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Phase II study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage ovarian cancer: primary analysis in the original cohort of KGOG3046/TRU-D

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ABSTRACT

Background This study assessed the antitumor activity and safety of durvalumab plus tremelimumab combined with neoadjuvant chemotherapy (NAC) in patients newly diagnosed with advanced ovarian cancer. Here, we report the primary endpoint of the original cohort of the KGOG 3046/TRU-D study.

Methods In this investigator-initiated single-arm, phase II trial, patients with stage IIIC-IVB ovarian cancer were administered three cycles of durvalumab (1500 mg) and tremelimumab (75 mg) with NAC, followed by interval debulking surgery (IDS). After surgery, three cycles of durvalumab (1120 mg) and adjuvant chemotherapy followed by durvalumab maintenance (1120 mg [total 12 cycles]) were administered. The primary endpoint of the study was 12-month progression-free survival (PFS) rate.

Results Twenty-three patients were enrolled. The median patient age was 60 years (range 44–77 years), and most patients presented with high-grade serous carcinoma (87.0%) and stage IV disease (87.0%). At the time of data cut-off on January 17, 2023, the median follow-up duration was 29.2 months (range 12.0–42.2). The 12-month, 24-month, and 30 month PFS rates were 63.6%, 45.0%, and 40.0%, respectively. All patients underwent IDS, with an R0 resection rate of 73.9%, and 17.4% achieved pathological complete response. Skin rashes were the most common treatment-related adverse events (TRAEs, 69.6%). However, all TRAEs completely resolved after steroid use.

Conclusion This study showed promising activity with a durable clinical response, supporting the potential of NAC with dual immune checkpoint blockade in advanced-stage ovarian cancer.

Trial registration number NCT03899610.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous clinical trials of neoadjuvant chemotherapy with immune checkpoint inhibitors for front-line advanced ovarian cancer have reported promising surgical and histopathological outcomes. However, no survival outcomes have been reported.

WHAT THIS STUDY ADDS

⇒ KGOG 3046 is the first study to report long-term survival outcomes of patients with advanced ovarian cancer receiving neoadjuvant chemotherapy with dual immune checkpoint blockade therapy (durvalumab [anti-PD-L1] and tremelimumab [anti-CTLA-4]).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Neoadjuvant chemoimmunotherapy may be a promising treatment option in terms of precision medicine for patients with advanced ovarian cancers. This study provides important evidence of the safety and efficacy of neoadjuvant chemoimmunotherapy for the treatment of front-line advanced epithelial ovarian cancer.

INTRODUCTION

Most patients with advanced-stage epithelial ovarian cancer (EOC) relapse despite an aggressive standard of care (SOC) (eg, upfront surgical cytoreduction followed by platinum-taxol combinational chemotherapy). The median progression-free survival (PFS) duration of patients with advanced EOC is approximately 12 months,[1–3] therefore, new treatment strategies are urgently needed to prevent recurrence and improve the survival outcomes of advanced-stage EOC.

The presence of tumor-infiltrating lymphocytes (TIL) is associated with improved survival in EOC.[4 5] Ovarian cancer is considered an immunologically cold tumor[6 7]; however, preclinical data indicate

that combining chemotherapy with immune checkpoint blockade (ICB) therapy can convert cold tumors into hot tumors.[8] Recently, the addition of ICB to chemotherapy has been attempted in several clinical trials as a first-line treatment for EOC. However, the JAVELIN Ovarian 100 trial (avelumab plus chemotherapy) and the IMagyn050 trial (atezolizumab plus chemotherapy) showed no significant PFS rate improvement compared with chemotherapy alone.[9 10]

Current evidence does not support the use of PD-L1 inhibitors in patients newly diagnosed with ovarian cancer. The optimal timing and use of ICB in ovarian cancer have been explored. First, the neoadjuvant treatment period was considered the optimal timing for ICB. Neoadjuvant treatment strategy has been shown to result in a high pathological response rate and prolonged relapse-free survival in randomized trials of other solid tumors, including ovarian cancer.[11–14] Second, combination strategies, such as dual immune checkpoint inhibition, have been suggested. Anti-PD-1/L1 and anti-CTLA-4 augment antitumor immunity through distinct, non-redundant cellular mechanisms in various cancers.[15–18] In the NRG-GY003 trial (NCT02498600), the combination of nivolumab and ipilimumab was more effective than nivolumab alone (objective response rate (ORR): 31.4% vs 12.2%).[19] In KGOG 3045 (NCT03699449), an umbrella study on biomarker-driven targeted therapy, the combination of durvalumab (a human IgG1κ anti-PD-L1 monoclonal antibody) and tremelimumab (a fully humanized IgG_2 anti-CTLA-4 monoclonal antibody) with chemotherapy was more effective than the addition of durvalumab to chemotherapy for recurrent ovarian cancer (ORR: 28.5% vs 20.0%).[20]

We hypothesized that neoadjuvant chemotherapy (NAC) with dual immune checkpoint inhibitors would improve survival outcomes without excessive adverse events (AEs) in patients newly diagnosed with advanced EOC. Therefore, the KGOG 3046 trial was designed to evaluate the efficacy and safety of durvalumab plus tremelimumab with NAC in patients with front-line advanced EOC. Here, we report the results of the primary analysis of the KGOG 3046/TRU-D trial.

