
# GYNECOLOGIC ONCOLOGY

## Advances in systemic treatment

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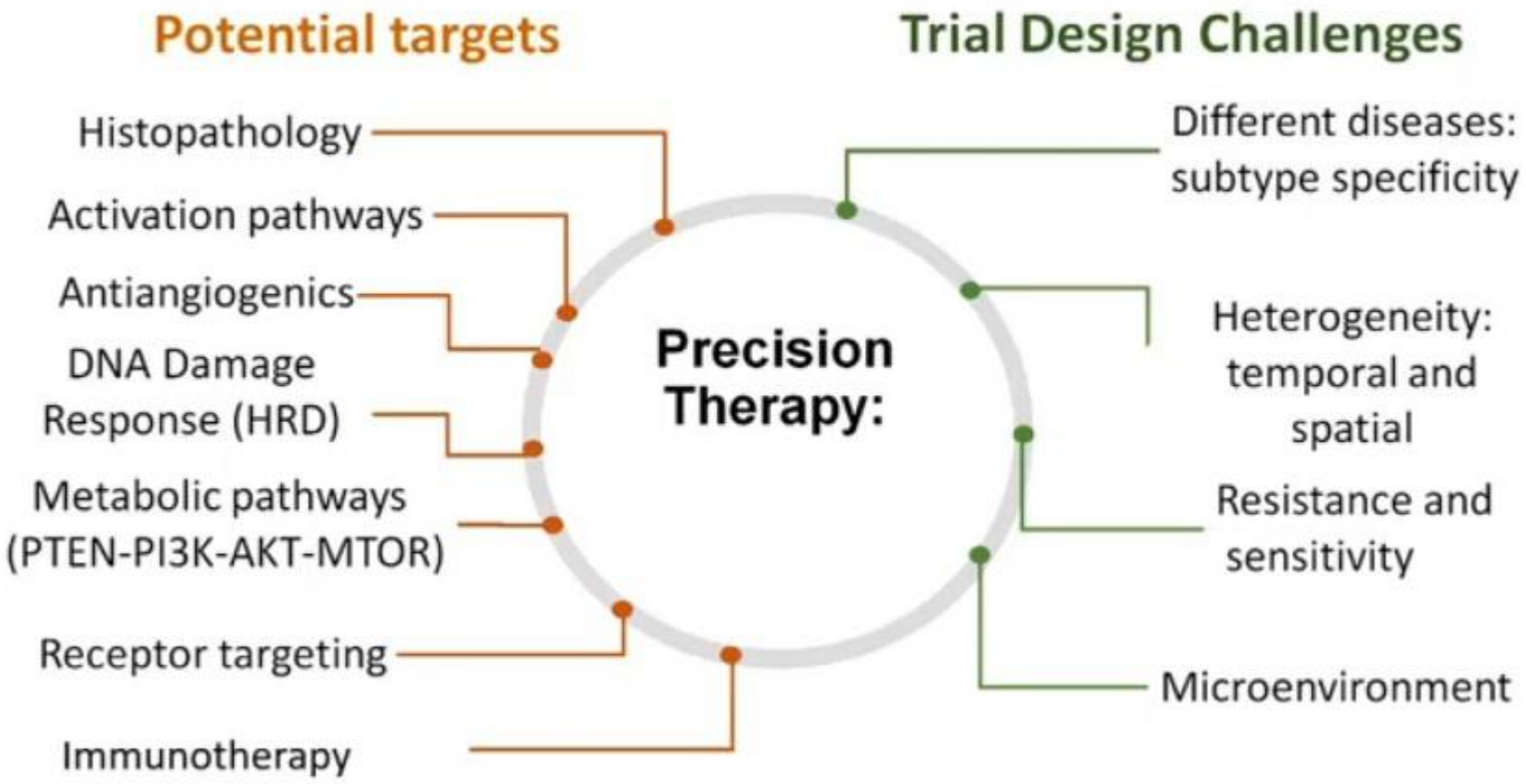
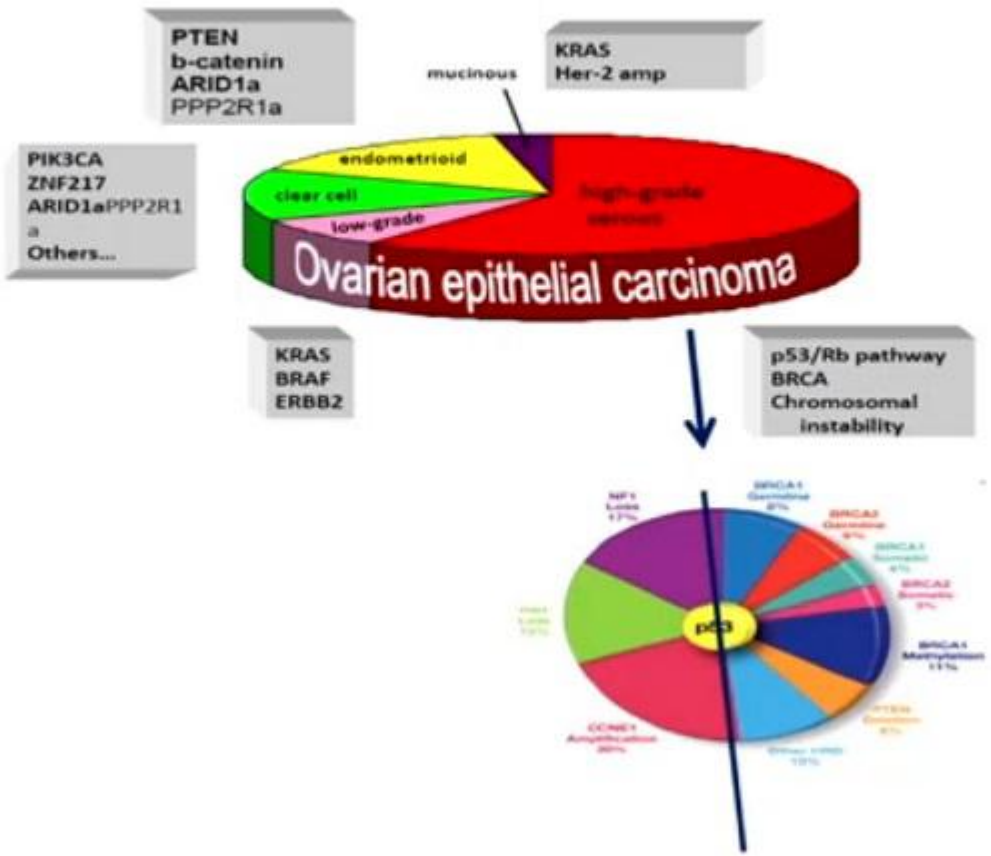
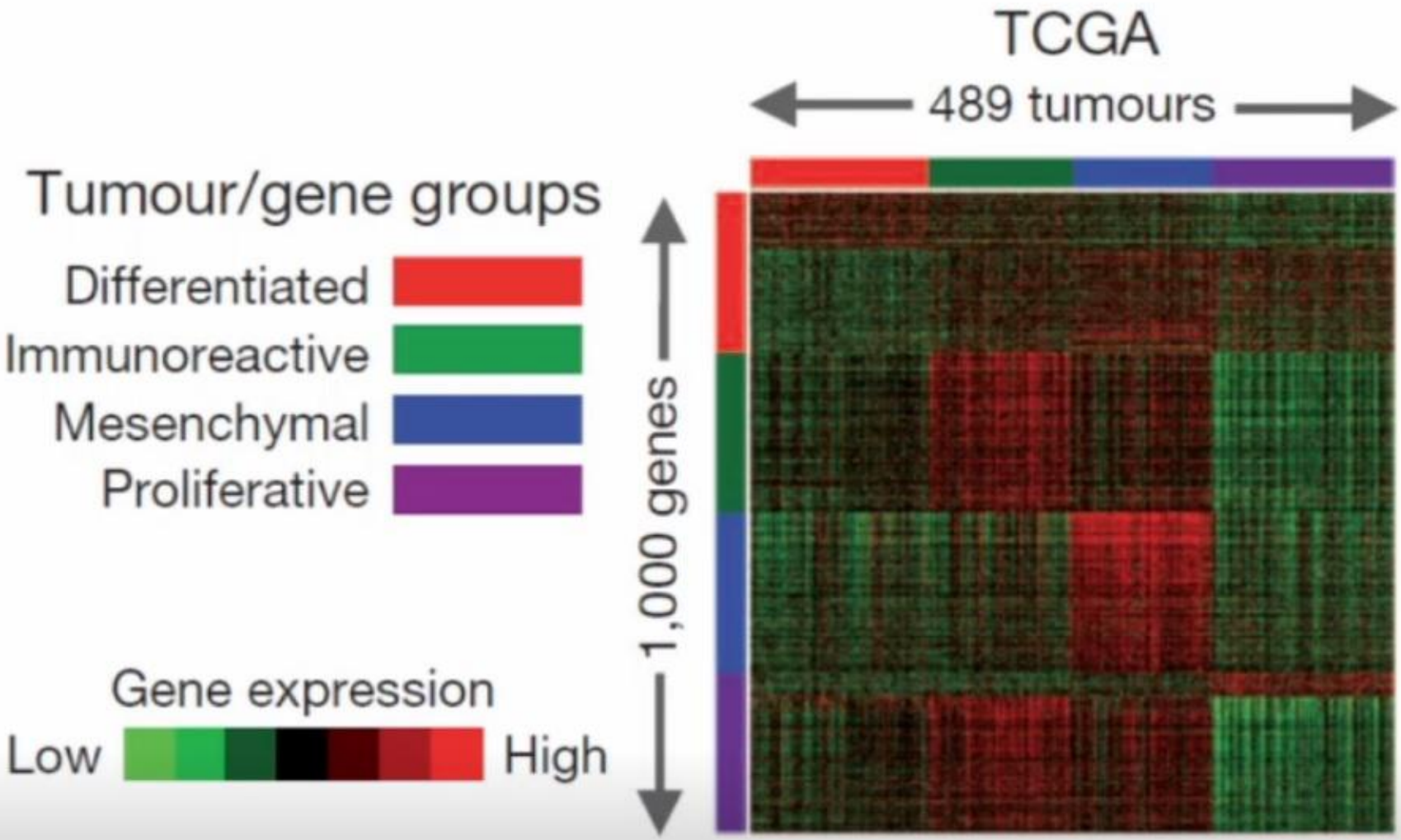

Potential targets
Histopathology
Activation pathways
Antiangiogenics
DNA Damage Response (HRD)
Metabolic pathways (PTEN-PI3K-AKT-MTOR)
Receptor targeting
Immunotherapy
Precision Therapy:
Trial Design Challenges
Different diseases: subtype specificity
Heterogeneity: temporal and spatial
Resistance and sensitivity
Microenvironment

# Distinctive molecular alterations in ovarian cancer subtypes




TCGA
489 tumours
Tumour/gene groups
Differentiated
Immunoreactive
Mesenchymal
Proliferative
1,000 genes
Gene expression
Low
High

## Anti-agiogenics in Ovarian Cancer
## Many studies
## Approval and use manly limited to Bevacizumab

### First line

- Improve PFS
- Improve Survival in high-risk disease
  - Sub-optimally debulked
  - Residual disease
- IV vs IP
  - Addition of Bev means no difference between IV and IP
- Standard IV vs Dose Dense paclitaxel
  - No difference in dose dense
  - Improves standard 3w schedule PFS

### Recurrent Disease

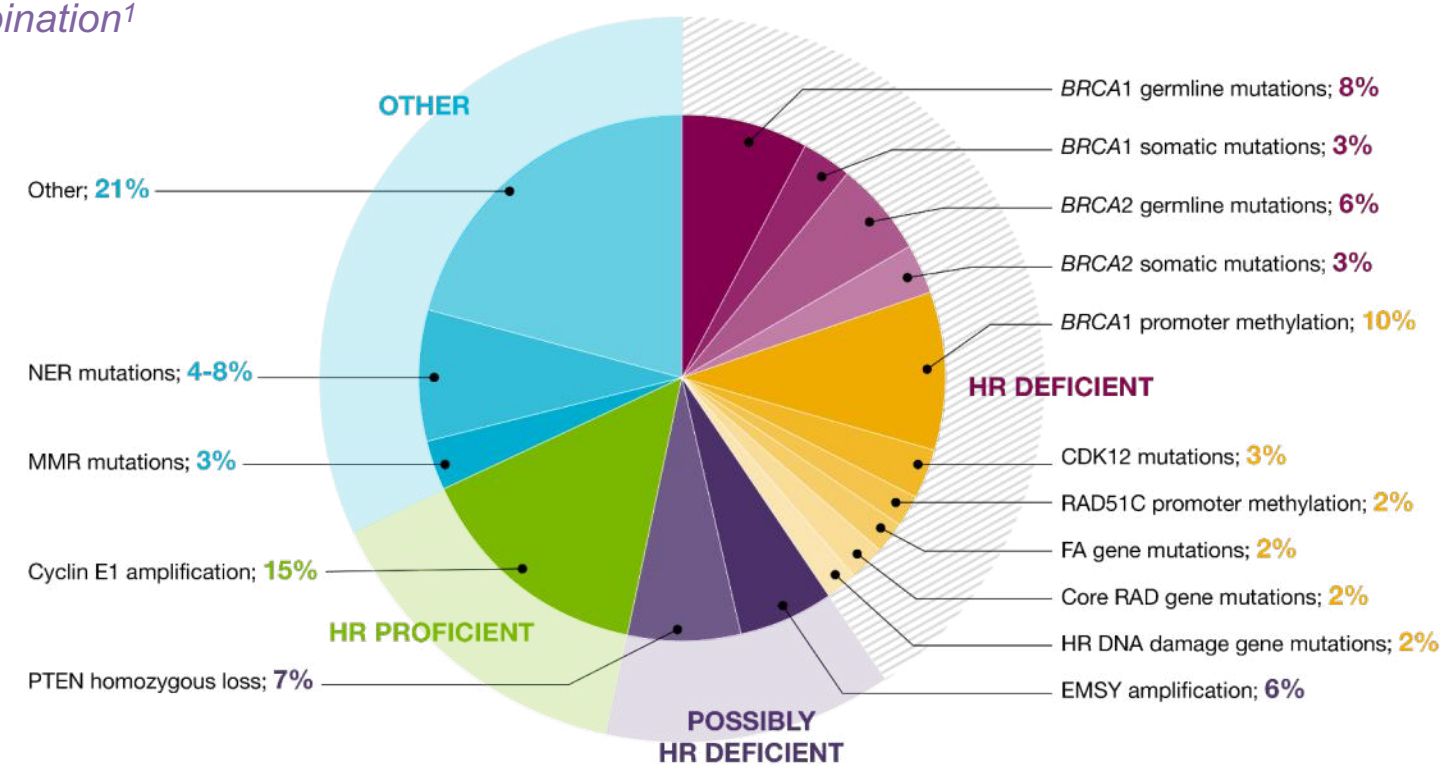
- Platinum Sensitive
  - Oceans Trial: Improved PFS (not OS)
  - GOG213: Improved PFS
  - ICON6: Cediranib improves PFS
    - Power and Toxicity
- Platinum Resistant
  - Aurelia: Improves PFS,
  - QL, OS in weekly taxol
- Single Agent Bevacizumab
  - Controls ascites/effusions
  - Palliative benefit

Predictive Biomarkers remain elusive

How best to combine with other targeted agents and immunotherapy

# Rationale for PARP inhibitor use in ovarian cancer

*Approximately half of high grade serous ovarian cancers harbour defects in homologous recombination[1]*





- Konstantinopoulos PA et al. *Cancer Discov*. 2015;5(11):1137-54.

# Olaparib in platinum-sensitive relapsed ovarian cancer

- There are two pivotal studies of olaparib maintenance therapy in relapsed, platinum-sensitive ovarian cancer; both of which found olaparib improved progression-free survival (PFS) in the patient population[1-5]

solo2
BRCAm Ovarian Cancer

**Study 19**

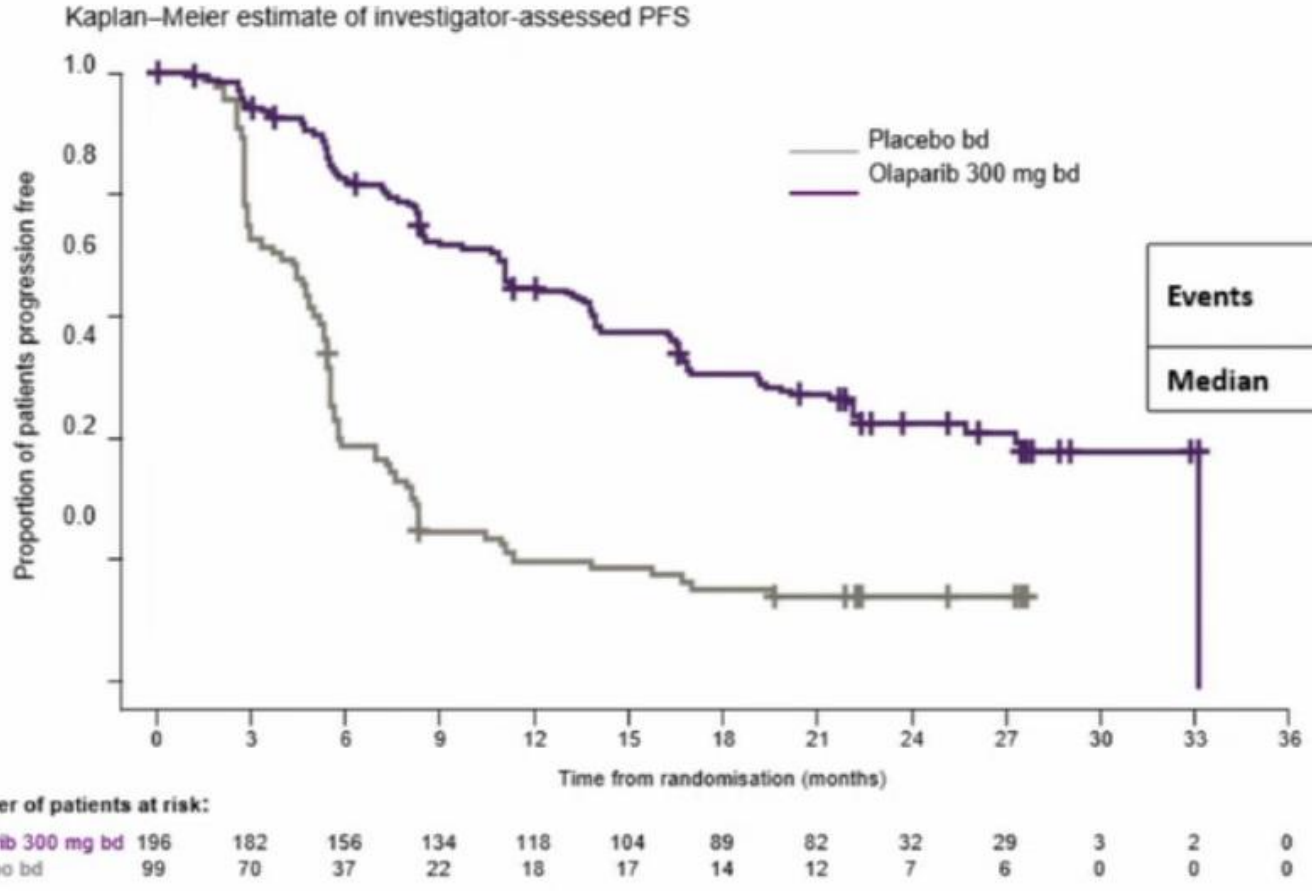
- Olaparib **tablets** significantly prolonged PFS in a *BRCA*m population compared with placebo (HR 0.30; 95% CI: 0.22–0.41; p<0.0001)[2]
- Olaparib **capsules** significantly prolonged PFS compared with placebo (HR 0.35; 95% CI: 0.25–0.49; p<0.001), regardless of *BRCA*m status[1]
- Unique dataset, with approximately 20% of patients still receiving olaparib treatment after 3 years and over 10% of patients remaining on treatment after 6 years[1,5]

- In both studies, adverse events reported were generally mild to moderate, and manageable with supportive treatment and dose modifications[1-5]


- 1. Ledermann J et al. *N Engl J Med* 2012;366(15):1382-92; 2. Pujade-Lauraine E et al. *Lancet Oncol* 2017;18(9):1274–1284; 3. Ledermann J, et al. *Lancet Oncol*. 2016;17(11):1579–1589; 4. Ledermann J, et al. *Lancet Oncol*. 2014;15:852–861; 5. Friedlander M et al. *Br J Cancer* 2018;119(9):1075-1085.

# SOLO-2: Olaparib maintenance therapy significantly extended investigator-assessed PFS compared with placebo[1]

*Risk of progression or death during the study was reduced by 70% for patients taking olaparib[1]*




| | Olaparib 300mg bd | Placebo |
|---|---|---|
| **Events** | 107/196 (54.6%) | 80/99 (80.8%) |
| **Median** | 19.1 m | 5.5 m |
| | **HR = 0.30** 95% CI: (0.22–0.41) p<0.0001 | |

Investigator-assessed PFS at 63% maturity. Median follow-up for PFS was 22.1 months in the olaparib group and 22.2 months for placebo.
Full assessment set n=295, data cut-off: 19 September 2016.

1. Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18:1274–1284

# The state of PARP Inhibitors in Ovarian Cancer

| Agent | Trial | Volunteer and Study criteria | | | | Efficacy | Toxicity |
|---|---|---|---|---|---|---|---|
| | | ROC | HGS | gBRCA | Maint | | |
| Niraparib | NOVA[1] (n=546) | ∫ | ∫ | | ∫ | +++PFS in gBRCA+ and gBRCA- | Nausea, Thrombocytopenia, Fatigue, Anemia |
| Olaparib | SOLO-2[2] (n=295) | ∫ | ∫ | ∫ | ∫ | +++PFS | Nausea, Fatigue, Anemia, Emesis |
| | Phase 2[3] (n=193) | ∫ | ∫ | ∫ | | 30%ORR 40%SD8w | Fatigue, Nausea, Anemia, Abdominal pain |
| Rucaparib | ARIEL-3[4] | ∫ ≥3 lines | ∫ | | ∫ | +++PFS in gBRCA+, LOH+, ITT | Nausea, Fatigue, Anemia, Constipation |
| | Phase 2[5] (n=106) | ∫ ≥2 lines | ∫ | ∫ Somatic allowed | | 54% ORR 9m mDOR | Nausea, Fatigue, Anemia, Abdominal pain |

(1) Mirza, et al. NEJM 2016; 375:2154-64; (2) Pujade-Lauraine, et al. Lancet Oncol 2017; 18:1274-84; (3) Ledermann, et al. Lancet Oncol 2014; 15:852-61; (4) Coleman, et al. Lancet 2017; 390:1949-61; (5) Oza, et al. Gynecol Oncol 2017; 147:267-75.



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# Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

# The first Phase III trial to investigate maintenance therapy with a PARP inhibitor in newly diagnosed ovarian cancer

SOLO1 BRCAm Ovarian Cancer

*SOLO-1 is a global randomised multicentre placebo controlled Phase III study*

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

Olaparib 300 mg bid (N=260)

2:1 randomisation

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- 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 years' treatment if no evidence of disease**

**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)

- *Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease
- BICR = blinded independent central review; 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; PARP = poly (ADP-ribose) polymerase; *BRCA*m = *BRCA* gene mutation

Moore K et al. *N Engl J Med* 2018;379(26):2495-2505.

# Baseline characteristics were well balanced between treatment groups

| Characteristic | Olaparib (N=260) | Placebo (N=131) |
|---|---|---|
| **Median age, years (range)** | 53.0 (29–82) | 53.0 (31–84) |
| **Response after platinum-based chemotherapy, N (%)** | | |
| Clinical complete response* | 213 (81.9) | 107 (81.7) |
| Partial response† | 47 (18.1) | 24 (18.3) |
| **ECOG performance status, N (%)** | | |
| 0 | 200 (76.9) | 105 (80.2) |
| 1 | 60 (23.1) | 25 (19.1) |
| Missing | 0 | 1 (0.8) |
| **Primary tumour location, N (%)** | | |
| Ovary | 220 (84.6) | 113 (86.3) |
| Fallopian tubes | 22 (8.5) | 11 (8.4) |
| Primary peritoneal | 15 (5.8) | 7 (5.3) |
| Other‡ | 3 (1.2) | 0 |
| **FIGO stage, N (%)** | | |
| III | 220 (84.6) | 105 (80.2) |
| IV | 40 (15.4) | 26 (19.8) |

- *Clinical complete response was defined as no evidence of (RECIST) measurable or non-measurable disease on the post-treatment scan and a normal CA-125 level.
- †Partial response was defined as a ≥30% reduction in tumour volume from the start to the end of chemotherapy or no evidence of disease on the post-treatment scan, but with a CA-125 level which had not decreased to within the normal range
- ‡Other includes ovary, fallopian tube, peritoneum, and omentum (N=1), ovary and peritoneum (N=1) and tubo-ovary (N=1)
- ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynecology and Obstetrics
- Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print

# Two thirds of patients had upfront surgery

| History of cytoreductive surgery, N (%) | Olaparib (N=260) | Placebo (N=131) |
|---|---|---|
| **Upfront surgery** | **161 (61.9)** | **85 (64.9)** |
| Residual macroscopic disease | 37 (23.0) | 22 (25.9) |
| No residual macroscopic disease | 123 (76.4) | 62 (72.9) |
| Unknown | 1 (0.6) | 1 (1.2) |
| **Interval cytoreductive surgery** | **94 (36.2)** | **43 (32.8)** |
| Residual macroscopic disease | 18 (19.1) | 7 (16.3) |
| No residual macroscopic disease | 76 (80.9) | 36 (83.7) |
| **No surgery** | **4 (1.5)** | **3 (2.3)** |

* Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print [supplementary appendix]

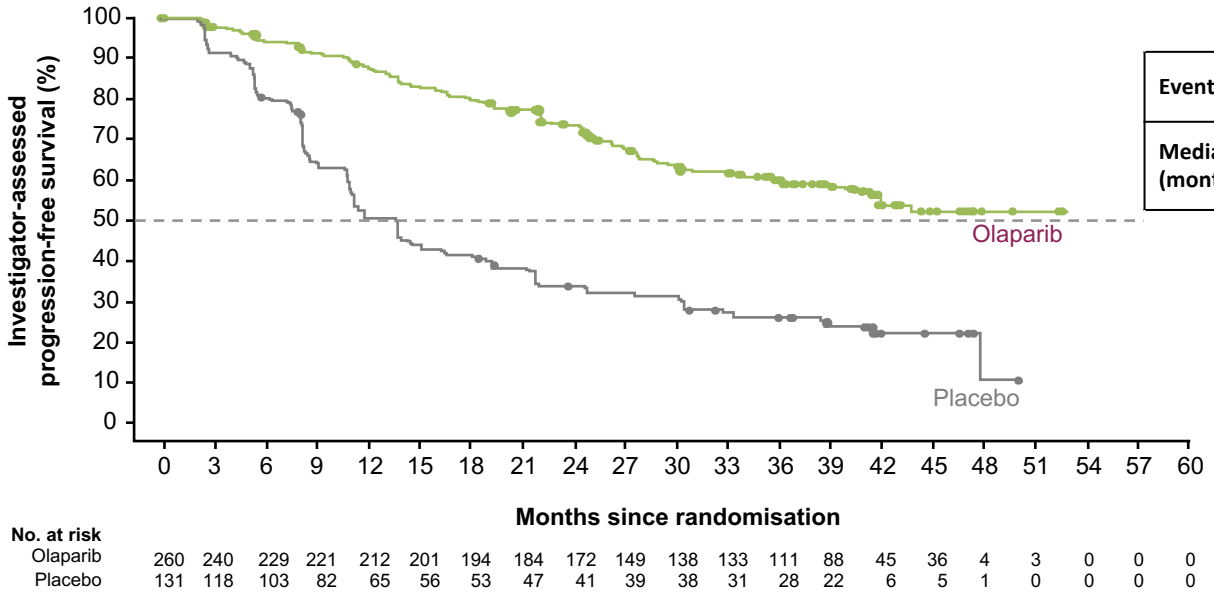
# The majority of patients received carboplatin and paclitaxel for 6 cycles

| Characteristic | Olaparib (N=260) | Placebo (N=131) |
|---|---|---|
| **Agents administered during platinum-based chemotherapy prior to randomisation** | | |
| Bevacizumab | 1 (0.4) | 0 |
| Carboplatin | 241 (92.7) | 115 (87.8) |
| Cisplatin | 46 (17.7) | 32 (24.4) |
| Cyclophosphamide | 1 (0.4) | 0 |
| Docetaxel | 15 (5.8) | 7 (5.3) |
| Doxorubicin | 1 (0.4) | 0 |
| Doxorubicin hydrochloride | 1 (0.4) | 0 |
| Gemcitabine | 2 (0.8) | 1 (0.8) |
| Nab-paclitaxel | 2 (0.8) | 0 |
| Paclitaxel | 253 (97.3) | 130 (99.2) |
| **Number of cycles of platinum-based chemotherapy, N (%)** | | |
| 4 | 2 (0.8) | 0 |
| 5 | 2 (0.8) | 1 (0.8) |
| 6 | 198 (76.2) | 106 (80.9) |
| 7 | 17 (6.5) | 10 (7.6) |
| 8 | 18 (6.9) | 7 (5.3) |
| 9 | 23 (8.8) | 7 (5.3) |

* Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print [supplementary appendix]

# Olaparib reduced the risk of progression or death by 70% vs. placebo[1]

*After a median follow-up of 41 months, the median PFS had not been reached in the olaparib arm (vs. 13.8 months in the placebo arm)[1]*




| | Olaparib | Placebo |
|---|---|---|
| **Events, N (%)** | 102 (39.2) | 96 (73.3) |
| **Median PFS (months)** | NR | 13.8 |
| | **HR=0.30** 95% CI: 0.23, 0.41 p<0.001 | |

**Primary endpoint:** investigator-assessed PFS

- DCO: May 2018; Median FU: olaparib, 40.7 months placebo, 41.2 months
- Analysis was performed after 198 progression events had occurred (in 50.6% of patients)
- PFS = progression-free survival; DCO = data cut-off; HR = hazard ratio; CI = confidence interval
- Moore K et al. *N Engl J Med* 2018;379(26):2495-2505.

