Current GCIG Trials in Ovarian Cancer

Andres Poveda, MD
GCIG Chair

PARSGO Marrakech April 2018

History of GCIG Collaboration

GYNECOLOGIC CANCER INTERGROUP

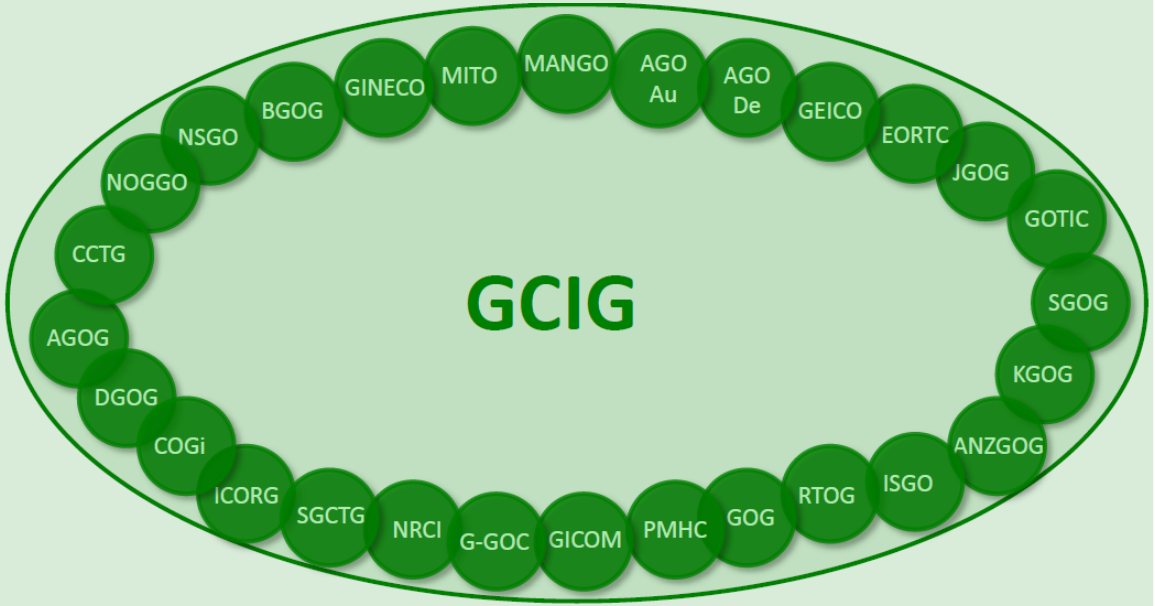
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

- **1992 Collaboration on two studies of paclitaxel in ovarian cancer between Europe and Canada**
- **In 1993**, it was felt that a network of national or international groups could facilitate this
- Need for an ongoing structure to facilitate intergroup activities discussed **1995-1997**
- Formalized in **1997**
- Incorporated in **2011** according to "Canada not-for- profit Corporations Act".

European-Canadian Randomized Trial of Paclitaxel in Relapsed Ovarian Cancer: High-Dose Versus Low-Dose and Long Versus Short Infusion

GCIG is a **collaborative network** of international and national **research groups** performing **clinical trials in gynecologic cancers**.

- Ovarian
- Cervix
- Endometrial
- Rare tumors



GCIG is a **non-profit organization**.

Achievements

Rapid accrual Phase III OC > 800 Pts

Study	N	Accrual time
NCIC CTG OV 9 TAXOL (Eisenhauer)	407	1991-1992
GOG182-ICON5 (Bookman)	4312	2001-2004
MITO-2 (Pignata)	820	2003-2007
SCOTROC 4 (Banerjee)	964	2004-2009
CALYPSO (Pujade-Lauraine)	976	2005-2007
TARCEVA (Vergote)	835	2005-2008
ICON 7 (Perren)	1528	2006-2009
MITO-7 (Pignata)	822	2008-2012
OVAR 16 (DuBois)	940	June 2009-August 2010
AURELIA (Pujade-Lauraine)	360	October 2009-April 2011
DESKTOP-III (DuBois)*	400	March 2012-March 2015

*80 sites in 12 countries

GYNECOLOGIC CANCER INTERGROUP

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Major GCIG Trials in Ovarian Cancer

Leading to The New Standard of Care

GOG-218 & ICON-7
Calypso
Aurelia
ENGOT-OV16/ NOVA
DESKTOP III
LION
ICON 8

May Change the Standard of Care

OVAR 17
iPOC
PAOLA 1
Prima
IMagyn050
OREO
NRG GY004
NRG GY009
NSGO-UMB1

Planned Trials

FIRST
AVANOVA IMMUNE 1
NRG OV 1719

Antiangiogenic therapy
Bevacizumab in primary Ovarian Cancer

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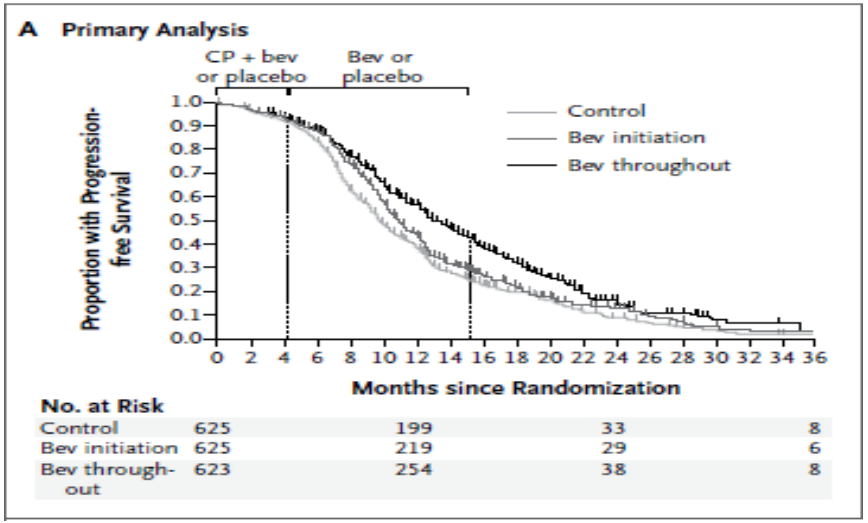
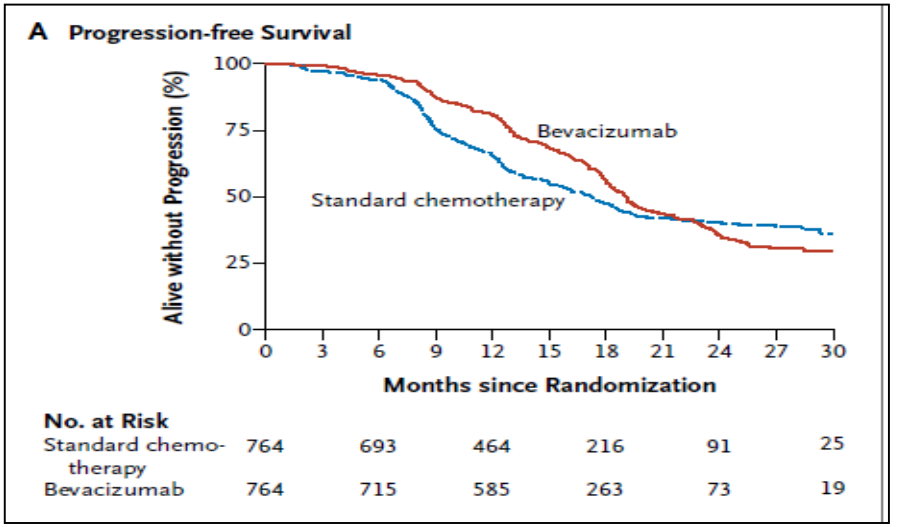
2 positive trials

Improved PFS by adding bevacizumab to carboplatin/paclitaxel and subsequent maintenance therapy





