Practice changing studies in Gynaecological Cancer in 2018

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Council member
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CONFLICT OF INTEREST DISCLOSURE

- Personal financial interests:
  Advisory boards, lectures, travel expenses- Astrazeneca, Clovis, Gamamabs, Merck, Pharmamar, Seattle Genetics, Roche and Tesaro

- Institutional financial interests (educational grants): Astrazeneca, Janssen Cilag

- Institutional financial interest (clinical trials/contracted research): Amgen, Astex, Astrazeneca, Aprea, Array, Astellas, Bristol Myer Squibb, Clovis, Endocyte, Enita, Glycotope, Roche, Genentech, GlaxoSmithLine, Immunogen, Lilly, Medimmune, Merck, Merck Sharpe Dhome, Millenium, Nucana, Pfizer, Pharmamar, Takeda, Tesaro
Areas to cover

OVARIAN CANCER
- Newly diagnosed - First Line
  - SOLO1
  - HIPEC

ENDOMETRIAL CANCER
- Levatinib+Pembrolizumab

CERVICAL CANCER
- Newly diagnosed, locally advanced
  - LACC

OVARIAN CANCER
- Recurrent
  - MITO16B-MANGO OV2B-ENGOT OV17
  - AGO-OVAR2.21/ENGOT OV18
  - GOG-0213
  - CORAIL
  - JAVELIN Ovarian 200
  - Granulosa– PARAGON, ALIENOR

CERVICAL CANCER
- Advanced, recurrent
  - KEYNOTE-158
SOLO-1: PHASE III TRIAL OF MAINTENANCE OLAPARIB FOLLOWING PLATINUM-BASED CHEMOTHERAPY IN NEWLY DIAGNOSED PATIENTS WITH ADVANCED OVARIAN CANCER AND A BRCA1/2 MUTATION

- Kathleen Moore, 1 Nicoletta Colombo, 2 Giovanni Scambia, 3 Byoung-Gie Kim, 4 Ana Oaknin, 5 Michael Friedlander, 6 Alla Lisyanskaya, 7
- Anne Floquet, 8 Alexandra Leary, 9 Gabe S. Sonke, 10
- Charlie Gourley, 11 Susana Banerjee, 12 Amit Oza, 13 Antonio González-Martin, 14 Carol Aghajanian, 15
- William Bradley, 16 Elizabeth S. Lowe, 17 Ralph Bloomfield, 18 Paul DiSilvestro 19

1Stephenson Oklahoma Cancer Center, Oklahoma City, OK, USA; 2University of Milan-Bicocca and IEO, European Institute of Oncology IRCCS, Milan, Italy; 3Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica, Rome, Italy; 4Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; 5Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; 6University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia; 7St Petersburg City Oncology Dispensary, St Petersburg, Russia; 8Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France; 9Gustave-Roussy Cancer Campus, Villejuif, France; 10The Netherlands Cancer Institute, Amsterdam, The Netherlands; 11Cancer Research UK Edinburgh Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK; 12The Royal Marsden NHS Foundation Trust, London, UK; 13Princess Margaret Cancer Centre, Toronto, ON, Canada; 14MD Anderson Cancer Centre Madrid, Madrid, Spain; 15Memorial Sloan Kettering Cancer Center, New York, NY, USA; 16Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA; 17AstraZeneca, Gaithersburg, MD, USA; 18AstraZeneca, Cambridge, UK; 19Women & Infants Hospital, Providence, RI, USA

ClinicalTrials.gov identifier: NCT01844986. This study was sponsored by AstraZeneca; part of an alliance between AstraZeneca and Merck & Co., Inc.
SOLO-1: Study Design

- Newly diagnosed, FIGO stage III-IV, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer and/or fallopian tube cancer
- Germline or somatic BRCAm
- ECOG performance status 0-1
- Cytoreductive surgery
- Completed platinum-based chemotherapy
- In clinical complete response or partial response

Olaparib 300 mg BID (n=260)
- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2:1 randomisation
Stratified by response to platinum-based chemotherapy

Placebo (n=131)

Primary endpoint
Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints
PFS using BICR
PFS2
Overall survival
Time from randomisation to first subsequent therapy or death
Time from randomisation to second subsequent therapy or death
HRQoL (FACT-O TOI score)

BICR=blinded independent central review; BID=twice daily; ECOG=Eastern Cooperative Oncology Group; FACT-O=Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO=International Federation of Gynecology and Obstetrics; HRQoL=health-related quality of life; PFS=progression-free survival; PFS2=time to second progression or death; RECIST=Response Evaluation Criteria In Solid Tumours; TOI= Trial Outcome Index.
Moore K et al. Presented at: ESMO annual meeting; 2018.
## SOLO-1: PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=260)</th>
<th>Placebo (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumour location, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>220 (84.6)</td>
<td>113 (86.3)</td>
</tr>
<tr>
<td>Fallopian tubes</td>
<td>22 (8.5)</td>
<td>11 (8.4)</td>
</tr>
<tr>
<td>Primary peritoneal</td>
<td>15 (5.8)</td>
<td>7 (5.3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>History of cytoreductive surgery, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upfront surgery</td>
<td>161 (61.9)</td>
<td>85 (64.9)</td>
</tr>
<tr>
<td>Residual macroscopic disease</td>
<td>37 (23.0)</td>
<td>22 (25.9)</td>
</tr>
<tr>
<td>No residual macroscopic disease</td>
<td>123 (76.4)</td>
<td>62 (72.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0.6)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Interval cytoreductive surgery</td>
<td></td>
<td></td>
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<tr>
<td>Residual macroscopic disease</td>
<td>18 (19.1)</td>
<td>7 (16.3)</td>
</tr>
<tr>
<td>No residual macroscopic disease</td>
<td>76 (80.9)</td>
<td>36 (83.7)</td>
</tr>
<tr>
<td>No surgery</td>
<td>4 (1.5)</td>
<td>3 (2.3)</td>
</tr>
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Moore K et al. Presented at: ESMO annual meeting; 2018.
## SOLO-1: Patient Characteristics (2)