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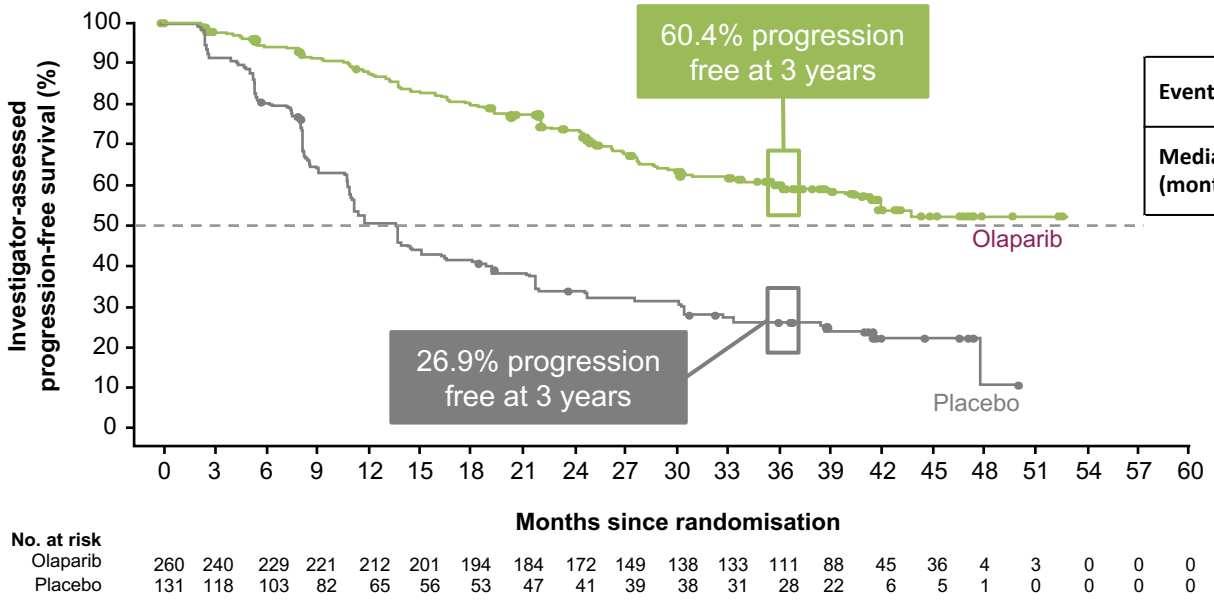


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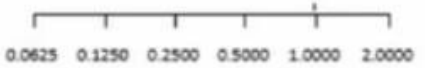
# A consistent benefit was seen across all PFS subgroups

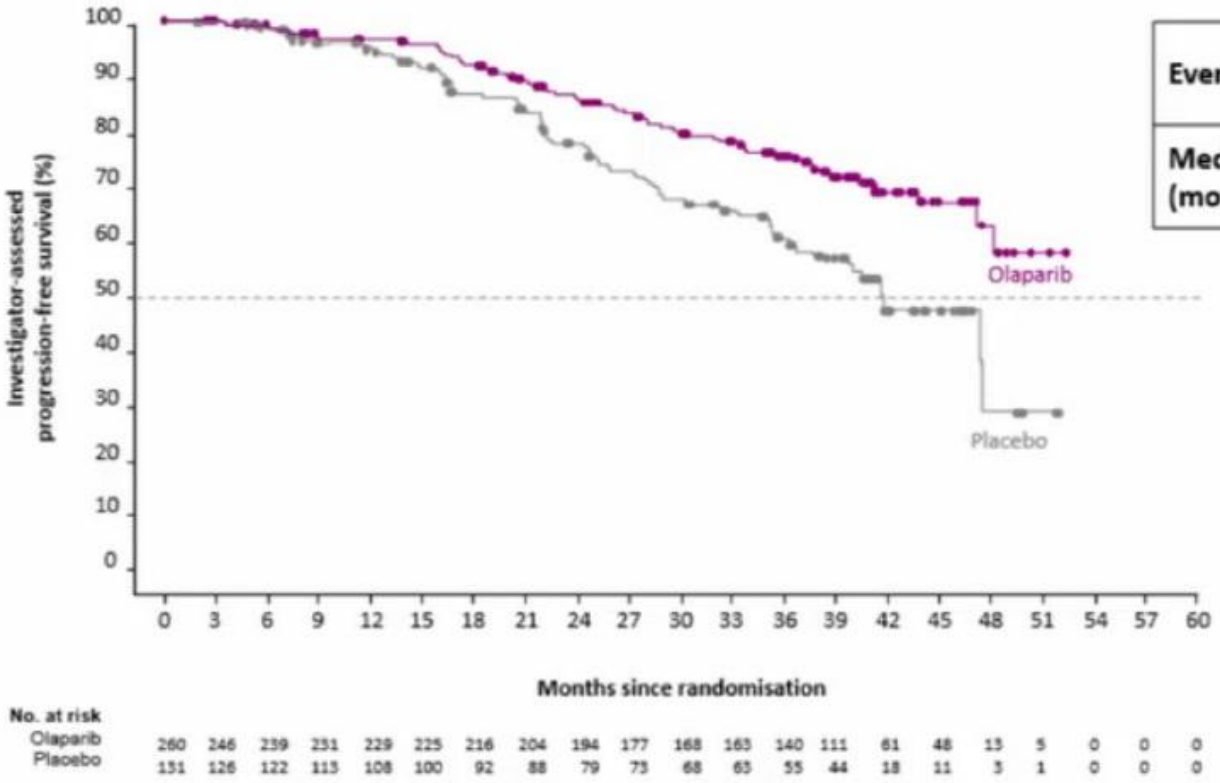
| Subgroup | Olaparib 300 mg bid<br>Number of patients with events/total number of patients (%) | Placebo bid<br>Number of patients with events/total number of patients (%) | HR (95% CI) |
|---|---|---|---|
| All patients | 102/260 (39.2) | 96/131 (73.3) | 0.30 (0.23, 0.41) |
| Response to previous chemotherapy | | | |
| Complete response | 73/213 (34.3) | 73/107 (68.2) | 0.35 (0.26, 0.49) |
| Partial response | 29/47 (61.7) | 23/24 (95.8) | 0.19 (0.11, 0.34) |
| ECOG performance status at baseline | | | |
| Normal activity | 75/200 (37.5) | 76/105 (72.4) | 0.33 (0.24, 0.46) |
| Restricted activity | 27/60 (45.0) | 20/25 (80.0) | 0.38 (0.21, 0.68) |
| Baseline CA-125 value | | | |
| ≤ULN | 92/247 (37.2) | 89/123 (72.4) | 0.34 (0.25, 0.46) |
| >ULN | 10/13 (76.9) | 7/7 (100.0) | NC |
| g*BRCA* mutation type by Myriad testing | | | |
| *BRCA1* | 84/188 (44.7) | 69/91 (75.8) | 0.40 (0.29, 0.56) |
| *BRCA2* | 15/62 (24.2) | 26/39 (66.7) | 0.20 (0.10, 0.38) |
| *BRCA1/2* (both) | 0/3 | 0/0 | NC |
| Negative | 3/7 (42.9) | 1/1 (100.0) | |
| Age | | | |
| <65 years | 85/225 (37.8) | 82/112 (73.2) | 0.33 (0.24, 0.45) |
| ≥65 years | 17/35 (48.6) | 14/19 (73.7) | 0.45 (0.22, 0.92) |
| Stage of disease at initial diagnosis | | | |
| Stage III | 83/220 (37.7) | 79/105 (75.2) | 0.32 (0.24, 0.44) |
| Stage IV | 19/40 (47.5) | 17/26 (65.4) | 0.49 (0.25, 0.94) |
| Following debulking surgery prior to study entry | | | |
| Residual macroscopic disease | 29/55 (52.7) | 23/29 (79.3) | 0.44 (0.25, 0.77) |
| No residual macroscopic disease | 70/200 (35.0) | 69/98 (70.4) | 0.33 (0.23, 0.46) |




- DCO: May 2018; Median FU: olaparib, 40.7 months placebo, 41.2 months
- ECOG = Eastern Cooperative Oncology Group; ULN = upper limit of normal; PFS = progression-free survival; CA-125 = cancer antigen 125; DCO = data cut-off; HR = hazard ratio
- 1. Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

# A 50% reduction in the risk of second progression or death was observed in SOLO-1

*This demonstrates that olaparib maintenance does not diminish the benefit conferred by subsequent therapy*

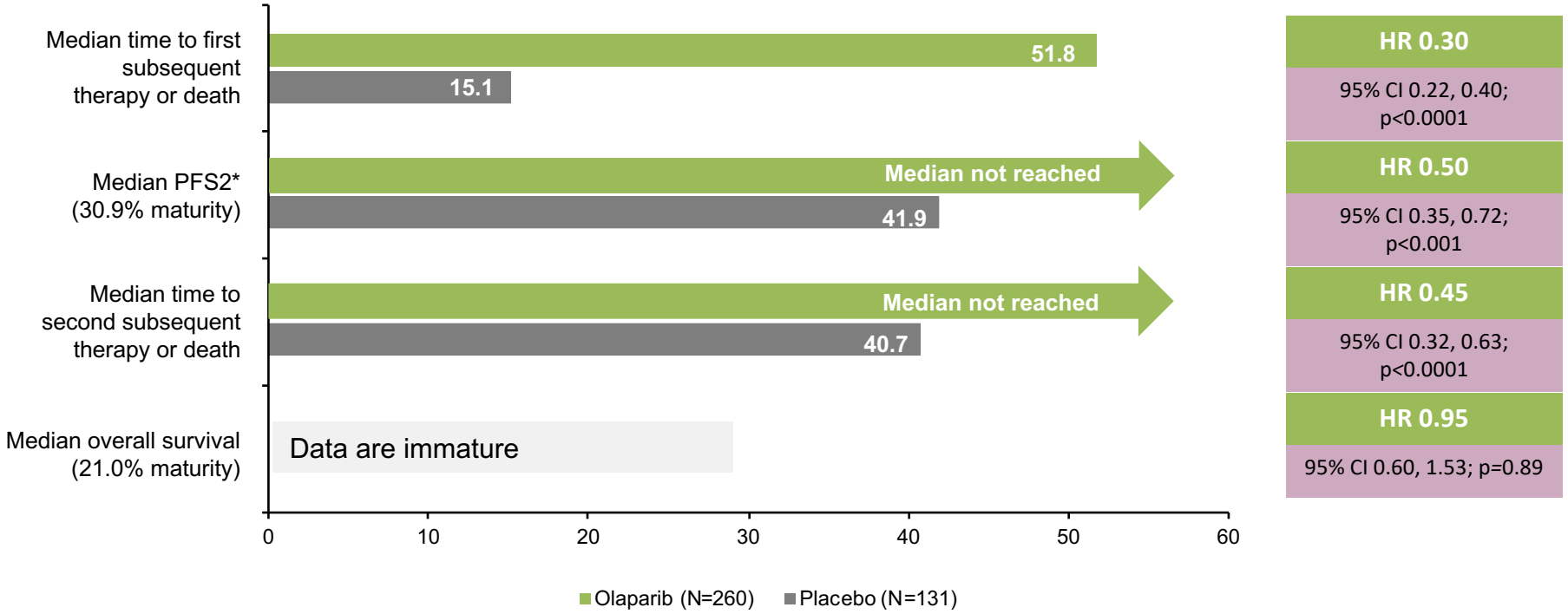



| | Olaparib | Placebo |
|---|---|---|
| **Events, N (%)** | 69 (26.5) | 52 (39.7) |
| **Median PFS2 (months)** | NR | 41.9 |
| | **HR=0.50** 95% CI: 0.35, 0.72; p<0.001 | |

In 2nd line, PARP inhibitor was used in 33/94 (35%) and 10/91 (11%) of patients who received a subsequent therapy in the placebo and olaparib arms respectively

- DCO: May 2018; Median FU: olaparib, 40.7 months placebo, 41.2 months
- Data maturity at 30.9%
- PFS2 = progression-free survival 2; DCO = data cut-off; HR = hazard ratio; PARP = poly (ADP-ribose) polymerase
- 1. Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

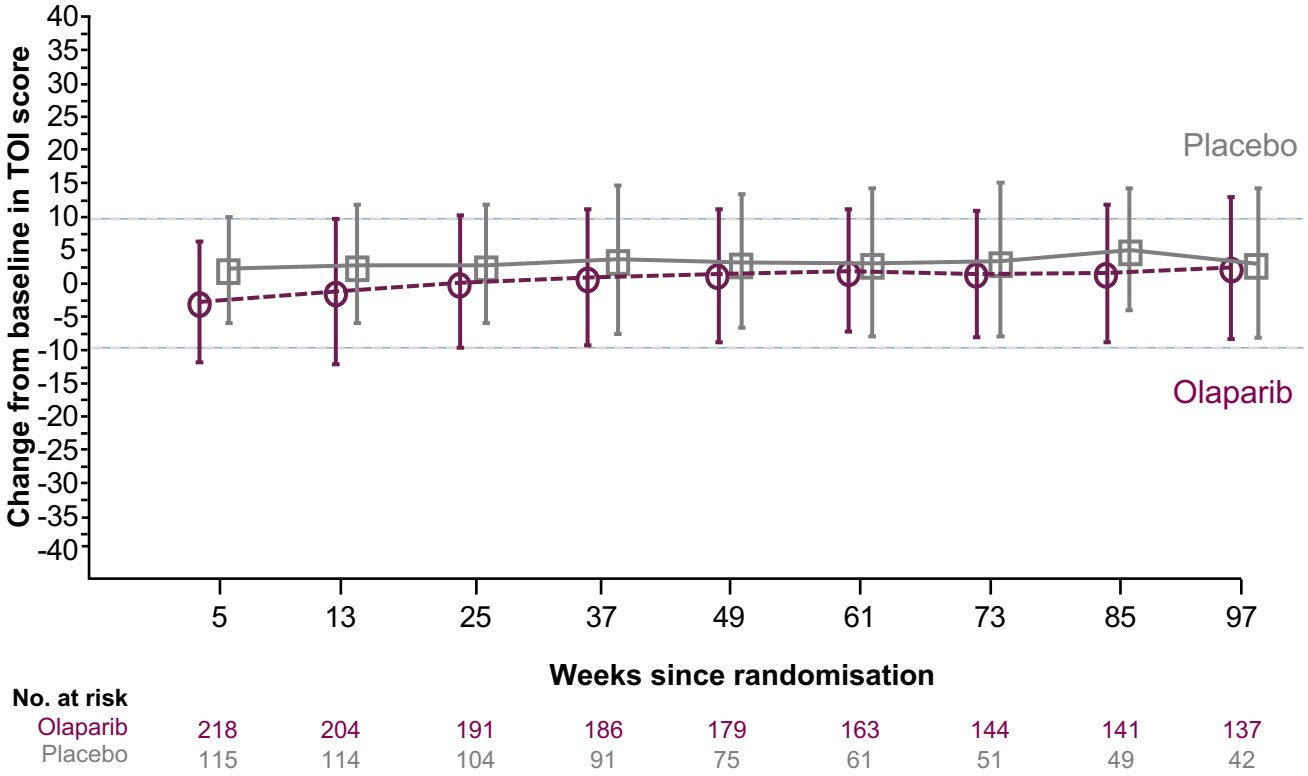
# Efficacy of olaparib was observed beyond a range of efficacy endpoints vs. placebo




- *Time from randomisation to second progression or death; in second line, a PARP inhibitor was used in 33/94 (35%) patients in the placebo arm and 10/91 (11%) patients in the olaparib arm
- DCO: May 2018
- PFS2 = progression-free survival 2; DCO = data cut-off; HR = hazard ratio; CI = confidence interval

Moore K et al. *N Engl J Med* 2018;379(26):2495-2505.

# There was no clinically meaningful difference in HRQoL between arms



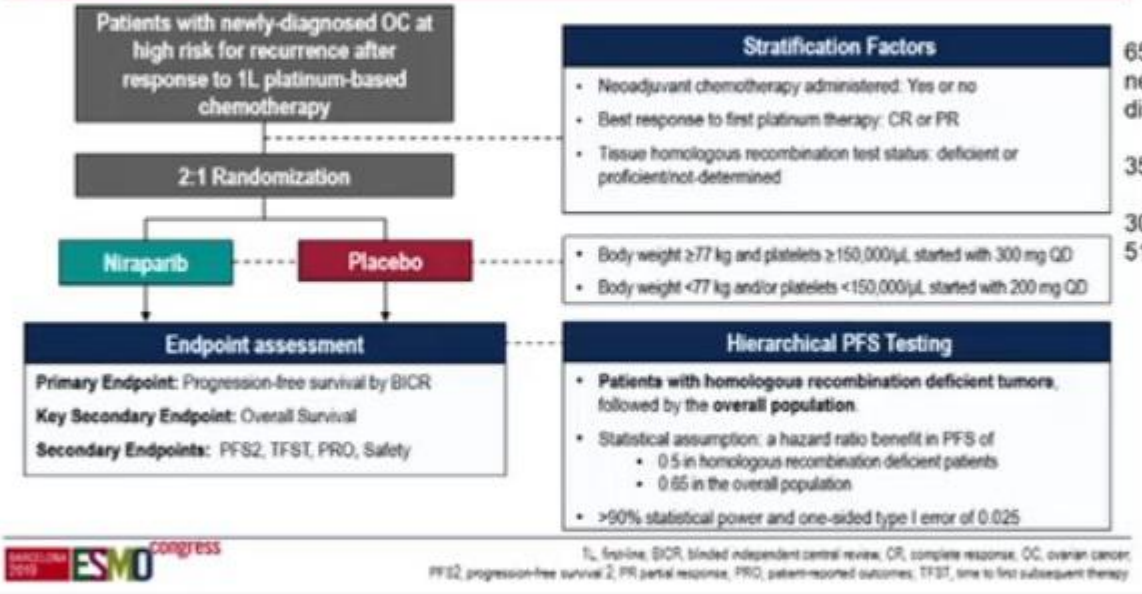

| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Olaparib | 218 | 204 | 191 | 186 | 179 | 163 | 144 | 141 | 137 |
| Placebo | 115 | 114 | 104 | 91 | 75 | 61 | 51 | 49 | 42 |

The difference between olaparib and placebo in the mean change from baseline in TOI score over 24 months (−3.00; 95% CI −4.779, −1.216) was not clinically meaningful

- *TOI scores range from 0 to 100, with higher scores indicating better HRQoL and a clinically meaningful difference defined as ±10 points
- HRQoL = health-related quality of life; TOI = trial outcome index; CI = confidence interval
- Moore K et al. *N Engl J Med* 2018;379(26):2495-2505.

# First line maintenance in Ovarian Cancer

## PRIMA Trial Design




65% stage III neoadjuvand with residual disease after surgery

35% stage IV

30% BRCA mut
51% HRD (+)

1L, first-line; BICR, blinded independent central review; CR, complete response; OC, ovarian cancer; PFS2, progression-free survival 2; PR partial response; PRO, patient-reported outcomes; TFST, time to first subsequent therapy

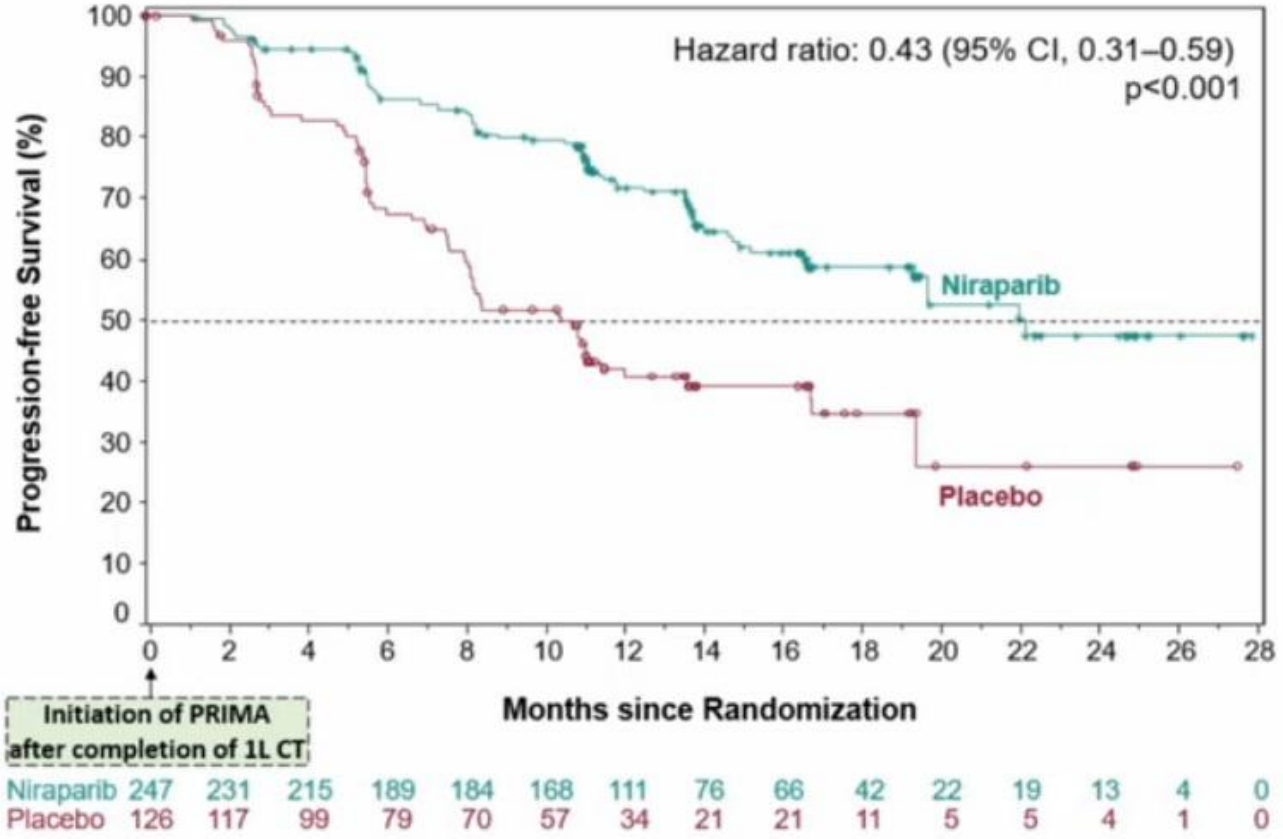
# PRIMA Patient Characteristics and Baseline Demographics

| Characteristic | Niraparib (n=487) | Placebo (n=246) | Overall (N=733) |
|---|---|---|---|
| Age, median (range), years | 62 (32, 85) | 62 (33,88) | 62 (32, 88) |
| Weight, median, kg | 66 | 66 | 66 |
| Stage at initial diagnosis, n (%) | | | |
| III | 318 (65) | 158 (64) | 476 (65) |
| IV | 169 (35) | 88 (36) | 257 (35) |
| Prior NACT, n (%) | | | |
| Yes | 322 (66) | 167 (68) | 489 (67) |
| No | 165 (34) | 79 (32) | 244 (33) |
| Best response to platinum-based CT, n (%) | | | |
| CR | 337 (69) | 172 (70) | 509 (69) |
| PR | 150 (31) | 74 (30) | 224 (31) |
| Homologous recombination test status, n (%) | | | |
| HRd | 247 (51) | 126 (51) | 373 (51) |
| *BRCA*mut | 152 (31) | 71 (29) | 223 (30) |
| *BRCA*wt | 95 (20) | 55 (22) | 150 (20) |
| HRp | 169 (35) | 80 (33) | 249 (34) |
| HRnd | 71 (15) | 40 (16) | 111 (15) |

- 35% of patients were Stage IV
- 99.6% with Stage III had residual disease post PDS
- 67% received NACT
- 31% achieved a PR to 1L CT
- 51% had HRd tumors
- 30% had *BRCA*mut tumors
- 34% had HRp tumors

1L, first-line; CR, complete response; CT, chemotherapy; HRd, homologous recombination deficient; HRp, homologous recombination proficient; HRnd, homologous recombination not determined; mut, mutation; NACT, neoadjuvant chemotherapy; PR, partial response; wt, wild-type.

# PRIMA Primary Endpoint, PFS Benefit in the HR-deficient Population



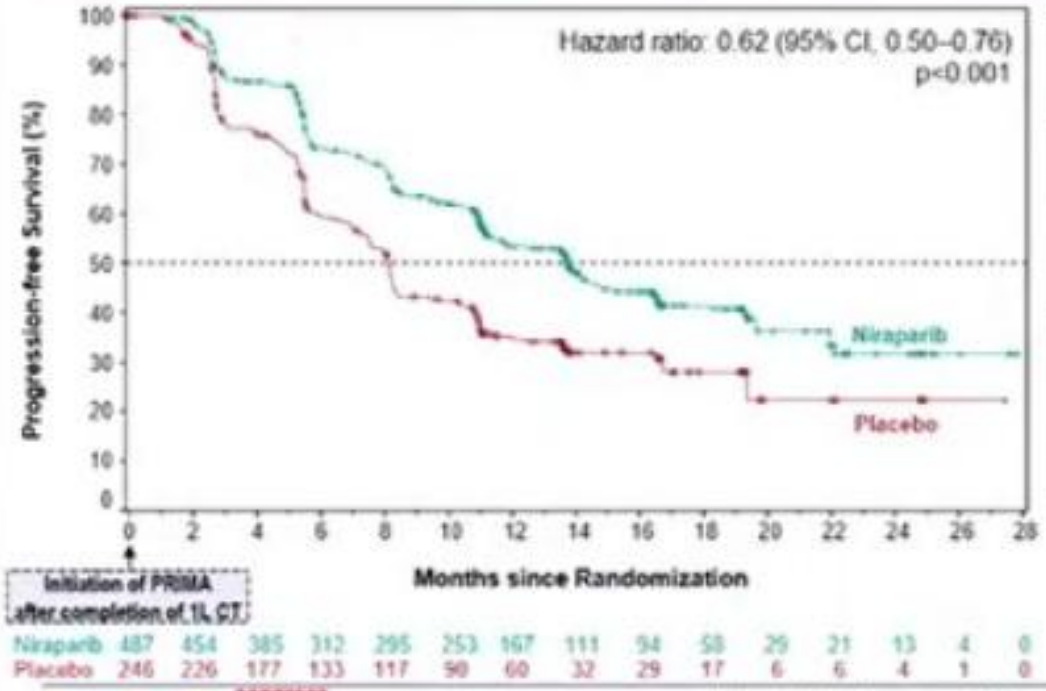

**57% reduction in risk of relapse or death with niraparib**

| | Niraparib (n=247) | Placebo (n=126) |
|---|---|---|
| **Median PFS** | | |
| months (95% CI) | 21.9 (19.3–NE) | 10.4 (8.1–12.1) |
| **Patients without PD or death (%)** | | |
| 6 months | 86% | 68% |
| 12 months | 72% | 42% |
| 18 months | 59% | 35% |

CI, confidence interval; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

# First line maintenance in Ovarian Cancer

## PRIMA Primary Endpoint, PFS Benefit in the Overall Population




| 38% reduction in hazard of relapse or death with niraparib | | |
|---|---|---|
| | Niraparib (n=487) | Placebo (n=246) |
| **Median PFS** | | |
| months (95% CI) | 13.8 (11.5–14.9) | 8.2 (7.3–8.5) |
| **Patients without PD or death (%)** | | |
| 6 months | 73% | 60% |
| 12 months | 53% | 35% |
| 18 months | 42% | 28% |

1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival
Discordance in PFS event between investigator assessment vs BICR >12%

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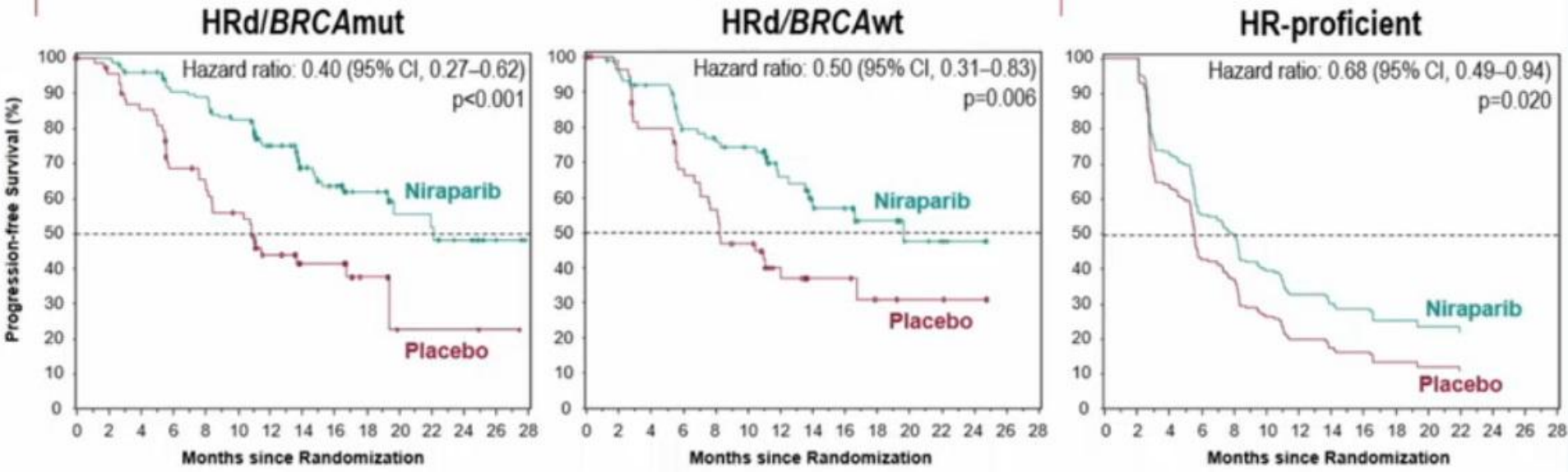
# PRIMA PFS Benefit in Biomarker Subgroups

## Homologous Recombination Deficient (HRd)




- Niraparib provided similar clinical benefit in the HRd subgroups (*BRCA*mut and *BRCA*wt)
- Niraparib provide clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

CI, confidence interval; HRd, homologous recombination deficient; mut, mutation; PFS, progression-free survival wt, wild-type.

