

Ovariecancer og HRD

Anja Ør Knudsen

Ledende Overlæge

Onkologisk Afdeling, OUH

Ovariecancer

Ovarie-, tuba- og primær peritonealcancer

Ca. 450 nye tilfælde årligt

Medianalder ved diagnose er 63 år

80 % postmenopausale

Histologiske grupper

Epitheliale tumorer (90 %) sex cord-stromale tumorer og germinalcelletumorer

Ovariecancer

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germinalcelletumorer

Histologiske typer:

STIC (serøst tubar intraepitelt carcinom)

High-grade serøst adenokarcinom

Low-grade serøst adenokarcinom

Endometrioidt adenokarcinom

Clear cell adenokarcinom

Mucinøst adenokarcinom

Karcinosarkom

Neuroendokrine tumorer

Andre sjældne

FIGO stadieinddeling

St. I Tumor begrænset til ovarie eller tuba (fimbriae) (5-y OS 86 %)

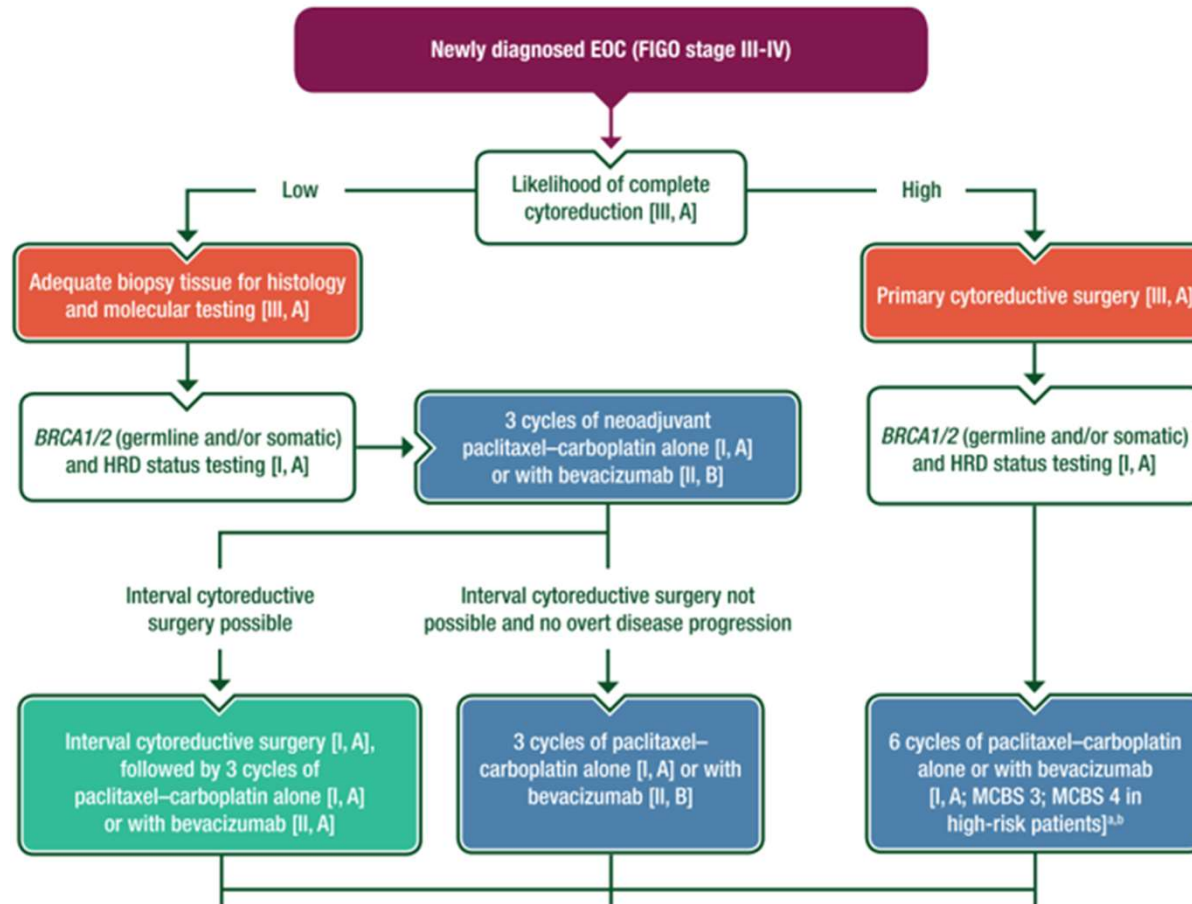
St. II Tumor på et eller to ovarier med spredning i det lille bækken (5-y OS 68 %)

St. III Tumor på et eller to ovarier med spredning uden for det lille bækken og/eller retroperitoneale lymfeknuder (5-y OS 36 %)

St. IV Tumor uden for abdominalhulen (5-y OS 20 %)