MATERIALS AND METHODS

Study design and participants

The KGOG 3046/TRU-D trial is an investigator-initiated, multicenter, single-arm, phase II trial. Four tertiary institutional hospitals in South Korea participated in this study: Severance Hospital, Samsung Medical Center, Seoul National University Hospital, and the National Cancer Center. The study was conducted in accordance with the Declaration of Helsinki and CONSORT (Consolidated Standards of Reporting Trials) 2010 guidelines. Patient enrolment began in June 2019. The full protocol is available in online supplemental data.

Eligible patients were at least 20 years old and had histologically confirmed non-mucinous ovarian, primary peritoneal, or fallopian tube cancer (hereafter referred to as EOC), with stages IIIC–IV disease (defined according to the International Federation of Gynecology and Obstetrics), an Eastern Cooperative Oncology Group performance status ≤1, and adequate organ function. Written informed consent was obtained from all the participants.

Procedures

Online supplemental figure S1 shows a schematic diagram of the study. The patients received the following treatments during the NAC period: durvalumab 1500 mg+tremelimumab 75 mg+paclitaxel 175 mg/m^2+carboplatin AUC 5–6 every 3 weeks. Interval debulking surgery (IDS) was performed 3 weeks after the completion of neoadjuvant therapy. After surgery, three cycles of durvalumab (1120 mg) and adjuvant chemotherapy followed by durvalumab maintenance (1120 mg (total 12 cycles)) were administered. Poly (ADP-ribose) polymerase (PARP) inhibitors or bevacizumab maintenance therapy were not planned for this cohort. After the initial treatment, the patients underwent CT or MRI of the pelvis, abdomen, and chest every 12 weeks. Investigators performed tumor assessments using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 up to 7 days before or after the designated time point. ^{18}F-FDG-PET/CT was performed before and after NAC. Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) version 1.0 was used for evaluation by nuclear medicine specialists. Patients were monitored for at least 2 years after treatment completion.

Safety and tolerability were assessed for each cycle until the treatment ended. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Doses of carboplatin and paclitaxel were reduced, interrupted, or discontinued at the investigator's discretion as per approved product labels and local regulations. Durvalumab and tremelimumab dosing was delayed until the resolution or medical stabilization of treatment-related toxicities associated with clinical symptoms.

We also conducted pre-specified exploratory analyses to identify potential biomarkers associated with clinical efficacy through integrative analysis of next-generation whole-transcriptome sequencing (WTS) data and immunohistochemistry (IHC) results. We collected tumor tissue and blood from the enrolled patients before treatment and at the IDS. Detailed methods of IHC, sample preparation for sequencing, WTS, and processing of WTS are described in online supplemental methods.

Outcomes

Patients who completed at least one study cycle were included for endpoint analysis (modified intention-to-treat (ITT) population). The primary end point was 12-month PFS. The secondary endpoints were: ORR using RECIST version 1.1, response rate using PERCIST after NAC, Chemotherapy Response Score (CRS) 3, complete cytoreduction (R0) rate at IDS, overall survival,

and safety. The genomic and immunological profiles of the TME during treatment were exploratory endpoints. PFS was defined as the time from treatment initiation to the date of disease progression or death from any cause. The censoring date was the date of the last response evaluation for participants with no disease progression and those who did not die. ORR was calculated as the percentage of participants with a confirmed complete response (CR) or partial response (PR). Overall survival was defined as the time from treatment initiation to death from any cause. The overall survival censoring date was the last date the participant was known to be alive and was used as the data cut-off date for analysis. The safety endpoints included the incidence and severity of AEs. Postoperative complications were graded according to the Memorial Sloan-Kettering Cancer Center Surgical Secondary Event grading system.[21] Major complications were defined as Memorial Sloan Kettering Cancer Center grade ≥3.

Statistical analysis

The sample size was calculated using the one-sample log-rank test. Assumed median PFS was 12 months in advanced-stage ovarian cancer based on the EORTC 55971 and CHORUS trials.[2 3] Fifty per cent of the patients were expected to have a disease-free status after 12 months of conventional chemotherapy (SOC). This rate is expected to increase to 70% with the addition of immunotherapy (combination of durvalumab+tremelimumab+SOC followed by durvalumab+SOC; HR=0.515). With 80% statistical power and 5% one-sided type I errors, a minimum sample size of 21 patients was required when the patients were accrued for 12 months and followed up for 30 months after the last patient was enrolled. The expected number of events was 14. Considering a drop-out rate of 10%, 24 patients were required.