# **Study Design:** VELIA/GOG-3005 (NCT02470585)

**Patient Population**

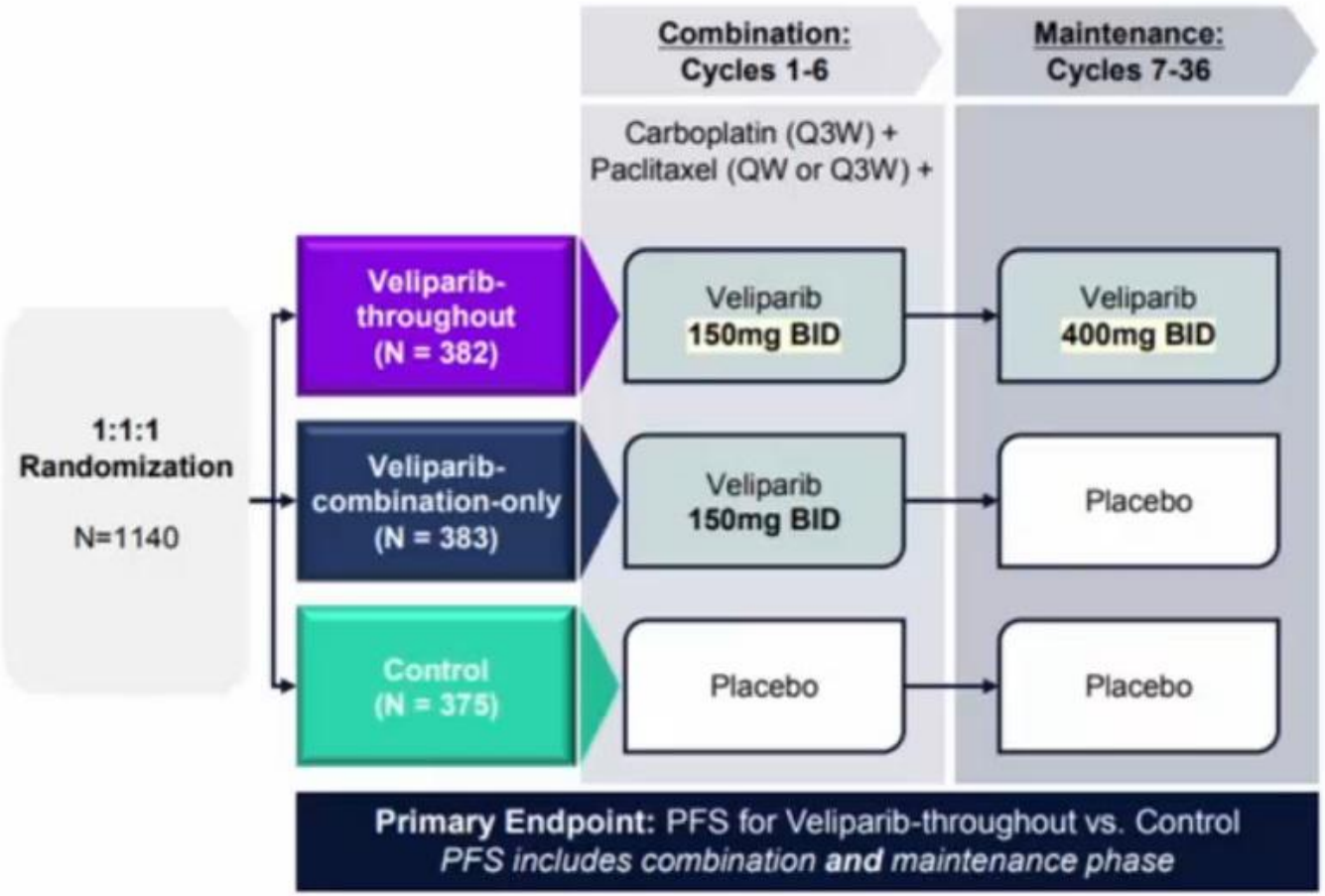
- High-Grade Serous Cancer
- FIGO Stage III or IV
- No Prior Systemic Therapy
- ECOG 0 to 2
- No CNS Metastases

**Stratification Factors**

- Stage of Disease
- Region
- Primary vs Interval Cytoreduction
- Residual Disease
- Chemotherapy Regimen*
- g*BRCA* Status **

* Carboplatin AUC 6 Q3W + Paclitaxel 80 mg/m² QW or 175 mg/m² Q3W

** Added as stratification factor ~14 months after trial initiation due to noted imbalance

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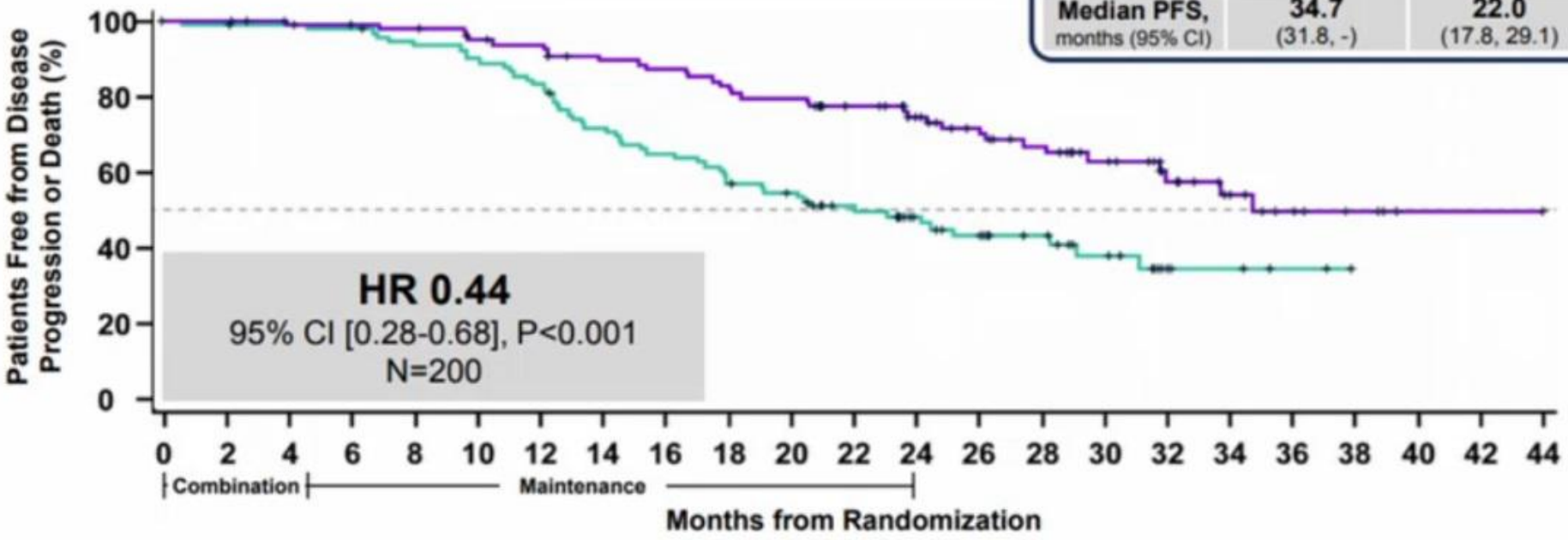
# PFS by Investigator Assessment
## *BRCA*m Population

*BRCA*m | HRD | Non-HRD

| *BRCA*m | Veliparib-throughout | Control |
|---|---|---|
| Events (%) | 34/108 (31.5) | 51/92 (55.4) |
| **Median PFS,** months (95% CI) | **34.7** (31.8, -) | **22.0** (17.8, 29.1) |




No. at Risk

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 92 | 90 | 89 | 88 | 84 | 80 | 74 | 63 | 57 | 50 | 46 | 38 | 29 | 24 | 19 | 13 | 6 | 4 | 2 | 0 | | |
| Veliparib-throughout | 108 | 102 | 99 | 97 | 95 | 90 | 88 | 82 | 80 | 76 | 73 | 65 | 53 | 45 | 38 | 30 | 21 | 14 | 9 | 5 | 1 | 1 | 0 |

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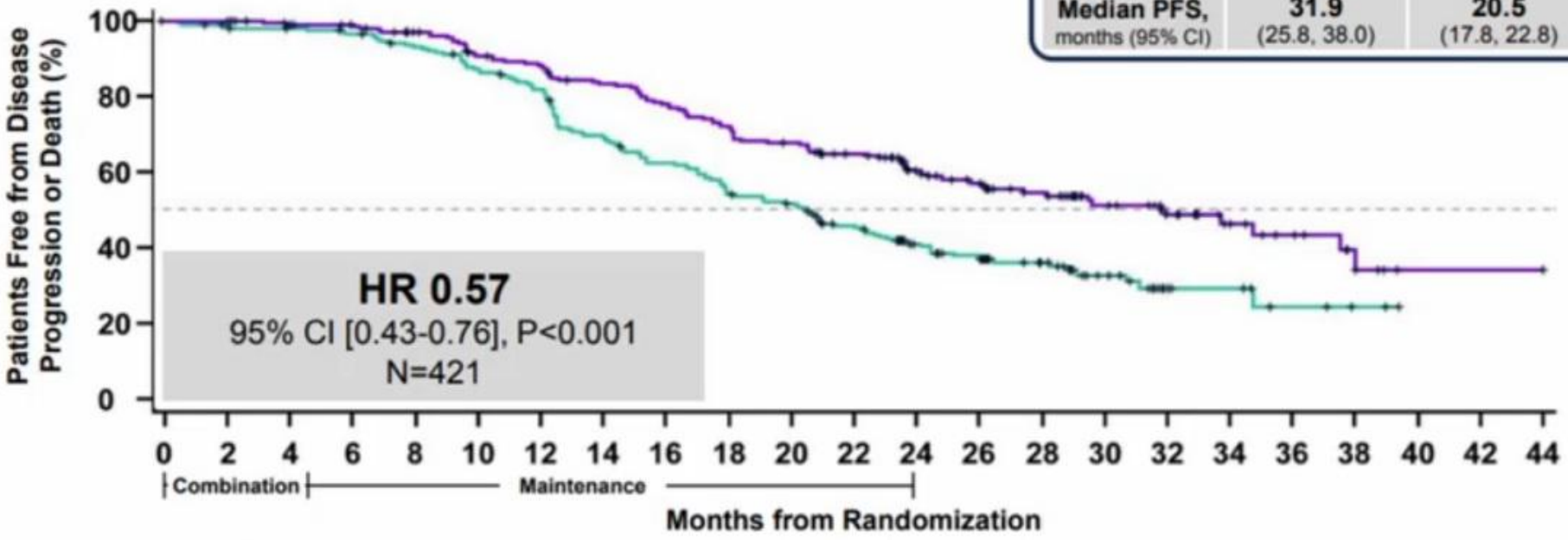
Median duration of follow-up was 28 months at the time of database lock.

# PFS by Investigator Assessment
## HRD Population

*BRCAm* HRD | Non-HRD

| HRD | Veliparib-throughout | Control |
|---|---|---|
| Events (%) | 87/214 (40.7) | 124/207 (59.9) |
| **Median PFS,** months (95% CI) | **31.9** (25.8, 38.0) | **20.5** (17.8, 22.8) |




No. at Risk

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 207 | 199 | 196 | 191 | 183 | 170 | 158 | 134 | 119 | 104 | 97 | 79 | 55 | 47 | 34 | 22 | 11 | 9 | 4 | 2 | 0 | |
| Veliparib-throughout | 214 | 203 | 195 | 191 | 182 | 167 | 161 | 150 | 140 | 130 | 121 | 109 | 82 | 72 | 58 | 44 | 30 | 19 | 14 | 5 | 1 | 1 | 0 |

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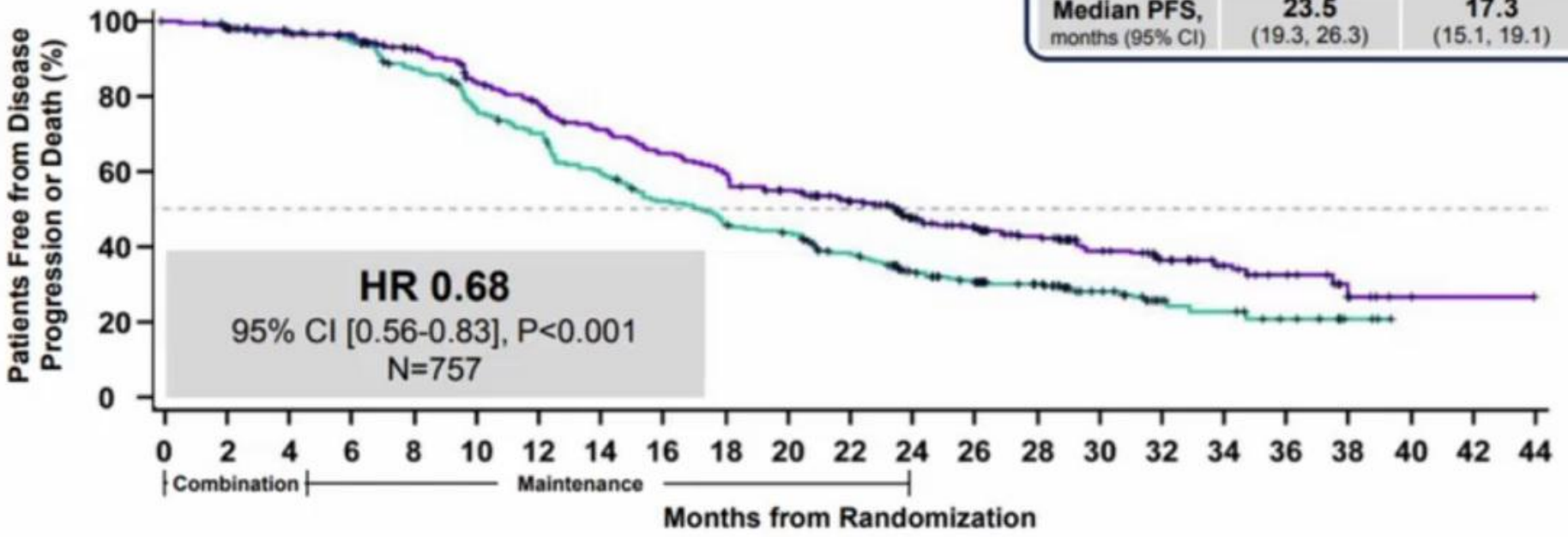
Median duration of follow-up was 28 months at the time of database lock.

# PFS by Investigator Assessment
## ITT Population

*BRCAm* | HRD | Non-HRD

| ITT | Veliparib-throughout | Control |
|---|---|---|
| Events (%) | 191/382 (50.0) | 237/375 (63.2) |
| **Median PFS,** months (95% CI) | **23.5** (19.3, 26.3) | **17.3** (15.1, 19.1) |




No. at Risk

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control | 375 | 356 | 340 | 328 | 297 | 260 | 236 | 202 | 172 | 153 | 143 | 119 | 84 | 70 | 55 | 36 | 21 | 16 | 10 | 3 | 0 | |
| Veliparib-throughout | 382 | 352 | 337 | 329 | 308 | 275 | 253 | 228 | 208 | 192 | 172 | 153 | 111 | 95 | 76 | 55 | 38 | 26 | 19 | 7 | 2 | 1 | 0 |

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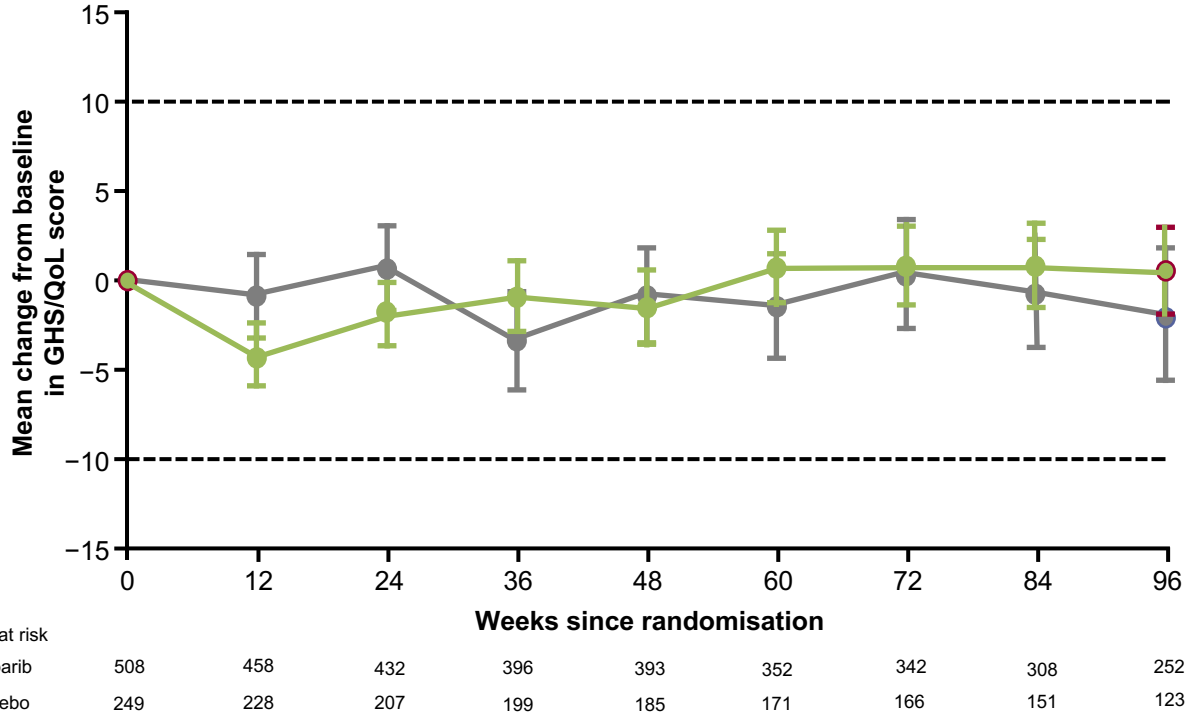
Median duration of follow-up was 28 months at the time of database lock.

# No clinically meaningful or statistically significant difference in HRQoL was seen between treatment arms




| | Olaparib + bevacizumab | Placebo + bevacizumab |
|---|---|---|
| **n** | 498 | 246 |
| **Adjusted mean** | −1.33 | −2.89 |
| **95% CI, *P*** | −2.47 to −0.19, *P*=0.022 | −4.52 to −1.26, *P*=0.0005 |
| **Estimated difference** | **1.56** | |
| **95% CI, *P*** | −0.42 to 3.55, *P*=0.123 | |

CI=confidence interval; GHS=Global health score; HRQoL=health related quality of life; QoL=Quality of life

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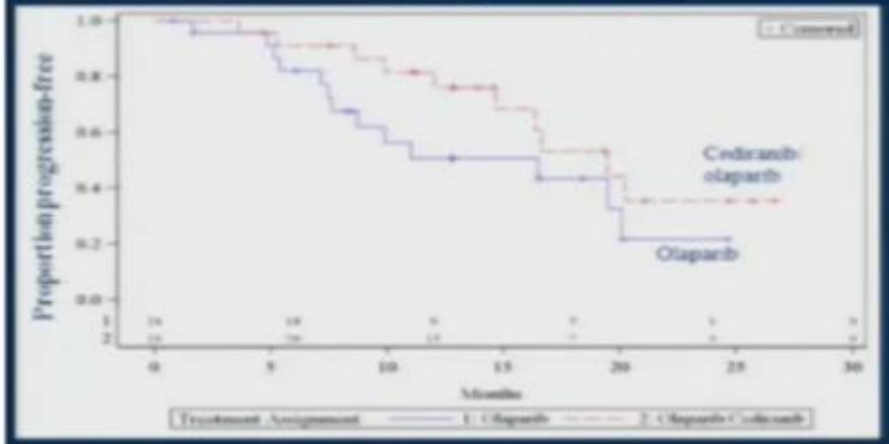
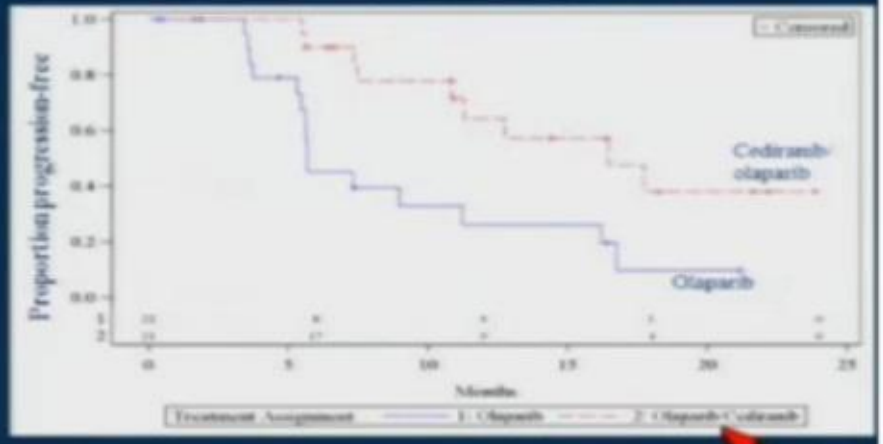
# Olaparib-cediranib combination

## BRCA mutation carrier




## BRCA non-carrier/unknown



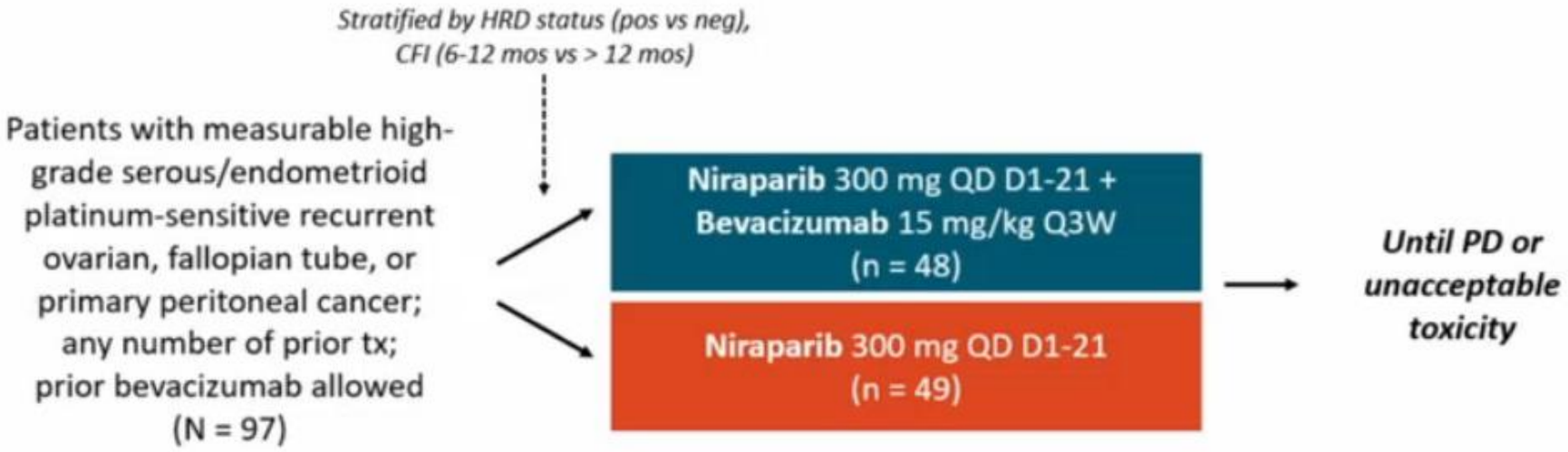

| | BRCA Mutation Carrier | | BRCA Non-carrier/Unknown | |
|---|---|---|---|---|
| | Olaparib | Ced/Olap | Olaparib | Ced/Olap |
| PFS events | 13 | 10 | 15 | 9 |
| Median PFS | 16.5 mo | 19.4 mo | 5.7 mo | 16.5 mo |
| | p=0.16 | | p=0.008 | |
| | HR 0.55 (95% CI: 0.24-1.27) | | HR 0.32 (95% CI: 0.14-0.74) | |

Presented by: Joyce Liu, MD, MPH

PRESENTED AT: ASCO 50 ANNUAL MEETING

# AVANOVA2: Study Design

- Prospective, randomized, open-label phase II trial




- Primary endpoint: PFS in ITT population (investigator assessed)
- Secondary endpoint: DCR

Mirza. ASCO 2019. Abstr 5505. NCT02354131.

# AVANOVA2: PFS in ITT Population (Primary Endpoint)

| Median PFS, Mos | Niraparib + Bevacizumab (n = 48) | Niraparib (n = 49) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| ITT | 11.9 | 5.5 | 0.35 (0.21-0.57) | < .0001 |

- Curves separated early at approximately 2 mos and remained separated until data cutoff

Mirza. ASCO 2019. Abstr 5505.

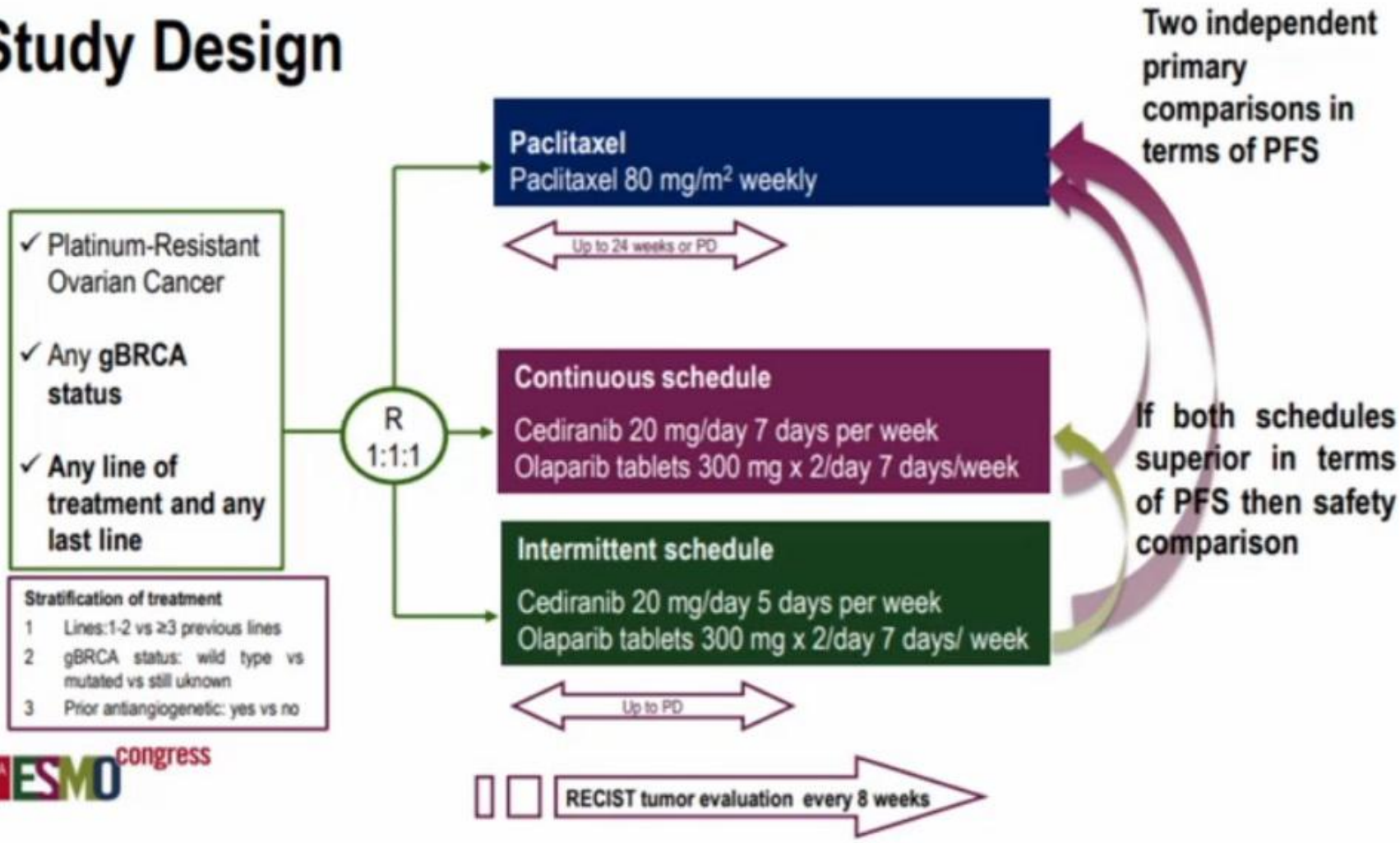
# AVANOVA2: PFS by Subgroup

| Median PFS, Mos | Niraparib + Bevacizumab (n = 48) | Niraparib (n = 49) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| ITT | 11.9 | 5.5 | 0.35 (0.21-0.57) | < .0001 |
| CFI | | | | |
| ▪ 6-12 mos* | 11.3 | 2.2 | 0.29 (0.14-0.62) | .0006 |
| ▪ > 12 mos† | 13.1 | 6.1 | 0.42 (0.20-0.80) | .0062 |
| HRD status | | | | |
| ▪ Positive‡ | 11.9 | 6.1 | 0.38 (0.20-0.72) | .0019 |
| ▪ Negative§ | 11.3 | 4.2 | 0.40 (0.19-0.85) | .0129 |
| *BRCA* status | | | | |
| ▪ Mutated¶ | 14.4 | 9.0 | 0.49 (0.21-1.15) | .0947 |
| ▪ WT‖ | 11.3 | 4.2 | 0.32 (0.17-0.58) | .0001 |

*N + B, n = 20; N, n = 17. †N + B, n = 28; N, n = 32. ‡N + B, n = 28; N, n = 30. §N + B, n = 20; N, n = 19. ¶N + B, n = 15; N, n = 18. ‖N + B, n = 33; N, n = 31.
CFI and HRD status are stratification factors.

Mirza. ASCO 2019. Abstr 5505.

