Paradigm Changes in Front Line Ovarian Cancer

Moderators: Thomas Herzog, MD, and Kathleen Moore, MD

April 29, 2020, 2:30 p.m. CST

Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by BRCA and homologous recombination status: PRIMA/ENGOT-OV26/GOG-3012 study

B.J. Monk[a] and A. Gonzalez Martin[b]. [a]*Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA,* [b]*Grupo Español de Investigación en Cáncer de Ovario (GEICO) and Medical Oncology Department, Clínica Universidad de Navarra, Madrid, Spain*

Objectives: Niraparib improves progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer after first-line (1L) platinum-based chemotherapy (CT). We report the efficacy of niraparib in pts by biomarker status.

Methods: This double-blind, placebo (PBO)-controlled, phase 3 study randomized 733 pts with newly diagnosed advanced ovarian, primary peritoneal, or fallopian tube cancer with a complete or partial response (CR or PR) to 1L platinum-based CT. Stratification factors were best response to the 1L CT (CR/PR), receipt of neoadjuvant CT (yes/no), and homologous recombination status (deficient/proficient/not determined). Pts received niraparib or PBO once daily. The primary endpoint of PFS assessed by blinded independent central review was analyzed using a stratified Cox proportional hazards model and hierarchically tested in homologous recombination deficient pts, then the overall population. Biomarker subgroup analysis of PFS was a prespecified exploratory analysis, and was performed using a stratified log-rank test and summarized using Kaplan-Meier methodology.

Results: Of 733 randomized pts (niraparib, 487; PBO, 246), 373 (51%) were homologous recombination deficient (niraparib, 247; PBO, 126) and 249 (34%) were homologous recombination proficient (niraparib, 169; PBO, 80). Overall, 35% had stage IV disease, 67% received neoadjuvant CT, and 31% had a PR to 1L CT. Niraparib-treated pts in all the biomarkers groups had a statistically significant and clinically meaningful benefit in PFS (Table). The most common grade ≥3 adverse events were anemia (31%), thrombocytopenia (29%), and neutropenia (13%).

Conclusions: Niraparib improved PFS as evidenced by reduction in the risk of recurrence or death due to any cause in the overall population of advanced ovarian cancer. No new safety signals were identified

Table 1.

Biomarker Subgroup	Hazard Ratio (95% CI)	*P* Value
Overall	0.62 (0.502-0.755)	<0.0001
Homologous recombination deficient	0.43 (0.310-0.588)	<0.0001
*BRCA*mut	0.40 (0.265-0.618)	<0.0001
*BRCA*wt	0.50 (0.305-0.831)	0.0064
Homologous recombination proficient	0.68 (0.492-0.944)	0.0203

mut = mutated; wt – wild type.

Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer

S.N. Han[a], B.J. Monk[b] and A. Gonzalez-Martin[c]. [a]*Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium,* [b]*Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA,* [c]*Grupo Español de Investigación en Cáncer de Ovario (GEICO) and Medical Oncology Department, Clínica Universidad de Navarra, Madrid, Spain*

Objective: Niraparib improves progression-free survival (PFS) in patients with newly diagnosed advanced ovarian cancer after response to first-line platinum-based chemotherapy. We report the key secondary endpoints of the PRIMA/ENGOT-OV26/GOG-3012 study.

Method: This double-blind, placebo-controlled, phase 3 study randomized 733 patients with newly diagnosed advanced ovarian, primary peritoneal, or fallopian tube cancer with a complete or partial response (CR or PR) to first-line platinum-

based chemotherapy. Patients received niraparib or placebo once daily for 36 months or until disease progression. The primary endpoint was PFS assessed by blinded independent central review. TFST and PFS2 were key secondary endpoints.

Results: In the overall population, median TFST was 6.6 months longer in patients receiving niraparib than in patients receiving placebo (HR = 0.65, 95% CI 0.52–0.80, *P* = 0.0001; **Table 1**). In the patients with homologous-deficient tumors, median TFST had not been reached for patients receiving niraparib, compared with 13.7 months in patients receiving placebo (HR = 0.46, 95% CI 0.33–0.64, *P* < 0.0001). In patients with homologous recombination-proficient tumors, the median TFST was 3.7 months longer in patients receiving niraparib than in patients receiving placebo (HR = 0.64, 95% CI 0.46–0.90, *P* < 0.0105). PFS2 data show point estimates HR < 1, as shown in **Table 1** (20% data maturity in overall population).

