SGO

Society of Gynecologic Oncology

SGO 20/20
VISION FOR THE FUTURE

ANNUAL MEETING ON WOMEN'S CANCER®

MARCH 28-31, 2020 // TORONTO, CANADA

Phase 2 OVARIO Study of Niraparib + Bevacizumab Therapy in Advanced Ovarian Cancer Following Front-Line Platinum-Based Chemotherapy With Bevacizumab

Melissa M. Hardesty,[1] Thomas Krivak,[2] Gail S. Wright,[3] Erika Hamilton,[4] Evelyn L. Fleming,[5] Divya Gupta,[6] Erika Keeton,[6] Jian Chen,[6] Aine Clements,[7] Heidi J. Gray,[8] Gottfried E. Konecny,[9] Richard Moore,[10] Debra Richardson[11]

[1]Alaska Women's Cancer Care, Anchorage, AK, USA; [2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Western Pennsylvania Hospital, Pittsburgh, PA, USA; [3]Florida Cancer Specialists and Research Institute, New Port Richey, FL, USA; [4]Medical Oncology, Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN, USA; [5]Division of Gynecologic Oncology, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [6]GlaxoSmithKline, Waltham, MA, USA; [7]Department of Gynecologic Oncology, Riverside Methodist Hospital, Columbus, OH, USA; [8]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA; [9]University of California Los Angeles, Los Angeles, CA, USA; [10]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [11]Division of Gynecologic Oncology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

SGO 20/20 VISION FOR THE FUTURE

ANNUAL MEETING ON WOMEN'S CANCER®
MARCH 28-31, 2020 // TORONTO, CANADA

SGO Society of Gynecologic Oncology

Disclosures – Dr. Melissa M. Hardesty

Dr. Melissa M. Hardesty has nothing to disclose

Background

- Niraparib is a PARPi approved in the United States and Europe in patients with OC regardless of biomarker status
  - Maintenance treatment for patients with platinum-sensitive recurrent OC who are in complete or partial response to platinum-based chemotherapy[1,2]
  - Based on the QUADRA study results, approved in the United States as treatment for adult patients with advanced OC who have been treated with ≥3 prior chemotherapy regimens and whose cancer is associated with HRd status, defined by either:
    - A deleterious or suspected deleterious *BRCA* mutation, or
    - Genomic instability and progression >6 months after response to the last platinum-based chemotherapy[1,3]

- In patients with newly diagnosed advanced OC, the PRIMA/ENGOT-OV26/GOG-3012 trial showed a significant improvement in PFS for patients receiving niraparib compared with those receiving placebo, regardless of biomarker status (HRd or HRp)[4]

- The PAOLA-1 study demonstrated a significant improvement in PFS for patients receiving bevacizumab + olaparib maintenance compared with those receiving bevacizumab alone in the ITT cohort, although the hazard ratio was 1.0 in the HRd-negative/HRp subgroup[5]

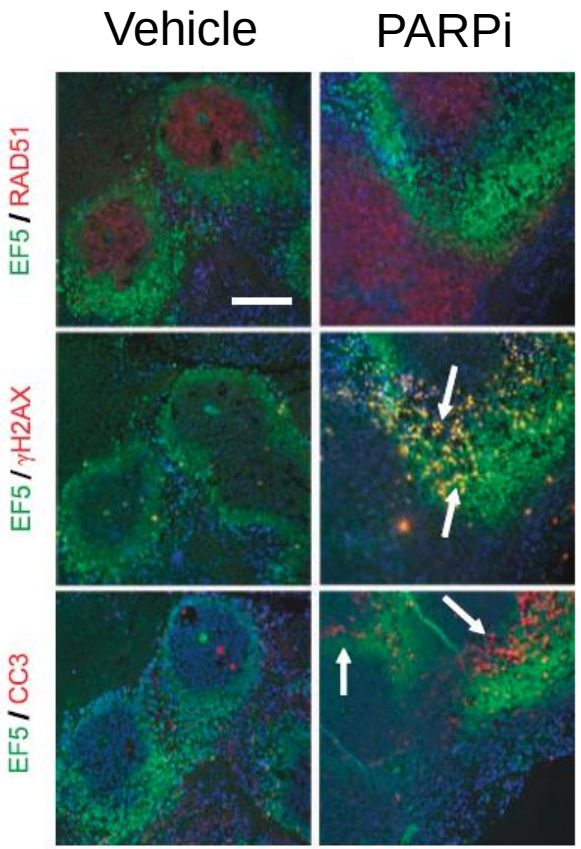
- The AVANOVA study of niraparib + bevacizumab demonstrated a significant improvement in PFS compared with niraparib alone in patients with platinum-sensitive OC[6]
  - Adjusted hazard ratio 0.35 (95% CI 0.21–0.57, P<0.0001)

