Atezolizumab Combined With Platinum and Maintenance Niraparib for Recurrent Ovarian Cancer With a Platinum-Free Interval >6 Months: ENGOT-OV41/GEICO 69-O/ANITA Phase III Trial

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ABSTRACT

PURPOSE To evaluate atezolizumab combined with platinum-based chemotherapy (CT) followed by maintenance niraparib for late-relapsing recurrent ovarian cancer.

METHODS The multicenter placebo-controlled double-blind randomized phase III ENGOT-OV41/GEICO 69-O/ANITA trial (ClinicalTrials.gov identifier: NCT03598270) enrolled patients with measurable high-grade serous, endometrioid, or undifferentiated recurrent ovarian cancer who had received one or two previous CT lines (most recent including platinum) and had a treatment-free interval since last platinum (TFIp) of >6 months. Patients were stratified by investigator-selected carboplatin doublet, TFIp, *BRCA* status, and PD-L1 status in de novo biopsy and randomly assigned 1:1 to receive either atezolizumab or placebo throughout standard therapy comprising six cycles of a carboplatin doublet followed (in patients with response/stable disease) by maintenance niraparib until progression. The primary end point was investigator-assessed progression-free survival (PFS) per RECIST v1.1.

RESULTS Between November 2018 and January 2022, 417 patients were randomly assigned (15% *BRCA*-mutated, 36% PD-L1–positive, 66% TFIp >12 months, 11% previous poly [ADP-ribose] polymerase inhibitor after frontline CT, and 53% previous bevacizumab). Median follow-up was 28.6 months (95% CI, 26.6 to 30.5 months). Atezolizumab did not significantly improve PFS (hazard ratio, 0.89 [95% CI, 0.71 to 1.10]; $P = .28$). Median PFS was 11.2 months (95% CI, 10.1 to 12.1 months) with atezolizumab versus 10.1 months (95% CI, 9.2 to 11.2 months) with standard therapy. Subgroup analyses generally showed consistent results, including analyses by PD-L1 status. The objective response rate (ORR) was 45% (95% CI, 39 to 52) with atezolizumab and 43% (95% CI, 36 to 49) with standard therapy. The safety profile was as expected from previous experience of these drugs.

CONCLUSION Combining atezolizumab with CT and maintenance niraparib for late-relapsing recurrent ovarian cancer did not significantly improve PFS or the ORR.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Platinum-based chemotherapy (CT) followed by maintenance therapy with a poly (ADP-ribose) polymerase (PARP) inhibitor if disease responds to CT is an established therapeutic option for patients with late-relapsing high-grade ovarian cancer (defined as relapse >6 months after the last platinum-containing regimen).[1] Three PARP inhibitors (olaparib, niraparib, and rucaparib) have demonstrated significantly improved clinical outcomes when given as maintenance therapy after response to platinum-based CT for PARP inhibitor-naïve late-relapsing recurrent high-grade ovarian cancer in placebo-controlled phase III trials.[2-5] Nevertheless, efforts to improve outcomes further continue.

CONTEXT

Key Objective

Does the addition of atezolizumab to platinum-based chemotherapy (CT) followed by maintenance niraparib improve outcomes for patients with late-relapsing recurrent ovarian cancer? This trial investigates the effect of combining immune checkpoint blockade and poly (ADP-ribose) polymerase inhibition (without bevacizumab) in recurrent ovarian cancer.

Knowledge Generated

Results do not support the use of immune checkpoint blockade in late-relapsing recurrent ovarian cancer, showing no significant improvement in progression-free survival or objective response rate. The safety profile was as expected from previous experience with these drugs.

Relevance *(G. Fleming)*

These data join the body of literature showing a lack of benefit from adding immune checkpoint blockade to CT in the treatment of ovarian cancer regardless of PD-L1 status.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

In many solid tumor types, including endometrial[6-9] and cervical cancers,[10-12] immune checkpoint blockade has shown impressive efficacy and has been integrated into standard regimens, often (but not exclusively) in biomarker-selected populations. In ovarian cancer, however, despite a strong preclinical rationale, previous phase III trials have so far shown no benefit from the addition of a PD-L1 inhibitor (atezolizumab or avelumab) to CT with or without bevacizumab for newly diagnosed or recurrent ovarian cancer.[13-17] None of these trials incorporated PARP inhibitors into either the standard or the experimental arm.

More recently, the DUO-O/ENGOT-Ov46/AGO-OVAR 23/GOG-3025 trial reported improved progression-free survival (PFS) with the addition of durvalumab (anti–PD-L1 agent) and olaparib to frontline CT plus bevacizumab for non–*BRCA*-mutated advanced ovarian cancer compared with CT and bevacizumab (without PARP inhibitor in the control arm).[18] However, the design of the trial does not allow assessment of the contribution of durvalumab to the triplet regimen, and the effect of PARP inhibition and immune checkpoint blockade without bevacizumab remains unknown.

