

13° CONGRESSO NAZIONALE AIOM GIOVANI
2019 NEWS IN ONCOLOGY

Terapia di mantenimento dopo trattamento di I linea nei tumori sierosi ad alto grado dell'ovaio

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Ovarian carcinoma is a common cancer that is often lethal

4th

most common female cancer
after breast, cervical, and corpus uteri*,¹

3.4%

of an estimated **8.6 million new cases of cancer** in women worldwide*¹

8th

most common cause of cancer-related mortality in women worldwide*,¹

1st

most lethal gynecological cancer in women in the United States²

Ovarian cancer is the most lethal gynecological malignancy³

*Based on GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions.

1. Bray F *et al. CA Cancer J Clin* 2018; 68 (6): 394–424. 2. Karakashev S *et al. Cell Rep* 2017; 21 (12): 3398–3405. 3. Chan JK *et al. Clin Exp Metastasis* 2018; 35 (5–6): 521–533.

There remains a significant unmet need for newly diagnosed ovarian cancer¹



Platinum-based
chemotherapy

Bevacizumab



~70%

of women relapse within 3
years of first line treatment¹



38%

5-year survival rate⁵

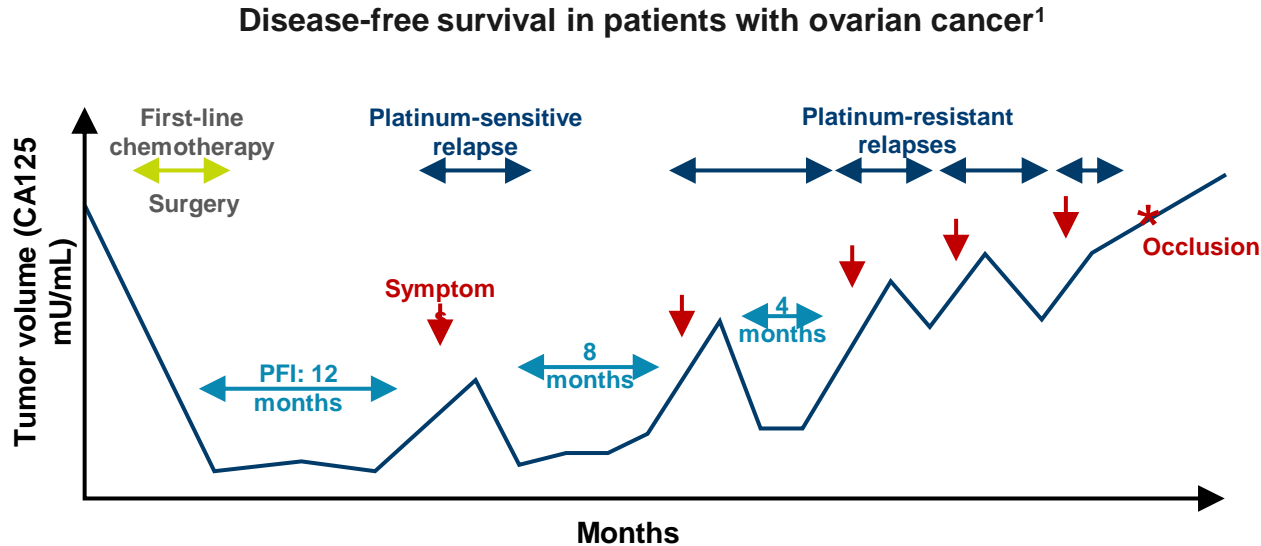
10-18 months

Median progression-free
survival^{2,3,4}

There is a significant need for better frontline treatment to improve
outcomes for women with ovarian cancer¹⁻⁵

Advanced ovarian cancer is a disease with multiple relapses

- Despite a high initial response rate, around 70% of patients with ovarian cancer will experience disease recurrence^{1,2}
- After the first recurrence, a definitive cure is almost impossible²

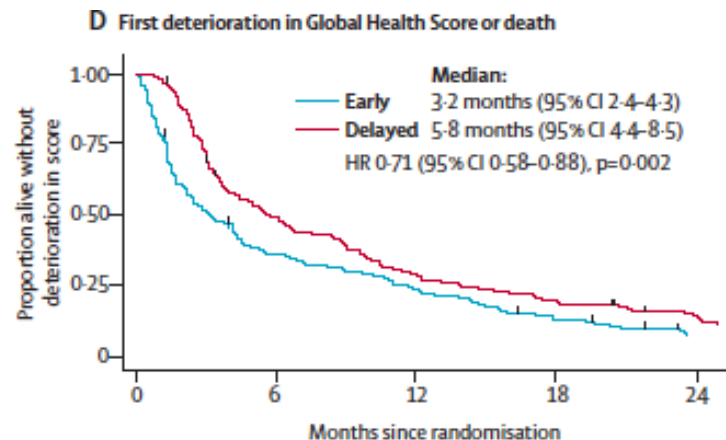
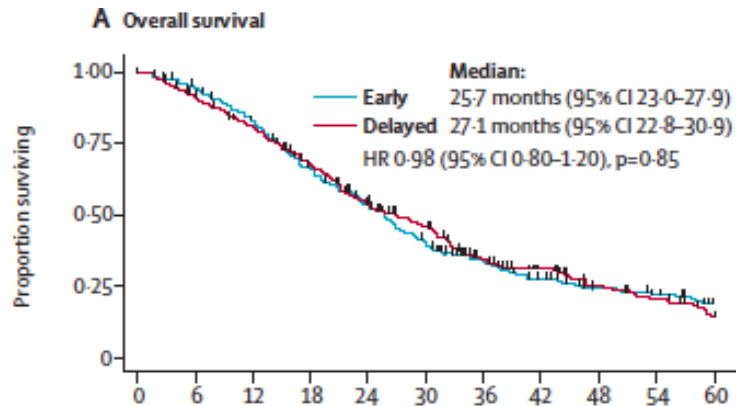


Adapted from Giomelli 2016.

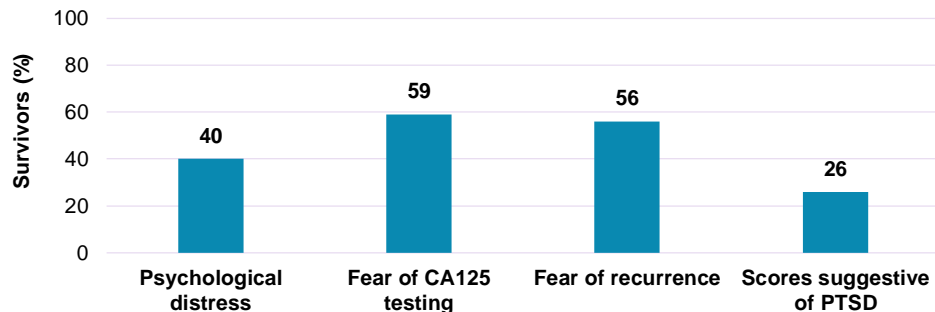
CA125, cancer antigen 125; PFI, progression-free interval or duration of disease control without chemotherapy.

1. Giomelli GH. *Springerplus* 2016; 5 (1): 1197. 2. About ovarian cancer: Recurrence. Available at: <https://ocrfa.org/patients/about-ovarian-cancer/recurrence/>. Accessed June 2019.

