Gynecologic Cancer InterGroup (GCIG)  
Ovarian Cancer Committee  
Wednesday, May 30, 2018, 1:30pm-3:00pm  
Palmer House Hilton, Chicago  

Chair: Antonio Gonzalez    Co-Chair: Aikou Okamoto
Closed and Published Trials
AGO-OVAR OP.3/LION
ENGOT Ov-31
Status Closed

ENGOT model: A
Sponsor: Philipps-Univ. Marburg
Supported by the Deutsche Forschungsgemeinschaft

Leading Group: AGO Study Group
Final No. of patients: 650
Timelines: FPI Dec 2008; LPI Jan 2012; LPO Apr 2016; trial closing 2017
Publications: ASCO 2017 Abstract presented (Harter et al.)
Practice changing results

Planned publications: Manuscript provided to co-authors for review; submission is planned soon
Planned substudies: tbd
ICON8 trials programme

Stage I-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
Pacitaxel 175mg/m² q3w

Arm 2
Carboplatin AUC 5
Pacitaxel 80mg/m² q3w

Arm 3
Carboplatin AUC 2
Pacitaxel 80mg/m² q1w

High-risk stage III-IV EOC/PPC/FTC

Randomise 1:1

Arm B1 6 cycles
Arm B2 6 cycles
Arm B3 6 cycles

Arm B1
Carboplatin AUC 5
Pacitaxel 175mg/m² q3w
Bevacizumab 7.5 mg/kg q3w

Arm B2
Carboplatin AUC 5
Pacitaxel 80mg/m² q1w
Bevacizumab 7.5 mg/kg q1w

Arm B3
Carboplatin AUC 5
Pacitaxel 80mg/m² q1w
Bevacizumab 7.5 mg/kg q1w

Maintenance bevacizumab (18 Cycles Total)

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

*High-risk defined as {1} FiGO (2013) stage IIIA(i), IIIB 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 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.
Trial setting: Maintenance 1st line with Niraparib

Patients: stage IV, stage III with macroscopic RD after PDS, and Stage III after NACT and IDS regardless residual disease

Study Design: ENGOT MODEL C

Sponsor(s): TESARO

Lead Group: GEICO (PI: A. González-Martín)

Planned No. of patients: 630 (Amendment 3)

End recruitment: may 2018 (646 patients)
AGO-OVAR 17
ENGOT Ov-15 Trial
Study Design

ENGOT model A
Sponsor AGO Study Group

No. Pts.: n = 900 planned / 927 randomized
First Patient In: 11-Nov-2011
Last Patient In: 06-Aug-2013
Enrolment Period: 22 months
Primary PFS analysis: after 697 events (~ Q4 2018)

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

1:1
N= 900

Bevacizumab 15mg/kg q21 days
Paclitaxel 175 mg/m²
Carboplatin AUC5 q21 days
15 months = 22 cycles

30 months = 44 cycles
Sponsor(s): **GINECO**

Planned No. of patients: **762 (+24 Japan)**

Final No. of patients: **782 (+24 in Japan)**

Timeline: **final PFS1 analysis: 458 events (summer 2018)**

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End of recruitment since 31 August 2017
PAOLA-1 status (15/05/2018)

Next steps:

- Steering Committee on 2\textsuperscript{nd} of June, at ASCO
- **Collection of all tumor blocks** at investigator sites by the end of June 2018
- Collection of blood samples at investigator sites by the end of September 2018
- **Cleaning of data in eCRF, ongoing**, for PFS1 analysis expected in Q4 2018
- 12th Substantial Amendment expected at the end of June/beginning of July 2018
- Translational Research: discussion ongoing
AGO-OVAR OP.4
AGO-DESKTOP OVAR III
ENGOT-ov20

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

Cytoreductive surgery

platinum-based ctx* recommended

no surgery

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

Status 28th March 2018
192 of 244 OS events observed

First Patient in 14-Jul-2010
Last Patient in 25-Mar-2015
Enrolment period 58 months

Interim analysis presented at ASCO 2017
OS follow-up ongoing
Final OS analyses ~ 2019
ENGOT model A
Sponsor AGO Study Group

Bevacizumab 15mg/kg q3w until PD
Gemcitabine 1000 mg/m² d1 and 8
Carboplatin AUC 4 d 1 q3w

Bevacizumab 10mg/kg q2w

Bevacizumab 15mg/kg q3w until PD
Pegylated Liposomal Doxorubicin 30 mg/m² d1
Carboplatin AUC 5 d1 q4w

No. pts : 654 planned/ 682 randomized
First Patient In: 01-Aug-2013
Last Patient In: 31-Jul-2015
Enrolment Period: 24 months
Primary PFS analysis: Events reached; primary PFS analysis is ongoing;
Abstract submitted to ESMO 2018

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)
❖ group language
A multicenter phase III randomized study with second line chemotherapy ± bevacizumab in patients with platinum sensitive epithelial ovarian cancer recurrence after a bevacizumab/chemotherapy first line

Non profit Sponsor: NCI Naples

Lead groups: MITO MaNGO

Final No. of patients: 406


Primary results: ASCO 2018 oral session

Translational: Q4 2018

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N. Patients</th>
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<tbody>
<tr>
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</table>
**Closed Trial – status update**

**MITO 8; ENGOT Ov-1**

A phase III international multicenter randomized study testing the effect on survival of prolonging platinum-free interval in patients with ovarian cancer recurring between 6 and 12 months after previous platinum based chemotherapy

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Nonprofit Sponsor: **NCI Naples**, MITO lead

Final No. of patients: **215**

Timeline: **FPI 1/2009** **LPI 10/2015**

Publications: Primary results


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### Enrollment by Group

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<td><strong>Total</strong></td>
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Phase III international, randomised 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.

