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Phase 2 OVARIO Study of Niraparib + Bevacizumab Therapy in Advanced Ovarian Cancer Following Frontline Platinum-Based Chemotherapy with Bevacizumab

Society of Gynecologic Oncology

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Background

- Niraparib monotherapy improves progression-free survival (PFS) in newly diagnosed, recurrent, and heavily pretreated ovarian cancer (OC) in patients after platinum-based chemotherapy in all biomarker-defined subgroups[1]
- Inhibition of vascular endothelial growth factor (VEGF) can lead to acute hypoxia that can drive genomic instability by altering DNA damage repair pathways, including homologous recombination (HR)[2,3]
- Therefore, it is hypothesized that bevacizumab may sensitize tumors to poly(ADP-ribose) polymerase inhibition (PARPi)
- The PAOLA-1 study demonstrated a significant improvement in PFS for patients receiving bevacizumab + olaparib first-line (1L) maintenance compared with those receiving bevacizumab alone in the intent-to-treat (ITT) cohort, although the hazard ratio (HR) was 1.0 in the homologous recombination deficiency (HRd)-negative/homologous recombination proficiency (HRp) subgroup[4]
- The AVANOVA study (NCT02354131) of niraparib + bevacizumab treatment demonstrated a significant improvement in PFS compared with niraparib alone in patients with recurrent platinum-sensitive OC[5]
  - Adjusted HR, 0.35 (95% CI, 0.21–0.57; *P*<0.0001)
- OVARIO (NCT03326193) is a single-arm, open-label study evaluating niraparib + bevacizumab maintenance treatment in advanced OC after response to 1L platinum-based chemotherapy + bevacizumab

Conclusions

- Preliminary data show that niraparib in combination with bevacizumab has antitumor activity in the overall population and across all biomarker subgroups, consistent with the continuum of clinical benefit observed with monotherapy niraparib maintenance treatment in the PRIMA trial (NCT02655016)
- At the 18-month landmark analysis, 62% of patients in the overall population and 76% in the HRd population remained progression free
- Consistent with other PARPi + bevacizumab studies, the rates of treatment discontinuation are higher for combination therapy than for monotherapy alone
- The safety of niraparib + bevacizumab was consistent with the known side effects of each drug as monotherapy

Poster #[XXX]

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Objectives

- Here we present the primary endpoint of PFS rate at 18 months and safety data from patients enrolled in the OVARIO study

Methods

- All patients with newly diagnosed high-grade serous or endometrioid stage IIIB-IV OC who had a complete response (CR), partial response (PR), or no evidence of disease (NED) after 1L platinum-based chemotherapy + bevacizumab were eligible (Figure 1)
- Patients receiving neoadjuvant chemotherapy (NACT) or primary debulking surgery (PDS) were eligible. All patients underwent tissue testing for HRd or HRp at enrollment
- Bevacizumab dosage was 15 mg/kg Q3W up to 22 cycles, including time on 1L chemotherapy
- Niraparib dosage was 300 or 200 mg QD based on baseline body weight and platelet count (200 mg QD was used in patients <77 kg or <150,000/µL), started within 12 weeks of completing 1L treatment and continued for 3 years or until progressive disease or unacceptable toxicity
- The primary endpoint was PFS rate at 18 months from treatment initiation of niraparib + bevacizumab maintenance

Figure 1. Trial Design

Patients with newly diagnosed high-grade serous or endometrioid stage IIIB to IV epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved a CR, PR, or NED result after frontline platinum-based chemotherapy + bevacizumab

All patients underwent tissue testing for HRd at enrollment

Niraparib (200 or 300 mg QD) + bevacizumab (15 mg/kg Q3W)

Starting niraparib dose, n (%)	N=105
200 mg (<77 kg and/or platelet count <150,000/µL)	82 (78)
300 mg (all others)	23 (22)

Endpoint assessment	
Primary endpoint	• PFS rate at 18 months (PFS18)
Secondary endpoints	• Overall survival • Time to first subsequent therapy • Time to second subsequent therapy • Safety • Patient-reported outcomes • RECIST or CA-125 PFS
Exploratory endpoints	• PFS rate at 6 months (PFS6) and 12 months (PFS12)
Statistical analysis plan	• Efficacy: the proportion will be estimated by frequency analysis, and corresponding 95% exact CI will be reported • KM method will be applied to estimate PFS18 – PFS6 and PFS12 • Progression will be assessed by RECIST v1.1 per investigator

