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Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39)

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abstract

PURPOSE To evaluate the addition of the humanized monoclonal antiprogrammed death ligand-1 (PD-L1) antibody, atezolizumab, to platinum-based chemotherapy and bevacizumab in newly diagnosed stage III or IV ovarian cancer (OC).

METHODS This multicenter placebo-controlled double-blind randomized phase III trial (ClinicalTrials.gov identifier: NCT03038100) enrolled patients with newly diagnosed untreated International Federation of Gynecology and Obstetrics (FIGO) stage III or IV OC who either had undergone primary cytoreductive surgery with macroscopic residual disease or were planned to receive neoadjuvant chemotherapy and interval surgery. Patients were stratified by FIGO stage, Eastern Cooperative Oncology Group performance status, tumor immune cell PD-L1 staining, and treatment strategy and randomly assigned 1:1 to receive 3-weekly cycles of atezolizumab 1,200 mg or placebo (day 1, cycles 1-22), with paclitaxel plus carboplatin (day 1, cycles 1-6) plus bevacizumab 15 mg/kg (day 1, cycles 2-22), omitting perioperative bevacizumab in neoadjuvant patients. The co-primary end points were investigator-assessed progression-free survival and overall survival in the intention-to-treat and PD-L1–positive populations.

RESULTS Between March 8, 2017, and March 26, 2019, 1,301 patients were enrolled. The median progression-free survival was 19.5 versus 18.4 months with atezolizumab versus placebo, respectively (hazard ratio, 0.92; 95% CI, 0.79 to 1.07; stratified log-rank $P = .28$), in the intention-to-treat population and 20.8 versus 18.5 months, respectively (hazard ratio, 0.80; 95% CI, 0.65 to 0.99; $P = .038$), in the PD-L1–positive population. The interim (immature) overall survival results showed no significant benefit from atezolizumab. The most common grade 3 or 4 adverse events were neutropenia (21% with atezolizumab *v* 21% with placebo), hypertension (18% *v* 20%, respectively), and anemia (12% *v* 12%).

CONCLUSION Current evidence does not support the use of immune checkpoint inhibitors in newly diagnosed OC. Insight from this trial should inform further evaluation of immunotherapy in OC.

ASSOCIATED CONTENT

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Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Epithelial ovarian cancer (OC) is a leading cause of cancer-related mortality among women worldwide: it is estimated that in 2018, there were almost 185,000 deaths from OC globally.[1] Standard-of-care therapy at initial diagnosis includes a combination of cytoreductive surgery and platinum–taxane chemotherapy. Adding the antiangiogenic agent bevacizumab to chemotherapy followed by maintenance bevacizumab significantly improves progression-free survival (PFS) for patients with advanced-stage OC and is a front-line therapy option in many countries, based on the results from the GOG-0218 and ICON7 phase III trials.[2,3] More recently, benefit from poly(ADP-ribose) polymerase (PARP) inhibitors, particularly in patients with *BRCA*-mutant or homologous recombination-deficient (HRD) tumors, has been demonstrated in the SOLO-1,[4] PAOLA-1,[5] PRIMA,[6] and VELIA[7] phase III trials. Nevertheless, there remains room for improvement, particularly in women whose disease is unresponsive to chemotherapy alone or in whom maintenance PARP inhibition has limited benefit.

Atezolizumab, a humanized monoclonal antibody targeting programmed death ligand-1 (PD-L1), has

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CONTEXT

Key Objective

Does adding the antiprogrammed death ligand-1 (PD-L1) antibody atezolizumab to a standard platinum-based chemotherapy regimen plus bevacizumab improve efficacy in patients with newly diagnosed stage III or IV ovarian cancer?

Knowledge Generated

In this placebo-controlled double-blind randomized phase III trial, atezolizumab did not significantly improve progression-free survival in either the intention-to-treat or the PD-L1–positive population. Post hoc exploratory analyses suggested an effect in patients with high PD-L1 expression; further exploration of this observation is warranted.

Relevance

Current evidence does not support adding PD-L1–targeted immune checkpoint inhibitors to the standard-of-care regimen for patients with newly diagnosed ovarian cancer.

demonstrated significantly improved PFS and overall survival (OS) when combined with first-line bevacizumab-containing therapy for non–small-cell lung cancer[8] and with bevacizumab versus single-agent sorafenib in hepatocellular carcinoma.[9] Single-agent atezolizumab demonstrated encouraging activity and tolerability in the PCD4989g study, with sustained responses in OC.[10]

In tumors associated with increased vascular endothelial growth factor production, such as OC, vascular endothelial growth factor blockade may promote T-cell infiltration into the tumor bed and reduce immunosuppression within the tumor microenvironment, providing the rationale to combine immunotherapeutic and antiangiogenic strategies. The atezolizumab and bevacizumab combination demonstrated durable responses and a safety profile consistent with the known effects of the individual agents in a single-arm study (GP28328) in platinum-resistant OC.[11]

IMagyn050 is the first randomized trial to provide efficacy and safety results for the addition of an immune checkpoint inhibitor to standard-of-care bevacizumab-containing therapy in epithelial ovarian, fallopian tube, or primary peritoneal cancer. In the PCD4989g study, responses to single-agent atezolizumab were limited to patients whose tumors showed high PD-L1 expression,[10] whereas responses to atezolizumab plus bevacizumab were seen irrespective of PD-L1 expression in the small OC cohort of the GP28328 study.[11] This provided the rationale to evaluate outcomes in both PD-L1–positive and all-comer populations in IMagyn050. Here, we report the primary results from the IMagyn050 trial.

METHODS

Study Design

This global randomized double-blind placebo-controlled two-arm phase III trial (ClinicalTrials.gov identifier: NCT03038100) was conducted in North and South America, Europe, Asia, and Australia according to the guidelines of Good Clinical Practice and the principles of the Declaration of Helsinki. The Protocol (online only) was approved by institutional review boards or ethics committees at each site.

Patients

Eligible patients had newly diagnosed untreated International Federation of Gynecology and Obstetrics (FIGO) stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer and either had undergone primary cytoreductive surgery resulting in gross (macroscopic or palpable) residual disease or were planned to receive neoadjuvant therapy followed by interval surgery. Additional eligibility criteria included the following: age $\geq$ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; adequate hematologic, renal, and hepatic function; and availability of a representative formalin-fixed paraffin-embedded tumor specimen for evaluation of PD-L1 status before random assignment. Patients with borderline epithelial ovarian tumors, non-epithelial ovarian tumors, or recurrent OC treated with surgery alone were ineligible, as were patients with contraindications for bevacizumab and atezolizumab. All patients provided written informed consent before any trial-specific procedures or treatment.

Procedures

Eligible patients were randomly assigned 1:1, stratified by FIGO stage (III *v* IV), ECOG performance status (0 *v* 1/2), PD-L1 status (PD-L1–expressing immune cells [ICs] as percentage of tumor in $< 1\%$ *v* $\geq 1\%$ [PD-L1–positive], assessed using VENTANA SP142 PD-L1 immunohistochemistry assay [VENTANA Medical Systems, Tucson, AZ]), and treatment strategy (primary cytoreductive surgery *v* neoadjuvant).

