Enhanced recovery after surgery in advanced ovarian cancer: a prospective randomized trial

-- JL. Sánchez-Iglesias et al.

Objectives & Methods (1/2)

OBJECTIVES

The primary goal of the study was to compare in a prospective randomized trial the enhanced recovery after surgery (ERAS) vs conventional perioperative care in terms of reduction in Median Length of Hospital Stay (LOH). The secondary outcomes were the type of intra- and postoperative complications, readmissions rate, and mortality within the 30-days follow-up period.

METHODS

Advanced ovarian carcinoma.
(FIGO Stage IIB-IVA)

Randomization

Conventional perioperative care	Enhanced recovery after surgery
49 patients with • primary CRS (21) • recurrent CRS (12) • interval CRS (16)	50 patients with • primary CRS (22) • recurrent CRS (8) • interval CRS (20)

Methods (2/2)

ERAS Protocol

Preoperative	Postoperative	Intraoperative
• pre-admission counselling • nutritional status assessment • administration of 35mg of maltodextrin 3h before surgery • no mechanical bowel preparation • no preanesthetic sedatives	• early mobilization (24-48h) • clear liquid intake (+6h) and protocolized diet • early (24h) urinary catheter removal	• ERAS based anesthetic protocol • no nasogastric intubation • no systematic use of drainages

Results

Overall compliance with the ERAS protocol was about 91 %.

No significant differences between the two groups related to operative time, blood loss, or cytoreduction rate.

The ERAS group had a median length of hospital stay of 2 days shorter as compared to the classic group (7 days vs 9 days, p=0,009).

No significant differences in the complications rate or re-interventions (30 days post-operative follow up period).

The ERAS group had a lower rate of readmissions as compared to the CM group (6% vs 20.4% p=0,03).

Conclusions

The ERAS protocol results in a shorter hospital stay due to earlier recovery, and a lower rate of readmissions with no increase in morbidity and mortality.

Ovarian cancer detection combining an innovative catheter for uterine and tubal lavage with ultra-sensitive TP53 sequencing

-- *P. Speiser et al.*

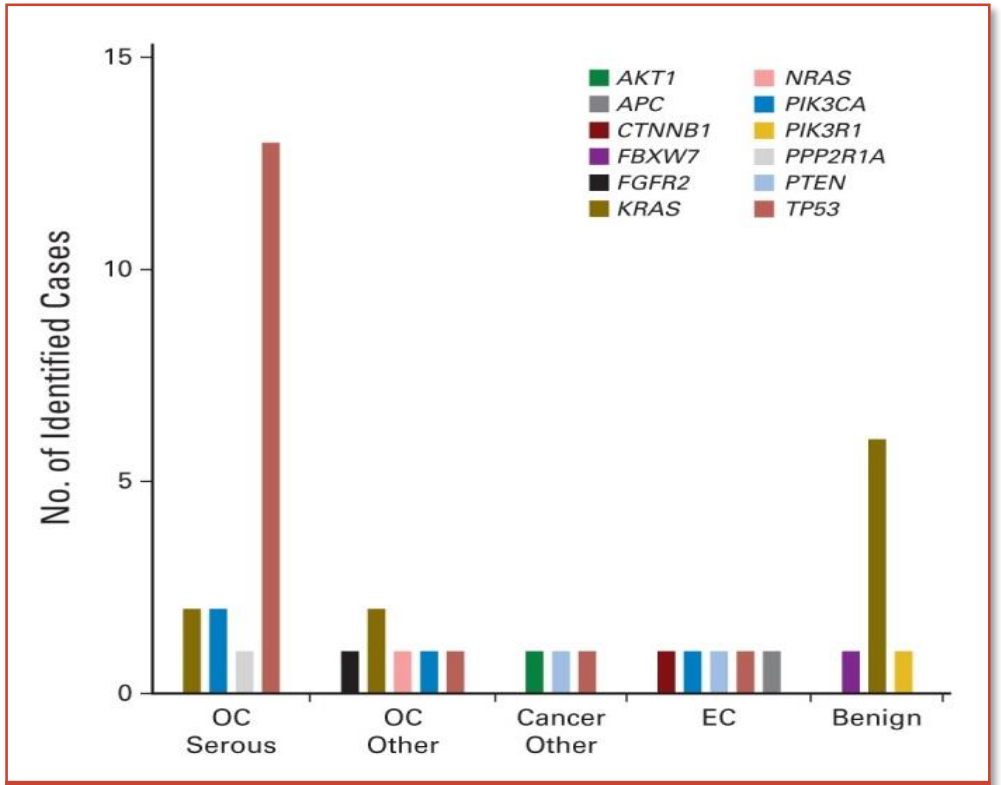
Objectives

To present rationale for the study aiming to investigate potential of Lavage Concept for the screening of BRCA 1 mutation carriers for occult high-grade serous carcinoma (HGSC) or serous tubal intraepithelial carcinoma (STIC) based on the 3 (already) finalized and published studies.

Background & Methods (1/3)

Proof of principle study n 1 (Maritschnegg E et al. J Clin Oncol. 2015):

- Cells shed from Müllerian duct cancers, including OC and EC, can be collected through a lavage of the uterine cavity, in which tumour-specific mutations can be detected through massively parallel sequencing.
- 60% of patients with OC had mutations in their lavage samples detected with the NGS approach.
- Singleplex analysis of mutations previously determined in corresponding tumour tissue led to further identification in 24 (80%) of 30 patients with OC.