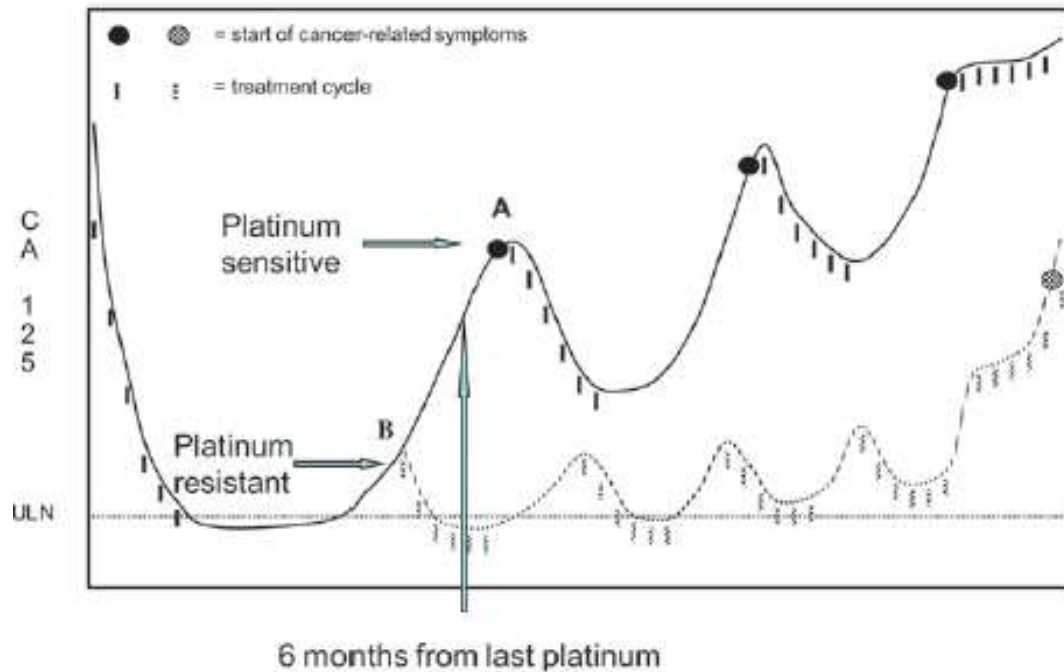
Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial



Psychological assessments of survivors of early-stage ovarian cancer (N=58)⁴

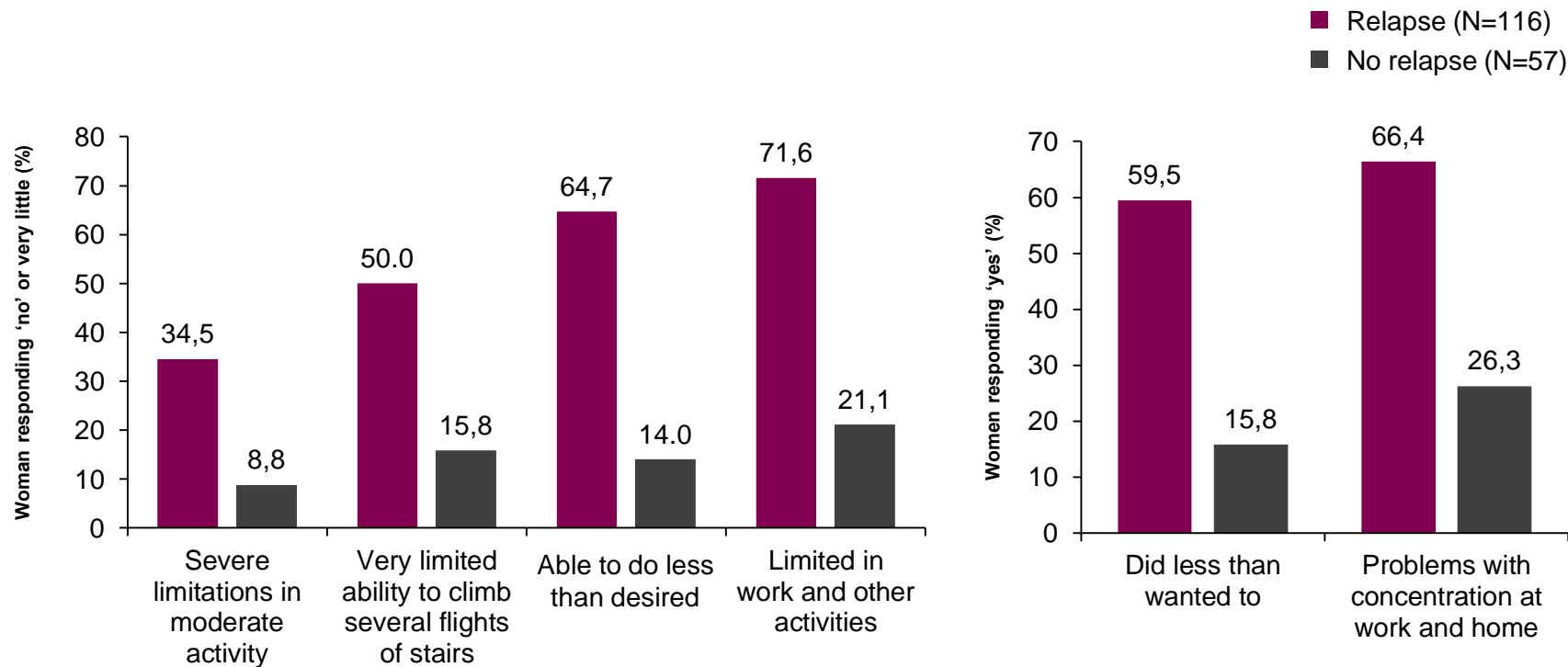


‘Watch and wait’ / surveillance has been the standard of care for recurrent ovarian cancer but is associated with an increase in anxiety



Hopefully, the DESKTOP 3 and GOG 213 trials will provide randomized trial data to demonstrate whether there is a survival benefit from surgery for relapse. Surgery is only of value if it can result in complete macroscopic removal of recurrent cancer. There is therefore no point in doing routine CA125 measurements in those patients who are not candidates for surgery, which is most patients during the first 12 months following first-line therapy. Data from DESKTOP

Disease recurrence leads to a decrease in patient reported physical and emotional wellbeing



The goal of maintenance therapy is to slow the rate of disease progression and lengthen life

Considerations for maintenance therapy for patients with recurrent ovarian cancer include:

Why treat?

- The watch and wait approach is burdensome to healthcare systems and patients¹
- Effective treatment is now available^{2,3}

Which treatment?

Maintenance therapy should:

- Be effective
- Be convenient
- Have low impact on QoL
- Have low cumulative toxicity

Who should be treated?

All patients with recurrent disease who have responded to chemotherapy treatment

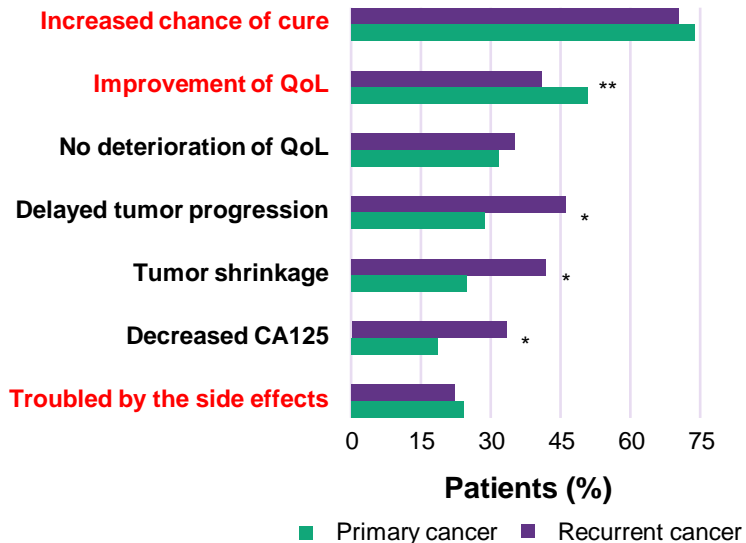
QoL, quality of life.

1. Harrow B *et al.* Abstract 962P presented at the European Society for Medical Oncology (ESMO) 2017 Congress; Madrid, Spain, September 8–12, 2017.

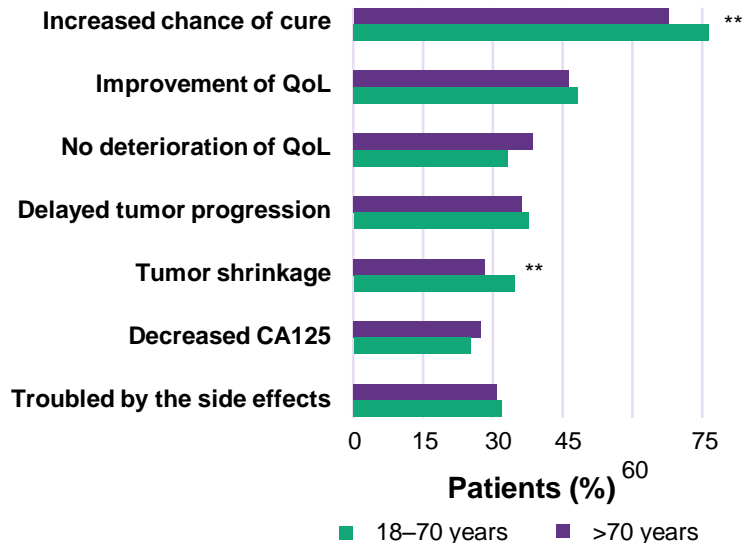
2. Pujade-Lauraine E *et al. Lancet Oncol* 2017; 18 (9): 1274–1284. 3. Mirza MR *et al. N Engl J Med* 2016; 375 (22): 2154–2164.