Udredning

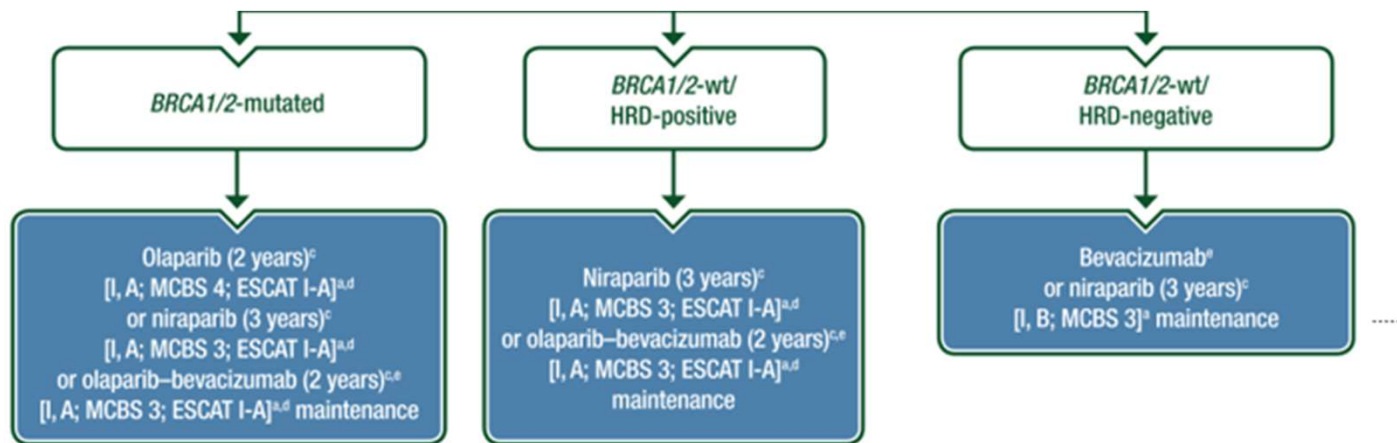
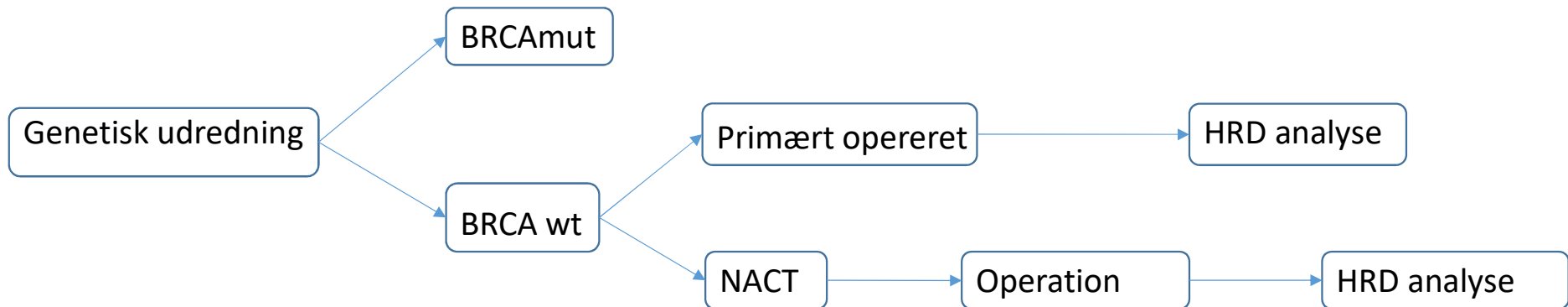
- UL
- CA-125
- PET-CT og MR
- Vurdering på MDT
- Fremmøde til plan som besluttet på MDT