In the primary cytoreductive surgery cohort, eligible patients were randomly assigned within 42 days after primary surgery to receive either atezolizumab 1,200 mg or placebo on day 1 of cycles 1-22, combined with paclitaxel

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175 mg/m^2 and carboplatin area under the curve 6 on day 1 during cycles 1-6, and bevacizumab 15 mg/kg on day 1 during cycles 2-22. In the neoadjuvant cohort, eligible patients were randomly assigned before starting study therapy to receive either atezolizumab 1,200 mg or placebo on day 1 of cycles 1-22, both combined with paclitaxel and carboplatin during cycles 1-6 as above. Patients who underwent interval surgery (planned to occur between cycles 3 and 4) omitted both perioperative cycles of bevacizumab. In both cohorts, cycles were repeated every 3 weeks. Treatment was discontinued in the event of disease progression, unacceptable toxicity, or patient or physician decision to discontinue.

PD-L1 expression was determined in the baseline tumor tissue sample collected during primary cytoreductive surgery in the primary surgery cohort and from pretreatment tumor tissue samples in the neoadjuvant cohort. Additional tissue samples were collected at the time of interval surgery in the neoadjuvant cohort. In post hoc exploratory analyses, tumors with $\geq$ 5% PD-L1 IC expression were categorized as PD-L1–positive high. Samples were also evaluated for tumor cell (TC) staining, with $<$ 1% TC staining considered to be PD-L1 TC–negative and $\geq$ 1% TC considered to be PD-L1 TC–positive.

In the primary cytoreductive surgery group, tumors were assessed by computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis within 28 days before random assignment, then every 9 weeks during the concurrent treatment phase, every 12 weeks in the maintenance phase, every 3 months for the first 2 years after completing treatment, and every 6 months for the next 3 years. Thereafter, patients were followed as clinically indicated. Patients in the neoadjuvant cohort followed a similar tumor assessment schedule; however, an additional tumor assessment was performed after interval surgery to determine a new baseline tumor status. The next scan was to be done 9 weeks later. Thereafter, the tumor assessment schedule matched that described for the primary cytoreductive surgery group.

Adverse events (AEs) were recorded at every cycle and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Outcomes

The co-primary end points were investigator-assessed PFS (according to RECIST v1.1) and OS in the intention-to-treat (ITT) population and in the population of patients with PD-L1–positive tumors.

Secondary end points included objective response rate (confirmed complete or partial response according to RECIST v1.1 in patients with measurable residual disease after primary surgery), duration of response in these patients, patient-reported outcomes, and the occurrence and severity of AEs.

Statistical Analysis

The planned sample size was 1,300 patients, calculated based on the number of deaths required to demonstrate improved OS in the PD-L1–positive and ITT populations.

PFS was tested in parallel in the PD-L1–positive and ITT populations (two-sided $P = .002$); OS was tested hierarchically (with the actual alpha spent dependent on the PFS results) first in the PD-L1–positive population; if statistical significance was reached, OS was tested further in the ITT population.[12]

The primary PFS analysis was prespecified to occur after approximately 601 PFS events in the ITT population and 347 PFS events in the PD-L1–positive subgroup. This provides 90% power to detect a PFS improvement with a hazard ratio (HR) of 0.70 in the ITT population and 91% power to detect an HR of 0.62 in the PD-L1–positive population, both with a two-sided significance level of 0.002. The first interim analysis of OS was prespecified to occur at the time of the primary PFS analysis.

PFS and OS were compared between treatment groups using stratified log-rank testing; 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 95% CIs were calculated using Brookmeyer-Crowley methodology.

Efficacy was analyzed in all randomly assigned patients in the relevant populations (ITT and PD-L1–positive). Safety was analyzed in the safety-evaluable population, defined as all randomly assigned patients who received at least one dose of study drug, with patients analyzed according to the treatment actually received.

RESULTS

Between March 8, 2017, and March 26, 2019, 1,301 patients were enrolled and randomly assigned: 651 to atezolizumab plus bevacizumab plus chemotherapy and 650 to placebo plus bevacizumab plus chemotherapy; of these, 784 (60%) had PD-L1–positive tumors. Overall, 1,286 patients received at least one dose of study treatment (Fig 1).

Baseline characteristics were well-balanced between treatment groups in the ITT and PD-L1–positive populations (Table 1).

At the data cutoff for the primary analysis (March 30, 2020), the median duration of follow-up was 19.9 months (interquartile range [IQR], 15.1-23.6 months) in the atezolizumab group and 19.8 months (IQR, 15.4-23.5 months) in the placebo group. In the PD-L1–positive population, the median duration of follow-up was 19.6 months (IQR, 15.1-23.2 months) versus 19.4 months (IQR, 15.4-23.4 months), respectively.

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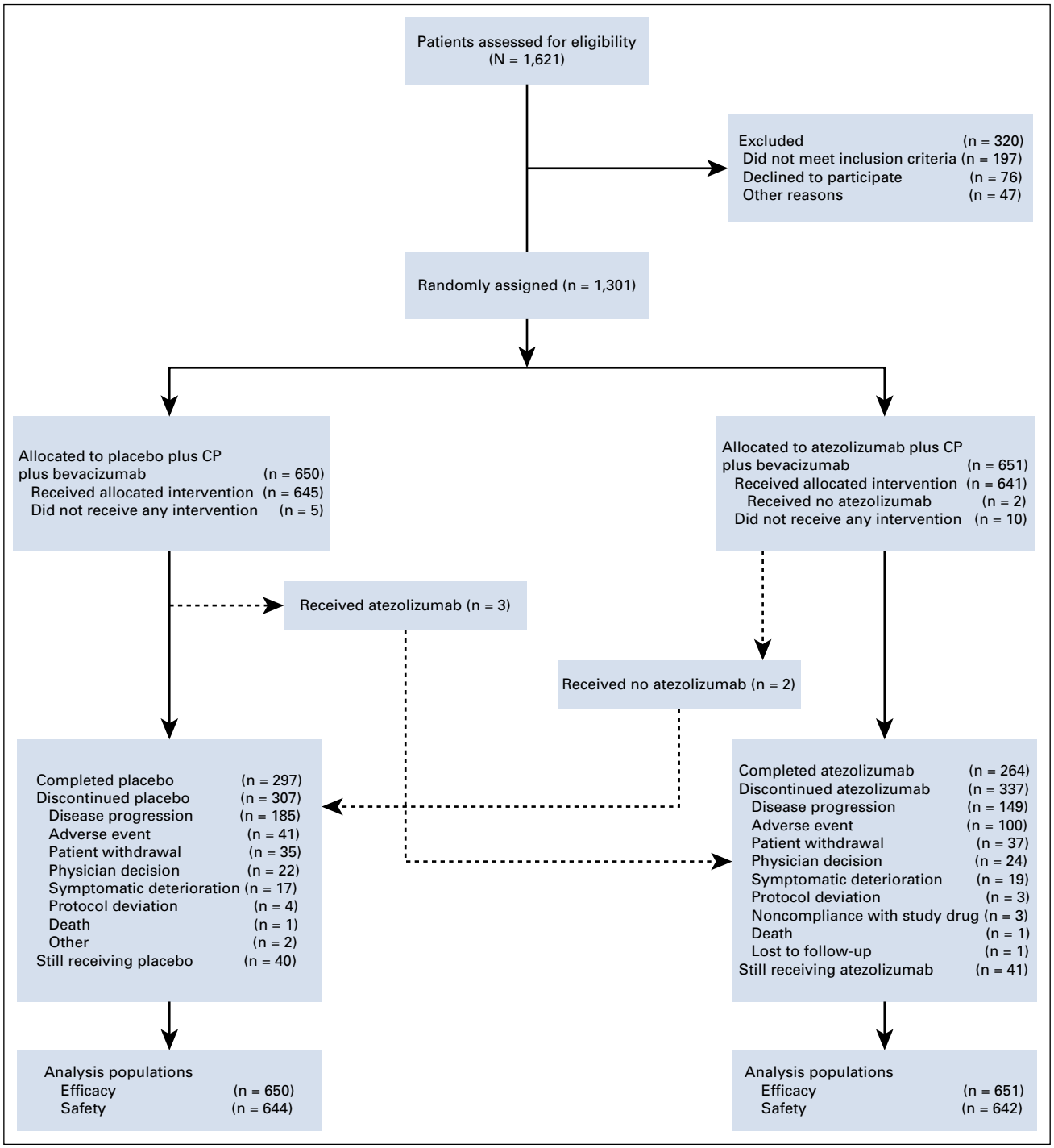