Conclusion: Preliminary data on TFST and PFS2 were supportive of a clinical benefit of niraparib therapy in a broad population of patients with ovarian cancer following response to first-line chemotherapy.

Table 1.

	Homologous Recombination Deficient		**Homologous Recombination Proficient**		**Overall Population**	
Endpoint	**Niraparib (*n* = 247)**	**Placebo (*n* = 126)**	**Niraparib (*n* = 169)**	**Placebo (*n* = 80)**	**Niraparib (*n* = 487)**	**Placebo (*n* = 246)**
Time to first subsequent therapy (47% data maturity in overall population)						
Median (95% CI) – mo	NE (24.7-NE)	13.7 (11.6-19.3)	11.6 (9.7-14.2)	7.9 (6.6-10.4)	18.6 (15.8-24.7)	12.0 (10.3-13.9)
HR (95% CI)	0.46 (0.33-0.64)		0.64 (0.46-0.90)		(0.65-0.80)	
Progression-free survival 2 (20% data maturity in overall population)						
HR (95% CI)	0.84 (0.49-1.45)		0.56 (0.34-0.91)		0.81 (0.58-1.14)	

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

I. Ray-Coquard. *Centre Léon Bérard and University Claude Bernard and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), Lyon, France*

Maintenance olaparib plus bevacizumab (bev) after platinum-based chemotherapy plus bev in patients (pts) with newly diagnosed advanced high-grade ovarian cancer (HGOC): Efficacy by timing of surgery and residual tumor status in the Phase III PAOLA-1 trial

C. Grimm[a], C. Cropet and I. Ray-Coquard[c]. [a]*Medical University of Vienna, Austria, Vienna, Austria,* [b]*Centre Leon Berard, Lyon, France*

Objective: In the PAOLA-1/ENGOT-ov25 (NCT01844986) trial, the addition of the PARP inhibitor olaparib to bevacizumab (BEV) maintenance therapy following first-line platinum-based chemotherapy plus BEV led to a statistically significant progression-free survival (PFS) benefit in patients with advanced high-grade ovarian cancer (HR = 0.59, 95% CI 0.49–0.72) (Ray-Coquard et al. *Annals Oncol* 2019: abst LBA2_PR). This analysis evaluates olaparib plus BEV efficacy in PAOLA-1 by timing of surgery and presence of residual tumor after surgery.

Method: PAOLA-1 is a randomized, double-blind, phase 3 trial in patients with newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer. Patients had received platinum-based chemotherapy plus BEV and were in clinical complete or partial response. Patients were randomized to olaparib tablets (300 mg bid for up to 24 months) plus BEV (15 mg/kg q3w, for 15 months in total) or placebo plus BEV, stratified by first-line treatment outcome and tumor *BRCA* mutation status. PFS was assessed by investigators and blinded independent central review (modified Response Evaluation Criteria in Solid Tumors [RECIST] v1.1).

Results: A total of 537 patients were randomized to olaparib plus BEV and 269 to placebo plus BEV. Median follow-up was 22.9 months. Of these, 51% and 42% of patients had upfront and interval surgery, respectively, and 60% and 33% had no

residual and residual macroscopic disease, respectively, after surgery regardless of timing (7% of patients had no surgery). For PFS, HR = 0.52 (95% CI 0.40–0.69, median 29.6 vs 18.2 months [olaparib plus BEV placebo plus BEV]) in patients undergoing upfront surgery; HR = 0.66 (0.50–0.87, median 21.4 vs 16.7 months) in patients undergoing interval surgery; HR = 0.54 (0.42–0.71, median 29.6 vs 19.3 months) in patients with no residual macroscopic disease after cytoreductive surgery; and HR = 0.63 (0.47–0.85, median 18.2 vs 12.9 months) in patients with residual macroscopic disease after cytoreductive surgery. Results of analyses combining timing of surgery, residual disease status, and/or disease stage are presented in **Table 1.**

Conclusion: Maintenance olaparib plus BEV improved outcomes compared with BEV alone in patients with newly diagnosed advanced high-grade serous ovarian cancer regardless of the timing of surgery or residual disease status after surgery. However, the magnitude of the PFS benefit is greatest when surgery achieved complete surgical debulking, particularly in the upfront setting.