GOG 218: Bev throughout vs placebo
HR 0.717; 95% CI 0.625-0.824, p<0.001

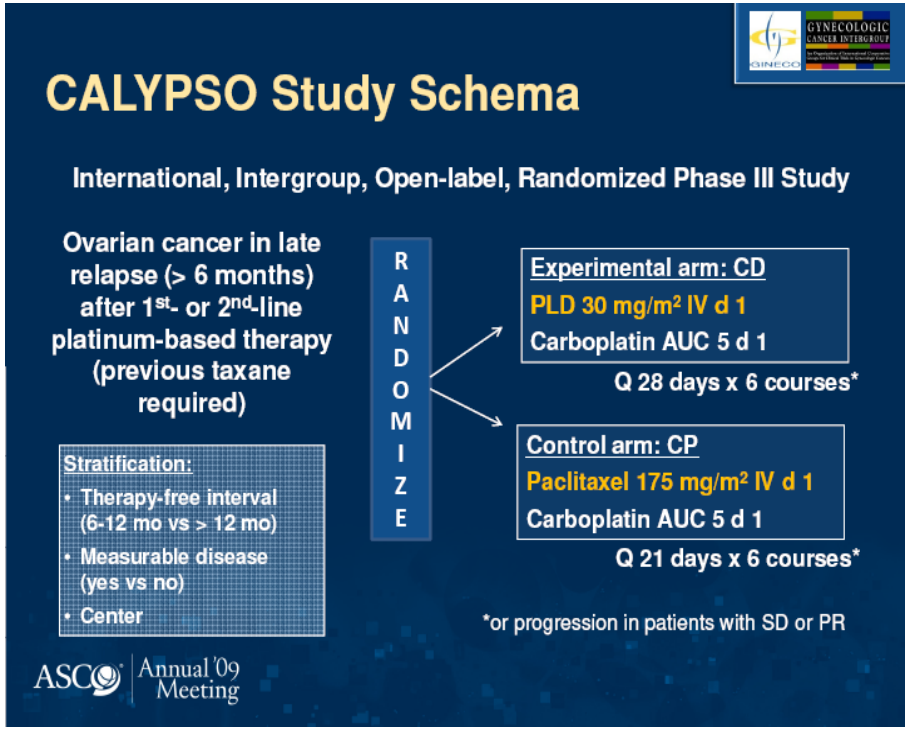
Burger RA et al. New Eng J Med 2011

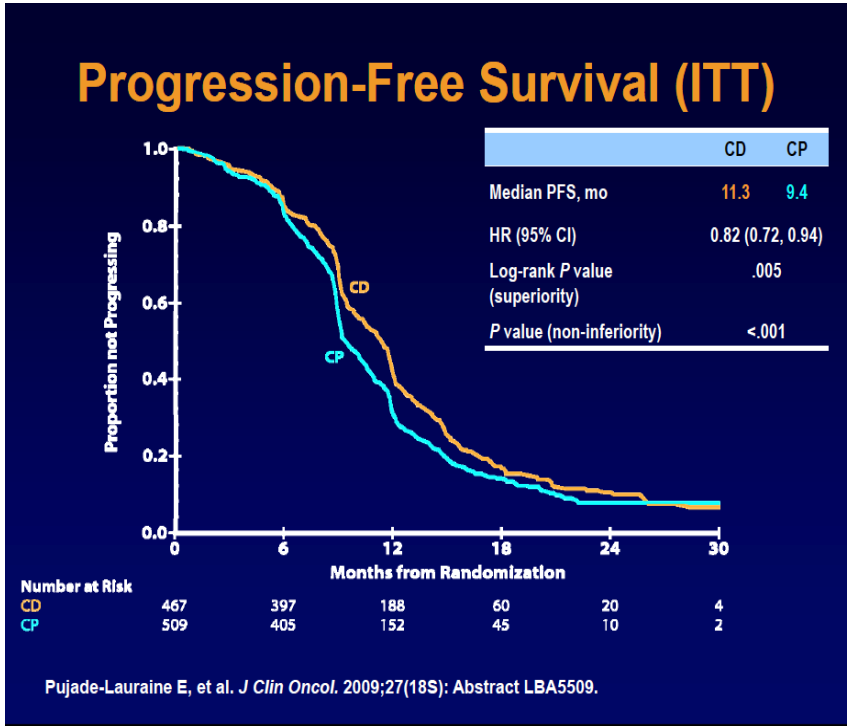
ICON 7: Bev vs control
HR 0.77; 95% CI 0.77-0.99; p=0.04

Perren TJ.... Mirza MR et al. New Eng J Med 2011

Better Combination Chemotherapy for Platinum- Sensitive Recurrent Ovarian Cancer

Phase 3 non-inferiority design: Improved PFS and quality of life in carboplatin/PLD arm





Pujade-Lauraine E et al. J Clin Oncol 2010

Antiangiogenic therapy
Bevacizumab in Recurrent Ovarian Cancer: *Platinum-Resistant Relapse*

GYNECOLOGIC CANCER INTERGROUP
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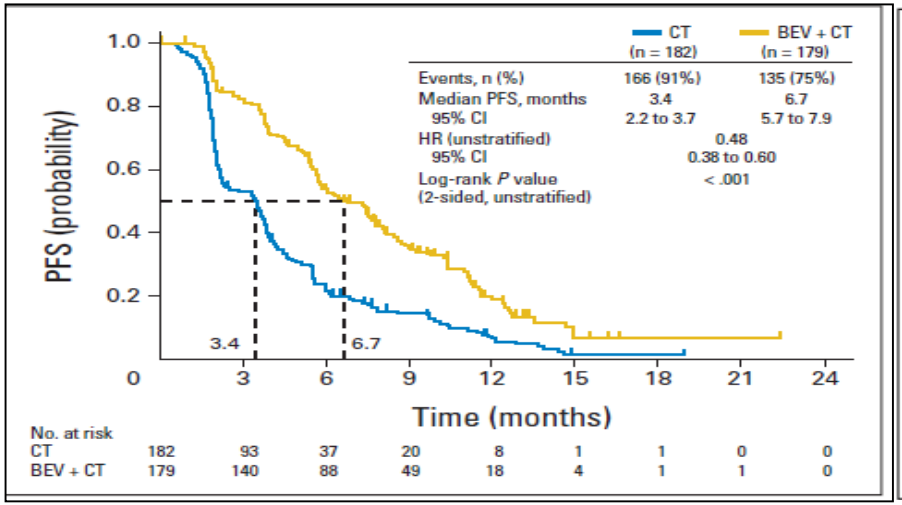
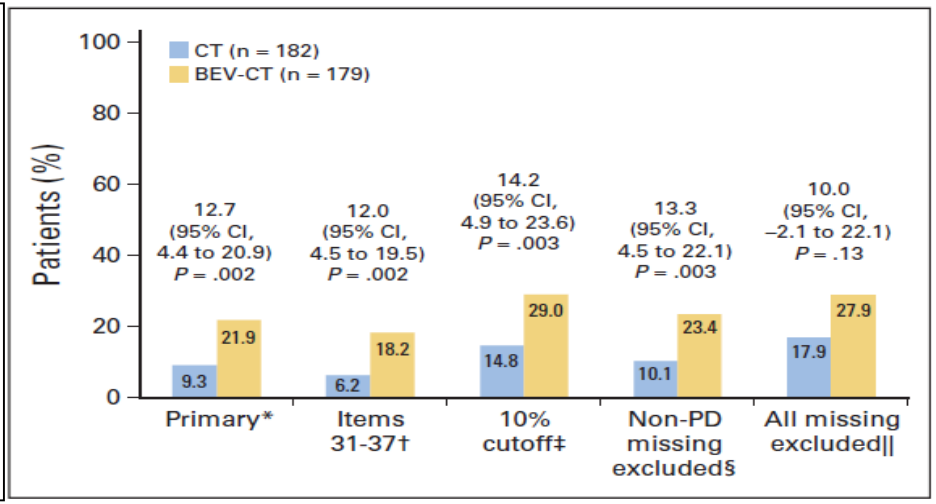
1 positive trial

Improved PFS by adding bevacizumab to non-platinum based chemo + QoL benefit in symptomatic pts.





AURELIA: PFS NonPlat +/- Bev
HR 0.48; 95% CI 0.38-0.60, p< 0.001

AURELIA: Primary and sensitivity analysis of the primary hypothesis (≥ 15% improvement in symptomatic pts)

Pujade-Lauraine E et al. J Clin Oncol 2014

Stockler MR et al. J Clin Oncol 2014

Antiangiogenic therapy
Bevacizumab in Recurrent Ovarian Cancer: *Platinum-Resistant Relapse*

GYNECOLOGIC CANCER INTERGROUP
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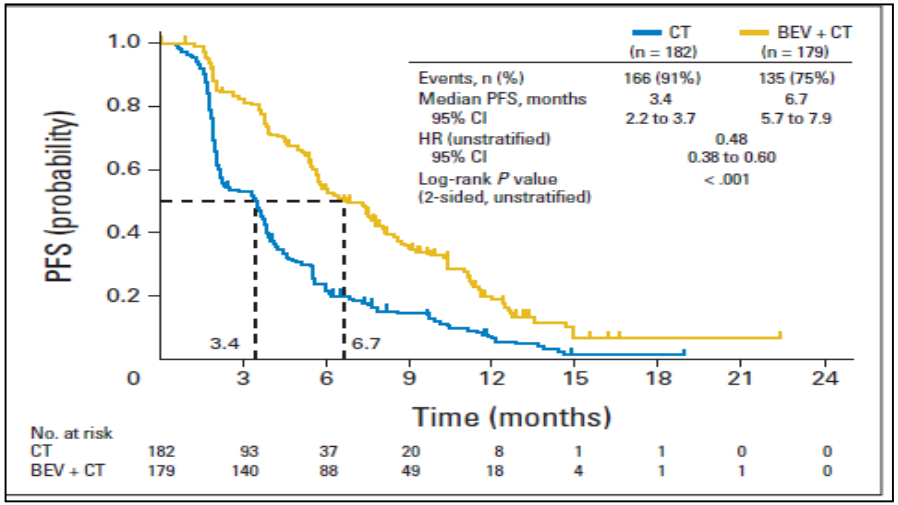
1 positive trial

Improved PFS by adding bevacizumab to non-platinum based chemo + OS benefit in PAC+Bev cohort.



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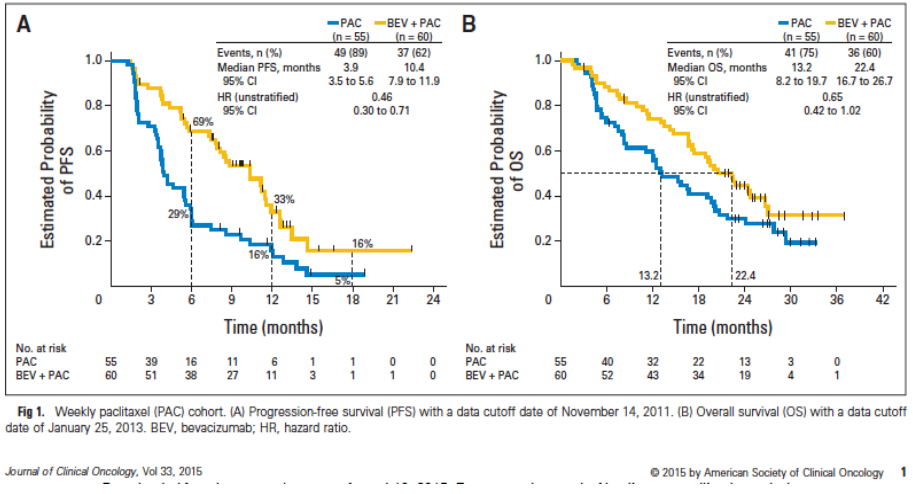


Fig 1. Weekly paclitaxel (PAC) cohort. (A) Progression-free survival (PFS) with a data cutoff date of November 14, 2011. (B) Overall survival (OS) with a data cutoff date of January 25, 2013. BEV, bevacizumab; HR, hazard ratio.