<table>
<thead>
<tr>
<th>Response after platinum-based chemotherapy, n (%)</th>
<th>Olaparib (N=260)</th>
<th>Placebo (N=131)</th>
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<tbody>
<tr>
<td>Clinical complete response</td>
<td>213 (81.9)</td>
<td>107 (81.7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>47 (18.1)</td>
<td>24 (18.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG performance status, n (%)</th>
<th>Olaparib (N=260)</th>
<th>Placebo (N=131)</th>
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<tbody>
<tr>
<td>0</td>
<td>200 (76.9)</td>
<td>105 (80.2)</td>
</tr>
<tr>
<td>1</td>
<td>60 (23.1)</td>
<td>25 (19.1)</td>
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<tr>
<td>Missing</td>
<td>0</td>
<td>1 (0.8)</td>
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<thead>
<tr>
<th>FIGO stage, n (%)</th>
<th>Olaparib (N=260)</th>
<th>Placebo (N=131)</th>
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</thead>
<tbody>
<tr>
<td>III</td>
<td>220 (84.6)</td>
<td>105 (80.2)</td>
</tr>
<tr>
<td>IV</td>
<td>40 (15.4)</td>
<td>26 (19.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRCAm,* n (%)</th>
<th>Olaparib (N=260)</th>
<th>Placebo (N=131)</th>
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</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>191 (73.5)</td>
<td>91 (69.5)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>66 (25.4)</td>
<td>40 (30.5)</td>
</tr>
<tr>
<td>Both BRCA1 and BRCA2</td>
<td>3 (1.2)</td>
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</table>

*Central germline testing confirmed that 388/391 patients had a BRCA1/2 mutation, 1 patient had a BRCA variant of uncertain significance, and 2 patients were BRCA wild-type.
Foundation Medicine testing confirmed that the 2 germline BRCA wild-type patients had somatic BRCA mutations.
Moore K et al. Presented at: ESMO annual meeting; 2018.
SOLO-1: PFS by Investigator Assessment (50.6% Maturity)

60.4% progression free at 3 years

26.9% progression free at 3 years

Based on Kaplan-Meier estimates, after 3 years, 60.4% of patients in the olaparib arm were progression-free, compared with 26.9% of patients in the placebo arm.

No. at risk

<table>
<thead>
<tr>
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<th>Placebo</th>
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</thead>
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<td>260</td>
<td>131</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>118</td>
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<tr>
<td>6</td>
<td>229</td>
<td>103</td>
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<td>9</td>
<td>221</td>
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<td>12</td>
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<td>15</td>
<td>201</td>
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<td>18</td>
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<td>33</td>
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<td>45</td>
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<td>48</td>
<td>4</td>
<td>1</td>
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<td>51</td>
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<tr>
<td>57</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.

Moore K et al. Presented at: ESMO annual meeting; 2018.
SOLO-1: PFS2* (30.9% maturity)

- Events (%): 69 (26.5) for Olaparib (n=260) vs. 52 (39.7) for Placebo (n=131)
- Median PFS2, mo: NR for Olaparib vs. 41.9 for Placebo
- HR=0.50
- 95% CI, 0.35-0.72
- P=0.0002

Of the patients who received subsequent therapy, first subsequent therapy included a PARP inhibitor in 33/94 (35%) patients in the placebo arm and 10/91 (11%) patients in the olaparib arm.

*Time from randomisation to second progression or death.
CI=confidence interval; HR=hazard ratio; PFS2=time to second progression or death.
Moore K et al. Presented at: ESMO annual meeting; 2018.
SOLO-1: Additional Secondary Efficacy Endpoints

- Median time to first subsequent therapy or death: Median not reached
  - Olaparib (N=260): 51.8
  - Placebo (N=131): 15.1

- Median time to second subsequent therapy or death: Median not reached
  - Olaparib (N=260): 40.7
  - Placebo (N=131): 95% CI, 0.32-0.63; P<0.0001

- Median overall survival: Data are immature (21.0% maturity)
  - Olaparib (N=260): 95% CI, 0.60-1.53; P=0.89
  - Placebo (N=131): HR 0.95

CI = confidence interval; HR = hazard ratio.
Moore K et al. Presented at ESMO annual meeting; 2018.
SOLO-1: Most Common Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Olaparib (n=260)</th>
<th>Placebo (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>77.3</td>
<td>37.7</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>63.5</td>
<td>41.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Anaemia</td>
<td>38.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>34.2</td>
<td>14.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>27.7</td>
<td>19.2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>26.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>25.4</td>
<td>26.9</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>23.1</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Grouped terms.
Moore K et al. Presented at: ESMO annual meeting; 2018.
Most interventions were managed through dose modifications without the need for discontinuation\textsuperscript{1,2}

11.5\% of patients in the olaparib arm discontinued treatment due to an AE

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=260)</th>
<th>Placebo (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE leading to a dose interruption, N (%)</td>
<td>135 (51.9)</td>
<td>22 (16.9)</td>
</tr>
<tr>
<td>Any AE leading to a dose reduction, N (%)</td>
<td>74 (28.5)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation of treatment, N (%)</td>
<td>30 (11.5)</td>
<td>3 (2.3)</td>
</tr>
</tbody>
</table>