FIG 1. Trial profile. CP, carboplatin plus paclitaxel.

The primary PFS analysis was performed after 664 PFS events had been recorded in the ITT population (323 [50%] atezolizumab-treated patients and 341 [52%] placebo-treated patients). The median PFS was 19.5 months (95% CI, 18.1 to 20.8) with atezolizumab versus 18.4 months (95% CI, 17.2 to 19.8) with placebo. The HR for PFS in the ITT population was 0.92 (95% CI, 0.79 to 1.07, stratified log-rank $P = .28$), which did not reach statistical significance (Fig 2A).

In the PD-L1–positive population, a total of 366 patients had PFS events (167 [43%] atezolizumab-treated and 199 [51%] placebo-treated patients). The median PFS was 20.8 months (95% CI, 19.1 to 24.2) with atezolizumab versus 18.5 months (95% CI, 16.6 to 21.4) with placebo.

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TABLE 1. Baseline Characteristics (ITT Population)

Characteristic	ITT Population		PD-L1–Positive Population	
	Placebo Plus CP Plus Bevacizumab (n = 650)	Atezolizumab Plus CP Plus Bevacizumab (n = 651)	Placebo Plus CP Plus Bevacizumab (n = 393)	Atezolizumab Plus CP Plus Bevacizumab (n = 391)
Median age, years (range)	59 (18-83)	60 (29-84)	60 (18-81)	59 (29-83)
Race				
White	461 (71)	464 (71)	292 (74)	281 (72)
Asian	155 (24)	150 (23)	81 (21)	93 (24)
Black or African American	13 (2)	8 (1)	9 (2)	4 (1)
Other	21 (3)	29 (4)	11 (3)	13 (3)
ECOG PS[a]				
0	353 (54)	355 (55)	225 (57)	226 (58)
1 or 2	297 (46)	296 (45)	168 (43)	165 (42)
Treatment approach[a]				
Neoadjuvant[b]	166 (25)	166 (25)	80 (20)	79 (20)
Primary surgery	484 (74)	485 (75)	313 (80)	312 (80)
PD-L1[a]				
IC < 1%	257 (40)	260 (40)	0	0
IC ≥ 1%	393 (60)	391 (60)	393 (100)	391 (100)
Stage[a,c]				
III	448 (69)	448 (69)	272 (69)	264 (68)
IV	201 (31)	203 (31)	121 (31)	127 (32)
Primary tumor site[c]				
Ovary	474 (73)	491 (75)	277 (70)	290 (74)
Fallopian tube	111 (17)	100 (15)	77 (20)	68 (17)
Primary peritoneal	64 (10)	60 (9)	39 (10)	33 (8)
Histology				
High-grade serous	489 (75)	504 (77)	302 (77)	322 (82)
Low-grade serous	58 (9)	67 (10)	33 (8)	29 (7)
Endometrioid	21 (3)	14 (2)	14 (4)	7 (2)
Grade 3	5 (1)	7 (1)	5 (1)	5 (1)
Grade 2	10 (2)	6 (1)	7 (2)	2 (1)
Grade 1	6 (1)	1 (< 1)	2 (1)	0
Clear cell	22 (3)	29 (4)	10 (3)	15 (4)
Mucinous/ undifferentiated/ mixed/other	60 (9)	37 (6)	34 (9)	18 (5)

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: CP, carboplatin plus paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cell; ITT, intention-to-treat; PD-L1, programmed death ligand-1.

[a]Stratification factor, as recorded in the electronic case report form.

[b]292 patients (88%; 143 [86%] in the atezolizumab arm *v* 149 [90%]) in the neoadjuvant cohort underwent interval surgery, 97% of whom had a re-baseline assessment.

[c]Missing in one patient in the placebo arm.

The HR for PFS in the PD-L1–positive population was 0.80 (95% CI, 0.65 to 0.99; stratified log-rank $P = .038$), which did not reach statistical significance (Fig 2B).

The OS results were immature at the data cutoff for the primary PFS analysis. Deaths had been recorded in 219 patients (17%) in the ITT population and 116 (15%) in the