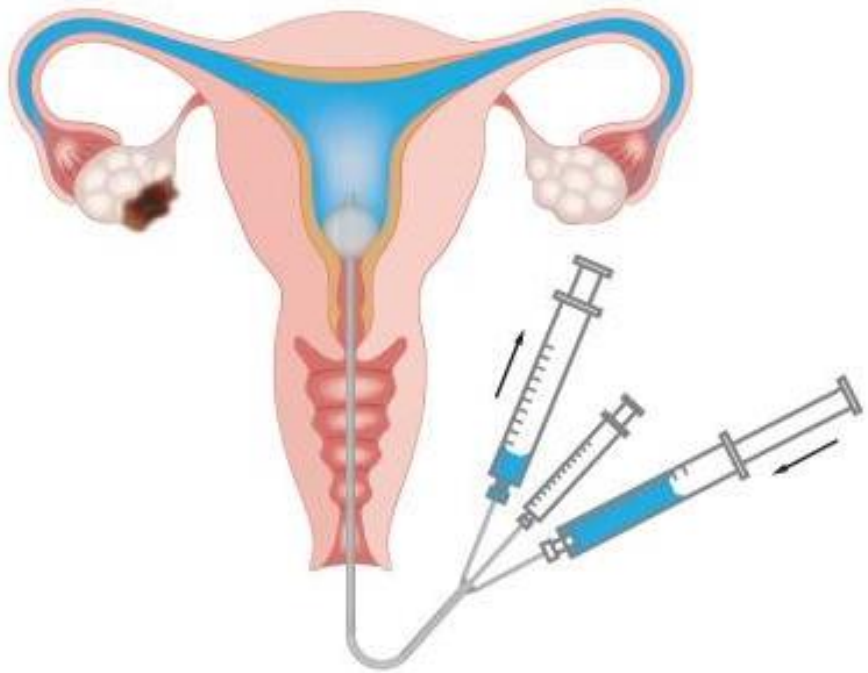


Distribution of genes affected by mutations: a mutation of the TP53 gene was the most important marker in identifying ovarian cancer (OC)

Background & Methods (2/3)

Proof of concept study n 2 (Maritschnegg E et al. Int J Gynecol Cancer. 2018):

- Uterine and tubal lavage (UtL) performed with the new catheter fulfills all prerequisites for a screening test.
- Specimens can be collected reliably, even after a short training.
- The procedure was proven to be safe and feasible to use in a clinical or outpatient setting.
- The uterine and tubal lavage took 6.5 minutes on average.
- The amount of extracted DNA was above the lower limit for a sensitive, deep-sequencing mutation analysis in all cases.

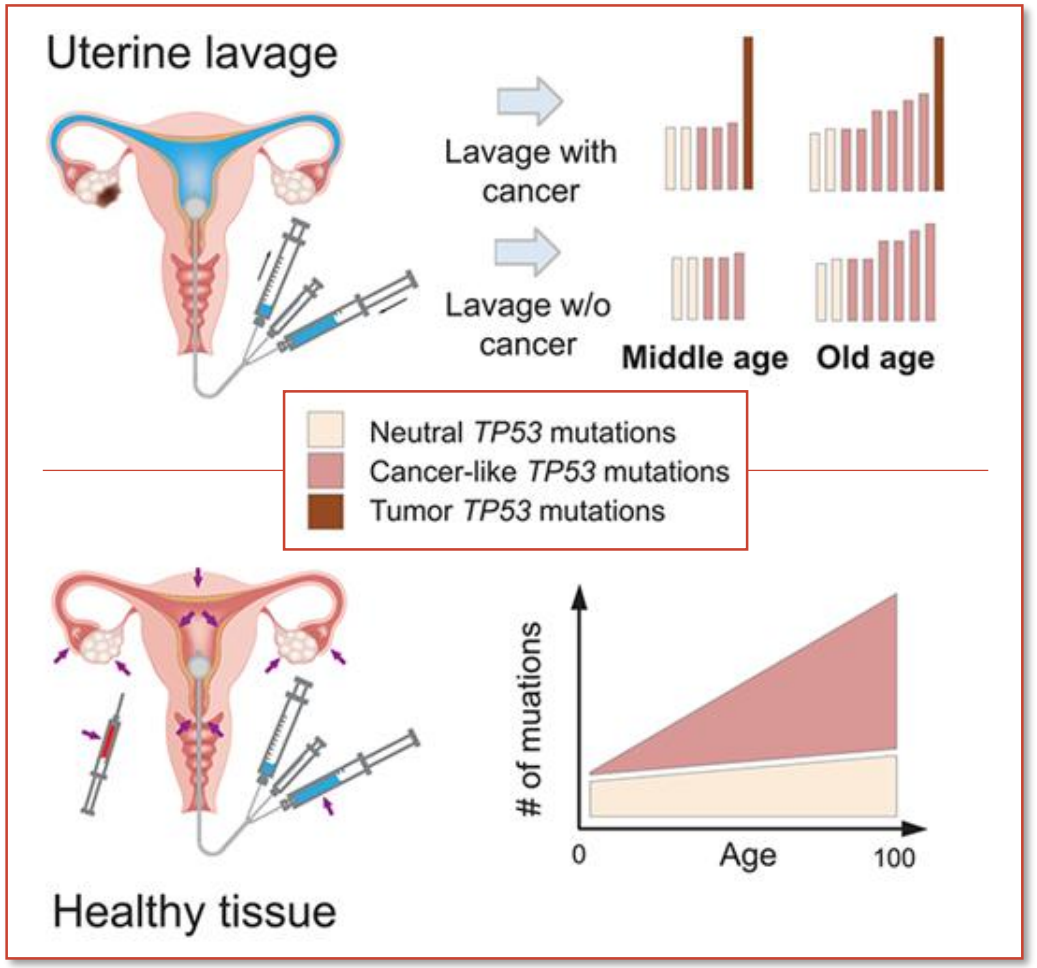


Sketch of the catheter for uterine and tubal lavage. It is carried out by passing a small catheter through the cervix, followed by concurrent flushing and aspiration with 10 mL of saline.