To our knowledge, ENGOT-OV41/GEICO 69-O/ANITA is the first reported phase III trial evaluating an immune checkpoint inhibitor (atezolizumab) with platinum-based CT and PARP inhibitor (niraparib) maintenance in recurrent ovarian cancer with a treatment-free interval since last platinum (TFIp) of >6 months.

METHODS

Study Design

This global randomized double-blind placebo-controlled two-arm phase III trial (ClinicalTrials.gov identifier: NCT03598270) was sponsored by Grupo Español de Investigación en Cáncer ginecológicO (GEICO) and conducted under the auspices of the European Network for Gynaecological Oncological Trial Groups (ENGOT) in Spain, France, Italy, Germany, Belgium, and Israel, according to the guidelines of Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol, informed consent form, other written material given to patients, and any other relevant documentation were approved by the relevant institutional review board or ethics committee at each site.

Patients

Eligible patients had measurable (by RECIST v1.1) high-grade serous, endometrioid, or undifferentiated recurrent ovarian cancer previously treated with one or two previous lines of CT, the last of which must have included platinum with recurrence >6 months after the last dose. Previous PARP inhibitor therapy for recurrent ovarian cancer was not permitted, although patients could have received a PARP inhibitor as maintenance after frontline therapy, provided it was continued for ≥18 months in patients with *BRCA*-mutated ovarian cancer and ≥12 months in those with *BRCA*-wildtype disease. Additional eligibility criteria included known *BRCA* mutational status (either germline or somatic); age ≥18 years; Eastern Cooperative Oncology Group performance status ≤1; and normal organ and bone marrow function. Following a protocol amendment after random assignment of 82 patients (whose PD-L1 status was analyzed in archival tissue), a de novo biopsy collected within 3 months before random assignment was mandatory for all patients for evaluation of PD-L1 status, which was assessed centrally using the VENTANA PD-L1 (SP142) immunohistochemistry assay (VENTANA Medical Systems, Tucson, AZ). PD-L1 status was classified according to the percentage of tumor area with PD-L1–expressing immune cells (ICs) as negative (<1%), positive (≥1%), or noninformative. The percentage of patients

with noninformative PD-L1 status was capped at 10%. All patients provided written informed consent before any trial-specific procedures or treatment.

Procedures

Before random assignment, investigators selected their preferred CT for each individual from one of three options: carboplatin AUC5 on day 1 plus paclitaxel 175 mg/m² once on day 1 every 21 days; carboplatin AUC4 once on day 1 plus gemcitabine 1,000 mg/m² once on days 1 and 8 every 21 days; or carboplatin AUC5 once on day 1 plus pegylated liposomal doxorubicin (PLD) 30 mg/m² once on day 1 every 28 days. Eligible patients were stratified by carboplatin partner (PLD *v* gemcitabine *v* paclitaxel), TFIp (6-12 *v* >12 months), *BRCA* mutation status (mutated *v* nonmutated), and PD-L1 status (IC <1% [PD-L1–negative] *v* IC ≥1% [PD-L1–positive] *v* noninformative) and randomly assigned in a 1:1 ratio to receive six cycles of the selected carboplatin doublet in combination with either placebo or atezolizumab at a dose of 1,200 mg on day 1 every 21 days or 840 mg on days 1 and 15 every 28 days, depending on the CT regimen. Patients with a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1 after six cycles of CT continued with randomized placebo or atezolizumab at a dose of 1,200 mg on day 1 every 21 days, given in combination with maintenance niraparib every day until disease progression. Niraparib was given at an individualized starting dose (300 mg, or 200 mg if baseline weight was <77 kg or baseline platelet count was <150,000 μL). Patients receiving at least four cycles of CT were eligible to start maintenance if toxicity prevented completion of six cycles, provided the disease had not progressed and patients were eligible for niraparib. Maintenance therapy had to be started between 3 and 12 weeks after completing CT.

Tumor imaging was undertaken during screening (within 28 days before random assignment), every 9 weeks during the CT phase, before starting maintenance therapy (to confirm CR, PR, or SD per RECIST after completing at least four cycles of CT), every 12 weeks during maintenance therapy, and (if treatment was discontinued before disease progression) within 30 days after discontinuing study treatment. Thereafter, patients were followed every 12 weeks to collect information on further anticancer therapy, survival, patient-reported outcomes, adverse events (AEs), and tumor assessment in patients who discontinued treatment before disease progression. AEs were recorded at every cycle and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

Outcomes

The primary end point was investigator-assessed PFS in the intention-to-treat (ITT) population, defined as the interval between random assignment and progression determined by RECIST v1.1 or death from any cause. Secondary end points analyzed at the time of the primary analysis included

