ENGOT-EN6/GOG-3031/NSGO-RUBY Part 2: a Phase 3, Randomized, Double-Blind, Study of Dostarlimab + Carboplatin-Paclitaxel Followed by Dostarlimab + Niraparib Versus Placebo + Carboplatin-Paclitaxel Followed by Placebo in Recurrent or Advanced Endometrial Cancer

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Mechanism of Action

Dostarlimab

- Dostarlimab is a programmed death 1 (PD-1)–blocking antibody that binds to PD-1 and effectively blocks the interaction with the PD-1 ligands 1 and 2 (PD-L1 and PD-L2)
- Dostarlimab is approved as a monotherapy in adult patients with mismatch repair deficient (dMMR; US) or dMMR/microsatellite instability–high (dMMR/MSI-H; EU) recurrent or advanced endometrial cancer (EC) that has progressed on or after prior treatment with a platinum-containing regimen
- Dostarlimab approval was based on positive results from the phase 1 GARNET trial, which demonstrated the antitumor activity of dostarlimab in patients with dMMR/MSI-H endometrial cancer[1,2]

Niraparib

- Niraparib is an orally available inhibitor of the poly(ADP-ribose) polymerase (PARP) enzymes PARP-1 and PARP-2, which play a role in DNA repair
- Niraparib is approved as maintenance therapy in the first-line and recurrent settings in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are considered responsive to platinum-based chemotherapy

The RUBY Trial

- The RUBY trial is a 2-part global, randomized, double-blind, placebo-controlled phase 3 trial evaluating the efficacy and safety of dostarlimab, alone or in combination with niraparib maintenance treatment, in patients with recurrent or primary advanced EC (clinical trial number: NCT03981796)
- Advanced/recurrent EC is associated with poor outcomes and limited treatment options[3,4]; RUBY part 2 is being conducted to see whether combining treatment approaches can improve outcomes in these patients

Part 1	• Evaluate the efficacy and safety of dostarlimab in combination with carboplatin-paclitaxel, compared with carboplatin-paclitaxel alone • Enrollment for part 1 is complete • Expected primary readout is late 2021
Part 2	• Evaluate the efficacy and safety of dostarlimab + carboplatin-paclitaxel followed by dostarlimab + niraparib compared with carboplatin-paclitaxel alone • Enrollment for part 2 is ongoing • Expected primary readout is mid 2023

- RUBY is part of an international collaboration of the European Network for Gynaecological Oncological Trial groups (ENGOT), Nordic Society of Gynecological Oncology Clinical Trial Unit (NSGO-CTU), and the GOG Foundation

Patients

- Patients with recurrent or primary advanced EC are eligible
  - All histologies (including carcinosarcoma) are eligible

Key inclusion criteria

Parts 1 and 2

- Female
- Aged ≥18 years
- Histologically or cytologically proven EC that is first recurrent or primary advanced (FIGO stage III or IV at diagnosis)
- Patient can provide a tumor sample for MMR status test
- ECOG score of 0 or 1
- Adequate organ function

Part 2 only

- Normal blood pressure or adequately treated and controlled hypertension
- Able to take medication orally

Key exclusion criteria

Parts 1 and 2

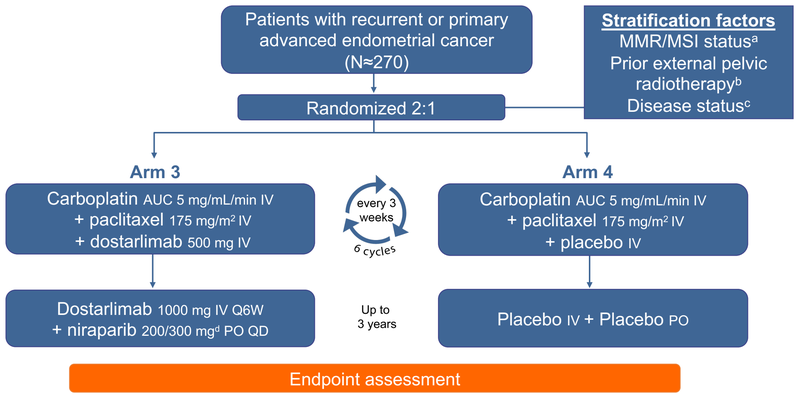
- Patients with primary advanced disease must not have received prior adjuvant or neoadjuvant chemotherapy
- Patients who recurred <6 months after completing chemotherapy
- >1 disease recurrence
- Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent
- Concomitant malignancies within the last 3 years
- Uncontrolled CNS metastases
- Immunocompromised/active autoimmune disease

Part 2 only

- Clinically significant cardiovascular disease
- Any known history or current diagnosis of MDS or AML
- At increased bleeding risk because of concurrent conditions
- Participation in part 1 of RUBY

AML, acute myeloid leukemia; CNS, central nervous system; EC, endometrial cancer; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; MDS, myelodysplastic syndrome; MMR, mismatch repair; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2.

