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Final overall survival results from SOLO2/ENGOT-ov21: a Phase III trial assessing maintenance olaparib in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation

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Background

- **Relapsed ovarian cancer**
  - Associated with poor outcomes[1]
  - Treatment goals:
    - Delay symptomatic disease progression
    - Delay the need for subsequent chemotherapy
    - Prolong survival[2]
- **Overall survival (OS)**
  - Difficult to demonstrate in ovarian cancer trials
    - Because of longer post-progression survival associated with crossover*[3,4]
  - Limited progress in the last two decades[5,6]

*Crossover to the investigational treatment and post-progression therapies
OS, overall survival

1. Ozols RF. *Semin Oncol* 2006;33(2 Suppl 6):S3–S11; 2. Gadduci A *et al. J Ovarian Res* 2019;12:9; 3. Colombo N *et al. Ann Oncol* 2019;30:672–705; 4. Wilson MK *et al. Ann Oncol* 2017;28:727–32; 5. McGuire WP *et al. N Engl J Med* 1996;334:1–6; 6. Parmar MK *et al. Lancet* 2003;361:2099–106

2

Background

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    - Delay the need for subsequent chemotherapy
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  - Limited progress in the last two decades[5,6]

Olaparib

PARP inhibitor approved globally as maintenance therapy

Patients with PSROC, regardless of BRCAm status[7–10]

Patients with newly diagnosed ovarian cancer and a BRCAm[7,8,11,12]

*Crossover to the investigational treatment and post-progression therapies

BRCAm, BRCA mutation; PARP, poly(ADP-ribose) polymerase; PSROC, platinum-sensitive relapsed ovarian cancer

1. Ozols RF. *Semin Oncol* 2006;33(2 Suppl 6):S3–S11; 2. Gadduci A *et al. J Ovarian Res* 2019;12:9; 3. Colombo N *et al. Ann Oncol* 2019;30:672–705; 4. Wilson MK *et al. Ann Oncol* 2017;28:727–32; 5. McGuire WP *et al. N Engl J Med* 1996;334:1–6; 6. Parmar MK *et al. Lancet* 2003;361:2099–106; 7. FDA. Lynparza prescribing information. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208558s010lbl.pdf; 8. EMA. Lynparza summary of product characteristics. 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf; 9. Parker A. China approves Lynparza in ovarian cancer. 2020. Available at: https://www.biocentury.com/article/297563/china-approves-lynparza-in-ovarian-cancer; 10. AstraZeneca. Lynparza receives approval in Japan for the treatment of advanced ovarian cancer. 2018. Available at: https://www.astrazeneca.com/media-centre/press-releases/2018/lynparza-receives-approval-in-japan-for-the-treatment-of-advanced-ovarian-cancer-19012018.htmlR; 11. AstraZeneca. Lynparza approved in China as a 1st-line maintenance therapy in BRCA-mutated advanced ovarian cancer. 2019. Available at: https://www.astrazeneca.com/media-centre/press-releases/2019/lynparza-approved-in-china-as-a-1st-line-maintenance-therapy-in-brca-mutated-advanced-ovarian-cancer.html; 12. AstraZeneca. Lynparza approved in Japan for 1st-line maintenance therapy in BRCA-mutated advanced ovarian cancer. 2019. Available at: https://www.astrazeneca.com/media-centre/press-releases/2019/lynparza-approved-in-japan-for-1st-line-maintenance-therapy-in-brca-mutated-advanced-ovarian-cancer-19062019.html

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Background

SOLO2 trial: primary analysis

Patients with PSROC and a BRCAm

Maintenance olaparib tablets led to median PFS improvement of 13.6 months over placebo (HR 0.30; *P*<0.0001)[1]

Olaparib tablets had a manageable tolerability profile[1]

Maintenance olaparib is the only PARP inhibitor with long-term follow-up data[2] → **SOLO2 is the first Phase III trial to provide OS data on maintenance olaparib**

HR, hazard ratio; PFS, progression-free survival

1. Pujade-Lauraine E *et al. Lancet Oncol* 2017;18:1274–84; 12. Friedlander M *et al. Br J Cancer* 2018;119:1075-85.

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Study design

FSI: Sep 2013

LSI: Nov 2014

Eligible patients had:
- Relapsed, high-grade serous or endometrioid ovarian cancer*
- BRCAm
- Received ≥2 previous lines of platinum-based chemotherapy
- In response to most recent platinum regimen