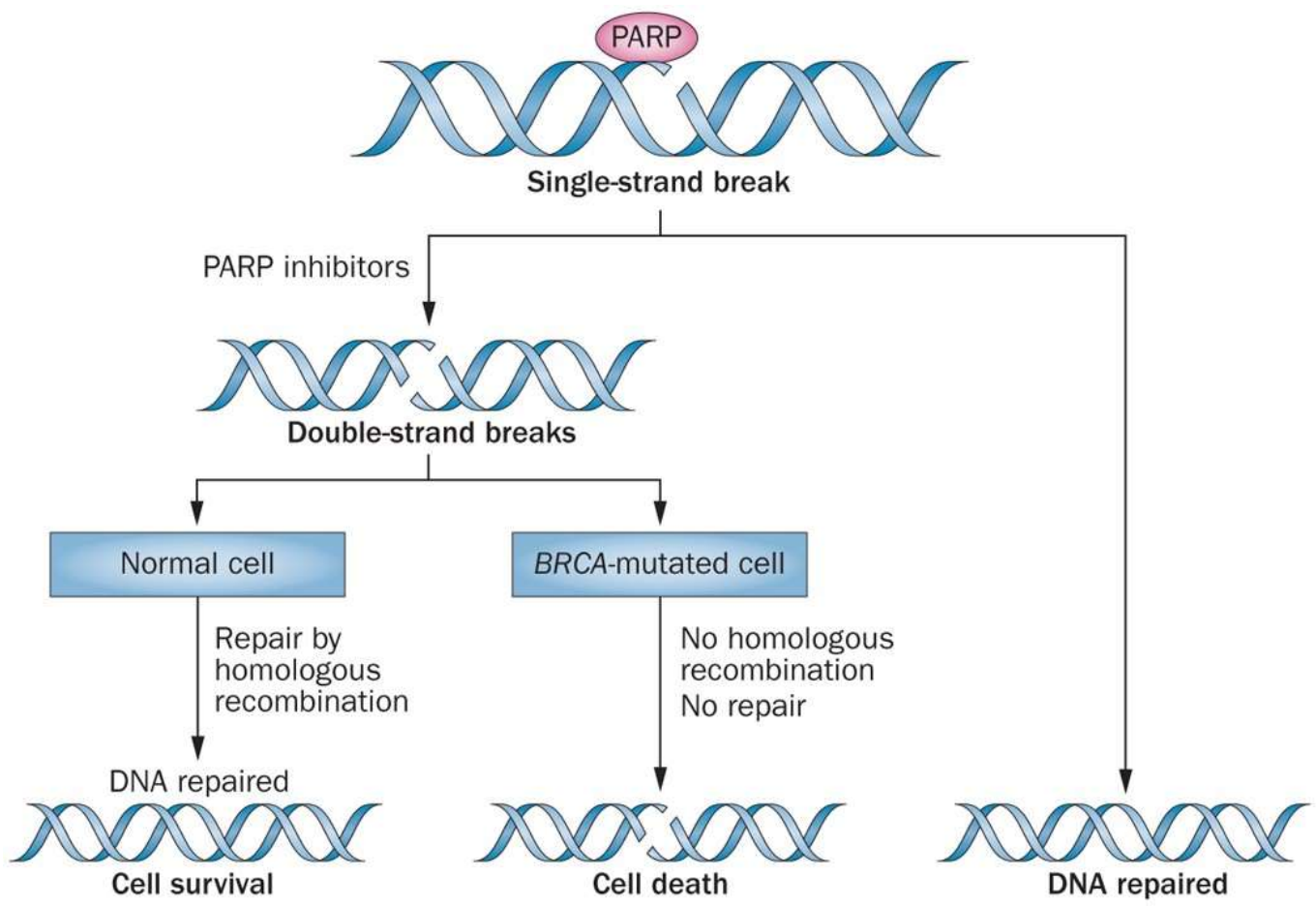


González-Martín A et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2023 Oct;34(10):833-848.

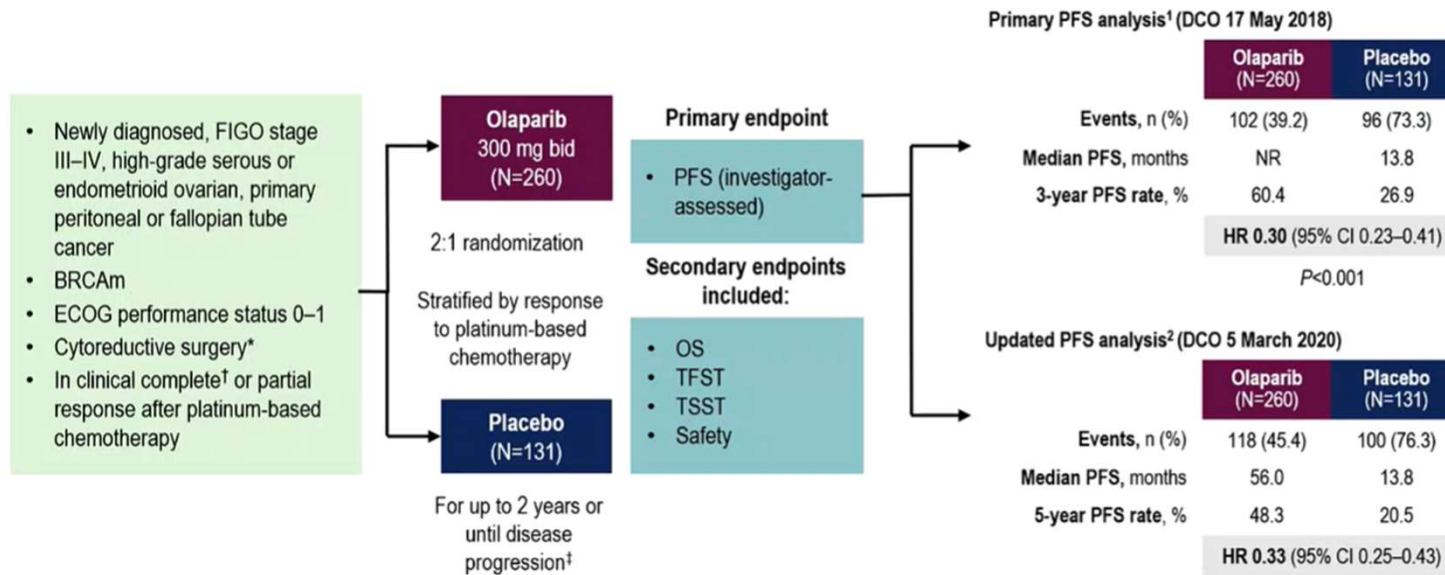
Genetisk udredning

- Alle kvinder med nydiagnosticeret ovariecancer henvises fra gynækologisk afdeling til genetisk udredning i Vejle eller Odense.
- Der tages fast track blodprøve på gynækologisk afdeling – sparer patienten for fremmøde til blodprøver.