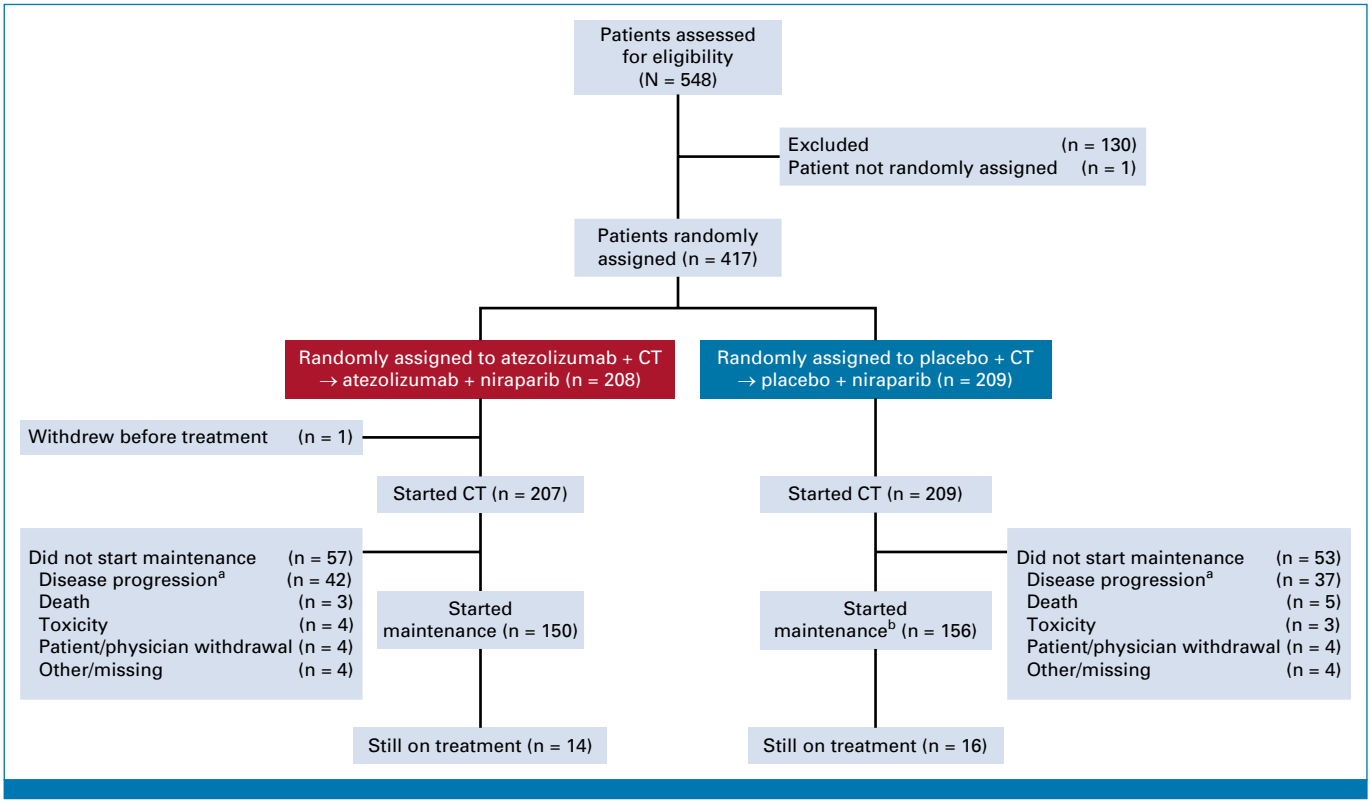

FIG 1. Trial profile. CT, chemotherapy. [a]Radiologic or clinical progression. [b]Seven patients received placebo without niraparib.

TABLE 1. Baseline Characteristics (intention-to-treat population)

Characteristic	Atezolizumab + CT → Atezolizumab + Niraparib (n = 208)	Placebo + CT → Placebo + Niraparib (n = 209)
Age, years, median (range)[a]	63 (37-85)	62 (23-82)
ECOG PS, No. (%)		
0	132 (63)	123 (59)
1	73 (35)	82 (39)
Missing/not available	3 (1)	4 (2)
Race, No. (%)		
White	161 (77)	166 (79)
Latin	5 (2)	0
Arab	2 (1)	1 (<1)
Asian	2 (1)	0
Black	2 (1)	0
Turkish	0	1 (<1)
Missing/not available	36 (17)	41 (20)
Histology, No. (%)		
High-grade serous	187 (90)	196 (94)
High-grade endometrioid	11 (5)	5 (2)
Mixed	7 (3)	5 (2)
Undifferentiated	3 (1)	3 (1)
Previous lines of therapy, No. (%)		
1	181 (87)	179 (86)
2	26 (13)	28 (13)
Missing	1 (4)	2 (1)
Previous therapy,[b] No. (%)		
Bevacizumab	115 (55)	108 (52)
PARP inhibitor	19 (9)	26 (12)
Treatment-free interval since last platinum,[c] No. (%)		
6-12 months	73 (35)	70 (33)
>12 months	135 (65)	139 (67)
BRCA mutation status, No. (%)		
Nonmutated	180 (87)	174 (83)
Mutated	28 (13)	35 (17)
Germline	18 (9)	23 (11)
Somatic	8 (4)	12 (6)
Missing	2 (1)	0
PD-L1 status, No. (%)		
Positive	76 (37)	73 (35)
Negative	117 (56)	112 (54)
Noninformative	14 (7)	21 (10)
Missing	1 (<1)	3 (1)
CT backbone, No. (%)		
PLD	155 (75)	162 (78)
Gemcitabine	33 (16)	30 (14)
Paclitaxel	20 (10)	17 (8)