What do patients expect from maintenance therapy?

Primary/recurrent cancer



Age <70 / >70 years



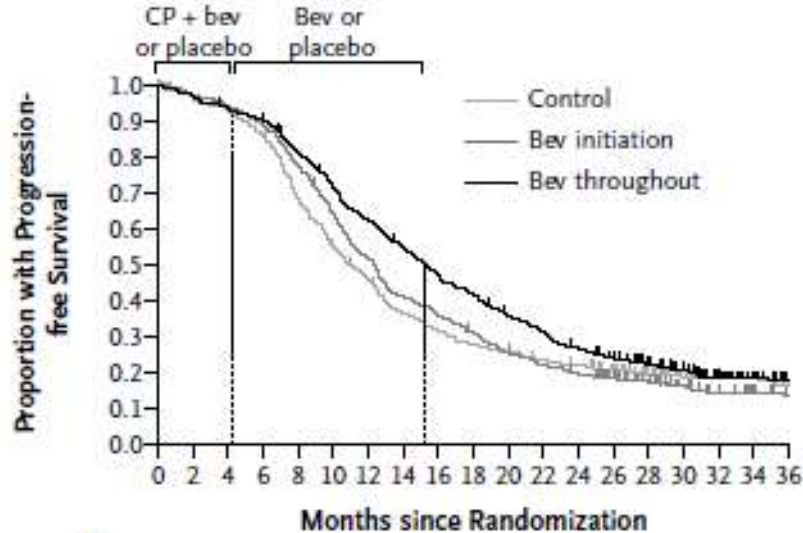
Survey results are from 1,954 patients.

* $P < 0.001$; ** $P < 0.05$.

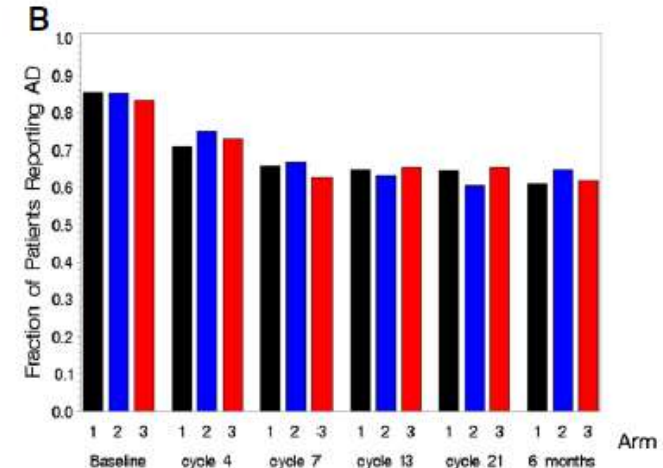
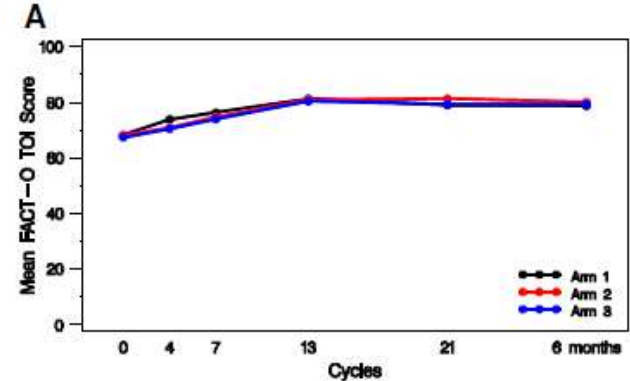
CA125, cancer antigen 125; QoL, quality of life.

Sehouli J *et al.* Abstract presented at the European Society of Gynaecological Oncology (ESGO) 2017 Congress; Vienna, Austria, November 4–7, 2017.

Bevacizumab was the first maintenance therapy approved for ovarian cancer

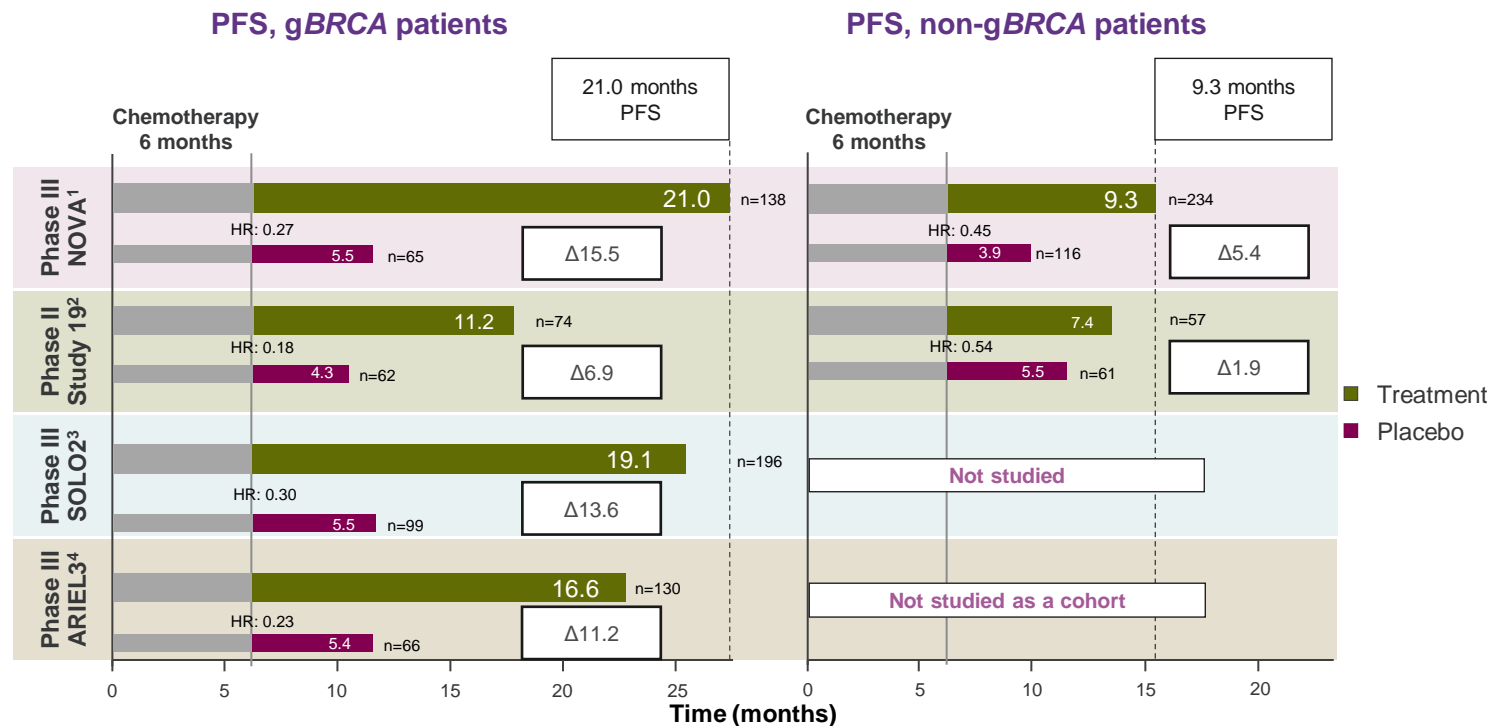


- Bevacizumab demonstrated to prolong PFS when administered in combination AND throughout chemotherapy
- Even if bevacizumab compromised QOL to a mild extent during chemotherapy, had no prolonged effect as maintenance treatment.



Note: The numbers above the bar are patient-reported AD scores by those reporting AD > 0.

