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Final overall survival and long-term safety in the ENGOT-OV16/NOVA phase III trial of niraparib in patients with recurrent ovarian cancer (LBA 6)

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Objectives

Primary results from the ENGOT-OV16/NOVA study showed that niraparib (nir) maintenance therapy (MT) significantly prolonged progression-free survival (PFS) in patients (pts) with platinum-sensitive recurrent ovarian cancer (PSROC) regardless of germline *BRCA* mutation (g*BRCA*m) or homologous recombination deficiency (HRD) biomarker status (median follow up 16.9 months). Previously reported long-term analyses on PFS2 indicated the benefit of nir MT beyond the first progression (median follow-up ≈67 months), but overall survival (OS) analyses were limited by missing data (Matulonis et al. *Gynecol Oncol.* 2021;162[suppl 1]: S24-S25). Recent data retrieval efforts reduced missing survival status from 17% to ≈2%, and the data cutoff was extended by 6 months. Here we report the final OS and long-term safety results in the updated dataset.

Methods

NOVA was a randomized, double-blind, placebo (PBO)-controlled phase III trial. Pts with PSROC were enrolled into independent g*BRCA*m and non-g*BRCA*m cohorts. Pts were randomized 2:1 to nir 300 mg once daily or PBO with stratification by PFS after penultimate platinum therapy (6 to <12 months vs ≥12 months), the best response to the last platinum-based therapy (complete/partial), and prior bevacizumab (yes/no). The primary endpoint, PFS, was assessed by a blinded independent central review. OS was a secondary endpoint. For the updated analysis, a vital status procedure was completed to retrieve the last known alive status for 92 pts. with missing survival data (data cutoff Mar 31, 2021). Final OS was evaluated in both cohorts and by non-g*BRCA*m HRD status.

Results

A total of 553 pts. were randomized. Median follow-up at data cutoff was >75 months across both cohorts and treatment arms. Survival status was available for 97.6% of pts. (540/553). Overall, OS maturity was 77.9%. Median OS was 40.9 months with nir and 38.1 months with PBO in the g*BRCA*m cohort (HR: 0.85; 95% CI: 0.61–1.20) and 31.0 and 34.8 months, respectively, in the non-g*BRCA*m cohort (HR: 1.06; 95% CI: 0.81–1.37). OS by HRD status is shown in the Table. No new safety signals were detected. Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) was reported in 14/367 pts. (3.8%; 10 [7.4%] g*BRCA*m, 4 [1.7%] non-g*BRCA*m) who received nir

Table. Final OS for the g*BRCA*m and non-g*BRCA*m cohorts and by HRD subgroup in the non-g*BRCA*m cohort

	Niraparib	Placebo
OS results by study cohort		
g*BRCA*m cohort (n=203)	(n=138)	(n=65)
Median OS (95% CI), months	40.9 (34.9–52.9)	38.1 (27.6–47.3)
Hazard ratio (95% CI)	0.85 (0.61–1.20)	
Non-g*BRCA*m cohort (n=350)	(n=234)	(n=116)
Median OS (95% CI), months	31.0 (27.8–35.6)	34.8 (27.9–41.4)
Hazard ratio (95% CI)	1.06 (0.81–1.37)	
Non-g*BRCA*m OS subgroup analysis		
HRd (n=162)	(n=106)	(n=56)
Median OS (95% CI), months	35.6 (28.3–43.4)	41.4 (33.9–57.6)
Hazard ratio (95% CI)	1.29 (0.85–1.95)	
HRp (n=134)	(n=92)	(n=42)
Median OS (95% CI), months	27.9 (22.6–32.8)	27.9 (19.2–44.0)
Hazard ratio (95% CI)	0.93 (0.61–1.41)	
HRnd (n=54)	(n=36)	(n=18)
Median OS (95% CI), months	29.8 (23.6–35.7)	20.2 (13.9–37.8)
Hazard ratio (95% CI)	0.62 (0.29–1.36)	

g*BRCA*m, germline breast cancer gene mutant; HRd, homologous recombination-deficient; HRnd, homologous recombination not determined; HRp, homologous recombination-proficient; OS, overall survival.

versus 3/179 (1.7%; 2 [3.1%] g*BRCA*m, 1 [0.9%] non-g*BRCA*m) PBO pts. There was no evidence suggesting that toxicity, including hematologic events, MDS/AML, or cardiovascular events, contributed to the OS results.