Background & Methods (3/3)

Proof of concept study n 3 (Salk JJ et al. Cell Rep. 2019):

- Ovarian cancer can be detected by ultra-accurate sequencing of uterine lavage DNA.
- However, low-frequency TP53 mutations also exist in normal tissue of healthy women.
- TP53 mutations are increasingly selected for with age, revealing somatic evolution.
- Age-associated, cancer-like mutations challenge specificity for cancer detection.



Results & Conclusions

Planned study: Uterine Lavage for Ovarian cancer Early detection – L.O.V.E. Trial Phase II Study on Sensitivity and Specificity of the Lavage Concept

Aim of the study

- Investigate potential of Lavage Concept for the screening of BRCA 1 mutation carriers for occult HGSC or STIC

Eligibility criteria

- ages eligible for study: 35 years to 70 years

Inclusion criteria

- BRCA1 mutation carriers

Exclusion criteria

- pregnant, incapacity, tubal ligation

Study intervention

- yearly uterine and tubal lavage under local anesthesia

Study endpoint

- STIC or occult HGSC on RRSO
- Spontaneous HGSC development
- End of the study

Statistics

- Lifetime incidence for HGSC ~45%
- Occult HGSC or STIC at RRSO is 7%
- Specificity of ≥94%, sensitivity = 80%
- 150 events requiring ~2000 patients

Phase III PAOLA-1/ENGOT-ov25 : maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care

-- P. Harter et al.

Background

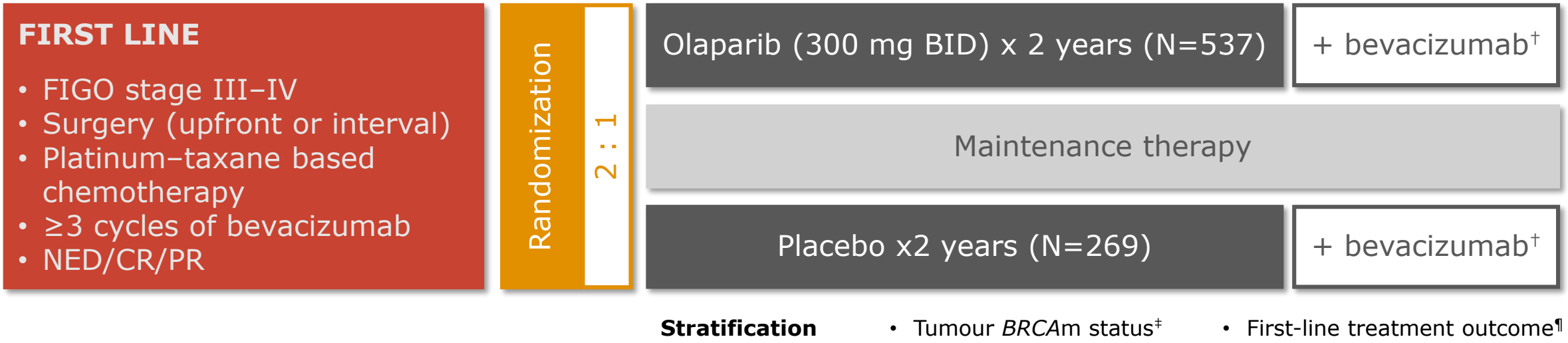
First-line bevacizumab in combination with chemotherapy and followed by bevacizumab maintenance is the current standard of care for most patients with newly diagnosed advanced ovarian cancer (AOC).

The PARP inhibitor olaparib showed a PFS benefit as first-line maintenance monotherapy for patients with a BRCA mutation (BRCAm). It is also well known that homologous recombination repair deficiency (HRD) affecting response to olaparib is not limited to BRCAm and is present in ~50% of high-grade serous ovarian tumours.