1. ZEJULA® [prescribing information]. Accessed December 16, 2019; 2. ZEJULA® [EPAR summary for the public]. Accessed December 16, 2019; 3. Moore KN, *Lancet Oncol* 2019;20:636–638; 4. González-Martín A, *N Engl J Med* 2019;381:2391–2402; 5. Ray-Coquard I, *N Engl J Med* 2019;381:2416–2428; 6. Mirza MR, *Lancet Oncol* 2019;20:1409–1419.
CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention-to-treat; OC, ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

Rationale for PARPi + VEGFi

Hypothesis: VEGFi-related hypoxia-induced functional HRd

- Acute hypoxia induces DNA damage and activates the DNA repair pathway[1]
- Chronic hypoxia leads to suppression of HR gene expression (*RAD51*, *BRCA1*) and functional deficiency in DNA repair through HR[1–2]
  - Mechanism linked to promotor methylation; therefore, induced HRd could be durable[3]
- PARP inhibition results in accumulation of damaged DNA in hypoxic tumor regions and triggers cell death[4]
- Combination of PARPi and VEGFi may confer contextual synthetic lethality



PARPi triggers DNA damage/ apoptosis in hypoxic tumor regions
EF5 = hypoxia marker

1. Scanlon SE, *Mol Cancer Res* 2014;12:1016–1028; 2. Bindra RS, *Mol Cell Biol* 2004;24:8504–8518; 3. Lu Y, *Mol Cell Biol* 2011;31:3339–3350; 4. Chan N, *Cancer Res* 2010;70:8045–8054.
HR, homologous recombination; HRd, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

Objectives

- OVARIO (NCT03326193) is a single-arm study evaluating niraparib + bevacizumab combination treatment in advanced OC after response to front-line platinum-based chemotherapy + bevacizumab

- The primary objective of the trial is PFS rate at 18 months, and today we will report the landmark 6 and 12-month PFS rates

- Identify possible new safety signals for niraparib + bevacizumab

OC, ovarian cancer; PFS, progression-free survival.

Trial Design

Patients with newly diagnosed high-grade serous or endometrioid stage IIIB or IV epithelial ovarian, fallopian tube, or peritoneal cancer who achieved a CR, PR, or NED result after front-line 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; PFS, progression-free survival; PR, partial response; Q3W, once every 3 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline Patient Demographics and Characteristics

Parameter	Overall N=105
Age, years	
Median (min–max)	60.0 (37–82)
Weight, kg	
Median (min–max)	67.7 (42.7–149.2)
ECOG, n (%)	
0	66 (63)
1	39 (37)
Stage at diagnosis, n (%)	
IIIA/IIIB	11 (10)
IIIC	72 (69)
IV	22 (21)
Histological subtype at diagnosis, n (%)	
Serous	100 (95)
Endometrioid	4 (4)
Undifferentiated	1 (1)

Parameter	Overall N=105
Biomarker status, n (%)	
HRd	49 (47)
*BRCA*mut	29 (28)
*BRCA*wt	16 (15)
HRp	38 (36)
HRnd*	18 (17)
Neoadjuvant chemotherapy, n (%)	
Yes	66 (63)
No	39 (37)
History of hypertension, n (%)	
Yes	51 (49)
No	54 (51)
Response after surgery/platinum-based CT, n (%)	
CR/NED	66 (63)
PR	39 (37)

*Test inconclusive or failed or insufficient tissue.
CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; mut, mutant; NED, no evidence of disease; PR, partial response; wt, wild-type.

