Long-Term Safety of Niraparib in Patients With Recurrent Ovarian Cancer: Results From the ENGOT-OV16/NOVA Trial

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BACKGROUND

- Niraparib is a selective poly(ADP-ribose) polymerase (PARP) 1/2 inhibitor approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy[1,2]
- In the pivotal phase 3 ENGOT-OV16/NOVA trial, niraparib significantly improved progression-free survival (PFS) in patients with recurrent ovarian cancer regardless of germline *BRCA* mutation (g*BRCA*mut) (**Figure 1**)[3] or homologous recombination deficiency status
- All patients in the ENGOT-OV16/NOVA trial started niraparib at a fixed dose of 300 mg once daily
- The dose reduction rate due to treatment-emergent adverse events (TEAEs) was 68.9%
  - Most dose reductions occurred during the first 3 months of treatment
  - Dose reductions did not appear to compromise efficacy[4]
- The discontinuation rate due to TEAEs was 14.7%, including 3.3% due to thrombocytopenia[4]
- Quality-of-life (QoL) measures for patients receiving niraparib showed no QoL impairment, regardless of g*BRCA*mut status, relative to patients receiving placebo[5]
- Long-term tolerability, which is crucial in the maintenance setting, has yet to be adequately studied for niraparib

OBJECTIVES

- To determine the long-term tolerability of niraparib, we assessed the incidence of TEAEs among patients receiving niraparib for up to 3.5 years in the ENGOT-OV16/NOVA trial

METHODS

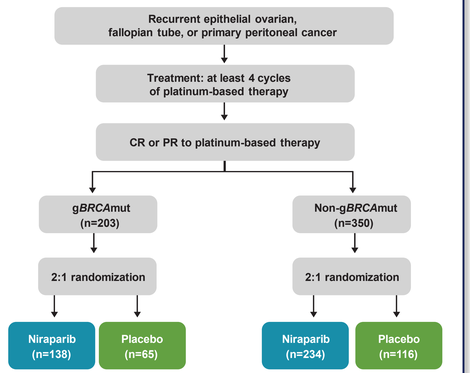
Study Design

- The ENGOT-OV16/NOVA trial (NCT01847274) was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of niraparib for the treatment of patients with platinum-sensitive ovarian cancer (**Figure 1**)

Patients

- Eligible patients were randomized 2:1 to receive niraparib 300 mg once daily or matched placebo in independent g*BRCA*mut or non-g*BRCA*mut cohorts
- The incidence of TEAEs was assessed by intervals of 0–3 months (when most dose reductions to 200 mg or 100 mg occurred), 3–12 months, 1–2 years, and 2–4 years

Figure 1. ENGOT-OV16/NOVA Trial Design



CR=complete response; PR=partial response; g*BRCA*mut=germline *BRCA* mutation.

RESULTS

- Of 553 patients enrolled, 203 were assigned to the g*BRCA*mut cohort and 350 were assigned to the non-g*BRCA*mut cohort (**Table 1**)
- Mean and median duration of exposure:
  - 16 and 13 months (range, 0–41 months) for niraparib and placebo, respectively, in the g*BRCA*mut cohort (n=136)
  - 11 and 7 months (range, 0–41 months) for niraparib and placebo, respectively, in the non-g*BRCA*mut cohort (n=231)

Table 1. Patient Demographics and Baseline Characteristics (Intent-to-Treat Population)

	g*BRCA*mut		Non-g*BRCA*mut	
Characteristic	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)
Age, years				
Median (min, max)	57.0 (36, 83)	58.0 (38, 73)	63.0 (33, 84)	60.5 (34, 82)
Baseline body weight, kg				
Mean	69.91	71.83	69.56	67.99
Median	66.65	69.00	66.11	66.50
Region, n (%)				
USA and Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe and Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
ECOG performance status, n (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Primary tumor site,[a] n (%)				
Ovarian	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneal	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Lines of previous chemotherapy,[a,b] n (%)				
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)
Time to progression after penultimate platinum therapy, n (%)				
6 to <12 months	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy, n (%)				
Complete response	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial response	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Prior bevacizumab use, n (%)				
Yes	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
No	105 (76.1)	48 (73.8)	172 (73.5)	86 (74.1)

[a]Data were missing for 1 patient.
[b]One patient had only 1 prior line of chemotherapy.
ECOG=Eastern Cooperative Oncology Group; g*BRCA*mut=germline *BRCA* mutation.

