SGO ANNUAL MEETING ON WOMEN'S CANCER TAMPA, FL • 2023

PATIENTS • PURPOSE • PROGRESS

# Cytochrome P450 Inhibiting/Inducing Medication Use Among Patients With Advanced Ovarian Cancer Who Receive or Are Eligible for Poly (ADP-Ribose) Polymerase Inhibitors as First-Line Maintenance Therapy

B.J. Rimel[1], Dana Chase[2]*, Jessica Perhanidis[3], Armen A. Ghazarian[4]*, Ella Xiaoyan Du[5], Travis Wang[5], Jinlin Song[5], Amanda K. Golembesky[6], Jean A. Hurteau[3], Ritu Salani[7], Bradley J. Monk[8]

[1]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]Arizona Center for Cancer Care, Phoenix, AZ, USA, USA; [3]GSK, Waltham, MA, USA; [4]GSK, Rockville, MD, USA; [5]Analysis Group, Los Angeles CA, USA; [6]GSK, Durham, NC, USA; [7]Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]HonorHealth Research Institute, University of Arizona, Creighton University, Phoenix, AZ, USA

*At time of study

## Introduction

- Three poly (ADP-ribose) polymerase inhibitor (PARPi) therapies have been approved in the United States (US) and European Union for clinical use as maintenance therapies in advanced epithelial ovarian cancer (aOC): olaparib, rucaparib, and niraparib.[1]
- While PARPi therapies share similar mechanisms of action by disrupting the DNA-repair process in tumor cells,[1] they are metabolized through separate pathways.[2]
  - For example, whilst niraparib is metabolized in the liver by carboxylesterase-catalyzed amide hydrolysis, other PARPi therapies (olaparib and rucaparib) are metabolized by the cytochrome P450 (CYP) system.[2]
- Of note, many other medications (including antifungals and antibiotics), which patients with aOC may be receiving, also interact with the CYP system.[2]
  - For these patients, potential drug–drug interactions (DDIs) could impact the efficacy, safety, and tolerability of PARPi therapies.
  - The metabolism enzymes, DDI effect on CYP enzymes, and interaction management of PARPi therapies are shown in **Table 1**.[2,3]

**Table 1. Pharmacology (metabolism enzymes), interaction management, and examples of PARPi therapies approved in aOC**

| PARPi | Metabolism enzymes | DDI effect on CYP enzymes[2] | Interaction management*[3] |
|---|---|---|---|
| **Olaparib** | • Primarily CYP3A4[4,5] | **PARPi effect on other drugs**<br>• CYP2B6 induced[4,5]<br>• CYP3A inhibited[6]<br>**Other drugs' effect on PARPi**<br>• CYP3A inhibitors increased AUC (i.e., increased exposure to the drug over time)[4,5]<br>• CYP3A inducers decreased AUC[4,5] | • Reduce olaparib dose if concomitant treatment with potent CYP3A inhibitors is required,[4,5] such as antibiotics (e.g., clarithromycin), anti(retro)-virals (e.g., indinavir), antifungals (e.g., itraconazole), and cardiovascular medications (e.g., diltiazem)<br>• Avoid use of potent CYP3A inducers such as antibiotics (e.g., rifampicin) and antiepileptics (e.g., phenytoin) |
| **Rucaparib** | • Primarily CYP2D6[7,8]<br>• Lesser extent CYP1A2 and CYP3A4[7,8] | **PARPi effect on other drugs**<br>• CYP1A2 (e.g., caffeine), CYP2C19 (e.g., omeprazole) CYP2C9 (e.g., warfarin), CYP3A (e.g., midazolam) and P-glycoprotein (e.g., digoxin) were reversibly inhibited and caused an increase in AUC[7,8]<br>**Other drugs' effect on PARPi**<br>• Currently not known DDI interactions | • Use of potent CYP3A4/5 substrates with a narrow therapeutic index should be avoided<br>• Affected drugs include some analgesics (e.g., alfentanil), antihistamines (e.g., astemizole), immunosuppressants (e.g., cyclosporine), and painkillers (e.g., fentanyl) |
| **Niraparib** | • Primarily by carboxylesterases[9,10] | • None[9,10] | • None |