Baseline Patient Demographics and Characteristics

Parameter	Overall N=105
Age, years	
Median (min–max)	60.0 (37–82)
Weight, kg	
Median (min–max)	67.7 (42.7–149.2)
ECOG, n (%)	
0	66 (63)
1	39 (37)
Stage at diagnosis, n (%)	
IIIA/IIIB	11 (10)
IIIC	72 (69)
IV	22 (21)
Histological subtype at diagnosis, n (%)	
Serous	100 (95)
Endometrioid	4 (4)
Undifferentiated	1 (1)

Parameter	Overall N=105
Biomarker status, n (%)	
HRd	49 (47)
*BRCA*mut	29 (28)
*BRCA*wt	16 (15)
HRp	38 (36)
HRnd*	18 (17)
Neoadjuvant chemotherapy, n (%)	
Yes	66 (63)
No	39 (37)
History of hypertension, n (%)	
Yes	51 (49)
No	54 (51)
Response after surgery/platinum-based CT, n (%)	
CR/NED	66 (63)
PR	39 (37)

*Test inconclusive or failed or insufficient tissue.
CR, complete response; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; mut, mutant; NED, no evidence of disease; PR, partial response; wt, wild-type.

PFS Rate at 6 Months and 12 Months

- There is a continuum of benefit of niraparib + bevacizumab in the biomarker subgroups

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)

6- and 12-month PFS efficacy population (N=105) includes all OVARIO patients dosed ≥6 and ≥12 months from data cutoff dates of August 14, 2019, and February 14, 2020 (last patient enrolled February 14, 2019). Median follow-up was 8.6 and 12.8 months.
CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; PFS, progression-free survival.

Treatment-Related TEAE Summary

- No new safety signals were identified

Parameter, n (%)	Overall N=105
Any TEAE	103 (98)
Any related grade ≥3 TEAE	77 (73)
Any serious TEAE	17 (16)
TEAE leading to treatment discontinuation	26 (25)
TEAE leading to dose reduction	75 (71)
TEAE leading to treatment interruption	85 (81)

Related to niraparib.
TEAE, treatment-emergent adverse event.

Any Treatment-Related TEAEs in ≥10% of Patients

Preferred term, n (%)	Any grade N=105	Grade ≥3 N=105
Thrombocytopenia*	74 (70)	39 (37)
Fatigue	59 (56)	9 (9)
Nausea	54 (51)	1 (1)
Anemia*	52 (50)	34 (32)
Hypertension	52 (50)	27 (26)
Proteinuria	40 (38)	3 (3)
Headache	33 (31)	5 (5)
Neutropenia*	29 (28)	13 (12)
Leukopenia*	25 (24)	0
Epistaxis	19 (18)	0
Vomiting	16 (15)	1 (1)
Dyspnea	14 (13)	1 (1)
Constipation	13 (12)	0
Stomatitis	12 (11)	4 (4)
Decreased appetite	12 (11)	0
Arthralgia	12 (11)	2 (2)

*Thrombocytopenia includes platelet count decreased; anemia includes hemoglobin decreased; neutropenia includes neutrophil count decreased; leukopenia includes white blood cell count decreased.
TEAE, treatment-emergent adverse event.

Conclusions

- Preliminary data suggest that niraparib in combination with bevacizumab is efficacious 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
- At the 12-month landmark analysis, 75% of patients in the overall population remained progression free
- Consistent with other PARPi + bevacizumab studies, the rates of treatment discontinuation are higher for combination than for monotherapy alone
- Safety of the niraparib + bevacizumab was consistent with the known side effects of each drug as monotherapy

HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARPi, poly (ADP-ribose) polymerase inhibitor.

Acknowledgments

We sincerely thank patients and their families for participating in this trial

Principal investigator	Affiliation
Robert Morris	Karmanos Cancer Institute
Cara Mathews	Women & Infants Hospital
Nana Tchabo	Morristown Medical Center
Rabbie Hanna	Henry Ford Hospital
Raul Mena	Providence Saint Joseph Medical Center
Prasanthi Ganesa	The Center for Cancer and Blood Disorders
Joanie Hope	Alaska Women's Cancer Care
Timothy Vanderkwaak	Hope Women's Cancer Center
Rodney Rocconi	University of South Alabama
Stephen DePasquale	Chattanooga's Program in Women's Oncology
Kristopher LyBarger	HCA Midwest Health Systems
Eirwen Miller	West Penn Hospital
Donald Paul Seago	St. Dominic-Jackson Memorial
Erin Tuller	University of Missouri Ellis Fischel Cancer Center
Nimesh Nagarsheth	Englewood Hospital and Medical Center
Fadi Kayali	FCS South
Andrea Jewell	Kansas University Medical Center
Paul Kramer	Wellmont Cancer Institute
Heidi Godoy	Vassar Brothers Medical Center
Dana Chase	Arizona Oncology Associates