2:1 randomization

Stratified by:
- Response to previous chemotherapy†
- Length of platinum-free interval‡

Olaparib 300 mg bid

Placebo

Study treatment continued until disease progression§

*Includes primary peritoneal of fallopian tube cancer; †Complete or partial response; ‡>6–12 or >12 months; §Study treatment continued under disease progression or discontinuation criteria were met, and patients could continue treatment beyond progression if deemed by the investigator to be experiencing benefit
bid, twice daily; FSI, first subject in; LSI, last subject in

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Study design

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Eligible patients had:
- Relapsed, high-grade serous or endometrioid ovarian cancer*
- BRCAm
- Received ≥2 previous lines of platinum-based chemotherapy
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2:1 randomization

Stratified by:
- Response to previous chemotherapy†
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Olaparib 300 mg bid

Placebo

Study treatment continued until disease progression§

Primary endpoint
- Investigator-assessed PFS

Key secondary endpoints
- **Overall survival**
- PFS2
- TFST
- TSST
- TDT

Final analysis

DCO: Feb 3, 2020
- Planned for 60% data maturity¶
- ***Post hoc* OS sensitivity analysis**: used eCRF§ stratification variables to correct for patients mis-stratified at randomization
- **Prespecified OS sensitivity analysis**: Myriad¶ gBRCAm subgroup

*Includes primary peritoneal of fallopian tube cancer; †Complete or partial response; ‡>6–12 or >12 months; §Study treatment continued under disease progression or discontinuation criteria were met, and patients could continue treatment beyond progression if deemed by the investigator to be experiencing benefit; ¶Approximately 177 events
bid, twice daily; DCO, data cut-off; eCRF, electronic case report form; gBRCAm, germline BRCA mutation; PFS2, time to second progression; TDT, time to study treatment discontinuation or death; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

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Patient disposition

Median duration of follow-up was 65.7 months for olaparib and 64.5 months for placebo

	Olaparib	Placebo
Randomized, n	196	99
Treated, n (%)	195* (99)	99 (100)
Discontinued study treatment before DCO, n (%)	152 (78)	91 (92)
Patient decision	7 (4)	4 (4)
Adverse events	35 (18)	3 (3)
Objective disease progression	96 (49)	79 (80)
Study-specific discontinuation	2 (1)	0
Other	12 (6)	5 (5)
Remained on study treatment at DCO, n (%)	43 (22)	8 (8)

*One patient was randomized in error, due to ineligibility for the trial, to the olaparib group

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Patient characteristics

	Olaparib (N=196)	Placebo (N=99)
Primary tumor location, n (%)		
Ovary	162 (83)	86 (87)
Fallopian tube or primary peritoneal	31 (16)	13 (13)
Other	2 (1)	0
Missing	1 (1)	0
Histology, n (%)		
Serous	183 (93)	86 (87)
Endometrioid	9 (5)	8 (8)
Mixed	3 (2)	5 (5)
Missing	1 (1)	0
gBRCAm by Myriad testing, n (%)		
BRCA1	132 (67)	61 (62)
BRCA2	58 (30)	35 (35)
Missing*	6 (3)	3 (3)
ECOG performance status, n (%)		
0	162 (83)	77 (78)
1	32 (16)	22 (22)
Missing	2 (1)	0

Percentages may not total 100% because of rounding
*Patients with a confirmed germline BRCAm by local testing, but without confirmed gBRCAm status as part of this trial
ECOG, Eastern Cooperative Oncology Group

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Patient characteristics

	Olaparib (N=196)	Placebo (N=99)
Response to previous platinum therapy, n (%)		
Complete response	91 (46)	47 (47)
Partial response	105 (54)	52 (53)
Number of prior platinum regimens, n (%)		
2	110 (56)	62 (63)
3	60 (31)	20 (20)
4	18 (9)	12 (12)
≥5	7 (4)	5 (5)
Unknown	1 (1)	0
Platinum-free interval, n (%)		
>6–12 months	79 (40)	40 (40)
>12 months	117 (60)	59 (60)
Prior use of bevacizumab, n (%)		
Yes	33 (17)	20 (20)
No	163 (83)	79 (80)
Patients with >2 cm target lesions at baseline, n (%)		
Yes	30 (15)	18 (18)