CA-125, cancer antigen 125; CI, confidence interval; CR, complete response; HRd, homologous recombination deficiency; KM, Kaplan–Meier; NED, no evidence of disease; PR, partial response; Q3W, once every 3 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Results

- The study completed enrollment at 105 patients
- Most patients were stage IIIB/IIIC (78%), had serous histology (95%), received NACT (63%), and had CR/NED at the completion of 1L (58%) (Table 1)
- Overall, 47% of patients were HRd, including HRd-*BRCA* mutated and HRd-*BRCA* wild type (wt)

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Results *(cont'd)*

Table 1. Baseline Characteristics and Patient Demographics

Parameter	Overall N=105
Age, years Median (range)	 60.0 (37–82)
Weight, kg Median (range)	 67.7 (43–149)
ECOG, n (%) 0 1	 66 (63) 39 (37)
Stage at diagnosis, n (%) IIIB IIIC IV	 11 (10) 71 (68) 23 (22)
Histological subtype at diagnosis, n (%) Serous Endometrioid Undifferentiated	 100 (95) 4 (4) 1 (1)
Primary tumor site, n (%) Ovarian Fallopian tube Primary peritoneal	 74 (70) 19 (18) 12 (11)
Debulking surgery, n (%) PDS NACT/IDS	 39 (37) 66 (63)
Postsurgery macroscopic residual disease, n (%) Yes No Unknown	 28 (27) 66 (63) 11 (10)
Biomarker status, n (%) HRd *BRCA*m *BRCA*wt HRp HRnd[a]	 49 (47) 29 (28) 16 (15) 38 (36) 18 (17)
History of hypertension, n (%) Yes No	 54 (51) 51 (49)
Response after surgery/platinum-based chemo, n (%) CR/NED PR	 61 (58) 44 (42)

[a]Test inconclusive or failed or insufficient tissue.
chemo, chemotherapy; HRnd, homologous recombination not determined; IDS, interval debulking surgery; m, mutation.

Efficacy

- The niraparib starting dose was 200 mg in 78% of patients
- At 6 and 12 months, PFS rates were 90% and 75% in the overall population, respectively (Table 2)
- At 18 months, the PFS rate was 62% in the overall population and 76% in the HRd population

Table 2. PFS Rate at 6, 12, and 18 Months

Parameter	Overall N=105	HRd n=49	HRp n=38	HRnd n=18
Events at 6 months, n	11	1	7	3
6-month PFS rate, % (95% CI)	90 (82–95)	98 (89–100)	82 (66–92)	83 (59–96)
Events at 12 months, n	26	6	13	7
12-month PFS rate, % (95% CI)	75 (66–83)	88 (75–95)	66 (49–80)	61 (36–83)
Events at 18 months, n	40	12	20	8
18-month PFS rate, % (95% CI)	62 (52–71)	76 (61–87)	47 (31–64)	56 (31–78)

6-, 12-, and 18-month PFS efficacy population (N=105) includes all OVARIO patients dosed ≥6, ≥12, and ≥18 months from the data cutoff dates of August 14, 2019; February 14, 2020; and August 14, 2020 (last patient enrolled February 14, 2019). Median follow-up was 8.6, 12.8, and 16.0 months.

Safety

- 99% of patients experienced a treatment-related treatment-emergent adverse event (TEAE) of any grade; 77% experienced a treatment-related grade ≥3 TEAE (Table 3)
- 27% of patients experienced a treatment-related TEAE that led to treatment discontinuation

Table 3. Treatment-Related TEAE Summary

Parameter, n (%)	Overall N=105
Any TEAE	104 (99)
Any related grade ≥3 TEAE	81 (77)
Any serious TEAE	19 (18)
TEAE leading to niraparib treatment discontinuation	28 (27)
TEAE leading to niraparib dose reduction	77 (73)
TEAE leading to niraparib treatment interruption	89 (85)

Related to niraparib.