- The most common treatment-emergent AEs leading to discontinuation were
  - Nausea (2.3\% in the olaparib group vs. 0.8\% in the placebo group)
  - Anaemia (2.3\% in the olaparib group vs. 0\% in the placebo group)

DCO: May 2018

AE = adverse event; DCO = data cut-off

FDA approves olaparib for first-line maintenance of BRCA-mutated advanced ovarian cancer

On December 19, 2018, the Food and Drug Administration approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Patients with gBRCAm advanced epithelial ovarian, fallopian tube or primary peritoneal cancer should be selected for therapy based on an FDA-approved companion diagnostic.
• Combination of hyperthermia and intraperitoneal chemotherapy
• Cytotoxic effect of hyperthermia, synergy with chemotherapy, enhanced penetration
OVARIAN CANCER – OVIHIPEC

Van Driel ASCO 2017, NEJM 2018

Questions:
- Tolerability- similar grade ¾ events
- Cost- effectiveness?
- Longer hospitalisation
- HIPEC post NACT and IDS
- What about post primary surgery?
- Highly technical procedure- training

IMPORTANT FIRST STEP

Not standard of care universally (ESMO/ESGO consensus conference April 2018, accepted for publication)
Areas to cover

OVARIAN CANCER
- Newly diagnosed- First Line
  - SOLO1
  - HIPEC

ENDOMETRIAL CANCER
- Levatinib+Pembrolizumab

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CERVICAL CANCER
- Advanced, recurrent
  - KEYNOTE-158
Primary Endpoint – PFS

IIIB-IV
1st relapse
>6 months
from last platinum
Received bevacizumab 1st line

Study Design

- Standard
- Experimental

Random 1:1

Platinum-Based Chemotherapy

Platinum-based Chemotherapy:
- Carboplatin + Paclitaxel +/- Beva 15mg/kg q 21
- Carboplatin + Gemcitabine +/- Beva 15mg/kg q 21
- Carboplatin + PLD q 28 +/- Beva 10mg/kg q 14

Stratification:
- center
- relapse during or after 1st line Beva
- performance status
- chemo backbone
PFS Investigator assessed (primary end-point)

Kaplan-Meier survival estimates

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Experimental</th>
<th>Log Rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td># events</td>
<td>161</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>8.8 mos</td>
<td>11.8 mos</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR* (95%CI)</td>
<td>0.51 (0.41-0.65)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*adjusted by: age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Overall Survival

27.1 months vs 26.6 months
HR 0.97 ns
Carboplatin/Pegylated Liposomal Doxorubicin/Bevacizumab (CD-BEV) vs. Carboplatin/Gemcitabine/Bevacizumab (CG-BEV) in patients with recurrent ovarian cancer.

A prospective randomized Phase III ENGOT/GCIG-Intergroup Study
(AGO Study Group, AGO-Austria, ANZGOG, GINECO, SGCTG)
AGO-OVAR 2.21 / ENGOT-ov 18
NCT 01837251


1 AGO Study Group & Gynecologic Oncology Center, Kiel, DE; 2 ANZGOG & St. John of God Hospital, Subiaco, Gynaecological Oncology, WA, AU; 3 AGO Study Group & Klinikum der Stadt Ludwigshafen ar Rhein gGmbH, Gynaecology, Ludwigshafen, DE; 4 AGO Study Group & Coordinating Center for Clinical Trials Philippus University Marburg, DE; 5 AGO Study Group & Kliniken Essen Mitte Evanger, Höxter, Gynecology, Gynecologic & Gynecologic Oncology, Essen, DE; 6 GINECO & Centre Francois Buclesse Caen, Gynaecology, Caen, FR; 7 AGO Study Group & Charité, Campus-Virchow-Klinikum, Department of Gynecology, Berlin, DE; 8 AGO Study Group & Medical Faculty and University Hospital Carl Gustav Carus, Technical University Dresden, Gynaecology, Dresden, DE; 9 AGO Study Group & Technical University of Munich - Klinikum rechts der Isar, current address: University of Medical Center Hamburg-Eppendorf, Gynaecology, Hamburg, DE; 10 ANZGOG & Sir Charles Gairdner Hospital, Gynaecology, Department, Sydney, AU; 11 AGO Study Group & Erlangen University Hospital, Gynaecology, Erlangen, DE; 12 AGO Austria & Innsbruck Medical University, Gynaecology, Innsbruck, AT; 13 AGO Study Group & University Hospital Schleswig-Holstein, Campus Lübeck, Gynaecology, Lübeck, DE; 14 GINECO & Paul Strauss Cancer Center and University of Strasbourg, Gynaecology, STRASBOURG, FR; 15 AGO Study Group & National Center for Tumor Disease, University of Heidelberg, Gynaecology, Heidelberg, DE; 16 AGO Study Group & University Hospital Frankfurt, Gynaecology, Frankfurt, DE; 17 SGCT & Beatson West of Scotland Cancer Centre, Gynaecology, Glasgow, GB; 18 AGO Study Group & University of Ulm, Gynaecology, Ulm, DE; 19 AGO Study Group & University Medical Center Hamburg-Eppendorf and University of Munich, Ludwig-Maximilian-University Munich, current address University of Munich, Gynaecology, Munich, DE; 20 GINECO & CHU de Strasbourg Hospital Civil, Hematology-Oncology, Strasbourg, FR.
STUDY DESIGN

**CG-BEV** standard arm

**CD-BEV** experim. arm

**N= 682 Aug 2013- July 2015**

**Stratification Factors**
- Platinum free interval (6-12 months vs. > 12 months)
- residual tumour (yes vs. no). In case of no debulking surgery for recurrence: all pts. categorized to residual tumor = yes
- Prior antiangiogenic treatment (yes vs. no)
- Participating study group language
PRIMARY OBJECTIVE: PROGRESSION-FREE SURVIVAL