Journal of Clinical Oncology, Vol 33, 2015

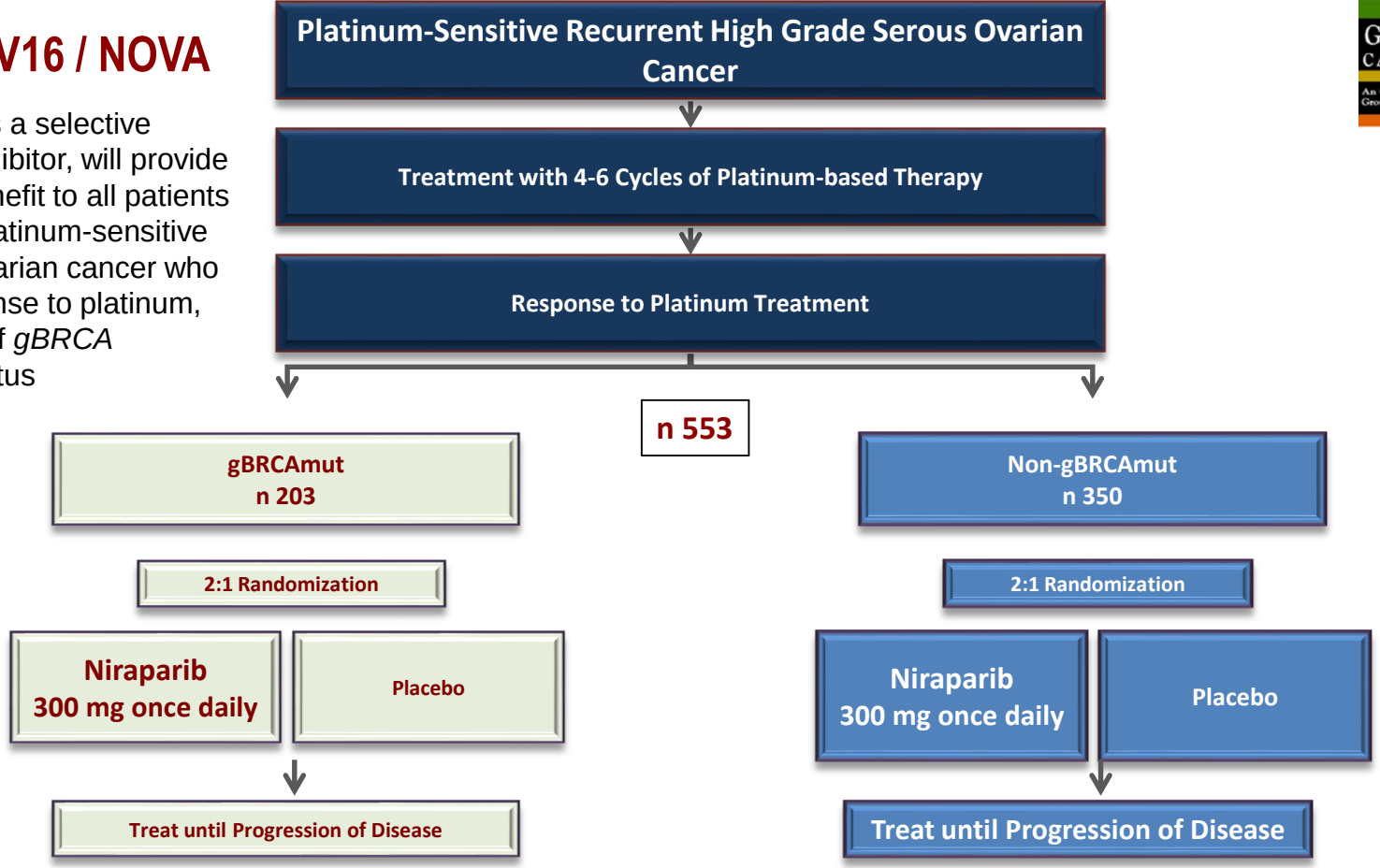
AURELIA: Analisys by chemotherapy cohort.
PACBev vs PAC OS HR: 0,65

Pujade-Lauraine E et al. J Clin Oncol 2014

Poveda A et al. J Clin Oncol 2015

ENGOT-OV16 / NOVA

Niraparib, as a selective PARP1/2 inhibitor, will provide a clinical benefit to all patients who have platinum-sensitive recurrent ovarian cancer who are in response to platinum, regardless of *gBRCA* mutation status



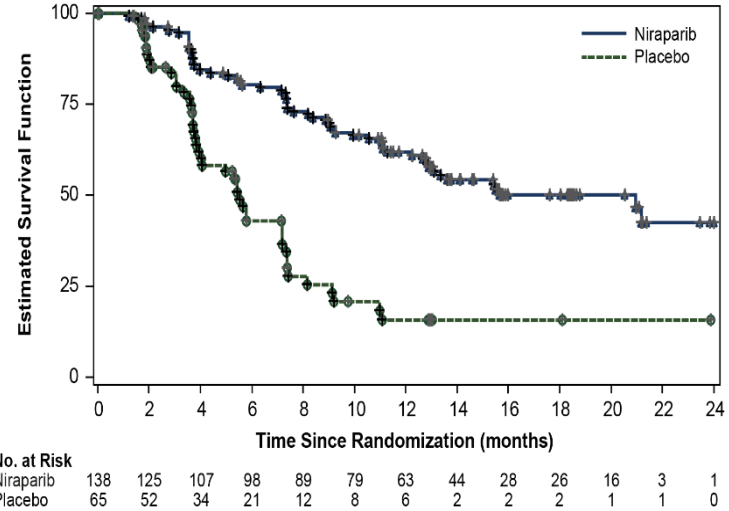
Mirza MR et al. N Engl J Med 2016;375:2154-64

ENGOT-OV16 / NOVA: PFS

Phase 3 randomised trial of maintenance niraparib in platinum-sensitive high-grade serous relapse OC

PFS: gBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	**21.0** (12.9, NE)	**0.27** (0.173, 0.410) p<0.0001	62%	**50%**
Placebo (N=65)	**5.5** (3.8, 7.2)		16%	16%



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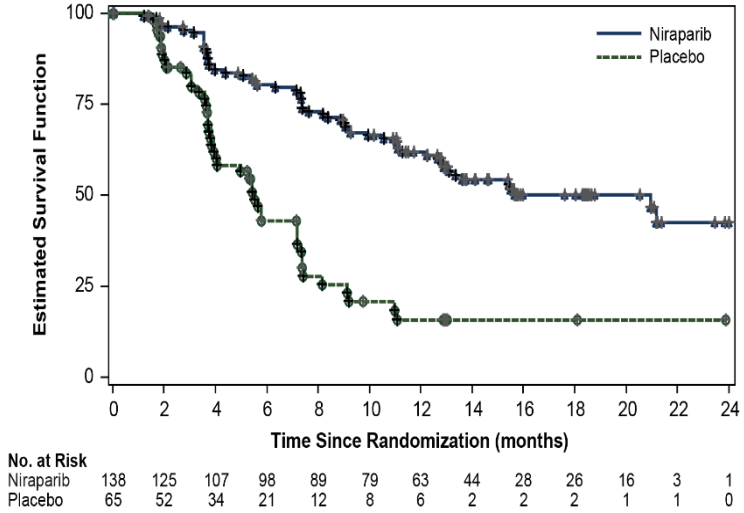
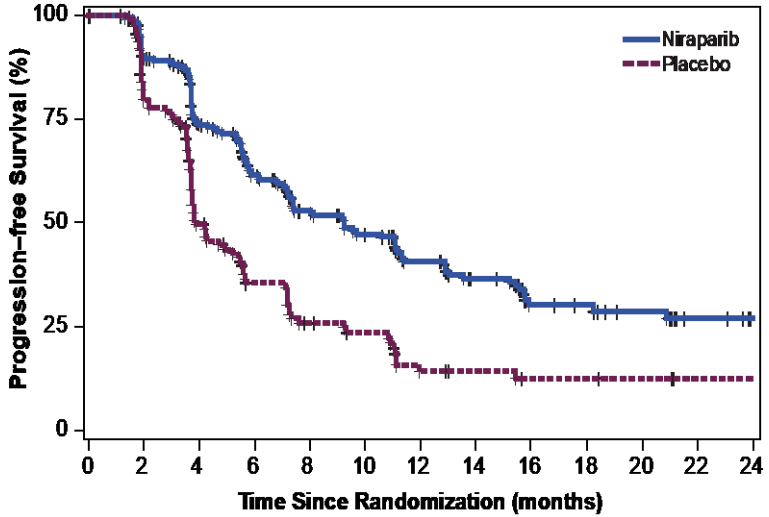


