ARIEL4: An International, Multicenter, Randomized Phase 3 Study of the PARP Inhibitor Rucaparib vs Chemotherapy in Germline or Somatic *BRCA1*- or *BRCA2*-Mutated, Relapsed, High-Grade Ovarian Carcinoma

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Abstract: TPS5603

INTRODUCTION

- In high-grade ovarian cancer, including fallopian tube and primary peritoneal cancers, approximately 18% of patients have tumors with a germline *BRCA1* or *BRCA2* mutation and approximately 7% of patients have tumors with a somatic *BRCA1* or *BRCA2* mutation[1]
- The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib has demonstrated efficacy in tumors with homologous recombination deficiency (HRD), including a *BRCA1* or *BRCA2* mutation[2-5]
  - In cells with HRD, PARP inhibition results in accumulation of double-strand DNA breaks that cannot be repaired, leading to cell death[6-8]
- Based on data from 2 single-arm clinical trials,[4-5] rucaparib has received accelerated approval in the United States as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥2 chemotherapies
- Although PARP inhibitors have demonstrated clinical activity in high-grade ovarian cancer in both treatment and maintenance settings, data comparing PARP inhibitors to standard of care (SOC) treatment for relapsed ovarian cancer are limited[9]
- Randomized studies in patients with *BRCA1*- or *BRCA2*-mutated, relapsed, high-grade ovarian cancer are needed to assess the benefit-risk profile of PARP inhibitors vs current SOC for this patient population, particularly in the third-line or later treatment setting

ARIEL4 TRIAL OVERVIEW

- ARIEL4 (CO-338-043; NCT02855944) is an international, multicenter, randomized phase 3 study evaluating rucaparib 600 mg twice daily vs SOC chemotherapy as treatment for patients with germline or somatic *BRCA1*- or *BRCA2*-mutated, relapsed, high-grade ovarian cancer (platinum sensitive or resistant) who have received ≥2 prior chemotherapy regimens (**Figure 1**)

PATIENT ELIGIBILITY

Table 1. Key Patient Inclusion/Exclusion Criteria

Key inclusion criteria

- ≥18 years of age
- Histologically or cytologically confirmed high-grade serous or grade 2 or grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer[a]
- Received ≥2 prior chemotherapy regimens and currently has relapsed or progressive disease as confirmed by radiologic assessment
  - Had treatment-free interval of ≥6 months following the ***first*** chemotherapy regimen received
- Evaluable disease, ie, ≥1 target or nontarget lesion that can be assessed per RECIST
- Deleterious *BRCA1* or *BRCA2* mutation by local testing or central laboratory HRD test[b]
  - Adequate screening and/or archival (formalin-fixed, paraffin-embedded) tissue available for analysis
- Adequate organ function

Key exclusion criteria

- Prior PARP inhibitor treatment or treatment with single-agent paclitaxel for platinum-resistant disease
- Prior known hypersensitivity to paclitaxel (patients with PFI <12 months) or hypersensitivity to platinum (patients with PFI ≥12 months)
- Platinum-refractory disease (ie, disease progression during or within 4 weeks of completion of most recent platinum-based therapy)
- Symptomatic and/or untreated CNS metastases
- Active secondary malignancy for which patient may be (but not necessarily) currently receiving treatment
- Ongoing grade ≥2 adverse event, with exception of peripheral neuropathy, which may be permitted with prior advanced approval

[a]Patients with a histology other than serous or endometrioid are also eligible if they are known to harbor a deleterious germline or somatic *BRCA1* or *BRCA2* mutation.
[b]Patients with a known deleterious *BRCA1* or *BRCA2* mutation based on local assessment must also submit archival tumor tissue for central laboratory testing.
CNS, central nervous system; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase; PFI, progression-free interval; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

STUDY ENDPOINTS

Primary Endpoint

- Investigator-assessed progression-free survival by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST)[10]