The D'Agostino and Pearson omnibus normality test was used to test for the normal distribution of continuous data. The independent samples t-test or Mann-Whitney U test was used to compare continuous variables. Survival was plotted using Kaplan-Meier curves and compared using the one-sample log-rank test. The median follow-up duration was estimated using reverse Kaplan-Meier methods, and the corresponding 95% CI was constructed based on the Brookmeyer and Crowley methods. A Cox proportional hazards regression model was used for multivariate analyses to assess the significant prognostic factors associated with survival, HR, and 95% CIs. Statistical analyses were performed using Prism software V.8 (GraphPad Software, San Diego, California, USA), SPSS software V.27 (IBM Corp., Chicago, IL, USA), and R statistical software V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A p<0.05 was considered significant. The study was registered at ClinicalTrilas.gov (NCT03899610).

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Study population

Between October 19, 2019 and April 9, 2020, 26 patients were assessed for eligibility. Two patients were excluded (one did not meet the eligibility criteria and the other withdrew). Twenty-four eligible patients were enrolled; however, one patient did not receive treatment (figure 1). After three cycles of NAC, the enrolled patients underwent IDS. Finally, 23 patients who completed at least one study cycle were included in the modified ITT population and evaluated for primary and secondary endpoints. The median patient age was 60 years (range 44–77 years), and most patients presented with high-grade serous carcinoma (20, 87.0%) and stage IV disease (14, 87.0%). The median Fagotti score of the study patients was 10 (range 8–12). Two (8.7%) had germline *BRCA1/2* mutations and five (21.7%) had somatic *BRCA1/2* mutations (table 1).

Efficacy outcomes

All 23 patients who completed at least one study cycle were included in the modified ITT population. ORR, CRS, and pathological CR (pCR) rates were evaluated in all patients after NAC. Fifteen patients were available for response evaluation using PERCIST. The clinical outcomes during the neoadjuvant period are presented in table 2. The ORR based on the RECIST was 95.7% in all patients. Three patients (13.0%) achieved a CR. Among the 15 patients evaluated using PERCIST, 5 (21.7%) achieved a complete metabolic response. After IDS, the level of residual disease was classified as complete (R0, no macroscopic residual disease), optimal (R1, largest diameter 0.1–1 cm), or suboptimal (R2, largest diameter >1 cm). Overall, 17 (73.9%) patients underwent complete cytoreductive surgery (R0), and 9 (39.1%) and 4 (17.4%) patients achieved CRS3 and pCR, respectively.

Primary endpoint and survival outcomes

At the time of data cut-off on January 17, 2023, the median follow-up was 29.21 months (range 12.0–42.2). The median PFS was 17.5 months (95% CI 10.6 to NE), and the median OS was not reached in the modified ITT population (figure 2A–B). Thirteen (56.5%) patients completed treatment, and seven (30.4%) remained alive without evidence of disease progression (figure 1 and figure 2C). The 12-month, 24-month and 30-month PFS rates were 63.6% (95% CI 44.4 to NE), 45.0% (95% CI 27.2 to NE), and 40.0% (95% CI 22.9 to NE), respectively. The PFS rates at 24 (p=0.031) and 30 months (p=0.018) were significant compared with those of the historical control based on the Z-test (figure 2A). When comparing the PFS curves themselves using the one-sample log-rank test, KGOG 3046 showed a significantly better PFS

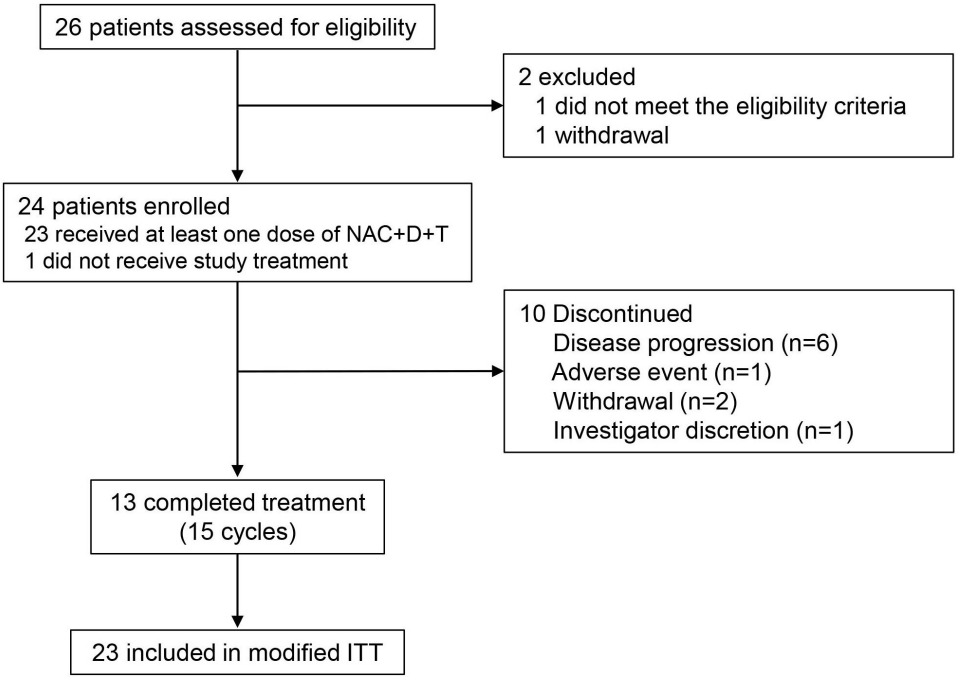


Figure 1 Trial flow diagram. D, durvalumab; ITT, intentionion-to-treat; NAC, neoadjuvant chemotherapy; T, tremelimumab.

curve than did the historical control with 30 months of follow-up (p=0.021) (figure 2A). The 30-month OS rate was 89.1% (figure 2B).

