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Efficacy and safety of niraparib as maintenance treatment in older patients (≥ 70 years) with recurrent ovarian cancer: Results from the ENGOT-OV16/NOVA trial

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HIGHLIGHTS

- Safety and efficacy of niraparib in pts. ≥70 years are similar to younger population.
- Niraparib significantly prolongs PFS in g*BRCA*mut and non-g*BRCA*mut pts. ≥70 years.
- Rates of myelosuppressive adverse events were similar in the <70 and ≥70 age groups.

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ABSTRACT

Objective. To analyze the safety and efficacy of niraparib in patients aged ≥70 years with recurrent ovarian cancer in the ENGOT-OV16/NOVA trial.

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Methods. The trial enrolled 2 independent cohorts with histologically diagnosed recurrent ovarian, fallopian tube, or peritoneal cancer who responded to platinum rechallenge, on the basis of germline breast cancer susceptibility gene mutation (g*BRCA*mut) status. Patients were randomized 2:1 to receive niraparib (300 mg) or placebo once daily until disease progression. The primary endpoint was progression-free survival (PFS) by blinded independent central review. Adverse events (AEs) of special interest were based on the known safety profile of poly(ADP-ribose) polymerase inhibitors.

Results. Patients aged ≥70 years in the g*BRCA*mut cohort receiving niraparib ($n = 14$) had not yet reached a median PFS compared with a median PFS of 3.7 months for the same age group in the placebo arm (hazard ratio [HR], 0.09 [95% confidence interval (CI), 0.01 to 0.73]). Non-g*BRCA*mut patients aged ≥70 years receiving niraparib ($n = 47$) had a median PFS of 11.3 months compared with 3.8 months in the placebo arm (HR, 0.35 [95% CI, 0.18 to 0.71]). Median duration of follow-up in the niraparib arm was 17.3 months in patients ≥70 years and 17.2 months in patients <70 years. Frequency, severity of AEs, and dose reductions in the niraparib arm were similar in patients aged <70 and ≥ 70 years population. The most common grade ≥ 3 AEs in patients ≥70 years were hematologic: thrombocytopenia event (34.4%), anemia event (13.1%), and neutropenia event (16.4%).

Conclusions. For patients ≥70 years of age receiving niraparib as maintenance treatment in the ENGOT-OV16/NOVA trial, PFS benefits and incidence of any grade or serious treatment-emergent AEs were comparable to results in the younger population. Use of niraparib should be considered in this population.

1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related death in women and the leading cause of death from gynecological malignancies [1]. The median age for ovarian cancer diagnosis is 63 years, and approximately one-third of patients with ovarian cancer are ≥70 years [2]. Increased age and factors associated with advanced age (advanced International Federation of Gynecology and Obstetrics [FIGO] stage, comorbid status, and poor tumor cytoreducibility) have been found to be independent prognostic factors of survival for patients with ovarian cancer [3–5].

Studies have shown that older patients are able to tolerate cytoreductive surgery and chemotherapy with safety and efficacy comparable to that of younger patients, with an independent effect of age on survival in older patients receiving standard-of-care treatment [6–9]. National Comprehensive Cancer Network (NCCN) guidelines for older

Table 1
Patient characteristics at baseline by age group and study arm.

Parameter	Niraparib		Placebo	
	Age < 70 y ($n = 311$)	Age ≥ 70 y ($n = 61$)	Age < 70 y ($n = 147$)	Age ≥ 70 y ($n = 34$)
Age, y				
Median	58	74	58	72
Mean (SD)	57.4 (7.74)	74.5 (3.48)	56.8 (7.83)	73.0 (3.29)
Min, max	33, 69	70, 84	34, 69	70, 82
ECOG PS, *n* (%)				
0	211 (67.8)	40 (65.6)	104 (70.7)	22 (64.7)
1	100 (32.2)	21 (34.4)	43 (29.3)	12 (35.3)
Cancer stage (FIGO) at time of initial diagnosis, *n* (%)[a]				
I/II	42 (13.5)	3 (4.9)	10 (6.8)	5 (14.7)
III	221 (71.1)	47 (77.0)	110 (74.8)	22 (64.7)
IV	48 (15.4)	10 (16.4)	26 (17.7)	7 (20.6)
Best response to penultimate platinum-based therapy, *n* (%)[b]				
CR	222 (71.4)	45 (73.8)	110 (74.8)	19 (55.9)
PR	88 (28.3)	15 (24.6)	35 (23.8)	15 (44.1)
Time to progression after penultimate platinum-based therapy, *n* (%)				
6 to <12 mo	117 (37.6)	27 (44.3)	55 (37.4)	15 (44.1)
≥ 12 mo	194 (62.4)	34 (55.7)	92 (62.6)	19 (55.9)
Best response to last platinum-based therapy, *n* (%)				
CR	162 (52.1)	26 (42.6)	79 (53.7)	14 (41.2)
PR	149 (47.9)	35 (57.4)	68 (46.3)	20 (58.8)
Previous bevacizumab use, *n* (%)				
Yes	80 (25.7)	15 (24.6)	36 (24.5)	11 (32.4)
Previous lines of chemotherapy, *n* (%)[c]				
1	1 (0.3)	0	0	0
2	185 (59.5)	40 (65.6)	85 (57.8)	22 (64.7)
>2	125 (40.2)	21 (34.4)	61 (41.5)	12 (35.3)
Previous lines of platinum-based chemotherapy, *n* (%)[c]				
1	1 (0.3)	0	0	0
2	207 (66.6)	46 (75.4)	100 (68.0)	24 (70.6)
>2	103 (33.1)	15 (24.6)	46 (31.3)	10 (29.4)

CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PR, partial response; PS, performance status; SD, standard deviation.

[a] One patient in the niraparib arm was stage 0 at diagnosis.

[b] One patient aged <70 years in the niraparib arm, 1 patient aged ≥70 years in the niraparib arm, and 2 patients aged <70 years in the placebo arm had missing data on best response to penultimate platinum-based therapy.

[c] One patient aged <70 years in the placebo arm had missing data on previous lines of therapy.

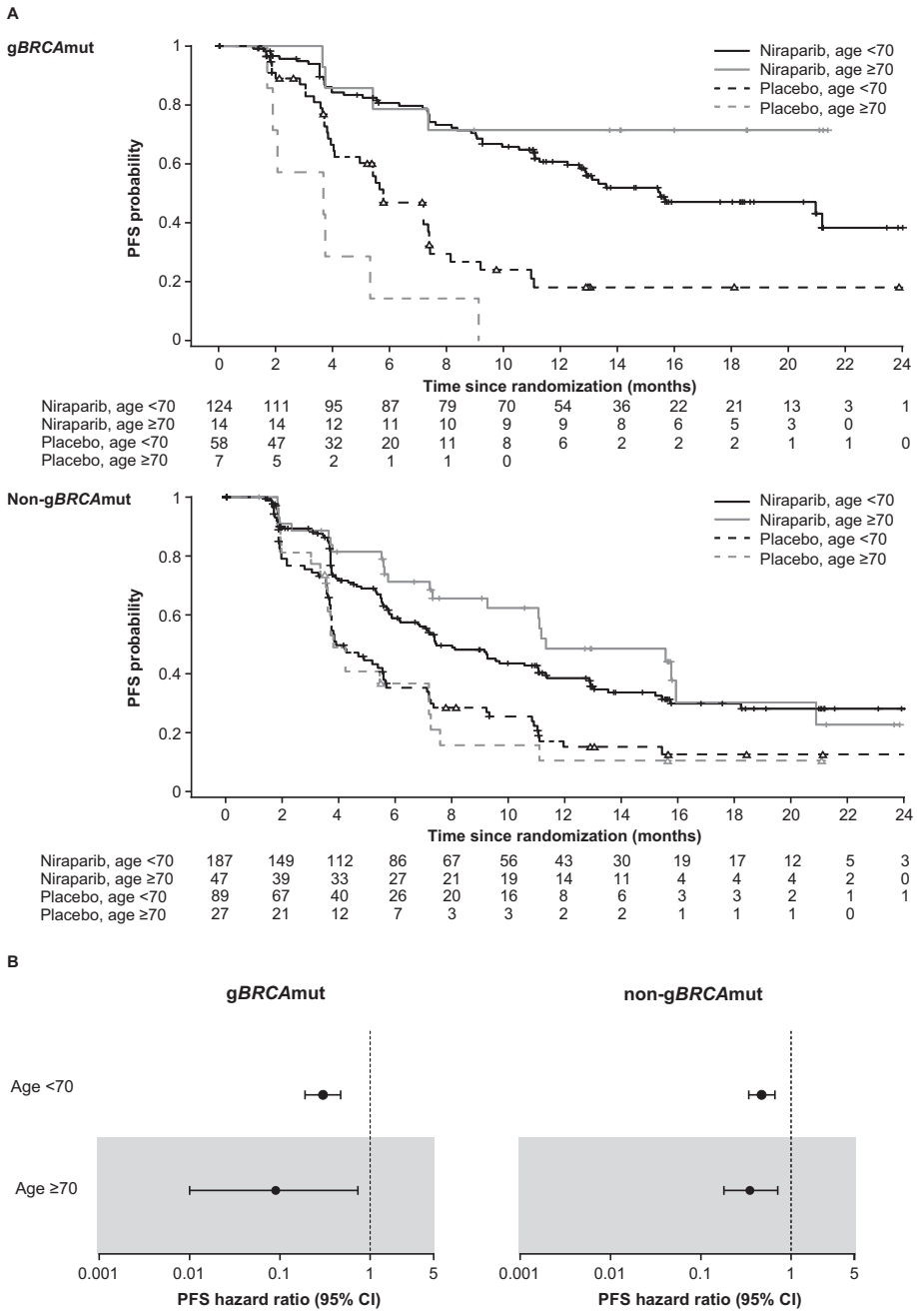

Fig. 1. (A) Progression-free survival with niraparib by treatment arm, age group, and cohort, and (B) hazard ratios by cohort in the niraparib arm by age. CI, confidence interval; g*BRCA*mut, germline breast cancer susceptibility gene mutation; PFS, progression-free survival.