Relapsed partially platinum sensitive Ovarian Cancer after end of 1st or 2nd-line platinum therapy

Group A: PLD 30 mg/m² + Carboplatin AUC 5 q4wks

At PD, subsequent platinum rechallenge is mandatory

Group B: PLD 30 mg/m² + Trabectedin 1.1 mg/m² q3wks

At PD, subsequent therapy at investigator discretion

Up to 6 cycles or PD

RECIST tumor evaluation at 12 and 24 weeks

Primary Endpoint: Overall Survival

Primary analysis: Intention to treat, 442 events/588 patients
Phase III international, randomised 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.

**Accrual closed September 2017**

117 enrolling sites/618 patients overall

**Next steps:**

Second Interim Analysis
September 2018

Final Analysis ~ July–August 2020
Phase 3 Randomized Double-Blind Trial of Maintenance with Niraparib

Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer

Study Design:

No. of patients: 553

Publications:

N Engl J Med

N Engl J Med

Annals of Oncology
Berek J et al. Ann Oncol 2018

Lancet Oncology
Quality of life in recurrent ovarian cancer patients treated with niraparib: results from the ENGOT-OV16/NOVA trial, Accepted
Study of OLaparib in Ovarian Cancer

Trial setting: **Platinum Sensitive Relapsed High grade serous ovarian cancer with a BRCA mutation or high grade endometrioid cancer**

Study Design: **A Phase III, Randomised, Double Blind, Placebo Controlled**

Sponsor(s): **AstraZeneca – GINECO Leading Group**

Final No. of patients: **295**


Publications: **Lancet Oncology July 2017**

Planned publications and substudies: **14 substudies in discussion – meeting with AZ at ASCO**
NRG GY004 (NCT02446600) Olaparib vs Olaparib-Cediranib vs PCT

(US, Canada, Japan, Korea)

Closed Trials – status update

Olaparib
vs
Olaparib-Cediranib vs PCT

- 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

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

Liu J, for NRG Oncology
NRG GY015 (NCT02122185)
NACT +/- Metformin

(Group-Wide)

- Epithelial ovarian, peritoneal, or fallopian carcinoma (EOPFC)
- Stage IIIC-IV and suitable for NACT with interval cytoreductive surgery
- No known diabetes or use of metformin
- Primary Endpoints: PFS and molecular/metabolic targeting

Open: JUN 2014
Status: Ongoing Accrual (U Chicago SPORE)
Target: 76 pts
Notes: Not Approved by NCI for Group-wide activation

Yamada D, for NRG Oncology and U Chicago SPORE
Ongoing trials
SUNNY TRIAL: Study of Upfront Surgery versus Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery for Patients with Stage IIIC and IV Ovarian Cancer

Trial setting: Ovarian cancer/stages IIIC and IV

Sponsor: SGOG

Group name: SGOG, KOG, JOG
Primary endpoint
  OS
Secondary endpoints
  PFS
  30-day post-operative complications
  QOL
  TFIs
  Long-term survival of IP

Open: Nov. 2015
Closed: Nov. 2020
Target accrual: 456
Current accrual: 173 (ITT)
updated on May 15, 2018
ENGOT model A
Sponsor AGO Study Group

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: Site, age-ECOG combination (EGOG 0 + age up to 65 y vs. ECOG >0 + 66y and older)
• Defined selection process for sites with high operative quality (minimum of 36 debulking-surgeries per year, complete resection rate at least 50%)

Recommended treatment: 6x Carboplatin/Paclitaxel + Bev
Also permitted: TC with weekly Paclitaxel (JGOG Regime) or TC without Bev or study participation, if treatment balanced in both arms
### T*R*U*S*T

#### Recruitment status 11.05.2018
388/686 patients randomized and eligible* (= 56.5 %)

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<thead>
<tr>
<th>Country</th>
<th>Sites (15 SIVs / 15 active)</th>
<th>Group</th>
<th>PI</th>
<th># pts screened</th>
<th># pts randomized</th>
<th># pts eligible*</th>
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* Status of February 7, 2018 (preliminary information; eligibility check via QA Board is ongoing)
YO39523/GOG-3015/ENGOT-ov39 (Joint International Steering Committee)

- 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

**Open:** MAR 2017
**Status:** Ongoing Accrual (NACT cohort closed)
**Target:** 1300 pts
**Notes:** NACT cohort closed MAY 2018 (20% cap)

Moore K and Pignata S, for GOG-F and ENGOT
Ongoing Trials – status update

NRG GY007 (NCT02713386)
NACT +/- Ruxolitinib
(US PIWG)

- Epithelial ovarian, peritoneal, or fallopian carcinoma (EOPFC)
- Stage IIIC-IV and suitable for NACT with interval cytoreductive surgery
- Phase I to evaluate acute toxicity (C1) and cumulative tolerability
- Maintenance ruxolitinib permitted in patients tolerating concurrent therapy (Phase I)
- Primary Endpoints: PFS and molecular targeting (stem cells and IL6)

Open: OCT 2016
Status: Ongoing Accrual (Phase I)
Target: Approximately 150 pts
Notes: Expansion Group-wide JUN2018

Burger R, for NRG Oncology
ICON8B

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

• Following ICON8 Primary PFS analysis in April 2017, the ICON8 TMG in consultation with IDMC and TSC immediately suspended recruitment to arm B2 in May 2017. Final approvals to continue ICON8B as a 2-arm randomised study comparing arm B1 and arm B3 were received in Aug 2017.
• **Modified recruitment target:** 660
• **Accrual total as of 14th May 2018:** 376 (omitting arm B2 patients)
• Interim analysis planned Summer 2018 to confirm it is favourable for the trial to continue.