**HR = 0.807 (95% CI: 0.681-0.956)**
Stratified log-rank test: \( P = 0.0128 \)

**CD-BEV: 345 pts. / 277 events**
median 13.3 (11.7 - 14.3) mos

**CG-BEV: 337 pts. / 294 events**
median 11.7 (11.1 - 12.8) mos

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>CD-BEV</th>
<th>CG-BEV</th>
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<tbody>
<tr>
<td>0</td>
<td>345</td>
<td>337</td>
</tr>
<tr>
<td>6</td>
<td>293</td>
<td>287</td>
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<td>12</td>
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</table>
OVERALL-SURVIVAL

CD-BEV: 345 pts. / 186 events
median 33.5 (29.3 - 36.7) mos

CG-BEV: 337 pts. / 203 events
median 28.2 (25.6 - 30.8) mos

HR = 0.833 (95% CI: 0.680-1.022)
Stratified log-rank test: \( P = 0.0787 \)
CONCLUSIONS

- This is the first phase III trial in ovarian cancer comparing two BEV containing regimens.
- CD-BEV resulted in superior efficacy (PFS HR 0.80, p= 0.01) compared to CG-BEV in patients with ROC PBT.
- CD-BEV improved efficacy also in the subgroup with previous antiangiogenic treatment (PFS HR 0.73, p < 0.05).
- Global QoL was superior for CD-BEV compared to CG-BEV.
- The safety data were consistent with BEV profile. There were no new safety signals.
- CD-BEV is a new treatment option for patients with recurrent ovarian cancer suitable for platinum based retreatment (ROC PBT), even after previous antiangiogenic treatment.
**OVARIAN CANCER – DESKTOP III**  Du Bois ASCO 2017

What is the role of cytoreductive surgery before chemotherapy in recurrent ovarian cancer?

Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: the interim analysis of AGO DESKTOP III / ENGOT ov20

AGO Score consisted of (1) good PS (ECOG 0), (2) complete resection during 1st line therapy, and (3) ascites less than 500 ml
Background: DESKTOP III

- Surgery was safe and feasible
- R0 rate: 72.5%
- Patients with residual disease after surgery had the same HR_{PFS} as those receiving chemotherapy alone
- Time to 3\textsuperscript{rd} line significantly longer
- OS: immature at interim analysis

DuBois, Proc ASCO, Abst 5501, 2017
A Phase III Randomized Controlled Trial of Secondary Surgical Cytoreduction followed by Platinum-Based Combination Chemotherapy, With or Without Bevacizumab in Platinum-Sensitive, Recurrent Ovarian Cancer: A NRG Oncology/Gynecologic Oncology Group Study

Robert L. Coleman, Nick Spirtos, Danielle Enserro, Thomas J. Herzog, Paul Sabbatini, Deborah Kay Armstrong, Byoung Kim, Keiichi Fujiwara, Joan L. Walker, Patrick J. Flynn, Angeles Alvarez Secord, David E. Cohn, Mark F. Brady, Robert S. Mannel
Women with recurrent ovarian, peritoneal primary or fallopian tube cancer and a treatment free interval greater than or equal to 6 months.

**Chemotherapy (2 options):**
- Paclitaxel 175 mg/m² +
- Carboplatin AUC5

- Gemcitabine 1000 mg/m² d1,8 +
- Carboplatin AUC5

**Bevacizumab (optional):**
- 15 mg/kg
- Starting cycle 2 for post-op to a max of 8 cycles
- Maintenance allowed until progression, intolerance or death

**Cycle Length:** 21 days
Primary Endpoint OS: Surgery vs. No Surgery

**Overall Survival**

- **HR_{TT}:** 1.28 (0.92-1.78)
- **HR_{Non USA}:** 1.28 (0.6-2.75)

**Progression-Free Survival**

- **HR: 0.88 (0.70-1.11)**
Conclusions

- Secondary cytoreduction was **NOT** associated with an improvement in either OS or PFS compared to no surgery in this population.
- Optimal surgical resection (R0) was 68% in the per protocol population and slightly lower than that reported in DESKTOP-III (72.5%, P=0.27).
  - R0 resection statistically improved PFS and OS relative to those with post-operative residual disease.
  - However, relative to chemotherapy alone, R0 was not associated with better OS despite extending PFS.
- High rate of adjuvant and maintenance bevacizumab use in GOG-0213 (84%).
  - Substantially higher than DESKTOP-III (~20%).
Phase III trial of Lurbinectedin versus PLD or Topotecan in platinum-resistant ovarian cancer patients: Results of CORAIL trial


¹ Duke University Medical Center, USA; ² Hospital Vall d’Hebron and Vall d’Hebron Institute of Oncology, Spain; ³ Centre Leon Berard, University Claude Bernard Lyon I & GINECO group, France; ⁴ University Hospital Leuven, Leuven Cancer Institute, Belgium, European Union; ⁵ Policlinico Agostino Gemelli - Universita’ Cattolica del Sacro Cuore, Italy; ⁶ University of Milan-Bicocca and Istituto Europeo di Oncologia, Italy; ⁷ Georgia Cancer Center at Augusta University, USA; ⁸ Pharma Mar, S.A., Spain; ⁹ Institut Catala Oncologia-Hospital Duran i Reynals, Spain; ¹⁰ Magyar Honvedseg Egeszsegugyi Kozpont, Onkologiai Osztaly, Hungary; ¹¹ University College London, United Kingdom; ¹² Ohio State University Wexner Medical Center, USA; ¹³ Arizona Center for Cancer Care, USA; ¹⁴ Institut Gustave Roussy & GINECO group, France; ¹⁵ Fondazione IRCCS Istituto Nazionale dei Tumori, Italy.
BACKGROUND