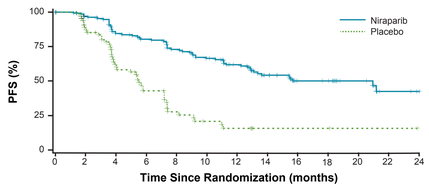
Efficacy

- Patients in both cohorts saw a dramatic improvement in PFS while taking niraparib (**Figure 2**)
- At 1 year, 49% of all patients receiving niraparib were without disease progression/death

Figure 2. PFS in the ENGOT-OV16/NOVA Trial

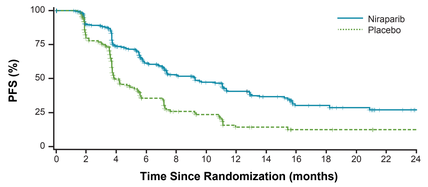
g*BRCA*mut

Treatment	Median PFS, mo (95% CI)	Hazard Ratio (95% CI)	Patients Without Progression or Death	
			12 mo	18 mo
Niraparib (n=138)	21.0 (12.9–NR)	0.27 (0.173–0.410) *P*<0.0001	62%	50%
Placebo (n=65)	5.5 (3.8–7.2)		16%	16%



Non-g*BRCA*mut

Treatment	Median PFS, mo (95% CI)	Hazard Ratio (95% CI)	Patients Without Progression or Death	
			12 mo	18 mo
Niraparib (n=234)	9.3 (7.2–11.2)	0.45 (0.338–0.607) *P*<0.0001	41%	30%
Placebo (n=116)	3.9 (3.7–5.5)		14%	12%



CI=confidence interval; g*BRCA*mut=germline *BRCA* mutation; mo=months; NR=not reached; PFS=progression-free survival.

- Long-term responders: at data cutoff, 39.0% of patients remained on niraparib for >1 year and 18.8% remained on niraparib for >2 years (**Table 2**)

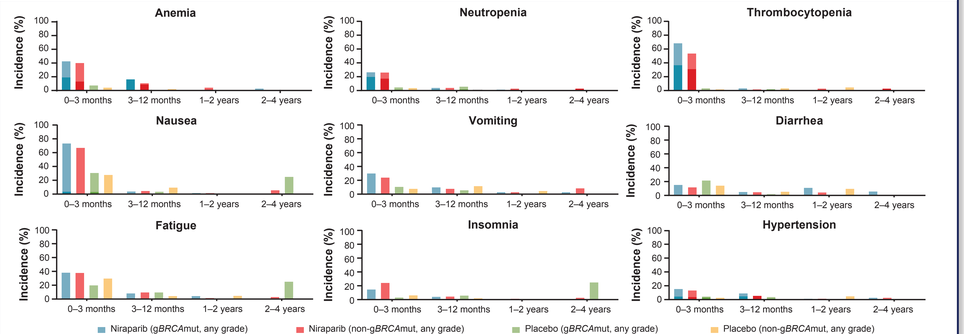
Table 2. Treatment Duration (Safety Population)

	Patients on Treatment, n (%)			
Treatment Arm	0–3 Months	3–12 Months	1–2 Years	2–4 Years
Niraparib	367 (100.0)	298 (81.2)	143 (39.0)	69 (18.8)
Placebo	179 (100.0)	145 (81.0)	31 (17.3)	10 (5.6)

Safety

- Hematologic TEAEs, such as anemia, neutropenia, and thrombocytopenia, occurred more frequently during early treatment
- Similar to other symptomatic TEAEs, these events resolved with dose adjustment within the first 3 months of treatment (**Figure 3**)
- *BRCA* status did not appear to impact TEAE incidence significantly
- The incidence of myelodysplastic syndrome (MDS) was 6 (1.55 cases per 100 patient-years) with niraparib and 1 (0.85 cases per 100 patient-years) with placebo (**Table 3**)
  - In all cases, the onset of MDS occurred after treatment discontinuation:
    - Niraparib: within 1 week to 5 months after discontinuation
    - Placebo: 8 months after discontinuation

Figure 3. TEAE Incidence by g*BRCA*mut Status



g*BRCA*mut=germline *BRCA* mutation; TEAE=treatment-emergent adverse event.