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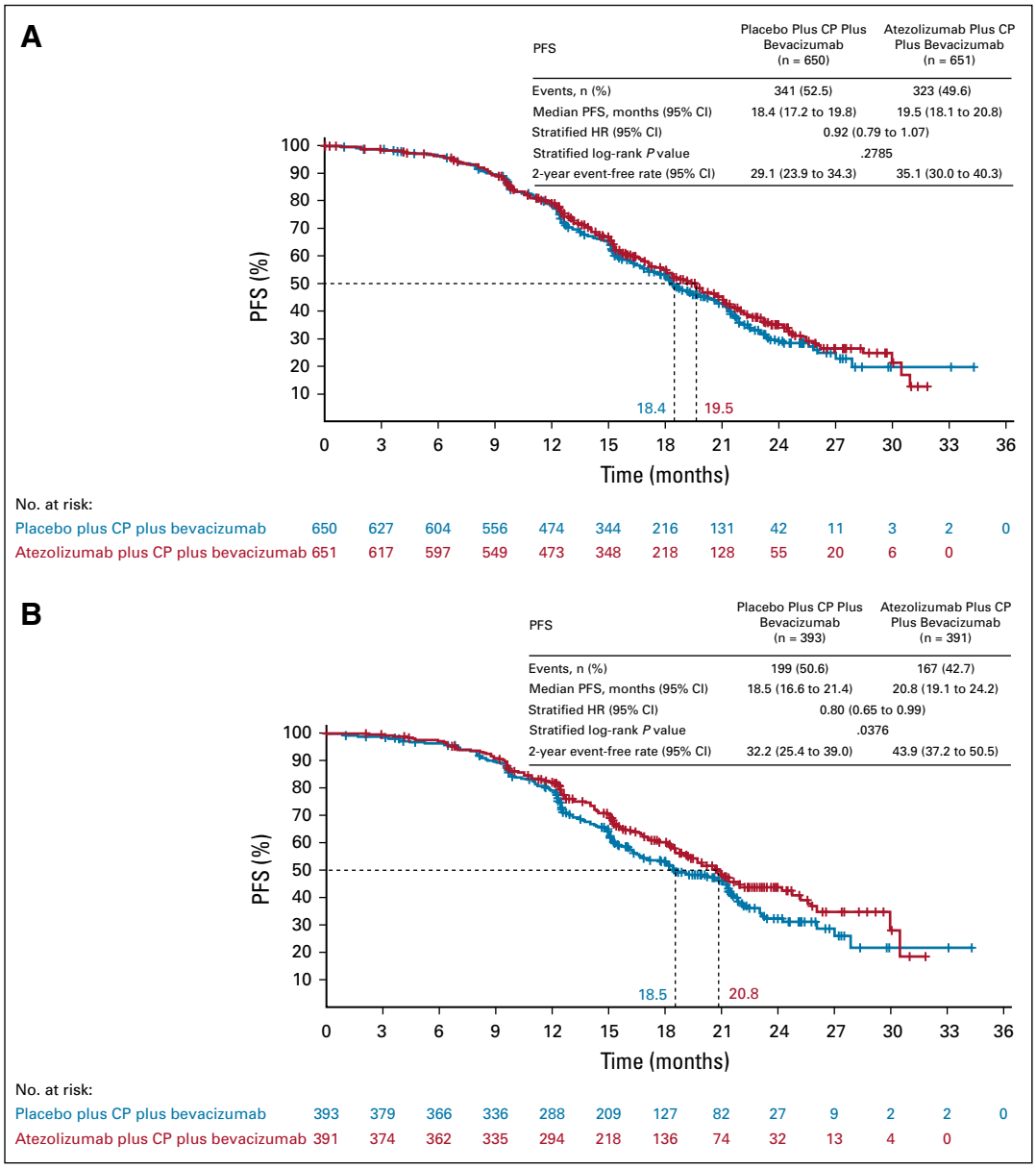


FIG 2. Efficacy: PFS in (A) ITT population and (B) PD-L1+ population; OS in (C) ITT population and (D) PD-L1+ population. CP, carboplatin plus paclitaxel; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

PD-L1–positive population (Figs 2C and 2D). Two-year OS rates were 81% (95% CI, 77 to 84) in atezolizumab-treated patients and 79% (95% CI, 75 to 83) in placebo-treated patients in the ITT population. In the PD-L1–positive population, 2-year OS rates were 82% (95% CI, 77 to 87) with atezolizumab versus 83% (95% CI, 78 to 87) with placebo.

In the ITT population, objective responses were achieved in 233 of 251 response-evaluable patients in the atezolizumab group (93%; 95% CI, 89 to 96) versus 212 of 239 in the placebo group (89%; 95% CI, 84 to 92). In the PD-L1–positive population, objective responses were achieved in 156 of 169 (92%; 95% CI, 87 to 96) and 142 of 158 (90%; 95% CI, 84 to 94) patients, respectively.

Exploratory subgroup analyses of PFS showed generally consistent effects irrespective of baseline characteristics, with the possible exception of FIGO stage (HR, 0.80 [95% CI, 0.67 to 0.97] in patients with stage III disease and 1.24 [95% CI, 0.95 to 1.63] in those with stage IV disease) (Fig 3). In post hoc subgroup analyses according to histologic subtype, the PFS HR was 1.01 (95% CI, 0.84 to 1.20) in patients with high-grade serous histology, representing

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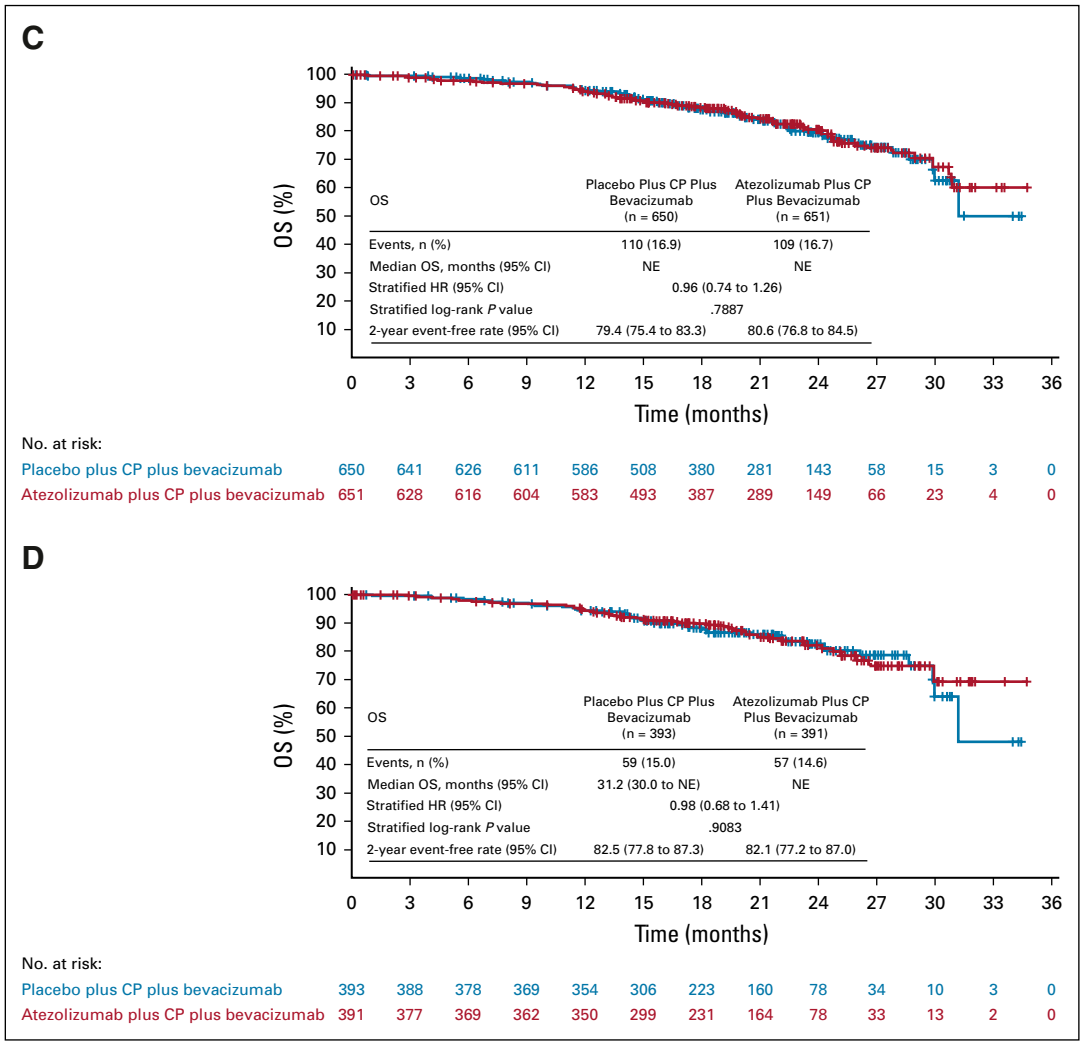


FIG 2. (Continued).