Modified comparator arms as of May 2018:

<table>
<thead>
<tr>
<th>Arm</th>
<th>Carboplatin AUC 5</th>
<th>q3w</th>
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<tr>
<td></td>
<td>Paclitaxel 175mg/m²</td>
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<tr>
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<td>Bevacizumab 7.5mg/kg</td>
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<table>
<thead>
<tr>
<th>Arm</th>
<th>Carboplatin AUC 5</th>
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<tr>
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<td>Paclitaxel 80mg/m²</td>
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<tr>
<td></td>
<td>Bevacizumab 7.5mg/kg</td>
<td>q3w</td>
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77 UK sites and 6 sites in Ireland open to recruitment. Will be an international trial with participation from Switzerland.
NB: On 5th May 2017 the modified ICON8B design opened to recruitment (2-arm randomisation, arms B1 vs B3). Monthly target accrual and overall accrual figures amended as per the sample size required in the modified trial design. Target accrual from July 2015-May 2017 is calculated from the original 3-arm study design target accrual / 0.66.
Trial setting: Ovarian Cancer
Sponsor: Hospices Civils LYON for GINECO
Planned No. of patients: 240
Current accrual: – 120 randomized (386 included)
(Randomization stopped since 28/04/2017 for the interim analysis)
Other important information:

- **Interim analysis timelines**
  - 20/09/2017: Cut-off date
  - 11/04/2018: Database lock
  - Q2/Q3: IDMC meeting

- **During the randomization suspension:**
  - Inclusions are still possible
  - Patients could sign the GVS consent to be screened
  - GVS ≥ 3 Patients have to be registered in the registry

### Table: Study Enrollment by Country

<table>
<thead>
<tr>
<th>Groups</th>
<th>Countries</th>
<th>Planned sites</th>
<th>Open sites</th>
<th>Active sites</th>
<th>Inclusions</th>
<th>Randomised Patients</th>
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<td><strong>TOTAL</strong></td>
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<td><strong>63</strong></td>
<td><strong>48</strong></td>
<td><strong>429</strong></td>
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</table>
Recurrent ovarian, primary peritoneal or fallopian tube cancers of BRCA mutated or BRCAness phenotype patients

Randomized phase III trial on Trabectedin (ET 743) vs clinician’s choice chemotherapy in recurrent ovarian, primary peritoneal or fallopian tube cancers of BRCA mutated or BRCAness phenotype patients

II line chemotherapy (physician choice):
- PLD 40 mg/mq d1 q28;
- Topotecan 4 mg/mq d1,8,15 q 28
- Weekly Paclitaxel 80 mg/mq d1,8,15 q28
- Gemcitabine 1000 mg/mq gg1,8,15 q28
- Carboplatin AUC 5 g 1 q 21

Trabectedin 1.3 mg/mq d1 q 21 in 3 hours (central line)

1° Endpoint: OS
2 ° Endpoints: PFS, RR, Duration of Response, Toxicity, Ca125 response, QOL

STRATIFICATION CRITERIA:
- Measurable Disease
- Platinum Sensitivity
- Number of Previous CHT Lines
- Mutational status
Randomized phase III trial on Trabectedin (ET 743) vs clinician’s choice chemotherapy in recurrent ovarian, primary peritoneal or fallopian tube cancers of BRCA mutated or BRCAness phenotype patients

Lead group: MITO
Academic trial - NCI of Milano sponsor
Data center: NCI of Milan
Trabectedin provided
Planned No. of patients: 244
No. of already recruited patients: 162
Timeline: FPI Feb 2016, LPI Q4 2018

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<th>GROUP</th>
<th>N. Patients</th>
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<tr>
<td>MITO</td>
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<tr>
<td>MANGO</td>
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<td>GEICO</td>
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<tr>
<td>Total</td>
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</table>
An international phase III randomised study to evaluate the efficacy of maintenance therapy with olaparib and cediranib or olaparib alone in patients with relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy
Following completion of 6 cycles (minimum 4 cycles) of platinum-based chemotherapy, if CT/MRI show 'CR' or 'PR' and patient remains eligible randomised 1:1* to receive:

Arm 1
- Oral olaparib 300mg BD
- Oral cediranib 20mg OD

Arm 2
- Oral olaparib 300mg BD

Stratified by:
- 6-12 vs >12 month platinum-free interval; surgery vs no surgery at relapse; prior bevacizumab therapy; BRCA status, country

Archival tissue sample collected for analysis

Primary Endpoints
- PFS
- OS

Eligibility & Registration
Patients with evidence of GCIG CA125 response or PR/CR on CT/MRI and who meet the inclusion criteria will be consented and registered

Randomisation

Mid-Treatment Chemotherapy Response
After 3 to 4 cycles of second line platinum-based chemotherapy patients are assessed for treatment response according to local practice

Trial treatment Follow up
Fortnightly for the first 8 weeks, 4 weekly during year 1 and 8 weekly for year 2 onwards until discontinuation of all trial drugs. Treatment may continue beyond progression until the next line of treatment if the patient is deemed to still be deriving clinical benefit. CT scan to be done at 16, 32 and 48 weeks after randomisation

Long term Follow up
Patients who have discontinued use of all trial drugs due to progression will have follow-up data collected every 12 weeks in the first two years then every 26 weeks in the third year (clinic attendance not required); patients who discontinue due to toxicity will continue to have follow-up assessments every 8 weeks until progression. QOL instruments will continue to be completed after relapse.