Percentages may not total 100% because of rounding

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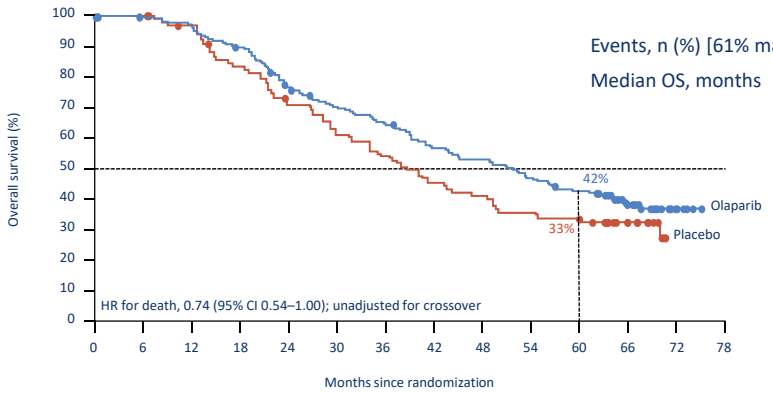
Final analysis of OS

Median OS improved by 12.9 months with maintenance olaparib over placebo, despite 39% of placebo patients crossing over to receive PARP inhibitor



No. at risk

Olaparib	196	192	187	172	145	130	120	105	98	86	77	39	7	0
Placebo	99	99	93	79	66	57	50	42	38	33	31	16	0	0

	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [61% maturity]	116 (59)	65 (66)
Median OS, months	51.7	38.8
HR 0.74		
95% CI 0.54–1.00; *P*=0.0537		

- **39% of placebo patients crossed over to receive PARP inhibitor therapy**
- **11% of olaparib patients received subsequent PARP inhibitor therapy**

CI, confidence interval

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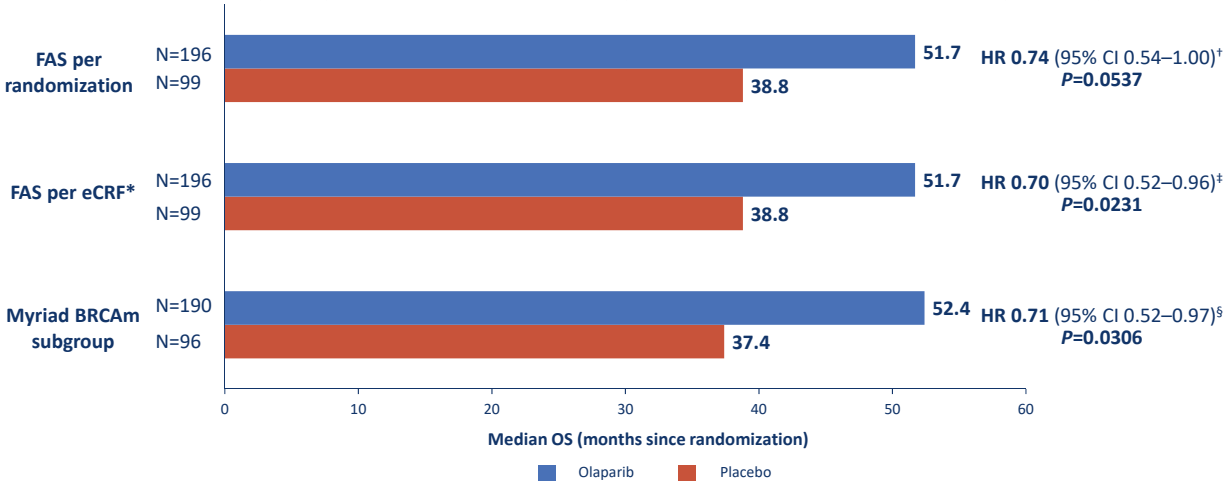
Summary of OS analyses

Final OS and sensitivity analyses show consistent OS improvements with maintenance olaparib vs placebo



*eCRF stratification variables were used to correct for any patients who were mis-stratified at randomization; †116 events for olaparib and 65 events for placebo; ‡116 events for olaparib and 65 events for placebo; §111 events for olaparib and 64 events for placebo
FAS, full analysis set