Lurbinectedin (PM01183) is a selective inhibitor of active transcription of protein-coding genes (1)

The mechanism involves the specific degradation of RNA polymerase II by the ubiquitin/proteasome machinery and the subsequent accumulation of DNA breaks and apoptosis as downstream events

Lurbinectedin also reduces tumour-associated macrophages and the inflammatory tumour microenvironment (2)

Pre-clinical studies:
- Strong Lurbinectedin antitumor activity in cisplatin-resistant epithelial ovarian cancer models (3)

Clinical study:
- Phase II trial in platinum resistant/refractory ovarian cancer (4)
  - In subgroup of platinum resistant patients (n=33), ORR (RECIST or GCIG criteria) was 30% (95% CI, 16%–49%), median PFS was 5.0 months (95% CI, 2.7–6.9 months).

Study Design

Patient population:
- Platinum Resistant (PFI 1-6 mo) Ovarian, Fallopian or Primary Peritoneal Cancer
- ECOG PS 0-2
- ≤ 3 prior Chemotherapy lines
- Measurable/non-measurable per RECIST v.1.1

12 countries / 102 sites
(Austria, Belgium, Bulgaria, Czech Republic, France, Hungary, Italy, Romania, Serbia, Spain, UK, USA)

Randomization 1:1

420 Patients

ARM A
Lurbinectedin
3.2 mg/m² D1 q3wk

ARM B*
PLD
50 mg/m² D1 q4wk or Topotecan
1.5 mg/m² D1-5 q3wk

Primary endpoint:
PFS by IRC
(30% reduction in the relative risk of progression or death (HR= 0.70))

Secondary endpoints:
- Overall Survival (OS)
- Anti-tumor activity (ORR, DoR, PFS by Investigator)
  - Safety
  - PK
  - PRO
- Pharmacogenetic and Pharmacogenomic (sub-studies)

* Primary GCSF prophylaxis allowed
PFS according to IRC

Median Lurbinectedin 3.5 months 95% CI (2.1-3.7) p-value=0.8599 95% CI (2.0-5.5)
Median PLD 3.6 months 95% CI (2.2-3.8) p-value=0.8599
Median Topotecan 3.6 months 95% CI (2.2-3.8)

PFS according to Investigator assessment

Median PM01183 (months): 3.7 95% CI (3.6-3.9)
Median Control (months): 3.7 95% CI (3.5-4.0)
HR: 0.971 95% CI (0.791-1.192)
log rank test p-value=0.7764
Overall Survival

Median Lurbinectedin (mo.): 11.2 95% CI (9.0-14.5)
Median Control (mo.): 11.1 95% CI (9.3-12.5)

HR: 0.97 95% CI (0.765-1.231) 
log rank test p-value=0.8038

Median PLD
Lurbinectedin 11.3 months 95% CI (8.9-12.7) 
Topotecan 10.2 months 95% CI (8.7-15.2)
Avelumab alone or in combination with pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase 3 JAVELIN Ovarian 200 trial


1ARCAGY-GINECO, Paris, France; 2Saitama Medical University International Medical Center, Hidaka, Japan; 3UCL Cancer Institute and UCL Hospitals, Gynecological Oncology, London, UK; 4Princess Margaret Cancer Centre, Toronto, ON, Canada; 5Centre Léon Bérard, Lyon, France, GINECO; 6Gabrielli Hospital, Malvern, VIC, Australia; 7Oncology Institute of Southern Switzerland (IOSI), Ospedale San Giovanni (Ospedale Bellinzona e Valli), Bellinzona, Switzerland; 8National Cancer Center Hospital, Tokyo, Japan; 9The Royal Marsden NHS Foundation Trust, Surrey, UK; 10Gustave Roussy Cancer Campus, Villejuif, France, GINECO; 11British Columbia Cancer Agency, Vancouver, BC, Canada; 12Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; 13Poznan University of Medical Sciences, Poznan, Poland; 14National Cancer Center Korea, Goyang-si, South Korea; 15Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA; 16Pfizer Oncology, Cambridge, MA, USA; 17Pfizer Oncology, San Diego, CA, USA; 18Pfizer, Inc., Groton, CT, USA; 19Arizona Oncology (US Oncology Network), Phoenix, AZ, USA
JAVELIN Ovarian 200: a randomized, open-label, phase 3 trial

Key eligibility criteria
- Platinum-resistant or refractory epithelial OC
- ≤ 3 prior lines for platinum-sensitive disease
- No prior therapy for platinum-resistant disease
- Unselected for PD-L1 expression

N=566

Stratification factors
- Platinum refractory vs resistant
- 1 prior anticancer regimen vs 2 or 3
- Tumor size ≥ 5 cm vs <5 cm

Endpoints
- 2 independent primary endpoints:
  - PFS (BICR assessed)
  - OS
- 2 independent comparisons
  - Avelumab vs PLD
  - Avelumab + PLD vs PLD
- 1 preplanned interim and 1 final analysis
- Various secondary endpoints*

NCT02580058

Tumor responses were assessed per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1
* PFS (investigator assessed), objective response, duration of response, disease control, tumor biomarkers, safety, PK, avelumab immunogenicity, and patient-reported outcomes

BICR, blinded independent central review; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PLD, pegylated liposomal doxorubicin; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomization

Avelumab 10 mg/kg Q2W
N=188

Avelumab 10 mg/kg Q2W + PLD 40 mg/m² Q4W
N=188

PLD 40 mg/m² Q4W
N=190

Treatment until confirmed disease progression, unacceptable toxicity, or withdrawal
**Progression-free survival by BICR**

<table>
<thead>
<tr>
<th></th>
<th>Avelumab (N=188)</th>
<th>Avel. + PLD (N=188)</th>
<th>PLD (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events, n (%)</td>
<td>154 (81.9)</td>
<td>134 (71.3)</td>
<td>125 (65.8)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>1.9 (1.8; 1.9)</td>
<td>3.7 (3.3; 5.1)</td>
<td>3.5 (2.1; 4.0)</td>
</tr>
<tr>
<td>Stratified HR vs PLD (repeated CI)</td>
<td>1.68 (1.320; 2.601)</td>
<td>0.78 (0.587; 1.244)</td>
<td>–</td>
</tr>
<tr>
<td>p value vs PLD*</td>
<td>&gt;0.999</td>
<td>0.0301†</td>
<td>–</td>
</tr>
</tbody>
</table>

* 1-sided log-rank test; nominal p values (futility boundary was crossed at interim analysis)  
† Did not meet significance threshold (<0.0002)
Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Avelumab (N=188)</th>
<th>Avel. + PLD (N=188)</th>
<th>PLD (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events, n (%)</td>
<td>109 (58.0)</td>
<td>102 (54.3)</td>
<td>104 (54.7)</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>11.8 (8.9; 14.1)</td>
<td>15.7 (12.7; 18.7)</td>
<td>13.1 (11.8; 15.5)</td>
</tr>
<tr>
<td>Stratified HR vs PLD (repeated CI)</td>
<td>1.14 (0.948; 1.580)</td>
<td>0.89 (0.744; 1.241)</td>
<td>–</td>
</tr>
<tr>
<td>p value vs PLD*</td>
<td>0.8253†</td>
<td>0.2082‡</td>
<td>–</td>
</tr>
</tbody>
</table>

* 1-sided log-rank test. † Nominal p value (futility boundary was crossed at interim analysis) ‡ Did not meet significance threshold (<0.0103)

Median follow-up for OS (95% CI): avelumab, 18.2 months (17.1; 19.4); avelumab + PLD, 18.4 months (17.3; 19.7); PLD, 17.4 months (16.5; 18.3)
## Confirmed objective responses by BICR

<table>
<thead>
<tr>
<th>Confirmed best overall response, n (%)</th>
<th>Avelumab (N=188)</th>
<th>Avelumab + PLD (N=188)</th>
<th>PLD (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>2 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (3.7)</td>
<td>23 (12.2)</td>
<td>8 (4.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>45 (23.9)</td>
<td>78 (41.5)</td>
<td>70 (36.8)</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>10 (5.3)</td>
<td>5 (2.7)</td>
<td>15 (7.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>101 (53.7)</td>
<td>60 (31.9)</td>
<td>61 (32.1)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>25 (13.3)</td>
<td>20 (10.6)</td>
<td>36 (18.9)</td>
</tr>
</tbody>
</table>

### Objective response rate (95% CI), %

<table>
<thead>
<tr>
<th></th>
<th>Avelumab (N=188)</th>
<th>Avelumab + PLD (N=188)</th>
<th>PLD (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate (95% CI), %</strong></td>
<td>3.7 (1.5; 7.5)</td>
<td>13.3 (8.8; 19.0)</td>
<td>4.2 (1.8; 8.1)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>0.890 (0.267; 2.901)</td>
<td>3.458 (1.463; 9.096)</td>
<td>–</td>
</tr>
<tr>
<td>p value*</td>
<td>0.8280</td>
<td>0.0018</td>
<td>–</td>
</tr>
</tbody>
</table>

### Median duration of response (range), months

<table>
<thead>
<tr>
<th></th>
<th>Avelumab (N=188)</th>
<th>Avelumab + PLD (N=188)</th>
<th>PLD (N=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median duration of response (range), months</strong></td>
<td>9.2 (6.4–NE)</td>
<td>8.5 (6.1–NE)</td>
<td>13.1 (5.5–NE)</td>
</tr>
</tbody>
</table>

*Nominal p values (test not prespecified in the overall testing strategy); 2-sided Cochran-Mantel-Haenszel test

CR, complete response; NE, not estimable; PD, progressive disease
**PFS (by BICR) and OS: PD-L1+ subgroup**

### Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Median, mo (95% CI)</th>
<th>HR vs PLD (95% CI)</th>
<th>p value vs PLD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>1.9 (1.8; 2.3)</td>
<td>1.45 (0.457; 0.919)</td>
<td>0.0303</td>
</tr>
<tr>
<td>Avelumab + PLD</td>
<td>3.7 (2.7; 6.1)</td>
<td>0.65 (0.457; 0.919)</td>
<td>0.0143</td>
</tr>
<tr>
<td>PLD</td>
<td>13.1 (10.5; 16.9)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

### Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Median, mo (95% CI)</th>
<th>HR vs PLD (95% CI)</th>
<th>p value vs PLD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>13.7 (9.6; 24.3)</td>
<td>0.83 (0.489; 1.048)</td>
<td>–</td>
</tr>
<tr>
<td>Avelumab + PLD</td>
<td>17.7 (13.8; 22.0)</td>
<td>0.72 (0.489; 1.048)</td>
<td>–</td>
</tr>
<tr>
<td>PLD</td>
<td>13.1 (10.5; 16.9)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Nominal p values; 2-sided log-rank test*
In JAVELIN Ovarian 200, avelumab + PLD showed clinical activity but the trial did not meet its primary objectives of significantly improving PFS or OS vs PLD in patients with platinum-resistant or refractory OC in an unselected population.