* The number of BRCA positive patients will be capped at approximately 250, to ensure that 350 BRCA wild-type patients will be randomised

1st relapse platinum sensitive ovarian, fallopian tube, primary peritoneal cancer N=618

Trial Schema
**Sponsor:** University College London

**Recruitment target:** 618

**Study Objectives**
To assess the efficacy, safety and tolerability of maintenance olaparib in combination with cediranib compared to maintenance of olaparib alone in patients who have received combination platinum-based chemotherapy

**Primary Endpoints**
PFS (RECIST v1.1) and OS (death from any cause), measured from randomisation

**Updates**
- 35 UK sites, 58 international sites from 7 countries
- Contract signed with AZ in December 2016
- UK REC approval December 2017, MHRA approval November 2017
- First set of SIVs have been held in UK
- Target FPI UK: Q2 2018
NRG GY005 (NCT02502266)
Olaparib-Cediranib vs PCT

(US, Canada)

Ongoing Trials – status update

- Recurrent HGSC with PFI < 6 months (following most recent platinum)
- No more than 2 prior regimens (including primary therapy)
- RECIST measurable or evaluable disease, biopsy accessible
- No prior PARPi therapy, prior bevacizumab permitted
- Stratify for BRCA status, number of prior treatment regimens
- Primary endpoint: OS 90% Power with HR 0.62

Open: FEB 2016
Status: Suspended for phase II interim analysis
Target: 460 pts (135 BRCA1/2 +)
Notes: Await Phase II Interim Analysis Outcome MAY2018
NRG GY009 (NCT02839707)
PLD +/- Bevacizumab +/- Atezolizumab

- 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
- Primary endpoints: Phase II PFS (selective) → Phase III OS

**Open:** MAY 2017
**Status:** Safety lead-in completed (Phase I Working Group)
**Target:** 272 Phase II, Cumulative 488 Phase III
**Notes:** Group-wide activation 11JUN2018

HR PFS \( \leq 0.783 \) (88% power)
HR OS* \( \leq 0.625 \) (90% power)
*one-tail \( \alpha \) 0.0115 (multiple comparisons)
Platinum-sensitive Ovarian Cancer

- HGSOC
- HGEOC
- Any BRCAmut OC

Randomize

**ARM 1**
- Niraparib
- Treat to PD/toxicity

**ARM 2**
- Bevacizumab + Niraparib
- Treat to PD/toxicity

**Stratification factors:**
- HRD positive/negative
- TFI: 6-12 mo vs. >12 mo

**Randomization:** 1:1
**n=94**

**Hypothesis:**
- Arm 1: niraparib median PFS 8mdr
- Arm 2: Nir + Bev median PFS 14mdr
- HR 0.57
- Power 80%
- alpha 0.1
- inclusion 18 months

Sponsor: NSGO
Platinum-sensitive Ovarian Cancer

Randomize

ARM 1
Niraparib

ARM 2
Bevacizumab + Niraparib

Bevacizumab + Niraparib + TSR042

Stratification factors:
HRD positive/negative
TFI: 6-12 mo vs. >12 mo

Stratification factors:
BRCAmut (yes/no)
TFI: 6-12 mo vs. >12 mo

Treat to PD/toxicity

Treat to PD/toxicity

Investigator’s choice (without niraparib)
Same Inclusion / exclusion criteria
Same sites
Number of BRCAmut patients capped to the same ratio as in part 2

Trial statistics:
To detect a PFS hazard ratio of 0.7 between dublet and triplet treatment
Power: 80%
one-sided significance level: 20%
Accrual: 18 months
Follow-up: 18 months
The doublet arm has included 55 patients which are already in follow-up.

The aim is to have additionally 72 (65+dropouts) patients in follow-up after treatment with triplet.

The below scenario is for 1:1 randomization between dublet and triplet, but since the dublet has already been included this is just a guide.
ENGOT-OV30 / NSGO / UMBRELLA
Sponsor: NSGO

A phase II umbrella trial in patients with relapsed ovarian cancer
ENGOT-OV30 / NSGO

**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:** Approved (DKMA, EC) in DK Sites: Rigshospitalet, DK / Vejle, DK activated, March 2018
- **Submission in NOR, FIN in Q2 2018**
- **Expected FPI: April 2018**
  Rigshospitalet: First patient signed CD73 PIC, April 2018, start treatment May 2018.
- **Cohort B (SGCTG UK)**
- **Cohort C (PMHC Canada)**
**ENGOT ov 29**

**Sponsor**: ARCAGY-GINECO  
**Principal Investigator**: J.E. KURTZ  
**Status**: RECRUITING

**ATEzolizumab and Avastin in LAtE recurreNT disease**

**ATALANTE DESIGN**

**Recurrent late relapse**

N=405

- Non-mucinous histology
- TF1 p (platinum-free interval) > 6 months
- One or 2 prior lines of Cx
- ECOG ≤1