There were no significant differences in PFS or OS when stratified according to baseline clinical characteristics (online supplemental figure S2). However, the patients who achieved R0 resection at IDS showed superior PFS (32.1 vs 12.6 months, p=0.034, HR 0.23, 95% CI 0.04 to 1.30), and there was a trend for better PFS in patients with CRS3 than in those with CRS1/2 (HR 0.22, 95% CI 0.04 to 1.25).

Table 1 Baseline demographics

Variables	
Age (median, range) (years)	60 (44–77)
Histology, n (%)	
High-grade serous	20 (87.0)
Clear cell	1 (4.4)
Carcinosarcoma	1 (4.4)
Other	1 (4.4)
Clinical FIGO stage at presentation, n (%)	
IIIC	3 (13.0)
IV	20 (87.0)
BRCA1/2 status, n (%)	
Non-mutated	15 (65.2)
Germline *BRCA1/2* mutation	2 (8.7)
Somatic *BRCA1/2* mutation	5 (21.7)
Unknown	1 (4.3)
CA-125 at diagnosis (U/mL)	
Median (range)	1882.3 (45.9–12 882.3)
Fagotti score at diagnosis (median, range)	10 (8–12)

FIGO, The International Federation of Gynecology and Obstetrics.

Biomarker analysis

We explored immunological changes between treatment-naïve and post-NACI tumor tissues. IHC analysis for TIL, CD8, FoxP3, and PD-L1 and WTS for T-cell inflamed gene expression profile (GEP), cytolytic activity, and immune scores were performed to explore immunological changes. After NACI, the expression of CD8 and PD-L1, T-cell inflamed GEP, cytolytic activity, and immune scores were significantly increased (online supplemental figure S3A–C). However, the levels of pretreatment CD8, FoxP3, and PD-L1 and changes in CD8 and PD-L1 levels were not correlated with survival outcomes (online supplemental figure S3D–H).

We also calculated homologous recombination deficiency (HRD) score, tumor mutation burden (TMB), mutational signature 3 (associated with HRD), and mutational signature 6 (associated with mismatch repair defects) based on whole exome sequencing (WES) data in pretreatment tumor tissues. HRD scores and mutational signatures were generated by applying the Sequenza[22] with BAM files of tumor samples followed by the scarHRD and deconstructSigs R package.[23 24] Patients with an HRD score ≥54 were classified in the HRD group. TMB was calculated by counting the number of somatic non-synonymous mutations derived from WES.[25] Excluding one patient for whom WES could not be performed due to insufficient tumor tissue, 11 of 22 patients were confirmed to have HRD. When PFS was compared according to genomic mutational status, patients with

Table 2 Outcomes of neoadjuvant therapy

Parameter		
Overall response by RECIST, n (%)		
CR	3	(13.0)
PR	19	(82.6)
SD	1	(4.3)
PD	0	(0.0)
Objective response rate by RECIST, n (%)	22	(95.65)
Overall response by PERCIST*, n (%)		
CMR	5	(21.7)
PMR	9	(39.1)
SMD	1	(4.3)
PMD	0	(0.0)
IDS residual tumor classification, n (%)		
R0 (no gross residual)	17	(73.9)
R1 (<1 cm)	5	(21.7)
R2 (>1 cm, suboptimal)	1	(4.3)
Chemotherapy Response Score (CRS), n (%)		
1	1	(4.3)
2	13	(56.5)
3	9	(39.1)
Pathological CR, n (%)		
Yes	4	(17.4)
No	19	(82.6)

*15 patients are available to evaluate PERCIST.
CMR, complete metabolic response; CR, complete response; IDS, interval debulking surgery; PD, progressive disease; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SMD, stable metabolic disease.

HRD score ≥54 had a numerically superior median PFS than did those with HRD score <54, but it was not statistically significant (online supplemental figure S4A, 32.1 vs 14.6 months, p=0.6702, HR 0.80, 95% CI 0.26 to 2.51). TMB and mutational signature 3 did not correlate significantly with PFS (online supplemental figure S4B,C). However, the high mutational signature 6 group showed better PFS than did the low mutational signature 6 group (online supplemental figure S4D, 32.1 vs 10.8 months, p=0.0316, HR 0.33, 95% CI 0.11 to 0.98).

For correlative analysis, we defined durable clinical benefit (DCB) as PFS longer than 24 months, and nine (39.1%) patients experienced DCB in the modified ITT population (figure 2C). The baseline clinical characteristics of DCB and non-DCB patients were comparable. However, DCB patients showed significantly better clinical outcomes during the neoadjuvant period than non-DCB patients in terms of CRS3, pCR, and R0 resection rates (table 3).

