ENGOT-OV44/FIRST Study: A Randomized, Double-Blind, Adaptive, Phase 3 Study of Platinum-Based Chemotherapy ± Dostarlimab Followed by Niraparib ± Dostarlimab Maintenance as First-Line Treatment of Stage III or Stage IV Ovarian Cancer

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Background

- Despite surgery and chemotherapy (paclitaxel + carboplatin ± bevacizumab), 5-year survival rates remain low for patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or stage IV ovarian cancer (OC)
- **Niraparib** is a poly(ADP-ribose) polymerase (PARP) inhibitor that is approved for treatment in heavily pretreated patients and maintenance treatment of patients with newly diagnosed or recurrent ovarian cancer following a response to platinum-based chemotherapy[1,2]
- **Dostarlimab** (TSR-042) is an anti–programmed cell death-1 (PD-1) humanized monoclonal antibody that has shown clinical activity as monotherapy in early phase trials[3,4]
- The currently enrolling ENGOT-OV44/FIRST trial (NCT03602859, EUDRACT 2018-000413-20) will compare the efficacy and safety of chemotherapy ± bevacizumab + niraparib (arm 2) vs chemotherapy ± bevacizumab + dostarlimab + niraparib (arm 3)[5]

Summary

- Projected enrollment is up to 1228 patients, including 1020 patients in arm 2 and arm 3 (**Figure 1**)
  - Stratification factors: Concurrent bevacizumab use, HRR mutation status, and disease burden
- Adaptive design allows for modification of the control arm to follow the evolution of the SOC
- This study is assessing the efficacy of dostarlimab + chemotherapy, followed by niraparib and dostarlimab maintenance therapy with standard platinum-based chemotherapy in patients with stage III or stage IV non-mucinous epithelial OC treated with platinum-based chemotherapy (**Table 1**)
- The primary endpoint is PFS by RECIST v1.1
- This study is currently recruiting patients (**Figure 2**)

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Prescribing Information

Presented at the American Society of Clinical Oncology (ASCO) Congress, May 29–31, 2020.

Methods

Stratification

Patients will be randomized according to the following stratification factors: (i) concurrent bevacizumab use, (ii) homologous recombination repair (HRR) mutation status (ie, patients with *BRCA*-mutated [*BRCA*mut], non-*BRCA*mut HRR-positive, and non-*BRCA*mut HRR-negative/not determined disease), and (iii) disease burden

Adaptive Study Design

The study has an adaptive design for modification of the control arm to follow the evolution of the standard of care (SOC). In 2018, after positive results from the SOLO-1 trial, all patients with *BRCA*mut disease were randomized to arm 2 or arm 3 to ensure they receive niraparib maintenance and not placebo. In 2019, after PRIMA demonstrated the efficacy of niraparib in all patients regardless of biomarker, amendment 4 closed arm 1 to ensure that all patients are receiving the current SOC

Key Inclusion Criteria

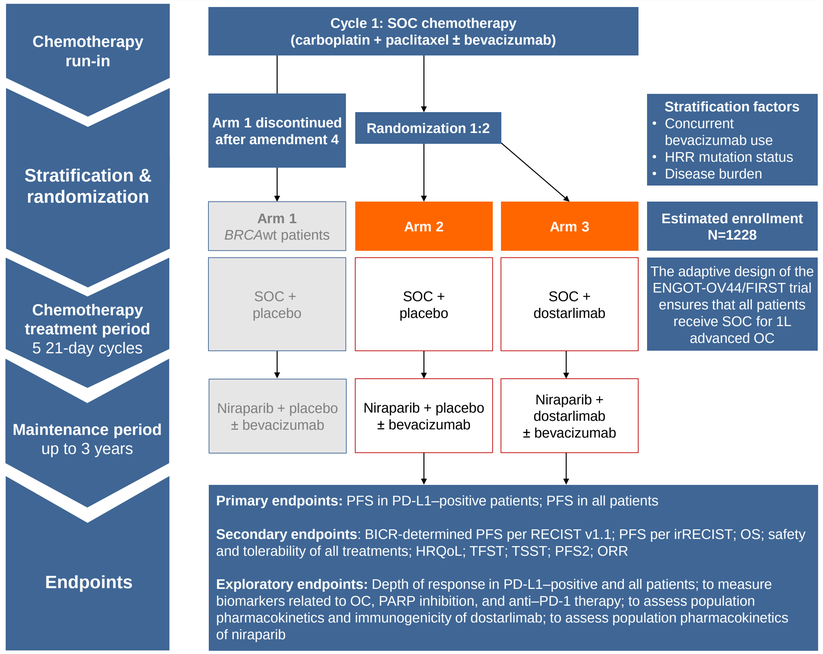
- Women ≥18 years of age
- Histologically confirmed diagnosis of non-mucinous epithelial ovarian, fallopian tube, or primary peritoneal cancer that is stage III or stage IV, according to FIGO or tumor, node, and metastasis staging criteria
- All patients with stage IV disease are eligible
- Patients with stage III disease are eligible if they are stage IIIC CC0 with ≥5-cm extrapelvic disease following PDS, inoperable stage III disease, macroscopic residual tumor following PDS, or NACT is planned
- Patients who undergo PDS or receive NACT are eligible
- Patients must have an ECOG score of 0 or 1 and provide blood and tumor tissue samples