Objectives & Methods

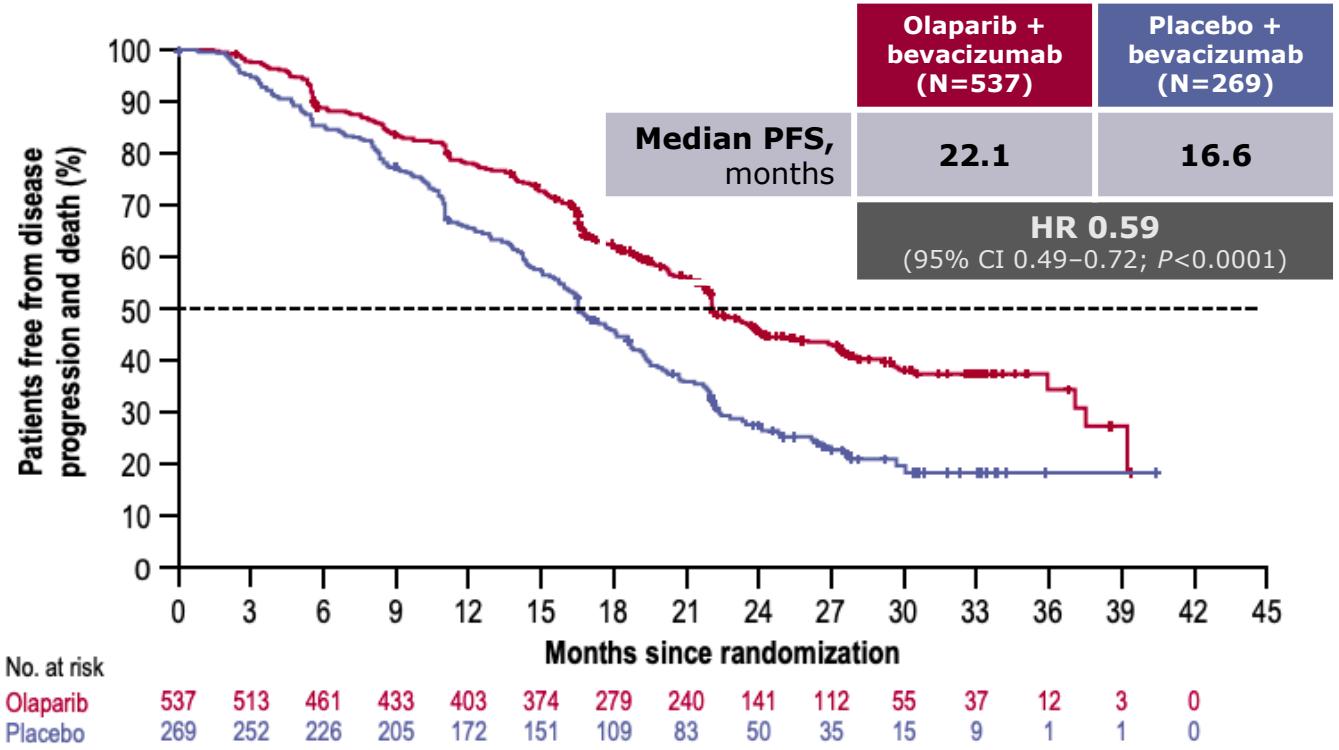
The aim of the study was to evaluate the efficacy and safety of maintenance therapy with a PARP inhibitor in patients with AOC regardless of BRCA mutation status who are receiving first-line standard-of-care treatment including bevacizumab.

METHODS



Results

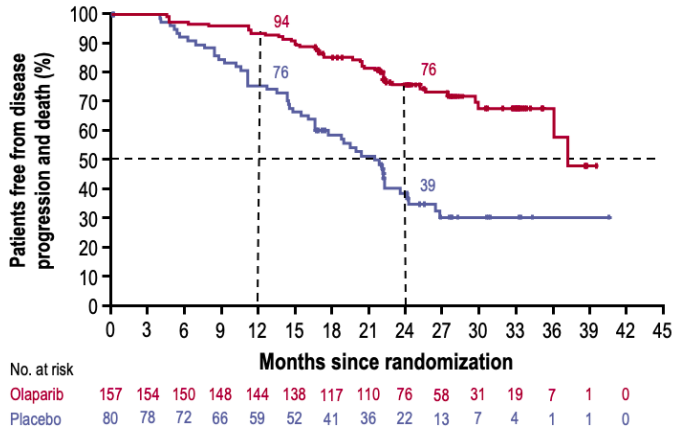
PFS BY INVESTIGATOR ASSESSMENT



PFS was significantly increased in the olaparib arm (22,1 vs 16,6 months), HR 0.59 (95% CI 0.49–0.72; P<0.0001) (59% maturity)

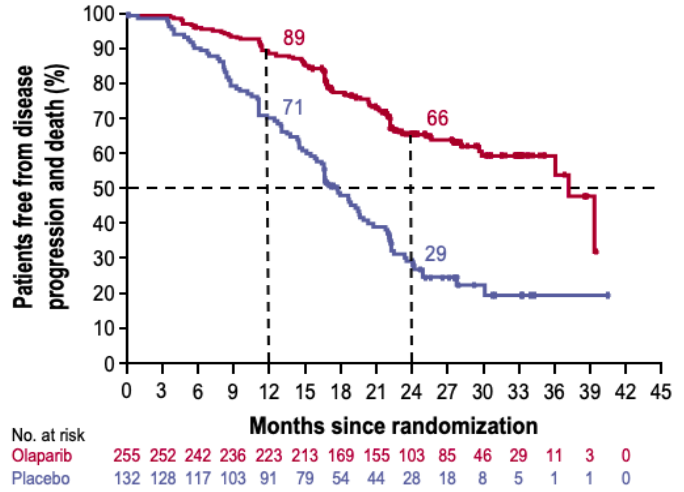
PFS IN PATIENTS WITH tBRCA MUTATION

(37.2vs 21.7 months)



PFS IN PATIENTS WITH HRD POSITIVE STATUS

(37.2 vs 17.7 months)



Conclusions

Addition of olaparib to bevacizumab maintenance therapy following first-line standard-of-care bevacizumab maintenance treatment led to a statistically significant and clinically meaningful PFS benefit in patients with advanced ovarian cancer. The PFS benefit in patients with a tBRCAm and in HRD-positive patients was substantial.

Exploratory subgroup analyses showed that all patients had PFS benefits regardless of disease stage and previous NACT; further biomarker analyses in both subgroups are ongoing.

The safety profile of olaparib in combination with bevacizumab was generally consistent with previous trials of each drug and the addition of olaparib did not impact on bevacizumab tolerability and HRQoL.