Abbreviations: CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly (ADP-ribose) polymerase; PLD, pegylated liposomal doxorubicin.
[a]Missing in 14 patients.
[b]Missing in three patients.
[c]As recorded in the interactive web response system.

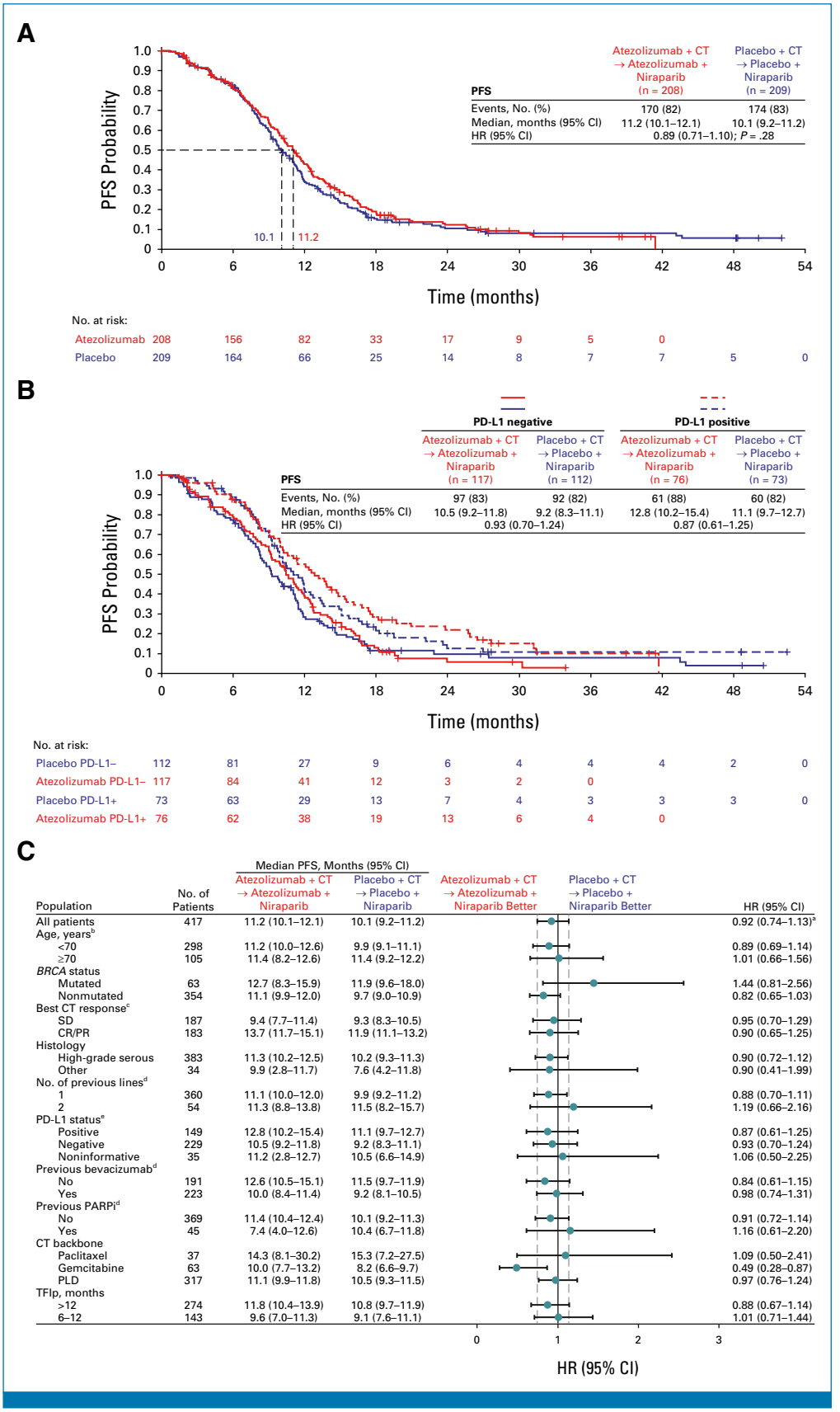

FIG 2. PFS. (A) Intention-to-treat population, (B) by PD-L1 status, and (C) in prespecified subgroups. CR, complete response; CT, chemotherapy; HR, hazard ratio; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, partial response; SD, stable disease; TFIp, treatment-free interval since last platinum. [a]On the basis of univariate (continued on following page)