- The most common any-grade treatment-related TEAEs were thrombocytopenia (70%), fatigue (57%), anemia (52%), and nausea (52%) (Table 4)
- The most common grade ≥3 treatment-related TEAEs were thrombocytopenia (39%), anemia (34%), and hypertension (27%)

Table 4. Treatment-Related TEAEs in ≥10% of Patients

Preferred term, n (%)	Any grade N=105	Grade ≥3 N=105
Thrombocytopenia[a]	74 (70)	41 (39)
Fatigue	60 (57)	10 (10)
Anemia[a]	55 (52)	36 (34)
Nausea	55 (52)	1 (1)
Hypertension[a]	53 (50)	28 (27)
Proteinuria	41 (39)	5 (5)
Headache	32 (30)	6 (6)
Neutropenia[a]	28 (27)	13 (12)
Leukopenia[a]	24 (23)	0
Epistaxis	20 (19)	0
Vomiting	19 (18)	1 (1)
Dyspnea	16 (15)	1 (1)
Constipation	15 (14)	0
Arthralgia	13 (12)	2 (2)
Decreased appetite	13 (12)	0
Stomatitis	12 (11)	4 (4)
Insomnia	11 (10)	2 (2)

[a]Thrombocytopenia includes platelet count decreased; anemia includes hemoglobin decreased; neutropenia includes neutrophil count decreased; leukopenia includes white blood cell count decreased and eosinophil count decreased; hypertension includes blood pressure increased.

Conflicts of Interest

Dr. Hardesty has nothing to disclose. **Dr. Krivak** reports personal fees from GlaxoSmithKline, Genentech, Clovis, and AstraZeneca. **Dr. Wright** reports she served as PI for a clinical trial for which the institute received payment for conducting the trial from GlaxoSmithKline, Macrogenics, Abbvie, Incyte, Genentech, Novartis, Lilly, Janssen, Astellas, Celgene, AstraZeneca, Bristol Myers/Squibb, Boehringer Ingelheim, Medivation, Merrimack, and Pfizer; and stock ownership at Roche Holdings Ltd., Odonate Therapeutics, Puma Biotech, and Macrogenics. **Dr. Hamilton** reports institutional consulting fees from Pfizer, Genentech/Roche, Lilly, Puma Biotechnology, Daiichi Sankyo, Mersana Therapeutics, Boehringer Ingelheim, AstraZeneca, Novartis, Silverback Therapeutics, Black Diamond, and NanoString; and institutional research/clinical trial support from Seattle Genetics, Puma, AstraZeneca, Hutchinson MediPharma, OncoMed, MedImmune, StemCentrx, Genentech/Roche, Curis, Verastem, Zymeworks, Syndax, Lycera, Rgenix, Novartis, Mersana, Millenium, TapImmune, Lilly, BerGenBio, Medivation, Pfizer, Tesaro, Boehringer Ingelheim, Eisai, H3 Biomedicine, Radius Health, Acerta, Takeda, Macrogenics, Abbvie, Immunomedics, FujiFilm, Effector, Merus, Nucana, Regeneron, Leap Therapeutics, Taiho Pharmaceutical, EMD Serono, Daiichi Sankyo, ArQule, Syros, Clovis, Cytomx, InventisBio, Deciphera, Unum Therapeutics, Sermonix Pharmaceuticals, Sutro, Aravive, Zenith Epigenetics, Arvinas, Harpoon, Fochon, Black Diamond, Orinove, Molecular Templates, Silverback Therapeutics, Compugen, G1Therapeutics, Karyopharm Therapeutics, and Torque Therapeutics. **Dr. Fleming** has nothing to disclose. **Dr. Clements** has nothing to disclose. **Dr. Gray** has nothing to disclose. **Dr. Konecny** reports personal fees from AstraZeneca, Clovis, and GlaxoSmithKline; and institutional grants from Pfizer, Merck, and Lilly. **Dr. Moore** reports personal fees from Fujirebio Diagnostics Inc., Abcodia Inc., and Humphries Pharmaceutical; and institutional grants from Angle Plc. **Dr. Richardson** reports personal fees from Genentech, Mersana, Deciphera, and GlaxoSmithKline. **Drs. Belotte, Keeton, and Chen** are employees of GlaxoSmithKline.