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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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 Gynaecology 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.

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 VELIA7 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...
demonstrated significantly improved PFS and overall survival (OS) when combined with first-line bevacizumab-containing therapy for non–small-cell lung cancer and with bevacizumab versus single-agent sorafenib in hepatocellular carcinoma. Single-agent atezolizumab demonstrated encouraging activity and tolerability in the PCD4989g study, with sustained responses in OC. 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.

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 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 ≥ 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 ≥ 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...
175 mg/m² 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 ≥ 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 ≥ 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. 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.
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.
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

### Table 1.Baseline Characteristics (ITT Population)

| Characteristic            | ITT Population Placebo Plus CP Plus Bevacizumab (n = 650) | Atezolizumab Plus CP Plus Bevacizumab (n = 651) | PD-L1–Positive Population 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\(b\)   |                                                         |                                                 |                                                                 |                                           |
| Neoadjuvant              | 166 (25)                                                | 166 (25)                                        | 80 (20)                                                         | 79 (20)                                   |
| Primary surgery           | 484 (74)                                                | 485 (75)                                        | 313 (80)                                                        | 312 (80)                                  |
| PD-L1\(c\)                |                                                         |                                                 |                                                                 |                                           |
| IC < 1%                   | 257 (40)                                                | 260 (40)                                        | 0                                                               | 0                                         |
| IC \(\geq\) 1%            | 393 (60)                                                | 391 (60)                                        | 393 (100)                                                       | 391 (100)                                 |
| Stage\(d,e\)              |                                                         |                                                 |                                                                 |                                           |
| III                       | 448 (69)                                                | 448 (69)                                        | 272 (69)                                                        | 264 (68)                                  |
| IV                        | 201 (31)                                                | 203 (31)                                        | 121 (31)                                                        | 127 (32)                                  |
| Primary tumor site\(f\)   |                                                         |                                                 |                                                                 |                                           |
| 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.
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...
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.
Baseline Risk Factors

| PD-L1 status | Placebo Plus CP | Atezolizumab Plus CP |
|--------------|----------------|----------------------|
| All patients | N=650          | N=651                |
| Age, years (by group) | | |
| 18-40        | 66            | 36                   |
| 41-64        | 813           | 415                  |
| ≥ 65         | 422           | 201                  |
| Race         |               |                      |
| White        | 925           | 456                  |
| Asian        | 305           | 150                  |
| Black or African American | 21 | 13 |
| Other        | 50            | 29                   |
| Baseline ECOG PS | 708 | 355         |
| 0            | 708           | 355                  |
| 1            | 529           | 263                  |
| 2            | 64            | 33                   |
| Treatment approach | | |
| Neoadjuvant  | 332           | 166                  |
| Primary surgery | 969 | 485         |
| No gross residual disease | 72 | 43 |
| Residual disease ≤ 1 cm | 499 | 254         |
| Residual disease > 1 cm | 398 | 198         |
| Disease stage |               |                      |
| Stage III    | 896           | 448                  |
| Stage IV     | 404           | 203                  |
| Histological type | | |
| High-grade serous | 993 | 504         |
| High-grade nonserous | 155 | 88 |
| Clear cell   | 51            | 29                   |
| Low-grade serous | 125 | 67          |
| PD-L1 IC status | | |
| IC < 1%      | 517           | 260                  |
| IC ≥ 1% to < 5% | 524 | 272         |
| IC ≥ 5%      | 260           | 119                  |
| PD-L1 TC status | | |
| TC < 1%      | 1,228         | 618                  |
| TC ≥ 1%      | 73            | 33                   |

Atezolizumab for Ovarian Cancer: IMagyn050 Phase III Trial

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,
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
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. Overall, adding atezolizumab to bevacizumab and chemotherapy did not compromise delivery of the backbone therapy. AEIs for bevacizumab were consistent with the known risks, indicating that adding atezolizumab did not worsen the established bevacizumab safety profile. The most common AEIs 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, 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. 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 200 trial. 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).