Prespecified analysis in PD-L1+ and PD-L1− subgroups indicate a potential role for PD-L1 expression as a predictor of clinical benefit.
PARAGON - A phase 2 study of Anastrozole (An) in patients with oestrogen receptor (ER) and progesterone receptor (PR) positive recurrent/metastatic granulosa cell tumors/sex-cord stromal tumors (GCT) of the ovary - ANZGOG 0903

Susana N. Banerjee¹, Monica Tang², Rachel O’Connell², Katrin Sjoquist³, Andrew R. Clamp³, Rosemary Lord⁴, Vinod Menon Mullaßery⁵, Marcia Hall⁶, Charlie Gourley⁷, Tony Bonaventura⁸, Jeffrey C. Goh⁹, Peter Sykes¹⁰, Peter T. Grant¹¹, Orla McNally¹², Laura Alexander¹³, Karen Carty¹³, James Paul¹³, Richard J Edmondson¹⁴, Michael Friedlander¹⁵ on behalf of PARAGON investigators

40 evaluable patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Response</th>
<th>n (%)</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit at 3 months</td>
<td>Clinical benefit</td>
<td>32 (80.0%)</td>
<td>(65.2% - 89.5%)</td>
</tr>
<tr>
<td></td>
<td>Progressive Disease</td>
<td>6 (15.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Progression</td>
<td>2 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Response at 3 months</td>
<td>Partial Response</td>
<td>1 (2.5%)</td>
<td>(0.4% - 12.9%)</td>
</tr>
<tr>
<td></td>
<td>Stable disease</td>
<td>31 (77.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progressive disease</td>
<td>8 (20.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Median PFS was 8.6 m (95% CI 5.5 – 13.5m)

Best response (RECIST) partial response (9.8% n=4)

23 (59%) patients were progression free at 6 months
2 patients remain on treatment at 14.8 and 53.5 months

This is the first prospective trial of an AI in recurrent GCTs
Although there was a high CBR, the objective response rate was much lower than in retrospective series


**ALIENOR/ENGOT-OV7**

Raq-Coquard et al

- First randomised trial in SCTs/GCTs
- Multicentre, International
- Example of Collaborative research and engagement in Rare Cancers

**Randomization**

- Paclitaxel alone
  - 80mg/m², IV, at D1, D8 and D15 every 4 weeks
  - Maximum of 6 cycles

- Paclitaxel
  - 80mg/m², IV, D1, D8 and D15 every 4 weeks

- Bevacizumab
  - 10mg/kg, IV, D1 and D15

**Standard surveillance**

**PD**

**Standard of care**

**Bevacizumab**

- 15mg/kg every 3 weeks
  - At the Investigator discretion

**PD**

**Standard of care**

- Up to 1 year or until PD / intolerance
ALIENOR/ENGOT-OV7

- 60 patients
- 87% adult GCTs
- 28% <12 month platinum-free interval
- 22% >2 chemotherapy lines; 28% prior hormonal therapy

- Did not meet primary endpoint- 6 month PFS rate (70.6% vs 72.4%)
- Median PFS 14.7 (taxol) vs 14.9 months (taxol+bevacizumab)
- Response rate higher with addition of bevacizumab 25% vs 44%
PRACTICE CHANGING AND LANDMARK STUDIES IN GYNECOLOGICAL CANCERS 2018

Areas to cover

OVARIAN CANCER
- Newly diagnosed- First Line
  - SOLO1
  - HIPEC

ENDOMETRIAL CANCER
- Levatinib+Pembrolizumab

CERVICAL CANCER
- Newly diagnosed, locally advanced
  - LACC

OVARIAN CANCER
- Recurrent
  - MITO16B-MANGO OV2B-ENGOT OV17
  - AGO-OVAR2.21/ENGOT OV18
  - GOG-0213
  - CORAIL
  - JAVELIN Ovarian 200
  - Granulosa– PARAGON, ALIENOR

CERVICAL CANCER
- Advanced, recurrent
  - KEYNOTE-158
**RR week 24 50%**

PFS 10.1 months
The U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for lenvatinib (Lenvima) in combination with pembrolizumab (Keytruda) for the potential treatment of patients with advanced and/or metastatic non–microsatellite instability high (MSI-H)/proficient mismatch repair (pMMR) endometrial carcinoma that has progressed following at least one prior systemic therapy.

This Breakthrough Therapy designation was based on interim results of the endometrial carcinoma cohort in Study 111/KEYNOTE-146, which were presented by Makker et al at the 2018 ASCO Annual Meeting (Abstract 5596). Study 111/KEYNOTE-146 is a multicenter, open-label, single-arm phase Ib/II basket trial evaluating the efficacy and safety of lenvatinib (20 mg/d) in combination with pembrolizumab (200 mg intravenously every 3 weeks) in patients with selected solid tumors (renal cell carcinoma, endometrial carcinoma, non–small cell lung cancer, urothelial cancer, squamous cell head and neck cancer, and melanoma).
Surgery for cervical cancer

**PRINCIPLES OF EVALUATION AND SURGICAL STAGING**

**Types of Resection and Appropriateness for Treatment of Cervical Cancer**

- Treatment of cervical cancer is stratified by stage as delineated in the Guidelines.
- Microinvasive disease, defined as FIGO stage IA-1 with no lymphovascular space invasion (LVSII), has less than a 1% chance of lymphatic metastasis and may be managed conservatively with cone biopsy for preservation of fertility (with negative margins) or with simple hysterectomy when preservation of fertility is not desired or relevant. The intent of a cone biopsy is to remove the ectocervix and endocervical canal en bloc using a scalpel. This provides the pathologist with an intact, non-frAGMENTED specimen without electro surgical artifact, which facilitates margin status evaluation. If a loop electrosurgical excision procedure (LEEP) is chosen for treatment, the specimen should not be fragmented, and care must be undertaken to minimize electrosurgical artifact at the margins. The shape and depth of the cone biopsy may be tailored to the size, type, and location of the neoplastic lesion. For example, if there is concern for invasive adenocarcinoma versus adenocarcinoma in situ in the cervical canal, the cone biopsy would be designed as a narrow, long cone extending to the internal os.