*As recommended by European Society for Medical Oncology Oncology in Practice[3]
aOC, advanced epithelial ovarian cancer; AUC, area under the curve; CYP, cytochrome P450; DDI, drug–drug interaction; PARPi, poly (ADP-ribose) polymerase inhibitors

## Aim

- To quantify the proportion of patients with aOC receiving CYP inhibiting/inducing (i/i) medications who have initiated or are eligible to receive PARPi therapy in the first-line maintenance (1Lm) setting, and describe their demographic/clinical characteristics.

## Methods

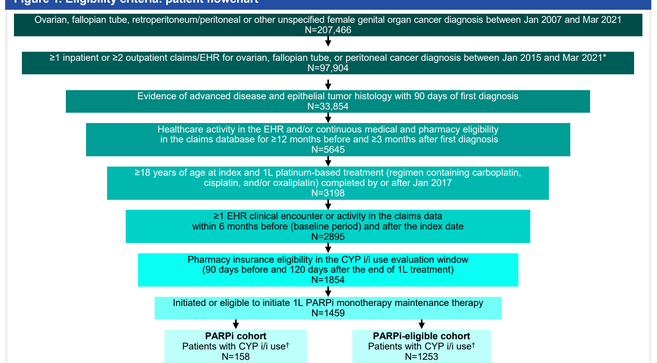
### Study design

- This retrospective cohort study used data extracted from Optum's de-identified Market Clarity Data between January 1, 2007 and March 31, 2021.
  - The database contains medical and pharmacy medication/prescription insurance claims linked with electronic health record (EHR) data from providers across the continuum of care.
- The index date was defined as the date of the last dose of 1L platinum-based treatment.
- Patients were followed from the index date to the earliest occurrence of either: the last clinical activity or enrollment date, the end of study period, or date of death.

### Study population

- Patients were included if they met the study criteria; key eligibility criteria are shown in **Figure 1**.

**Figure 1. Eligibility criteria: patient flowchart**




*Defined using the International Classification of Diseases (ICD), Ninth Revision Clinical Modification: 183.0, 183.2, 158.x or ICD Tenth Revision Clinical Modification: C56.x, C57.0x, C48.x; †114 and 34 patients were not receiving CYP i/i medication and thus were excluded from the PARPi-cohort and PARPi eligible cohort, respectively.
1L, first-line; CYP i/i, Cytochrome P450 inhibiting/inducing; EHR, electronic health record; PARPi, poly (ADP-ribose) polymerase inhibitor

- Ineligible patients included those who were pregnant during the baseline period (defined as the 6 months prior to the index date), those with bleomycin use and those flagged as deceased with a missing death date.
- Eligible patients were split into two cohorts:
  - PARPi cohort: Patients who initiated 1Lm PARPi monotherapy (olaparib, rucaparib, or niraparib).
  - PARPi-eligible cohort: Patients who did not initiate either 1Lm or second-line treatments within 60 days of the index date but who would have been eligible to receive 1Lm PARPi monotherapy.

### Data analysis

- Descriptive statistics were used to describe patient demographic and clinical characteristics.
- Strong/moderate CYP inhibitors were defined as therapies with an area under the plasma concentration–time curve ratio (AUCR) of ≥2 or clearance (CL) ratio ≤0.5.
- Strong/moderate CYP inducers were defined as therapies with AUCR ≤0.5 or CL ratio ≥2.
- The top 4 strong/moderate CYP i/i medications were selected based on the total number of patients in the PARPi cohort who received olaparib or rucaparib.
- Lines of therapy were defined according to Market Clarity data using a prespecified algorithm.

## Results

- Of the 1411 patients included in the study, 158 were in the PARPi cohort and 1253 were in the PARPi-eligible cohort (**Figure 1**).
  - The median (quartile 1 and 3 [Q1, Q3]) time from initial diagnosis to initiation of 1L therapy was 1.0 (0.6, 1.5) month for the PARPi cohort and 1.2 (0.8, 1.7) months for the PARPi-eligible cohort.