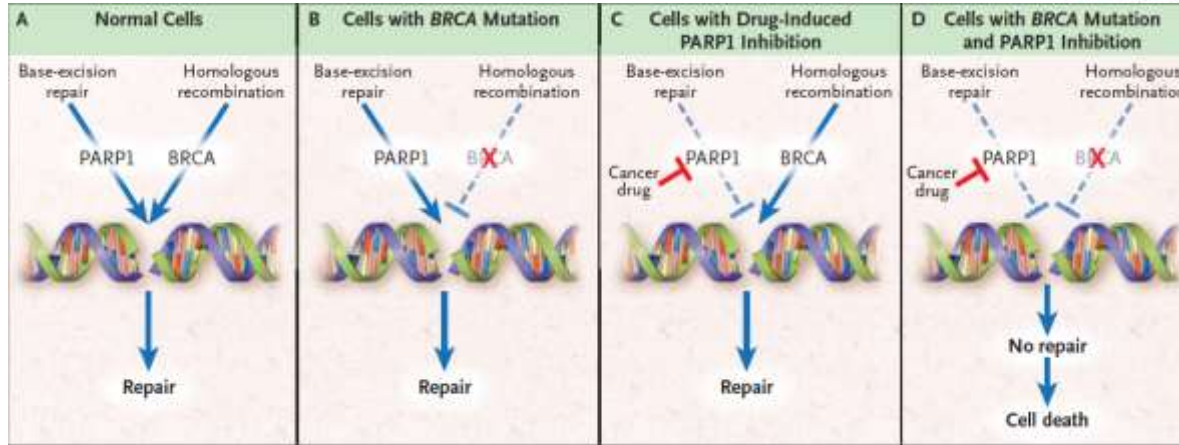
Published primary endpoint results of maintenance studies in recurrent ovarian cancer



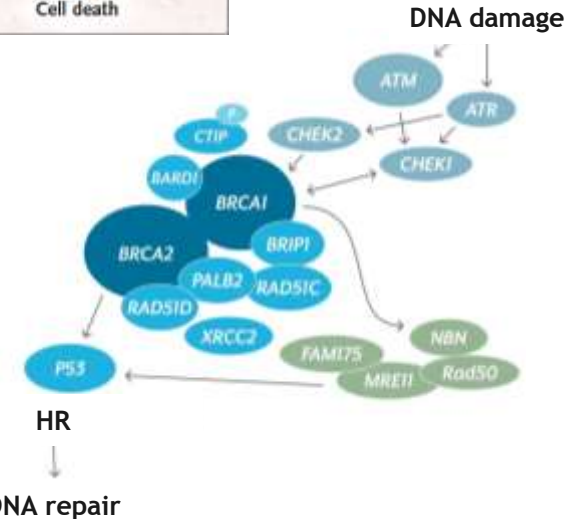
BRCA, breast cancer susceptibility gene; gBRCA, germline BRCA mutation; HR, hazard ratio; non-gBRCA, no germline BRCA mutation; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

1. Mirza MR *et al. N Engl J Med* 2016; 375: 2154–2164. 2. Ledermann J *et al. Lancet Oncol* 2014; 15 (8): 852–861. 3. Pujade-Lauraine E *et al. Lancet Oncol* 2017; 18 (9): 1274–1284. 4. Coleman RL *et al. Lancet* 2017; 390 (10106): 1949–1961.

Synthetic lethality



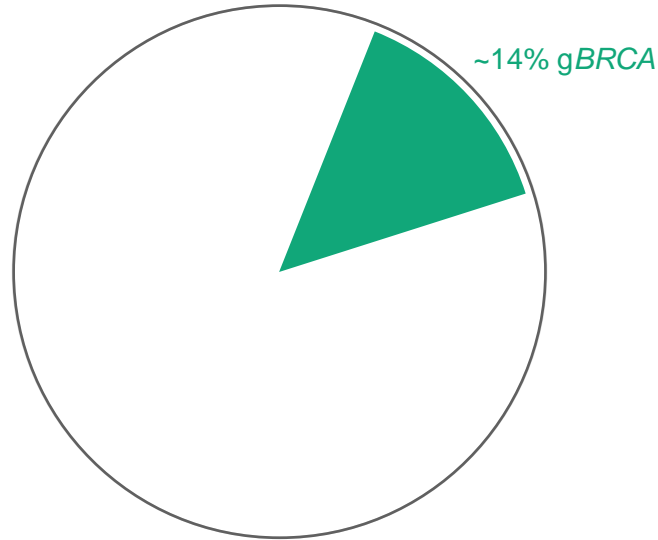
But things are not that simple...



BRCA, breast cancer susceptibility gene; PARP, poly(ADP-ribose) polymerase.
Iglehart JD *et al. N Engl J Med* 2009; 361 (2): 189–191.

Germline *BRCA* mutations are present in a small proportion of patients with ovarian cancer

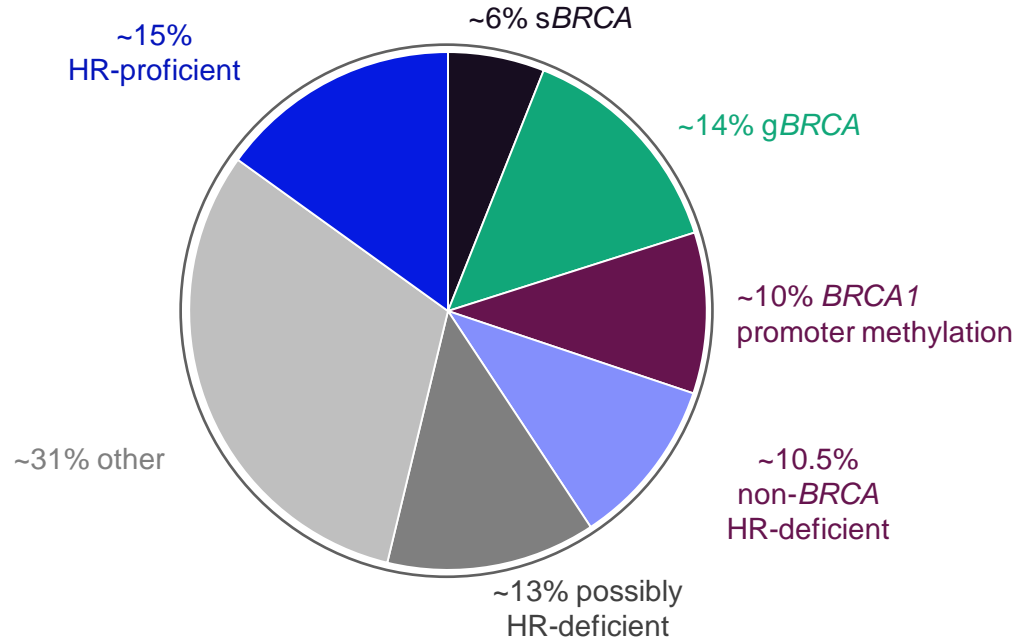
- Germline *BRCA* mutations are hereditary¹
- Approximately 14% of patients with high-grade serous ovarian cancer have a germline *BRCA* mutation²



Adapted from Konstantinopoulos PA et al. 2015

DNA repair defects other than *BRCA* mutations are present in a high proportion of patients

- About one-quarter of women with high-grade serous ovarian cancer have other HR deficiencies