Table 1.

	Median PFS, months		HR (95% CI)
	Olaparib + bev arm	Placebo + bev arm	*P* value
PFS, investigator-assessed (*n* = 806)	22.1	16.6	0.59 (0.49-0.72) *P* <0.0001
Upfront surgery and no residual disease (*n* = 245)	39.3	22.1	0.47 (0.29-0.75)
Interval surgery and no residual disease (*n* = 238)	22.1	17.7	0.61 (0.41-0.91)
Interval surgery with residual disease (*n* = 100)	18.7	12.3	0.70 (0.41-1.2)
Upfront surgery with residual disease (*n* = 164)	17.6	13.0	0.74 (0.48-1.15)
PFS, assessed by blinded independent central review (*n* = 806)	26.1	18.3	0.63 (0.51-0.77) *P* <0.0001
Stage III pts with upfront surgery and no residual disease (*n* = 211)	NR	24.9	0.45 (0.27-0.75)
Stage III pts with upfront surgery and residual disease or who had received NACT and stage IV pts† (*n* = 595)	22.0	16.6	0.65 (0.51-0.82)

NACT, neoadjuvant chemotherapy; NR, not reached

Population adjusted indirect comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 studies of olaparib with or without bevacizumab, bev alone and placebo in the maintenance treatment of women with newly diagnosed stage III/IV ovarian cancer with BRCA mutation

I.B. Vergote[a], K.N. Moore[b], R. Hettle[c], K. Rhodes[d], M. Ouwens[e] and I. Ray-Coquard[f]. *[a]University Hospital Leuven, Leuven, Belgium, [b]The University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA, [c]AstraZeneca, Cambridge, United Kingdom, [d]AstraZeneca UK, Cambridge, United Kingdom, [e]AstraZeneca, Gothenberg, Sweden, [f]Centre Leon Berard, Lyon, France*

Objective: Our goal was to assess the comparative efficacy of olaparib with versus without bevacizumab, olaparib versus bevacizumab, and bevacizumab versus placebo in the maintenance treatment of newly diagnosed advanced ovarian cancer with *BRCA* mutation.

Method: An unanchored population-adjusted indirect comparison (PAIC) was performed on the endpoint of progression-free survival (PFS) (Response Evaluation Criteria to Solid Tumor [RECIST] version 1.1), according to the study investigator, using individual patient data from the SOLO1 (olaparib versus placebo phase 3 trial and pooled with individual patient data from the *BRCA* mutation subset of the PAOLA-1/ENGOT-ov25 (olaparib plus bevacizumab versus placebo plus bevacizumab) phase 3 trial. Inverse probability of treatment weights was used to match each arm of PAOLA-1 to the SOLO1 cohort, such that key baseline clinical and demographic characteristics were similar across populations. All analyses were performed in patients with complete baseline data. Weighted Cox regression analysis was performed to estimate the comparative efficacy of different treatment strategies and was supplemented by weighted Kaplan-Meier analyses.

Results: Data for 380 patients with complete baseline data from SOLO1 (*n* = 254 olaparib, *n* = 126 placebo) were pooled with data from 222 *BRCA*-mutated patients with complete baseline data in PAOLA-1 (*n* = 151 olaparib plus bevacizumab, *n* = 71 bevacizumab plus plaebo). Prior to matching, PFS at 2 years was 76% olaparib plus bevacizumab, 73% olaparib, 44% bevacizumab, and 36% placebo. The weights allocated to the PAOLA-1 cohort ranged from 0.12 to 3.98 (median 0.88), with an

effective sample size of 166. The matched PAOLA-1 cohort had baseline data comparable to SOLO1, with 85% FIGO stage III, 81% complete response after first-line chemotherapy, and 75% no residual disease after surgery. **Table 1** presents the results of the matched comparison.