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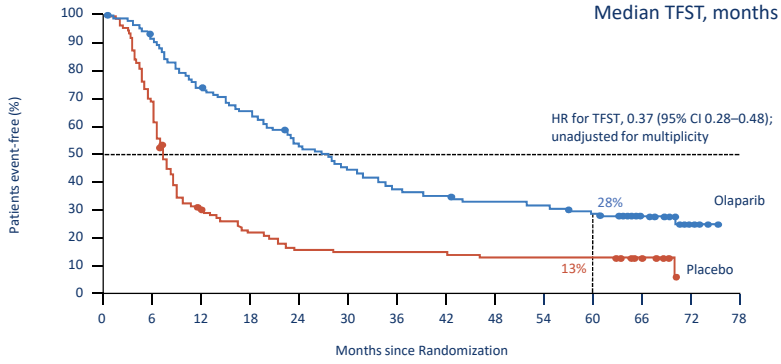
Time to first subsequent therapy

At 5 years, 28% of olaparib patients were alive and had not received subsequent therapy

	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [76% maturity]	139 (71)	86 (87)
Median TFST, months	27.4	7.2
HR 0.37		
95% CI 0.28–0.48; *P*<0.0001		



No. at risk

Olaparib	196	176	142	125	101	84	70	66	61	59	52	27	5	0
Placebo	99	67	28	21	15	14	14	13	12	12	12	5	0	0

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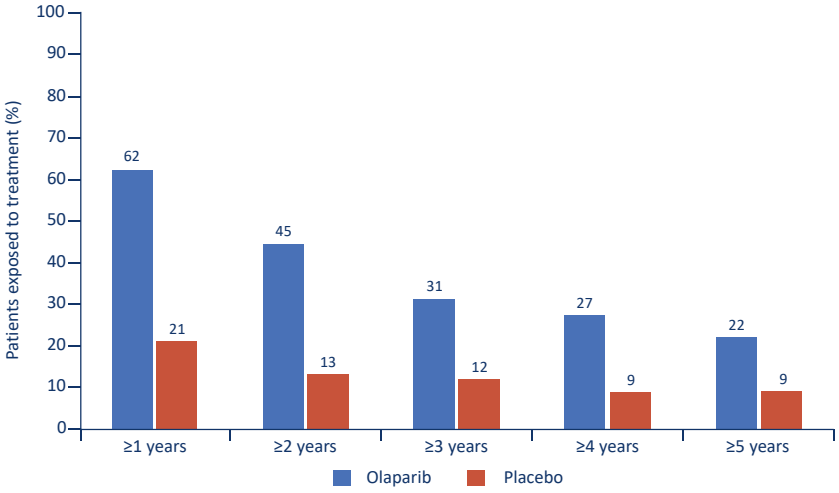
Duration of treatment exposure*

22% of patients received maintenance olaparib for ≥5 years, reflecting the therapeutic benefit and manageable tolerability of olaparib



*In the safety analysis set (N=195 with olaparib and N=99 with placebo); AE, adverse event

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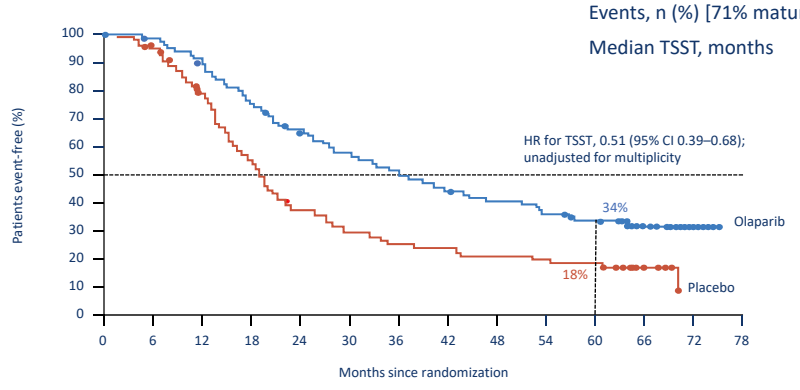
Time to second subsequent therapy

At 5 years, 34% of olaparib patients versus 18% of placebo patients were alive and had not received a second subsequent therapy

	Olaparib (N=196)	Placebo (N=99)
Events, n (%) [71% maturity]	130 (66)	79 (80)
Median TSST, months	35.8	18.9
HR 0.51		
95% CI 0.39–0.68; *P*<0.0001		



No. at risk

Olaparib	196	190	172	145	123	107	92	82	74	65	60	29	5	0
Placebo	99	93	72	50	33	25	22	20	18	17	16	5	0	0

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Safety overview – Primary and final analyses

Small increase in TEAEs, dose modifications and treatment discontinuations in the olaparib group, compared with the primary analysis, despite longer treatment duration