Niraparib therapy in patients with newly diagnosed advanced ovarian cancer after chemotherapy: PRIMA/ENGOT-OV26/GOG-3012 Study

-- *A. González-Martín et al.*

Objectives

Niraparib has shown progression-free survival (PFS) benefit in recurrent ovarian cancer (OC) after platinum-based chemotherapy (CT) in all patients regardless of BRCA status.

The efficacy of niraparib in patients with newly diagnosed advanced ovarian cancer after a response to first-line platinum-based chemotherapy was unknown.

The aim of this study was to show the efficacy and safety of niraparib after first line chemotherapy in newly diagnosed advanced ovarian cancer patients.

Methods

KEY INCLUSION CRITERIA

- High grade serous or endometroid pathology
- Stage III: primary debulking surgery (PDS) with visible residual disease post surgery, NACT, or inoperable
- Stage IV: PDS regardless of residual disease, NACT, or inoperable
- CR or PR following platinum first-line treatment

KEY EXCLUSION CRITERIA

- Patients with Stage III disease who have had complete cytoreduction (i.e., no visible residual disease) after PDS

733 patients with newly-diagnosed OC at high risk for recurrence after first line platinum-based chemotherapy

Randomization 2 : 1

484 patients with niraparib

244 patients with placebo

Primary Endpoint:
Progression-free survival

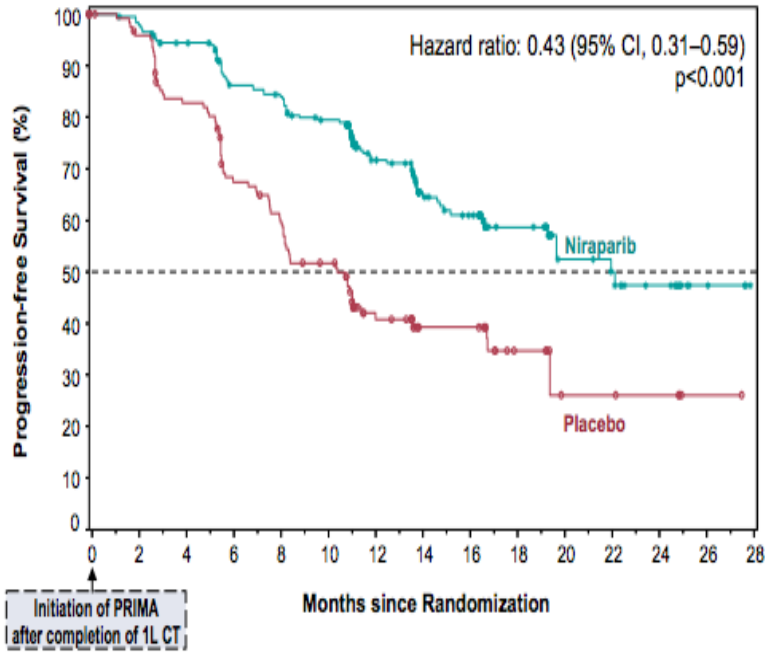
Key Secondary Endpoint:
Overall Survival

Patient characteristics were well balanced across each arm.

Median follow up of 13.8 months

Results (1/2)

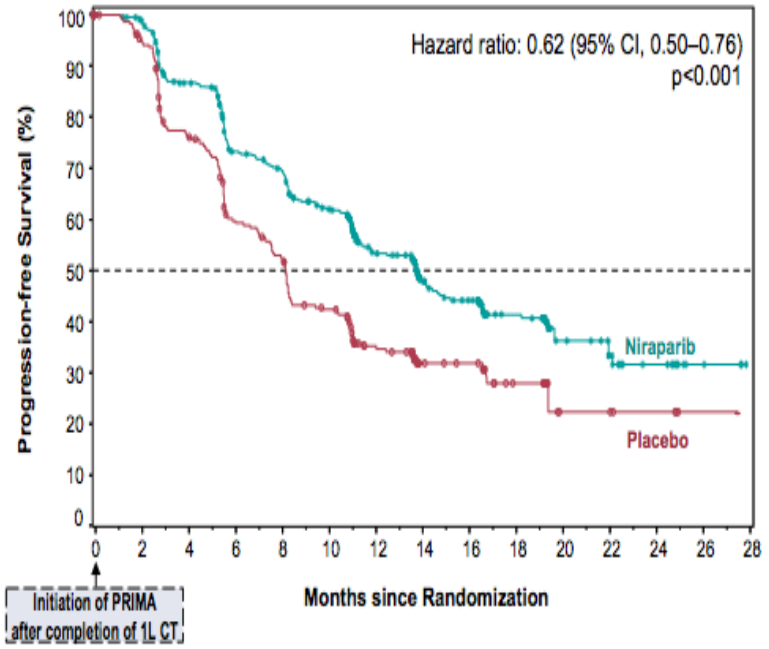
PFS BENEFIT IN THE HR-DEFICIENT POPULATION



57% reduction in hazard 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%

Niraparib reduced the risk of relapse or death by 57% and **prolonged median PFS from 10.4 to 21.9.**