Conclusion: The results of the PAIC suggest that the combination of olaparib plus bevacizumab leads to a potentially meaningful improvement in PFS versus olaparib alone in women with *BRCA*-mutated newly diagnosed ovarian cancer. The relative clinical benefit of bevacizumab appears to be additive and consistent across regimens, such that its use leads to a similar level of benefit when combined with olaparib and compared with olaparib alone or used as monotherapy and compared with placebo. Despite matching, the results of this analysis should be viewed with the limitation that it is a nonrandomized comparison.

Table 1. Results of PAIC.

Regimen 1	Regimen 2	Kaplan-Meier estimate of PFS at 24 months for regimen 1 [95% confidence interval]	Kaplan-Meier estimate of PFS at 24 months for regimen 2 [95% confidence interval]	Hazard Ratio for regimen 1 versus regimen 2 [95% confidence interval]**
Olaparib plus bevacizumab*	Olaparib	82% [76% to 89%]	73% [68% to 79%]	0.71 [0.45 to 1.09]
Olaparib	Bevacizumab plus placebo*	73% [68% to 79%]	50% [39% to 64%]	0.48 [0.30 to 0.75]
Bevacizumab plus placebo*	Placebo	50% [39% to 64%]	36% [28% to 45%]	0.65 [0.43 to 0.95]

Table note: *Results based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval versus initial), residual disease status after surgery (yes or no), response to first-line treatment and age to SOLO1; **Confidence intervals generated via bootstrapping.

Integration of veliparib (V) with front-line chemotherapy and maintenance in women with high-grade serous carcinoma of ovarian, fallopian tube, or primary peritoneal origin (HGSC)

R.L. Coleman. *The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Anti-tumor activity of veliparib during combination phase with chemotherapy in velia study

D.M. O'Malley[a], M.A. Bookman[b], K.N. Moore[c], G.F. Fleming[d], M.F. Brady[e], E.M. Swisher[f], C. Aghajanian[g], K.D. Steffensen[h], M. Friedlander[i], A. Okamoto[j], N.M. Spirtos[k], M.S. Shahin[l], T.J. Reid[m], D.M. Sullivan[n], V. Sehgal[n], P.J. Ansell[n], M.H. Dinh[n] and R.L. Coleman[o]. *[a]The Ohio State University, Columbus, OH, USA, [b]Kaiser Permanente Northern California, San Francisco, CA, USA, [c]Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, [d]The University of Chicago Medicine, Chicago, IL, USA, [e]NRG Oncology Statistical and Data Center, Roswell Park Cancer Institute,, Buffalo, NY, USA, [f]University of Washington Medical Center, Seattle, WA, USA, [g]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [h]Vejle University Hospital of Southern Denmark, Vejle, Denmark, [i]Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia, [j]The Jikei University School of Medicine, Tokyo, Japan, [k]Women's Cancer Center, Las Vegas, NV, USA, [l]Abington Jefferson Hospital, Asplundh Cancer Center of Sidney Kimmel Cancer Center,, Willow Grove, PA, USA, [m]University of Cincinnati College of Medicine, Cincinnati, OH, USA, [n]AbbVie Inc., North Chicago, IL, USA, [o]The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Objective: The VELIA study evaluated progression-free survival (PFS) with veliparib added to carboplatin and paclitaxel with and without veliparib maintenance in newly diagnosed high-grade serous ovarian carcinoma (HGSC) patients. As anticipated, few patients experienced PFS events during carboplatin and paclitaxel, and we evaluated other parameters to explore the impact of veliparib during carboplatin and paclitaxel.

Method: Patients with previously untreated stage III–IV HGSC received 6 cycles (21-day interval) of carboplatin and paclitaxel following primary cytoreduction or as neoadjuvant chemotherapy (NACT) with interval cytoreduction. Randomization was 1:1:1: veliparib-throughout, carboplatin and paclitaxel + veliparib then veliparib maintenance; veliparib-combo-only, carboplatin and paclitaxel + veliparib then placebo maintenance; and control, carboplatin and paclitaxel + placebo then