patients (≥65 and ≥ 70 years) recommend the same standard-of-care treatment as for the general population but note that older patients may be at higher risk of severe toxicities and have a higher rate of treatment discontinuation [10].

A recent randomized, placebo-controlled, pivotal phase 3 study conducted in patients with recurrent ovarian cancer (ENGOT-OV16/NOVA; NCT01847274) demonstrated significantly longer progression-free survival (PFS) in patients receiving niraparib than in those receiving placebo [11]. NCCN guidelines recommend maintenance treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor such as niraparib following a complete response (CR) or partial response (PR) to second-line or later treatment with platinum-based chemotherapy.

Hematologic adverse events (AEs) were classified as AEs of special interest (AESI) in the ENGOT-OV16/NOVA study, and they are of particular concern in the older population due to the reduction of hematopoietic reserves in this population [12]. Here we present a retrospective subanalysis on the safety and efficacy of niraparib in the subgroup of patients aged ≥70 years in the ENGOT-OV16/NOVA trial.

2. Patients and methods

The ENGOT-OV16/NOVA study design has previously been published [11]. The ENGOT-OV16/NOVA trial enrolled 2 independent cohorts on the basis of germline breast cancer susceptibility gene mutation (g*BRCA*mut) status (determined by BRAC*Analysis* Testing, Myriad Genetics, Salt Lake City, UT, USA). Patients were at least 18 years of age and had histologically diagnosed recurrent ovarian, fallopian tube, or peritoneal cancer. All patients had disease progression >6 months after completion of their penultimate platinum-based round of chemotherapy. Patients also had to have achieved a CR or PR to their

Table 2
Summary of TEAEs and dose reductions, interruptions, and discontinuations by treatment arm and age.

Characteristic	Niraparib ($n = 367$)		Placebo ($n = 179$)	
	Age < 70 y ($n = 306$)	Age ≥ 70 y ($n = 61$)	Age < 70 y ($n = 145$)	Age ≥ 70 y ($n = 34$)
Median treatment exposure, d	**250.0**		**163.0**	
Median duration of follow-up, mo	17.2	17.3	16.4	16.0
Total number of TEAEs, *n*	5950	1132	1300	235
Any TEAE, *n* (%)	306 (100.0)	61 (100.0)	138 (95.2)	33 (97.1)
Any grade ≥ 3 TEAE, *n* (%)	229 (74.8)	43 (70.5)	32 (22.1)	9 (26.5)
Any serious TEAE, *n* (%)	90 (29.4)	20 (32.8)	20 (13.8)	7 (20.6)
Any TEAE leading to death, *n* (%)	0	0	0	0
Any TEAE leading to dose reduction, *n* (%)	211 (69.0)	42 (68.9)	6 (4.1)	3 (8.8)
Any TEAE leading to dose interruption, *n* (%)	210 (68.6)	34 (55.7)	22 (15.2)	4 (11.8)
Any TEAE leading to treatment discontinuation, *n* (%)	42 (13.7)	12 (19.7)	3 (2.1)	1 (2.9)

TEAE, treatment-emergent adverse event.

last platinum-based chemotherapy prior to being randomized in the study.

Patients in each cohort (g*BRCA*mut and non-g*BRCA*mut) were randomized 2:1 to receive niraparib (300 mg) or placebo once daily until disease progression. Randomization within each cohort was stratified based on time to progression following the penultimate platinum-based regimen, prior use of bevacizumab, and best response (CR or PR) to the last platinum-based regimen. The primary endpoint was duration of PFS as determined by blinded independent central review.

For this analysis, patients were dichotomized according to an age split of <70 or ≥ 70 years based on age at time of study entry. The decision to use 70 as the defining age was based on clinical relevance and established guidelines [10,13]. The objective of this analysis was to evaluate the safety and efficacy of niraparib in older patients. AESI assessed included hematologic toxicities, fatigue, pneumonitis, and overdose. Patient-reported outcomes were examined using the Functional Assessment of Cancer Therapy–Ovarian Symptoms Index (FOSI) and European Quality of Life Five Dimension Five Level Scale (EQ-5D-5L) questionnaires.

Table 3
Grade ≥ 3 treatment-emergent AEs occurring in ≥2% of any group by treatment arm and age.