Pretreated tumor tissue from 19 patients was evaluated by IHC analysis to identify predictive biomarkers for DCB. TIL and CD8, FoxP3, and PD-L1 expression were compared, with no significant differences between the DCB and non-DCB groups (online supplemental file 1). We further analyzed the whole transcriptome of the available 15 pretreatment tumor tissue samples, but the molecular subtype, immune score, and stromal score were not significantly different between the DCB and non-DCB groups (online supplemental file 1).

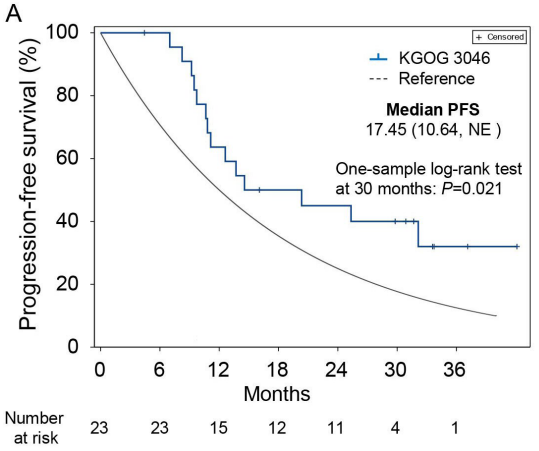
Safety and feasibility

Safety and AEs were analyzed after completion of adjuvant therapy. Treatment-related AEs (TRAEs) of any grade were evaluated for all study populations. All patients experienced TRAEs during treatment, with the most common AE being skin rashes (table 4, n=16, 69.6%). The most common grades 3–4 TRAEs were decreased neutrophil count (table 4; n=9, 39.1%), skin rash (n=3, 13.0%), and increased aspartate aminotransferase levels (n=3, 13.0%).

All of the TRAEs, including severe AEs, were manageable, with no new safety concerns in this study. Among 23 patients, 2 patients discontinued the study because of grade 4 skin rash and pneumonitis. Patient #1, who experienced grade 4 skin rashes, was a woman in her mid-60s with stage IVB disease with hepatic metastasis. Large bullae on the palms, soles, and trunk developed 14 days after the second cycle of NACI. After 21 days of hospitalization, the skin rashes had completely resolved with high-dose steroid therapy, and she underwent IDS on day 47 after the second cycle of NACI. The patient received adjuvant chemotherapy and completed a total of six cycles of chemotherapy. In contrast, Patient #2, who experienced grade 4 pneumonitis, was a woman in her early 50s with stage IVB disease with left supraclavicular lymph node metastasis. Pneumonitis occurred 35 days after the third cycle of NACI. After 70 days of hospitalization with steroid therapy, the patient received three more cycles of chemotherapy as soon as she recovered from pneumonitis. After six cycles of NAC, IDS was performed. This was the reason for patient #2 undergoing IDS on day 202 after the third cycle of NACI. The median time to surgery from the first day of the last NAC cycle was 24 days (range 19–202 days). However, all other patients, except those with severe AEs, underwent IDS within 39 days after the last NAC cycle. No grade 4 or 5 surgical complications were observed. The most common complications were abdominal pain (n=5; 21.8%) and ileus (n=3; 13.1%; online supplemental table S1). No surgery-related death occurred during the study period.

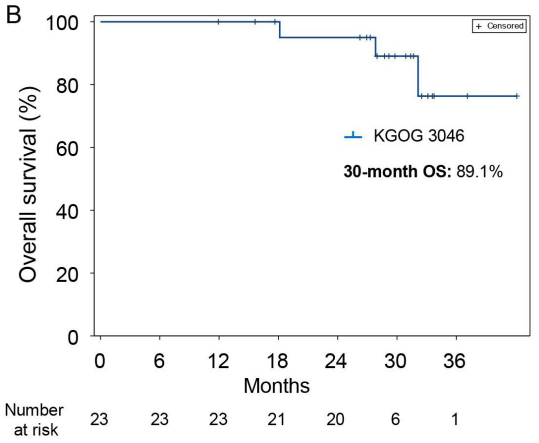
DISCUSSION

In this multi-institutional, single-arm, phase II study, front-line NAC with dual ICB therapy (durvalumab plus tremelimumab) showed promising activity against advanced-stage EOC. To our knowledge, this is the first prospective study to report the survival outcomes of NAC



PFS rate	KGOG 3046 (%, 95% CI)	Reference[a] (%)	Z-test[b] *P*-value
12 months	63.6 (44.4, NE)	50.0	0.092
24 months	45.0 (27.2, NE)	25.0	0.031
30 months	40.0 (22.9, NE)	17.7	0.018

a. Reference: exponential survival distribution (assumed median PFS of 12 months)
b. PFS rates of each fixed time point were compared using one-sided Z-test.