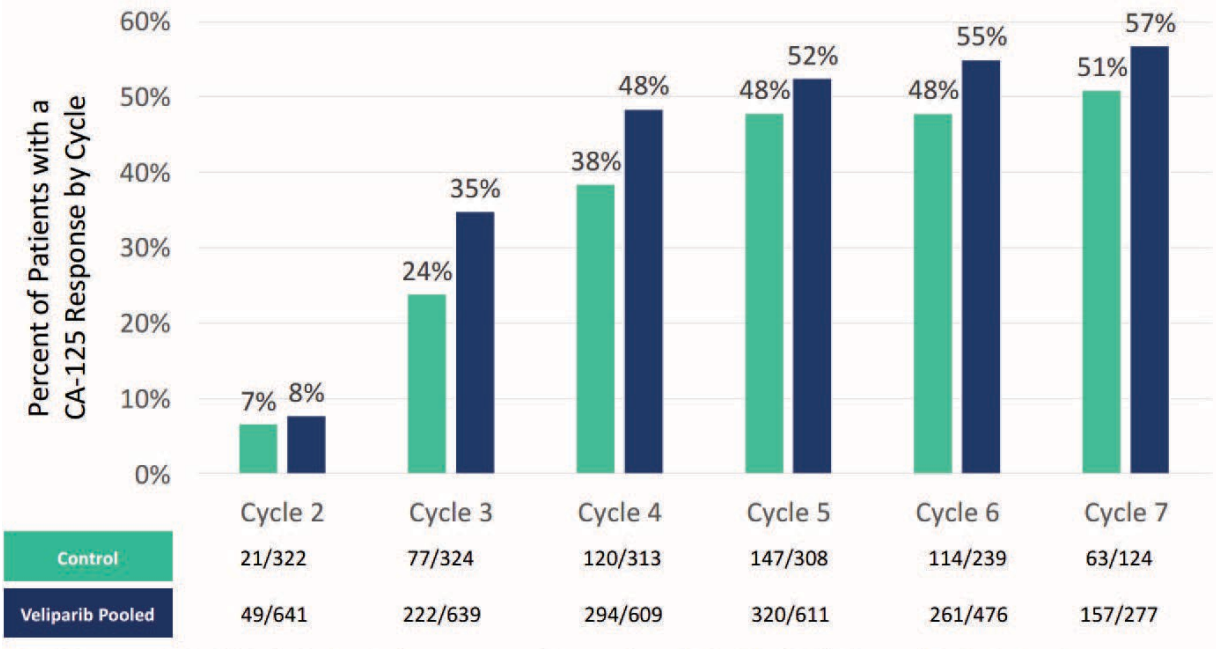
placebo maintenance. These exploratory analyses evaluated responses during the combination phase, as assessed by CA-125 levels (response defined as ≥90% reduction from baseline or normalization) or Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Results: A total of 1,140 patients were enrolled, and 67% underwent primary cytoreduction (stratified prior to randomization). At baseline, the distribution of CA-125 levels was similar across each arm. By cycle 3, more patients receiving veliparib achieved a CA-125 response compared to control (**Figure 1**); a similar trend was seen among patients undergoing NACT. Among patients with measurable disease after primary surgery (*n* = 197), more patients in the veliparib-containing arms had complete response (CR) than those in the control arm.

Conclusion: Veliparib added to frontline carboplatin and paclitaxel during induction resulted in a modest increase in CA-125 responses and CRs in women with newly diagnosed HGSC. These exploratory analyses suggest that veliparib added to carboplatin and paclitaxel during combination phase may provide antitumor activity above carboplatin and paclitaxel alone.

	V-throughout (N=382)	V-combo-only (N=383)	Control (N=375)
Baseline CA-125 > ULN (all evaluable*)	323/377 (86%)	319/376 (85%)	323/369 (86%)
CA-125 response by cycle 3**	121/316 (38%)	101/323 (31%)	77/324 (24%)
CA-125 response by cycle 3 (NAC**)	49/86 (57%)	46/101 (46%)	38/100 (38%)
Complete responses+ (primary surgery with measurable disease)	25/98 (26%)	23/99 (23%)	17/93 (18%)
Stable disease+	8/98 (8%)	9/99 (9%)	18/93 (19%)

*Among those with documented values; missing values at baseline = 5, 7, 6 in each arm, respectively.
**Among those with documented values at baseline and cycle 3.
+RECIST v1.1



CA-125 Response criteria: ≥90% reduction from baseline or return to within normal range (0-35 units/mL); CA-125 measured Day 1 of each cycle.

Fig. 1.