76% (993 of 1,301) of the study population. In other histologic subtypes (high-grade nonserous including clear cell, and low-grade serous), PFS was more favorable with atezolizumab, but the numbers of patients in these subgroups were small and 95% CIs for the HRs crossed 1. There was no apparent enrichment of any particular histologic subtype in the PD-L1–positive population (Table 1).

Additional prespecified exploratory analyses exploring the effect of atezolizumab on PFS in 260 patients (20%) with PD-L1 expression on ≥ 5% of ICs suggested a potential benefit from atezolizumab in this subgroup. The median PFS was not reached in the atezolizumab group after events in 39 of 119 patients (33%) and was 20.2 months (95% CI, 17.1 to 21.9) after events in 66 of 141 patients (47%) in the placebo group (Fig 4). The PFS HR in this subgroup was 0.64 (95% CI, 0.43 to 0.96). A small subgroup of patients displayed PD-L1 expression on ≥ 1% of TCs, representing 6% of the ITT population. The median PFS in the PD-L1 TC ≥ 1% subgroup was not reached in atezolizumab-treated patients and was 15.0 months (95% CI, 13.1 to 20.8 months) in placebo-treated patients (HR, 0.41 [95% CI, 0.19 to 0.90]; Fig 4).

The median number of atezolizumab cycles administered was 18 (range, 1-22). In both groups, the median number of cycles administered was 17 (range, 1-21) for bevacizumab and 6 (range, 1-6) for both carboplatin and paclitaxel.

Table 2 summarizes the safety results in the safety-evaluable population, with the most common AEs by treatment group in Table 3. Findings were consistent in the safety-evaluable and PD-L1–positive populations (data not shown). AEs with fatal outcome occurred in 1% of patients in both groups.

The incidence of grade 3 or 4 AEs was numerically higher with atezolizumab than placebo (79% *v* 73%, respectively). The most common grade 3 or 4 AEs were neutropenia, hypertension, and anemia (Table 3). The only serious AEs

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Baseline Risk Factors	N	Placebo Plus CP Plus Bevacizumab (n = 650) n	Placebo Plus CP Plus Bevacizumab (n = 650) Median (months)	Atezolizumab Plus CP Plus Bevacizumab (n = 651) n	Atezolizumab Plus CP Plus Bevacizumab (n = 651) Median (months)	HR (95% Wald CI)
All patients	1,301	650	18.4	651	19.5	0.92 (0.79 to 1.07)
Age, years (by group)						
18-40	66	30	19.6	36	20.6	0.58 (0.35 to 1.30)
41-64	813	399	18.2	414	19.6	0.90 (0.74 to 1.10)
≥ 65	422	221	18.8	201	18.0	1.01 (0.78 to 1.32)
Race						
White	925	461	18.1	464	18.2	0.97 (0.82 to 1.16)
Asian	305	155	21.2	150	21.6	0.78 (0.55 to 1.10)
Black or African American	21	13	19.1	8	24.2	0.52 (0.13 to 2.07)
Other	50	21	18.2	29	19.7	1.06 (0.48 to 2.32)
Baseline ECOG PS						
0	708	353	18.4	355	20.2	0.87 (0.70 to 1.07)
1	529	266	18.7	263	18.3	1.00 (0.79 to 1.27)
2	64	31	18.2	33	17.1	0.87 (0.42 to 1.81)
Treatment approach						
Neoadjuvant	332	166	17.2	166	16.6	1.12 (0.85 to 1.47)
Primary surgery	969	484	18.4	485	19.8	0.84 (0.70 to 1.01)
No gross residual disease	72	41	22.1	31	19.3	2.27 (0.89 to 5.77)
Residual disease ≤ 1 cm	499	245	18.3	254	21.1	0.78 (0.60 to 1.01)
Residual disease > 1 cm	398	198	17.1	200	18.6	0.80 (0.61 to 1.05)
Disease stage						
Stage III	896	448	18.4	448	20.6	0.80 (0.67 to 0.97)
Stage IV	404	201	18.4	203	17.1	1.24 (0.95 to 1.63)
Histological type						
High-grade serous	993	489	19.0	504	19.3	1.01 (0.84 to 1.20)
High-grade nonserous	155	87	15.7	68	19.9	0.69 (0.45 to 1.07)
Clear cell	51	22	12.3	29	13.6	0.64 (0.33 to 1.24)
Low-grade serous	125	58	20.4	67	19.7	0.83 (0.50 to 1.38)
PD-L1 status						
PD-L1 IC status						
IC < 1%	517	257	18.3	260	17.4	1.06 (0.84 to 1.33)
IC ≥ 1% to < 5%	524	252	18.2	272	19.3	0.89 (0.55 to 1.13)
IC ≥ 5%	260	141	20.2	119	NE	0.64 (0.43 to 0.96)
PD-L1 TC status						
TC < 1%	1,228	610	18.4	618	19.2	0.96 (0.82 to 1.12)
TC ≥ 1%	73	40	15.0	33	NE	0.41 (0.19 to 0.90)

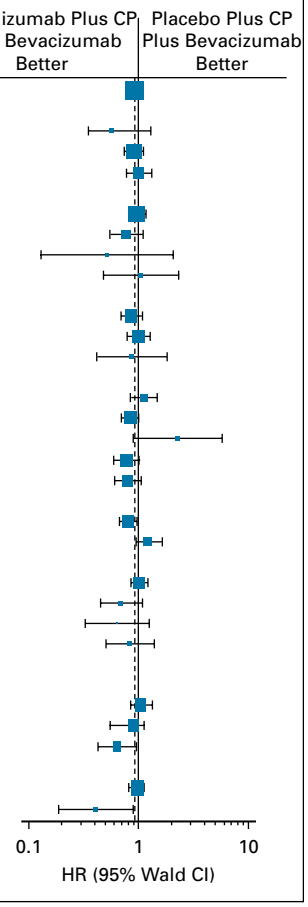


FIG 3. PFS by subgroup. CP, carboplatin plus paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IC, immune cell; NE, not evaluable; PD-L1, programmed death ligand-1; PFS, progression-free survival; TC, tumor cell.

(irrespective of investigator-assessed causality) in ≥ 2% of patients in either group were febrile neutropenia (8% *v* 4% with atezolizumab *v* placebo, respectively) and pyrexia (4% *v* 1%, respectively).