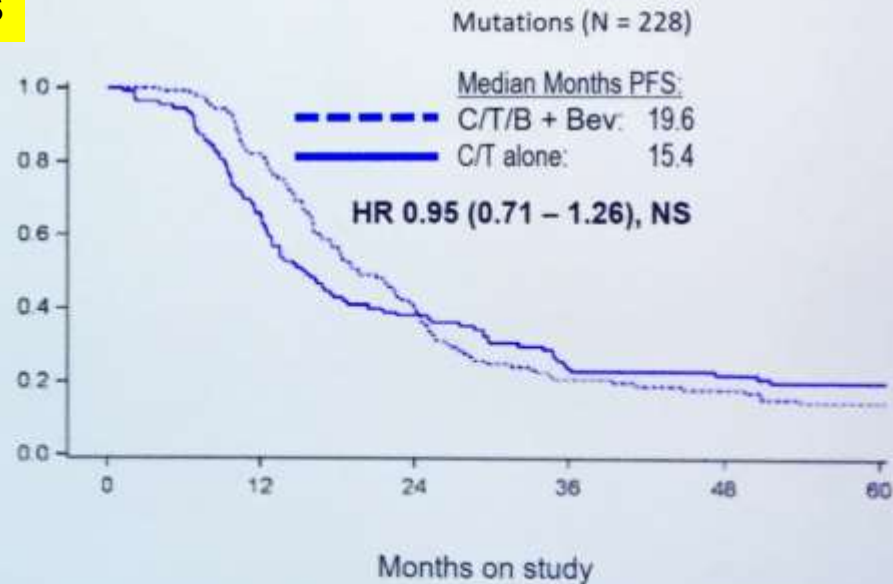
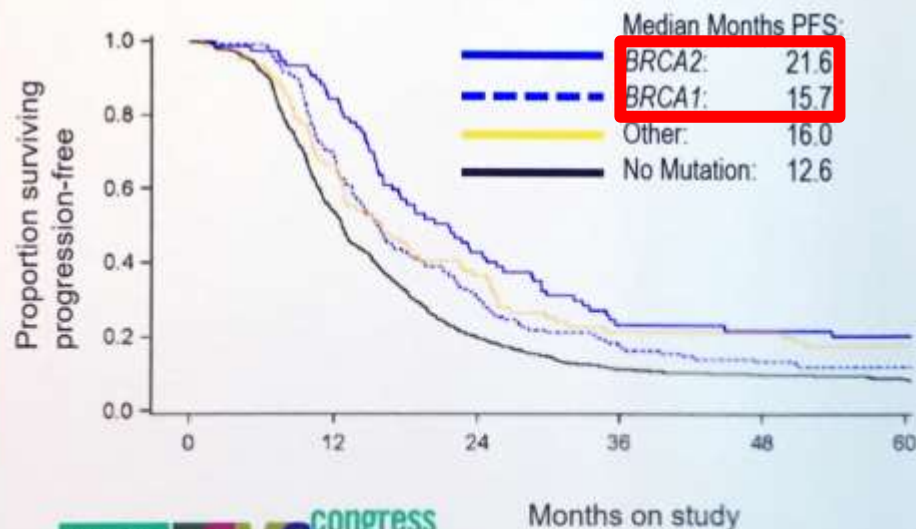
Adapted from Konstantinopoulos PA et al. 2015

BRCA, breast cancer susceptibility gene; *gBRCA*, germline *BRCA* mutation; HR, homologous recombination; *sBRCA*, somatic *BRCA* mutation.
Konstantinopoulos PA et al. *Cancer Discov.* 2015; 11: 1137–1154.

BRCA mutations confer a better prognosis – what is the outcome of these patients with ‘standard of care’ chemotherapy and bevacizumab?

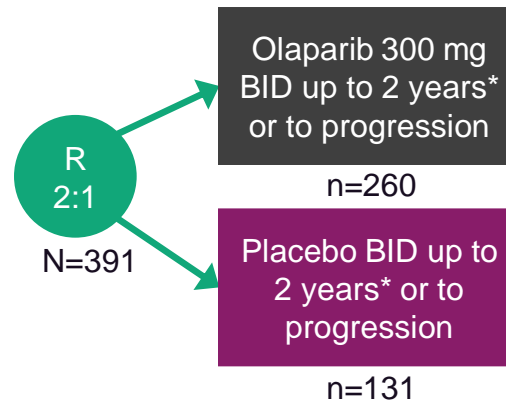
GOG 218 : Carboplatin/paclitaxel versus carboplatin/paclitaxel+ bevacizumab with bevacizumab maintenance

20 months



SOLO-1 trial design and patient inclusion^{1,2}

- Newly diagnosed Stage III or IV ovarian, primary peritoneal, or fallopian tube cancer
- High grade serous or endometrioid history
- **Only patients with documented deleterious *BRCA* 1/2 mutation**
- Stage III: 1 optimal upfront debulking attempt
- Stage IV: Biopsy, or 1 upfront or interval debulking
- In CR or PR at the end of frontline platinum-based chemotherapy



- **Primary endpoint:** Investigator-assessed **PFS by RECIST v1.1**
- **Secondary endpoints:**
 - OS, PFS2, best ORR, health-related quality of life, TFST, TSST, safety and tolerability

*At investigators' discretion.

BID, twice daily; *BRCA*, breast cancer susceptibility gene; CR, complete response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to second disease progression or death; PR, partial response; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

1. ClinicalTrials.gov SOLO-1. Available at: <https://clinicaltrials.gov/ct2/show/NCT01844986>. Accessed June 2019. 2. Moore K *et al. N Engl J Med* 2018; 379 (26): 2495–2505.

SOLO-1: Baseline patient characteristics¹

	Olaparib group (n=260)	Placebo group (n=131)
Clinical response after platinum-based chemotherapy*, n (%)		
Complete response	213 (82)	107 (82)
Partial response	47 (18)	24 (18)
International FIGO Stage†, n (%)		
Stage III	220 (85)	105 (80)
Stage IV	40 (15)	26 (20)
CA125 level, n (%)		
≤ULN	247 (95)	123 (94)
>ULN	13 (5)	7 (5)
Missing data	0	1 (1)
Histologic type, n (%)		
Serous	246 (95)	130 (99)
Endometrioid	9 (3)	0
Mixed serous and endometrioid	5 (2)	1 (1)
BRCA mutation‡, n (%)		
BRCA1	191 (73)	91 (69)
BRCA2	66 (25)	40 (31)
BRCA1 and BRCA2	3 (1)	0

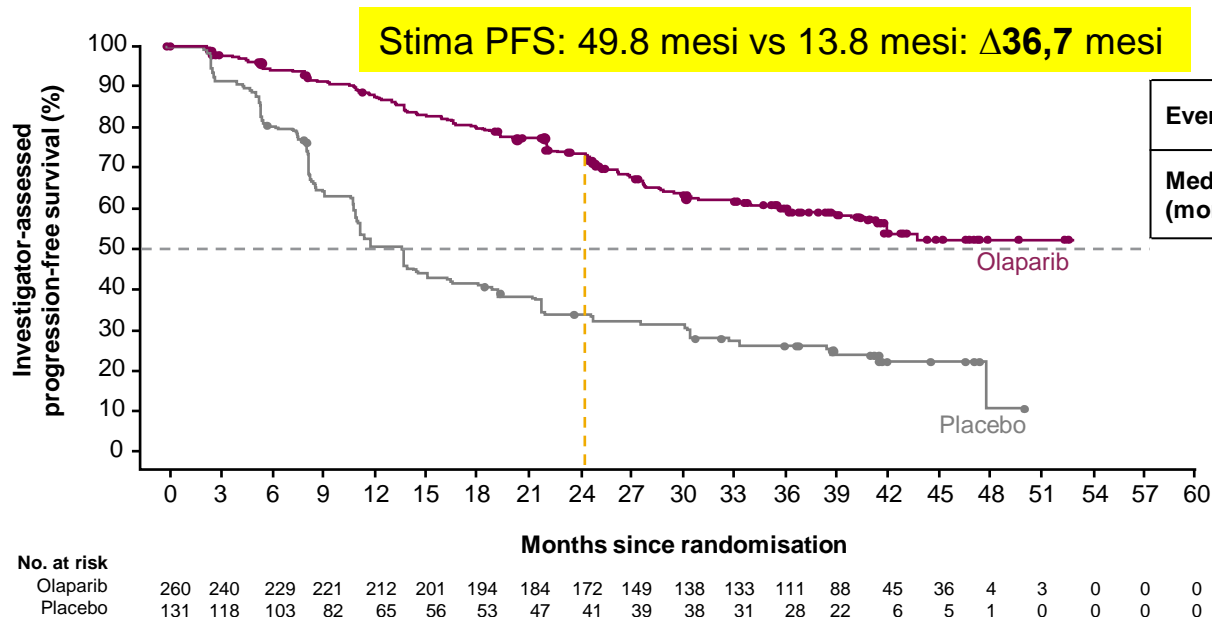
- At baseline, the majority of patients had no evidence of disease, a good performance status, and a CA125 level within the normal range¹

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)