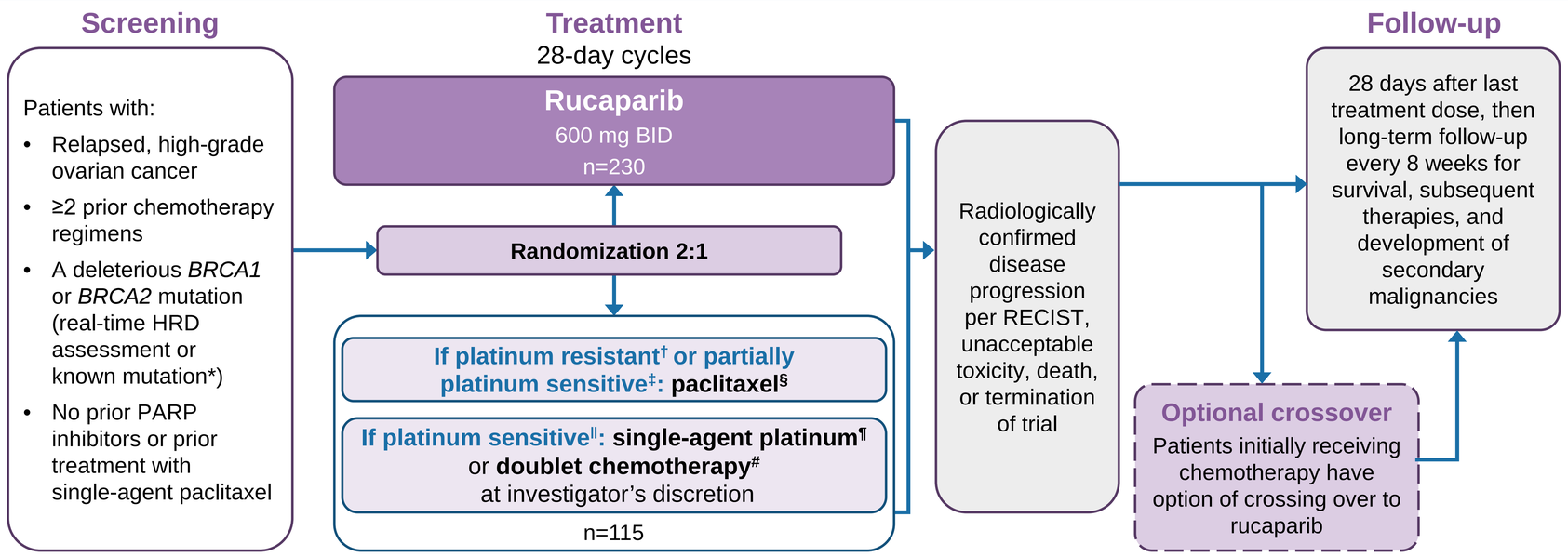
Secondary Endpoints

- Overall survival
- Objective response rate by RECIST and by RECIST/cancer antigen 125 (CA-125) criteria
- Duration of response
- Patient-reported outcomes by European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (QLQ-C30) and the ovarian cancer module (QLQ-OV28)[11,12]
- Safety and tolerability of rucaparib vs SOC chemotherapy

TRIAL SUMMARY

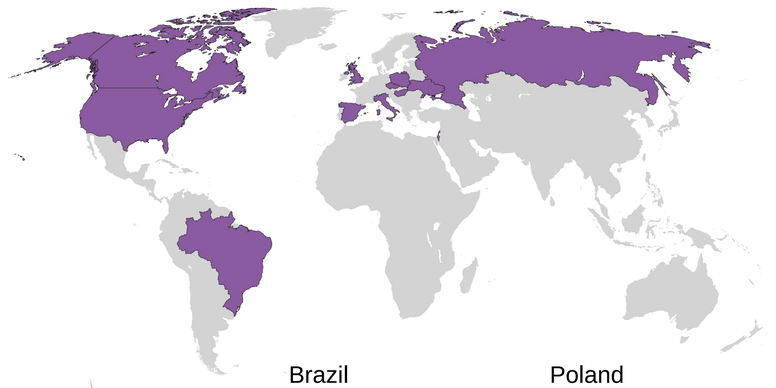
- Rucaparib has demonstrated efficacy in the treatment setting in patients with ovarian cancer and a deleterious *BRCA1* or *BRCA2* mutation[4,5,13]
- The ARIEL4 phase 3 study aims to assess the benefit-risk profile of rucaparib vs current SOC chemotherapy as treatment for patients with *BRCA1*- or *BRCA2*-mutated, relapsed, high-grade ovarian cancer
- ARIEL4 is actively recruiting patients, with a goal of enrolling 345 patients from >100 sites worldwide (**Figure 2**)

Figure 1. ARIEL4 Trial Schema



*Patients with a known *BRCA* mutation based on local test result must also submit tumor tissue; however, enrollment is not contingent on this tumor analysis.
†Progressed ≥1 to <6 months after last dose of platinum.
‡Progressed ≥6 to <12 months after last dose of platinum.
§Paclitaxel 60 to 80 mg/m^2 on days 1, 8, and 15; administered per local standard of care and regulations.
‖Progressed ≥12 months after last dose of platinum.
¶Cisplatin or carboplatin; administered per local standard of care and regulations.
#Carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine; administered per local standard of care and regulations.
BID, twice daily; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Figure 2. Countries Participating in ARIEL4



ARIEL4 Assessment of Rucaparib In ovarian cancEr: phase 3 trial

Brazil	Poland
Canada	Ukraine
Czech Republic	Russia
Hungary	Spain
Italy	United Kingdom
Israel	United States

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ACKNOWLEDGMENTS

This study is funded by Clovis Oncology, Inc. Medical writing and editorial support was funded by Clovis Oncology and provided by Nathan Yardley and Shannon Davis of Ashfield Healthcare Communications.