PFS BENEFIT IN THE OVERALL POPULATION

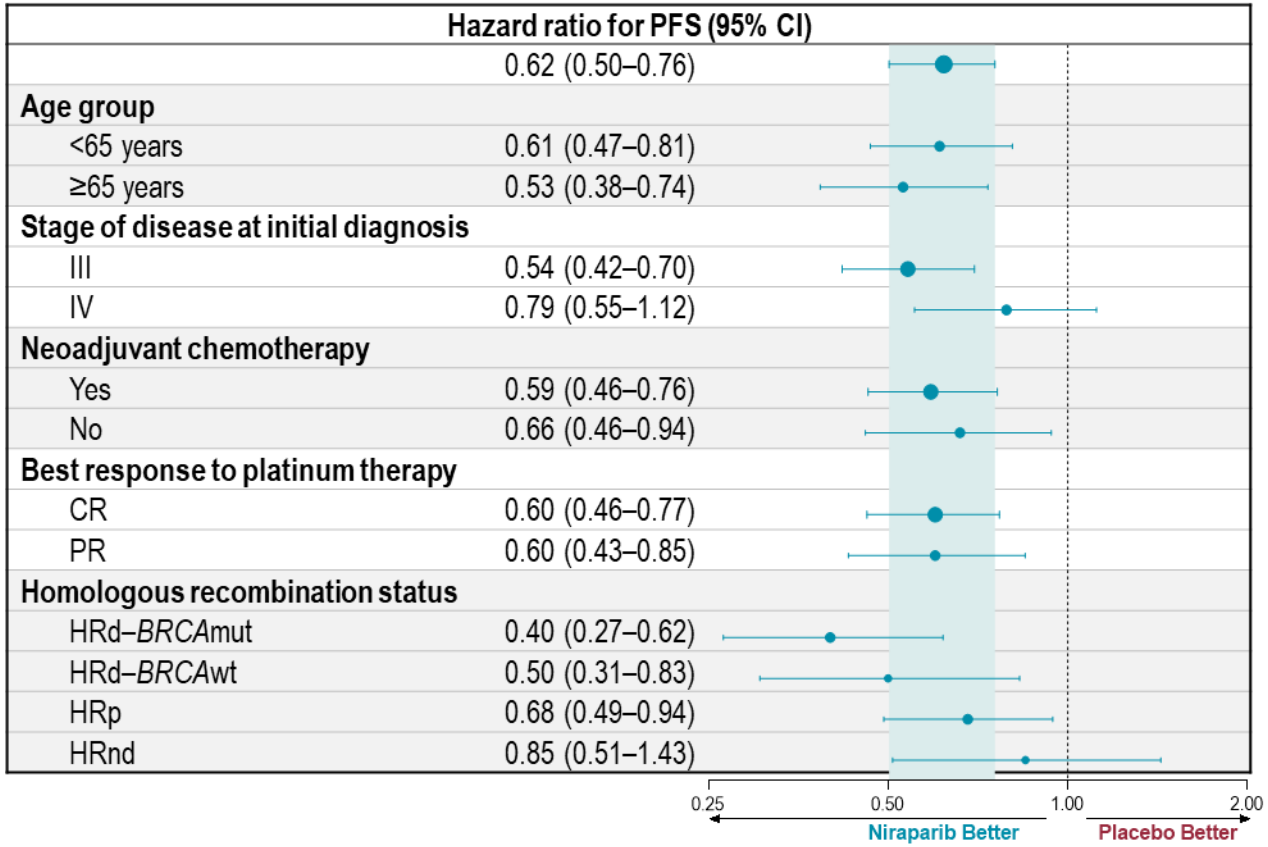


38% reduction in hazard of relapse or death with niraparib	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

Niraparib reduced the risk of relapse or death of 38% and **prolonged median PFS from 8.2 months to 13.8 months.**

Results (2/2)

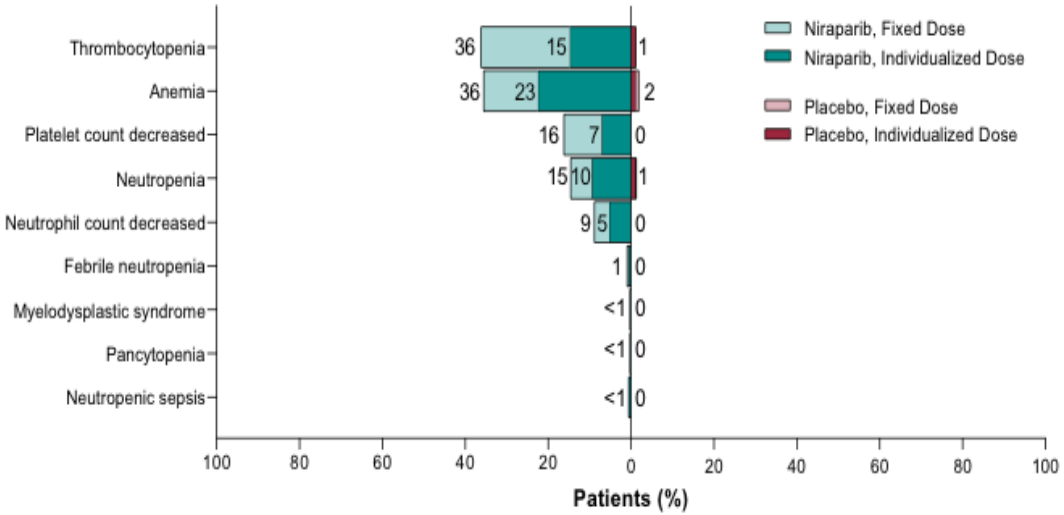
PFS BENEFIT IN PRE-SPECIFIED GROUPS



- Niraparib provided similar clinical benefit in the HRd subgroups (BRCAmut and BRCAwt)
- Niraparib also provide benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