Olaparib reduced the risk of progression or death by 70% vs. placebo¹

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

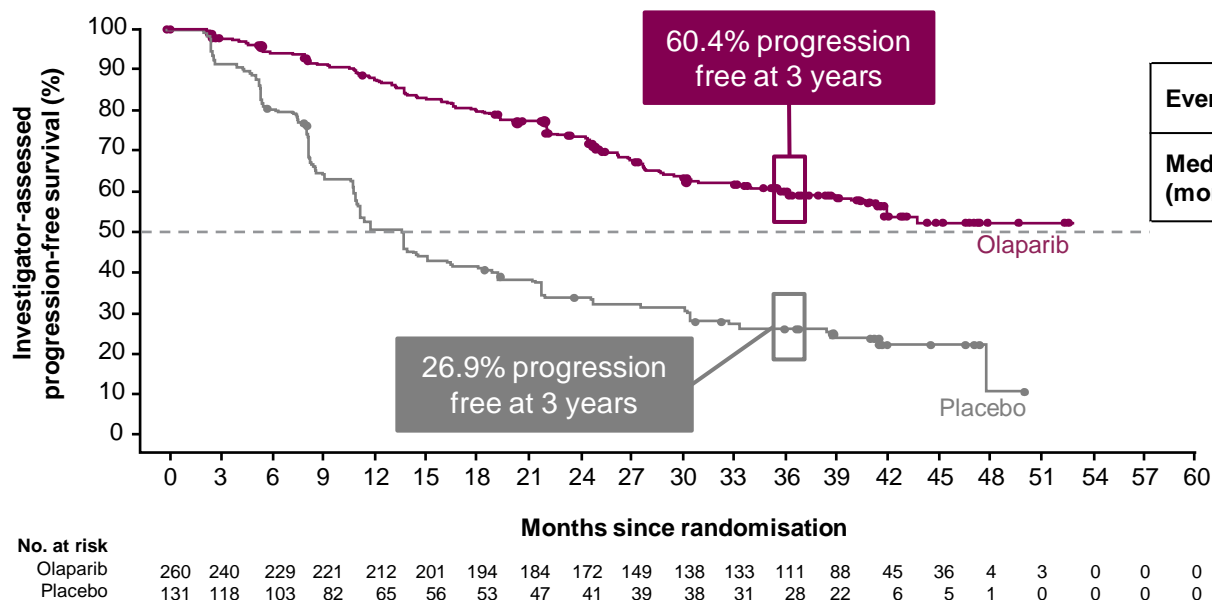
Analysis was performed after 198 progression events had occurred (in 50.6% of patients)

PFS = progression-free survival; DCO = data cut-off; HR = hazard ratio; CI = confidence interval

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)

Olaparib reduced the risk of progression or death by 70% vs. placebo¹

A 3 anni solo il 40% delle pazienti trattate con olaparib ricade, contro il 70% delle pazienti trattate con placebo



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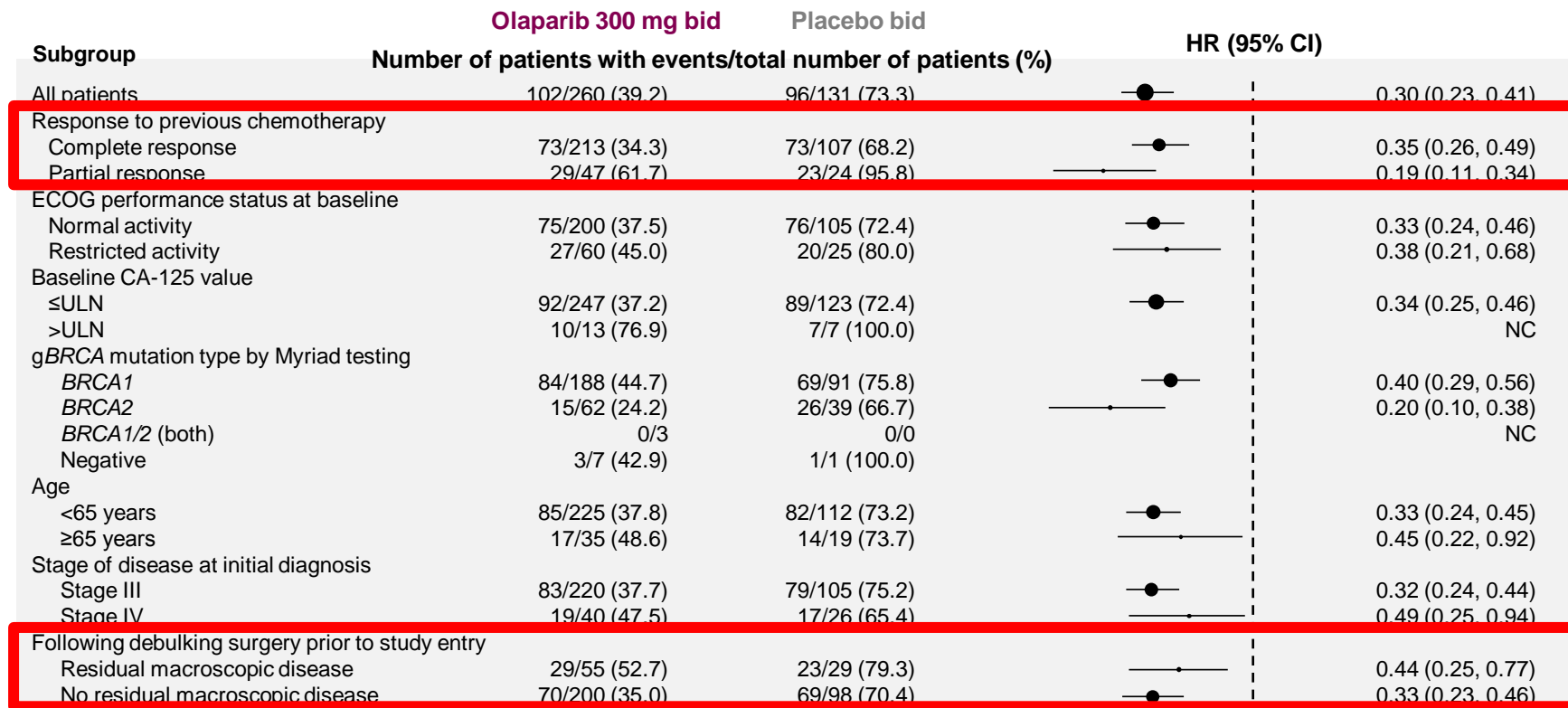
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1. Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

A consistent benefit was seen across all PFS subgroups^{1,2}



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)

0.0625 0.1250 0.2500 0.5000 1.0000 2.0000

← Olaparib better

→ Placebo better

Subgroup analyses focused on surgery

Kaplan-Meier estimate of investigator-assessed PFS based on timing of surgery

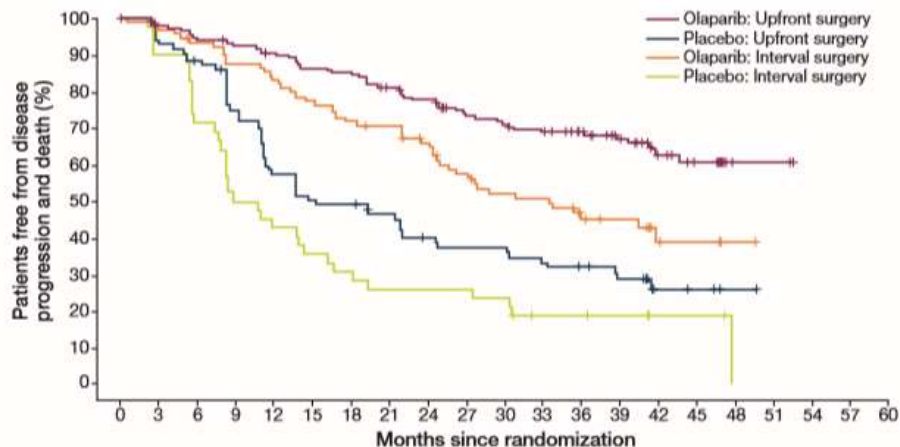


Figure 2. Kaplan-Meier estimate of investigator-assessed PFS based on residual disease status following surgery