AE preferred term, *n* (%)	Niraparib ($n = 367$)		Placebo ($n = 179$)	
	Age < 70 y ($n = 306$)	Age ≥ 70 y ($n = 61$)	Age < 70 y ($n = 145$)	Age ≥ 70 y ($n = 34$)
Thrombocytopenia event[a]	103 (33.7)	21 (34.4)	1 (0.7)	0
Anemia event[b]	85 (27.8)	8 (13.1)	0	0
Leukopenia event[c]	67 (21.9)	12 (19.7)	4 (2.8)	0
Neutropenia event[d]	62 (20.3)	10 (16.4)	3 (2.1)	0
Hypertension	26 (8.5)	4 (6.6)	3 (2.1)	1 (2.9)
Fatigue event[e]	25 (8.2)	5 (8.2)	1 (1.7)	0
Gamma-glutamyltransferase increased	12 (3.9)	1 (1.6)	3 (2.1)	0
Nausea	10 (3.3)	1 (1.6)	2 (1.4)	0
Vomiting	6 (2.0)	1 (1.6)	1 (0.7)	0
Hypokalemia	5 (1.6)	0	2 (1.4)	1 (2.9)
Dyspnea	3 (1.0)	1 (1.6)	1 (0.7)	1 (2.9)
Abdominal pain	2 (0.7)	2 (3.3)	3 (2.1)	0
Constipation	2 (0.7)	0	0	1 (2.9)
Hyponatremia	2 (0.7)	2 (3.3)	1 (0.7)	1 (2.9)
Pleural effusion	2 (0.7)	1 (1.6)	0	2 (5.9)
Small intestinal obstruction	2 (0.7)	3 (4.9)	3 (2.1)	2 (5.9)
Ascites	1 (0.3)	0	1 (0.7)	2 (5.9)
Diarrhea	1 (0.3)	0	1 (0.7)	1 (2.9)
Abdominal distension	0	0	0	1 (2.9)
Atrial fibrillation	0	0	0	1 (2.9)
Device-related infection	0	0	0	1 (2.9)
Empyema	0	0	0	1 (2.9)
Ileus	0	0	1 (0.7)	1 (2.9)
Metastases to central nervous system	0	0	1 (0.7)	1 (2.9)
Peripheral sensory neuropathy	0	0	0	1 (2.9)

AE, adverse event.
[a] Includes reports of thrombocytopenia and decreased platelet count.
[b] Includes reports of anemia and decreased hemoglobin counts.
[c] Includes leukopenia, white blood cell count decreased, lymphocyte count decreased, lymphopenia, monocyte count decreased, and neutropenia event.
[d] Includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.
[e] Includes fatigue, malaise, lethargy, and asthenia.

3. Results

3.1. Baseline characteristics

The baseline characteristics of the general population were previously reported [11]. Baseline demographics were generally well balanced between the age groups (Table 1). Of the 553 patients in the study, 95 (17%) were aged ≥70 years and 31 (6%) were aged ≥75 years. The median age in the ≥70 years subgroup was 74 years in the niraparib arm and 72 years in the placebo arm. In both arms, patients aged ≥70 years were more likely to have progressed <12 months after the penultimate platinum-based therapy and to have had a PR to their last platinum-based therapy compared with younger patients.

3.2. Efficacy

The primary efficacy readouts were previously reported [11]. Briefly, maintenance treatment with niraparib extended PFS in both the g*BRCA*mut cohort (hazard ratio [HR], 0.27 [95% confidence interval (CI), 0.17 to 0.41]) and overall non-g*BRCA*mut cohort (HR, 0.45 [95% CI, 0.34 to 0.61]) [11].

In the g*BRCA*mut cohort, patients aged <70 years receiving niraparib had a median PFS of 15.5 months compared with a median PFS of 5.8 months for the same age group in the placebo arm (HR, 0.30 [95% CI, 0.19 to 0.47]; Fig. 1A and B). Patients aged ≥70 years in the g*BRCA*mut cohort receiving niraparib had not yet reached a median PFS compared with a median PFS of 3.7 months for the same age group in the placebo arm (HR, 0.09 [95% CI, 0.01 to 0.73]).

In the non-g*BRCA*mut cohort, patients aged <70 years receiving niraparib had a median PFS of 7.5 months compared with a median PFS of 3.9 months for the same age group in the placebo arm (HR, 0.47 [95% CI, 0.34 to 0.66]; Fig. 1A and B), a 53% reduction in risk of progression. Patients aged ≥70 years in the non-g*BRCA*mut cohort receiving niraparib had a median PFS of 11.3 months compared with a median PFS of 3.8 months for the same age group in the placebo arm (HR, 0.35 [95% CI, 0.18 to 0.71]), a 65% reduction in risk of progression.