TREATMENT EMERGENT ADVERSE EVENTS (TAETS)

- manageable and consistent with the PARP inhibitor class, most commonly reversible myelosuppression.
- discontinuation due to TAETs was 12,4%
- no death due to treatment



- Incidence of grade ≥3 hematologic TEAEs were lower in patients who received an individualized dose of niraparib

Conclusions

- Niraparib therapy in patients with advanced ovarian cancer provided a clinically significant improvement in PFS after response to first-line platinum-based chemotherapy in all patients.
- Niraparib demonstrates benefit in patients across biomarker subgroups
- Patients with ovarian cancer at the highest risk of early disease progression (NACT, partial responders to first-line platinum chemotherapy) had significant benefit
- No new safety signals were observed, and quality of life was maintained
- Niraparib monotherapy after first-line platinum-based chemotherapy should be considered a new standard of care

Maintenance olaparib after platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: efficacy by the timing of surgery and residual tumor status following upfront or interval cytoreductive surgery in the phase III SOLO1 trial

-- *N. Colombo et al.*

Objectives

- The Phase III SOLO1 trial evaluated maintenance therapy with the PARP inhibitor olaparib in women with primary, advanced ovarian cancer (OC) and a BRCA1 or BRCA2 mutation (BRCAm) who were in clinical complete or partial response following platinum-based chemotherapy
- Maintenance with olaparib provided a substantial PFS benefit versus placebo (HR 0.30; 95% CI 0.23–0.41; P<0.001)
- The probability of progression free of disease or being alive at 3 years was 60.4% with olaparib versus 26.9% with placebo
- SOLO1 recruited patients regardless of prior surgical status.
- The main aim of this study was to analyze the efficacy of olaparib in stage III OC patients who underwent upfront surgery and had no residual macroscopic disease.

Methods

- Newly diagnosed, FIGO stage III-IV, high grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic BRCAm
- Cytoreductive surgery
- In clinical complete response or partial response after platinum based chemotherapy

STUDY DESIGN

2:1 Randomization (stratified by response to platinum-based chemotherapy)

Olaparib tablets 300mg bid (N=260)

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with an ongoing partial response at 2 years could continue treatment