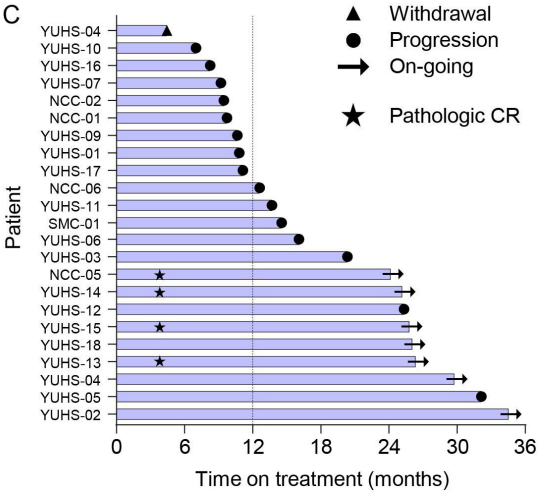


Figure 2 PFS and overall survival in the modified ITT population. (A) PFS. The reference is assumed to have an exponential survival distribution and a median PFS of 12 months. (B) Overall survival. (C) A swimmer plot showing outcomes in all patients from the start of treatment to either disease progression or the date of last-follow-up. CR, complete response; ITT, intention-to-treat; PFS, progression-free survival.

with dual ICB therapy in patients with advanced EOC. This study did not meet its primary endpoint because the 12-month PFS rate was not significant (63.6%, 95% CI 44.4 to NE). However, the PFS rates at 24 and 30 months were significant compared with those of the historical control based on the Z-test (figure 2A). In addition, KGOG 3046 showed a significantly better PFS curve than did the historical control with 30 months of follow-up (p=0.021 by one-sample log-rank test) (figure 2A). When the primary outcome is negative, positive findings for secondary outcomes are usually considered to be hypothesis-generating.[26] Considering the inherent nature of phase II study to generate hypothesis to support proceeding with a phase III confirmatory trial, this study is meaningful that it showed the potential of neoadjuvant chemoimmunotherapy to long-term survival benefit in advanced EOC.

Nine (39.1%) patients underwent DCB (PFS>24 months), and seven patients with DCB were still ongoing without disease progression. Considering that the patients in this study did not receive PARP inhibitor or bevacizumab maintenance therapy, the number of patients with DCB was remarkable. Historically, the median PFS was approximately 12 months,[1–3 7] and the CRS3 and pCR rates after NAC were 25%–30%[27 28] and <5%,[29] respectively. However, this study showed a median

Table 3 Comparison of clinical characteristics and neoadjuvant period outcomes according to durable clinical benefit (DCB)

Variables	DCB (n=9)	Non-DCB (n=14)	P value
Age (median, range) (years)	59 (50–68)	61 (44–77)	0.663
Histology, n (%)			0.825
High-grade serous	8 (88.9)	12 (85.7)	
Non-serous	1 (11.1)	2 (22.2)	
Clinical FIGO stage at presentation, n (%)			0.825
IIIC	1 (11.1)	2 (22.2)	
IV	8 (88.9)	12 (85.7)	
BRCA1/2 status, n (%)			0.405
Non-mutated	5 (55.6)	10 (71.4)	
BRCA1/2 mutation	4 (31.8)	3 (21.4)	
Unknown	0 (0.0)	1 (7.1)	
Chemotherapy Response Score, n (%)			0.002
1/2	2 (22.2)	12 (85.7)	
3	7 (77.8)	2 (14.3)	
Pathological CR, n (%)			0.022
Yes	4 (44.4)	0 (0)	
No	5 (55.6)	14 (100)	
No gross residual disease at IDS, n (%)			0.022
Yes	9 (100)	8 (57.1)	
No	0 (0)	6 (42.9)	

DCB was defined as PFS longer than 24 months.
FIGO, The International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; PFS, progression-free survival.

Table 4 Treatment-related adverse events

	Patients (n=23)			
Events	Any grade		Grades 3–4	
Rash	16	(69.6)	3	(13.0)
Neutrophil count decreased	12	(52.2)	9	(39.1)
Anemia	9	(39.1)	2	(8.7)
Aspartate aminotransferase elevated	8	(34.8)	3	(13.0)
Pruritus	8	(34.8)	0	(0.0)
Alanine aminotransferase elevated	7	(30.4)	2	(8.7)
Amylase increased	5	(21.7)	1	(4.3)
Fever	5	(21.7)	0	(0.0)
Febrile neutropenia	4	(17.4)	3	(13.0)
Feeding disorder	4	(17.4)	0	(0.0)
Hypothyroidism	4	(17.4)	0	(0.0)
Lipase increased	4	(17.4)	1	(4.3)
Neuropathy peripheral	4	(17.4)	0	(0.0)
Constipation	3	(13.0)	0	(0.0)
Peripheral sensory neuropathy	3	(13.0)	0	(0.0)
Thyroiditis	3	(13.0)	0	(0.0)
Decreased appetite	2	(8.7)	0	(0.0)
Dyspepsia	2	(8.7)	0	(0.0)
Hepatitis	2	(8.7)	2	(8.7)
Hypoalbuminemia	2	(8.7)	0	(0.0)
Platelet count decreased	2	(8.7)	1	(4.3)
Stomatitis	2	(8.7)	0	(0.0)
Urticaria	2	(8.7)	1	(4.3)
White cell count decreased	2	(8.7)	2	(8.7)
Pneumonitis	1	(4.3)	1	(4.3)
Gamma-glutamyltransferase elevated	1	(4.3)	1	(4.3)
Hyponatremia	1	(4.3)	1	(4.3)
Hypotension	1	(4.3)	1	(4.3)
Ileal perforation	1	(4.3)	1	(4.3)
Renal failure	1	(4.3)	1	(4.3)
Blood thyroid stimulating hormone elevated	1	(4.3)	0	(0.0)
Diarrhea	1	(4.3)	0	(0.0)
Myalgia	1	(4.3)	0	(0.0)
Nausea	1	(4.3)	0	(0.0)

