additional Authors: Topic CoChairs (2), Presenters & Discussants (6), Assigned Delegates (9), CoChairs (3)