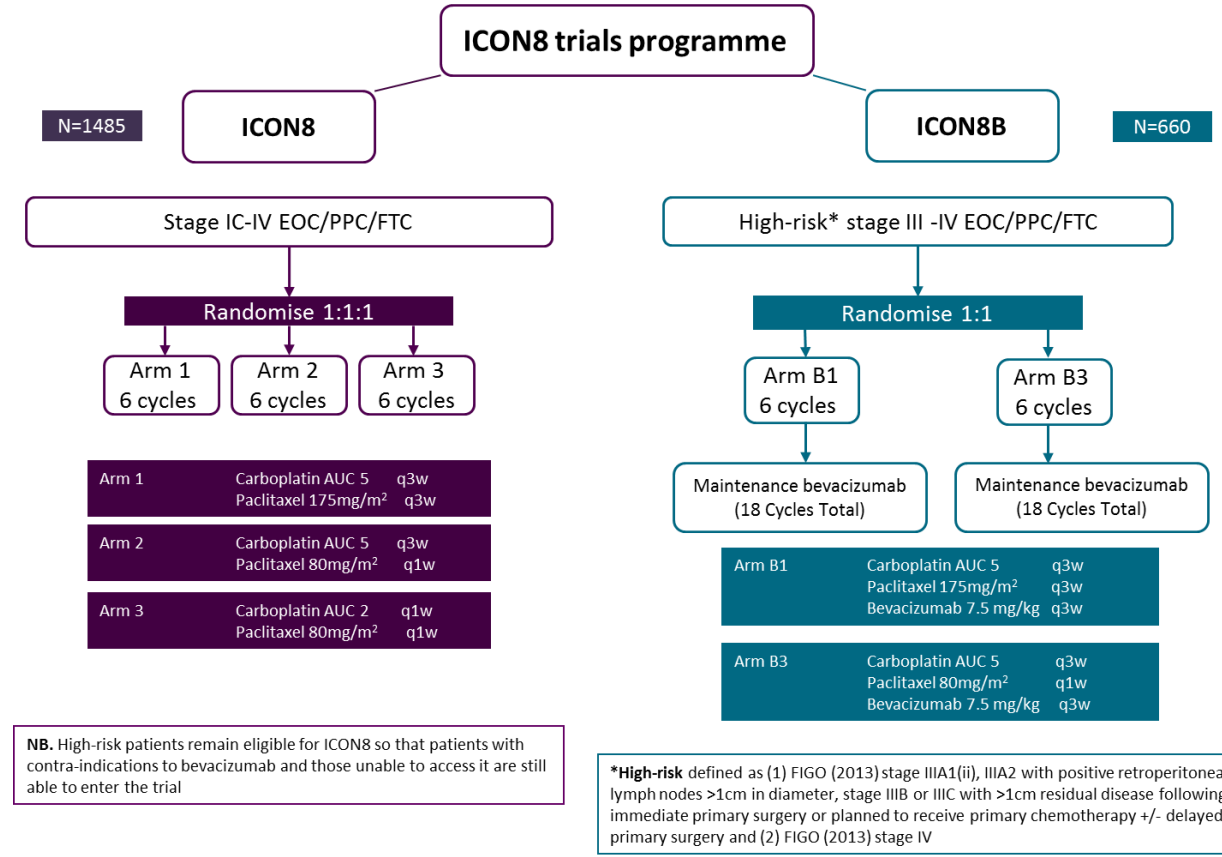
PFS: non-gBRCAmut

Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=234)	**9.3** (7.2, 11.2)	**0.45** (0.338, 0.607) p<0.0001	41%	**30%**
Placebo (N=116)	**3.9** (3.7, 5.5)		14%	12%



Mirza MR et al. N Engl J Med 2016;375:2154-64

ICON 8 Design

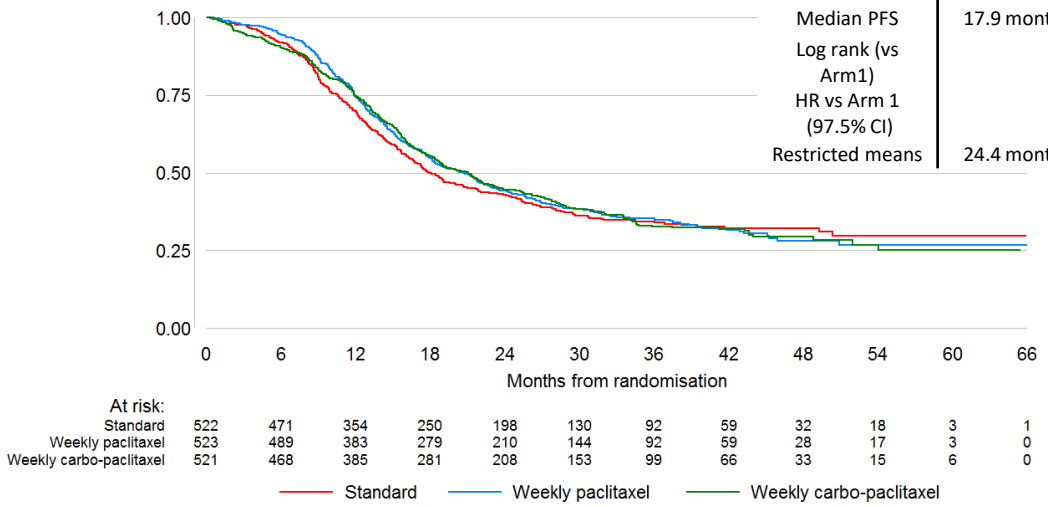


NB. High-risk patients remain eligible for ICON8 so that patients with contra-indications to bevacizumab and those unable to access it are still able to enter the trial

***High-risk** 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

ICON 8 PFS

ICON8 Progression Free Survival



Total Patients	Arm 1 Standard N=522	Arm 2 Weekly paclitaxel N=523	Arm 3 Weekly carbo-paclitaxel N=521
Progressions	330 (63%)	335 (64%)	338 (65%)
Median PFS	17.9 months	20.6 months	21.1 months
Log rank (vs Arm1)		p=0.45	p=0.56
HR vs Arm 1 (97.5% CI)		0.92 (0.77, 1.09)	0.94 (0.79, 1.12)
Restricted means	24.4 months	24.9 months	25.3 months

- Accrual began 6th June 2011 and ICON8 pathway closed to recruitment 28th November 2014
- Final recruitment figure = **1566**
- UK= 1397, ANZGOG= 70, GICOM= 43, KGOG= 32, ICORG= 24
- Primary PFS analysis presented at ESMO 2017. **Conclusions:** although weekly dose-dense chemotherapy can be delivered successfully as first-line EOC treatment without substantial toxicity increase, it does not significantly improve PFS compared to standard 3-weekly CT.

SURGERY

Role of Surgery at Relapse
AGO-OVAR DESKTOP III

AGO-OVAR OP.4

AGO-DESKTOP OVAR III

ENGOT-ov20

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ENGOT model A
Sponsor AGO Study Group

n=408 Pts with

+ AGO-Score

Stratification:

Platinum-free-interval

6-12 vs > 12 months

1st line platinum based ctx: yes vs no

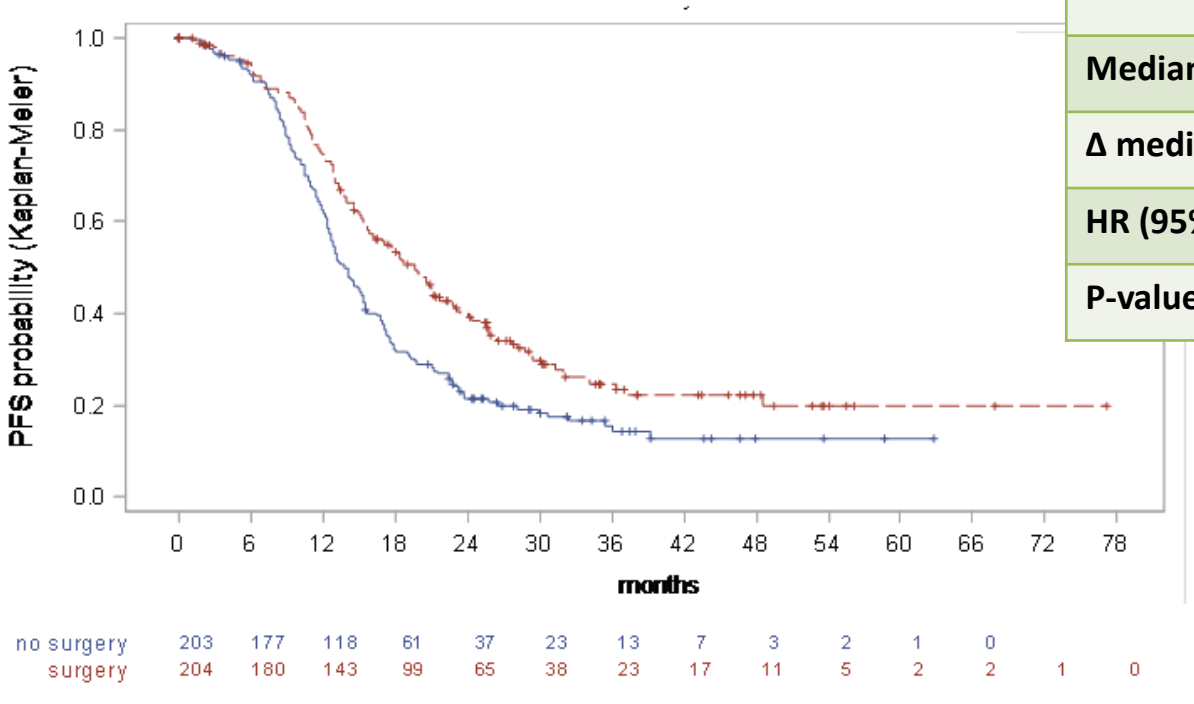
R A N D O M

- Cytoreductive surgery
- no surgery

→ platinum-based chemotherapy* recommended

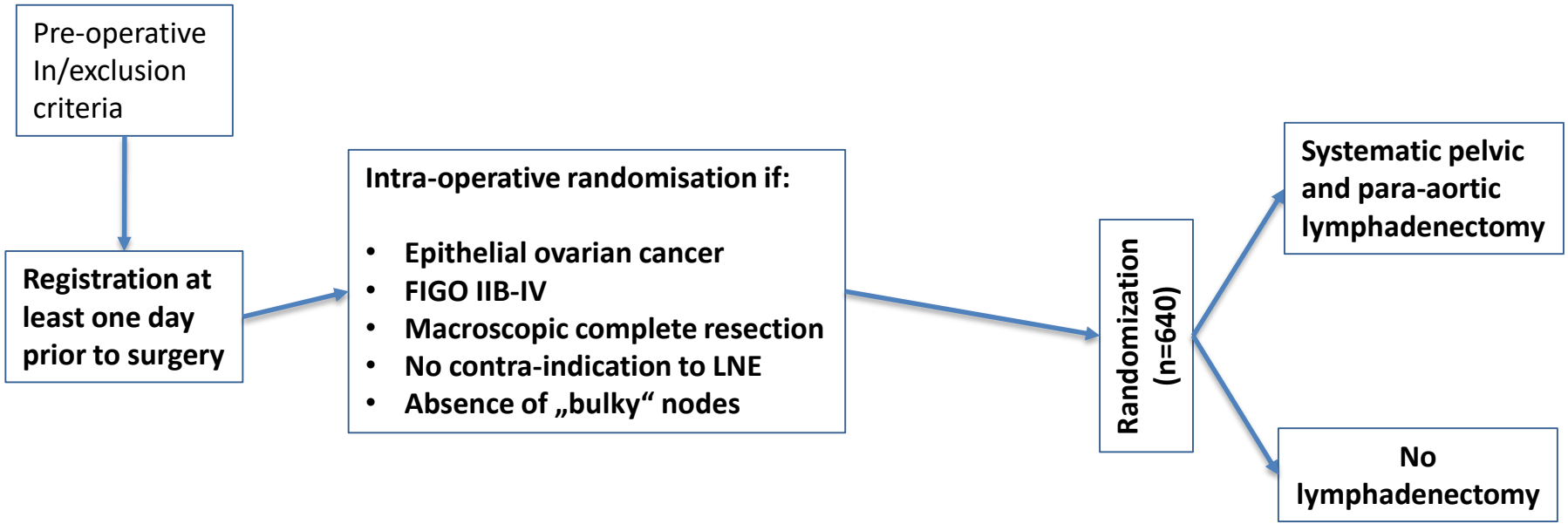
* Recommended platinum-based chemotherapy regimens:
- carboplatin/paclitaxel
- carboplatin/gemcitabine
- carboplatin/pegliposomal doxorubicin
-or other platinum combinations in prospective trials

AGO DESKTOP III
PFS, ITT population



	Surgery	No surgery
Median PFS	19.6 mos	14.0 mos
Δ median PFS	5.6 mos	
HR (95% CI)	0.66 (0.52 – 0.83)	
P-value	< 0.001	

AGO-OVAR OP.3 / LION
Design

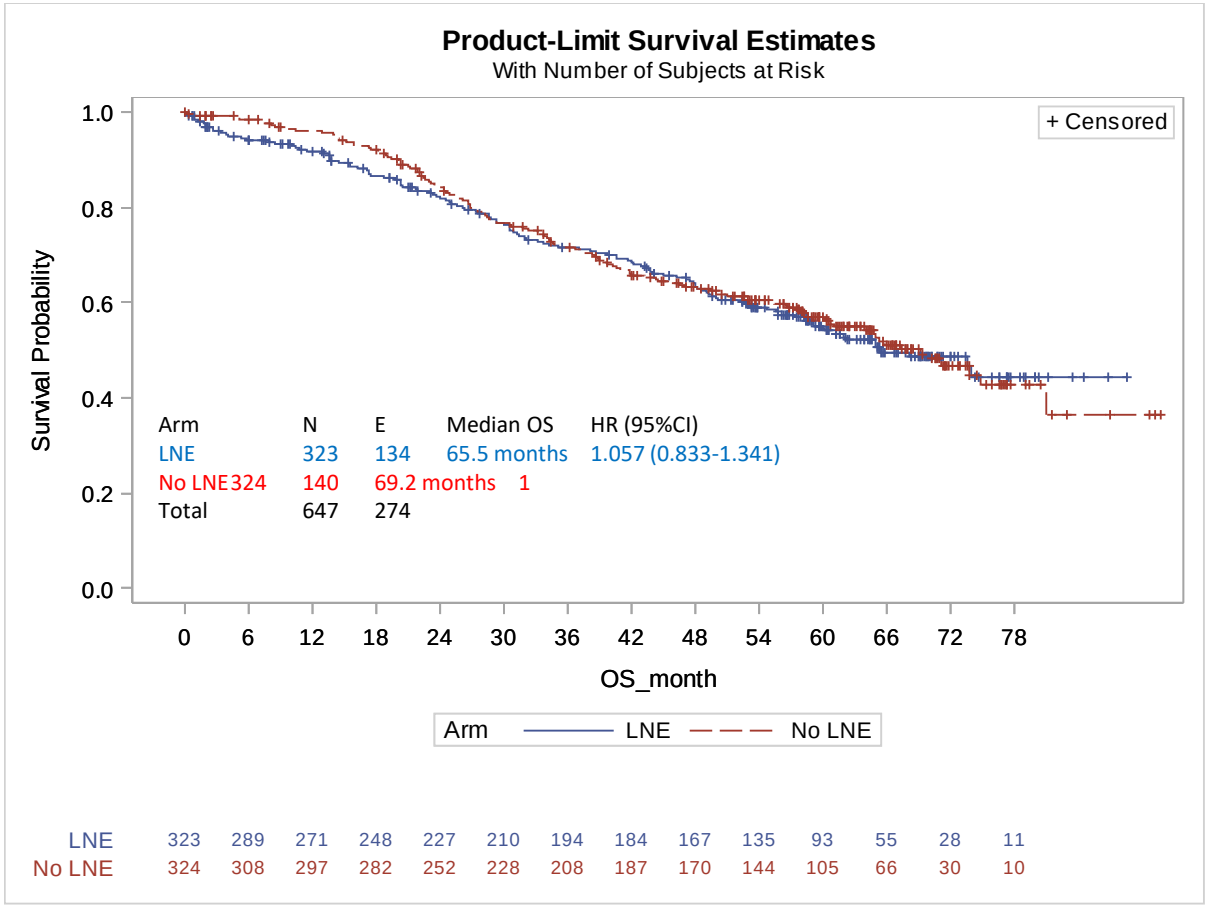


Sponsor(s) Philipps-Univ. Marburg
Supported by the Deutsche Forschungsgemeinschaft
Leading Group AGO Study Group

Final No. of pt 650

Strata:
- Center
- Age
- PS ECOG

AGO-OVAR OP.3 / LION
Primary endpoint OS



Stratified Log-Rank Test (Strata Age >60J vs <=60J und ECOG 0 vs >0): p=0.65

Leading to The New Standard of Care

- GOG-218 & ICON-7
- Calypso
- Aurelia
- ENGOT-OV16/ NOVA
- DESKTOP III
- LION
- ICON 8

May Change the Standard of Care

- ***OVAR 17***
- ***iPOC***
- ***PAOLA 1***
- ***Prima***
- ***IMagyn050***
- ***OREO***
- ***NRG GY004***
- ***NRG GY009***
- ***NSGO-UMB1***