Study design and updated PFS analysis



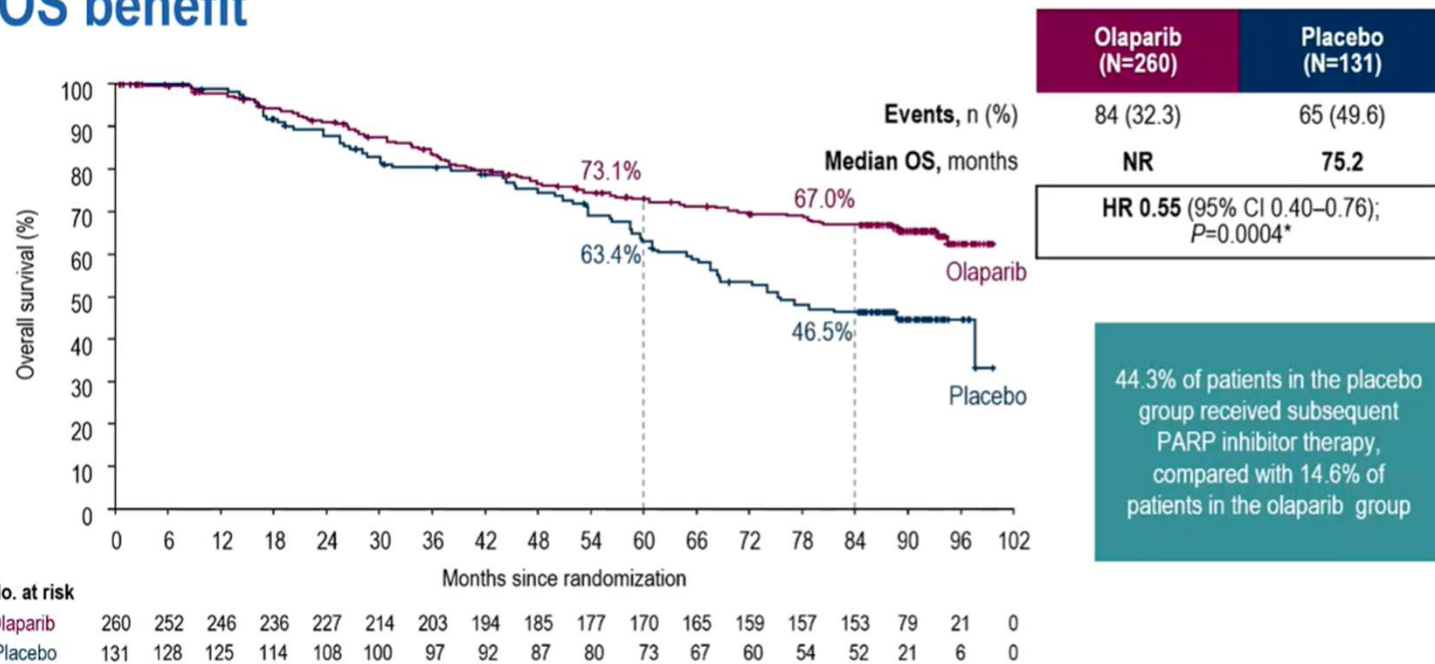
*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease;

[†]Including patients with no evidence of disease; [‡]Patients with evidence of disease at 2 years could continue to receive study treatment if, in the investigator's opinion, this was in the patient's best interest

bid, twice daily; CI, confidence interval; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NR, not reached; PFS, progression-free survival; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death

1. Moore K *et al. N Engl J Med* 2018;379:2495–505; 2. Banerjee S *et al. Lancet Oncol* 2021;22:1721–31

Maintenance olaparib provided a clinically meaningful OS benefit

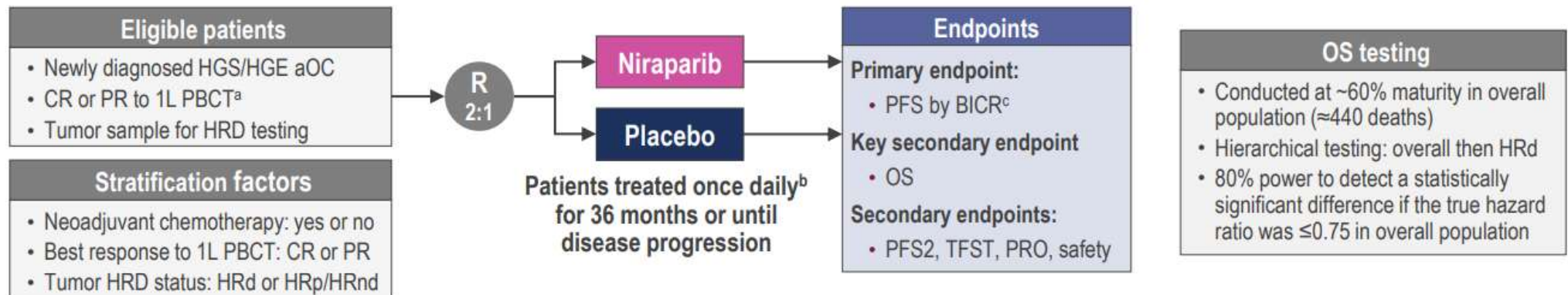


44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

*P<0.0001 required to declare statistical significance

PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib 1L maintenance

Phase 3 PRIMA trial enrolled patients with newly diagnosed aOC at a high risk for disease recurrence