**Stratification factors**

- PDL-1 expression
- TF1 p (6-12, >12 mos)
- Chemotherapy cohort

**Chemotherapy-based schedule options (investigator’s choice):**
- Carboplatin AUC5 + PLD (30mg/m² q 4wks) or paclitaxel (175mg/m² q 3wks) or gemcitabine (1000mg/m² DT#D8 q 3wks)
- BEV 15mg/kg q 3 wks or 10mg/kg q 2 wks. ATEZOL/PLACEBO: 1200mg, I V q 3wks or 800mg q 2wks.
• 3 countries are recruiting France (38 sites), Austria (2 sites), Spain (7 sites).
• 4 countries expected to start in the coming months (Germany, Belgium, Czech republic, Israel)

**Next step:** discussion on-going about the increase to 600 patients
**OREO – ENGOT-Ov38**
*(Olaparib Retreatment in late recurrent Ovarian cancer)*

**Eligible patients**
- Relapsed non-mucinous EOC
- Documented *BRCA1/2* status
- Treatment with one course of PARPi maintenance therapy
- PR/CR after ≥4 cycles of platinum-based chemo

**Cohort 1**
**BRCAm**
- 136 patients with a germline or somatic mutation in *BRCA1/2*
- Exposure for ≥18 months after first-line Cx or ≥12 months after second-/later-line chemotherapy

**Cohort 2**
**non-BRCAm**
- 280 patients
- Exposure for ≥12 months after first-line Cx or ≥6 months after second-/later-line chemotherapy

**Randomization**
- PR or CR to most recent course of platinum-based chemotherapy (no bevacizumab)

**Olaparib tablets**
- 300 mg bid or last tolerable dose

**Placebo**

**Stratification factors:**
- Prior bevacizumab
- ≤3 vs ≥4 prior lines of chemotherapy

**Endpoints:**
- PFS, OS, TTP, TDT, TFST, TSST, HRQoL

**Cohort 1**
- BRCAm
- 280 patients
- Exposure for ≥12 months after first-line Cx or ≥6 months after second-/later-line chemotherapy

**Cohort 2**
- non-BRCAm
- 136 patients with a germline or somatic mutation in *BRCA1/2*
- Exposure for ≥18 months after first-line Cx or ≥12 months after second-/later-line chemotherapy

**Primary endpoint**
- PFS (RECIST 1.1)
**Sponsor(s):** AstraZeneca – Leading group GINECO

**Planned No. of patients:** 416 patients (coming from PAOLA-1, SOLO1 for 1st line and SOLO 2, ARIEL 3, NOVA for relapse trials and patients treated with Lynparza as per label)

**Current accrual:** 30 (17 in France, 6 in Spain, 2 in Israël, 2 in Germany, 2 in Italy, 1 in Danemark)

**Global amendment submitted:** This will specifically include exclusion of patients who are not certain to have received a prior PARPi, and the inclusion of an interim analysis.
Planned Trials
FIRST Trial
First-line ovarian cancer treatment with Niraparib plus TSR-042

A RANDOMIZED, DOUBLE-BLIND, PHASE 3 COMPARISON OF PLATINUM-BASED THERAPY WITH TSR-042 AND NIRAPARIB VERSUS STANDARD OF CARE PLATINUM-BASED THERAPY AS FIRST-LINE TREATMENT OF STAGE III OR IV NONMUCINOUS EPITHELIAL OVARIAN CANCER

ENGOT model C (id NOVA & PRIMA): ENGOT ov-Sponsor: TESARO 1L OvCaStudy (3000-01-0005)
ENGOT group leader: GINECO
**Newly diagnosed advanced ovarian cancer**

**RANDOMIZATION 1:1:2**

**Cycle 1 Carboplatin-Paclitaxel**

- **Arm 1**
  - Carboplatin-Paclitaxel + I.V. placebo ± bevacizumab
  - Placebo (oral and I.V.)* ± bevacizumab

- **Arm 2**
  - Carboplatin-Paclitaxel + I.V. placebo ± bevacizumab
  - Niraparib + I.V. placebo* ± bevacizumab

- **Arm 3**
  - Carboplatin-Paclitaxel + TSR-042 + bevacizumab
  - Niraparib + TSR-042 + bevacizumab

*N.I.V. placebo up to 15 months in total

**Endpoints**

- **Primary endpoint:** PFS
- **Secondary endpoints:** ORR, DOR, DCR, PROs, TFST, TSST, PFS2, OS
Inclusion criteria

- All patients with FIGO stage III and IV epithelial OC
  except:- mucinous adenocarcinoma
    - complete surgical resection at primary debulking surgery and low risk of relapse *

Stratification

- bevacizumab use (investigator choice)
- HRR and BRCA status based on ctDNA with tumor sample as back-up
- Stage III < 1 cm at PDS versus others

* High risk: Aggregate 5 cm extra-pelvic disease during PDS AND require procedures including one or more of the following: resection of colon, diaphragm/diaphragmatic peritoneum, liver, spleen, or porta-hepatis.
Specificity (2)

**Treatment**

- Randomization at chemotherapy cycle 2
- During chemotherapy; I.V. TSR-O42/placebo every 3 weeks
- During maintenance:
  - **I.V. TSR-042 every 6 weeks** up to 3 years or I.V. placebo every 6 weeks during 15 months in total (simultaneously with bevacizumab)
  - During maintenance: **oral niraparib/placebo at 200 mg/d** (except if \( \geq 77 \) kg + platelets \( \geq 150,000 \)) up to 3 years

**Follow-up**

- CT-scan at baseline every 4 months during 2 years, every 6 months during the 3rd year and then according to routine practice
Objectives

**Primary objective: PFS**
The primary PFS analysis will be based upon Investigator assessment per RECIST v1.1. PFS based upon blinded independent central review committee (BICR) will be a sensitivity analysis.