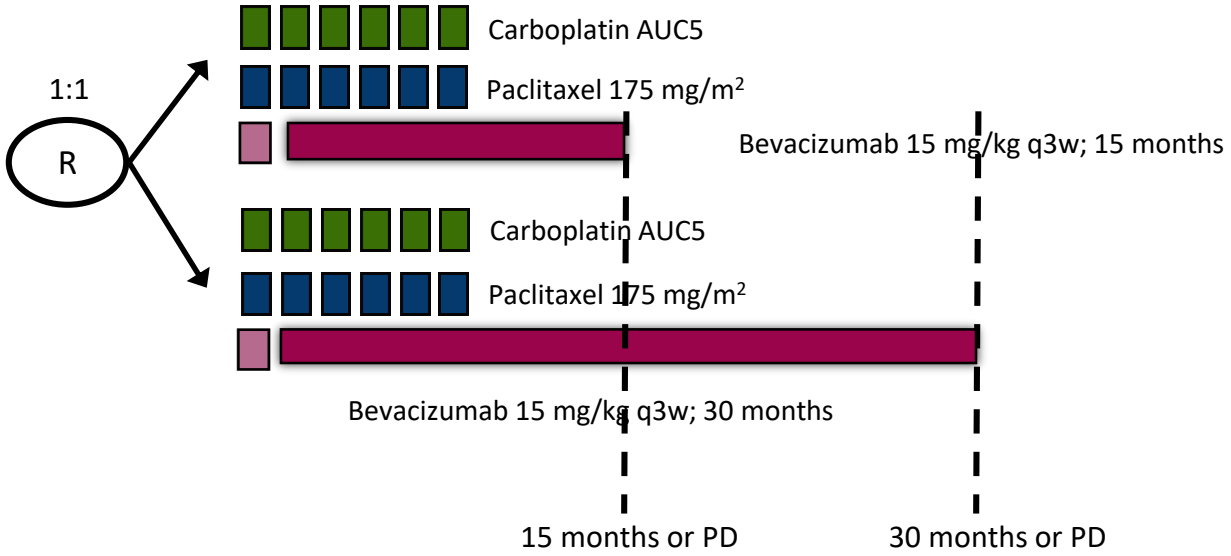
Planned Trials

- ***FIRST***
- ***AVANOVA IMMUNE 1***
- ***NRG OV 1719***

Duration of Bevacizumab therapy
AGO-OVAR-17; ENGOT-OV-15

- FIGO stage IIB–IV
- PDS or biopsy
- histologically confirmed OC

N=796



IV or IP therapy
iPocc Trial

Stage II to IV
Ovarian cancer

Including
Suboptimal/Exploratory
Laparoscopy Cases
IDS Allowed

RANDOMIZE

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

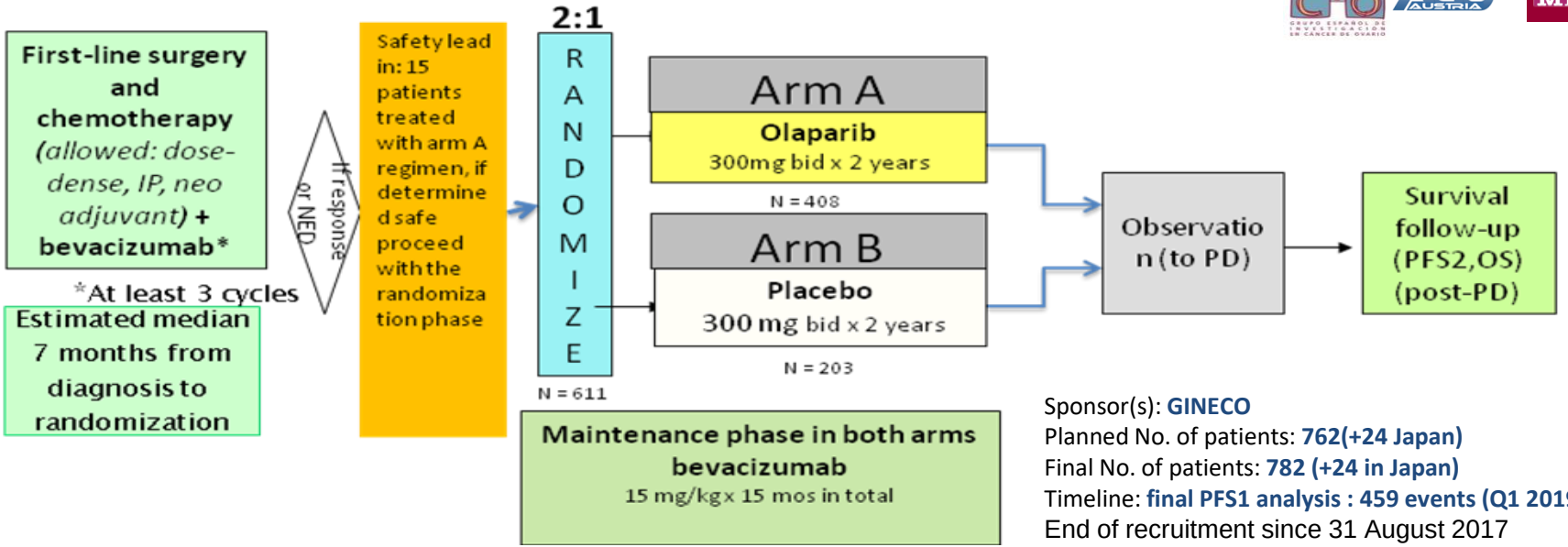
Paclitaxel 80 mg/m^2/1h IV, weely, Cycles 1-6
Carboplatin AUC 6 IP, Day 1, Cycles 1-6

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

PAOLA 1 / ENGOT-OV25

Platine, Avastin and OLAparib in 1st line of advanced high grade epithelial OC

- **Olaparib tablets administered at 600 mg daily for up to 2 years.**



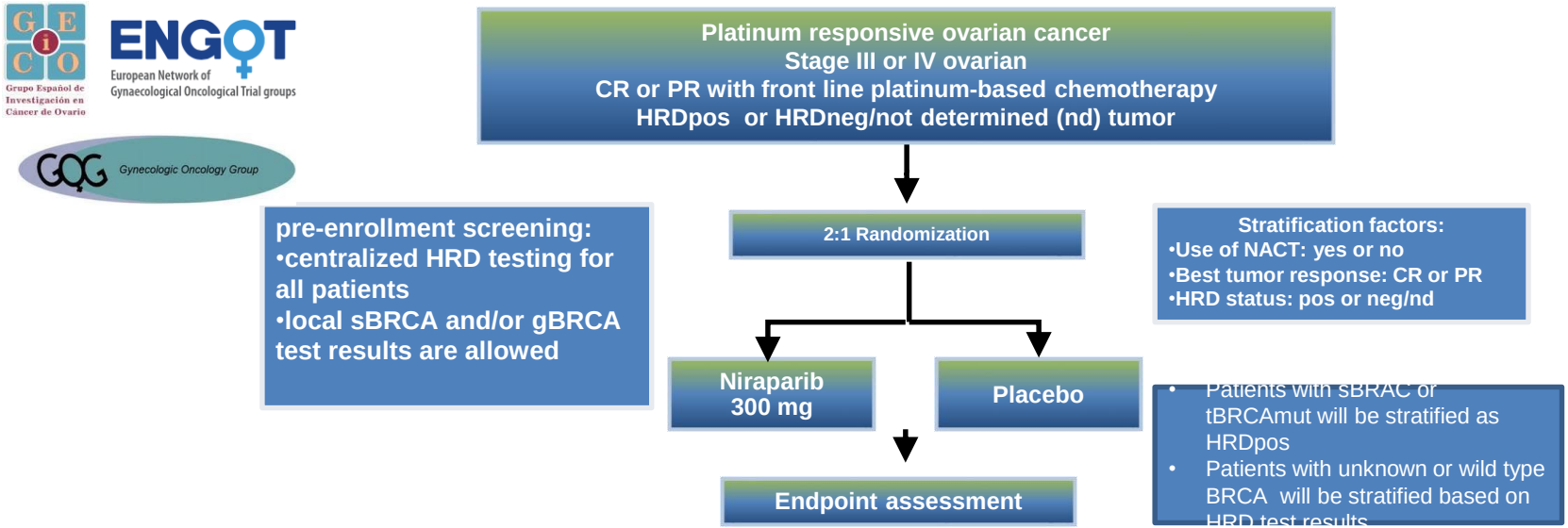
Sponsor(s): **GINECO**
Planned No. of patients: **762(+24 Japan)**
Final No. of patients: **782 (+24 in Japan)**
Timeline: **final PFS1 analysis : 459 events (Q1 2019)**
End of recruitment since 31 August 2017

Stratification factors:

First-line treatment outcome (complete resection after initial surgery and NED at screening, complete resection at interval debulking surgery and NED at screening, incomplete resection at initial or interval debulking surgery and in CR at screening, PR at screening) & gBRCA status (yes, no, unknown)

ENGOT-OV26 / PRIMA

Niraparib Maintenance Treatment in Patients with HRD-Positive OC



Primary Endpoint	PFS in HRDpos patients; hierarchical analysis for all patients regardless of HRD status
Key Secondary Endpoints	Overall survival (OS), patient reported outcomes (PRO's), time to first subsequent treatment, progression- survival-2 , time to CA-125 progression, safety and tolerability of study therapy

HRD=homologous recombination deficiency; CR=complete response; PR=partial response; PFS=progression-free survival;

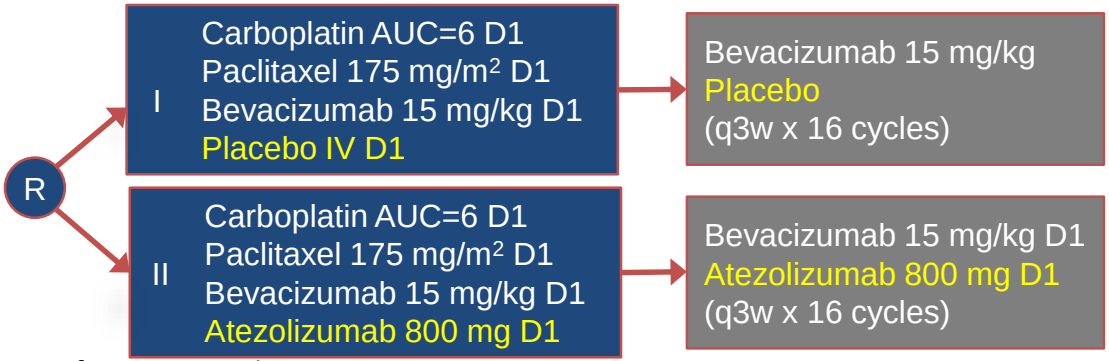
GOG 3015

CP + Bevacizumab +/- Atezolizumab

(Global)

YO39523/GOG-3015/ENGOT-ov39

- Previously untreated high-grade cancer
- Stage III macroscopic or Stage IV (allows election of NACT), Bx cohort
- Stratification PDL1 0 vs 1+, Stage, PS, NACT
- Co-Primary endpoints (PDL1+): OS HR 0.72 (81%, 0.046), PFS HR 0.7