PFS of 17.5 months, CRS3 rate of 39.1% and pCR rate of 17.4%. In other words, the pCR rate was higher than that previously reported for NAC alone, and all patients who achieved pCR exhibited DCB. In the long-term survival data, we observed the plateau or tail of the curve with 30 months of follow-up (figure 2A). We speculate that this long-term survival benefit was induced by a durable clinical response. Therefore, we would like to emphasize that some of the patients had DCBs from NAC with dual ICB. NAC combined with dual immune checkpoint inhibition improved the pCR rate during the neoadjuvant period and led to a durable clinical response. The toxicity profile and surgical complications were manageable with no new safety concerns.

By the way, the response rate after NAC based on PERCIST was one of the secondary endpoints in this study, but not all patients underwent PET/CT scans after neoadjuvant therapy. As only 15 patients were available for response evaluation using PERCIST, we could analyze the response rate using PERCIST for an exploratory purpose. Clinical response based on the RECIST and pathological response after NAC were analyzed as main secondary endpoints. In addition, there was discordance among PERCIST, RECIST, and pathological evaluation. Five patients achieved complete metabolic response based on PERCIST, three patients achieved CR based on RECIST, and four patients had pCR. Indeed, discordance between PERCIST and RECIST is well known in ovarian cancer as well as in various solid tumors,[30–33] and the discordance rates were reported to be between 18.3% and 56.5%.[34]

In this study, the pathological response showed a more reliable correlation with prognosis than did responses assessed using RECIST or PERCIST.

Five prospective studies are currently investigating NAC with ICBs for front-line treatment of advanced ovarian cancer. These studies have reported encouraging R0 rates for IDS and histopathological responses after NAC; however, no survival outcomes have been reported.[13 35 36] In clinical trials investigating the efficacy of durvalumab and tremelimumab with NAC, a randomized phase Ib trial, INEOV (NCT03249142), reported an R0 rate at IDS (70%) and pCR rate (18%).[37] The KGOG 3046 study reported similar R0 (73.9%) and pCR rates (17.4%) to this study. As the dose and sequence of tremelimumab in the INEOV study (single low dose during the second cycle) were different from those used in the KGOG 3046 trial, the most appropriate neoadjuvant chemoimmunotherapy regimen for tremelimumab in aEOC was determined when the final results were published. Another randomized phase II trial, iPRIME (ACTRN12618000109202), has been conducted; however, the results of this study have not yet been reported. Therefore, this is the first study to report long-term survival outcomes of aEOC patients receiving NAC with dual ICB therapy.

A major breakthrough in immunotherapy is its potential to achieve a durable response in a subset of patients with advanced cancer; the response can be maintained for several years, even after stopping treatment. Therefore, we hoped to achieve a durable clinical response in some patients with advanced EOC, and long-term follow-up of more than 30 months was required to identify patients who experienced DCB. However, no standardized definition of a durable response exists in the literature, and the optimal treatment duration in cases that experienced durable responses has not been clearly established. In the EORTC 55971 and CHORUS trials, median PFS and OS of NAC were 11.6 months and 27.6 months, respectively.[1] Therefore, we defined DCB patients as those with PFS longer than 24 months and attempted to identify predictive biomarkers in a correlative analysis. Since PARP inhibitors and bevacizumab were not used as maintenance therapy in this study, it is assumed that ICB contributed to DCB. In post hoc analyses, surgical outcomes (R0 resection) were correlated with DCB; however, baseline clinical characteristics, TIL, and CD8, FoxP3, and PD-L1 expression in pretreatment tumors were not significantly correlated with DCB. Further exploratory analyses are required to identify predictive biomarkers and dynamic changes in the TME during neoadjuvant chemoimmunotherapy (NACI).

Several phase II clinical trials have explored the optimal combination regimen of NACI for front-line treatment of advanced EOC. The expansion cohort of KGOG 3046 of NAC with durvalumab+tremelimumab (300 mg×1; STRIDE regimen), the FLORA-6 trial (NCT05605535) of NAC with oregovomab (anti-CA125 monoclonal antibody), and the MK-4830-002 trial (NCT05446870) of NAC with pembrolizumab±MK-4830 (anti-ILT4 monoclonal antibody) are actively ongoing. Although these trials have different research objectives and primary endpoints, they may provide clues for developing optimal strategies to induce durable clinical responses and improve survival outcomes in patients with advanced EOC. The expansion cohort of KGOG 3046 was designed to permit PARP inhibitor maintenance therapy, according to the current SOC. Therefore, we believe that the expanded cohort may provide additional insights into the relative contribution of dual immune checkpoint inhibition to the current SOC.