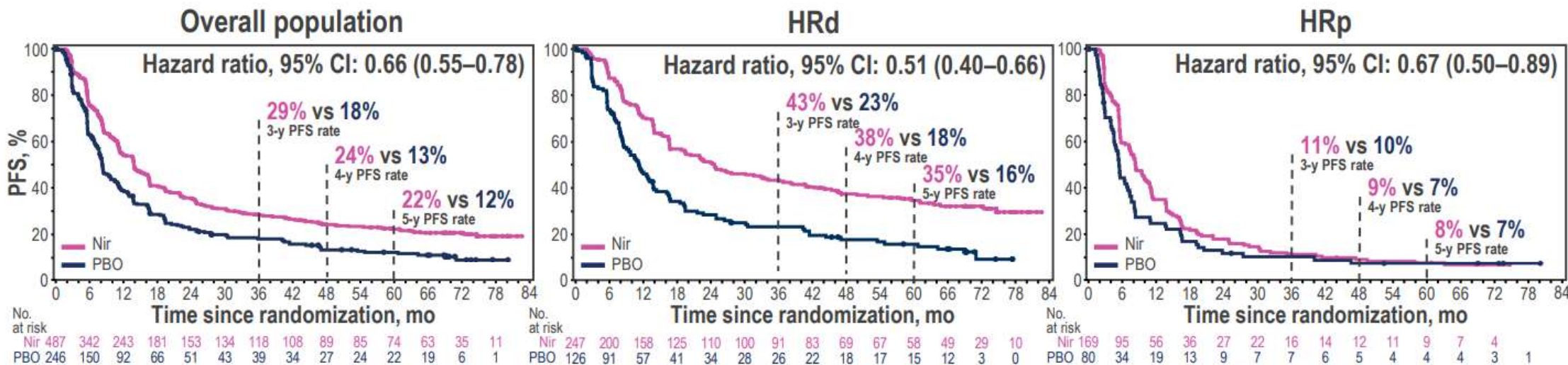
Key risk characteristics of PRIMA population ^{1,2}			
Disease stage	Residual disease		Tumor HRD/ <i>BRCA</i> status
35.1% stage IV disease at diagnosis	>99%	stage III disease at diagnosis with residual disease after primary debulking surgery	50.9% HRd
Initial treatment			30.4% HRd/ <i>BRC</i> Am
66.7% received neoadjuvant chemotherapy	47.5%	postoperative visible residual disease or no debulking surgery	34.0% HRp
30.6% achieved partial response to 1L PBCT			

PRIMA/ENGOT-OV26/GOG-3012 trial (NCT02655016). ^aPatients must have either had CA-125 in the normal range or a $\geq 90\%$ decrease in CA-125 during 1L treatment that was stable for at least 7 days. At baseline, 7.1% of the overall population had CA-125 above the upper limit of normal. ^bAt study start, all patients received a fixed starting dose of 300 mg once daily. Subsequently, the protocol was updated to use an individualized starting dose adjusted according to baseline body weight/platelet count. ^cPrimary endpoint of PFS by BICR assessed by hierarchical testing, first in patients with HRd tumors and then in the overall population. 1L, first-line; aOC, advanced ovarian cancer; BICR, blinded independent central review; *BRC*Am, *BRCA*-mutated; CA-125, cancer antigen 125; CR, complete response; HGE, high-grade endometrioid; HGS, high-grade serous; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRnd, homologous recombination status not determined; HRp, homologous recombination proficient; OS, overall survival; PBCT, platinum-based chemotherapy; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; PRO, patient-reported outcomes; TFST, time to first subsequent therapy.

1. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391–2402. 2. O’Cearbhaill RE, et al. *Gynecol Oncol*. 2022;166(1):36–43.

Updated long-term PFS (ad hoc, investigator-assessed)^{a,b}

Niraparib PFS benefit sustained with additional follow-up in the overall and HRd populations