FIG 2. (Continued). analysis of electronic case report form data, which differed from interactive web response system data in 17 patients (*BRCA* status) and 21 patients (CT backbone). [b]Missing in 14 patients. [c]Missing in one patient, disease progression in 31 patients, not evaluable/not done in 15 patients. [d]Missing in three patients. [e]Missing in four patients.

objective response rate (ORR) assessed by RECIST v1.1 during the CT phase, investigator-assessed PFS from the start of maintenance therapy in all patients starting maintenance therapy, primary and secondary end points in subgroups according to stratification factors, and the occurrence and severity of AEs. Additional secondary end points, which were not analyzed or mature at the time of the primary analysis and will be reported with the final analysis, include duration of response in responding patients, time to first subsequent therapy or death, time to second subsequent therapy or death, time to second progression or death, overall survival (OS), and patient-reported outcomes. The final OS analysis is planned when ≥50% of patients have died or at study closure, whichever occurs first.

Statistical Analysis

The primary PFS analysis was prespecified to occur after PFS events in 332 (80%) of the planned 414 patients. This would provide approximately 90% power at a two-sided alpha of .05 to detect a target hazard ratio (HR) of 0.70, representing an increase in median PFS of 6 months. PFS was compared between treatment groups using a two-sided log-rank test at a 5% level of significance, stratified by the four randomization stratification factors. Treatment HRs were estimated using a stratified Cox proportional hazards model and reported with associated 95% CIs. Kaplan-Meier methodology was used to estimate medians and associated two-sided 95% CIs.

Efficacy was analyzed in the ITT population, comprising all randomly assigned patients analyzed in the group to which they were allocated, regardless of whether they received treatment. Safety was analyzed in the safety-evaluable population, defined as all patients who received at least one dose of study drug and had at least one valid postbaseline safety assessment, with patients analyzed according to the treatment actually received. Safety was analyzed in two separate periods: the CT phase, describing all AEs with onset during the CT phase in patients who received at least one dose of atezolizumab or placebo in the CT phase; and the maintenance phase, describing all AEs occurring from day 1 of maintenance in patients who started maintenance therapy.

RESULTS

Between November 8, 2018, and January 24, 2022, 417 patients enrolled from 68 sites were randomly assigned: 208 to atezolizumab plus CT and 209 to placebo plus CT. All patients except one started CT, 68% completed six cycles of CT, and 73% started maintenance therapy (Fig 1). The most common reason for not starting maintenance therapy was radiologic or clinical disease progression. Seven patients received maintenance placebo without niraparib.

Baseline characteristics were well balanced between treatment groups (Table 1). Most patients had high-grade serous histology (92%) and had received only one previous line of therapy (86%). Approximately two-thirds had a TFIp of >12 months, 15% had *BRCA*-mutated tumors, and approximately one-third had PD-L1-positive tumors. The most commonly selected carboplatin partner was PLD (76% of patients).

At the data cutoff for the primary analysis (July 1, 2023), the median duration of follow-up was 28.6 months (95% CI, 26.6 to 30.5 months); 30 patients remained on treatment,

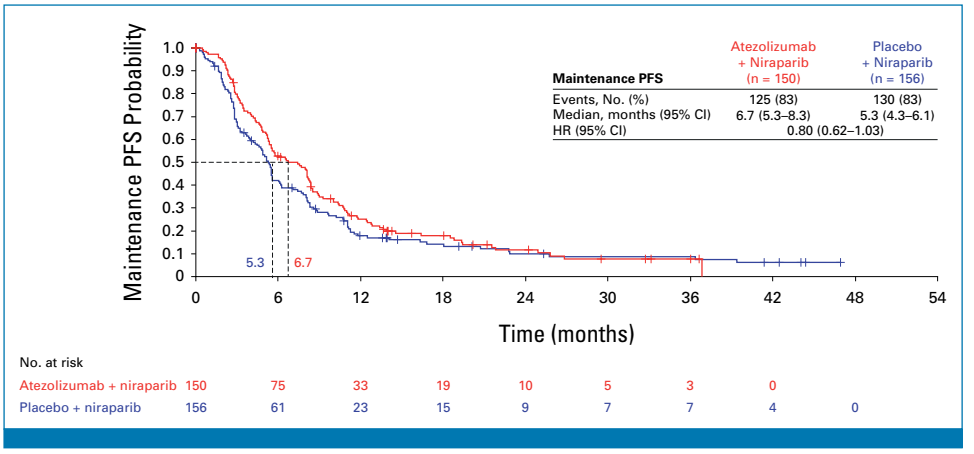

FIG 3. Maintenance PFS from start of maintenance. HR, hazard ratio; PFS, progression-free survival.