AEs of special interest (AESIs) for atezolizumab (Appendix Table A1, online only) were generally manageable and typically grade 1 or 2 (77% of 469 atezolizumab-treated patients with AESIs; 89% of 336 placebo-treated patients). One atezolizumab-treated patient experienced a grade 5 AESI (myasthenia gravis). AESIs (any grade) with a numerical difference between treatment groups were rash (any grade: 41% with atezolizumab *v* 26% with placebo; grade 3 or 4: 6% *v* 1%), hypothyroidism (any grade: 26% *v* 13%; grade 3 or 4: 0.5% *v* 0.2%), infusion-related reactions (12% *v* 8%), and hyperthyroidism (grade 1 or 2: 8% *v* 4%, respectively; no grade ≥ 3). Grade ≥ 3 severe cutaneous reactions occurred in 1% of atezolizumab-treated patients versus none of the placebo group. AESIs for bevacizumab were well-balanced between the two treatment groups (data not shown).

AEs led to discontinuation of any treatment in 26% of atezolizumab-treated patients and 22% of placebo-treated patients. This difference was driven by a higher proportion of patients discontinuing atezolizumab than placebo; the proportion of patients with AEs leading to bevacizumab discontinuation was similar in the two treatment groups.

DISCUSSION

In the IMagyn050 randomized phase III trial in newly diagnosed OC, adding atezolizumab to a chemotherapy plus bevacizumab backbone did not improve PFS compared with chemotherapy plus bevacizumab alone in either the ITT or the PD-L1–positive (IC ≥ 1%) populations. The results are immature for the co-primary end point of OS (deaths in only 17% of patients in the ITT population). OS follow-up continues.

IMagyn050 showed no significant PFS improvement in patients with PD-L1–positive tumors defined as IC ≥ 1%. However, in an exploratory analysis using a threshold of PD-L1 IC ≥ 5% (the cutoff used in urothelial carcinoma,

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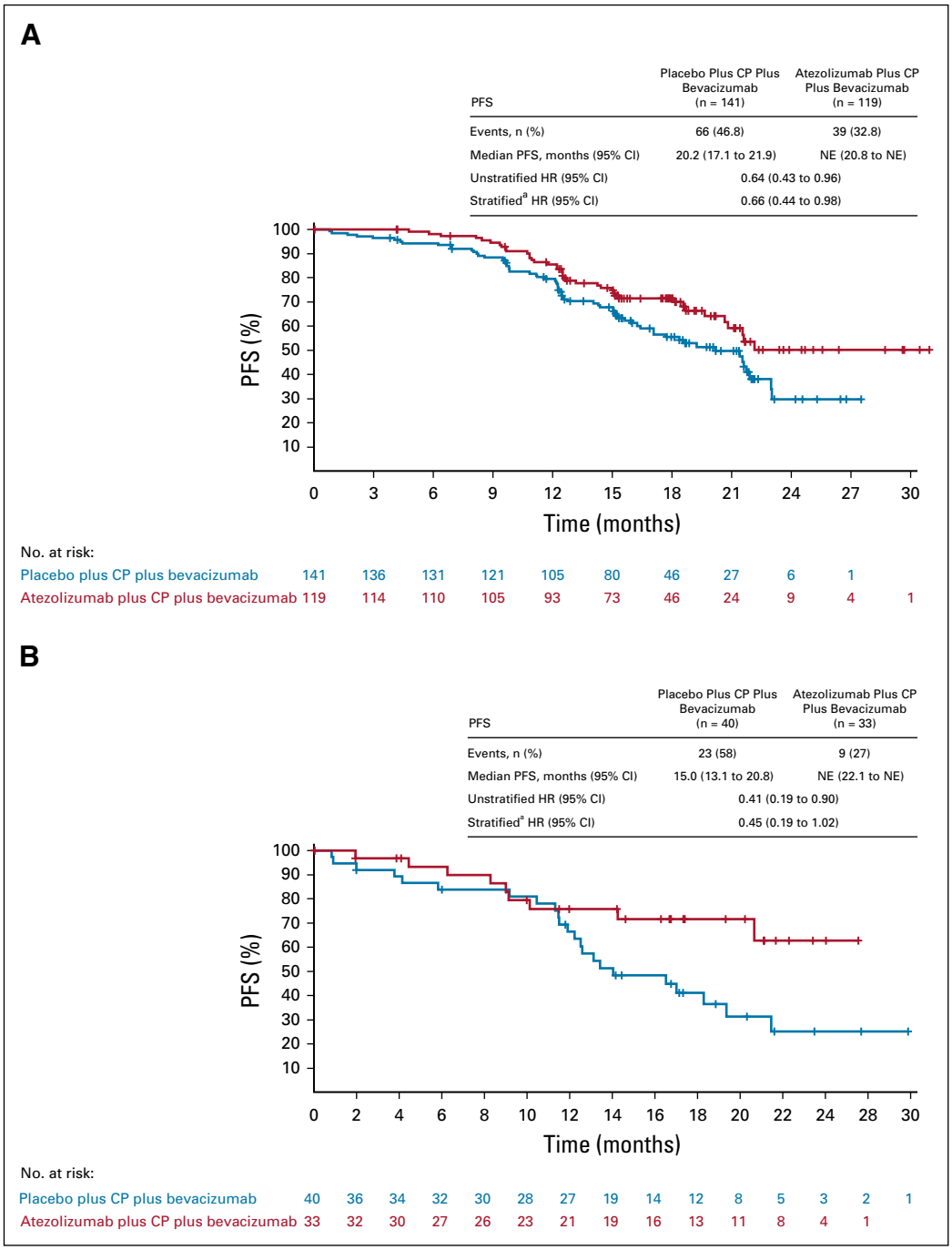


FIG 4. PFS in the subgroup of patients with PD-L1: (A) IC ≥ 5% (20% of the ITT population) and (B) TC ≥ 1% (6% of the ITT population). Of note, 67 of the 73 patients with TC ≥ 1% were also PD-L1 IC ≥ 1%. Only six patients whose tumors were identified as PD-L1–positive by TC staining were not considered to have PD-L1–positive tumors by IC staining. [a]Using the stratification factors, disease stage, ECOG performance status, and treatment approach. CP, carboplatin plus paclitaxel; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IC, immune cell; ITT, intention-to-treat; NE, not evaluable; PD-L1, programmed death ligand-1; PFS, progression-free survival; TC, tumor cell.

representing 20% of the ITT population in IMagyn050), the PFS HR was 0.64 (95% CI, 0.43 to 0.96). The median PFS was 20.2 months with placebo but was not reached in atezolizumab-treated patients, with an early and sustained separation (Fig 4). The distribution of these biomarkers appeared to be balanced across subgroups. This intriguing signal may warrant further evaluation of atezolizumab in a population with high PD-L1 expression. Additional

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TABLE 2. Overview of Safety (Safety-Evaluable Population)