	Olaparib (N=195)		Placebo (N=99)	
	Primary	Final	Primary	Final
All-grade TEAEs, n (%)	192 (98)	**194 (99)**	94 (95)	**94 (95)**
Grade ≥3 TEAEs, n (%)	72 (37)	**90 (46)**	18 (18)	**19 (19)**
Serious TEAEs, n (%)	35 (18)	**50 (26)**	8 (8)	**8 (8)**
TEAEs leading to dose interruption, n (%)	88 (45)	**97 (50)**	18 (18)	**19 (19)**
TEAEs leading to dose reduction, n (%)	49 (25)	**54 (28)**	3 (3)	**3 (3)**
TEAEs leading to treatment discontinuation, n (%)	21 (11)	**33 (17)**	2 (2)	**3 (3)**
Median total treatment duration (range), months	19.4 (0.2–34.8)	**19.4 (0.2–75.3)**	5.6 (0.9–31.5)	**5.6 (0.9–70.2)**
Mean total treatment duration (SD), months	17.4 (9.8)	**29.1 (24.7)**	9.0 (8.1)	**13.1 (18.6)**

Most patients in the olaparib group had onset of AEs within the first year of treatment, with only 1.7% of grade ≥3 AEs occurring after 2 years of treatment[1]

1. Korach J *et al. Ann Oncol.* 2018;29(Suppl 8):abst 952P

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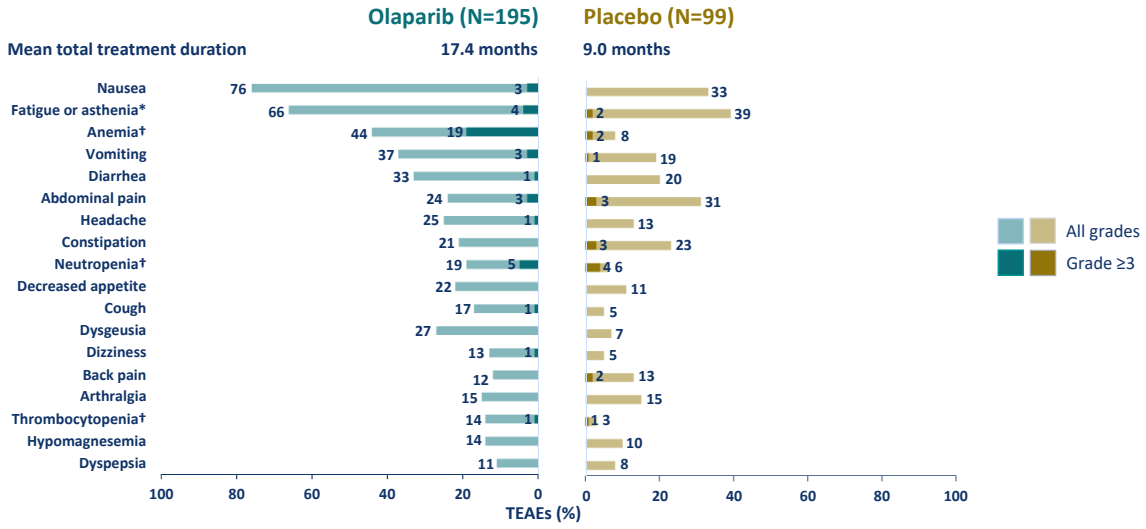
Most common TEAEs – Primary analysis