### Baseline demographics

- Baseline demographic and clinical characteristics are shown in **Table 2**.

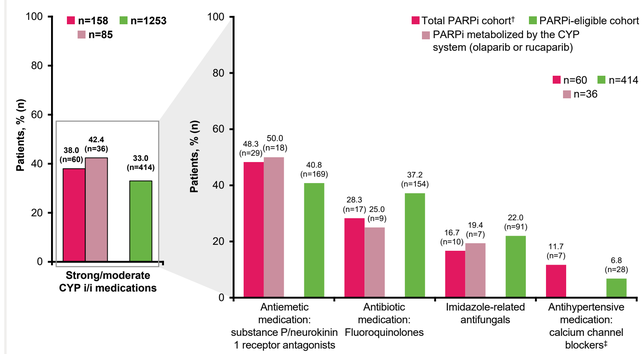
**Table 2. Baseline demographic and clinical characteristics**

| | PARPi cohort (n=158) | PARPi-eligible cohort (n=1253) |
|---|---|---|
| **Age, median (Q1, Q3)** | 63.0 (56.0, 71.8) | 64.0 (56.0, 73.0) |
| **Race/ethnicity, n (%)** | | |
| Hispanic/Latino | 6 (3.8) | 51 (4.1) |
| Non-Hispanic African American | NR* | 77 (6.1) |
| Non-Hispanic Asian | NR* | 25 (2.0) |
| Non-Hispanic White | 108 (68.4) | 740 (59.1) |
| Other/Unknown | 38 (24.1) | 360 (28.7) |
| **Region, n (%†)** | | |
| Midwest | 77 (48.7) | 525 (41.9) |
| South | 28 (17.7) | 260 (20.8) |
| West | 9 (5.7) | 121 (9.7) |
| Northeast | 38 (24.1) | 306 (24.4) |
| Other/Unknown | 6 (3.8) | 41 (3.3) |
| **PARPi maintenance therapy, n (%)** | | |
| Olaparib | 77 (48.7) | – |
| Niraparib | 73 (46.2) | – |
| Rucaparib | 8 (5.1) | – |
| **Stage at initial diagnosis,‡ n (%)** | | |
| Stage I | 0 | 14 (1.1) |
| Stage II | 0 | 22 (1.8) |
| Stage III | 15 (9.5) | 108 (8.6) |
| Stage IV | 143 (90.5) | 1104 (88.1) |
| Unknown | 0 | 5 (0.4) |

*n<5 , thus not reported to maintain patient confidentiality; †due to rounding of values, percentages may not add up to 100%; ‡defined using the non-missing stage reported during the 6 months period before or 90 days after the initial aOC diagnosis
aOC, advanced epithelial ovarian cancer; NR, not reported; PARPi, poly (ADP-ribose) polymerase inhibitors; Q1/3, quartile 1/3

- Most patients were Non-Hispanic White (PARPi, 68.4% [n=108]; PARPi-eligible, 59.1% [n=740]) and the median age was 63.0 (Q1, Q3: 56.0, 71.8) and 64.0 (Q1, Q3: 56.0, 73.0) years for PARPi and PARPi-eligible patients, respectively.
- In the PARPi cohort, 46.2% (n=73) of patients received niraparib, and 53.8% (n=85) received other PARPi therapies (olaparib: 48.7% [n=77]; rucaparib: 5.1% [n=8]).