balanced between treatment groups. A total of 344 patients (82%) had experienced disease progression or died. The HR for PFS was 0.89 (95% CI, 0.71 to 1.10; stratified log-rank $P = .28$), which did not reach statistical significance (Fig 2A). Median PFS was 11.2 months (95% CI, 10.1 to 12.1 months) with atezolizumab-containing therapy versus 10.1 months (95% CI, 9.2 to 11.2 months) with standard therapy. The 12-month PFS rate was 44% (95% CI, 37 to 51) with atezolizumab-containing therapy and 35% (95% CI, 29 to 42) in the standard arm.

Subgroup analyses according to PD-L1 status (IC ≥1% *v* <1%) showed consistent results, with no clear benefit in the PD-L1–positive population (Fig 2B). As only 31 patients (7% of the ITT population) had IC ≥5% and 12 (3%) had IC ≥10%, meaningful assessment of different cutoffs for PD-L1 positivity was not possible. Subgroup analyses across prespecified subgroups according to age, best response to CT, histology, number of previous lines of therapy, previous bevacizumab exposure, previous PARP inhibitor therapy, and TFIp showed no relevant differences between treatment arms, with 95% CIs for the HR point estimates crossing 1 (Fig 2C). Subgroup analyses according to *BRCA* mutation status and investigator-selected carboplatin partner suggested differing directions of treatment effect, with an HR of 0.49 (95% CI, 0.28 to 0.87) in the small subgroup of patients treated with gemcitabine (Fig 2C). However, exploratory analyses in these subgroups (which were very small in the case of *BRCA* mutation, gemcitabine, and paclitaxel) revealed imbalances in baseline characteristics between subgroups and arms, inconsistent directions of effect for secondary end points, and no clear difference in Kaplan-Meier curves (Data Supplement, Tables S1-S4 and Figs S1 and S2, online only); therefore, these findings should be interpreted with caution.

Among 416 patients with tumor assessment information, the ORRs were 45% (95% CI, 39 to 52) in the atezolizumab group and 43% (95% CI, 36 to 49) in the standard group; CR rates were 7% and 6%, respectively (Data Supplement, Fig S1). An additional 44% and 46% of patients in the atezolizumab and standard groups, respectively, had SD.

Among the 306 patients starting maintenance therapy, 255 (83%, balanced between treatment groups) experienced disease progression or died. The HR for maintenance PFS was 0.80 (95% CI, 0.62 to 1.03). Median maintenance PFS was 6.7 months (95% CI, 5.3 to 8.3 months) in the atezolizumab plus niraparib group versus 5.3 months (95% CI, 4.3 to 6.1 months) in the standard arm (Fig 3).

In both treatment groups, patients received a median of six (range, 1-6) cycles of carboplatin and six cycles of paclitaxel, gemcitabine, or PLD. The proportion of patients receiving all six planned cycles of carboplatin was 63% in both treatment groups, with a slightly lower proportion of patients completing six 4-week cycles of carboplatin in the PLD subgroup (61%-62%) than the gemcitabine (67%) and paclitaxel (70%-77%) subgroups, in which cycles were repeated every 3 weeks.

Similar proportions of patients in the two treatment groups experienced grade ≥3 treatment-related AEs and AEs leading to niraparib dose reduction (Table 2). There were two treatment-related deaths, both in the atezolizumab arm (sepsis due to CT in cycle 1 in one patient, pericarditis and disease progression in one patient). One patient (0.5%) in each arm had myelodysplastic syndrome/acute myeloid leukemia. The higher incidence of immune-mediated AEs with atezolizumab was driven by higher incidences of rash, hypothyroidism, and pruritus (Table 3; Data Supplement, Fig S3). There was no relevant increase in hematologic AEs with atezolizumab in either the CT phase or the maintenance phase (Data Supplement, Table S5).