*Includes patients with fatigue and patients with asthenia; †Grouped terms

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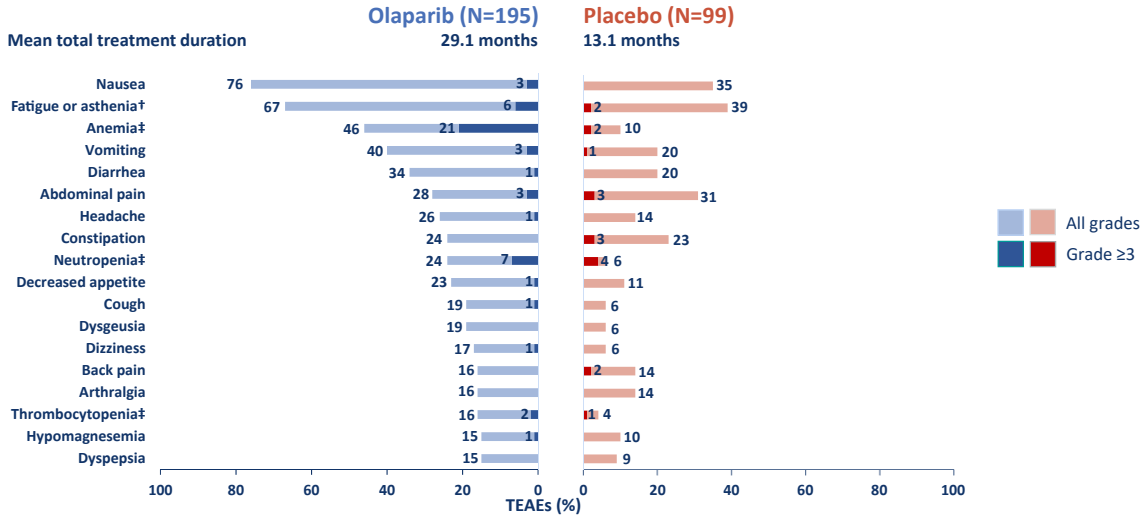
Most common TEAEs – Final analysis*

Small increase in TEAEs in the olaparib group, compared with the primary analysis, despite longer treatment duration



*Frequency ≥15%; †Includes patients with fatigue and patients with asthenia; ‡Grouped terms

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AEs of special interest*

Note to authors: MDS/AML data will be added when available

	Olaparib (N=195)	Placebo (N=99)
MDS/AML, n (%)	X (X)	X (X)
New primary malignancies, n (%)	8 (4)	2 (2)
Pneumonitis, n (%)	3 (2)	0

*Include AEs that occurred outside the 30-day follow-up period for safety
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

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Conclusions

- **SOLO2, the first randomized Phase III trial to provide final OS data on maintenance PARP inhibitor therapy, represents progress in improving OS for women with PSROC and a BRCAm, which had been limited since the introduction of platinum-based chemotherapy**
- **In the final SOLO2 analysis, maintenance olaparib provided a clinically meaningful improvement of 12.9 months in median OS over placebo:**
  - At 5 years, 42% of patients in the olaparib group and 33% of patients in the placebo group were alive
- **Few additional adverse events, and dose modifications or discontinuations due to adverse events, occurred in the olaparib group with longer-term treatment:**
  - 22% of patients remained on maintenance olaparib treatment for ≥5 years
- **The SOLO2 results demonstrate that olaparib maintenance monotherapy not only delays disease progression, but also improves OS in women with PSROC and a BRCAm:**
  - The SOLO2 results raise hope that an OS benefit may also be seen with maintenance olaparib in the first-line setting

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JA Pérez Fidalgo

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H Denys

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Supplementary Materials

Note to authors: The supplementary materials will be accessible via a QR code

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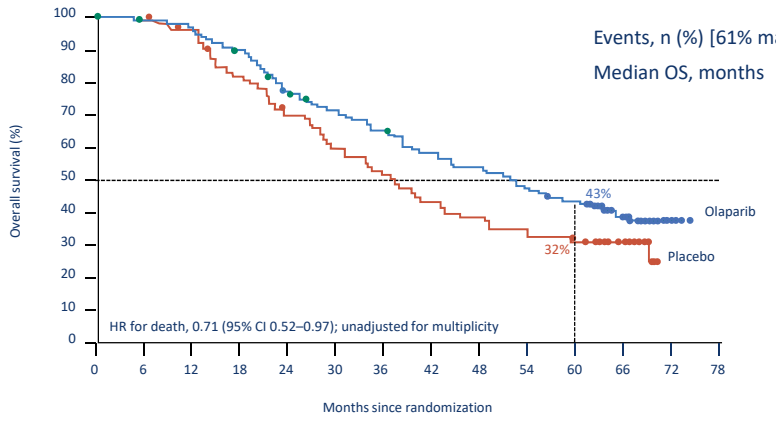
Prespecified OS analysis in the Myriad gBRCAm subgroup



	Olaparib (N=190)	Placebo (N=96)
Events, n (%) [61% maturity]	111 (58)	64 (67)
Median OS, months	52.4	37.4
HR 0.71		
95% CI 0.52–0.97; *P*=0.0306		

No. at risk

Olaparib	190	186	182	167	141	127	117	102	96	85	76	38	7	0
Placebo	96	96	90	76	63	54	47	39	35	31	29	14	0	0

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