**Secondary objectives**
- OS
- ORR/DOR/DCR
- Safety and tolerability of all treatments
- Patient-reported outcomes (PROs)
- Time to first subsequent therapy (TFST)
- Time to second subsequent therapy (TSST)
- PFS2

**Exploratory objectives**
- Evaluate biomarkers related to OC, PARP inhibition and PD-1 therapy
- PK for niraparib and TSR-042 and immunogenicity for TSR-042 only
Overview of the Adaptive Design

Four likely scenarios for the composition of the final SOC control group

<table>
<thead>
<tr>
<th>Final active control group: 4 scenarios</th>
<th>Non-BRCAmut HRR+</th>
<th>Non-BRCAmut HRR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm-1</td>
<td>Arm-1</td>
<td>Arm-1</td>
</tr>
<tr>
<td>Arm-2</td>
<td>Arm-1</td>
<td>Arm-1</td>
</tr>
<tr>
<td>Arm-2</td>
<td>Arm-2</td>
<td>Arm-1</td>
</tr>
<tr>
<td>Arm-2</td>
<td>Arm-2</td>
<td>Arm-2</td>
</tr>
</tbody>
</table>

To detect a PFS HR of 0.70 between the final active control group and Arm-3 (TSR -042 + niraparib), with 92% power and 1-sided alpha of 0.025, and a 1:2 randomization, a minimum of 401 PFS events are required.

With a 18 to 24 months of accrual and an additional FU ranging from 7 to 15 months, approximately 720 to 960 ITT patients will be randomized depending upon the timing and results of cited pivotal studies.

Arm-2: with niraparib as maintenance
STUDY Status

- Selection of sites on going
- 220 sites are planned
- first regulatory submission planned in June
- first patient planned during summer
A randomized phase III, two-arm trial of paclitaxel/carboplatin followed by maintenance letrozole versus letrozole monotherapy in patients with stage II-IV, primary low-grade serous carcinoma of the ovary or peritoneum

Amanda N. Fader, MD
David M. Gershenson, MD
Carcinoma is Similar to ER⁺ Breast Cancer

- Series of studies indicate that LGSC is strikingly similar to ER⁺ breast cancer
  - At least 80% of LGSC are ER⁺
  - Women < 35 yrs have significantly worse survival
  - LGSC responds to anti-estrogen hormonal therapy (AI, tamoxifen, leuprolide, fulvestrant, etc.) in the recurrent setting
  - Following primary surgery and platinum/taxane chemotherapy, hormonal maintenance therapy is associated with superior PFS and OS compared to observation
  - Adjuvant hormonal monotherapy demonstrates promising results

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al.</td>
<td>Int J Gynecol Pathol 2007</td>
</tr>
<tr>
<td>Gershenson et al.</td>
<td>Gynecol Oncol 2012</td>
</tr>
<tr>
<td>Sieh et al.</td>
<td>Lancet Oncol 2013</td>
</tr>
<tr>
<td>Fader et al.</td>
<td>Gynecol Oncol 2017</td>
</tr>
<tr>
<td>Gershenson et al.</td>
<td>J Clin Oncol 2017</td>
</tr>
</tbody>
</table>
Hormonal Therapy: Maintenance or Adjuvant

MD Anderson Study
- 203 pts (133 OBS, 70 HMT)

Johns Hopkins Study
- 27 pts with stage II-IV LGSC
- Primary CRS + HT
- Median duration HT = 18 mo
- After median FU = 41 mo, 6 (22%) pts relapsed
- Median PFS and OS not reached
- 3-yr PFS = 79.0%
- 3-yr OS = 93.1%

Gershenson et al. 
*J Clin Oncol* 2017

Fader et al.
*Gynecol Oncol* 2017
Eligible Patients

Primary endpoint: PFS

- Paclitaxel + Carboplatin x 6 cycles
- Letrozole x 6 cycles

Randomization #1 will be done in a 5:2 ratio (250 to CT, and 100 to L)
Stratified by residual disease (< 1 cm vs > 1 cm)

Randomization #2 will be done in a 1:1 ratio
Stratified by no persistent vs persistent disease

- Observation until disease progression or severe toxicity
- Letrozole until disease progression or severe toxicity

- Randomization #1
- Randomization #2
### Progression-free Survival

<table>
<thead>
<tr>
<th>Population/ Study/ Endpoint</th>
<th>HMT following chemo</th>
<th>Obs following chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (events)</td>
<td>Median (95% CI)</td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD Anderson (LGS)</td>
<td>70</td>
<td>65 (44, 86)</td>
</tr>
<tr>
<td>GOG 0182 (Gr 1 serous)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No gross residual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD Anderson (LGS)</td>
<td>14 (4)</td>
<td>3yr: 70%†</td>
</tr>
<tr>
<td>GOG 0182 (Gr 1 serous)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hopkins HMT alone, <strong>NOT</strong> after chemo</td>
<td>27 (8)</td>
<td>3yr: 79%†</td>
</tr>
<tr>
<td>Gross residual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD Anderson (LGS)</td>
<td>49 (36)</td>
<td>46 (30, 62) 3yr: 59%</td>
</tr>
<tr>
<td>GOG 0218 (Gr 1 serous)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

=GOG 0182 (Gr 1 serous): 0.1-1.0

†Median not reached
Consensus Design

Primary Cytoreductive Surgery

Paclitaxel + Carboplatin X 6

Letrozole 2.5 mg daily

Letrozole 2.5 mg daily
Primary objective: PFS

Secondary objectives:
- PRO
- QOL
- Toxicity
- Response (measurable disease)
- OS
- Compliance