# Study Design

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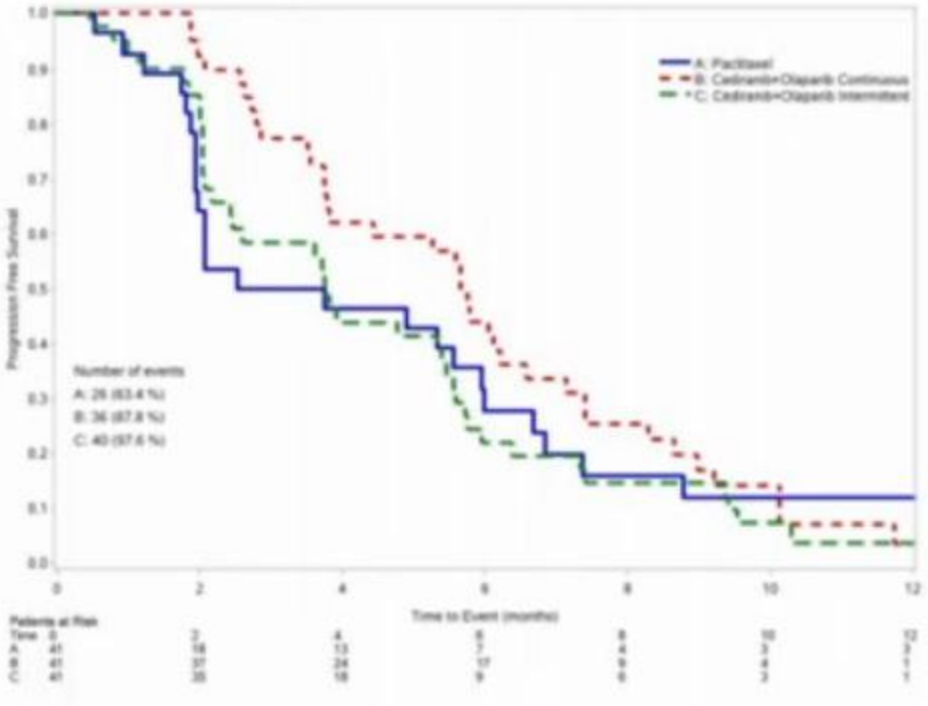
# Primary Endpoint: Progression-free Survival (by Investigator assessment)




**Median PFS (Q1 - Q3):**

Paclitaxel 3.1 (1.9 – 6.7) months

Continuous 5.7 (3.5 – 8.3) months

Intermittent 3.8 (2.0 – 5.8) months

**HR PFS [90% CI]; p-value Log-rank:**

Paclitaxel vs Continuous 0.76 [0.49-1.17]; 0.29

Paclitaxel vs Intermittent 1.08 [0.71-1.64]; 0.76

**Test for proportional hazard:**

Paclitaxel vs Continuous **p=0.004 - Not proportional**

**Difference of area under the PFS curves**:

1.25 months (95% CI: -0.33 to 2.83; p=0.12) in favor of Continuous

# Olaparib maintenance in newly diagnosed advanced OC patients treated with chemotherapy and bevacizumab

PAOLA-1
Platine, Avastin and OLAparib in 1st line
*Sponsored by ARCAGY research*

- FIGO stage III–IV high-grade ovarian cancer (serous or endometrioid)* or non mucinous BRCAm
- Surgery (upfront or interval)
- Platinum–taxane based chemotherapy
- ≥3 cycles of bevacizumab**

**NED/ CR/PR**

**Olaparib** (300mg bid) x 2 years
+ bevacizumab**

2:1 randomisation; **n=806**
Stratification by tumour BRCA status† and 1L treatment outcome

**Placebo** (300mg bid) x 2 years
+ bevacizumab**

**2 years' MTX treatment**

**Primary endpoint**
- Investigator-assessed PFS (RECIST 1.1)‡
  Sensitivity analysis by BICR

**Secondary endpoints**
- PFS2
- TSST
- OS
- Safety
- PRO/HRQoL

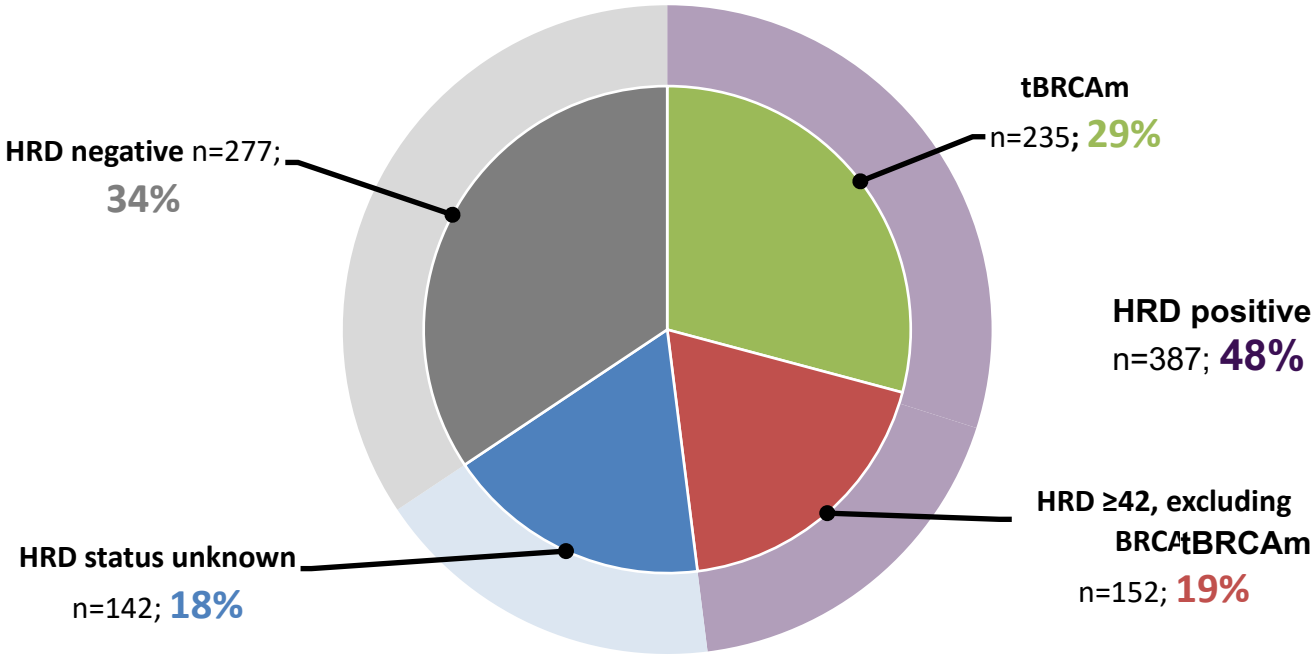
**Pre-specified exploratory endpoints**
- PFS in pre-defined subgroups including tBRCAm and Myriad HRD test

n=**762** / 458 events will give >80% power, at 5% alpha, to show **HR 0.75,** mPFS from 15.8 months (control) to 21.1 months (olaparib)
*Also includes fallopian tube and primary peritoneal cancer; **Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; †By central labs; ‡PFS by BICR as a key sensitivity 1l= first line; bid=twice daily; BICR=blinded independent centralised review; BRCAm=BRCA mutated; CR=complete response; DCO=data cut-off; ECOG= Eastern Cooperative Oncology Group; FIGO=Fédération Internationale de Gynécologie Obstétrique; FSI=first subject in; HRD=homologous recombination repair deficiency; HRQoL=health-related quality of life; LSI=last subject in; MTX=maintenance; NED=no evidence of disease; OS=overall survival; PFS=progression-free surivival;PFS2=progression-free survival 2; PR=partial response; PRO=patient reported outcomes; q3w=every three weeks; RECIST=Response Evaluation Criteria in Solid Tumours 1.1; tBRCA=tumour BRCA; TSST=time to subsequent treatment

1. Ray-Coquard I et al. J Clin Oncol. 2016;34 (suppl; abstr TPS5607 and poster); 2. Study NCT02477644. Available at https://clinicaltrials.gov. Accessed September 2019.

# Approximately 50% of patients in PAOLA-1 were HRD test positive

*Around half of HRD test positive patients were tBRCAm*




HRD positive is either tumour BRCA mutation and/or HRD score ≥42 by Myriad MyChoice HRD Plus
Reasons for HRD status unknown: 4.2% missing; 2.1% fail; 11.3% inconclusive
HRD=homologous recombination deficient; tBRCAm=tumour BRCA mutation;
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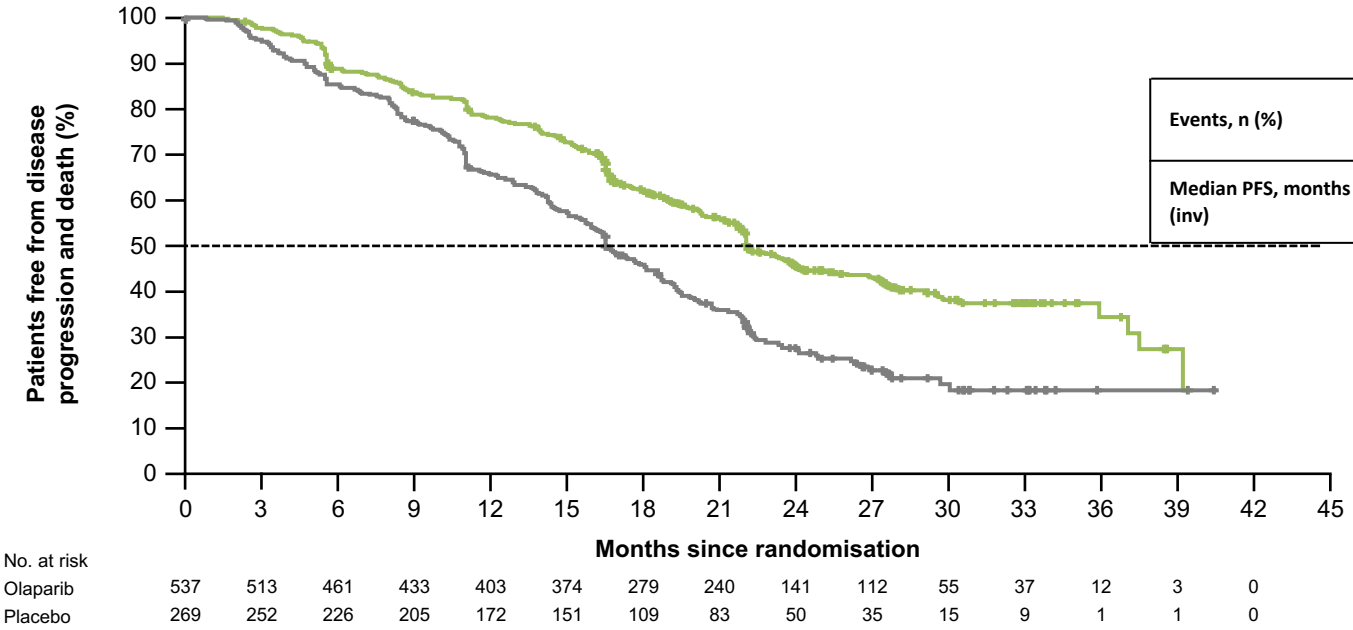
# Primary endpoint: Olaparib significantly improved PFS in the ITT population




| | Olaparib + bevacizumab N=537 | Placebo + bevacizumab N=269 |
|---|---|---|
| **Events, n (%)** | 280 (52) | 194 (72) |
| **Median PFS, months (inv)** | 22.1 | 16.6 |
| | **HR=0.59** 95% CI (0.49-0.72) p<0.0001 | |

Median time from first cycle of chemotherapy to randomisation = **7 months**

PFS by investigator assessment; analysis per eCRF; data maturity = 59%
Median duration of follow-up for primary analysis: olaparib, 24.0 months; placebo, 22.7 months. Data cut-off: 22 March 2019
CI=confidence interval; HR=hazard ratio; inv=investigator; ITT=intent to treat; PFS=progression-free survival
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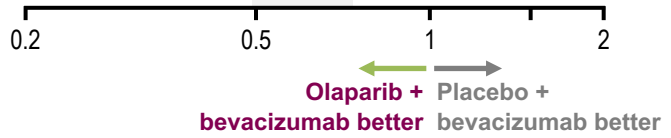
# Results of pre-specified PFS subgroup analyses evaluating clinical characteristics were consistent with primary PFS analysis

| Subgroup | Olaparib + bevacizumab | Placebo + bevacizumab | HR (95% CI) |
|---|---|---|---|
| | *No. of events/no. of patients (%)* | | |
| **All** | 280/537 (52) | 194/269 (72) | **0.59** (0.49–0.72) |
| **Age group** | | | |
| <65 years old | 171/332 (52) | 126/182 (69) | **0.61** (0.49–0.77) |
| ≥65 years old | 109/205 (53) | 68/87 (78) | **0.55** (0.41–0.75) |
| **FIGO stage** | | | |
| III | 184/378 (49) | 125/186 (67) | **0.64** (0.51–0.80) |
| IV | 96/159 (60) | 69/83 (83) | **0.49** (0.36–0.67) |
| **ECOG baseline** | | | |
| 0 | 193/378 (51) | 132/189 (70) | **0.63** (0.50–0.78) |
| 1 | 85/153 (56) | 61/76 (80) | **0.51** (0.37–0.71) |
| **Cytoreductive surgery outcome** | | | |
| Debulking surgery with no residual macroscopic disease | 135/323 (42) | 104/160 (65) | **0.54** (0.42–0.71) |
| Debulking surgery with residual macroscopic disease | 113/176 (64) | 71/88 (81) | **0.63** (0.47–0.85) |
| No debulking surgery | 32/38 (84) | 19/21 (90) | **0.56** (0.32–1.01) |
| **Timing of cytoreductive surgery** | | | |
| Upfront | 116/271 (43) | 92/138 (67) | **0.52** (0.40–0.69) |
| Interval debulking | 132/228 (58) | 83/110 (75) | **0.66** (0.50–0.87) |
| No debulking surgery | 32/38 (84) | 19/21 (90) | **0.57** (0.32–1.02) |
| **Response to first line CT** | | | |
| NED | 119/290 (41) | 92/141 (65) | **0.53** (0.40–0.70) |
| CR | 54/106 (51) | 42/53 (79) | **0.44** (0.29–0.66) |
| PR | 107/141 (76) | 60/75 (80) | **0.86** (0.63–1.19) |




BRCAm=BRCA1 and/or BRCA2 mutation; CI=confidence interval; CR=complete response; CT=chemotherapy; ECOG=Eastern Cooperative Oncology Group; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; HR=hazard ratio; NED=no evidence of disease; PFS=progression free survival; PR=partial response

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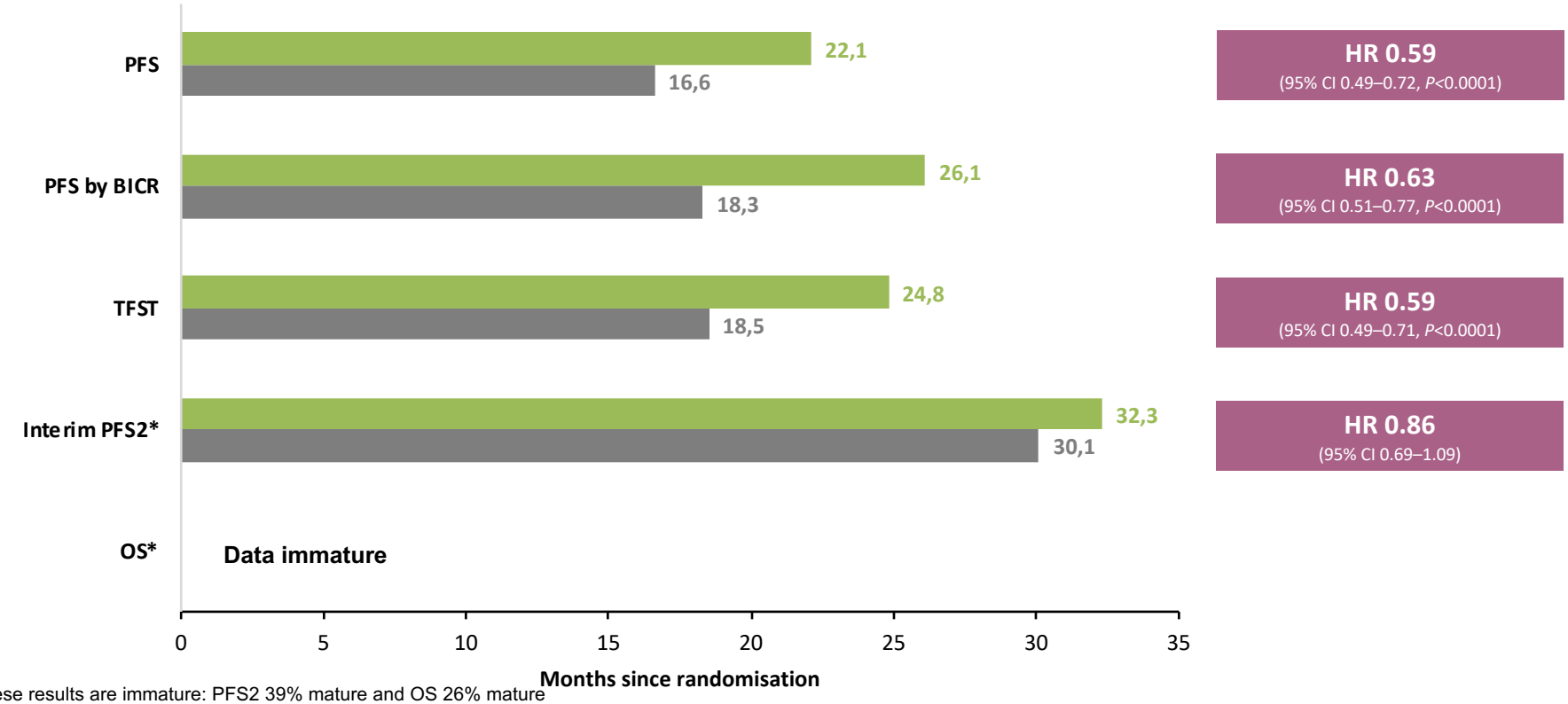
# Summary of secondary efficacy endpoints




*These results are immature: PFS2 39% mature and OS 26% mature

BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival; PFS2=time to second progression or death; TFST=time to first subsequent therapy or death

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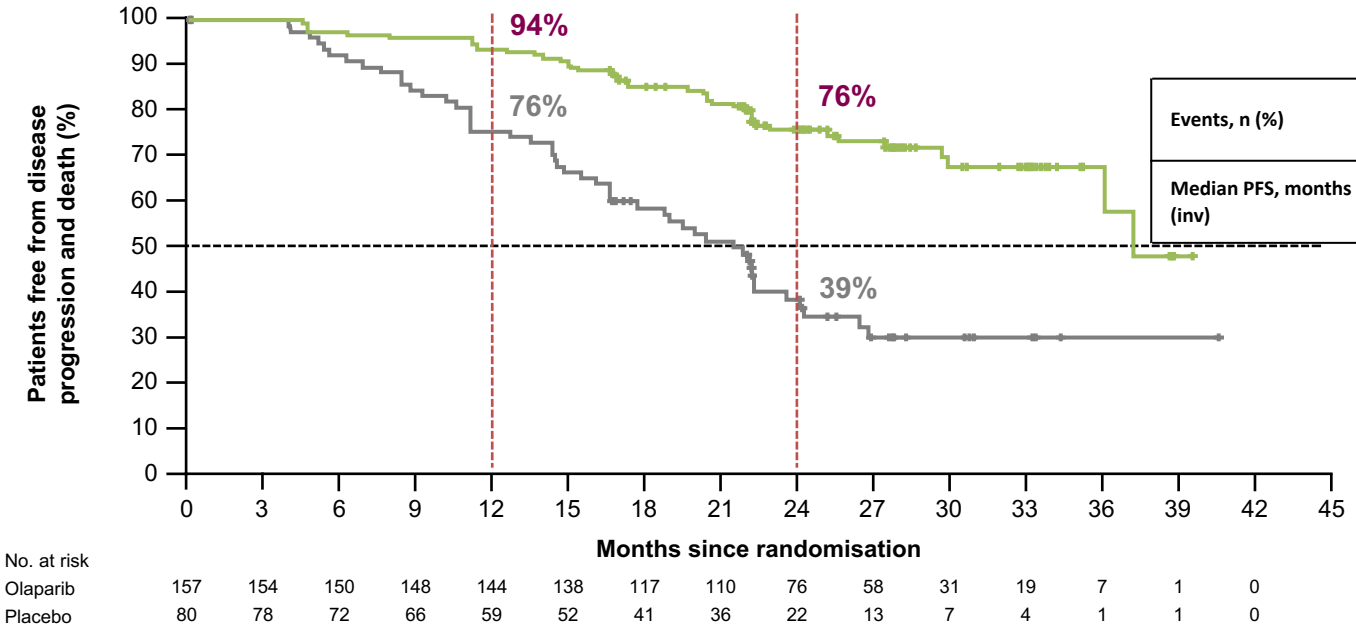
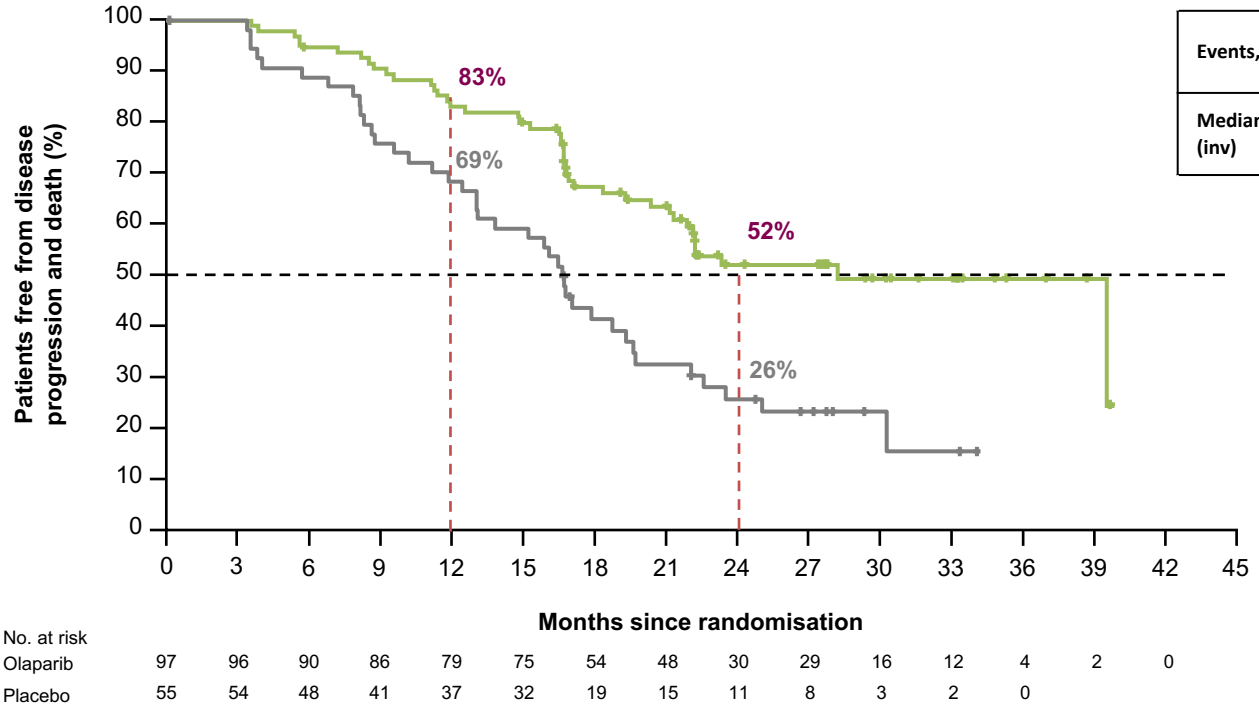
# Pre-specified subgroup analysis showed PFS benefit in tBRCAm patients



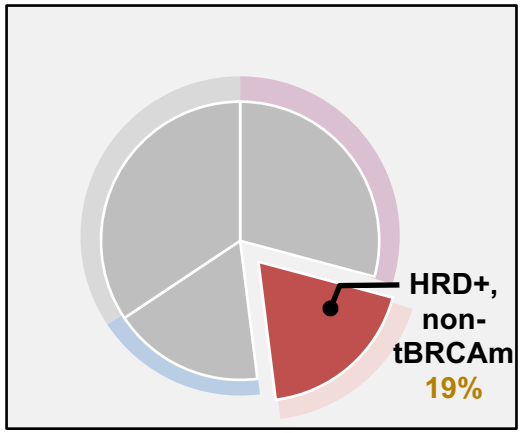

| | Olaparib + bevacizumab N=157 | Placebo + bevacizumab N=80 |
|---|---|---|
| Events, n (%) | 41 (26) | 49 (61) |
| Median PFS, months (inv) | 37.2* | 21.7 |
| | **HR=0.31** 95% CI (0.20-0.47) | |

*This median is unstable due to a lack of events – less than 50% maturity ; Based on Kaplan-Meier estimates
Analysis per eCRF; data maturity = 38%
CI=confidence interval; HR=hazard ratio; inv=investigator; PFS=progression-free survival; tBRCAm=tumour BRCA mutation
Ray-Coquard I et al. Presentation LBA2_PR presented at

# Pre-specified subgroup analysis showed PFS benefit in HRD-positive, non-tBRCAm patients




| | Olaparib + bevacizumab N=97 | Placebo + bevacizumab N=55 |
|---|---|---|
| **Events, n (%)** | 43 (44) | 40 (73) |
| **Median PFS, months (inv)** | 28.1* | 16.6 |
| | **HR=0.43** 95% CI (0.28-0.66) | |




The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates; HRD positive is an HRD score ≥42

*This median is unstable due to a lack of events – less than 50% maturity ; Data maturity = 55%

CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficient; inv=investigator; PFS=progression-free survival; tBRCAm=tumour BRCA mutation

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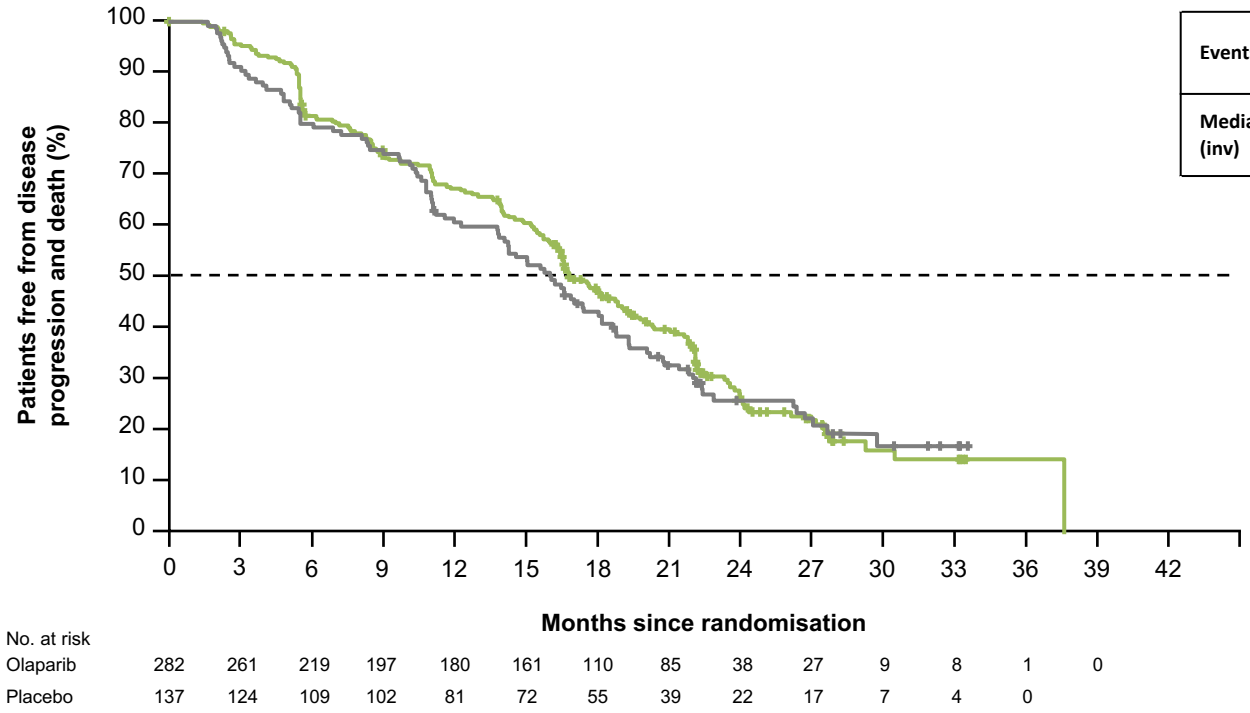
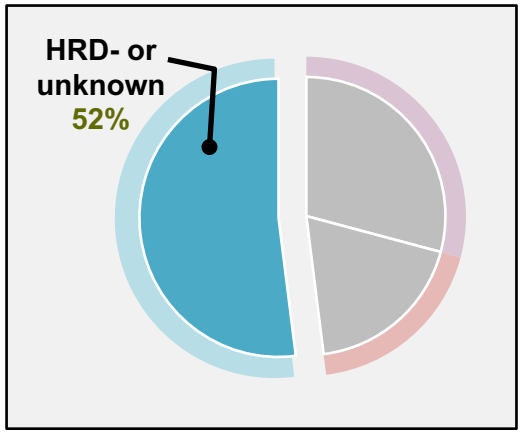
# Subgroup analysis in HRD-negative or unknown patients




| | Olaparib + bevacizumab N=282 | Placebo + bevacizumab N=137 |
|---|---|---|
| **Events, n (%)** | 193 (68) | 102 (74) |
| **Median PFS, months (inv)** | 16.9 | 16.0 |
| | **HR=0.92** 95% CI (0.72-1.17) | |




Data maturity = 70%
CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficient; inv=investigator; PFS=progression-free survival
Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1

# Adverse events were generally mild to moderate and manageable through dose adjustments

| | Olaparib + bevacizumab N=535 | Placebo + bevacizumab N=267 |
|---|---|---|
| **Median duration of treatment with olaparib/placebo**, months (range) | 17.3 (0.03-33.0) | 15.6 (0.07-26.2) |
| Median duration of treatment with bevacizumab since randomisation, months (range) | 11.0 (0.69-21.4) | 10.6 (0.69-17.1) |
| **All grade AEs**, n (%) | 531 (99) | 256 (96) |
| **Grade ≥3 AEs**, n (%) | 303 (57) | 136 (51) |
| **Serious AEs**, n (%) | 167 (31) | 83 (31) |
| **AEs leading to death**, n (%) | 1 (0.2) | 4 (1.5) |
| **AEs leading to dose interruption of olaparib or placebo**, n (%) | 291 (54) | 65 (24) |
| **AEs leading to dose reduction of olaparib or placebo**, n (%) | 220 (41) | 20 (7) |
| **AEs leading to treatment discontinuation of olaparib or placebo**, n (%) | 109 (20) | 15 (6) |

AE=adverse event

Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain

# COMPARING PARP INHIBITOR & BEVACIZUMAB TRIALS IN FIRST-LINE HAZARD RATIO OF PFS

ENGOT

| | PRIMA [1] Niraparib | SOLO-1 [2] Olaparib | PAOLA-1 [3] Olaparib | VELIA [4] Veliparib | GOG-218 [5] Bevacizumab | ICON7 [6] Bevacizumab |
|---|---|---|---|---|---|---|
| N | 733 | 391 | 806 | 1140 | 1873 | 1528 |
| Overall population | 0.62 | | 0.59 | 0.68 | 0.73 | 0.87 |
| HR deficient *BRCAmut* | 0.40 | 0.30 | 0.31 | 0.44 | 0.95 | ND |
| HR deficient *BRCAwt* | 0.50 | | 0.43 | 0.74 NS | | ND |
| HR proficient BRCAwt | 0.68 | | 0.92 NS | 0.81 NS | 0.71 | ND |

ESMO congress

(1) Gonzalez, ESMO 2019. (2) Moore, NEJM 2018. (3) Ray-Coquard ESMO 2019. (4) Coleman ESMO 2019. (5) Burger NEJM 2011. (6) Perren NEJM 2011

*Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study*

In patients with no mutations , extended bevacizumab significantly prolonged PFS (15.7months vs. 10.6 months; (HR: 0.71)

***In those with mutations , extended bevacizumab conferred a median PFS of 19.6 months versus 15.4 months (HR 0.95).***

# What next?

- Moving PARP inhibitors to first-line for all or subset BRCA/ HRD +ve?
- How will first-line PARP inhibitors impact on use in recurrent disease?
- Can patients benefit from a rechallenge with same or different PARP inhibitor?
- Will combination therapy be needed in recurrent disease?