3.3. Safety

AEs for the NOVA population by age are summarized in Tables 2, 3, and Supplemental Table S1, and the full list of AEs for the ENGOT-OV16/NOVA study were previously reported [11]. In the niraparib arm, the frequency and severity of serious treatment-emergent AEs (TEAEs) were similar regardless of age (Fig. 2 and Table 2). The most common AEs of any grade were nausea, thrombocytopenia events, fatigue events, anemia events, constipation, and vomiting.

Of the AESI, the incidence of myelosuppression events was higher in the niraparib arm than in the placebo arm but showed no age-related difference (75.5% and 78.7% with niraparib vs. 20.0% and 11.8% with placebo; Supplemental Table S2). In the niraparib arm, thrombocytopenia events were slightly more frequent in patients aged ≥70 years (65.6%) than in those aged <70 years (60.5%), while leukopenia events (32.8% vs. 35.6%), neutropenia events (24.6% vs.

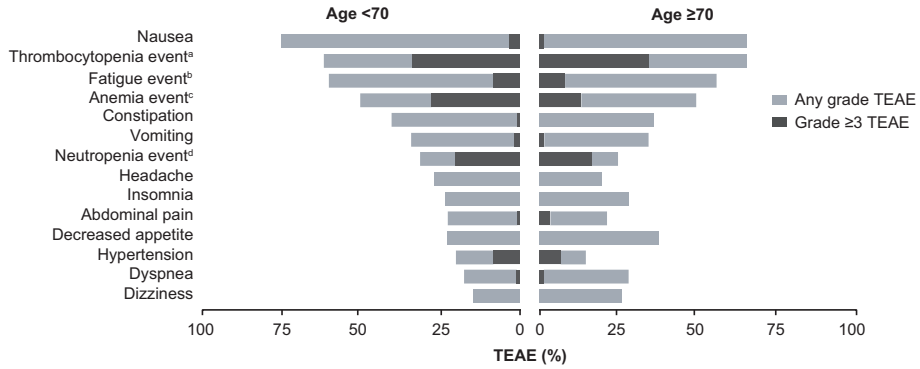

Fig. 2. Most frequent TEAEs in the niraparib arm by age. TEAEs, treatment-emergent adverse events. [a]Includes reports of thrombocytopenia and decreased platelet count; [b]Includes fatigue, malaise, lethargy, and asthenia; [c]Includes reports of anemia and decreased hemoglobin counts; [d]Includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

31.4%), and fatigue events (55.7% vs. 60.1%) were slightly less frequent in patients aged ≥70 years compared with patients aged <70 years (Fig. 3 and Supplemental Table S2). The incidence of anemia events was similar among patients aged ≥70 years (49.2%) and < 70 years (50.3%).

The incidence of grade ≥3 TEAEs was approximately similar for patients in the niraparib arm, regardless of age (≥70 years, 70.5%; <70 years, 74.8%; Table 2). No grade 5 TEAEs were reported in the niraparib or placebo arms. In the niraparib arm, dose reduction rates were similar regardless of age (≈69% in both cohorts; Table 2). Dose interruptions were less common in patients aged ≥70 years (55.7%) than in those aged <70 years (68.6%). By contrast, treatment discontinuations were more common in patients aged ≥70 years (19.7%) than in those aged <70 years (13.7%) (Supplemental Table S3 provides further details on dose discontinuations in patients aged ≥70 years receiving niraparib).

In the niraparib arm, the most common grade ≥3 TEAEs among patients aged ≥70 and <70 years, respectively, were thrombocytopenia events (34.4% and 33.7%; Table 3), anemia events (13.1% and 27.8%), neutropenia events (16.4% and 20.3%), hypertension (6.6% and 8.5%), and fatigue events (8.2% and 8.2%).

3.4. Patient-reported outcomes

Analysis of FOSI scores by age did not reveal any specific quality of life differences in patients aged ≥70 years when compared with patients aged <70 years (Fig. 4). The tendency for great volatility (higher highs, lower lows, and larger wings) is likely due to the smaller group size, as this trend was also evident in patients receiving placebo. EQ-5D-5L utility scores were similar regardless of patient age (Supplemental Table S4).

4. Discussion

The study demonstrates that for older patients receiving niraparib as a maintenance treatment in the ENGOT-OV16/NOVA trial, PFS benefits and the incidence of any grade or serious TEAEs were comparable to the results seen in the younger population. Maintenance treatment with niraparib was associated with hematologic toxicities, but rates of any grade or grade ≥ 3 myelosuppressive TEAEs were similar among patients aged <70 and ≥70 years.

While the ENGOT OV-16/NOVA population comprised patients with both g*BRCA*mut and non-g*BRCA*mut disease, previously published data on the safety of olaparib in older patients are limited to patients with g*BRCA* mutations. In these patients, Dockery et al. reported no special safety concerns in older patients relative to younger patients [14]. Our results with niraparib are concordant with this and further demonstrate the safety of PARP inhibitors in non-g*BRCA*mut patients who tend to be older. This study also provides efficacy data for niraparib in both populations.