Correlative translational research
- NGS
- ER, PR, Ki-67, AR
Sample size = 450

Non-inferiority design

Stratification factors: Age, Residual

Non-inferiority bound at HR = 1.18

80% power to detect increase in PFS of 9 mos (HR = 0.87)

Study duration: 56 mos accrual, 40 mos FU

2 interim analyses
NRG Concept OV1741
NACT +/- ICS

(9 Group-Wide)

- Epithelial ovarian, peritoneal, or fallopian carcinoma (EOPFC)
- Stage IIIC-IV and suitable for NACT with interval cytoreductive surgery
- Registered after CT with minimal residual disease, prior to planned ICS
- Permits minimally-invasive ICS
- Primary Endpoints: PFS and PRO/QoL

Open: Concept in planning
Status: Approximately 150 pts
Target: Preparation for NCI Review
Notes: Ahmed A, Bregar A and Fleming G for NRG Oncology

Core Bx → CP (x3) → CT-MRD → R → ICS → CP (x3)
Core Bx → CP (x3) → CT-MRD → R → No ICS → CP (x3)

CP = Carboplatin AUC 6 (D1), Paclitaxel 80 mg/m2 (D1,8,15)
CT-MRD = CT post-chemotherapy with minimal residual disease
ICS = Interval Cytoreductive Surgery (minimally invasive allowed)
NRG Concept OV1719
Olaparib-Tremelimumab vs PCT

New Concept (Revised)

- 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 (except primary maintenance). No prior immune checkpoint inhibitors
- Primary endpoint: PFS (pre-specified sequential analysis by whole population and subgroups)

Open:
Status: Concept in planning
Target: 250 pts
Notes: Revised Concept MAY 2018 (Pending Review)

Adams S, for NRG Oncology
ENGOT-OV41/GEICO 69-O/ ANITA

Atezolizumab and Niraparib Treatment Association in patients with recurrent ovarian cancer and platinum as option

ENGOT model: MODEL B

Sponsor: GEICO

Colaborative Groups: AGO, GINECO, MITO, MANGO, BGOG, ISGO, PGOG

PI: Antonio González

Financed by: ROCHE and TESARO

Planned No. of patients: 414 PATIENTS

Status: NOT YET RECRUITING. FPI expected in Q3 2018
ENGOT-OV41/GEICO 69-O/ANITA

N= 414 patients

- Recurrent high-grade serous or endometrioid, or undifferentiated ovarian, primary peritoneal or tubal carcinoma
- TFIp >6 months
- ≤ 2 prior lines
- Measurable disease
- ECOG≤ 1

**Stratification factors:**
- Platinum based regimen selected
- PFI (6-12 months vs > 12 months)
- BRCA mutation status (mutated vs. non-mutated)

**Randomization**

A

Platinum doublet+ Placebo
6 cycles

B

Platinum doublet + Atezolizumab
6 cycles

1:1

REGIST v1.1 CT SCAN

If CR, PR or SD

Niraparib+ Placebo
until disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

Niraparib+ Atezolizumab
disease progression, unacceptable toxicity, death, withdrawal of consent, or study termination by sponsor

**Primary Endpoint:**
- PFS by RECIST v.1.1

Secondary endpoints:
- Safety and tolerability
- TFST, TSST, PFS2, OS
- ORR, DOR
- QoL/PRO

The addition of atezolizumab is expected to increase the median PFS of Arm A from 16 months to 22.9 months, corresponding to a 30% reduction of the risk of progression (average HR of 0.70)
A randomized phase II trial of atezolizumab, niraparib and bevacizumab combination for patients with recurrent ovarian cancer.

ENGOT-OV42 / NSGO / AVANOVA-Immune1

Sponsor: NSGO
Study Chair: Mansoor Raza Mirza
ENGOT-OV42 / NSGO
AVANOVA-Immune1

Design

ENGOT-Ov42-NSGO / AVANOVA-Imune1
Multicenter, Open-Label, Phase 2 Randomized Trial
n=212

- **Arm A**: Standard of Care Therapy
- **Arm B**: Niraparib + Bevacizumab + Atezolizumab

**Recruitment Criteria**
- Recurrent Ovarian Cancer
- TFI 1-6 months or TFI >6 months

**Randomization**
- 2:1

**Stratification**
- Cohort 1 (TFI 1-6 months): BRCA status (positive/negative)
- Numbers of lines of therapy as platinum resistant disease.
- Cohort 2 (TFI >6 months):
  - BRCA status (positive/negative)
  - TFI 6-12mo vs >12mo
Objectives

Primary objective:
Compare Progression-Free Survival (PFS) of niraparib-bevacizumab-atezolizumab against Standard of care (SoC) therapy in both cohorts (TFI 1-6months and TFI >6months).