Key Exclusion Criteria

- Has a mucinous, germ cell, transitional cell, or undifferentiated tumor
- Has a low-grade or grade 1 epithelial OC
- Diagnosed and/or treated with any therapy for invasive cancer <5 years from study enrollment
- Completed adjuvant chemotherapy and/or targeted therapy <3 years from enrollment, or completed adjuvant hormonal therapy <4 weeks from enrollment
- Investigational therapy administered within 4 weeks or within a time interval of <5 half-lives of an investigational agent, whichever is longer
- Known contraindication or uncontrolled hypersensitivity to components of paclitaxel, carboplatin, niraparib, bevacizumab, dostarlimab, or their excipients

BP=blood pressure; CC0=complete cytoreduction score 0; DBP=diastolic BP; FIGO=International Federation of Gynecology and Obstetrics; HRQoL=health-related quality of life; NACT=neoadjuvant chemotherapy; OC=ovarian cancer; PDS=primary debulking surgery; SBP=systolic BP.

Figure 1. Study Design



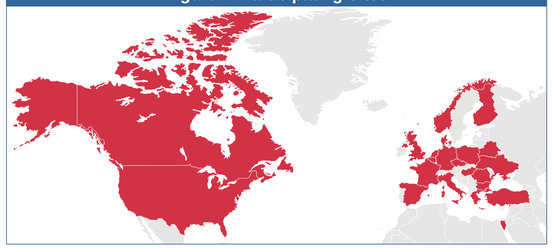
1L=first line; BICR=blinded independent central review; HRQoL=health-related quality of life; HRR=homologous recombinant repair; IDS=interval debulking surgery; OC=ovarian cancer; ORR=objective response rate; OS=overall survival; PARP=poly(ADP-ribose) polymerase; PD-1=programmed death 1; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PFS2=progression-free survival 2; SOC=standard of care; TFST=time to first subsequent treatment; TSST=time to second subsequent treatment; wt=wild-type.
All patients previously randomized to placebo and not receiving bevacizumab will be unblinded and provided the option to receive niraparib maintenance if they have received chemotherapy or discontinued chemotherapy <12 weeks. The study is open to patients with inoperable ovarian cancer, patients who have macroscopic residual disease at the end of the primary debulking surgery (PDS) and have recovered from PDS, and patients for whom platinum-based combination neoadjuvant chemotherapy (NACT) is planned.

Table 1. Therapy and Dosing by Treatment Arm

Drug	Dosage	Administration	Arm 2	Arm 3
Chemotherapy treatment period				
Paclitaxel	175 mg/m^2 Q3W	IV	✓	✓
Carboplatin	AUC of 5 or 6 mg/mL/min Q3W	IV	✓	✓
Dostarlimab	500 mg Q3W	IV	–	✓
Bevacizumab	7.5 mg/kg or 15 mg/kg Q3W (up to 15 months)	IV	Optional treatment	
Maintenance treatment period				
Niraparib[a]	200 or 300 mg QD	Oral	✓	✓
Dostarlimab[a]	1000 mg Q6W	IV	–	✓
Bevacizumab	7.5 mg/kg or 15 mg/kg Q3W (up to 15 months)	IV	May be continued from chemotherapy treatment period	

AUC=area under the curve; Q3W=every 3 weeks; Q6W=every 6 weeks; QD=once daily.
[a]Placebo capsules and/or infusion will be administered in arms where active treatment is indicated as not provided.

Figure 2. Participating Sites



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Acknowledgements

The authors thank the patients and their families for their participation in this study, as well as the study teams at each of the study sites. Writing and editorial support, funded by GlaxoSmithKline (Waltham, MA, USA) and coordinated by Ashujit Tagde, PhD, of GlaxoSmithKline, were provided by Eric Scocchera, PhD, and Michele Salernitano of Ashfield Healthcare Communications (Middletown, CT, USA).