The current study had some limitations. This study had a single-arm design with a relatively small sample size and did not have a control arm (NAC only). We acknowledge the limitations of the single-arm phase II study using historical control. The null hypothesis (median PFS of 12 months) was based on the result of the EORTC 55971 and CHORUS trials.[1 2 38] Therefore, we designed a historical control curve (exponential curve with median PFS of 12 months and constant HR, figure 2A, dot line) and compared the KGOG 3046 study results with the historical control results at 12 months, 24 months, and 30 months using the Z-test and the one-sample log-rank test. In this way, we tried to indirectly show the promising long-term survival benefits of neoadjuvant chemoimmunotherapy in front-line advanced EOC. All participants originated from a single Asian country, but were from multiple centers. In addition, this study did not provide bevacizumab/PARP inhibitors. At the beginning of this study, the SOC for newly diagnosed advanced-stage ovarian cancer was paclitaxel-carboplatin±bevacizumab. In Korea, bevacizumab was reimbursed only for patients who underwent suboptimal resection after primary debulking surgery. Bevacizumab had no indication for use in NAC in Korea. The first patient was registered in June 2019. However, olaparib was approved only for patients with *BRCA1/2* mutations by the Korean Food and Drug Administration (KFDA) in October 2019 and could be covered by the National Health Insurance Service from October 2020. Therefore, there were limitations to providing bevacizumab/PARP inhibitor to the patients newly diagnosed with advanced-stage ovarian cancer during this study. KGOG 3046 showed a promising survival outcome in response to neoadjuvant chemo-immunotherapy, even in high-risk patients. In the era of maintenance therapy, further clinical trials are needed to investigate the role of neoadjuvant chemoimmunotherapy.

Despite these limitations, a strength of the study is the long-term follow-up to evaluate durable responses. When we compared the long-term outcomes for NAC in our study with those of other phase III studies[2 38 39] including the EORTC 55971 and CHORUS trials, the 30-month PFS rates for NAC ranged from 5.6% to 14.5% based on the best approximation from the PFS Kaplan-Meier curve. This is in contrast with results from the KGOG 3046 study, where the 30-month PFS rate was 40.0%.

In addition, when we compared the KGOG 3046 study results with the long-term follow-up data of historical

control, the PFS rates at 24 and 30 months were significant compared with those of the historical control (Z-test, figure 2A), and KGOG 3046 showed a significantly better PFS curve than did the historical control with 30 months of follow-up (one-sample log-rank test, figure 2A).

We reasoned that this long-term survival benefit was caused due to a durable clinical response. Durable clinical response is a distinct characteristic of immunotherapy[40 41] and is an important issue in advanced EOC.[42] The benefit of the ICBs is not properly captured by classical endpoints because ICBs may have a delayed effect resulting in a variable proportion of long-term survivors (plateau or tail of the curve).[43] In a pooled analysis of long-term survival data from trials of ipilimumab in melanoma, a plateau was observed in the survival curve, beginning at approximately 3 years.[44] We would like to emphasize the plateau or tail of the curve was observed in this study with 30 months of follow-up. We believe that the response rate and long-term survival outcomes observed in this study may provide some insight into the design of a confirmatory randomized study on NACI in patients with newly diagnosed advanced EOC.

In conclusion, we report promising long-term survival outcomes of NAC combined with dual ICBs in front-line advanced EOC. The addition of durvalumab and tremelimumab to NAC is safe and feasible. Further evaluation in large-scale randomized clinical trials of combined NACI is warranted in patients with advanced-stage EOC.

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Contributors J-YL is the principal investigator and has responsibility for the overall content as guarantor. The study was designed by J-YL, B-GK and J-WK. J-YL and JP acquired the funding. MCL, B-GK, J-WK, SK, CHC, HSK, SYP and J-YL recruited study participants and aided in data collection. JP did the formal analyses. JP and J-YL interpreted the data. JBL and D2S led the statistical analysis. JP and J-YL validated the data. JP and J-YL wrote original draft. All other authors contributed to the writing and review of the manuscript. JP and J-YL directly accessed and verified the underlying data reported in this manuscript. J-YL had final responsibility for the decision to submit for publication on behalf of the collaborative authors' group. All authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

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Patient consent for publication Not applicable.

Ethics approval We obtained approval from the Institutional Review Board (IRB) before initiating patient accrual at each institution. The representative board was the IRB of Yonsei University (No. 4-2019-0083). This study was done in accordance with Good Clinical Practice guidelines. Peripheral blood and tumor tissues were obtained from patients before treatment and at interval debulking surgery. All patients provided written informed consent before study participation based on the principles of the Declaration of Helsinki.

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Data availability statement Data are available on reasonable request. The raw clinical and imaging data are protected by patient privacy laws. The datasets generated and/or analyzed during the study are available from the corresponding author, J-YL, on request, and deidentified clinical data and experimental data is available on request sharing, which will require the approval of the institutional ethical committees. Deidentified data will then be transferred to the investigator via secure file transfer.

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