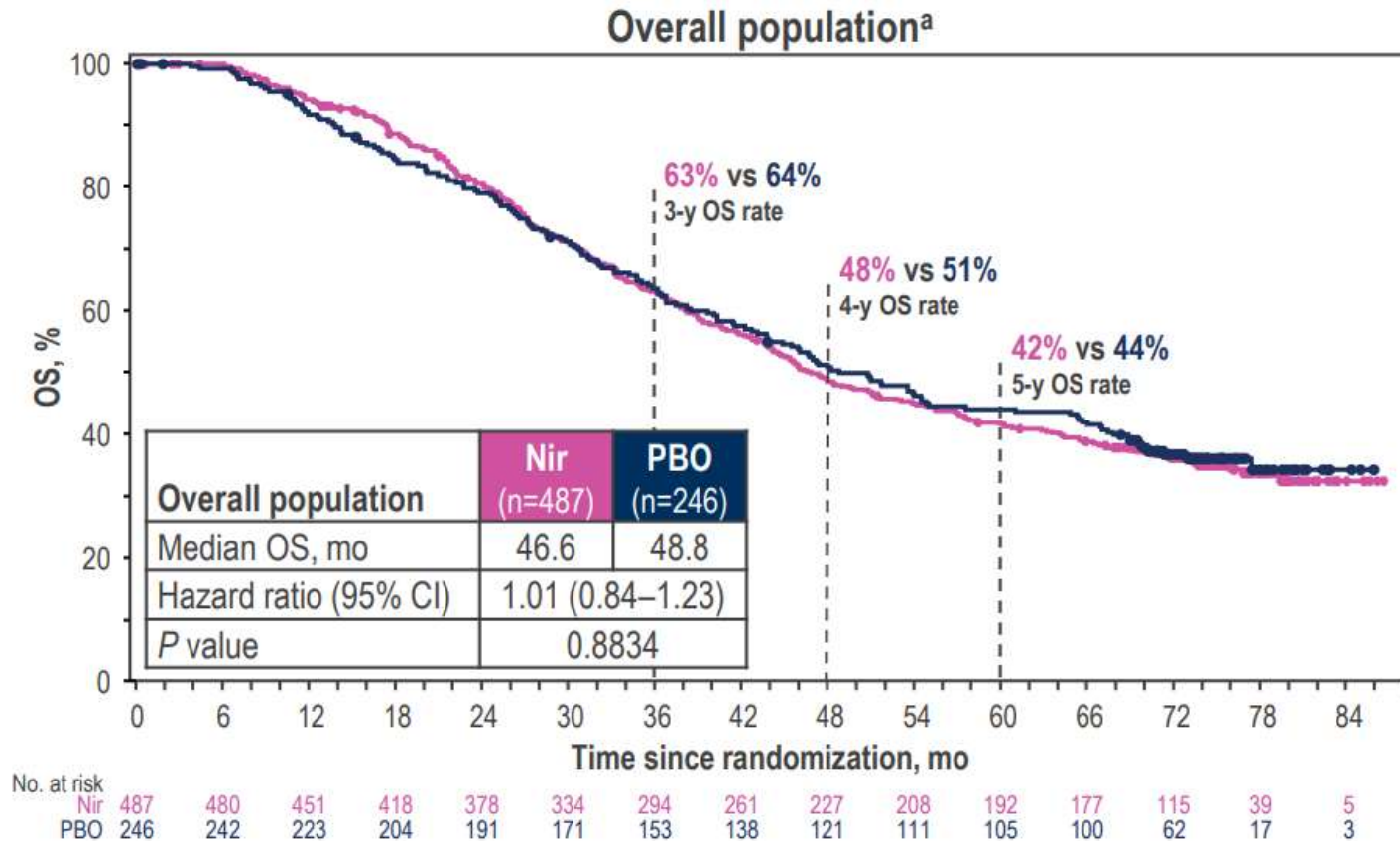


- Data cutoff date, 8 April 2024; median follow-up, 6.2 years
- Among patients alive at 5 years in the HRd population, patients who received niraparib were twice as likely to be progression free (35%) than patients who received placebo (16%)
- Delaying progression is critical to maintain health-related quality of life¹

^aAt study start, patients were monitored for disease progression (CT/MRI) every 12 weeks (3 cycles); in August 2019, the protocol was amended to monitor patients who stayed on study treatment for more than 2 years for disease progression every 24 weeks (6 cycles).
^bPFS hazard ratios and associated 95% CI calculated using stratified Cox proportional hazards model. For all analyses, stratification factors were those used in randomization. CT, computed tomography; HRd, homologous recombination deficient; HRp, homologous recombination proficient; MRI, magnetic resonance imaging; Nir, niraparib; PBO, placebo; PFS, progression-free survival. 1. Chase DM, et al. *Gynecol Oncol*. 2022;166(3):494–502.

Final OS (62.5% maturity in overall population)

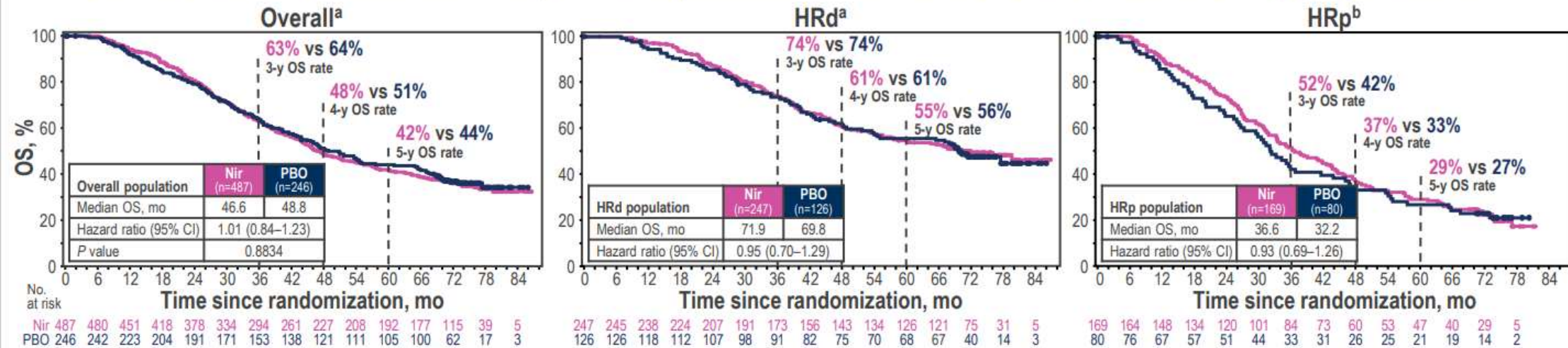
No difference in OS between niraparib and placebo arms



^aResults for overall population evaluated with stratified log-rank test. Hazard ratio and 95% CI calculated using stratified Cox proportional hazards model with randomization stratification factors. Nir, niraparib; OS, overall survival; PBO, placebo.

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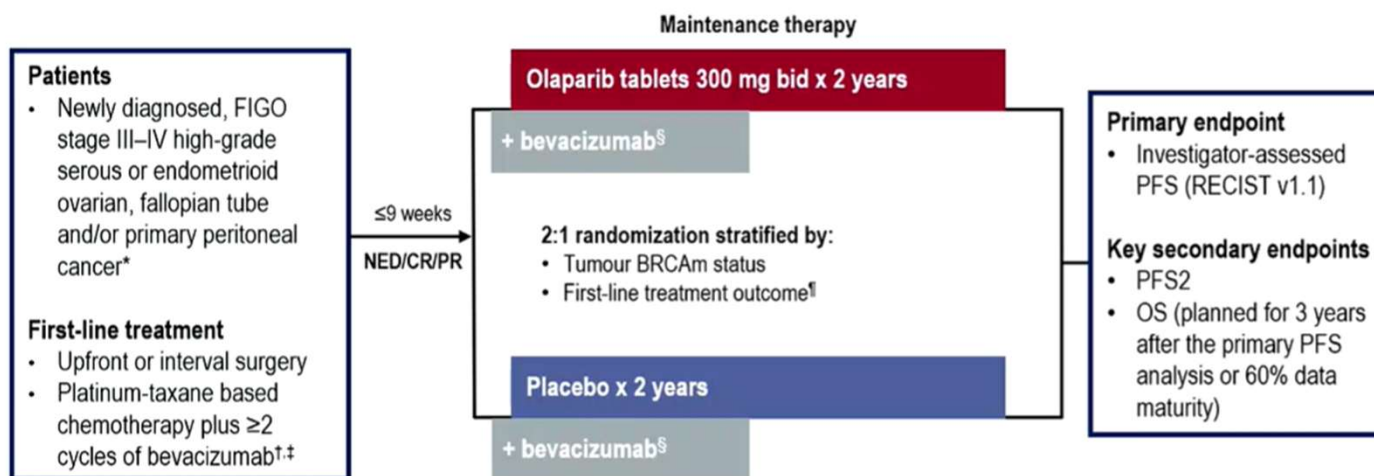
No difference in OS between niraparib and placebo arms in the overall, HRd, and HRp populations