PAOLA 1
No olaparib only arm
Does the addition of BEV add to outcome?

PRIMA
No bevacizumab arm

# Ongoing and future research strategies to improve OS in AOC

Better characterization of molecular biology of the disease

- Not all HRD patients are the same
- Not all BRCA 1/2 muts patients are the same
- Biomarkers for patients that will respond
- mechanism of resistance to PARPi

Adaptive design in future trials with proper comparators

- NACT-IDS strategy provides valuable translational information
- CRS pts have definitely better survival

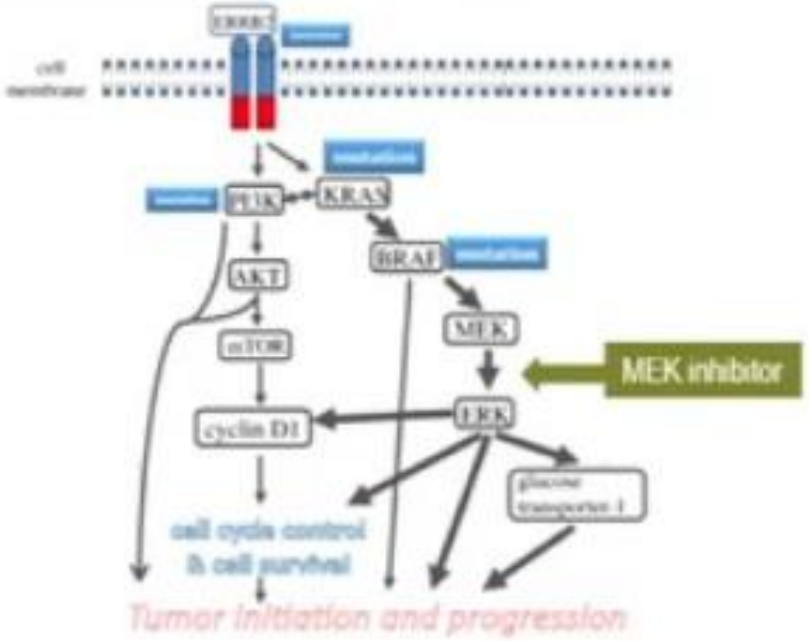
# Low grade serous OC

## RECURRENT LOW GRADE SEROUS OVARIAN CANCER

Responds poorly to chemotherapy

| | ORR | SD | Number |
|---|---|---|---|
| Carboplatin | 3 | 15 | 25 |
| PLD | 0 | 11 | 21 |
| Paclitaxel | 1 | 11 | 18 |
| Carbo/Paclitaxel | 0 | 7 | 10 |
| Topotecan | 0 | 5 | 10 |
| Carbo/ Gemcitabine | 0 | 1 | 1 |
| Percentage | 5% | 59% | N=85 |

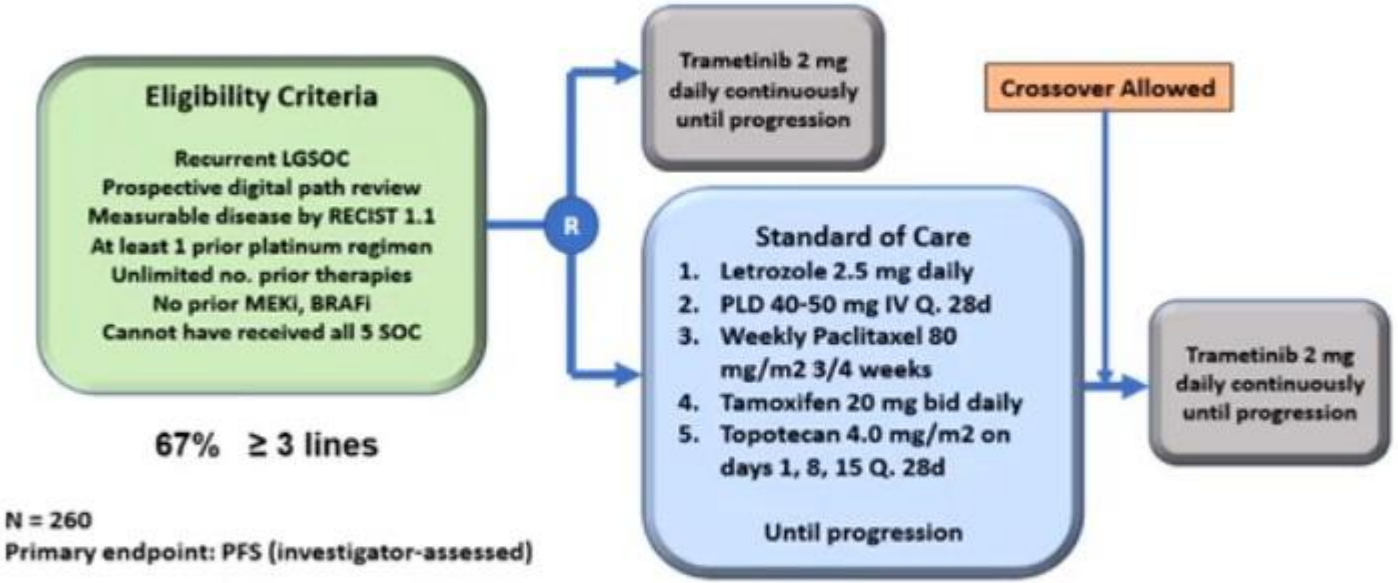
Gershenson et al Gyne Oncol 2009




Kurman & Shih 2011

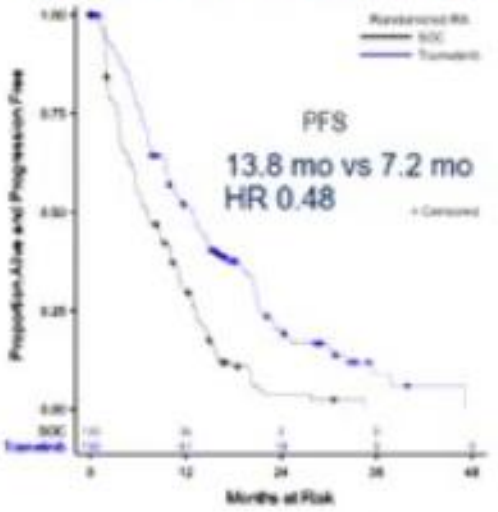
ESMO congress

# Study Design

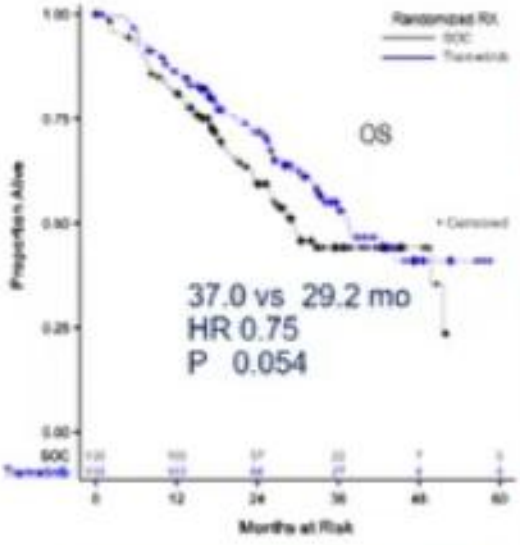



N = 260
Primary endpoint: PFS (investigator-assessed)

# TREMETANIB IN LGSOC




| | Trametinib | Control (SOC) |
|---|---|---|
| Median (Months) 95% CI | 13.8 (9.9 – 15.8) | 7.2 (5.6 - 9.9) |
| Hazard Ratio 95% CI | 0.48 (0.36 – 0.64) | |
| One-sided p-value | <0.0001 | |




| | Trametinib | Control (SOC) |
|---|---|---|
| Median (Months) 95% CI | 37.8 (30.3 to NE) | 29.2 (23.5 to 51.8) |
| Hazard Ratio 95% CI | 0.75 (0.51 – 0.1.11) | |
| One-sided p-value | 0.054 | |

- Significant benefit in PFS
- Borderline OS benefit but cross over in 68%
- In cross-over patients Trametinib is active median PFS10.8 months
- Skin rash; Fatigue; diarrhoea
- 35% stopped due to AE
- Cardiac function; pneumonitis ?

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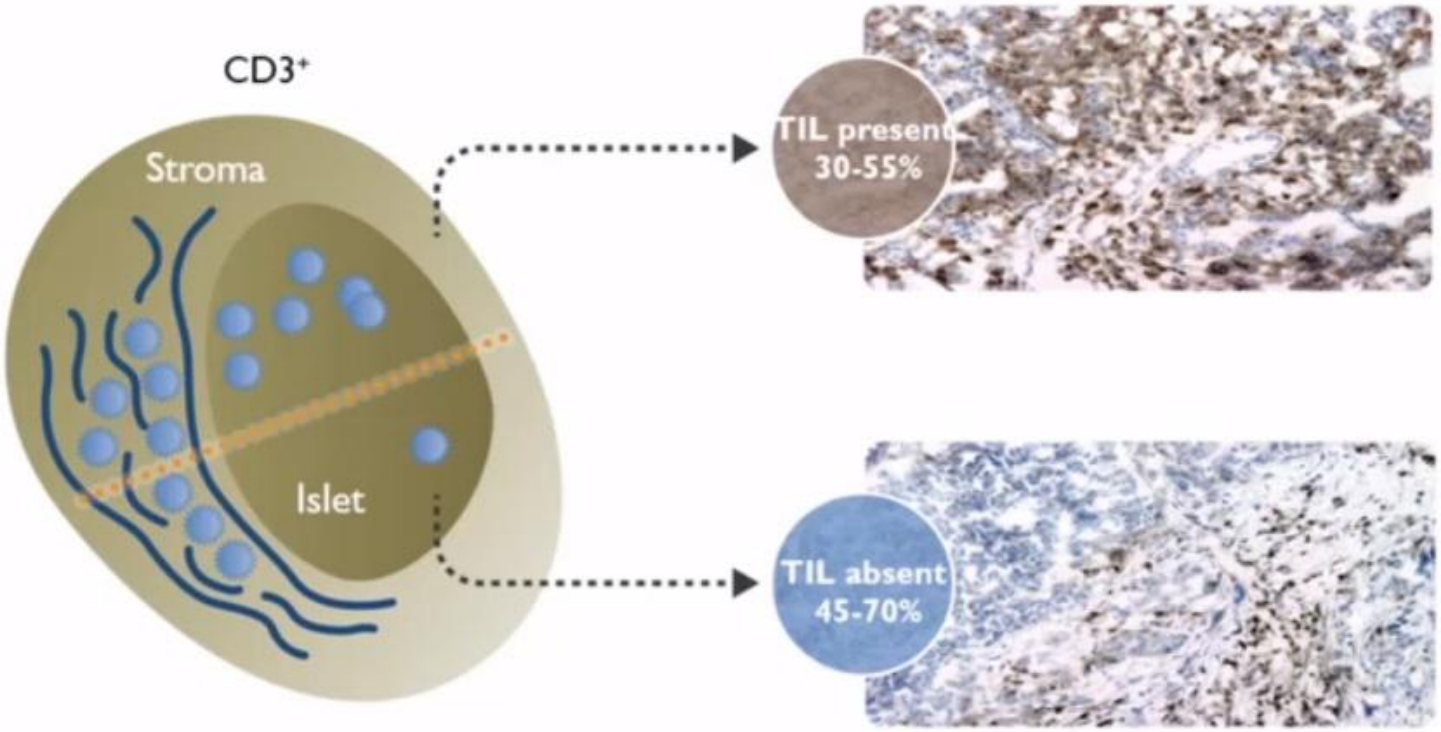
ORR 26.2% vs 6.2 % (p< 0.0001)

# IS THERE A ROLE FOR IMMUNOTHERAPY IN OC?



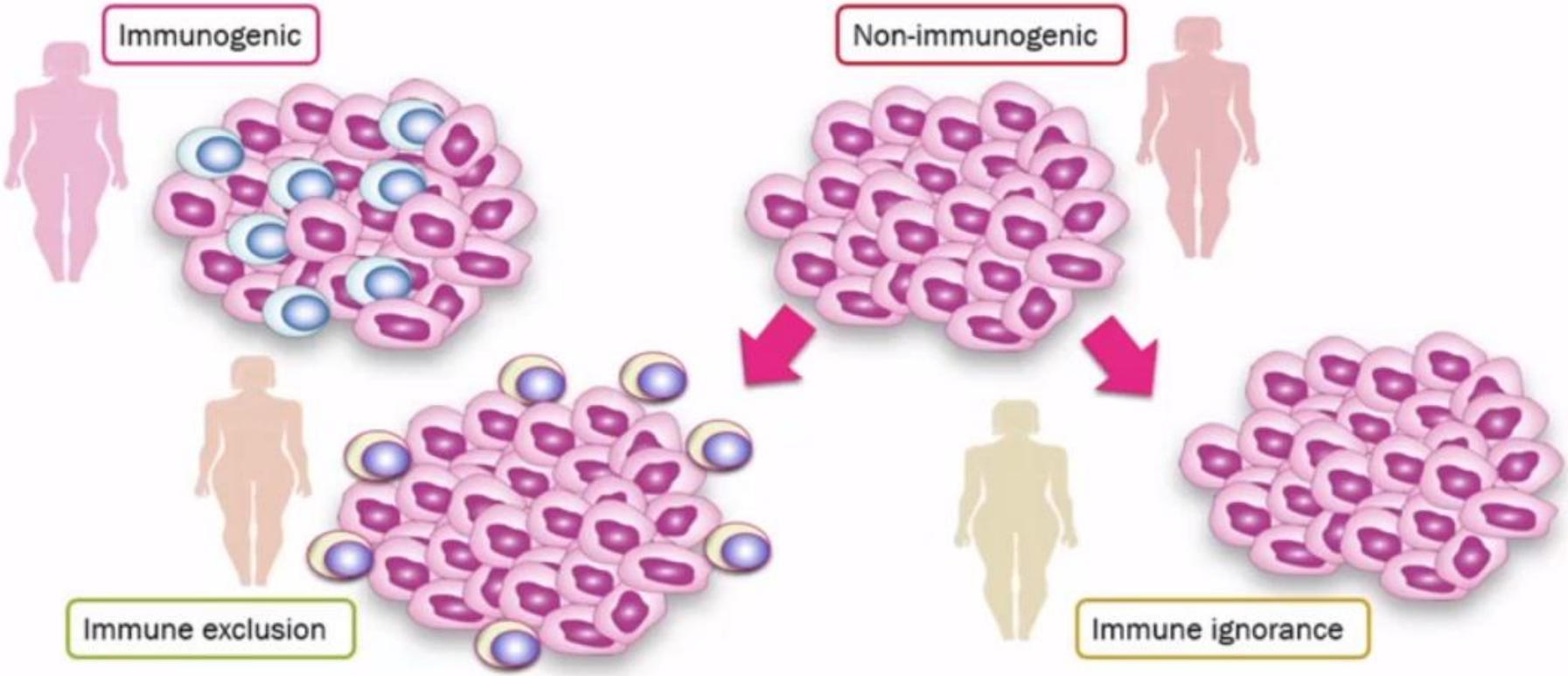

OC, ovarian cancer; TIL, tumour-infiltrating lymphocyte

Zhang L *et al. N Engl J Med* 2003;348:203–213

- Presence of intratumoral T cells is a prognostic factor in OC (HR 2.24 for OS; CI 95% 1.71 - 2.91) [1-2], **but** TIL subpopulation is relevant [3].
- Ovarian cancer shows lower tumor mutational burden than others tumors (melanoma, NSCLC, CC…) **but** patients with HRD tumors demonstrated significantly higher neo-antigen expression [4]
- **Combination** of HR-deficient and High CD3+ TILs had longer median OS than HR-proficient and low CD3+ TILs (HR 0.38, 95% CI (0.25–0.59)[5]
- **PD-L1** is expressed in ovarian cancer although its role as prognostic factor is **contradictory**
  - Negative prognostic factor [6-7]
  - Positive prognostic factor [8-910]

1. Zhang…Coukos. NEJM 2003; 2. Hwang…Coukos. Gyn Oncol 2012; 3. Nelson. Current Opinion Inmunol 2015
4. Strickland et al. Oncotarget 2016; 5. Morse et al. Gynecol Oncol 2019; 6. Hamanishi et al. PNAS 2007; 7. Chatterjee et al. Clin Cancer Res 2017; 8. Silvia Darb-Esfahani et al. Oncotarget 2016; 9. Stefanie Aust et al. Sci Rep 2017; 10. Webb et al. Gyn Oncol 2016

# DIFFERENT IMMUNOPHENOTYPES OF OC




Gajewski TF *et al. Nat Immunol* 2013;14:1014–1022

# Check-point inhibitors monotherapy in ROC have limited activity that is poorly correlated with PD-L1 expression

| | Nivolumab[1] | Pembrolizumab[2] Keynote-028 | Avelumab[3] Phase Ib | Atezolizumab[4] |
|---|---|---|---|---|
| Population | 20<br>Plat-resistant<br>55%> 4 lines | 26<br>Phase Ib<br>73%> 3 lines | 125<br>PROC<br>65%> 3 lines | 12<br>Phase Ib<br>58%> 6 lines |
| ORR global | 15%(10%CR) | 11.5%(4%CR) | 9.6%(0.8%CR) | 25%(2/8) |
| Cut-off PD-L1 | IHC 2/3+ (80%) | ≥ 1%(100%) | ≥ 1%(77%) | IHC 2/3+ (83%) |
| ORR PD-L1- | 1/4 (25%) | - | 7.9%(3/38) | - |
| ORR PD-L1+ | 2/16 (12.5%) | 3/26 (11.5%) | 11.8%(9/76) | - |

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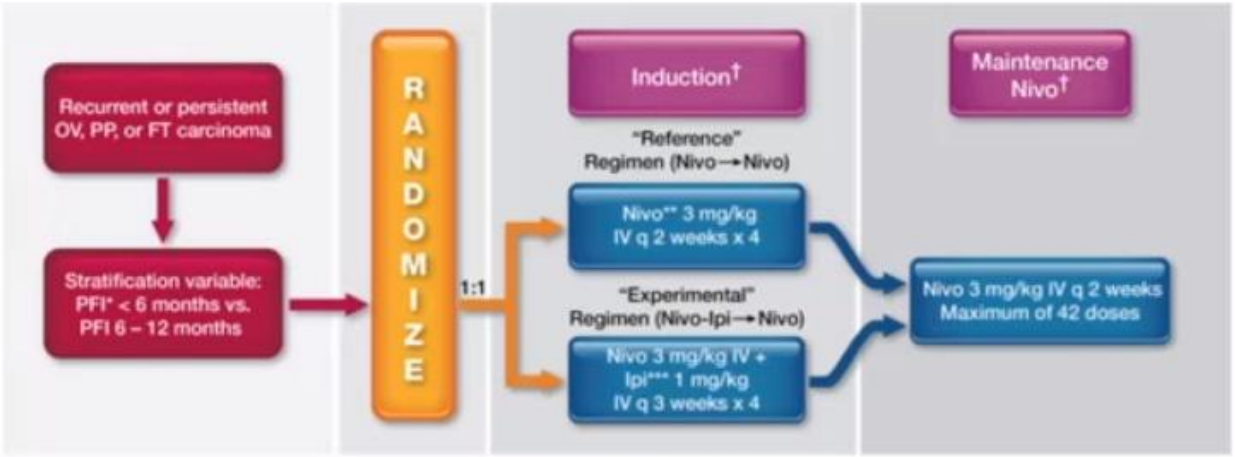
1. Hamanishi et al. J Clin Oncol 2015; 2. Varga et al. Gynecologic Oncology 2019; 3. Disis ML, et al. JAMA Oncology 2019; 4. Infante et al. Ann Oncol 2016: 27 (Supple 6) Abstract 871P

NRG ONCOLOGY
Advancing Research. Improving Lives.™

# Phase II Randomized Trial of Nivolumab With or Without Ipilimumab in Patients with Persistent or Recurrent Ovarian Cancer (NRG GY003)

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

- Presented at IGCS 2018 (Kyoto)
- Induction with Nivo-Ipi induced higher response rate 33.3% vs 12.2% and longer PFS 3.9bs 2.0months (0.528
- (0.339–0.821



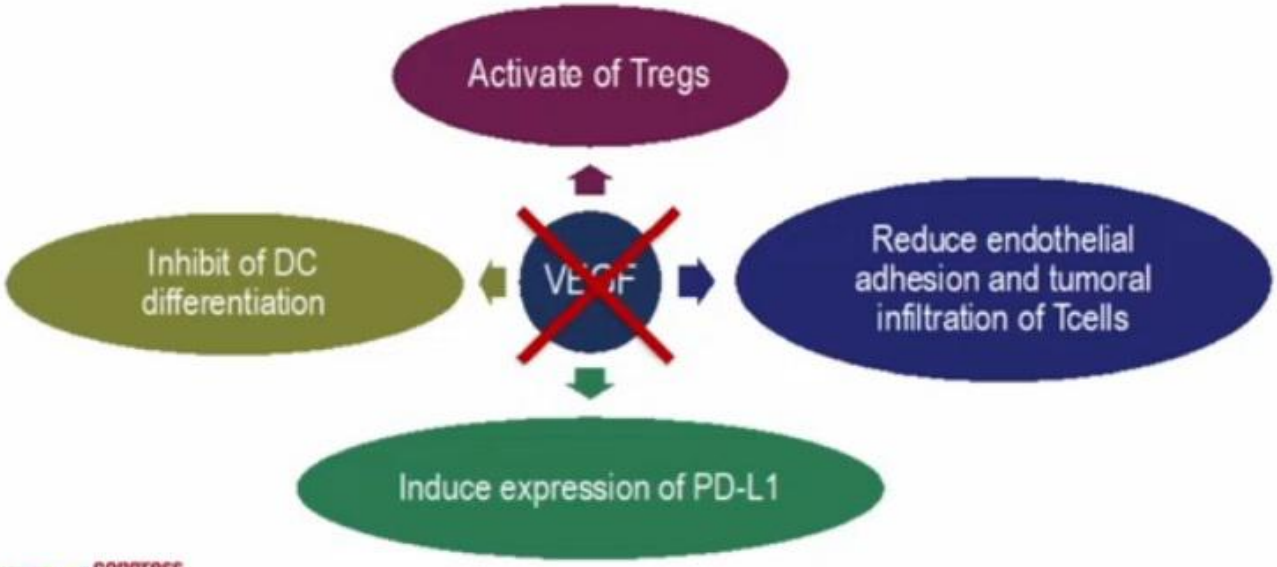

* Platinum-Free Interval
** Nivolumab
*** Ipilimumab
† Protocol-directed therapy until progression or unacceptable toxicity

ClinicalTrials.gov Identifier: NCT02498600

Burger, for NRG Oncology

# Rational for combining anti-VEGF and IO

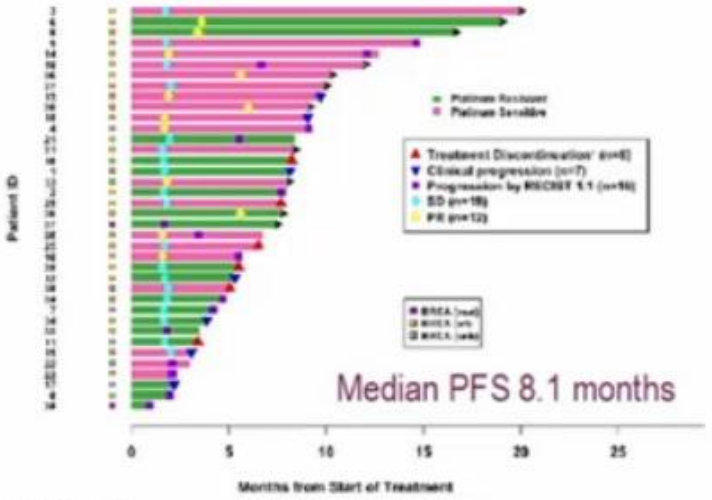
## VEGF has immunosupressive properties



# Phase II of nivolumab (anti-PD-1) and bevacizumab in ROC

| Best Overall Response | Platinum-Sensitive (N=20) | | Platinum-Resistant (N=18) | | Overall (N=38) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Unevaluable | - | - | 1 | 5.6 | 1 | 2.6 |
| Partial response | | | | | | |
| Confirmed | 8 | 40.0 | 3 | 16.7 | 11 | 28.9 |
| Unconfirmed | 1 | 5.0 | | | | |
| Stable disease | | | | | | |
| >24 weeks | 6 | 30.0 | 3 | 16.7 | 9 | 23.7 |
| <24 weeks | 3 | 15.0 | 7 | 38.9 | 10 | 26.3 |
| Progressive disease | 2 | 10.0 | 4 | 22.2 | 6 | 15.8 |
| **Overall confirmed response rate** | 8 | 40.0 | 3 | 16.7 | **11** | **28.9** |
| **Total clinical benefit rate (CBR)** | 15 | 75.0 | 6 | 33.3 | **21** | **55.3** |

Durable responses or prolonged stable disease (including in platinum-resistant patients)

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Liu et al. ESMO 2018, PD937

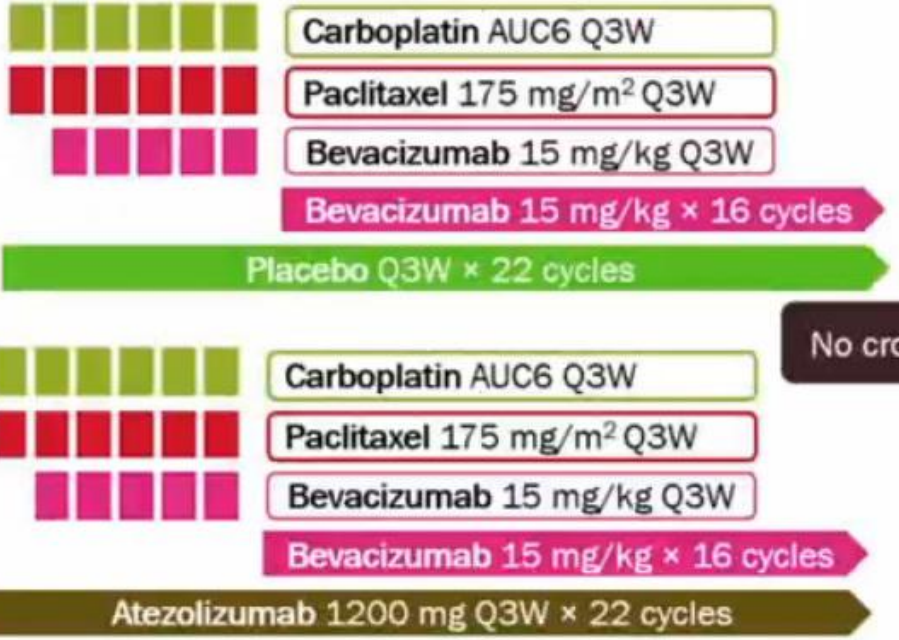
# ENGOT-OV39 TRIAL, IMAGYN050

## Study design in primary surgery cohort

- Previously untreated ovarian, fallopian tube or peritoneal cancer
- Post-operative Stage III with macroscopic residual disease: Stage IV
- ECOG PS 0–2