AE	Placebo Plus CP Plus Bevacizumab (n = 644)	Atezolizumab Plus CP Plus Bevacizumab (n = 642)
Any grade AE	643 (100)	642 (100)
Grade 3 or 4	471 (73)	509 (79)
Grade 5	8 (1)	9 (1)
Serious	211 (33)	304 (47)
Any treatment-related AE	642 (100)	636 (99)
Grade 3 or 4	429 (67)	479 (75)
Grade 5	5 (1)	4 (1)
Serious	135 (21)	222 (35)
AE leading to discontinuation of any study drug	140 (22)	167 (26)
Atezolizumab or placebo	40 (6)	98 (15)
Bevacizumab	109 (17)	116 (18)
Paclitaxel	49 (8)	64 (10)
Carboplatin	23 (4)	43 (7)
AE of special interest	336 (52)	469 (73)
Grade 3 or 4	38 (6)	109 (17)
Grade 5	0	1 (< 1)
Serious	20 (3)	55 (9)

NOTE. Data are presented as No. (%).
Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel.

exploratory analysis in populations defined by PD-L1 expression on TCs was encouraging but difficult to interpret, as this population represents only 6% of the trial population and overlaps largely with PD-L1 IC–positive tumors (IC ≥ 1%). Subgroup analyses according to stage (a stratification factor) suggested an effect in patients with stage III but not stage IV disease. Reasons for such a difference are unclear and require elucidation. All the results from subgroup analyses should be interpreted with caution given their exploratory nature, the small sample sizes of some of the subgroups, and differences in event rates and prognosis between subgroups, biasing toward early events in some groups more than others, and should be considered only as hypothesis generating.

The safety profile of the atezolizumab, bevacizumab, and chemotherapy combination was consistent with previous experience with this regimen.[8] Overall, adding atezolizumab to bevacizumab and chemotherapy did not compromise delivery of the backbone therapy. AESIs for bevacizumab were consistent with the known risks, indicating that adding atezolizumab did not worsen the established bevacizumab safety profile. The most common AEs with atezolizumab-containing therapy were typical of chemotherapy and bevacizumab, with the exception of hypothyroidism, hyperthyroidism, and rash, which were more common with atezolizumab.

HRD and *BRCA* mutation status have both shown prognostic value in OC and are associated with sensitivity to platinum-based chemotherapy and PARP inhibitors. *BRCA* and HRD status were unavailable at the time of random assignment; imbalances between the two treatment arms may exist. Further exploratory analyses according to HRD and *BRCA* mutation status in IMagyn050 are ongoing. Although the backbone regimen in IMagyn050 represents a standard front-line regimen for OC, the hypothesis that the type of chemotherapy backbone has an impact on outcomes with immunotherapeutic approaches remains unanswered. Exposure to immunogenic chemotherapy agents, such as anthracyclines, may sensitize cells to immune checkpoint inhibitors, converting 'cold' tumors to 'hot' tumors,[13] although the combination of avelumab and pegylated liposomal doxorubicin (PLD) did not significantly improve outcomes in patients with platinum-resistant or platinum-refractory OC versus PLD alone in the JAVELIN-OVARIAN 200 trial.[14] Ongoing trials evaluating checkpoint inhibitors with other chemotherapy backbones, including PLD, may help to elucidate this hypothesis and include NRG-GY009 (ClinicalTrials.gov identifier: NCT02839707), ATALANTE (ClinicalTrials.gov identifier: NCT02891824), and AGO-OVAR 2.29/ENGOT-ov34 (ClinicalTrials.gov identifier: NCT03353831).

The lack of PFS benefit from immunotherapy in IMagyn050 is consistent with findings from the JAVELIN-OVARIAN 100 and 200 trials evaluating avelumab in the front-line and recurrent settings, respectively,[14,15] albeit the two front-line trials differed with respect to eligibility criteria, backbone regimen (with *v* without bevacizumab), and the assay used to determine PD-L1 status.

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TABLE 3. Clinical[a] AEs (Any Grade in ≥ 25% of Patients in Either Arm and Grade ≥ 3 AEs in > 0.5% of Patients in Either Arm)

AE	Placebo Plus CP Plus Bevacizumab (n = 644)			Atezolizumab Plus CP Plus Bevacizumab (n = 642)		
Grade	All	3 or 4	5	All	3 or 4	5
Nausea	338 (52)	6 (1)	0	324 (50)	15 (2)	0
Constipation	245 (38)	6 (1)	0	225 (35)	4 (1)	0
Diarrhea	207 (32)	16 (2)	0	225 (35)	18 (3)	0
Abdominal pain	173 (27)	11 (2)	0	186 (29)	25 (4)	0
Vomiting	158 (25)	8 (1)	0	152 (24)	14 (2)	0
Colitis	11 (2)	7 (1)	0	19 (3)	11 (2)	0
Ileus	11 (2)	5 (1)	0	15 (2)	9 (1)	0
Small intestinal obstruction	7 (1)	6 (1)	0	10 (2)	9 (1)	0
Intestinal obstruction	7 (1)	6 (1)	0	8 (1)	5 (1)	0
Dental caries	5 (1)	0	0	7 (1)	4 (1)	0
Alopecia	410 (64)	0	0	385 (60)	0	0
Rash	99 (15)	3 (< 1)	0	153 (24)	13 (2)	0
Pruritus	59 (9)	0	0	87 (14)	4 (1)	0
Rash maculopapular	17 (3)	1 (< 1)	0	48 (7)	16 (2)	0
Urticaria	10 (2)	0	0	34 (5)	5 (1)	0
Peripheral sensory neuropathy	163 (25)	5 (1)	0	178 (28)	6 (1)	0
Headache	178 (28)	4 (1)	0	147 (23)	3 (< 1)	0
Neuropathy peripheral	165 (26)	9 (1)	0	153 (24)	11 (2)	0
Syncope	7 (1)	7 (1)	0	16 (2)	13 (2)	0
Peripheral motor neuropathy	7 (1)	2 (< 1)	0	7 (1)	4 (1)	0
Cerebrovascular accident	3 (< 1)	1 (< 1)	2 (< 1)	3 (< 1)	1 (< 1)	0
Arthralgia	267 (41)	10 (2)	0	266 (41)	10 (2)	0
Myalgia	165 (26)	3 (< 1)	0	144 (22)	5 (1)	0
Fatigue	251 (39)	9 (1)	0	243 (38)	16 (2)	0
Pyrexia	59 (9)	2 (< 1)	0	123 (19)	4 (1)	0
Asthenia	79 (12)	3 (< 1)	0	77 (12)	10 (2)	0
Anemia	269 (42)	76 (12)	0	285 (44)	80 (12)	0
Neutropenia	198 (31)	137 (21)	0	200 (31)	138 (21)	0
Thrombocytopenia	136 (21)	38 (6)	0	138 (21)	47 (7)	0
Leukopenia	77 (12)	32 (5)	0	72 (11)	40 (6)	0
Febrile neutropenia	34 (5)	34 (5)	0	64 (10)	64 (10)	0
Lymphopenia	7 (1)	3 (< 1)	0	11 (2)	5 (1)	0
Bone marrow failure	3 (< 1)	2 (< 1)	0	5 (1)	4 (1)	0
Pancytopenia	4 (1)	4 (1)	0	3 (< 1)	1 (< 1)	0
Urinary tract infection	107 (17)	7 (1)	0	114 (18)	14 (2)	0
Pneumonia	12 (2)	6 (1)	0	18 (3)	6 (1)	0
Sepsis	11 (2)	9 (1)	1 (< 1)	3 (< 1)	2 (< 1)	0
Wound infection	9 (1)	5 (1)	0	3 (< 1)	0	0
Abdominal abscess	5 (1)	2 (< 1)	0	6 (1)	5 (1)	0
Infection	3 (< 1)	1 (< 1)	0	7 (1)	4 (1)	0
Pyelonephritis	3 (< 1)	2 (< 1)	0	5 (1)	4 (1)	0
Urosepsis	2 (< 1)	2 (< 1)	0	4 (1)	4 (1)	0