A similar analysis that includes both patients with g*BRCA*mut and non-g*BRCA*mut ovarian cancer has been previously published for platinum/taxane chemotherapy in the AGO OVAR-3 study, which found that although rates of hematologic AEs were similar for patients aged <70 and ≥ 70 years, there were significantly more reports of febrile neutropenia among patients aged ≥70 years [8]. We did not find an increase in febrile neutropenia in older patients receiving niraparib.

The use of PARP inhibitors has the potential to increase the chemotherapy-free interval in patients [11,15], which may be advantageous in older patients, who are often unable to receive successive lines of chemotherapy following progression due to comorbidities [7]. In this analysis, two-thirds of discontinuations in patients aged ≥70 years were for grade 1 or 2 AEs. The lower level of treatment interruptions and higher level of discontinuations in patients aged ≥70 years may indicate

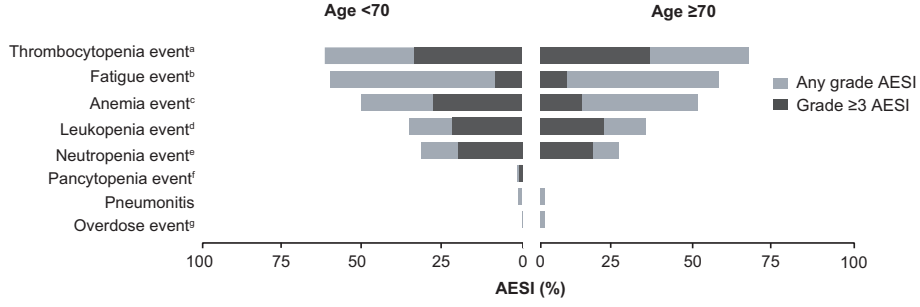

Fig. 3. Incidence of AESI in the niraparib arm by age. AESI, adverse event of special interest. [a]Includes reports of thrombocytopenia and decreased platelet count; [b]Includes fatigue, malaise, lethargy, and asthenia; [c]Includes reports of anemia and decreased hemoglobin counts; [d]Includes leukopenia, white blood cell count decreased, lymphocyte count decreased, lymphopenia, monocyte count decreased, and neutropenia event; [e]Includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; [f]Includes myelodysplastic syndrome and pancytopenia; [g]Includes overdose and accidental overdose.