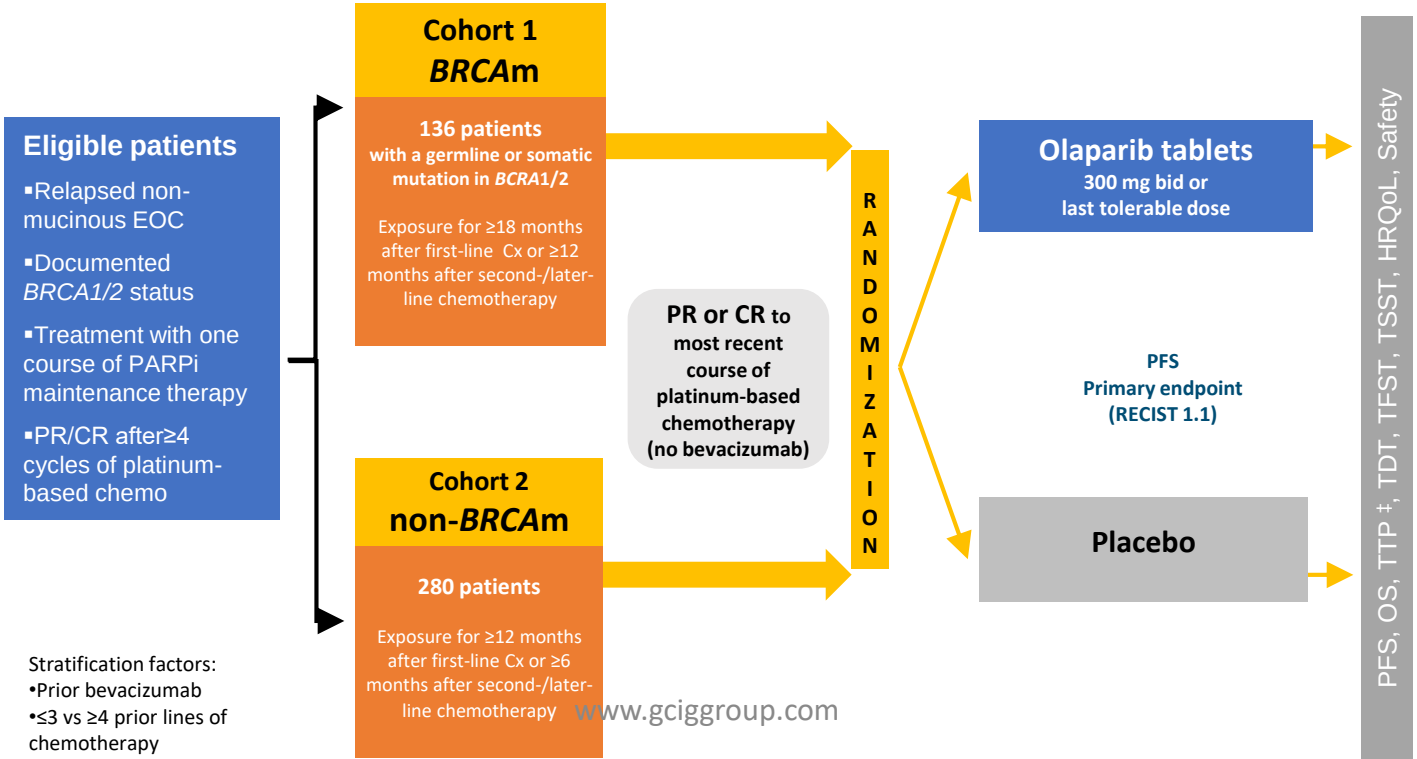


Moore K and Pignata S, for GOG-F and ENGOT

Open:	MAR 2017
Status:	Ongoing Accrual
Target:	1300 pts
Notes:	Joint protocol steering committee (GNE, GOG-F, ENGOT)

OReO – ENGOT-Ov38

Olaparib Retreatment in late recurrent Ovarian cancer



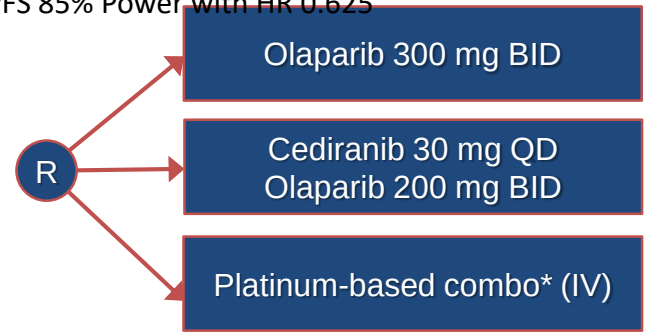
www.gciggroup.com

NRG GY004

Olaparib *vs* Olaparib-Cediranib *vs* PCT

(US, Canada, Japan, Korea)

- Recurrent HGSC with PFI > 6 months (following most recent platinum)
- No more than 3 prior regimens (including primary therapy)
- RECIST measurable or evaluable disease with accessible tumor
- No prior PARPi therapy, prior bevacizumab permitted
- Stratify for BRCA status, number of prior treatment regimens
- Primary endpoint: PFS 85% Power with HR 0.625



*Carboplatin + gemcitabine or paclitaxel or PLD

Open:	FEB 2016
Status:	Ongoing Accrual
Target:	550 pts (135 BRCA1/2 +)
Notes:	Anticipate closure NOV2017

NRG ONCOLOGY
Advancing Research. Improving Lives.™

(US PIWG)

NRG GY009 (NCT02839707)
PLD +/- Bevacizumab +/- Atezolizumab

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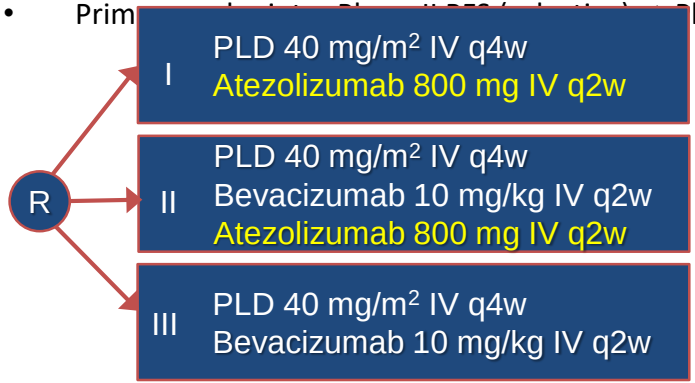
- Recurrent high-grade with PFI < 6 months (following most recent platinum)
- No more than 2 prior regimens (including primary therapy)
- RECIST measurable or evaluable disease with accessible tumor
- No prior anti-angiogenic therapy for platinum-resistant recurrence
- Prim[illegible] Phase III OS



HR PFS	≤ 0.783 (88% power)
HR OS*	≤ 0.625 (90% power)

*one-tail α 0.0115
(multiple comparisons)

Open:	MAY 2017
Status:	Ongoing safety lead-in (Phase I Working Group)
Target:	272 Phase II, Cumulative 488 Phase III
Notes:	Anticipate Group-wide activation JAN2018

A phase II umbrella trial in patients with relapsed ovarian cancer

NSGO-OV-UMB1
ENGOT-OV30 / NSGO

EudraCT number: 2017-002805-36

Sponsor: NSGO

Study Chair: Mansoor Raza Mirza

Participating groups & Lead PIs:

NSGO:	MR Mirza
SGCTG UK:	C Gourley
PMHC Canada:	A Oza
BGOG Belgium:	I Vergote
ANZGOG Australia:	M Friedlander
COGI US:	J Barek
GOTIC Japan:	K Fujiwara
KGOG S Korea	SY Ryu
NOGGO Germany:	Jalid Sehouli

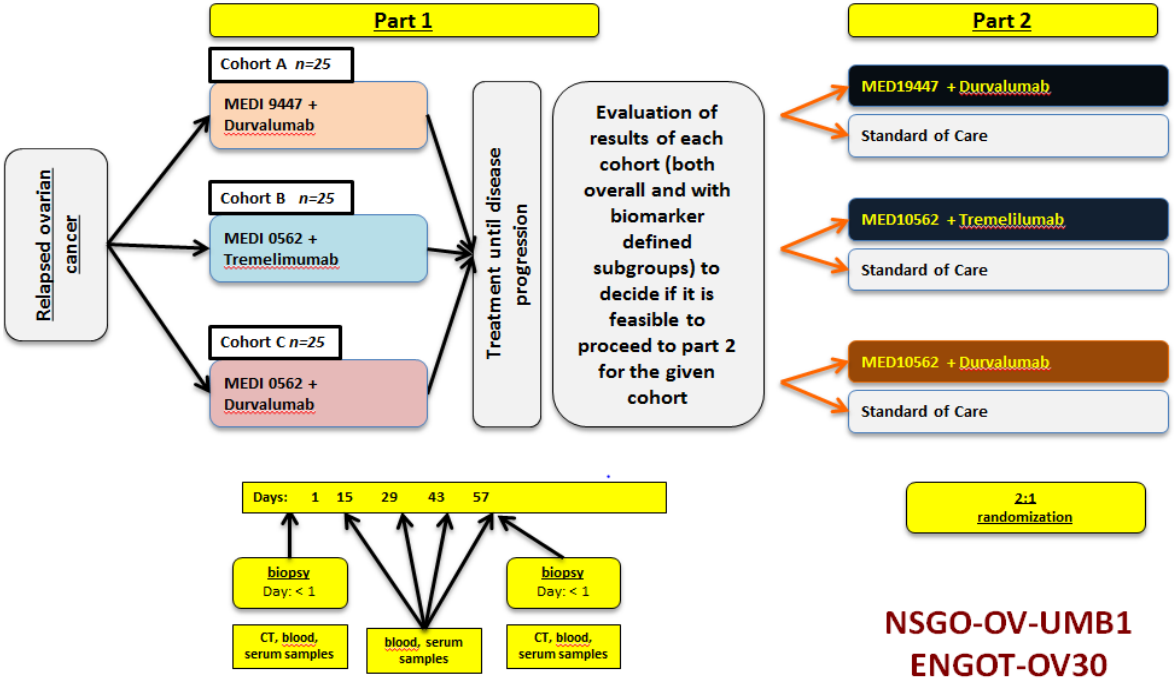
Study Status

- Cohort A submitted (DKMA, EC) in DK
- Submission in NOR, FIN, SWE in Q4 17
- Expected FPI: Jan 18