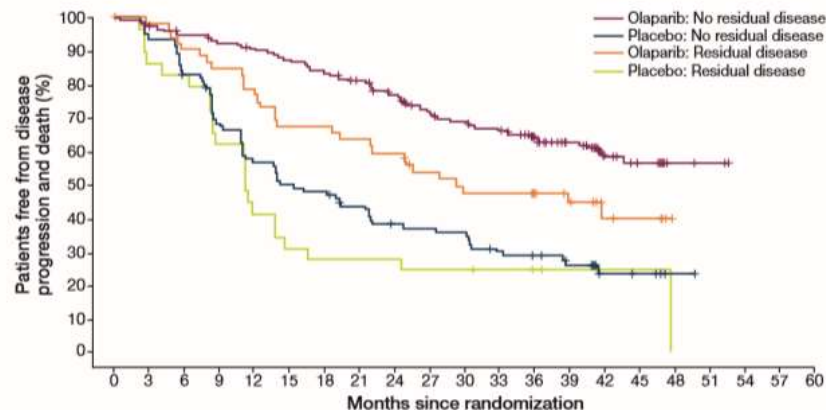


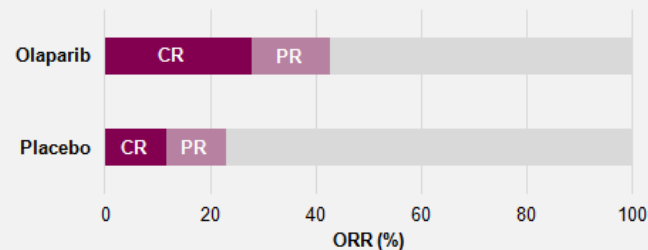
Table 2. Investigator-assessed PFS in patients who underwent upfront surgery based on residual disease status

	Olaparib	Placebo
Upfront surgery and no residual disease	n=123	n=62
Number of events	35	39
Median PFS, months	NR	22.0
HR (95% CI)	0.33 (0.20–0.51)	
Upfront surgery and residual disease	n=37	n=22
Number of events	16	18
Median PFS, months	NR	11.3
HR (95% CI)	0.29 (0.15–0.58)	

NR, not reached

Colombo et al ASCO 2019

1/4 patients with measurable disease were converted to a complete response



More than 50% of patients in the olaparib arm completed protocol-defined treatment

	Olaparib	Placebo
Randomised, N	260	131
Treated, N	260	130
Discontinued treatment before 2 years	111 (42.6)	92 (70.7)
Completed treatment at 2 years per protocol, N (%)	123 (47.3)	35 (26.9)
Continued treatment beyond 2 years	26 (10.0)	3 (2.3)
Still receiving treatment at data cut-off, N (%)	13 (5.0)	1 (0.8)
Median (mean) total treatment duration (months)	24.6 (0–52.0)	13.9 (0.2–45.6)
Median (IQR) duration of follow-up, months	40.7 (34.9–42.9)	41.2 (32.2–41.6)

DCO: May 2018

IQR = interquartile range

1. Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print; 2. Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print [supplementary appendix]

The most common reason for discontinuation was disease progression

	Olaparib	Placebo
Randomised, N	260	131
Treated, N	260	130
Discontinued treatment other than protocol defined stopping rule, N (%)	124 (47.7)	94 (72.3)
Objective disease progression	51 (19.6)	78 (60.0)
Adverse event	30 (11.5)	3 (2.3)
Patient decision	22 (8.5)	2 (1.5)
Other*/unknown reason	21 (8.1)	11 (8.5)

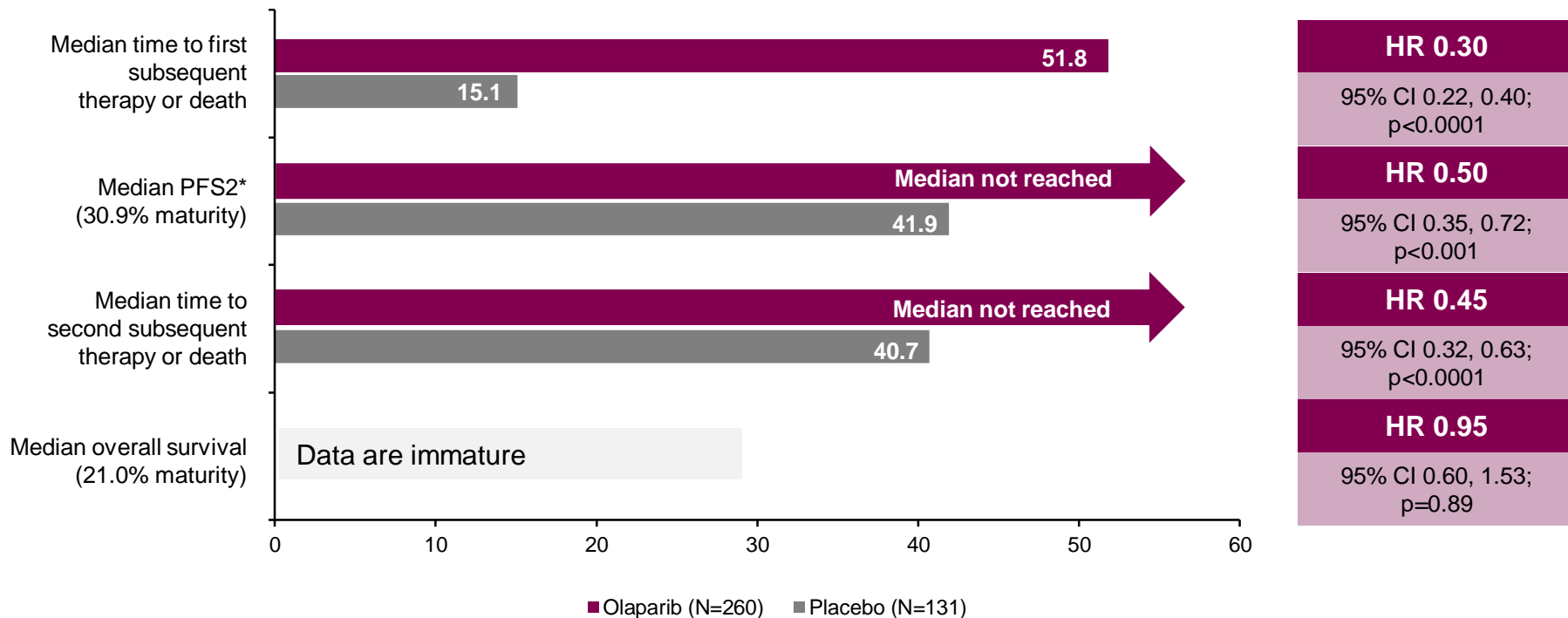
*Other includes study-specific discontinuation criteria, severe non-compliance to protocol and lost to follow-up, among other reasons

DCO: May 2018; Median duration of treatment: olaparib 24.6 months; placebo 13.9 months

IQR = interquartile range

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^{1,2}



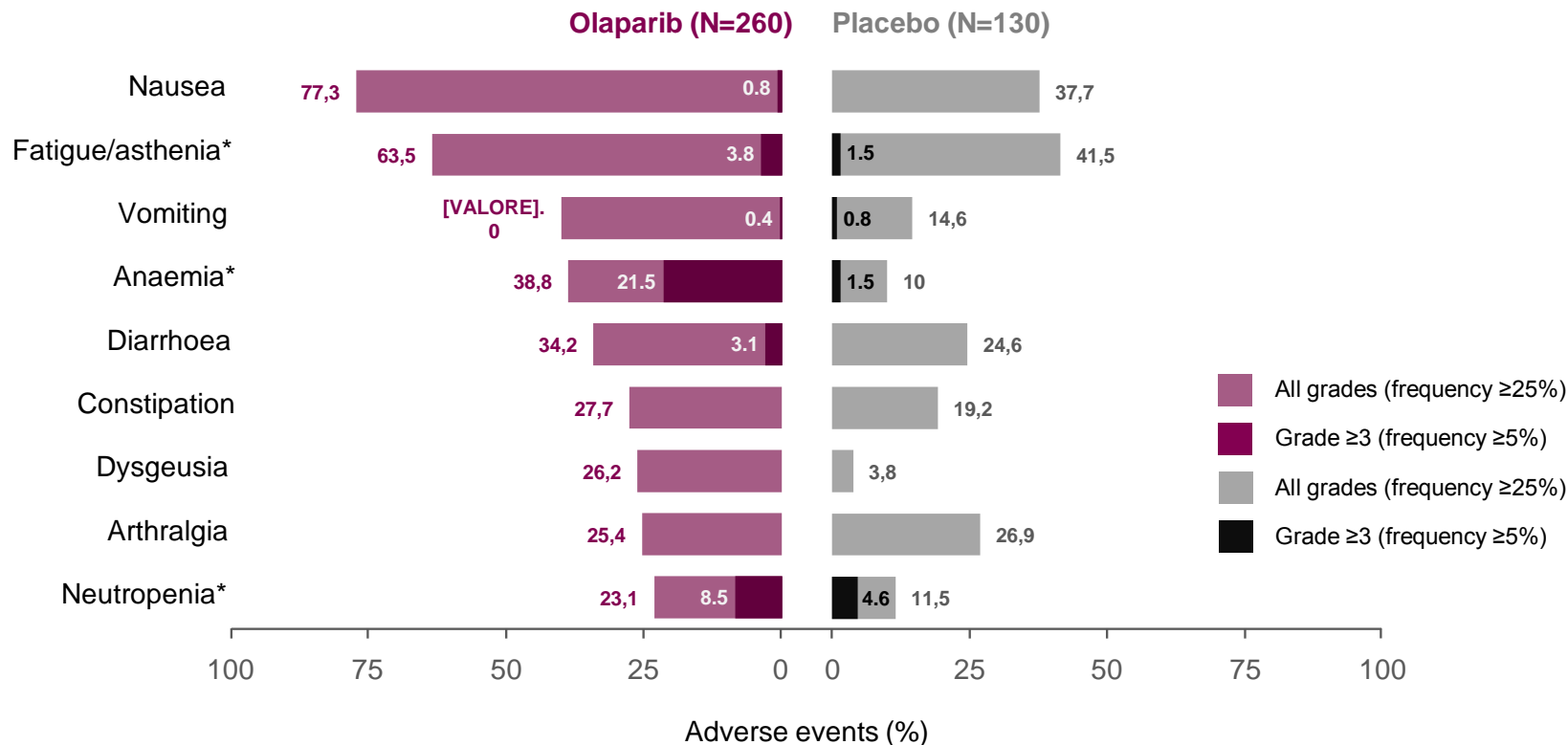
*Time from randomisation to second progression or death; in second line, a PARP inhibitor was used in 33/94 (35%) patients in the placebo arm and 10/91 (11%) patients in the olaparib arm