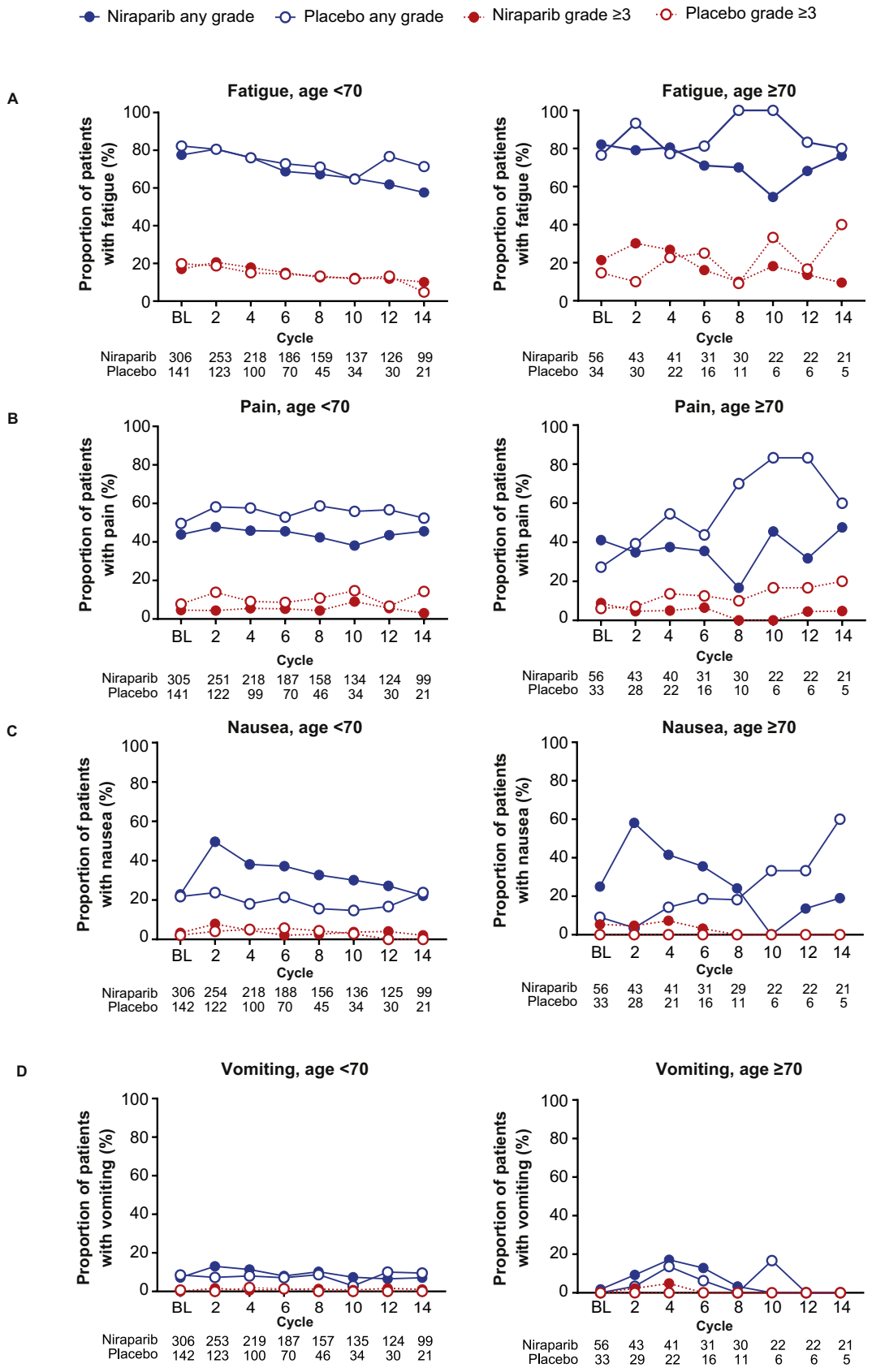

Fig. 4. Individual Functional Assessment of Cancer Therapy–Ovarian Symptoms Index measures over time. Symptoms include (A) fatigue, (B) pain, (C) nausea, (D) vomiting, (E) bloating, (F) cramps, and (G) worry. BL, baseline.