Cohort B (SGCTG UK), submission end Q1 18

- Cohort C (PMHC Canada), submission Q3 18

NSGO-OV-UMB1
ENGOT-OV30 / NSGO
UMBRELLA



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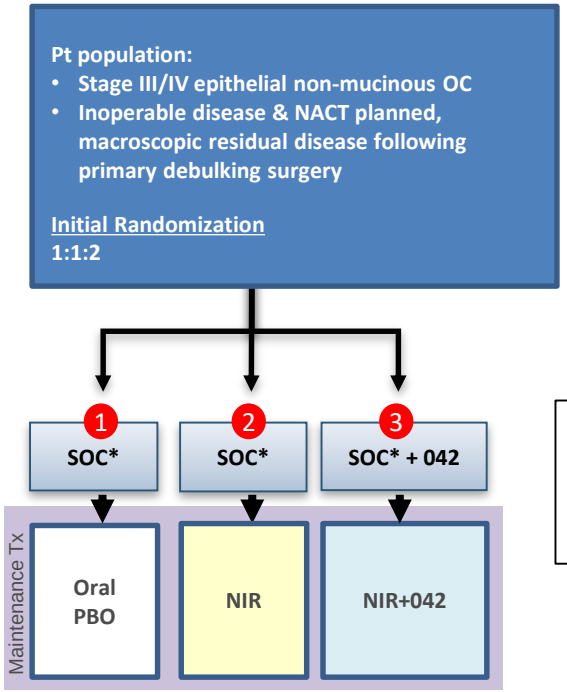
- ***AVANOVA IMMUNE 1***
- ***NRG OV 1719***

ENGOT-OV44 / GINECO / FIRST

First-line ovarian cancer treatment with Niraparib plus TSR-042

Study Schema



Stratification factors

- tRCA/HRD status (test to be determined)
- Concurent use of bevacizumab
- ECOG PS OR REGION?

Primary endpoint: PFS

SOC: Standard chemotherapy with paclitaxel/carboplatin ± bevacizumab and bevacizumab maintenance per local

- **Niraparib dose: 200 mg once daily**
  No PBO for 042
  screening for first cycle; randomization at 2nd cycle

ENGOT European Network of Gynaecological Oncological Trial groups

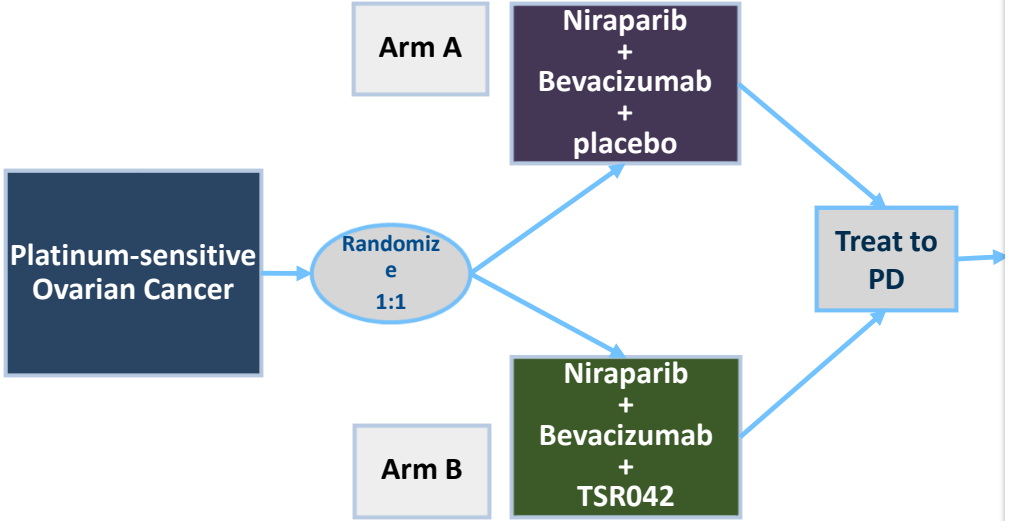
GYNECOLOGIC CANCER INTERGROUP An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

GINECO

TESARO

ENGOT-OV42-NSGO / AVANOVA-Immune1
Multicenter, Double-blind, Phase 2 Randomized Trial

Part 1: n=238

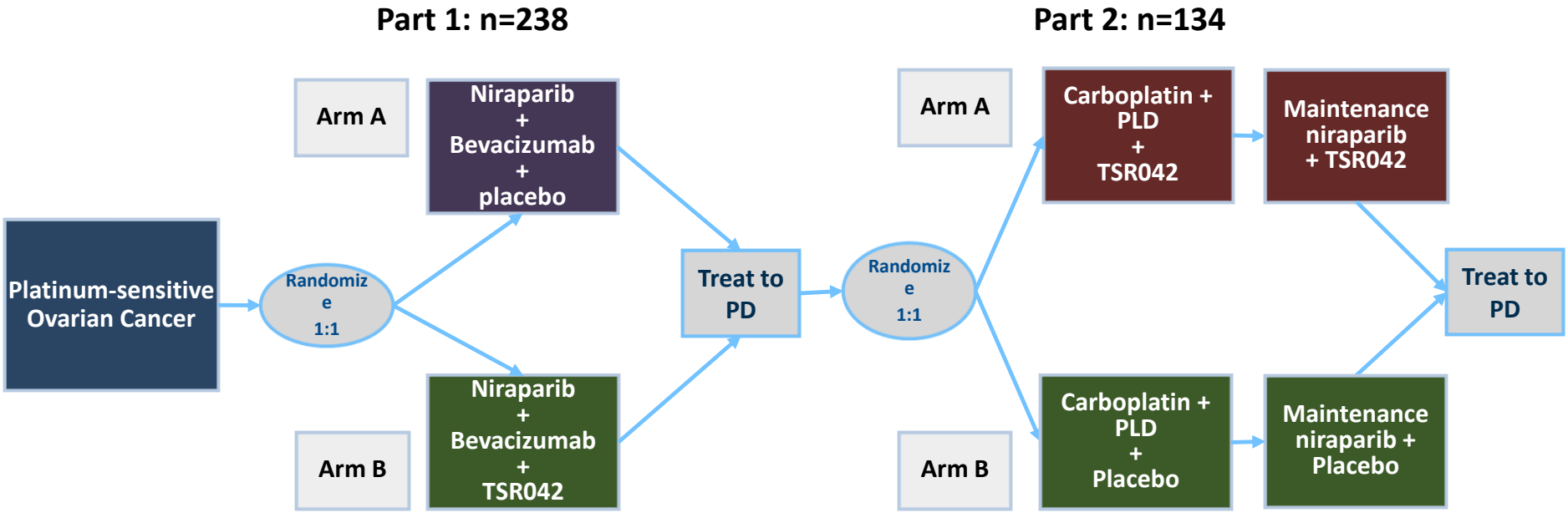


Stratification factors Part 1

- BRCAmut vs BRCAwt
- Chemotherapy-Free Interval: 6-12mo vs >12 mo

Mirza MR, for NSGO

ENGOT-OV42-NSGO / AVANOVA-Immune1
Multicenter, Double-blind, Phase 2 Randomized Trial



Stratification factors Part 1

- BRCAmut vs BRCAwt
- Chemotherapy-Free Interval: 6-12mo vs >12 mo

Stratification factors Part 2

- BRCA status
- Duration of treatment in part 1: 0-6mo vs >6 mo

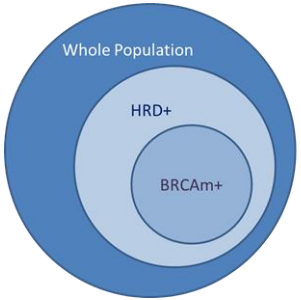
Mirza MR, for NSGO

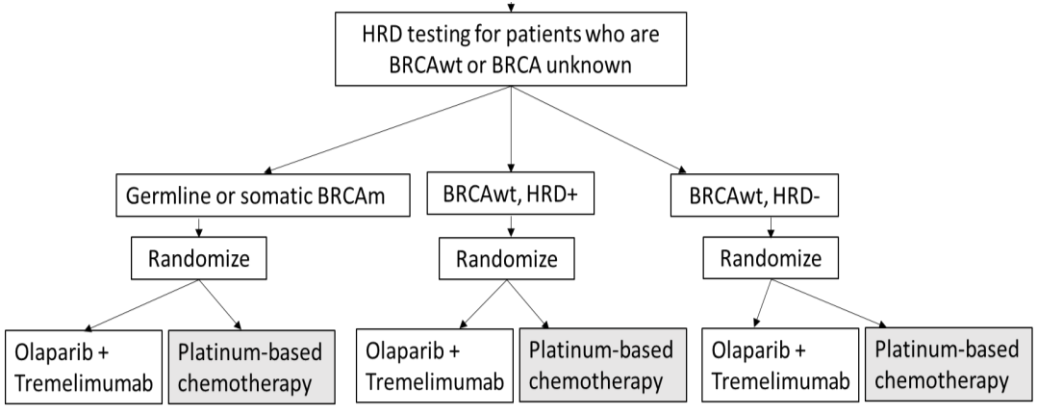
NRG Concept OV1719

Olaparib-Tremelimumab *vs* PCT

(Group-Wide)

- Recurrent HGSC with PFI > 6 months (following most recent platinum)
- No more than 3 prior regimens (including primary therapy)
- RECIST measurable disease
- No prior PARPi therapy or immune checkpoint inhibitors
- Primary endpoint: PFS (pre-specified sequential analysis by whole population and subgroups)





Status: Concept in planning
Target: 420 pts (126 BRCAm+, 168 HRD+, 126 HRD-)
Notes: OTF review 20-OCT-2017 then GCSC

JOIN GCIG
Gynecologic Cancer InterGroup