Conclusions
After a comprehensive effort to reduce missing data, we provide an updated, exploratory analysis of NOVA long-term follow-up data. The differences in OS between treatment arms were not interpreted to be significant in either cohort, though the OS hazard ratio numerically favored nir in the g*BRCA*m cohort. NOVA was not powered to show OS, and analyses were confounded by imbalances in post-progression therapy (including subsequent PARP inhibitors) by the treatment arm in both the g*BRCA*m and non-g*BRCA*m cohorts, including the exploratory HRD status subgroups. No new safety signals were observed with long-term follow-up.

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Anlotinib enhanced the efficacy of pembrolizumab in refractory or recurrent High-Grade Serous Ovarian Cancer by regulating the tumor microenvironment (LBA 7)

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Objectives
In 2022 ASCO, we reported that the anlotinib–pembrolizumab combination showed promising efficacy and favorable safety as treatment for refractory or recurrent high-grade serous ovarian cancer (HGSOC). The ARID1A are potential biomarkers for predicting the efficacy of this novel regimen. As a continuation of the study, we have updated the data here.

Methods
Patients with refractory or recurrent HGSOC randomly received pembrolizumab (200 mg, intravenously over 60 min, once every 3 weeks) plus anlotinib (12 mg/day, orally, 2 weeks on and 1 week off, every 3 weeks) therapy or pembrolizumab (200 mg, intravenously over 60 min, once every 3 weeks) monotherapy, respectively. The primary endpoints were progression-free survival (PFS) and overall survival (OS). The relationships of potential biomarkers with clinical efficacy were also evaluated, and the tumor environment has been analyzed here.

Results
A total of 75 patients were enrolled, with 30 participants receiving the anlotinib-pembrolizumab combination regime and 35 with pembrolizumab monotherapy, respectively. Grade 3 treatment-related adverse events (TRAEs) were recorded in 5 participants (16.7%) who received the combination treatment and 3 (8.6%) in the pembrolizumab monotherapy group, respectively. The PFS was 8.0 months and 4.3 months in the anlotinib-pembrolizumab combination regime and pembrolizumab mono-treatment, respectively. In the anlotinib-pembrolizumab combination treatment group, patients with *ARID1A* mutation indicated a significant survival benefit compared to patients with the wide type (PFS: 12.5 vs 7.0, $P = 0.004$). The tumor environment analysis by single-cell sequencing indicated that the anlotinib increased the expression of $CD4^{+}$T and enhanced the susceptibility of patients to pembrolizumab.

Conclusions
The anlotinib-pembrolizumab combination showed promising efficacy and favorable safety as a treatment for refractory or recurrent HGSOC. The ARID1A are potential biomarkers for predicting the efficacy of this novel regimen. Anlotinib could enhance the efficacy of pembrolizumab in refractory or recurrent HGSOC by regulating the tumor microenvironment.

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Final primary analysis in the original cohort of KGOG3046/TRU-D: A phase II study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage ovarian cancer (LBA 8)

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Objectives
We hypothesized that adding durvalumab and tremelimumab to neoadjuvant chemotherapy (NACT) in advanced-stage epithelial ovarian cancer (aEOC) would increase progression-free survival (PFS) with minimal adverse effects. Here, we report the final primary endpoint in the original cohort of the KGOG 3046 study on NACT with dual immune checkpoint blockade (durvalumab and tremelimumab) in newly diagnosed aEOC.

Methods
This open-label, investigator-initiated study enrolled patients with FIGO stage IIIC-IV EOC. Enrolled patients in the original cohort received the following neoadjuvant chemo-immunotherapy (NACI) (durvalumab 1500 mg q3w + tremelimumab 75 mg q3w + paclitaxel 175 mg/m2 + carboplatin AUC 5 [3 cycles]). After NACT, all patients underwent interval debulking surgery (IDS). After IDS, three cycles of durvalumab (1120 mg) and adjuvant chemotherapy followed by durvalumab maintenance (1120 mg [total 12 cycles]) were administered. Tumor response was assessed using RECIST v1.1. The primary endpoint was the 12-month PFS rate, and secondary endpoints were the objective response rate (ORR), rate of chemotherapy response score (CRS) 3, and pathologic complete response (pCR) rates, overall survival, and safety. The 12-month PFS rate in the treatment arm was expected to be 70% against that of 50% in the historical control group. The study is registered with Clinicaltrials.gov (NCT03899610).

Results
Between October 2019 and April 2020, 23 patients were enrolled in the original cohort. The median patient age was 60 years (range: 44–77 years). The majority of the patients presented with high-grade serous carcinoma (87.0%) and stage IV disease (87.0%). PFS of the original cohort showed a promising 12-month PFS rate of 63.6%, and this was significant with a durable response with 30 months follow-up ($P = 0.026$). After NACT, the ORR was 95.7%, and the R0 resection rate was 73.9%. Nine patients (39.1%) had a CRS 3, and 4 (17.4%) had