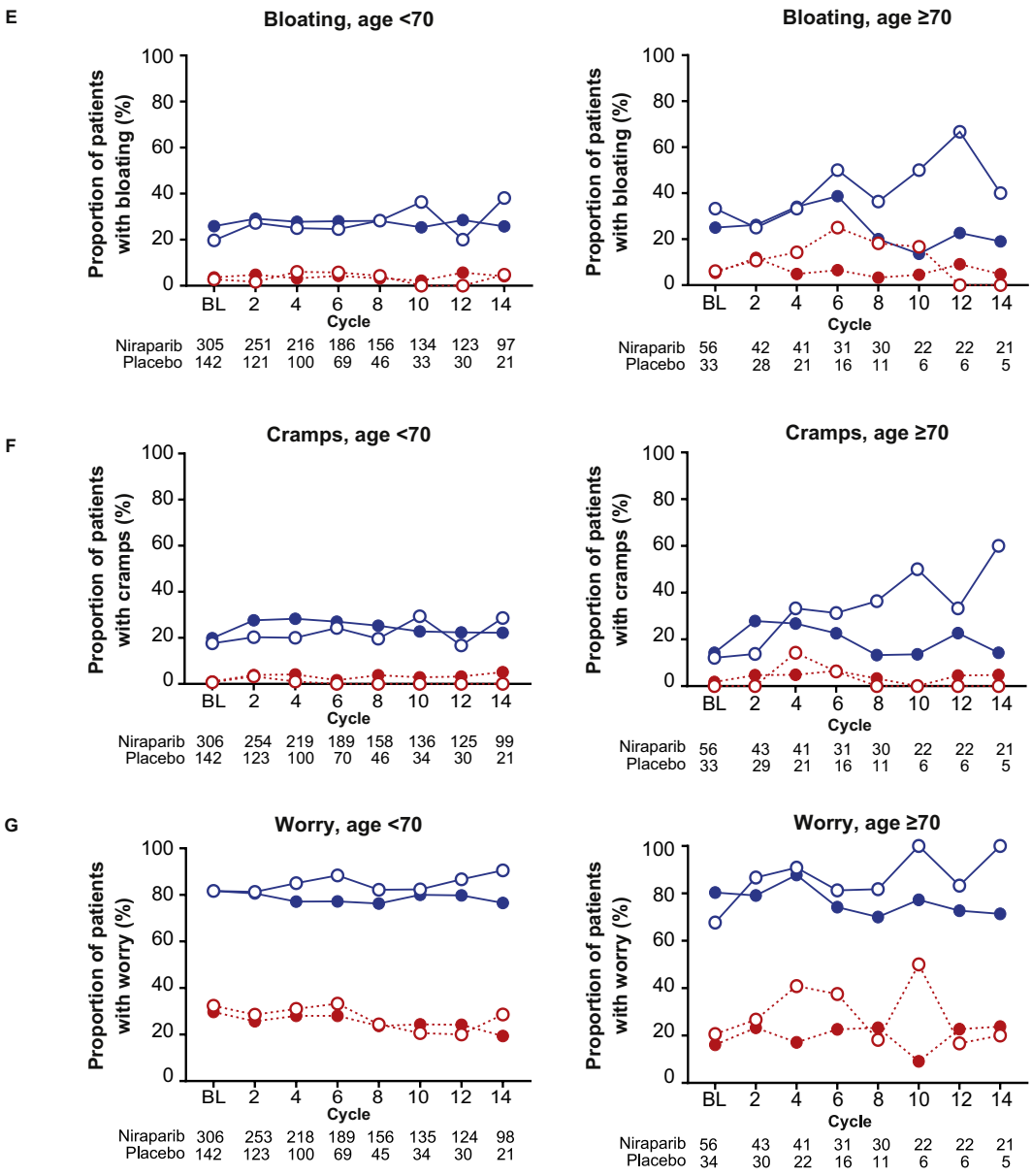

Fig. 4 (*continued*).

an investigator bias toward treatment discontinuations in older patients. A similar pattern suggesting investigator bias in discontinuation rates has previously been noted for doublet chemotherapy in patients aged ≥70 years [8].

In both cohorts, we observed a reduced risk with niraparib in patients aged ≥70 years compared with the younger patients. While this could be associated with a genetic driver, such as the well-known increase in p53 mutations with age [16], this result should be interpreted with caution. The ENGOT-OV16/NOVA trial was not designed with a prespecified geriatric assessment, and there were low numbers of patients ≥70 years of age in either cohort; therefore, the results are descriptive in nature. Further results from real-world treatment of older patients will be necessary to establish any benefit beyond the increased PFS observed in the ENGOT-OV16/NOVA trial.

There are other limitations of this post hoc analysis. Approximately 20% of the ENGOT-OV16/NOVA study population were ≥70 years of age, less than the 30% approximated for the total ovarian cancer population [2]. This discrepancy may be due to a number of factors: clinician bias against referring older patients for clinical trial enrollment, greater incidence of comorbidities in patients ≥70 years of age, and ineligibility for enrollment in this trial due to exclusion criteria. Additionally, patients enrolled in ENGOT-OV16/NOVA were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1, a factor more likely to exclude older patients.

In the ENGOT-OV16/NOVA study, niraparib treatment significantly prolonged PFS in patients with recurrent ovarian cancer. The safety and efficacy of niraparib in patients aged ≥70 years were comparable to the results observed for the younger population. This study provides encouraging results that older patients who meet the criteria for ENGOT-OV16/NOVA can benefit from the same standard-of-care therapy as younger patients.

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Conflict of interest statement

MF: Has nothing to disclose.

KNM: Outside the submitted work reports honorarium/Advisory Boards from TESARO, Inc., Genentech Roche, Clovis, AstraZeneca (for agents not involved in the SOLO-1 study), Immunogen, VBL Therapeutics, and Janssen.

AD: Has nothing to disclose.

AVT: Outside the submitted work reports grants and personal fees from AstraZeneca.

SM: During the conduct of the study: reports grants and personal fees from TESARO, Inc., AstraZeneca, and Roche; personal fees from Clovis. Outside the submitted work: reports grants and personal fees from TESARO, Inc., AstraZeneca, Medac, Merck Sharp & Dohme, PharmaMar, Roche, and Teva; personal fees from Clovis and Sensor Kinesis.

IB: Has nothing to disclose.

SB: Outside the submitted work reports Advisory Boards for TESARO, Inc., Clovis, and AstraZeneca.

GT: Has nothing to disclose.

FG: Has nothing to disclose.

RSF: Has nothing to disclose.

RMW: Outside the submitted work reports grants and personal fees from Genentech and Merck, personal fees from TESARO, Inc., Clovis, Janssen, Mersana, Ovation Diagnostics, and Amgen, and Steering Committee for TapImmune.

KH: Has nothing to disclose.

DP: Outside the submitted work reports consulting/advisory and Speaker's Bureau from AstraZeneca.

PH: During the conduct of the study: reports personal fees from TESARO, Inc. Outside the submitted work: reports personal fees from AstraZeneca, Roche, Lilly, and PharmaMar.

IPV: Outside the submitted work reports personal fees from AstraZeneca, Novartis, and TESARO, Inc. and non-financial support from PharmaMar and Roche.

PF: Outside the submitted work: reports consulting fees from TESARO, Inc. and AstraZeneca and personal fees from Novartis.

MJP: Has nothing to disclose.

MM: Outside the submitted work reports consulting/advisory fees from Clovis Oncology.

SD: Employee and stockholder of TESARO, Inc.

UAM: Outside the submitted work reports consulting/advisory fees from Merck KGaA, Clovis, Geneos, Eli Lilly, and 2x Oncology.

Author contributions

- All authors provided substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work.
- MF drafted the work or revised it critically for important intellectual content.
- All authors provided final approval of the version to be published.

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Appendix A. Supplementary data

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