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TABLE 3. Clinical[a] AEs (Any Grade in ≥ 25% of Patients in Either Arm and Grade ≥ 3 AEs in > 0.5% of Patients in Either Arm) (continued)

AE	Placebo Plus CP Plus Bevacizumab (n = 644)			Atezolizumab Plus CP Plus Bevacizumab (n = 642)		
Grade	All	3 or 4	5	All	3 or 4	5
Infected lymphocele	1 (< 1)	0	0	4 (1)	4 (1)	0
Peritonitis	0	0	0	4 (1)	3 (< 1)	1 (< 1)
Hypertension	264 (41)	131 (20)	0	225 (35)	118 (18)	0
Embolism	8 (1)	6 (1)	0	6 (1)	3 (< 1)	0
Lymphocele	6 (1)	4 (1)	0	3 (< 1)	2 (< 1)	0
Dyspnea	88 (14)	2 (< 1)	0	87 (14)	5 (1)	0
Pulmonary embolism	12 (2)	10 (2)	0	17 (3)	15 (2)	1 (< 1)
Decreased appetite	120 (19)	6 (1)	0	120 (19)	5 (1)	0
Hypomagnesemia	83 (13)	4 (1)	0	92 (14)	10 (2)	0
Hypokalemia	63 (10)	24 (4)	0	72 (11)	22 (3)	0
Hyponatremia	48 (7)	25 (4)	0	50 (8)	28 (4)	0
Hyperglycemia	49 (8)	14 (2)	0	47 (7)	9 (1)	0
Hypoalbuminemia	32 (5)	1 (< 1)	0	30 (5)	4 (1)	0
Dehydration	29 (5)	2 (< 1)	0	32 (5)	7 (1)	0
Hypocalcemia	22 (3)	2 (< 1)	0	22 (3)	4 (1)	0
Proteinuria	140 (22)	23 (4)	0	136 (21)	14 (2)	0
Acute kidney injury	6 (1)	2 (< 1)	0	11 (2)	4 (1)	0
Urinary tract obstruction	4 (1)	3 (< 1)	0	0	0	0
Infusion-related reaction	52 (8)	2 (< 1)	0	81 (13)	6 (1)	0
Wound complication	25 (4)	4 (1)	0	10 (2)	0	0
Depression	39 (6)	4 (1)	0	35 (5)	4 (1)	0

NOTE. Data are presented as No. (%).
Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel.
[a]System organ class investigations not included.

Unlike findings in non–small-cell lung cancer,[8] combining atezolizumab with bevacizumab and chemotherapy did not improve efficacy in OC, highlighting intrinsic biologic and molecular differences between the tumor types. Currently, there is no evidence to support using immune checkpoint inhibitors in newly diagnosed OC. Insights from this trial should be considered for further research. Combining observations from this large trial with plausible biologic hypotheses will enable us to embrace specific trial designs in more focused, selected populations and settings.

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DATA SHARING STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the sharing of clinical information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Atezolizumab, Bevacizumab, and Chemotherapy for Newly Diagnosed Stage III or IV Ovarian Cancer: Placebo-Controlled Randomized Phase III Trial (IMagyn050/GOG 3015/ENGOT-OV39)

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Research Funding: Roche, AstraZeneca, MSD, Pfizer

No other potential conflicts of interest were reported.

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TABLE A1. AEs of Special Interest for Atezolizumab

	Placebo Plus CP Plus Bevacizumab (n = 644)		Atezolizumab Plus CP Plus Bevacizumab (n = 642)	
Immune-Mediated AEs by Medical Concept	**Any Grade**	**Grade 3 or 4[a]**	**Any Grade**	**Grade 3 or 4[a]**
Hepatitis[b]	14 (2.2)	4 (0.6)	17 (2.6)	7 (1.1)
Pneumonitis	4 (0.6)	0	12 (1.9)	1 (0.2)
Hypothyroidism	83 (12.9)	1 (0.2)	166 (25.9)	3 (0.5)
Hyperthyroidism	23 (3.6)	0	51 (7.9)	0
Adrenal insufficiency	2 (0.3)	0	5 (0.8)	1 (0.2)
Infusion-related reactions	49 (7.6)	2 (0.3)	78 (12.1)	5 (0.8)
Colitis	11 (1.7)	7 (1.1)	21 (3.3)	11 (1.7)
Rash	165 (25.6)	6 (0.9)	265 (41.3)	41 (6.4)
Severe cutaneous reactions	3 (0.5)	0	15 (2.3)	8 (1.2)
Myositis plus rhabdomyolysis	5 (0.8)	0	6 (0.9)	3 (0.5)
Myositis	5 (0.8)	0	4 (0.6)	2 (0.3)
Rhabdomyolysis	0	0	2 (0.3)	1 (0.2)
Meningoencephalitis[c]	3 (0.5)	0	3 (0.5)	1 (0.2)
Meningitis[c]	3 (0.5)	0	2 (0.3)	0
Encephalitis	0	0	1 (0.2)	1 (0.2)
Pancreatitis	0	0	5 (0.8)	4 (0.6)
Vasculitis	1 (0.2)	0	9 (1.4)	1 (0.2)
Nephritis	2 (0.3)	0	4 (0.6)	1 (0.2)
Ocular inflammatory toxicity	0	0	6 (0.9)	2 (0.3)
Diabetes mellitus	3 (0.5)	0	2 (0.3)	1 (0.2)
Autoimmune hemolytic anemia	3 (0.5)	0	0	0
Guillain-Barré syndrome	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Myocarditis	1 (0.2)	1 (0.2)	1 (0.2)	0
Myasthenia gravis	0	0	1 (0.2)[d]	0

NOTE. Data are presented as No. (%). There were no cases of hemophagocytic lymphohistiocytosis or hypophysitis in either treatment group.

Abbreviations: AE, adverse event; CP, carboplatin plus paclitaxel.

[a]Grade 3 or 4 AE refers to highest grade experienced.

[b]Sponsor-defined group of terms that represent events suggestive of hepatitis diagnosis (as opposed to events associated with liver function test abnormalities only).

[c]No cases of meningitis, one patient with encephalitis within the meningoencephalitis category, and remaining events were photophobia.

[d]Grade 5.

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