- OS results for all prespecified biomarker-defined subgroups consistent with overall population^c

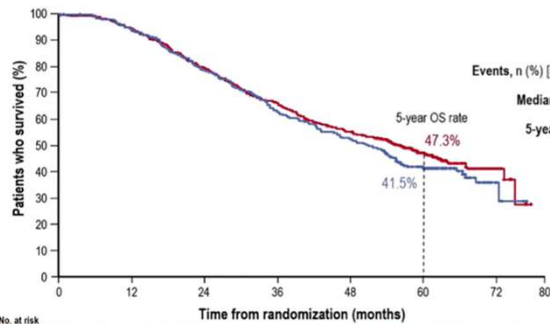
^aHazard ratios and 95% CIs for overall and HRd populations calculated using stratified Cox proportional hazards model with randomization stratification factors. ^bHazard ratio and 95% CI for HRp population calculated using unstratified Cox proportional hazards model. ^cOS results for the HRnd population (unstratified): hazard ratio (95% CI), 1.39 (0.88–2.19). aOC, advanced ovarian cancer; HRd, homologous recombination deficient; HRnd, homologous recombination status not determined; HRp, homologous recombination proficient; OS, overall survival; Nir, niraparib; PBO, placebo. 1. Matulonis UA, et al. *Cancer*. 2015;121(11):1737–1746. 2. Siegel RL, et al. *CA Cancer J Clin*. 2024;74(1):12–49. 3. Elattar A, et al. *Cochrane Database Syst Rev*. 2011;201(8):CD007565. 4. Sun C, et al. *PLoS One*. 2014;9(5):e95285. 5. Delgado A, et al. *Am J Cancer Res*. 2021;11(4):1121–1131.

PAOLA-1 trial design



*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; †Patients must have received ≥ 4 and ≤ 9 cycles of platinum-based chemotherapy; ‡Patients must have received ≥ 3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; §Bevacizumab 15 mg/kg every 3 weeks for a total of 15 months, including when administered with chemotherapy; ¶According to timing of surgery and NED/CR/PR, bid, twice daily; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline BRCA mutation; NED, no evidence of disease; PBC, platinum-based chemotherapy; PFS2, time from randomization to second progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

OS analysis: ITT population



	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [55% maturity]	288 (53.6)	158 (58.7)
Median OS, months	56.5	51.6
5-year OS rate, %	47.3	41.5

HR 0.92 (95% CI 0.76-1.12);
P=0.4118

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: 19.6% (105/537)
Placebo + bevacizumab: 45.7% (123/269)

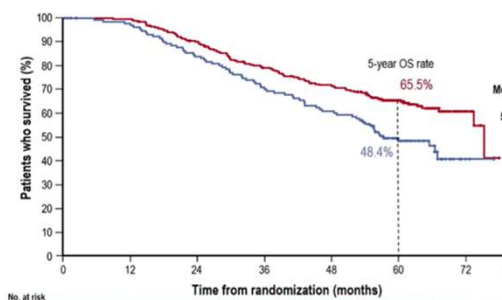
Median time from first cycle of chemotherapy to randomization = 6 months

No. at risk	537	530	528	517	503	480	463	440	420	398	376	357	347	329	308	295	286	276	262	217	199	113	82	40	19	4	0
Olaparib + bevacizumab	537	530	528	517	503	480	463	440	420	398	376	357	347	329	308	295	286	276	262	217	199	113	82	40	19	4	0
Placebo + bevacizumab	269	267	264	261	250	242	229	220	208	199	188	179	166	160	154	148	139	132	121	96	76	51	37	20	5	2	0



PARP, poly(ADP-ribose) polymerase.

OS was prolonged in the HRD-positive subgroup



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	75.2 (unstable)*	57.3
5-year OS rate, %	65.5	48.4

HR 0.62 (95% CI 0.45-0.85)