### 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.
### TABLE 3. Clinical 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) |
|-----------------------------------------|-------------------------------------------|-----------------------------------------------|
|                                         | 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 |
| Neutropathy 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 |
| Anemia                                   | 79 (12) | 3 (< 1) | 0 | 77 (12) | 10 (2) | 0 |
| Neutropenia                              | 269 (42) | 76 (12) | 0 | 285 (44) | 80 (12) | 0 |
| Thrombocytopenia                         | 198 (31) | 137 (21) | 0 | 200 (31) | 138 (21) | 0 |
| Leukopenia                               | 136 (21) | 38 (6)  | 0 | 138 (21) | 47 (7)  | 0 |
| Febrile neutropenia                      | 77 (12) | 32 (5)  | 0 | 72 (11) | 40 (6)  | 0 |
| Lymphopenia                              | 34 (5)  | 34 (5)  | 0 | 64 (10) | 64 (10) | 0 |
| Bone marrow failure                      | 7 (1)   | 3 (< 1) | 0 | 11 (2)  | 5 (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 |
| Uroseps                                  | 2 (< 1) | 2 (< 1) | 0 | 4 (1)   | 4 (1)  | 0 |

(continued on following page)
Unlike findings in non–small-cell lung cancer,\textsuperscript{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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### TABLE 3. Clinical AE (Any Grade in $\geq 25\%$ of Patients in Either Arm and Grade $\geq 3$ AE 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   | 0      | 0           | 4   | 1      | 0           |
| Peritonitis                            | 0   | 0      | 0           | 4   | 1      | 0           |
| Hypertension                           | 264 | 131    | 0           | 225 | 118    | 0           |
| Embolism                               | 6   | 4      | 0           | 3   | 2      | 0           |
| Lymphocele                             | 88  | 4      | 0           | 87  | 5      | 0           |
| Pulmonary embolism                     | 12  | 10     | 0           | 17  | 15     | 1 (< 1)     |
| Decreased appetite                     | 120 | 6      | 0           | 120 | 5      | 0           |
| Hypomagnesemia                         | 83  | 4      | 0           | 92  | 10     | 0           |
| Hypokalemia                            | 63  | 24     | 0           | 72  | 22     | 0           |
| Hyperglycemia                          | 48  | 25     | 0           | 50  | 28     | 0           |
| Hypocalcemia                           | 49  | 14     | 0           | 47  | 7      | 0           |
| Hypoalbuminemia                        | 32  | 1      | 0           | 30  | 4      | 0           |
| Dehydration                            | 29  | 2      | 0           | 32  | 7      | 0           |
| Hypocalcemia                           | 22  | 2      | 0           | 22  | 4      | 0           |
| Proteinuria                            | 140 | 23     | 0           | 136 | 14     | 0           |
| Acute kidney injury                    | 6   | 2      | 0           | 11  | 4      | 0           |
| Urinary tract obstruction              | 4   | 1      | 0           | 0   | 0      | 0           |
| Infusion-related reaction              | 52  | 2      | 0           | 81  | 6      | 0           |
| Wound complication                     | 25  | 4      | 0           | 10  | 0      | 0           |
| Depression                             | 39  | 4      | 0           | 35  | 4      | 0           |

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

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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 (IMagn1050/GOG 3015/ENGOT-OV39)

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# AEs of Special Interest for Atezolizumab

| Immune-Mediated AEs by Medical Concept | Placebo Plus CP Plus Bevacizumab (n = 644) | Atezolizumab Plus CP Plus Bevacizumab (n = 642) |
|---------------------------------------|------------------------------------------|-----------------------------------------------|
|                                       | Any Grade | Grade 3 or 4<sup>a</sup> | Any Grade | Grade 3 or 4<sup>a</sup> |
| Hepatitis<sup>b</sup> | 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<sup>c</sup> | 3 (0.5) | 0 | 3 (0.5) | 1 (0.2) |
| Meningitis<sup>c</sup> | 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)<sup>d</sup> | 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.  
<sup>a</sup>Grade 3 or 4 AE refers to highest grade experienced.  
<sup>b</sup>Sponsor-defined group of terms that represent events suggestive of hepatitis diagnosis (as opposed to events associated with liver function test abnormalities only).  
<sup>c</sup>No cases of meningitis, one patient with encephalitis within the meningoencephalitis category, and remaining events were photophobia.  
<sup>d</sup>Grade 5.