Secondary objectives:
Safety and tolerability of atezolizumab when given in combination with niraparib-bevacizumab.
PFS according to trial stratification factors in both cohorts.
Objective response rate according to RECIST (ORR) both in cohort 1 and cohort 2
Objective response rate according to irRECIST (irORR) both in cohort 1 & cohort 2
Disease control rate (DCR) (CR+PR+SD)
Patient Reported Outcomes (PROs)
PFS1 + PFS2

Exploratory objectives:
Overall survival (OS) in each group according to trial stratification factors
Study population of Cohort 1 (TFI 1-6months)

- Recurrent epithelial ovarian, fallopian tube, or peritoneal cancer within 1-6 months of last receipt of chemotherapy.
- Biopsy proven epithelial ovarian cancer.
- BRCA\textit{mut} or BRCA\textit{wt} or BRCA status unknown
- Prior treatment:
  - Patients must have received platinum-containing therapy for primary disease.
  - Maximum two series of prior therapies for platinum-resistant relapse.
  - Patients may have received bevacizumab.
  - Prior PARP inhibitors: patients may have participated in a placebo-controlled PARPi trial
  - Patient may have participated in a placebo-controlled IO trial.
Study population of Cohort 2 (TFI >6months)

• Recurrent epithelial ovarian, fallopian tube, or peritoneal cancer and no recurrence within 6 months of last receipt of chemotherapy.

• Biopsy proven epithelial ovarian cancer.

• BRCAmut or BRCAwt or BRCA status unknown

• Prior treatment:
  • Patients must have received platinum-containing therapy for primary disease.
  • Maximum two series of prior platinum-based therapies for relapse.
  • Patients may have received bevacizumab.
  • Prior PARP inhibitors: patients may have participated in a placebo-controlled PARPi trial
  • Patient may have participated in a placebo-controlled IO trial
**Experimental arm:**

Arm B combination:
- Niraparib 200mg PO once daily until disease progression.
- Bevacizumab 15mg/kg IV q 21 days until disease progression
- Atezolizumab until progression (dose to be added)

**Standard arm**

**Cohort 1**
- Arm A: chemotherapy alone (weekly paclitaxel or PLD or gemcitabin) or chemotherapy + bevacizumab.

**Cohort 2**
- Arm A: platinum combination chemotherapy (carboplatin-PLD or carboplatin-paclitaxel or carboplatin-gemcitabine) or platinum combination chemotherapy with concomitant and maintenance bevacizumab or platinum combination chemotherapy followed by maintenance parp inhibitor.
ENGOT-OV42 / NSGO
AVANOVA-Immune1

Design

ENGOT-Ov42-NSGO / AVANOVA-Imune1
Multicenter, Open-Label, Phase 2 Randomized Trial
n=212

- Arm A: Standard of Care Therapy
- Arm B: Niraparib + Bevacizumab + Atezolizumab

Randomize 2:1

Recrrent Ovarian Cancer
TFI 1-6months or TFI>6months

Treat to PD

Stratification
Cohort 1 (TFI1-6 months)
BRCA status (positive/negative)
Numbers of lines of therapy as platinum resistant disease.
Cohort 2 (TFI >6 months):
BRCA status (positive/negative)
TFI 6-12mo vs >12mo
Less chemotherapy with PARP inhibitor in newly diagnosed advanced ovarian cancer patients: a randomised phase 2 study

LEE, Jung-Yun
KIM, Jae Weon
Debulking surgery + Chemotherapy for 20 years

No significant survival change during 20 years

Survival benefit is anticipated for next decades

From Korean National Cancer Database

Targeted agents: PARPi, IO drug
In the era of targeted agents, 6 cycles of chemotherapy, Should it be?

- Toxicity from taxane-platinum combination chemotherapy
- CIPN
- CINV
- Neutropenic fever
- Hair loss
- Related to Cumulative dose
IDEA
(International Duration Evaluation Adjuvant Chemotherapy)

- 3 months vs. 6 months.

**Hypothesis:** Reduction of adjuvant treatment duration may decrease toxicities without loss of efficacy in stage III colon cancer

- Dramatic reduction in neurotoxicity
- CAPOX regimen, lower-risk subgroup
Targeted agent as front-line therapy

• Lung cancer
  - IO drug superior to chemotherapy in phase III trial
  - NCCN guideline changed

• Targeted agent vs. Chemotherapy (NRG-GY004, NRG-GY005)

- Cediranib 30 mg QD
- Olaparib 200 mg BID
- Platinum-based combo* (IV)
  *Carboplatin + gemcitabine or paclitaxel or PLD
Less chemotherapy
Concept 1: 6 cycle vs. 3 cycle

- FIGO stage IIB–IV
- PDS or IDS
- HGSC

N=44

Bevacizumab 15 mg/kg q3w; 15 months
Olaparib 300mg BID (24 months)

Primary endpoints:
✓ PFS by investigator
Stratification variables
✓ No residual vs residual or IDS

Randomised phase II study
N=44; HR (0.35) based on Study19, alpha=0.1; beta=0.2
Less chemotherapy
Concept 2: 6 cycle vs. 3 cycle

- FIGO stage IIB–IV
- PDS or IDS
- HGSC
  $N=86$

Randomised phase II study

We hypothesize that RR of severe CIPN is assumed with 0.5 in patients with 3 cycles compared to those with 6 cycles, $alpha=0.1; beta=0.2$

Primary endpoints:
✓ QOL
Stratification variables
✓ No residual vs residual or IDS
**Less chemotherapy**

**Concept 3: 6 cycle vs. 0 cycle**

- FIGO stage **IIB–IIIB**
- PDS, R0 resection
- HGSC

N=44

1:1

**R**

Bevacizumab 15 mg/kg q3w; 15 months

Carboplatin AUC5

Paclitaxel 175 mg/m²

Bevacizumab 15 mg/kg q3w; 15 months

Olaparib 300mg BID (24 months)

Durvalumab 1125 mg q3w; 15 months

Primary endpoints:

✓ PFS by investigator

Randomised phase II study

N=44 ; HR (0.35) based on Study19, alpha=0.1; beta=0.2