Primary objective

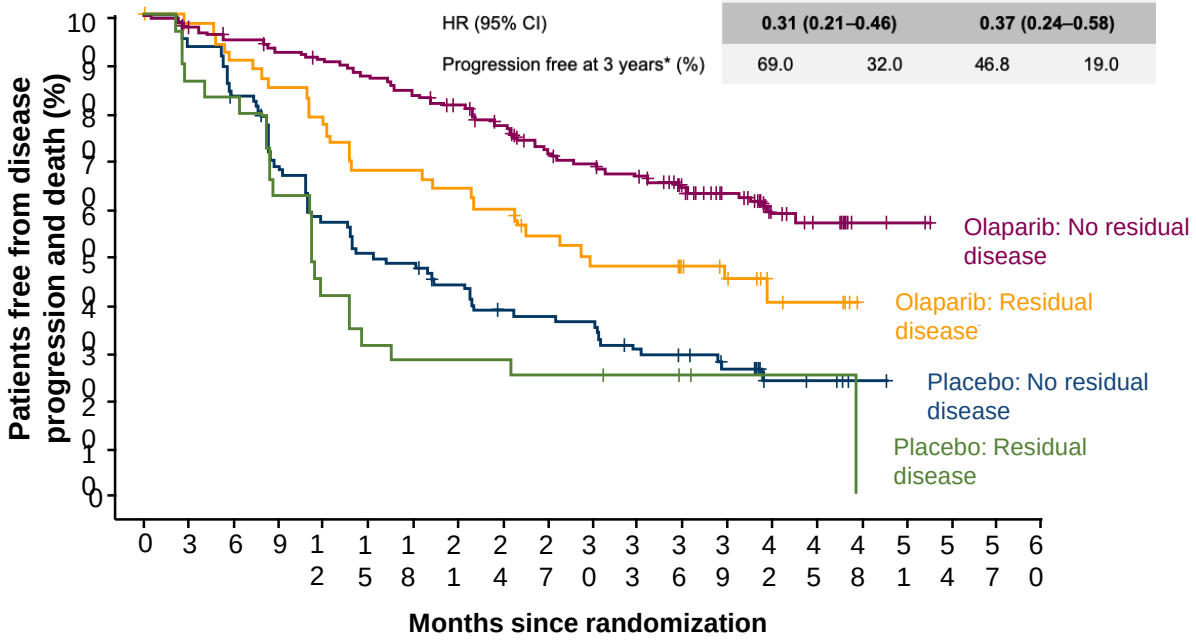
Investigator-assessed PFS

2 years' treatment if no evidence of disease

Results

PFS BASED ON TIMING OF SURGERY

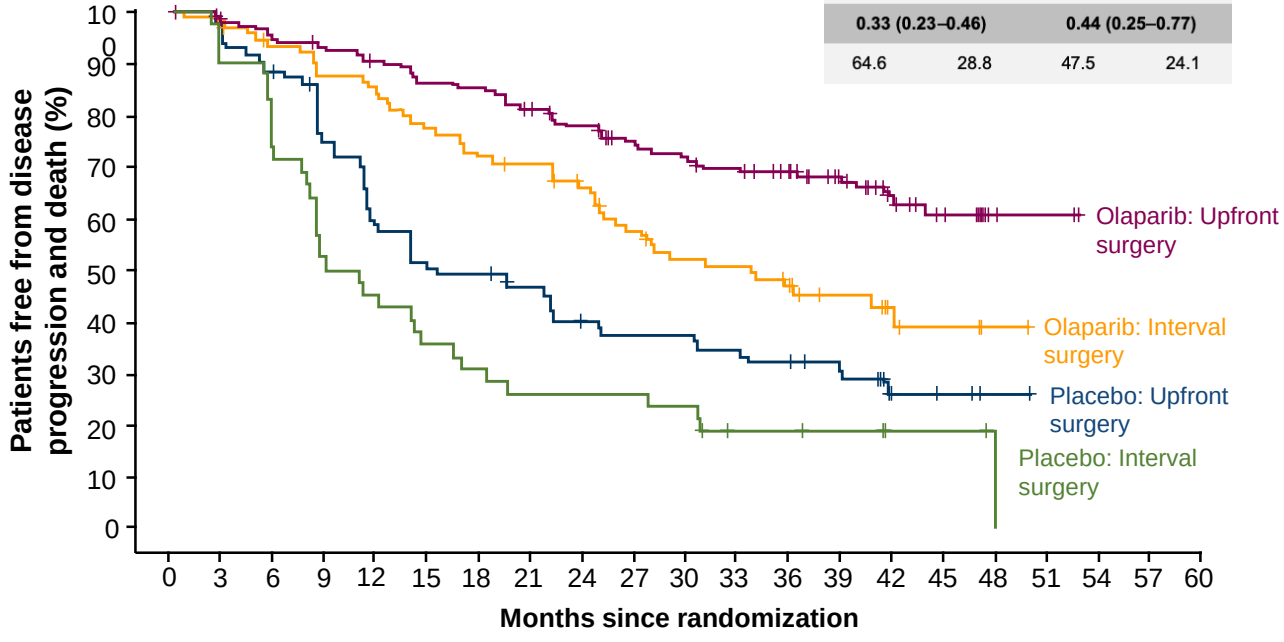
	Upfront surgery		Interval surgery	
	Olaparib (n=161)	Placebo (n=85)	Olaparib (n=94)	Placebo (n=43)
Median PFS, months	NR	15.3	33.6	9.8
HR (95% CI)	0.31 (0.21–0.46)		0.37 (0.24–0.58)	
Progression free at 3 years* (%)	69.0	32.0	46.8	19.0



PFS was significantly improved regardless of the timing of surgery

PFS BASED ON RESIDUAL DISEASE STATUS FOLLOWING SURGERY

	No residual disease		Residual disease	
	Olaparib (n=200)	Placebo (n=98)	Olaparib (n=55)	Placebo (n=29)
NR	15.3	29.4	11.3	
0.33 (0.23–0.46)		0.44 (0.25–0.77)		
64.6	28.8	47.5	24.1	



PFS was significantly improved regardless of the residual disease status after surgery

Conclusions

Consistent with the PFS benefit seen in the overall population in SOLO1, maintenance olaparib provided a substantial PFS benefit across all patient subgroups including:

- Patients with a complete cytoreduction
- Patients who had undergone upfront surgery and had no residual disease

A substantial PFS benefit was seen regardless of the timing of surgery or residual disease status after surgery, indicating that all patients with newly diagnosed, advanced high-grade ovarian cancer and a BRCAm are at high risk of progression and achieve substantial benefit from maintenance olaparib

TP53 mutations in cell-free DNA as early marker of therapy response in platinum-resistant ovarian cancer

-- *A. Vanderstichele et al.*

Objectives & Methods

OBJECTIVES

Detecting tumour-specific genetic alterations in cell-free DNA (cfDNA) obtained from cancer patients allows for a quantification of the tumoral fraction, i.e. the circulating tumour DNA (ctDNA).

This hypothesis was tested on cfDNA samples collected in GANNET53 trial investigating the addition of Hsp90-inhibitor ganetespib to standard paclitaxel weekly regimen (P +/-G) in platinum-resistant ovarian cancer (PROC);

- Cohort: 133 patients were randomized (90 P+G vs 43 P);
- Primary endpoint: PFS;
- Results: addition of ganetespib to paclitaxel did NOT improve PFS.

Objectives & Methods

The aim of this study was to explore the predictive role of early negativation of TP53 mutations in circulating tumour DNA (ctDNA) in outcome / therapy response.

METHODS

- Archival FFPE tissue (central review + somatic TP53 / BRCA sequencing);
- Blood samples for plasma extraction (EDTA) at start and during treatment.

Results

ctDNA was detectable in 64.6% of baseline samples. Baseline CA125 did not differ between cases with and without detectable ctDNA at baseline.

- Detection of ctDNA predicted a **worse overall survival.**
- ctDNA **negative status after 4 weeks** of treatment predicts **better overall survival;**
  - Paclitaxel mono + ctDNA negative: PFS HR 0.65 (0.33-1.29) / OS HR 0.28 (0.16-0.65).
- ctDNA **negative status after 4 weeks** of treatment predicts **better response rate;**
  - ORR 40.5% in ctDNA negative ⇔ 16.1% in ctDNA positive (p=0.047).
- Highest objective response rate (ORR) was in patients where ctDNA was detectable and disappeared.
- Patients, where ctDNA remained or became detectable, had worst ORR.

Conclusions

Quantification of TP53 mutations in cfDNA of platinum-resistant ovarian cancer patients has prognostic value at baseline.

Favorable early changes during treatment may predict therapeutic response (early identification of non-responders).