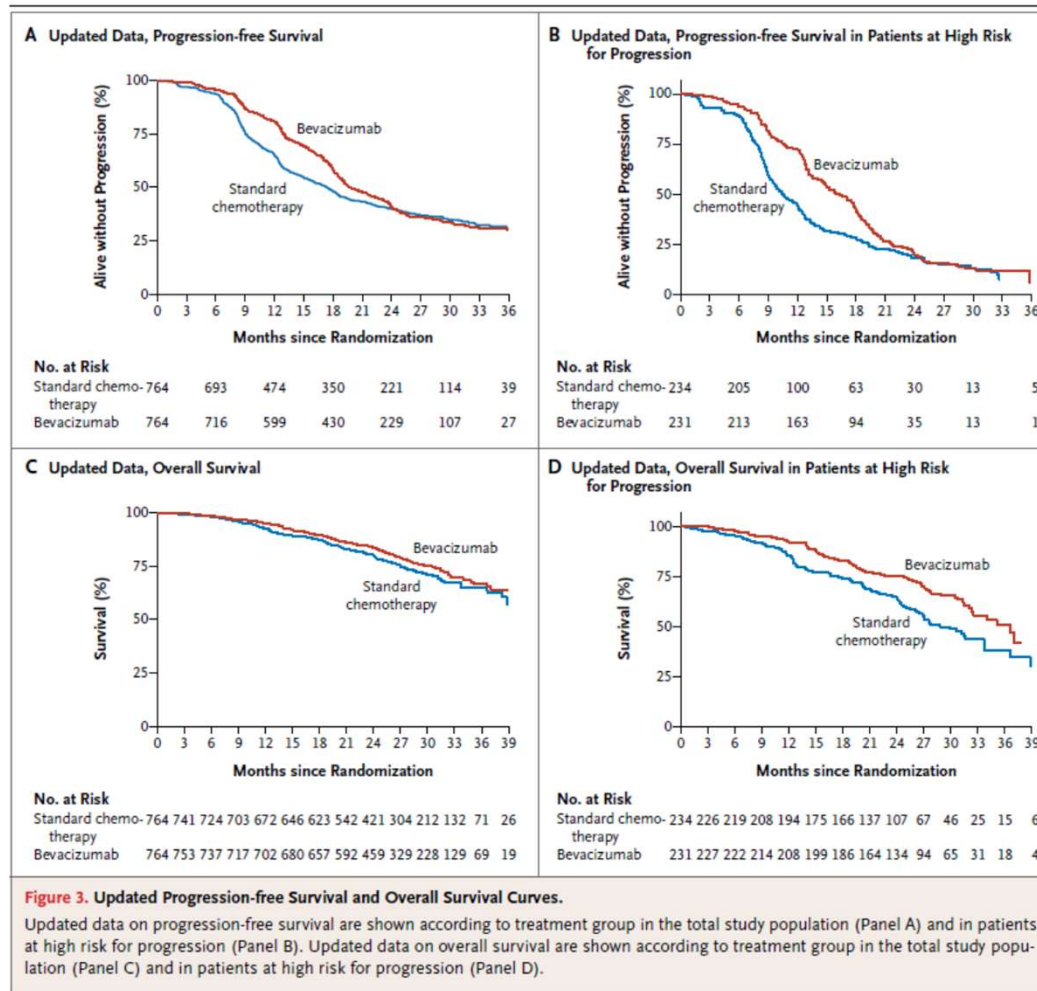
38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: 17.3% (44/255)
Placebo + bevacizumab: 50.8% (67/132)

No. at risk	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0



*Median unstable; <50% data maturity.
HRD positive defined as a BRCAm and/or genomic instability score of >42 on the Myriad myChoice HRD Plus assay.



PARP-hæmmere

Vedligeholdelsesbehandling

3. Kvinder med ny diagnosticeret FIGO stadium III/IV high-grade serøs (HGSOC) eller endometrioid karcinom (HGEOC) med patogen BRCA1 eller 2 mutation, som responderer på første linje platinbaseret kemoterapi, bør tilbydes enten:

a: olaparib vedligeholdelsesbehandling i 24 mdr. (A)

b: niraparib vedligeholdelsesbehandling i 36 mdr. (A)

c: kombinationsregime med bevacizumab og olaparib i 24 mdr. baseret på data fra PAOLA1 studiet. *

*Der foreligger ikke en godkendelse fra Medicinrådet til denne indikation.

4. Kvinder med ny diagnosticeret FIGO st. III/IV, HGSOC/HGEOC BRCAwt, men HRD positiv, som responderer på første linje platinbaseret kemoterapi, bør tilbydes:

a: niraparib vedligeholdelsesbehandling i 36 mdr. (A)

5. Kvinder med ny diagnosticeret HGSOC/HGEOC BRCAwt, HRDnegativ, med FIGO st. III sygdom med makroskopisk tumurvæv efter primær kirurgi/interval debulking, alle patienter med st. IV sygdom, og inoperable patienter, som responderer på første linje platinbaseret kemoterapi, kan tilbydes:

a: bevacizumab initialt i kombination med kemoterapi, efterfulgt af vedligeholdelses behandling med bevacizumab som monoterapi, i op til sammenlagt 15 mdr. (A)

b: niraparib vedligeholdelsesbehandling i 36 mdr. *

*Der foreligger ikke en godkendelse fra Medicinrådet til denne indikation.

Anbefaling

Godkendt den 24. april 2024

Medicinrådets anbefaling vedr. olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af avanceret kræft i æggestokkene, æggeledeerne eller primær kræft i bughinden - version 2.0

Medicinrådet **anbefaler** olaparib i kombination med bevacizumab til 1. linje vedligeholdelsesbehandling af fremskreden kræft i æggestokkene, æggeledeerne eller primær kræft i bughinden for patienter med epitelcelle highgrade karcinom og homolog rekombinationsdefekt (HRD+), men uden BRCA1/2-mutation.

Medicinrådet vurderer, at olaparib i kombination med bevacizumab ikke er et dårligere behandlingsalternativ end den nuværende standardbehandling niraparib. Begge behandlinger kan udskyde tid til sygdomsforværring. Der er dog også bivirkninger ved begge behandlinger, som hyppigst er kvalme og træthed.

Omkostningerne for de to behandlinger er på samme niveau. Derfor anbefaler Medicinrådet olaparib i kombination med bevacizumab som en mulig standardbehandling.