**STRATIFICATION FACTORS**
- Stage/debulking status
- ECOG PS
- PD-L1 IC0 vs IC1+
- Adjuvant/neo-adjuvant

RANDOMISATION 1:1



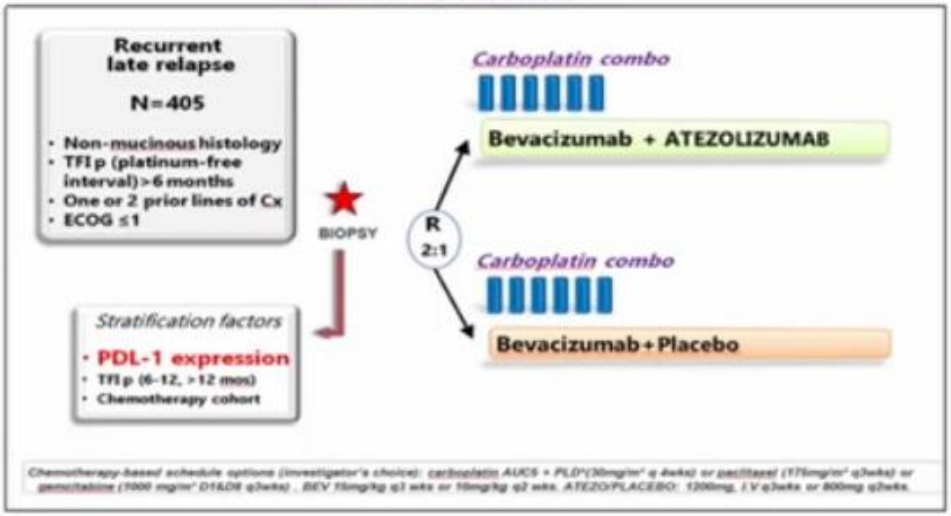

CLINICALTRIALS.GOV, NCT03038100

# ENGOT ov 29

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

## ATezolizumab and Avastin in LAte recurreNT diseasE

## ATALANTE DESIGN

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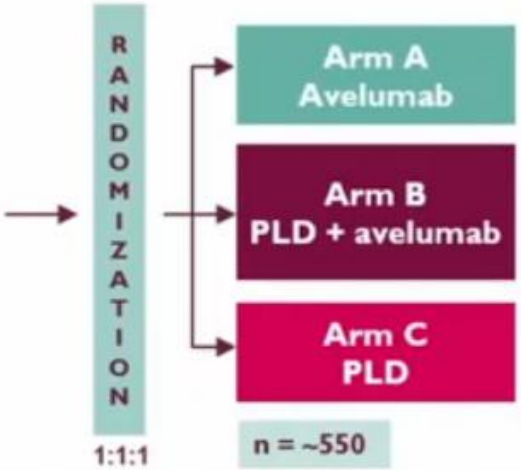
# JAVELIN OVARIAN 200
# AVELUMAB IN PLATINUM RESISTANT OC

## Randomized Phase 3 Study (NCT02580058)

### Enrollment Criteria

- Progression ≤6 mo or no response to most recent platinum-based therapy
- Up to 3 lines of chemotherapy for platinum-sensitive disease, most recently platinum-containing, and no prior therapy for platinum-resistant disease
- Measurable disease
- ECOG PS 0 or 1
- No prior immune checkpoint inhibitor therapies
- Doxil-resistant (disease progression within 6 mo) excluded
- Mandatory archival tissue
- Baseline biopsy required unless contraindicated




**Stratification: Platinum refractory vs resistant, number of prior therapies, bulky disease**

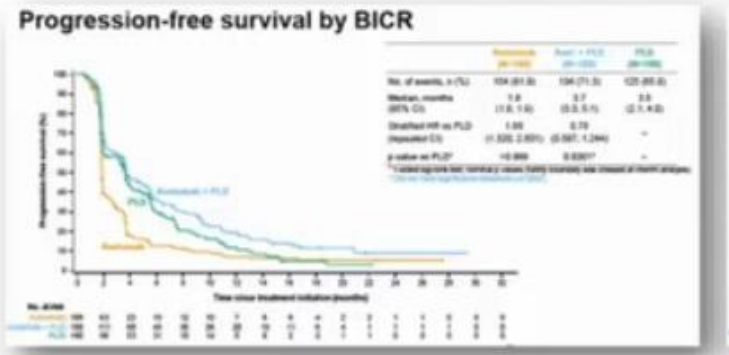
| | |
|---|---|
| **Primary Endpoint:** | OS |
| **Secondary Endpoints:** | ORR, PFS, duration of response, PROs, safety |

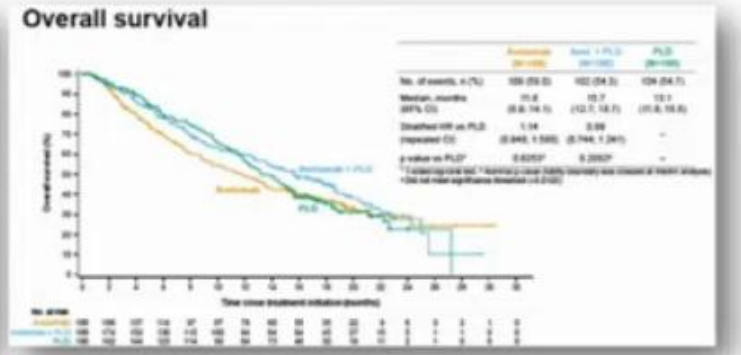
ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes.

Clinicaltrials.gov. Accessed October 11, 2016.

# JAVELIN OVARIAN 200

## Co-primary Endpoints: PFS (BICR assesed) and OS

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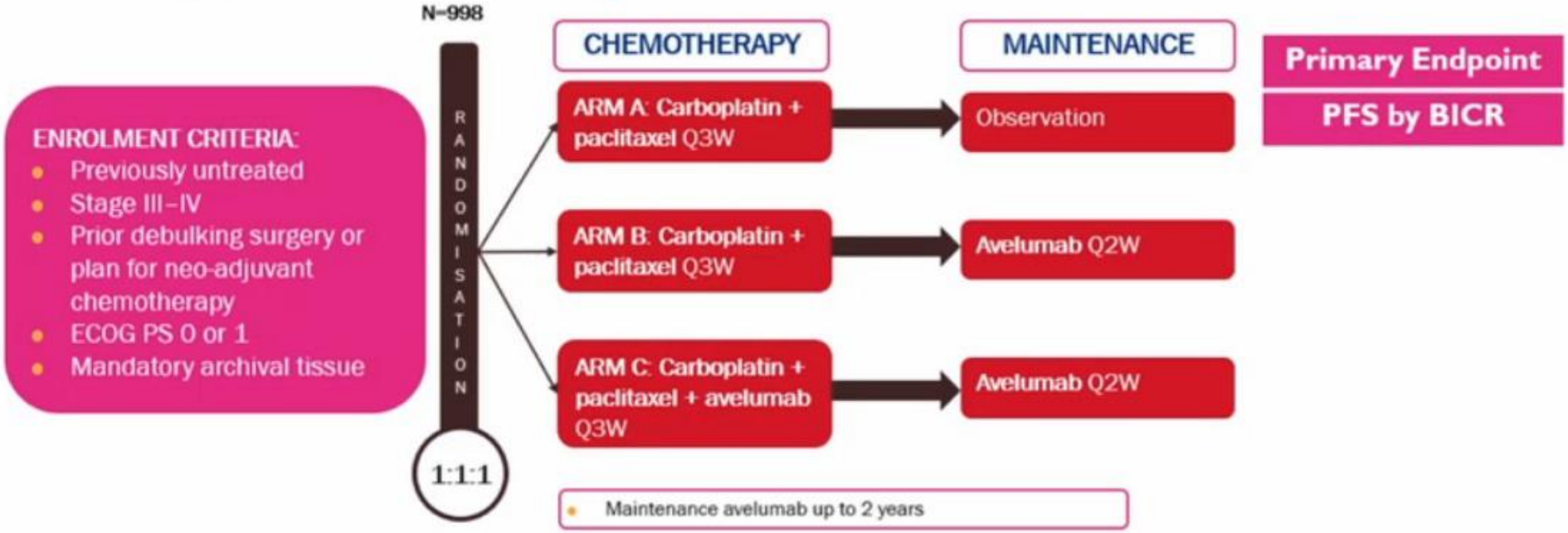
Pujade et al . SGO 2019

# JAVELIN OVARIAN 100: AVELUMAB PLATINUM COMBO + MAINTENANCE IN FIRST-LINE

## Randomised Phase III study

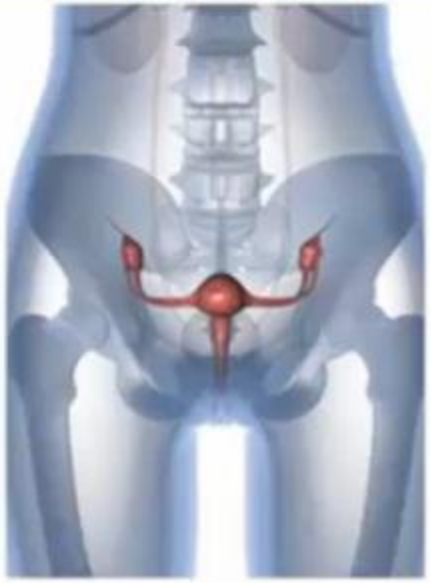



CLINICALTRIALS.GOV. NCT02718417; LEDERMANN *ET AL. INT J GYNECOL CANCER.* IGCS 2016; ABSTRACT 753

# Phase III Ovarian Cancer Study Terminated After Frontline Avelumab Falls Short

Targeted Oncology Staff
**Published Online:**4:57 PM, Thu January 3, 2019





At a planned interim analysis of the phase III JAVELIN Ovarian 100 study evaluating frontline avelumab (Bavencio) in ovarian cancer, an independent panel determined the study would not meet its primary endpoint of progression-free survival (PFS). Merck KGaA and Pfizer, the co-developers of the PD-L1 inhibitor, have announced they will terminate the trial on this basis.

A total of 998 treatment-naive patients with locally advanced or metastatic (stage III/IV) epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer were included in the trial. Patients were randomized to carboplatin/paclitaxel; carboplatin/paclitaxel with maintenance avelumab; or avelumab plus carboplatin/paclitaxel followed by maintenance avelumab.

# Optimizing check point inhibitors in AOC

- Better patient selection:
  - Search for more efficient biomarker
- Check-point inhibitors combination
  - Anti-angiogenic
  - PARPi
  - Multiple combinations Chemo +/- Bev +/- PARPi

# Biomarkers for checkpoint blockade immunotherapy response

**Indicative of a T cell–inflamed tumor microenvironment (TME)**

- (PD-L1) protein expression on tumor and immune cells
- Gene signatures of activated T cells (i.e T cell–inflamed gene expression profile, GEP)

**Related to tumor neoantigen burden**

- Microsatellite instability (MSI)
- High tumor mutational burden (TMB)

# ANTI-PD-1/PD-L1 AND PARP INHIBITOR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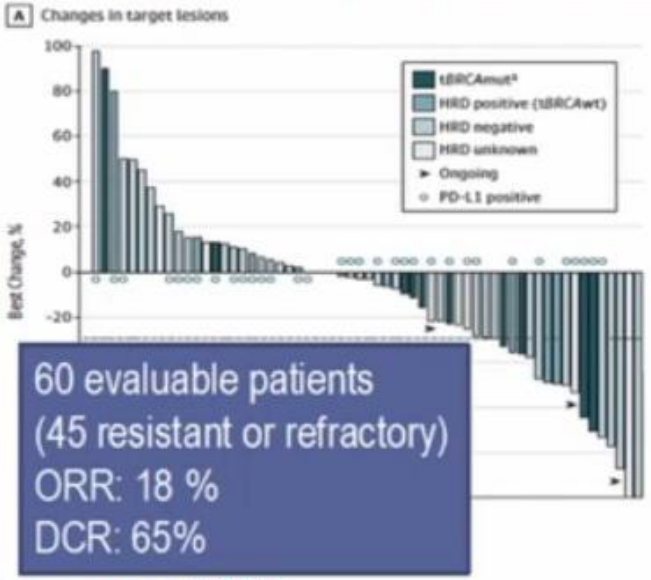
Adapted from: Lee and Kostantinopoulos. Trends in Cancer 2019

# TOPACIO/Keynote-162 (PROC)

## Niraparib 200 mg/d + pembrolizumab 200 mg/21d




60 evaluable patients
(45 resistant or refractory)
ORR: 18 %
DCR: 65%

| Subgroup | ORR | 90% CI |
|---|---|---|
| Plat-resistant | **21%** | 9-37 |
| Plat-refractory | **13%** | 2-34 |
| tBRCAmut | **18%** | 3-47 |
| tBRCAwt | **19%** | 10-31 |
| HR-deficient | **14%** | 4-33 |
| HR-proficient | **19%** | 9-34 |

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Kostantinopoulos et al. Jama Oncol 2019

# Durvalumab + Olaparib

| Author | N | Population | ORR (%) | DCR (%) |
|---|---|---|---|---|
| MEDIOLA<br>Drew et al. ESMO 2019 | 34 | gBRCA<br>Platinum-sensitive | 71%<br>(CI 95%:<br>53.3-86.6) | 81.3 % @ 12w<br><br>65.6 % @ 24w |
| Lee et al.<br>ESMO 2018 | 35 | 83% Plat-R | 14%<br>(all PR) | 37% |

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# ENGOT-OV41/GEICO 69-O/ANITA

N= 414 patients

- Recurrent high-grade serous or endometrioid, or undifferentiated
- TFIp >6 months
- [redacted]
- Measurable disease
- [redacted]

IP: A. González

RANDOMIZATION 1:1

A: Platinum doublet 6 cycles → Niraparib Until PD

A: Placebo → Placebo until PD

B: Platinum doublet 6 cycles → Niraparib Until PD

B: Atezolizumab → Atezolizumab Until PD

RECIST v1.1 CT SCAN

If CR, PR or SD

**Stratification factors:**

- Platinum based regimen selected
- PFI (6-12 months vs > 12 months)
- BRCA mutation status (mutated vs. non-mutated)
- **PD-L1 positive/negative-**

**Primary Endpoint:**

- PFS by RECIST v.1.1

Secondary endpoints:

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

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# Ongoing front line randomized trials

## Stratification factors, biomarkers, and primary endpoint

| | ENGOT Ov43 | ENGOT Ov44 FIRST (BRCAm) | ENGOT Ov44 FIRST (BRCAwt) | ENGOT Ov45 ATHENA | ENGOT Ov46 DUO-O |
|---|---|---|---|---|---|
| Arm 1 | CP +/- Bev<br>Placebo-Placebo | CP +/- Bev<br>**Niraparib**-Placebo | CP +/- Bev<br>Placebo-Placebo | Rucaparib<br>**Nivolumab** | CP + Bev<br>Placebo-Placebo |
| Arm 2 | CP +/- Bev<br>**Pembro**-Placebo | CP +/- Bev<br>**Niraparib-TSR042** | CP +/- Bev<br>**Niraparib**-Placebo | **Rucaparib**<br>Placebo | CP + Bev<br>**Durva**-Placebo |
| Arm 3 | CP +/- Bev<br>**Pembro-Olaparib** | | CP +/- Bev<br>**Niraparib-TSR042** | **Placebo**<br>**Nivolumab** | CP + Bev<br>**Durva-Olaparib** |
| Arm 4 | | | | Placebo<br>Placebo | |

Maintenance

# ENDOMETRIAL CANCER

# The Cancer Genome Atlas (TCGA) project

ARTICLE

OPEN

doi:10.1038/nature12113

# Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

We performed an integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas using array- and sequencing-based technologies. Uterine serous tumours and ~25% of high-grade endometrioid tumours had extensive copy number alterations, few DNA methylation changes, low oestrogen receptor/progesterone receptor levels, and frequent *TP53* mutations. Most endometrioid tumours had few copy number alterations or *TP53* mutations, but frequent mutations in *PTEN*, *CTNNB1*, *PIK3CA*, *ARID1A* and *KRAS* and novel mutations in the SWI/SNF chromatin remodelling complex gene *ARID5B*. A subset of endometrioid tumours that we identified had a markedly increased transversion mutation frequency and newly identified hotspot mutations in *POLE*. Our results classified endometrial cancers into four categories: *POLE* ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high. Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas. We demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may affect post-surgical adjuvant treatment for women with aggressive tumours.

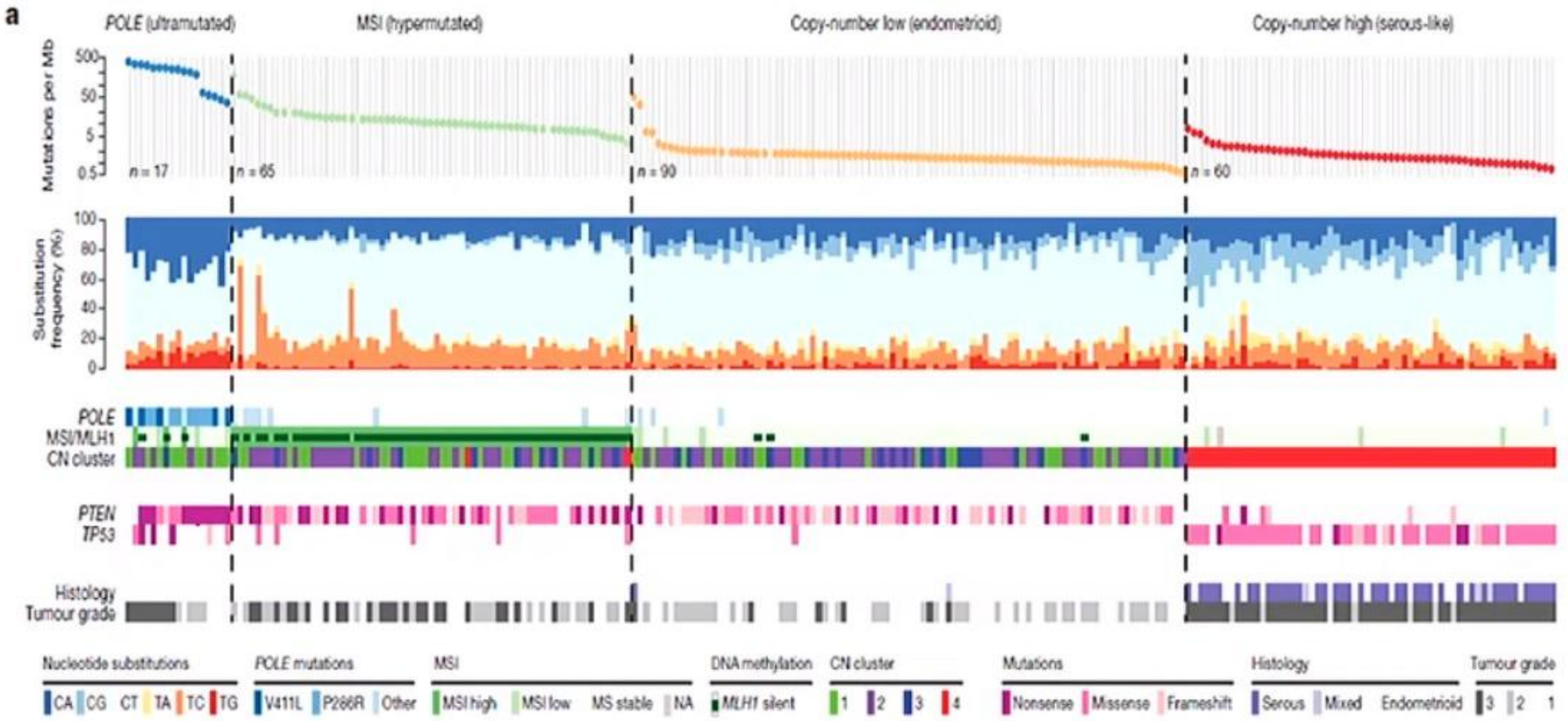
Nature 2013.

# TCGA

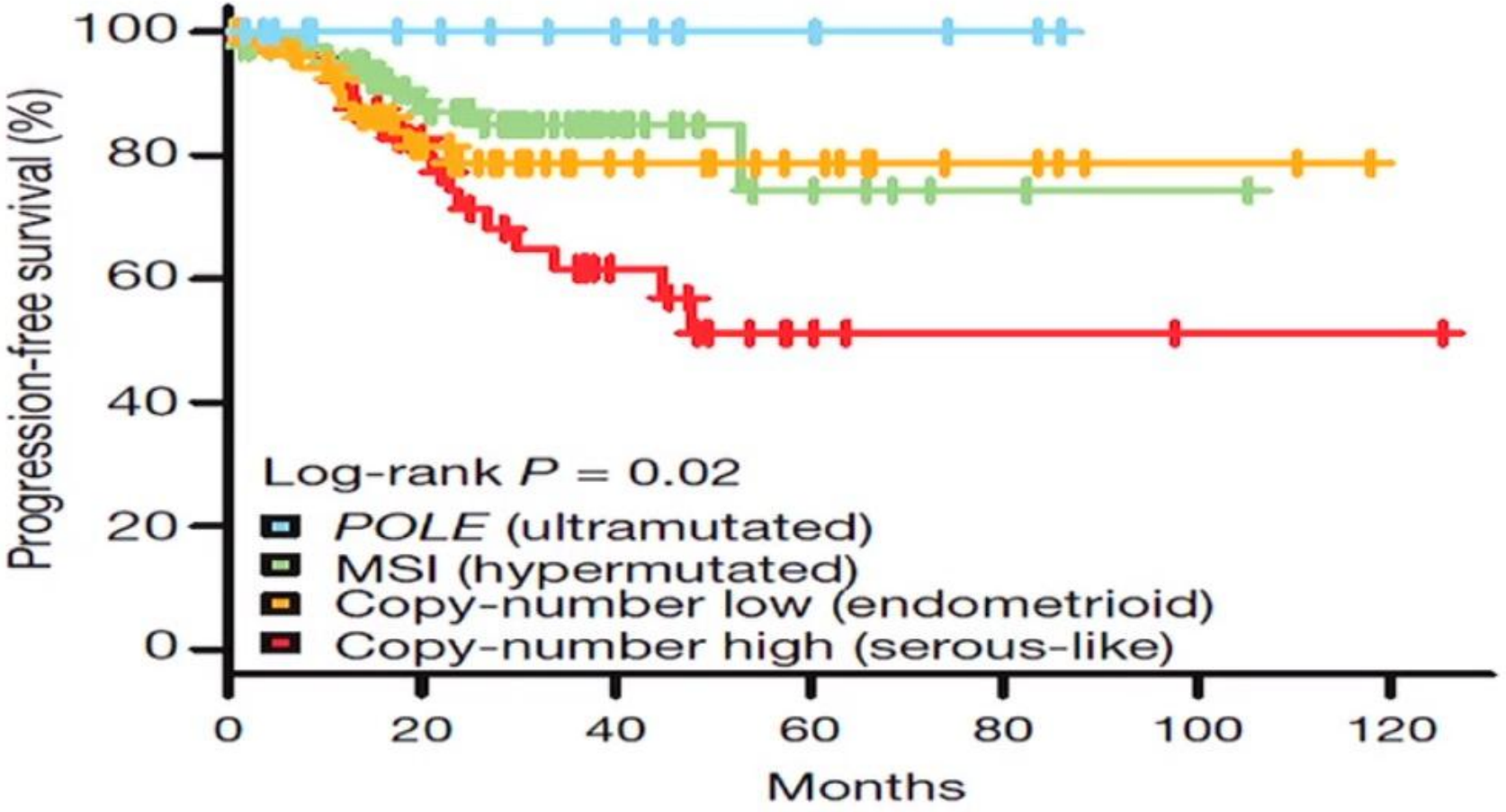
- combination of whole genome sequencing, exome sequencing, microsatellite instability (MSI) assays, and copy number analysis

- Tumour samples and corresponding germline DNA was analyzed to classify 373 endometrioid and serous endometrial cancers into four groups:
  - *POLE* (DNA polymerase-ε)ultramutated
  - MSI hypermutated
  - Copy-number low
  - Copy Number high

# TCGA Spectrum



# TCGA PFS analysis



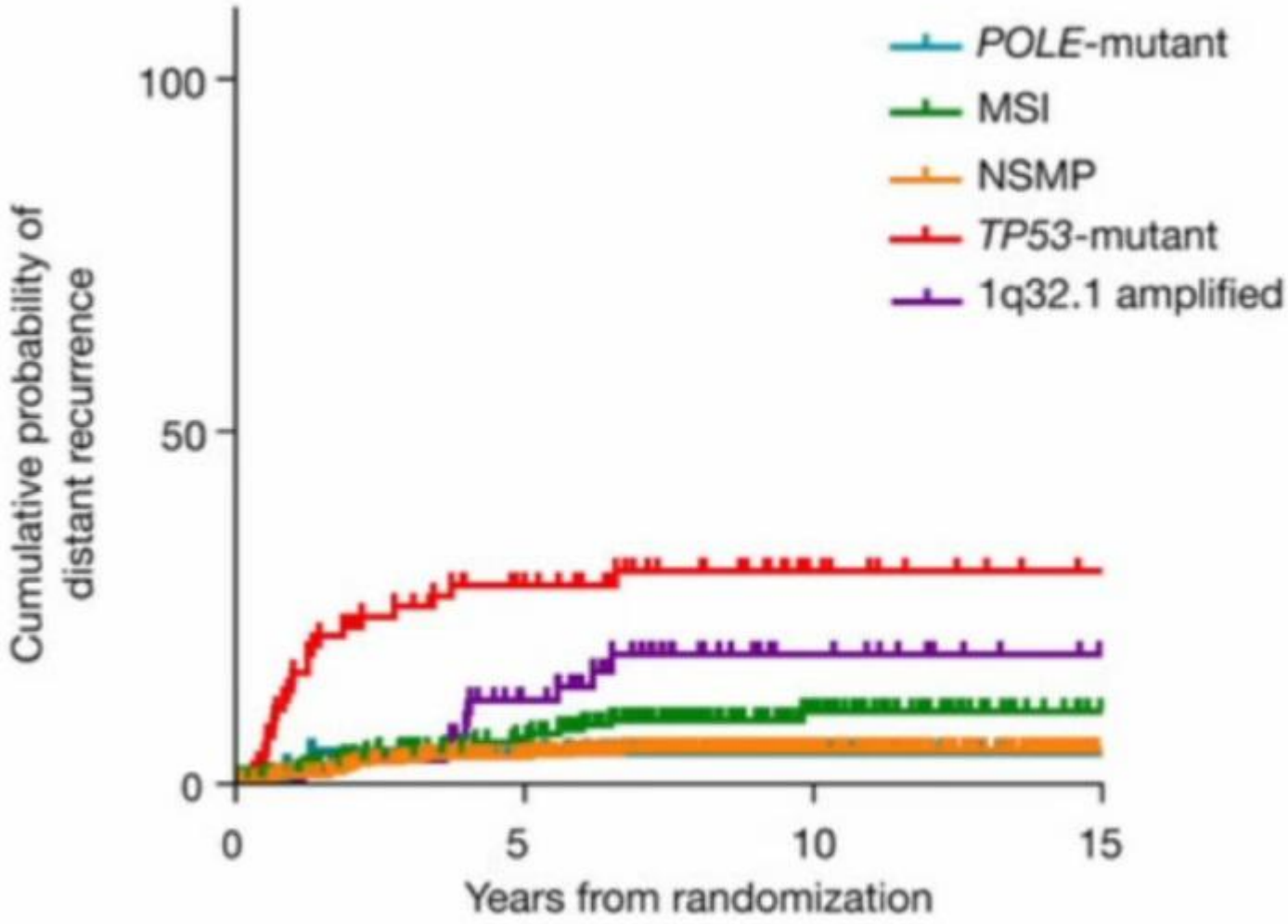
Published OnlineFirst September 22, 2017; DOI: 10.1158/1078-0432.CCR-17-0566

Personalized Medicine and Imaging

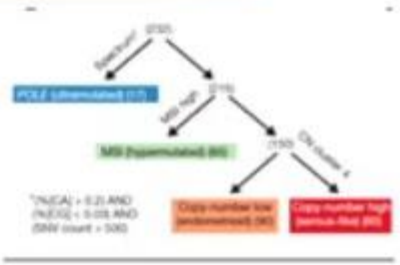
Clinical Cancer Research

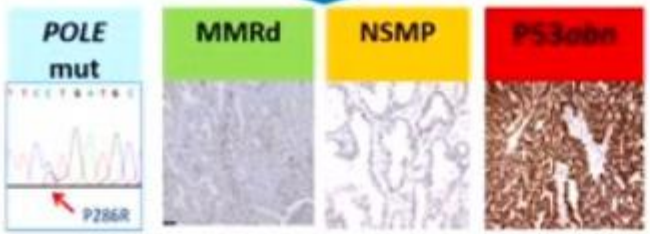
# Amplification of 1q32.1 Refines the Molecular Classification of Endometrial Carcinoma

Jeroen Depreeuw[1,2,3], Ellen Stelloo[4], Elisabeth M. Osse[4], Carien L. Creutzberg[5], Remi A. Nout[5], Matthieu Moisse[2,3], Diego A. Garcia-Dios[1,2,3], Michael Dewaele[6,7], Karen Willekens[6,7], Jean-Christophe Marine[6,7], Xavier Matias-Guiu[8], Frédéric Amant[1,9], Diether Lambrechts[2,3], and Tjalling Bosse[4]


POLE-mutant
MSI
NSMP
TP53-mutant
1q32.1 amplified
Cumulative probability of distant recurrence
100
50
0
0
5
10
15
Years from randomization

# TCGA molecular groups by surrogate markers




- Immunohistochemistry for p53 and mismatch repair proteins
- DNA sequencing for *POLE* exonuclease domain mutations

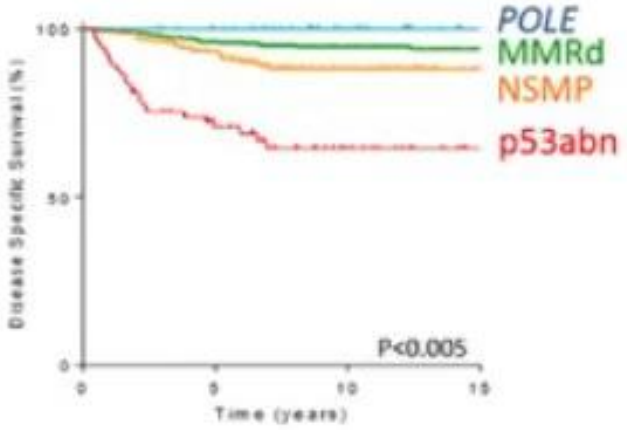
However ....