**Figure 2. Strong/moderate CYP i/i medications* use in PARPi and PARPi-eligible cohorts**




*The number of patients in the PARPi cohort who received topical antifungals was the same as those who received antihypertensive medication (i.e., both were listed as the fourth most frequently used strong/moderate CYP i/i medication); however, these data are not reported here to maintain patient confidentiality; †includes olaparib, rucaparib, and niraparib; ‡n<5 patients in the PARPi metabolized by the CYP system (olaparib and rucaparib), thus not reported to maintain patient confidentiality
CYP i/i medications, cytochrome P450 inhibiting/inducing medications; PARPi, poly (ADP-ribose) polymerase inhibitors

### Concomitant CYP i/i medications

- In total, 38.0% (n=60) of the PARPi cohort and 33.0% (n=414) of the PARPi-eligible cohort received strong/moderate CYP i/i medications (**Figure 2**).
  - Among the patients who received either olaparib or rucaparib, 42.4% (n=36) received strong/moderate CYP i/i medications.
  - Antiemetics were the most commonly received strong/moderate CYP i/i medications in both the PARPi and PARPi-eligible cohort (48.3% [n=29] and 40.8% [n=169], respectively), followed by antibiotics (PARPi, 28.3% [n=17]; PARPi-eligible, 37.2% [n=154]), imidazole-related antifungals (16.7% [n=10]; 22.0% [n=91]), and antihypertensive medication (11.7% [n=7]; 6.8% [n=28]).
  - Of note, imidazole-related antifungals excluded topical formulations and are therefore likely capturing systemic use.

### Limitations

- This study was limited by the real-world data available in the Market Clarity data. For example, clinical characteristics including *BReast CAncer gene (BRCA)* mutation status, epithelial histology subtype, and Eastern Cooperative Oncology Group (ECOG) performance status had high levels of missingness. Moreover, homologous recombination deficient data were not available.
- The clinical activity requirement was implemented before and after the index date to ensure that the patients had clinical activity following the aOC diagnosis, which could lead to potential selection bias of patients.
- The study population identified in the Market Clarity data may not be fully representative of the aOC patient population in the US.

## Conclusions and implications

- In total, 33.0% of patients with aOC who were eligible to receive PARPi therapies and 42.4% of patients who received olaparib or rucaparib, received a strong/moderate CYP i/i medication, which has the potential to lead to a DDI, and may interfere with the efficacy, safety, and tolerability of PARPi therapies. In contrast, previous studies have shown that niraparib has no known interactions with CYP i/i medication and no known DDIs.[9,10]
- The findings shown here warrant future studies to understand any potential impact of concomitant CYP i/i use on PARPi efficacy, safety, and tolerability.

## Disclosures

**BJR** has received consulting or advisory fees from AstraZeneca, Genentech/Roche, and Tesaro: a GSK company. **DC** declares advisory/consultancy for AstraZeneca, GSK, Clovis Oncology; speaker bureaus for AstraZeneca, GSK; and travel/accommodation/expenses from AstraZeneca, GSK. JP is an employee of GSK and holds stock/shares at GSK and Boston Scientific. **AKG**, and **JAH** are employees of GSK. **AAG** is a former GSK employee. **EXD**, **TW**, and **JS** are employees of Analysis Group, which received consulting fees from GSK. **RS** reports honoraria from Arcus, Clovis, Genentech, GSK, Immunogen, Instil Bio, Merck, and Seagen; and advisory fees from Genentech. **BJM** reports consulting fees (AbbVie, Amgen, Aravive, AstraZeneca, Clovis, GOG Foundation, Gradalis, ImmunoGen, Laekna Health Care, Merck, Mersana, Myriad, Nucana, Oncomed, Oncoquest, Pfizer, Roche/Genentech, GSK), speakers' bureau fees (AstraZeneca, Clovis, Merck, Roche/Genentech, GSK), honoraria (AbbVie, Amgen, Aravive, AstraZeneca, Clovis, GOG Foundation, Gradalis, ImmunoGen, Laekna Health Care, Merck, Mersana, Myriad, Nucana, Oncomed, Oncoquest, Pfizer, Roche/Genentech, GSK).

## Acknowledgments

This study was funded by GSK (OneCDP217728). Medical writing support was provided by Nicholas Thomas, PhD and Eithne Maguire, PhD, at Fishawack Indicia Ltd, UK, part of Fishawack Health, funded by GSK.

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**Author email address:** drdanamchase@gmail.com

**Presented at the Society of Gynecologic Oncology (SGO) Annual Meeting, Tampa, FL; March 25–28, 2023**