- The incidence of acute myeloid leukemia (AML) was 2 (0.52 cases per 100 patient-years) with niraparib and 1 (0.85 cases per 100 patient-years) with placebo (**Table 3**)
- The incidence of AML/MDS with niraparib was consistent with that of other PARP inhibitors[6,7]; no causal relationship has been established between PARP inhibitors and AML/MDS

Table 3. Incidence of AML and MDS

Incidence	Niraparib (386.8 Patient-years)	Placebo (117.8 Patient-years)
AML		
No. of cases	2	1
Cases per 100 patient-years	0.5	0.8
MDS		
No. of cases	6	1
Cases per 100 patient-years	1.6	0.8

AML=acute myeloid leukemia; MDS=myelodysplastic syndrome.

- Liver transaminase elevations (>5 times the upper limit of normal) were reported in 6 patients (1.6%) receiving niraparib and 3 patients (1.7%) receiving placebo (**Table 4**)
- No patient receiving niraparib had concurrent elevations in transaminase and bilirubin levels (data not shown)

Table 4. Incidence of Transaminase Elevations

Incidence	Niraparib (n=367)	Placebo (N=179)
AST/ALT >3 × ULN		
No. of cases (%)	15 (4.1)	6 (3.4)
AST/ALT >5 × ULN		
No. of cases (%)	6 (1.6)	3 (1.7)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

- Grade ≥3 renal TEAEs were rare (≤1%) regardless of *BRCA* status (**Table 5**)

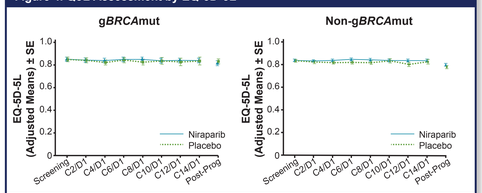
Table 5. Incidence of Renal TEAEs

Incidence	g*BRCA*mut Cohort (n=136)	Non-g*BRCA*mut Cohort (n=231)	Niraparib Arm Total (n=367)
All grades TEAE	66 (48.5%)	90 (38.9%)	156 (42.5%)
Grade ≥3 TEAE*	1 (0.7%)	1 (0.4%)	2 (0.6%)

*Creatinine levels >3 x ULN.
TEAE=treatment-emergent adverse event; ULN=upper limit of normal.

- Baseline QoL (adjusted Health Utilities Index score) was similar among niraparib- and placebo-treated patients (**Figure 4**)[5]
- European Quality of Life Scale, 5-Dimensions (EQ-5D-5L) scores during treatment were similar among niraparib- and placebo-treated patients
  - g*BRCA*mut cohort: niraparib, 0.812; placebo, 0.803
  - Non-g*BRCA*mut cohort: niraparib, 0.845; placebo, 0.828

Figure 4. QoL Assessment by EQ-5D-5L



C=cycle; D=day; EQ-5D-5L=European Quality of Life Scale, 5-Dimensions; g*BRCA*mut=germline *BRCA* mutation; QoL=quality of life; Post-Prog=post-progression; SE=standard error.

CONCLUSIONS

- Hematologic TEAEs occurred more frequently during early treatment and tended to decline after dose adjustments at 3 months
- Liver transaminase elevations and grade ≥3 renal abnormalities were rare during treatment
- Niraparib demonstrated good long-term tolerability in the ENGOT-OV16/NOVA trial, with 39.0% of patients receiving treatment for >1 year and 18.8% receiving treatment for >2 years
- Quality-of-life (QoL) measures for patients receiving niraparib showed no QoL impairment, regardless of g*BRCA*mut status, relative to patients receiving placebo[5]
- These data support the safe long-term use of niraparib for maintenance treatment in recurrent ovarian cancer

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ACKNOWLEDGMENTS

Writing and editorial support, funded by TESARO, Inc. (Waltham, MA, USA) and coordinated by Teodor G. Paunescu, PhD, of TESARO, Inc., were provided by Eric Scocchera, PhD, of Ashfield Healthcare Communications (Middletown, CT, USA) and Adrienne Schreiber of TESARO, Inc.