- Multiple classifying alterations (3%) – essential to do **all** tests
  - *a p53abn cancer may harbor a pathogenic POLE mutation*

Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

# Prognostic significance of the TCGA groups

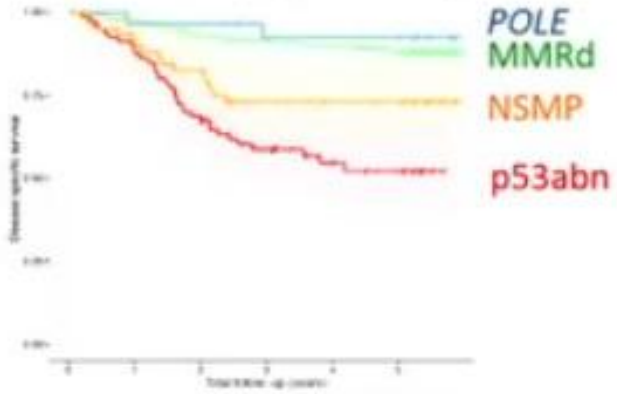
N=834 (PORTEC)




**High-intermediate risk EC**

*Stelloo et al, Clin Cancer Res 2016*

N=319 (Vancouver)




**Unselected EC**

*Talhouk et al, Cancer 2017*

- Few data from high grade tumors

Stelloo et al, Clin Cancer Res 2016; Talhouk et al, Cancer 2017; Leon del Castillo et al, USCAP 2018

# PORTEC-4a trial design

- Molecular integrated vs standard indications for adjuvant treatment:

Endometrial carcinoma

↓

Surgery and pathology diagnosis

↓

FIGO 2009 – high intermediate risk
Stage IA (with invasion), any age and grade 3 (with or without LVSI)
Stage IB, grade 1-2 and age > 60
Stage IB, grade 1-2 and LVSI+
Stage IB, grade 3 without LVSI
Stage II (microscopic), grade 1

↓

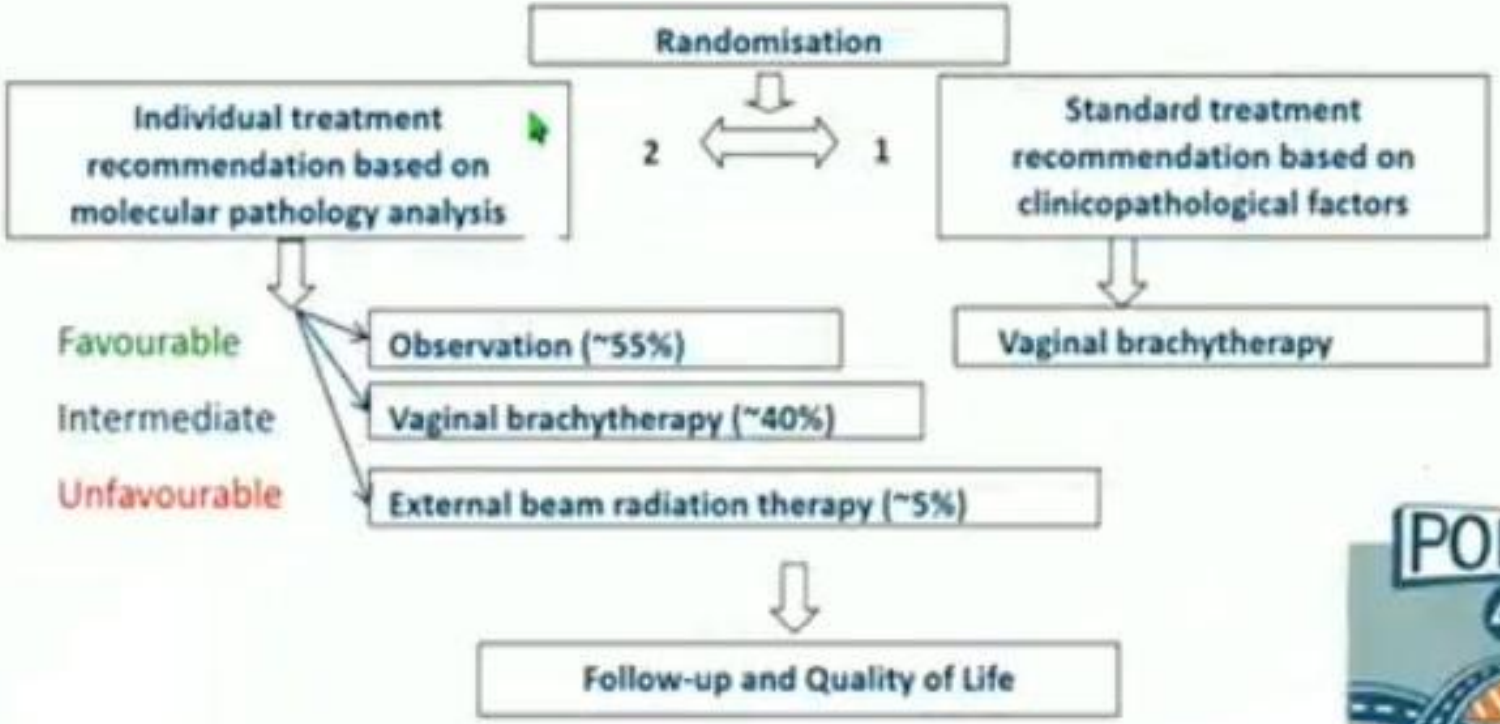
Randomisation


DGOG

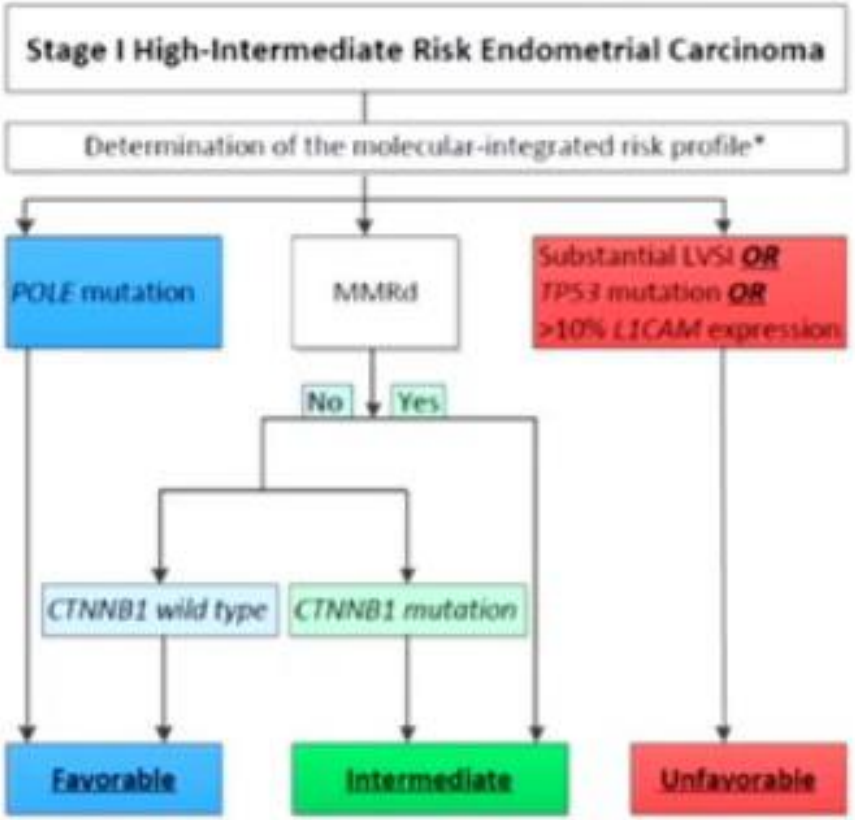
DUTCH CANCER SOCI

# PORTEC-4a trial design

- Molecular integrated vs standard indications for adjuvant treatment:




# PORTEC decision tree




*Patients with multiple characteristics (double classifiers) were designated intermediate risk. MMRd = Mismatch repair-deficiency.


Wortman et al, Gynecol Oncol 2018

## PORTEC-4a pilot phase completed

**Pilot phase (n=50) endpoints:**

- Logistics of molecular analysis (< 2 wks)
- Patient acceptance
- **Completed: 50 pts**

**PORTEC-4a study endpoints (n=500):**

- Vaginal recurrence
- RFS and OS; pelvic and distant recurrence
- Quality of life and freedom from symptoms
- Costs and use of health care resources
- **Current total: 252**

- Requirement to determine molecular profile within 2 working weeks
- Pilot phase has shown 2 weeks to be feasible
  - Involves microscopy, IHC and DNA sequencing
  - Dedicated pathologists
  - Efficient logistics, NGS runs 2-3/wk


D GOG
Dutch Gynaecological Oncology Group

GYNECOLOGIC CANCER INTERGROUP

Wortman et al, Gynecol Oncol 2018

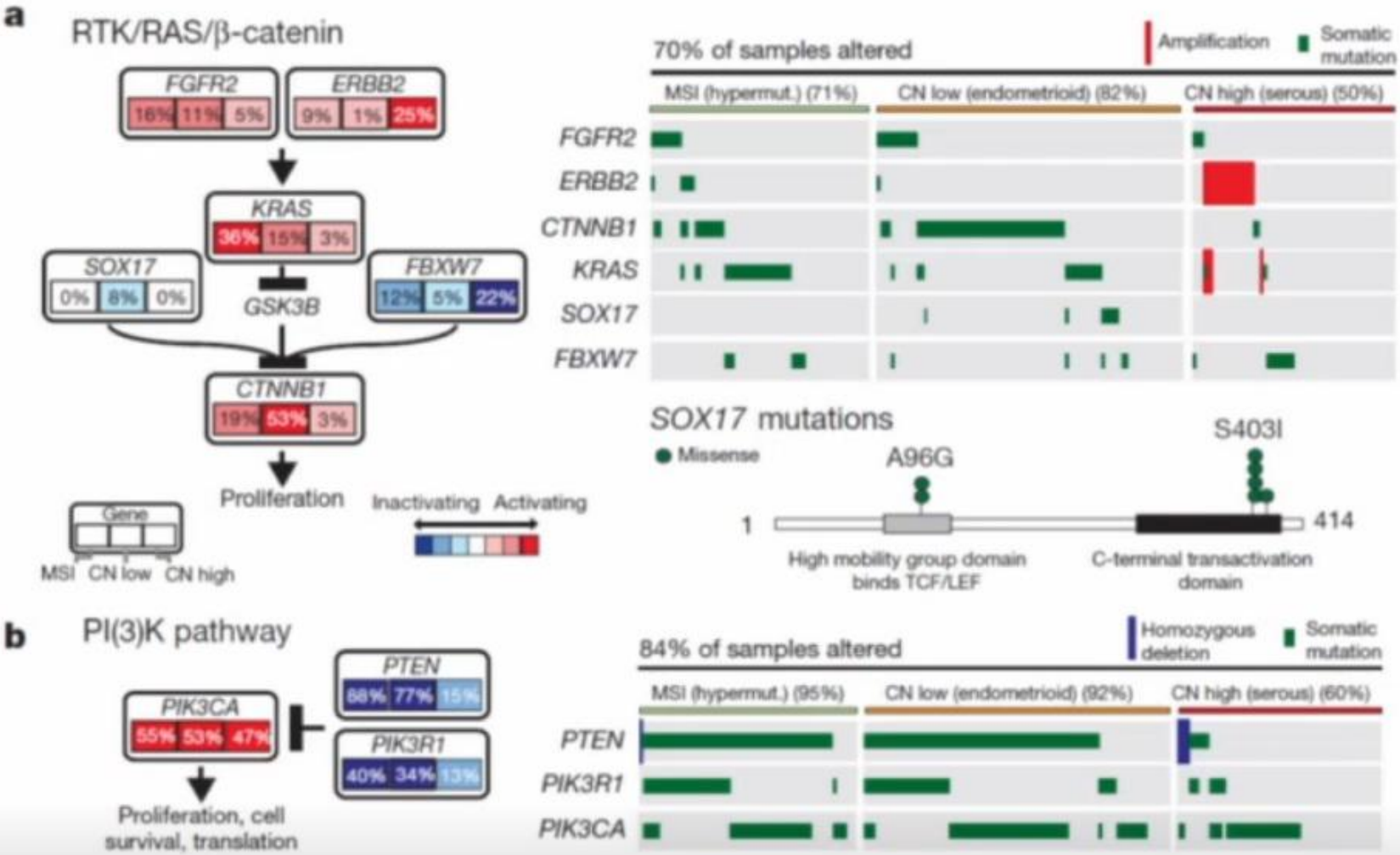



**Figure 4 | Pathway alterations in endometrial carcinomas.**

# Endometrial Cancer: Targeted Trials

## MTOR Inhibitors

**Single agent**

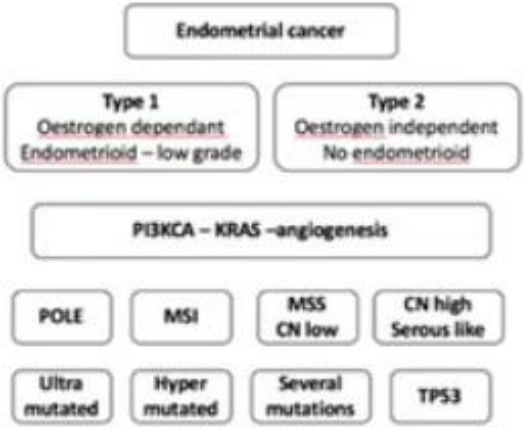
- Temsirolimus
- Ridaforolimus
- Everolimus

**Combinations**

- Temsirolimus with Megace
- Everolimus with Letrozole
- Temsirolimus with CT chemo
- Temsirolimus + Bevacizumab

## PI3K inhibitors

## AKT inhibitors




## Anti-angiogenic

**Single agent**

- Bevacizumab
- Sunitinib
- Cabozantinib

**Combinations**

- Bevacizumab with CT chemo

## Checkpoint inhibitors

## DNA Repair Inhibitors

## Folate Receptor Targeting

# Endometrial cancer

## Single Agent IO

| | Patient Population | Agent | Results |
|---|---|---|---|
| **Single agent IO** | | | |
| Le et al. (2018) | MMRd tumors (2EC pts included) | Pembrolizumab | ORR 71% |
| Ott et al. (2017) Keynote 028 | 24 PD-L1+ pts | Pembrolizumab | ORR 13% |
| Keynote 158 | Multicohort MSI-H (17EC pts included) | Pembrolizumab | ORR 37.7% |
| Fader et al. (2016) | MMRd tumors recurrent EC | Pembrolizumab | ORR 56%<br>DCR 88.9% |
| Santin et al. (2016) | 2pts (POLE and MSI-H) | Nivolumab | Prolonged response (>7mo) in 2 patients |
| Hasegawa et al. (2018) | 23 Metastatic EC pts | Nivolumab | ORR 23%<br>PFS 3.6mo |
| Fleming et al. (2017) | 15 Metastatic EC pts | Atezolizumab | ORR 13% (1MSI-H)<br>PFS 1.7mo |
| GARNET | MSI-H recurrent/advanced EC | TSR-042 | ORR 52% |

# GARNET, PHASE 1 TSR-042 (anti-PD-1) in patients with Recurrent or Advanced MSI-H EC

**Part 2B Key Objectives**

- Evaluate safety and tolerability at the RP2D in advanced solid tumors
- Objective response rate (ORR), duration of response (DOR), and DOR per irRECIST assessed by investigators
- To further characterize the pharmacokinetic profile and receptor occupancy (RO) of TSR-042
- **Primary Efficacy Endpoints**
- ORR and DOR per irRECIST assessed by investigators

**Parts 1 and 2A Completed**

**Part 1: DLT-Based Dose Escalation**
- 1-10 mg/k Q2W
- N=21, all comers

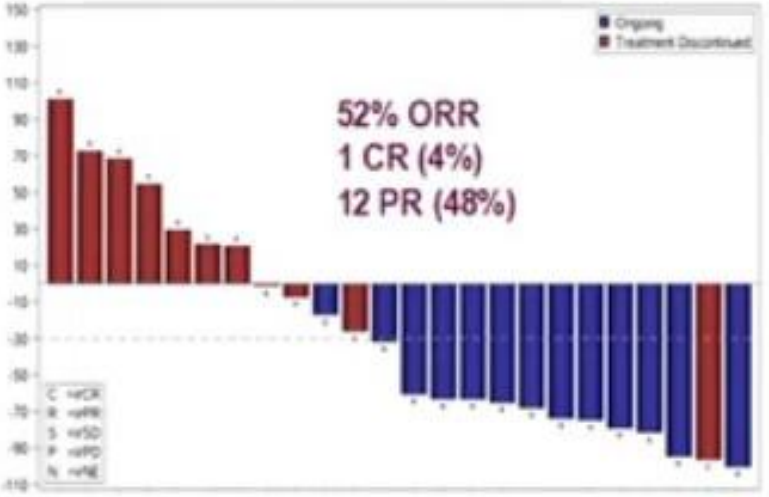
**Part 2A: Fixed-Dose Safety Cohorts**
- 500 mg Q3W or 1000 mg Q6W
- N=13, all comers

**RP2D**
500 mg Q3W x4; 1000 mg Q6W thereafter

**Part 2B: Expansion Cohorts at RP2D Ongoing**

- **MSI-H Endometrial Cancer** N=65
- **Endometrial Cancer (MSS)** N=65
- **NSCLC** N=65
- **Nonendometrial MSI-H Basket** N=100

Best irRECISt ORR in 25 MSI-H EC



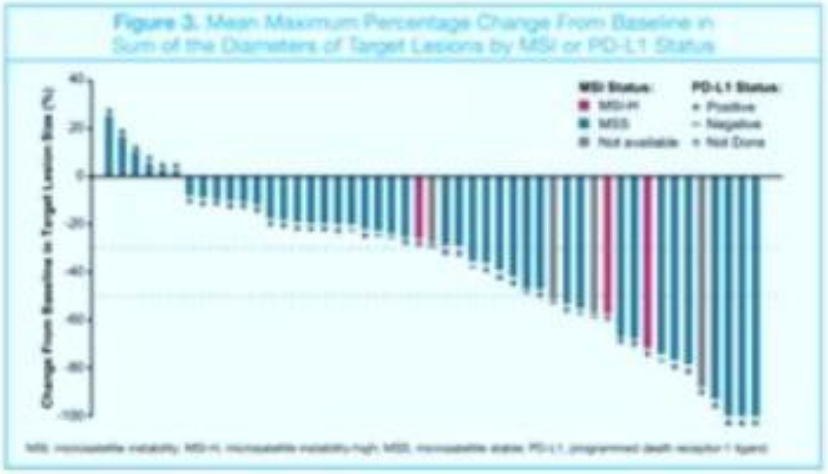

Oaknin et al. ESMO 2018 (PD)

# Lenvatinib+Pemprolizumab in AEC

ORR 39.6%

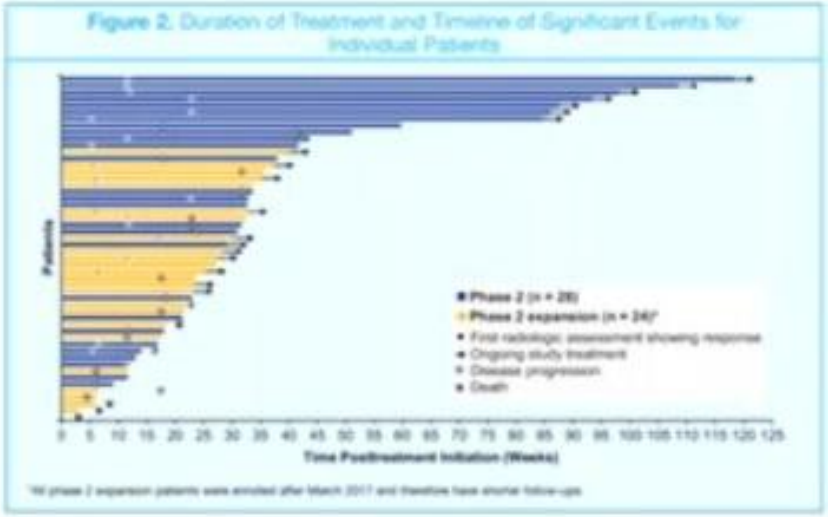
85% MSS: ORR 35.6% (16/45)

8% MSI-H: ORR 50% (2/4)




83% of responses ≥ 6 months

65% of response ≥ 12 months




Makker et al. ASCO 2018

Abs 9940

# Primary endpoint:

## Tumor Response at 24 weeks (Investigator Assessment; irRECIST)

| Response Category | Total (n = 108) | Not MSI-H or dMMR (n = 94)[a] | MSI-H / dMMR (n = 11)[a] |
|---|---|---|---|
| | Week 24 | | |
| Objective response rate (complete response + partial response), n (%)[b] | 41 (38.0) | 34 (36.2) | 7 (63.6) |
| 95% CI | 28.8–47.8 | 26.5–46.7 | 30.8–89.1 |

## Tumor Response at Data Cut-off (Independent Imaging Review; RECIST version 1.1)

| Endpoint | Not MSI-H or dMMR (n = 94) |
|---|---|
| Objective response rate (complete response + partial response) | |
| ORR (95% CI) | 38.3 % (29,49) |
| Complete response | 10.6 % |
| Partial response | 27.7 % |
| Duration of response | |
| Median in months ( range) | NR ( 1.2+,33.1+ ) |
| % with duration ≥ 6 months | 69% |

Data reported In the label

## TOXICITY

- Grade 3-4 AEs in 69,4% of pts ( Hypertension 32.4%)
- Most frequent AEs of any grade : hypertension, diarrhoea, decrease appetite, fatigue, hypothyroidism, nausea)
- Study drug discontinuation in 20% of pts, interruption in 72.2 %, reduction in 65%

NO CONTROL ARM

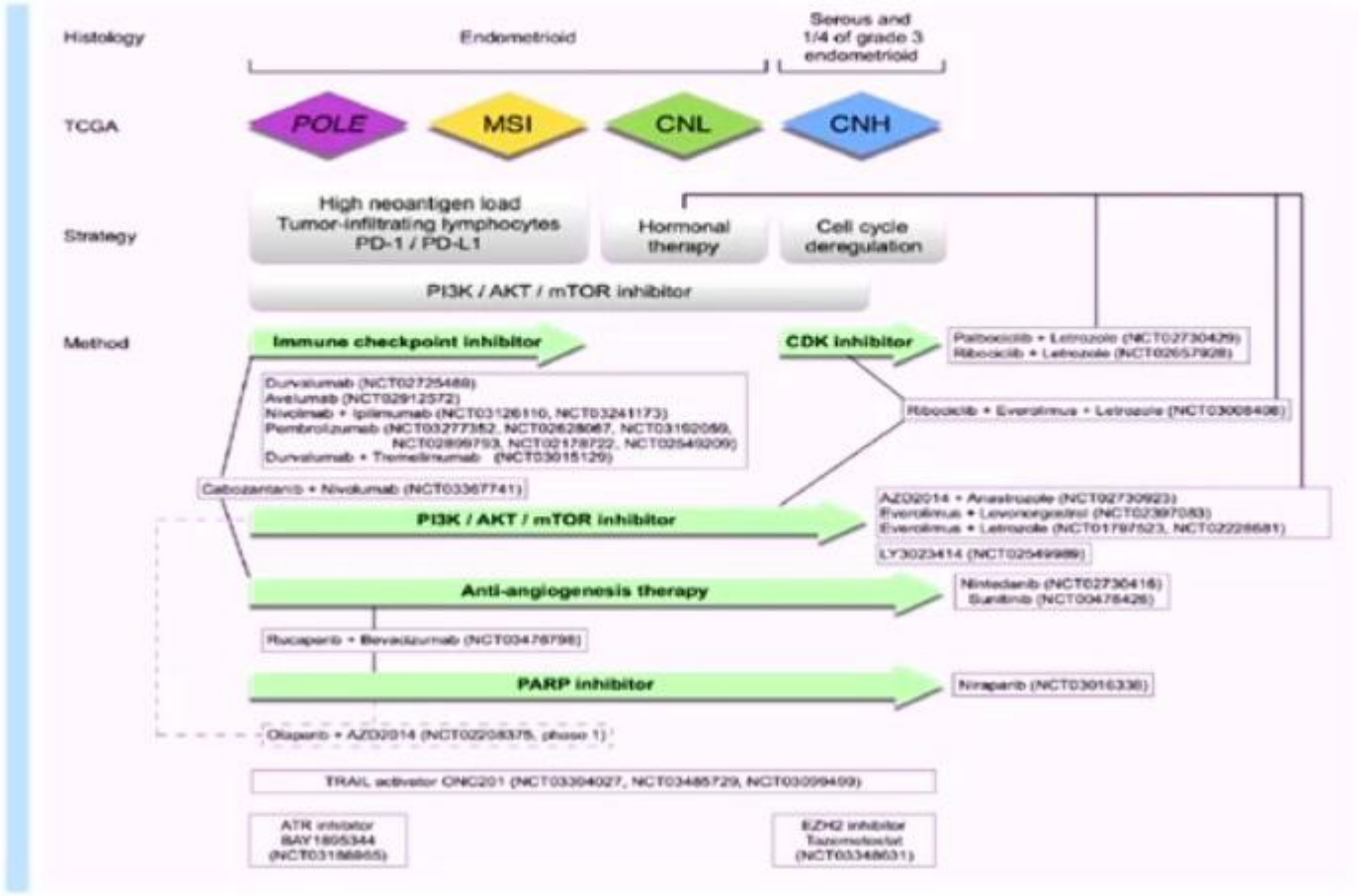
PHASE III trial is ongoing

**TUESDAY, SEPTEMBER 17, 2019**

# FDA Approves KEYTRUDA® (pembrolizumab) plus LENVIMA® (lenvatinib) Combination Treatment for Patients with Certain Types of Endometrial Carcinoma

- *Disease Progression Following Prior Systemic Therapy*
- *Not candidate for curative surgery or radiation*
- *Not Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR)*
- *Under New FDA-Initiated Program, Project Orbis, Combination Treatment Is the First to Receive Simultaneous Review Decisions in the U.S., Australia and Health Canada*

# Genetic background and develop individual optimal treatment **with molecular –targeted drugs**



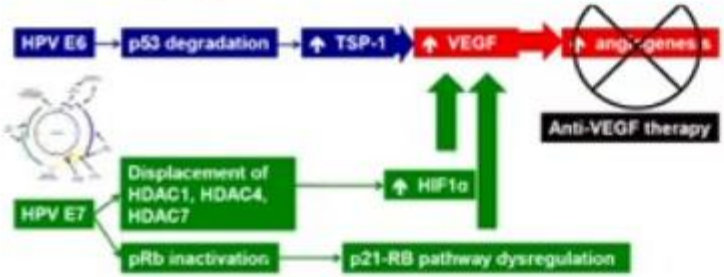
# CERVICAL CANCER

# Incorporation of molecular targeted therapy

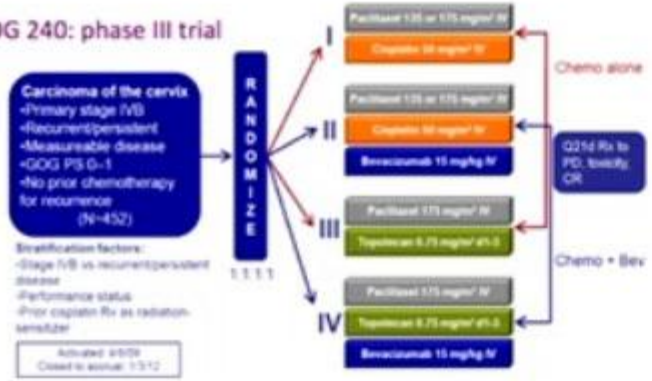
- Anti-angiogenic agents
  - Bevacizumab
  - Cediranib
- Antibody-Drug conjugates
  - Tisotumab vedotin
- Immunotherapeutic strategies