Trial Design for RUBY Part 2



Primary endpoint

- Compare PFS evaluated by blinded independent review committee per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary endpoints

- PFS by investigator assessment
- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- PFS-2[e]
- Patient-reported outcomes for quality of life assessment

Safety assessment

- All adverse events will be assessed for intensity according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03

[a]MMR/MSI status: dMMR/MSI-H or MMRp/MSS; [b]Prior external pelvic radiotherapy: yes or no; [c]Disease status: recurrent, primary stage III, or primary stage IV; [d]Niraparib dosing is 200 mg PO QD for patients with baseline BW <77 kg or PC <150,000/μL or 300 mg QD for patients with baseline BW ≥77 kg and PC ≥150,000/μL; [e]PFS-2 is defined as the time from randomization to objective tumor progression on next-line treatment or death from any cause, whichever is earlier.
AUC, area under the curve; BW, body weight; dMMR, mismatch repair deficient; IV, intravenously; MMR, mismatch repair; MMRp, mismatch repair proficient; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSS, microsatelite stable; PC, platelet count; PFS, progression-free survival; PO, by mouth; Q3W, every 3 weeks; Q6W, every 6 weeks; QD, once daily.

Enrolling Countries

ENGOT

- Belarus (CEEGOG)
- Belgium (BGOG)
- Czech Republic (CEEGOG)
- Denmark (NSGO-CTU)
- Finland (NSGO-CTU)
- Germany (AGO)
- Greece (HeGOG)
- Hungary (CEEGOG)
- Israel (ISGO)
- Italy (MITO)
- Netherlands (DGOG)
- Norway (NSGO-CTU)
- Poland (PGOG)
- Spain (GEICO)
- Sweden (NSGO-CTU)
- Turkey (TRSGO)
- Ukraine (CEEGOG)
- United Kingdom (NCRI)
- Canada
- United States (GOG Foundation)

Summary

- RUBY is a randomized, double-blind, placebo-controlled, multicenter phase 3 study of dostarlimab in patients with recurrent or primary advanced EC
- Part 2 of RUBY is evaluating the efficacy and safety of dostarlimab + carboplatin-paclitaxel followed by dostarlimab + niraparib
- Enrollment is ongoing
- Expected primary readout is mid 2023

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Conflicts of Interest

- **Dr. Mirza** reports personal fees and other from Karyopharm Therapeutics; personal fees and other from Roche and Sera Prognostics; grants and personal fees from AstraZeneca, BioCad, Boehringer Ingelheim, Clovis Oncology, Genmab, Geneos Therapeutics, GlaxoSmithKline, Merck, Oncology Venture, Pfizer, Sotio, Seattle Genetics, Sera Prognostics, Takeda Pharmaceutical Company Ltd, and Zailab. **Dr. Coleman** reports consulting fees from AbbVie, Arrivive, AstraZeneca, Clovis, Eisai, Janssen, Merck, Novocure, OncoMed/Mateo, Oncoquest, Oncosec, Roche/Genentech, and Tesaro/GlaxoSmithKline; grants from AbbVie, AstraZeneca, Clovis, Genmab, Janssen, Merck, Roche/Genentech, and V-Foundation; and honoraria/reimbursement from Arrivive, AstraZeneca, Clovis, Eisai, Janssen, Merck, Novocure, OncoMed/Mateo, OncoQuest, Oncosec, Roche/Genentech, and Tesaro/GlaxoSmithKline. **Dr. Hanker** reports consulting/advisory fees from AstraZeneca, Clovis Oncology, Roche, and Tesaro. **Dr. Slomovitz** reports consulting/advisory fees from GlaxoSmithKline. **Dr. Valabrega** reports consulting/advisory fees from Amgen, AstraZeneca, Clovis Oncology, GlaxoSmithKline, PharmaMar, Roche, and Tesaro. **Dr. Powell** reports consulting/advisory fees from AstraZeneca, Clovis Oncology, Roche/Genentech, and Tesaro; and speakers' bureau at AstraZeneca, Clovis Oncology, Genentech/Roche, and Tesaro. **Drs. DeMars and Duan and Monica Walker** are employees of GlaxoSmithKline.

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