- Radical hysterectomy with bilateral pelvic lymph node dissection (with or without SLN mapping) is the preferred treatment for FIGO stage IA-2, IB, and IIA lesions when fertility preservation is not desired. Radical hysterectomy results in resection of much wider margins compared with a simple hysterectomy, including removal of parts of the cardinal and uterosacral ligaments and the upper 1–2 cm of the vagina; in addition, pelvic and sometimes para-aortic nodes are removed. Radical hysterectomy procedures may be performed either via laparotomy or laparoscopy, and the laparoscopy approach may be either with conventional or robotic techniques. The Quereuil & Morrow classification system is a modern surgical classification that describes degree of resection and nerve preservation in 3-dimensional planes of resection. Procedural details for the most commonly used types of hysterectomy are described in Table 1 [see CERV-B 5 of 7].

- The radical vaginal trachelectomy with laparoscopic lymphadenectomy procedure (with or without SLN mapping) offers a fertility-sparing option for carefully selected individuals with stage IA-2 or stage IB-1 lesions of 2 cm diameter or less. The cervix, upper vagina, and supporting ligaments are removed as with a type B radical hysterectomy, but the uterine corpus is preserved. In the more than 300 subsequent pregnancies currently reported, there is a 10% likelihood of second trimester loss, but 72% of patients carry their gestation to 37 weeks or more. The abdominal radical trachelectomy has emerged as a reasonable fertility-sparing strategy. It provides larger resection of parametra than the vaginal approach, is suitable for select stage IB1 cases, and has been utilized in lesions up to 4 cm in diameter. The operation mimics a type C radical hysterectomy.1,2,3,4
LACC trial

Compare **disease-free survival at 4.5 years** amongst patients who underwent a total **laparoscopic or robotic radical hysterectomy (TLRH/TRRH)** vs. a total **abdominal radical hysterectomy (TARH)** for early stage cervical cancer.

- International, multicenter, randomized, phase III trial to test for non-inferiority of TLRH/TRRH vs. standard care (TARH)

- Therefore, the **primary intent** to demonstrate that minimally invasive surgery was within 7.2% of the DFS rate of the standard care (TARH) arm

- Test for non-inferiority was based upon a 97.5% one-sided confidence interval. Based on exponential survival times, for a 4.5-year follow-up, a total of **740 patients (370 per arm)** was determined to have at least 90% power for non-inferiority.
LACC trial

Open: June 2008
Accrual: 631
Closed: June 2017*

Stage IA1 LVSI, IA2, IB1
Squamous, Adenocarcinoma, or Adenosquamous Cervical Cancer

Randomize

Total Abdominal Radical Hysterectomy
N= 312

Total Laparoscopic/Robotic Radical Hysterectomy
N= 319

Largest, prospective, randomised trial
Multicentre, international

- Confirmed primary squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix
- FIGO stage IA1 (with LVSI), IA2, or IB1
- Type II or III radical hysterectomy (Piver-Rutledge Classification)
- Performance status of ECOG 0-1
- Age 18 years or older
LACC trial results

Primary Outcome: DFS at 4.5 years

- **TARH**
  - Intention to Treat: 88.5 (92.7 - 94.4)
  - Per Protocol: 97.6 (94.1 - 99.3)

- **TLRH/TRRH**
  - Intention to Treat: 86.0 (75.7 - 90.4)
  - Per Protocol: 87.1 (81.0 - 93.2)

**P-values for non-inferiority (2 sided):**
- TarH vs TARH, p=0.87
- Per Protocol vs TARH, p=0.99

**Disease-Free Survival (DFS)**
- HR: 3.74 (95% CI 1.63 - 8.58), p=0.002
- **Events/N**
  - TARH: 7/312
  - TLRH/TRRH: 27/319

**Cumulative Local/Regional Recurrence**
- HR: 4.26 (95% CI 1.44-12.6), p=0.009

**Overall Survival**
- HR: 6.00 (95% CI 1.77 - 20.3), p=0.004
- **Events/N**
  - TARH: 3/312
  - TLRH/TRRH: 19/319
FDA approval June 2018

98 patients
RR 12%
82 pts PD-L1+ 14.6%
No response PD-L1-ve

CR 3pts
PFS 6 months 25%
Median OS 9.4 months
Summary: Implications for Practice

- SOLO1- Maintenance Olaparib first line BRCA mutated ovarian cancer (FDA)
- MITO16B-MANGO OV2B-ENGOT OV17 and AGO-OVAR2.21/ENGOT OV18
  - Role of bevacizumab rechallenge with platinum-based chemotherapy in relapse (after receiving in first line setting)
- Levatinib+pembrolizumab endometrial cancer (FDA breakthrough designation nonMSI-H)
- KEYNOTE-158- Pembrolizumab PD-L1+ recurrent cervical cancer (FDA)
- LACC trial: Total radical abdominal hysterectomy 1A1/2 1B1 cervical cancer

Look forward to practice changing studies in 2019