# Cervical cancer

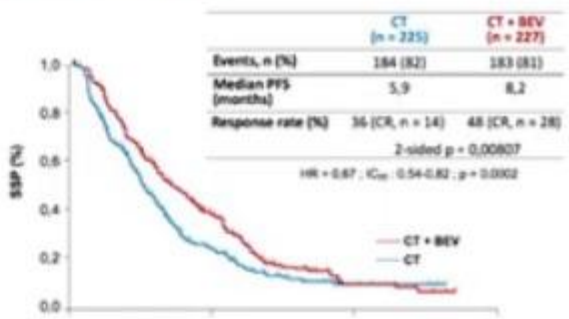
- **Antiangiogenics**



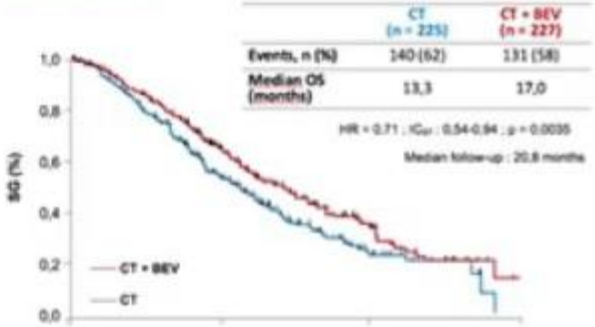

GOG 240: phase III trial




*Progression-free-survival*

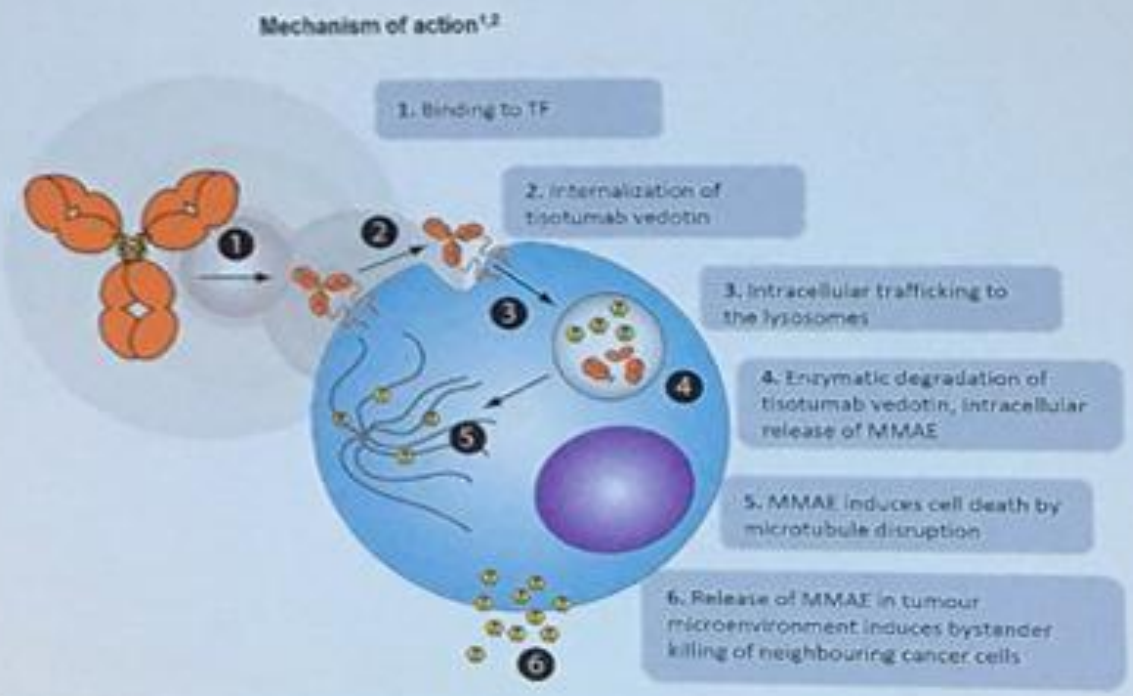



*Overall survival*



# Tisotumab Vedotin Mechanism of Action

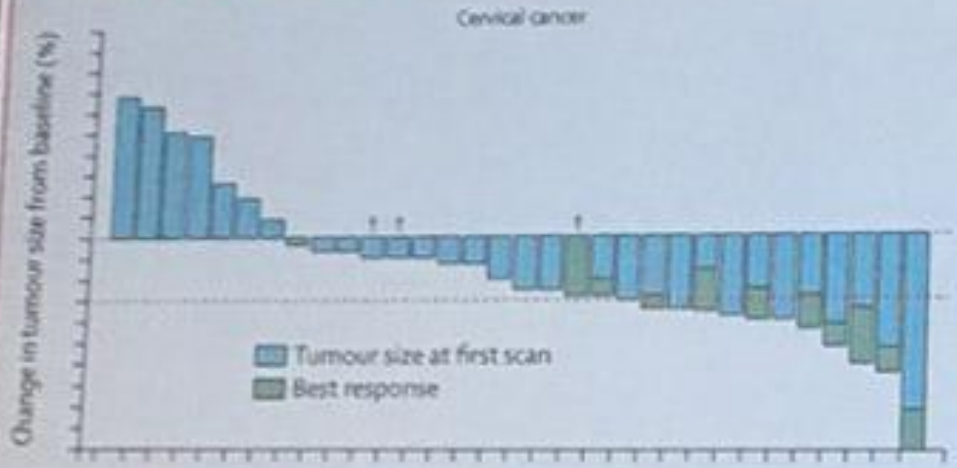
- **Tisotumab vedotin is an antibody-drug conjugate (ADC) composed of a human mAb specific for tissue factor (TF), a protease-cleavable linker, and the microtubule-disrupting agent MMAE[1,2]**
- **TF is a transmembrane protein that is the main physiologic initiator of coagulation and is involved in angiogenesis, cell adhesion, motility, and cell survival[3]**
- **TF is aberrantly expressed in a broad range of solid tumors, including cervical cancer, and is associated with poor prognosis[4,5]**



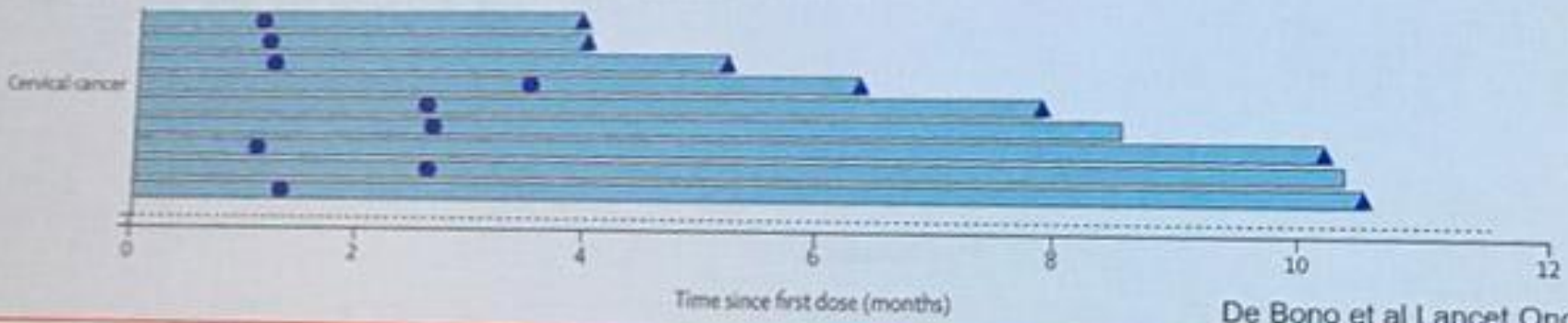

MMAE, monomethyl auristatin E
*Tissue factor is known as TF, CD142, and thromboplastin.

1. Breij EC et al. *Cancer Res*. 2014;74(4):1214-1226. 2. De Goeij BE et al. *Mol Cancer Ther*. 2015;14(5):1130-1140. 3. Chu AJ. *Int J Inflam*. 2011;2011:367284. 4. Förster Y et al. *Clin Chim Acta*. 2006;364(1-2):12-21. 5. Cocco E et al. *BMC Cancer*. 2011;11:263.

# Tisotumab vedotin in cervical cancer (cohort)




Partial Response: 9 out of 34 patients
(26.5% [ 95% CI 12.9-44.4])




De Bono et al Lancet Oncol 2019

# Check point inhibitors in cervical cancer

| | Lheureux et al.[1] | KEYNOTE-028[2] | KEYNOTE-158[3] (Cohort E)[a] | Checkmate 358[4] |
|---|---|---|---|---|
| Phase(s) | 2 | 1b | 2 | 1/2 |
| Population | Metastatic or recurrent cervical cancer with progression after prior platinum chemotherapy | PD-L1+ advanced cervical squamous cell cancers after failure of prior systemic therapy | Advanced cervical cancer with progression on or intolerance to ≥1 line of prior therapy, PD-L1+ (CPS ≥1) | HPV-associated tumors, including recurrent or metastatic cervical, vaginal, vulvar cancers |
| Patients, n | 42[a] | 24 | 77[d] | 24 |
| Treatment | Ipilimumab | Pembrolizumab | Pembrolizumab | Nivolumab |
| ORR, % | 8.8[c] | 12.5[c] | 14.3 | ITT: 20.8[c] Cervical cancer pts: 26.3% |
| DCR, % | 32.3 | 25.0 | — | 70.8 |
| mDOR | — | 19.3 wk | NR (range: 4.1–18.6+ mo) | NR |
| PFS | mPFS: 2.5 mo | 6-mo PFS: 13.0% | — | mPFS: 5.5 mo |
| OS | — | 6-mo OS: 66.7% | — | NR |
| Safety | Manageable toxicities | ≥Gr 3 TRAEs: 20.8% | Serious AEs: 39% | Gr 3/4 TRAEs: 12.5% |
| Follow-up | — | 48.9 wk | 11.7 mo | 31 wk |

heureux S, et al. Presented at ASCO Annual Meeting, 2015. Abstract 3061. 2. Frenel JS, et al. Presented at ASCO Annual Meeting, 2016. Abstract 5515. 3. J Clin Oncol. 2019 Jun 10;37(17):1470-1478. 4. Hollebecque A, et al. Presented at ASCO Annual Meeting, 2017. Abstract 5504.

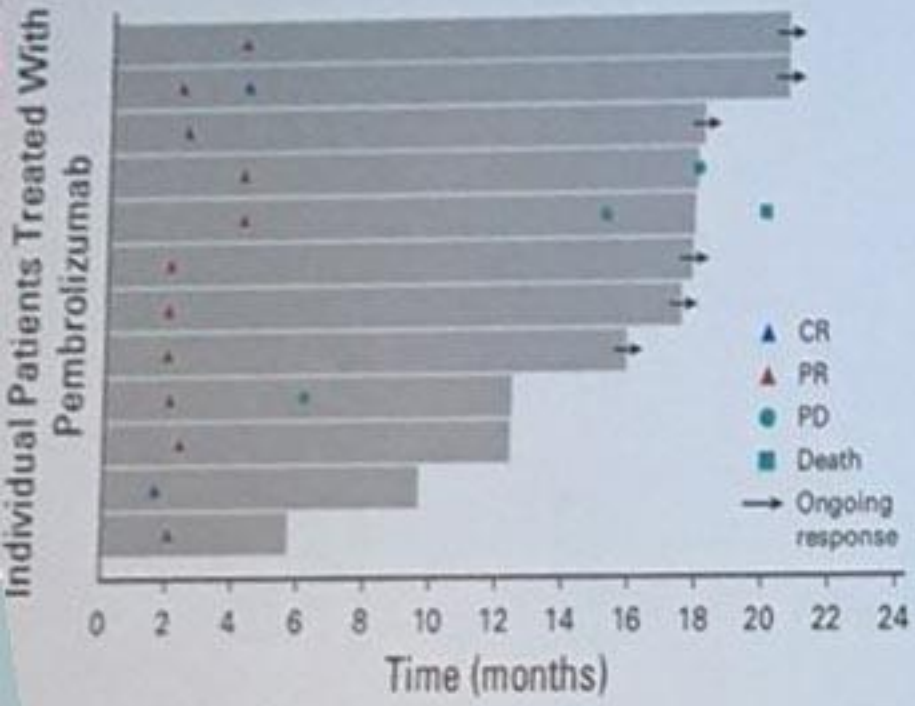
# Keynote 158: Pembrolizumab in recurrent cervical cancer

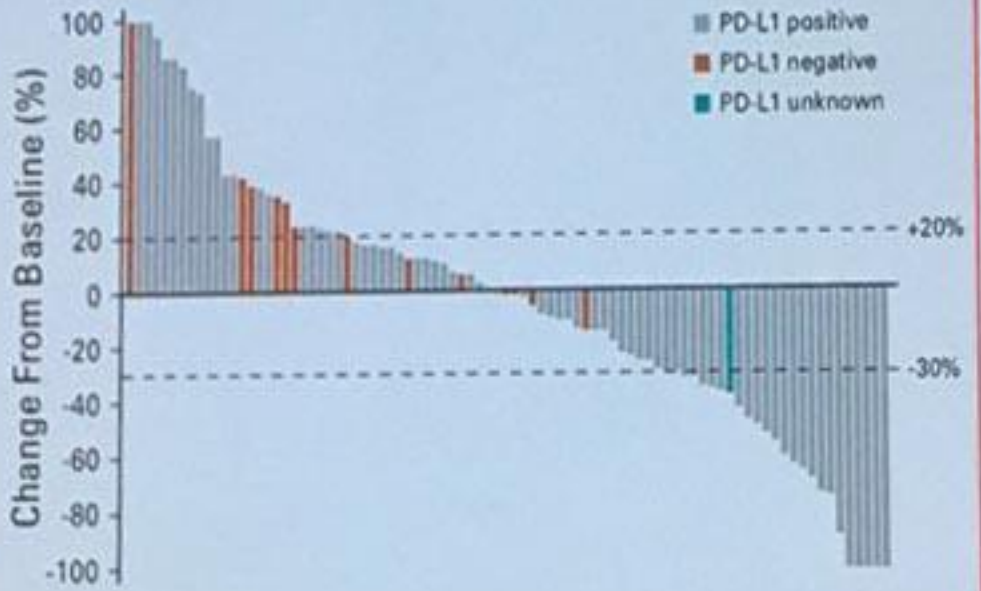
98 patients

**ORR 12.2 %**

All responses in PDL-1 +ve tumours

Median duration of response not reached

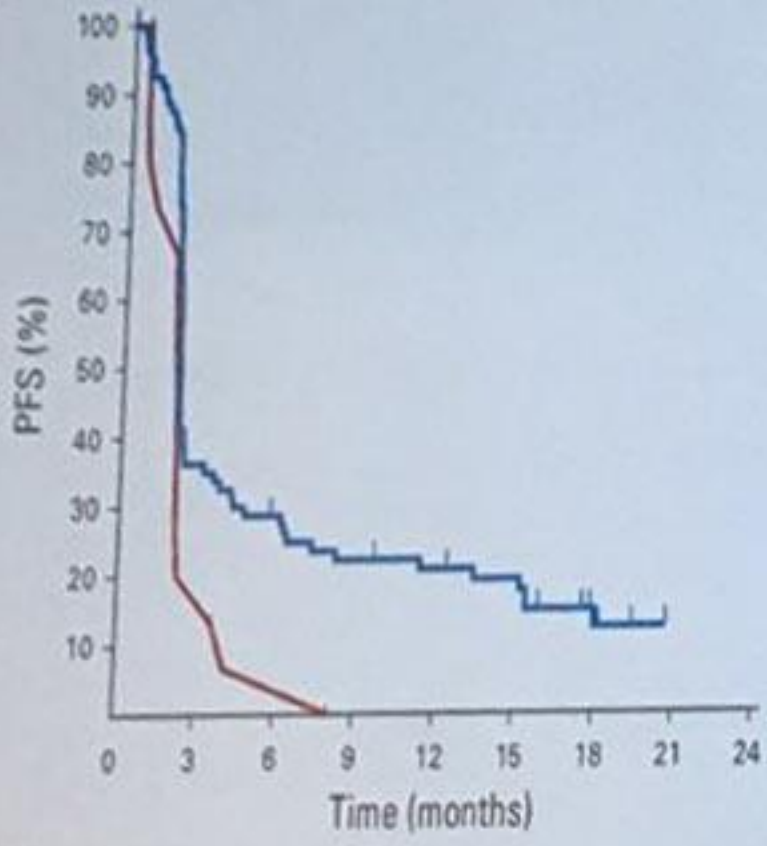



Chung et al J Clin Oncol 2019

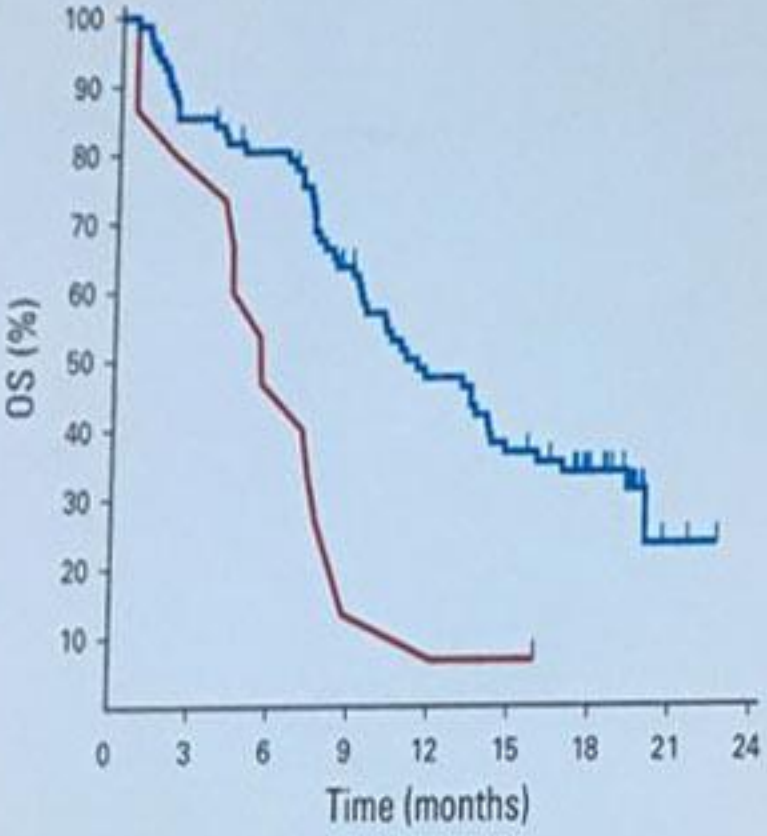
# Keynote 158: Pembrolizumab in recurrent cervical cancer- PDL1 +ve and PDL1 -ve

A




| No. at risk: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PD-L1+ | 82 | 29 | 22 | 17 | 15 | 13 | 6 | 0 | 0 |
| PD-L1- | 15 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

C




| No. at risk: | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| PD-L1+ | 82 | 69 | 63 | 46 | 35 | 27 | 18 | 2 | 0 |
| PD-L1- | 15 | 12 | 7 | 2 | 2 | 1 | 0 | 0 | 0 |

Chung et al J Clin Oncol 2019

## Drugs



Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

# FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

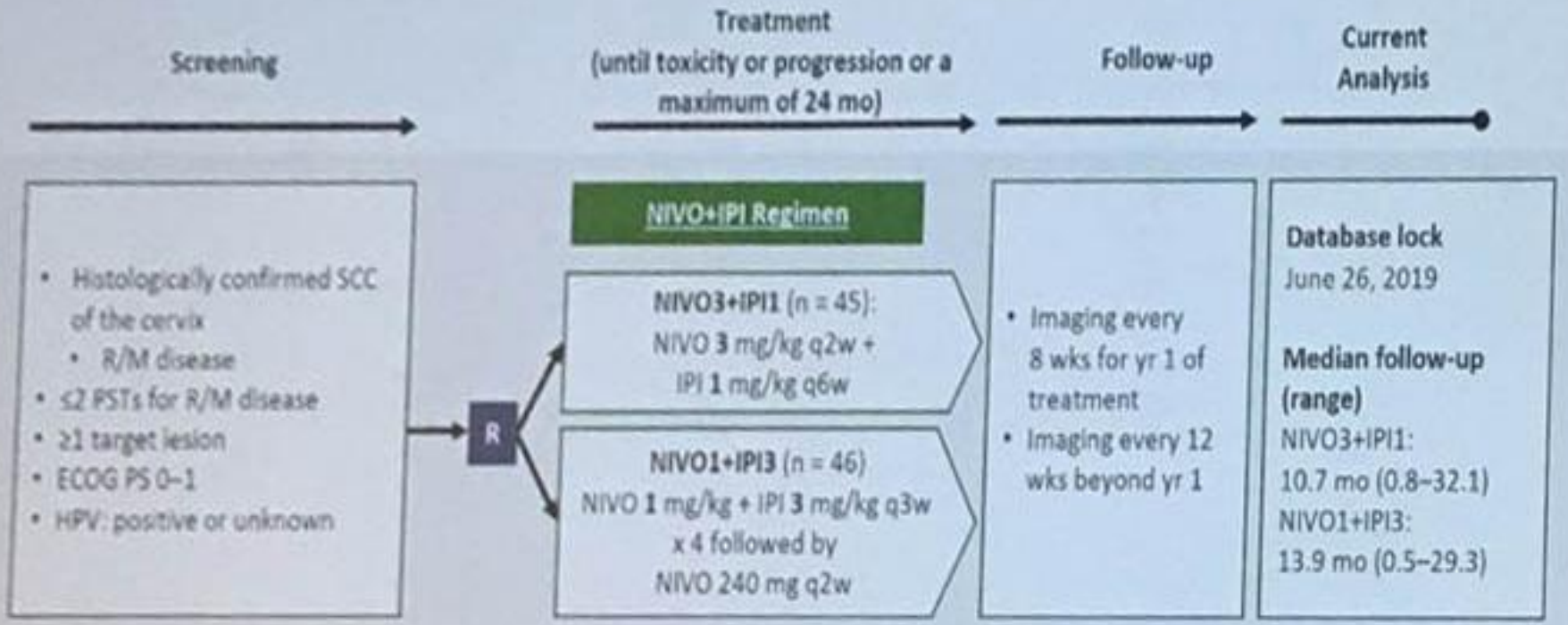
On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

# Phase III trials with immune checkpoint inhibitors in cervical cancer

| Trial | Indication | Investigational arm | Comparator | Primary Outcome |
|---|---|---|---|---|
| Keynote - 826 (N= 600) | Primary systemic therapy: (Persistent or recurrent cervical cancer | Pembrolizumab | Investigator choice: Paclitaxel + Cis/carboplatin +/- bevacizumab | PFS |
| BEATcc (n=404) | Primary systemic therapy: (Persistent or recurrent cervical cancer | Cisplatin + paclitaxel + bevacizumab + Atezolizumab | Cis/Carboplatin +paclitaxel + bevacizumab (GOG # 240) | OS |
| EMPOWER-CERVICAL-1 | Metastatic cervical cancer: resistant to platinum | cemiplimab | Investigator choice: Pemetrexed Gemcitabine Topotecan vinorelbine | OS |

# Combinations of nivolumab and ipilumumab

## Randomized cervical cancer cohorts of CheckMate 358 (NCT02488759) in relapsed or metastatic cervical cancer




- **Study start date:** October 2015
- **Estimated completion date:** December 2019
- **Primary endpoint:** Investigator-assessed ORR by RECIST 1.1
- **Secondary endpoints:** OS, PFS, duration of response

ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PFS, progression-free survival; PS, performance status; PST, prior systemic therapy; SCC, squamous cell carcinoma.

Neumann, Oaknin et al ESMO 2019

# CheckMate 358 nivolumab and ipilumumab

## Tumour Response

| | NIVO3+IPI1 | | NIVO1+IPI3 | |
|---|---|---|---|---|
| Response in all treated patients | No PST for R/M disease, n = 19 | PST for R/M disease, n = 26 | No PST for R/M disease, n = 24 | PST for R/M disease, n = 22 |
| ORR, % (95% CI) | 31.6 (12.6–56.6) | 23.1 (9.0–43.6) | 45.8 (25.6–67.2) | 36.4 (17.2–59.3) |
| Clinical benefit rate,* % (95% CI) | 63.2 (38.4–83.7) | 53.8 (33.4–73.4) | 70.8 (48.9–87.4) | 72.7 (49.8–89.3) |
| Best overall response† | | | | |
| Complete response | 3 (15.8) | 1 (3.8) | 1 (4.2) | 3 (13.6) |
| Partial response | 3 (15.8) | 5 (19.2) | 10 (41.7) | 5 (22.7) |
| Stable disease | 6 (31.6) | 8 (30.8) | 6 (25.0) | 8 (36.4) |
| Progressive disease | 7 (36.8) | 11 (42.3) | 6 (25.0) | 5 (22.7) |
| Duration of response, median, mo (95% CI) | NR (6.6–NR) | 14.6 (7.5–NR) | NR (4.6–NR) | 9.5 (1.9–NR) |
| ORR by tumor cell PD-L1 expression,‡ | | | | |
| PD-L1 ≥1%, # responders/# treated (%) [95% CI] | 4/13 (30.8) [9.1–61.4] | 4/10 (40.0) [12.2–73.8] | 4/11 (36.4) [10.9–69.2] | 2/12 (16.7) [2.1–48.4] |
| PD-L1 <1%, # responders/# treated (%) [95% CI] | 1/3 (33.3) [0.8–90.6] | 1/11 (9.1) [0.2–41.3] | 0/4 (0) [0.0–60.2] | 4/7 (57.1) [18.4–90.1] |

*Proportion of patients with a complete response, a partial response, or stable disease; †Responses could not be determined in 1 patient with PST in NIVO3+IPI1 and in 1 patient each with and without PST in NIVO1+IPI3. ‡Tumor cell PD-L1 expression was defined as the percentage of tumor cells exhibiting plasma membrane staining at any intensity.
CI, confidence interval; NR, not reached; PST, prior systemic therapy.

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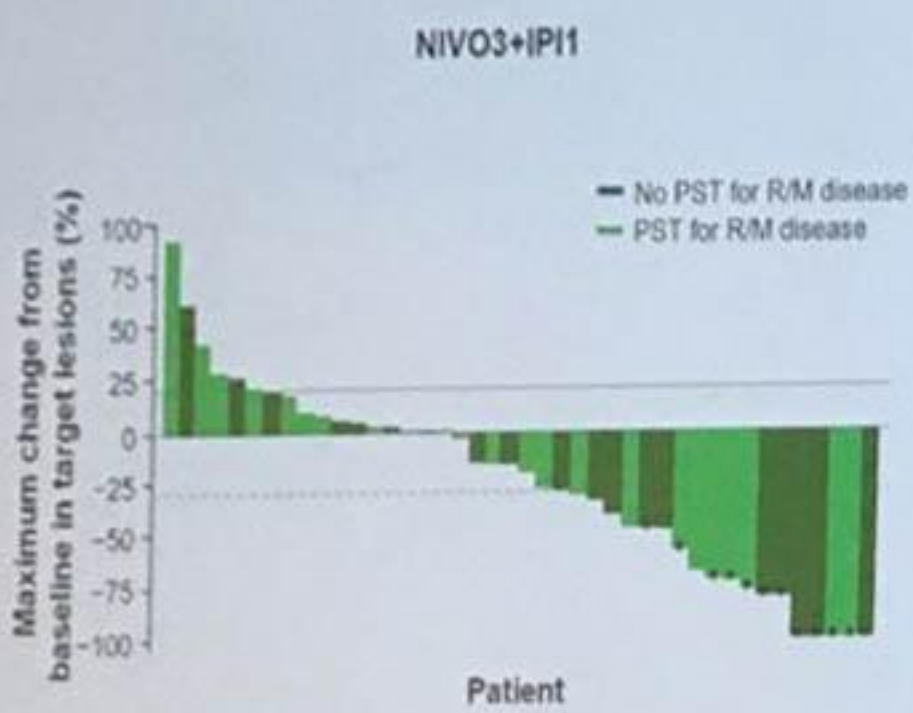
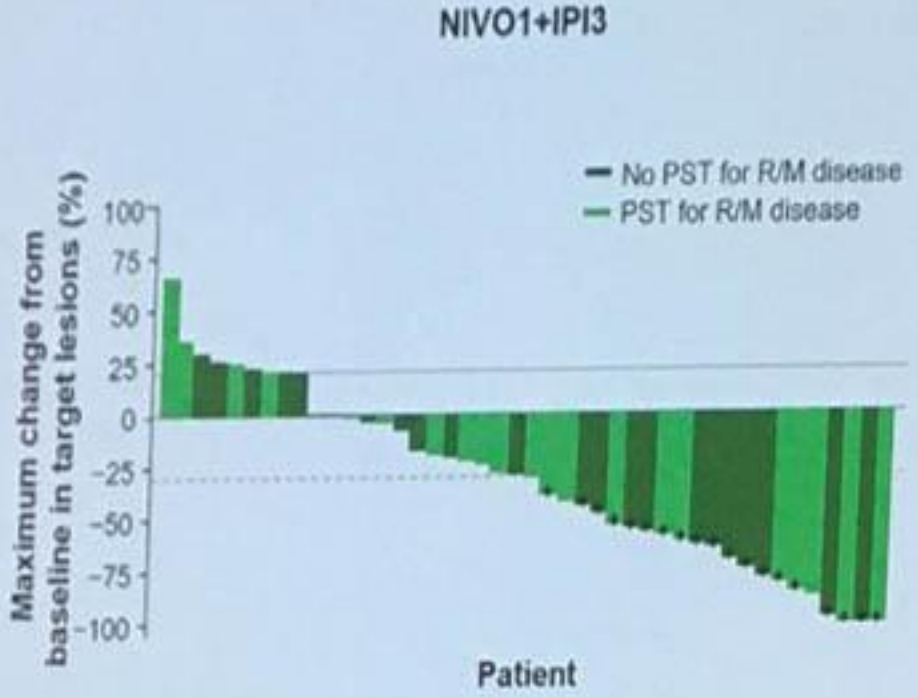
# CheckMate 358 nivolumab and ipilumumab

## Change From Baseline in Target Lesion Size




rs with asterisks represent confirmed responses (complete or partial response).
, prior systemic therapy.

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# CheckMate 358 nivolumab and ipilumumab

Summary of Treatment Related Adverse Events

| Event, n (%) | NIVO3+IPI1 (n = 45) | | NIVO1+IPI3 (n = 46) | |
|---|---|---|---|---|
| | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| TRAEs | 36 (80.0) | 13 (28.9) | 38 (82.6) | 17 (37.0) |
| Treatment-related SAEs | 12 (26.7) | 8 (17.8) | 16 (34.8) | 10 (21.7) |
| TRAEs leading to treatment discontinuation | 6 (13.3) | 2 (4.4) | 9 (19.6) | 6 (13.0) |
| Treatment-related SAEs leading to treatment discontinuation | 2 (4.4) | 1 (2.2) | 5 (10.9) | 5 (10.9) |

- No new safety signals
- Higher incidence of TRAEs and treatment-related SAEs leading to treatment discontinuation in NIVO1+IPI3 compared with NIVO3+IPI1
- Higher incidence of gastrointestinal AEs with Nivo1 +IPI3 compared to Nivo3+ IPI1
- No treatment-related deaths

SAE, serious adverse event; TRAE, treatment-related adverse event.

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# Phase III CALLA in frontline treatment of Locally advanced Cervical Cancer

A Phase III, Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With and Following Chemoradiotherapy Compared to Chemoradiotherapy Alone for Treatment in Women With Locally Advanced Cervical Cancer

- Adeno or Squamous carcinoma
- Stage IB2, IIA, or IIB node positive or IIA-IVA any node
- ECOG 0-1
- At least one measurable lesions. No distant metastases
- Adequate hematologic & renal function

N=714

**Experimental**

Chemoradiation with Durvalumab up to 2 years

**Control**

Chemoradiation

Sponsor: AZ

Sponsor: Primary endoint:PFS

# Conclusions

Personalized medicine in gynecologic oncology remains an evolving science

- Precision medicine use is growing included in community practices

- Rapid gene sequencing to identify targets in individual tumors (Precision Oncology)
- Tumor heterogeneity and tumor resistance contribute to the complexity of developing effective personalized treatment
- Cost?
- Well designed clinical trials designs and translational studies are essential