DISCUSSION

In the randomized phase III ENGOT-OV41/GEICO 69-O/ANITA trial, the addition of atezolizumab to CT and

TABLE 2. Overview of Safety (safety-evaluable population)

AE	Atezolizumab + CT → Atezolizumab + Niraparib (n = 207), No. (%)	Placebo + CT → Placebo + Niraparib (n = 209), No. (%)
Any grade AE	200 (97)	202 (97)
Grade ≥3	156 (75)	154 (74)
Grade ≥3 treatment-related	135 (65)	132 (63)
Serious AE	77 (37)	63 (30)
Immune-mediated AE	47 (23)	19 (9)
AE of special interest for atezolizumab	59 (29)	29 (14)
AE leading to niraparib dose reduction	74/150 (49)	64/149 (43)
AE leading to treatment discontinuation		
Maintenance niraparib	9/150 (6)	18/149 (12)
Maintenance placebo/atezolizumab	10/150 (7)	7/156 (4)

Abbreviations: AE, adverse event; CT, chemotherapy.

maintenance niraparib did not statistically significantly improve clinical outcomes (PFS, ORR, or maintenance PFS) in patients with recurrent ovarian cancer and TFIp of >6 months. There was a modest separation of the maintenance PFS curves, possibly suggesting a later effect of atezolizumab, or an effect in those without early progression. OS results are immature and follow-up is ongoing. In some tumor types, including metastatic triple-negative breast cancer, modest (yet statistically significant) effects on PFS have translated to clinically relevant OS improvement in subsets of patients.[19] To date, however, this has not been seen in ovarian cancer. The HR for OS at the final analysis of the IMagyn050 trial (adding atezolizumab to paclitaxel, carboplatin, and bevacizumab for newly diagnosed disease) was 0.92 (95% CI, 0.78 to 1.09) in the ITT population,[20] almost identical to the PFS HR at the primary analysis (0.92; 95% CI, 0.79 to 1.07).[16] Likewise, in the PD-L1–positive population, the OS HR was 0.83 (95% CI, 0.66 to 1.06), similar to the PFS HR of 0.80 (95% CI, 0.65 to 0.99). In ATALANTE, which assessed the incorporation of atezolizumab into carboplatin- and bevacizumab-based therapy for late-relapsing recurrent disease, the PFS HR was 0.83 (95% CI, 0.69 to 0.99) and the (immature) OS HR was 0.81 (95% CI, 0.65 to 1.01).[15]

Subgroup analyses of the ANITA trial showed no difference in treatment effect according to PD-L1 status. In the *BRCA*-mutated subgroup, median PFS, ORR, and median

TABLE 3. Most Common (>10%) AEs (safety-evaluable population)

	Atezolizumab + CT → Atezolizumab + Niraparib (n = 207), No. (%)		Placebo + CT → Placebo + Niraparib (n = 209), No. (%)	
AE	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anemia	135 (65)	51 (25)	135 (65)	39 (19)
Thrombocytopenia	127 (61)	63 (30)	131 (63)	68 (33)
Nausea	126 (61)	3 (1)	132 (63)	1 (<1)
Asthenia	125 (60)	8 (4)	122 (58)	10 (5)
Neutropenia	121 (58)	86 (42)	137 (66)	95 (45)
Constipation	98 (47)	1 (<1)	95 (45)	3 (1)
Vomiting	61 (29)	10 (5)	62 (30)	5 (2)
Diarrhea	60 (29)	4 (2)	49 (23)	3 (1)
Abdominal pain	55 (27)	3 (1)	52 (25)	4 (2)
Decreased appetite	51 (25)	2 (1)	53 (25)	1 (<1)
Fatigue	45 (22)	1 (<1)	36 (17)	2 (1)
Pyrexia	45 (22)	2 (1)	25 (12)	1 (<1)
Mucosal inflammation	44 (21)	1 (<1)	41 (20)	2 (1)
Rash	40 (19)	4 (2)	23 (11)	1 (<1)
Hypomagnesemia	37 (18)	5 (2)	43 (21)	3 (1)
Headache	36 (17)	0	32 (15)	0
Back pain	34 (16)	1 (<1)	28 (13)	1 (<1)
Abdominal pain upper	33 (16)	0	47 (22)	0
Arthralgia	33 (16)	0	34 (16)	0
Dyspnea	31 (15)	1 (<1)	27 (13)	2 (1)
Hypothyroidism	31 (15)	0	10 (5)	0
Insomnia	30 (14)	0	27 (13)	0
Urinary tract infection	29 (14)	0	23 (11)	1 (<1)
Hypertension	29 (14)	11 (5)	19 (9)	4 (2)
Pruritus	29 (14)	1 (<1)	16 (8)	0
Blood creatinine increased	27 (13)	0	20 (10)	0
Cough	24 (12)	0	21 (10)	0
Palmar-plantar erythrodysesthesia	23 (11)	2 (1)	14 (7)	0
Dysgeusia	23 (11)	0	23 (11)	0
AST increased	22 (11)	1 (<1)	21 (10)	2 (1)
WBC count decreased	19 (9)	8 (4)	24 (11)	10 (5)
Alopecia	16 (8)	0	24 (11)	0

Abbreviations: AE, adverse event; CT, chemotherapy.