DCO: May 2018

PFS2 = progression-free survival 2; DCO = data cut-off; HR = hazard ratio; CI = confidence interval

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)

The most common AEs reported in patients on olaparib in SOLO-1 were gastrointestinal disturbances, fatigue and anaemia



*Grouped term

AE = adverse event

1. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

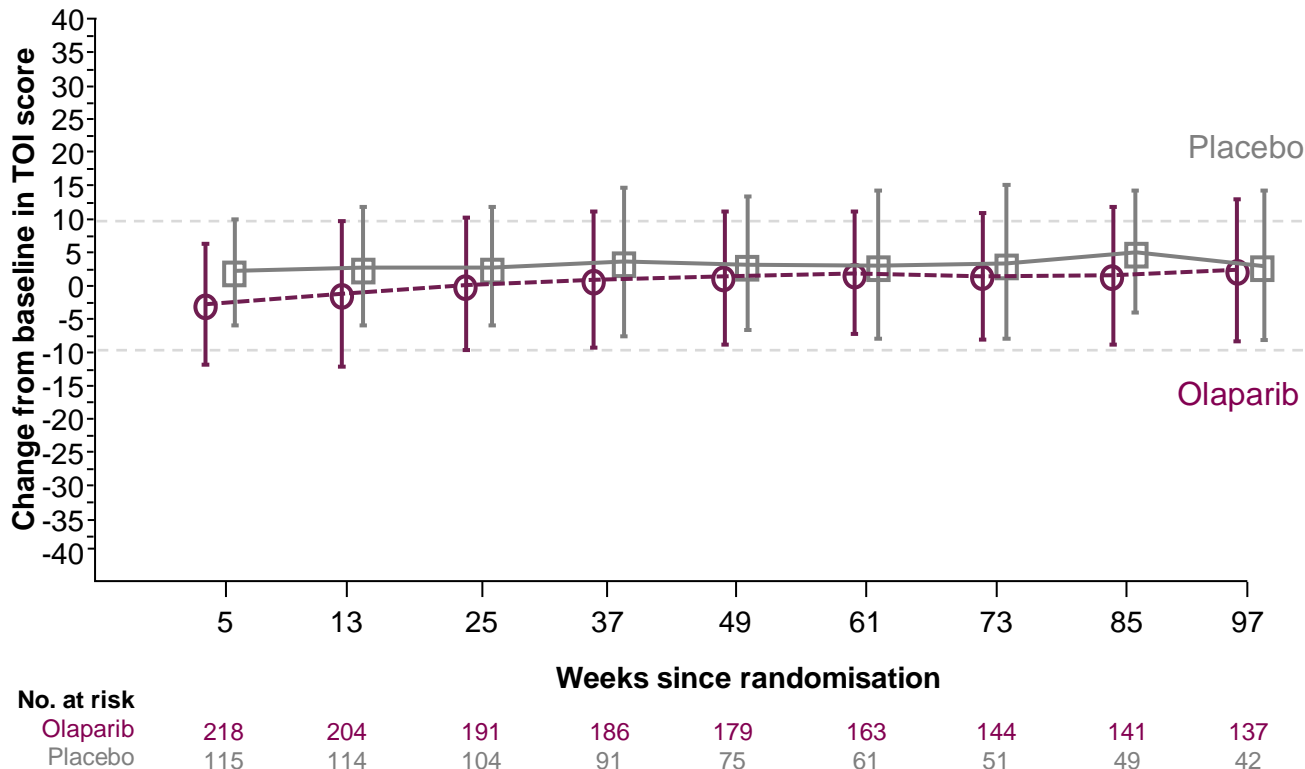
AEs of special interest were in line with rates seen in previous trials of olaparib^{1,2}

	Olaparib (N=260)	Placebo (N=130)
MDS/AML,* N (%)	3 (1.2)	0
New primary malignancies,† N (%)	5 (1.9)	3 (2.3)
Pneumonitis/ILD, N (%)	5 (1.9)	0

*The three cases of MDS/AML occurred 1.7–5.7 months after stopping olaparib (duration of olaparib therapy of 14.3–24.9 months); †Including breast cancer (n=3), head and neck cancer (n=1) and thyroid cancer (n=1) in the olaparib group and breast cancer (n=3) in the placebo group
AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome; ILD = interstitial lung disease

1. Moore K et al. Oral presentation LBA7_PR, ESMO (2018); 2. Moore K et al. N. Engl. J. Med. (2018) ePub ahead of print

There was no clinically meaningful difference in HRQoL between arms



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

1. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

Two key ongoing trials are exploring PARP inhibition for first-line treatment of advanced ovarian cancer

PRIMA¹

A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy

Randomized, double-blind, placebo-controlled (2:1 **niraparib:placebo**) Phase III study in patients with Stage III or IV ovarian cancer. Patients must have **completed front-line platinum-based chemotherapy with a CR or PR**, and have a normal or >90% decrease in CA125 following front-line platinum treatment.

PAOLA-1²

Platine, Avastin and OLaparib in 1st Line (PAOLA-1)

Randomized, double-blind, Phase III trial of **olaparib vs. placebo** in patients with advanced FIGO Stage IIIb–IV high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer treated with standard **first-line treatment**, combining **platinum-taxane chemotherapy** and **bevacizumab** concurrent with chemotherapy and in maintenance.

Niraparib is not licensed for the first-line treatment of advanced ovarian cancer. Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade, serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Please consult the summary of product characteristics.

CA125, cancer antigen 125; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; PARP, poly(ADP-ribose) polymerase; PR, partial response.

1. ClinicalTrials.gov PRIMA. Available at: <https://clinicaltrials.gov/ct2/show/NCT02655016>. Accessed June 2019. 2. ClinicalTrials.gov PAOLA-1. Available at: <https://clinicaltrials.gov/ct2/show/NCT02477644>. Accessed June 2019.

Conclusions

Maintenance olaparib led to a substantial, unprecedented improvement in PFS in patients with newly diagnosed, advanced ovarian cancer and a BRCAm, with a 70% reduction in risk of disease progression or death

The safety profile is consistent with previous olaparib data with most AEs being mild or moderate in severity and generally not leading to dose reduction or permanent discontinuation

A reduction in the risk of second progression or death was observed demonstrating that olaparib maintenance does not diminish the benefit conferred by subsequent therapy

There was no decrease in HRQoL from baseline for olaparib-treated patients over the 24-month treatment period and no clinically important differences in HRQoL compared with placebo-treated patients

The results provide a strong indication for swift BRCAm testing at diagnosis, especially if considering first-line bevacizumab, waiting for PAOLA results
Overall survival data are awaited (olaparib increased PFS in pancreatic cancer, but failed in OS prolongation – POLO trial)

Waiting for the next future at...



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Thank you!