maintenance PFS numerically favored atezolizumab-containing therapy, whereas HRs favored the standard arm. Compared with the non–*BRCA*-mutated population, the *BRCA*-mutated population included more patients with previous PARP inhibitor exposure and/or TFIp >12 months. The small patient numbers in this subgroup limit interpretation and may contribute to the apparent discordance. Of note, there was no signal of enhanced benefit from atezolizumab in subgroups with *BRCA* mutation or homologous recombination deficiency in the phase III IMagyn050 trial evaluating atezolizumab in newly diagnosed ovarian cancer,[21] or in the ATALANTE trial in the recurrent setting (although sample sizes were small).[15] In ANITA, there was a suggestion of benefit from atezolizumab among the small subgroup of patients treated with gemcitabine plus carboplatin, but these patients were more heavily pretreated, received a lower median carboplatin dose (inherent in the protocol), and had shorter median PFS and lower ORR than patients in the PLD or paclitaxel subgroups, suggesting some selection bias complicating interpretation.

An important difference between the ANITA trial and the NOVA trial,[4] which established maintenance niraparib as a standard of care in platinum-sensitive ovarian cancer, is that ANITA allowed patients with SD (45% of randomly assigned patients) as well as responding patients to continue to maintenance therapy. By contrast, to be eligible for NOVA, patients had to be in CR or PR after platinum-based CT. This may have contributed to the shorter maintenance PFS in the control arm of the present trial (median 5.3 months compared with 21.0 and 9.3 months in the *BRCA*-mutated and non–*BRCA*-mutated populations, respectively, of the niraparib arm in the NOVA trial). In the present trial, median PFS in both treatment groups was considerably shorter in the subgroup of patients with SD as best response compared with CR or PR.

Combining atezolizumab with standard CT and maintenance niraparib was tolerable, with no new safety signals. Immune-mediated AEs (grade 1/2 rash, hypothyroidism, and pruritus) were increased with atezolizumab, consistent with experience from previous trials of atezolizumab in ovarian cancer (IMagyn050[16] and ATALANTE[15]), and there was a slight increase in fatigue and asthenia during maintenance niraparib. However, niraparib administration was not compromised.

To the best of our knowledge, these are the first results from a trial evaluating the impact of immune checkpoint blockade and PARP inhibition in a randomized trial for ovarian cancer. The DUO-O/ENGOT-Ov46/AGO-OVAR 23/GOG-3025 trial reported improved PFS with the addition of durvalumab and olaparib to frontline CT plus bevacizumab for non–*BRCA*-mutated advanced ovarian cancer.[18] However, the exact contribution of immune checkpoint blockade and PARP inhibition remains unknown as all patients also received bevacizumab in the triplet combination and there was no PARP inhibitor control arm. Despite its disappointing outcomes, the ENGOT-OV41/GEICO 69-O/ANITA trial provides relevant information for interpreting other phase III trials of PD-(L)1 inhibitors and PARP inhibition in ovarian cancer, including the FIRST/ENGOT OV44 (ClinicalTrials.gov identifier: NCT03602859), KEYLYNK-001/ENGOT-ov43 (ClinicalTrials.gov identifier: NCT03740165), and ATHENA/ENGOT-ov45 (ClinicalTrials.gov identifier: NCT03522246) trials evaluating immune checkpoint inhibitors and PARP inhibitors in the frontline setting. Immune checkpoint blockade has shown remarkable efficacy in other gynecologic cancers, but whether it plays a role in ovarian cancer remains to be elucidated.

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Atezolizumab Combined With Platinum and Maintenance Niraparib for Recurrent Ovarian Cancer With a Platinum-Free Interval >6 Months: ENGOT-OV41/GEICO 69-O/ANITA Phase III Trial

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Speakers' Bureau: AstraZeneca, PharmaMar, Roche, GlaxoSmithKline/Tesaro
Expert Testimony: AstraZeneca, GlaxoSmithKline/Tesaro, Roche, PharmaMar, Clovis Oncology
Travel, Accommodations, Expenses: Roche, GlaxoSmithKline/Tesaro

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Speakers' Bureau: Roche/Genentech, Novartis, Pfizer, AstraZeneca, Lilly
Research Funding: Tesaro
Travel, Accommodations, Expenses: Roche/Genentech, Novartis, Tesaro, MSD Oncology, GlaxoSmithKline

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Research Funding: GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: Eisai, AstraZeneca

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Travel, Accommodations, Expenses: Roche, MSD Oncology, GlaxoSmithKline, Teva

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Research Funding: AbbVie (Inst), Advaxis (Inst), Aeterna Zentaris (Inst), Aprea Therapeutics (Inst), Clovis Oncology Inc (Inst), Eisai (Inst), Roche (Inst), Regeneron (Inst), Bristol Myers Squibb International Corporation (BMS) (Inst), Immunogen (Inst), Merck Sharp & Dohme (Inst), Tesaro (Inst), Amgen (Inst), Millennium Pharmaceuticals Inc (Inst), PharmaMar (Inst)
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