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Cytochrome P450 inhibitor/inducer treatment patterns among patients in the United States with advanced ovarian cancer who were prescribed or were eligible for poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors in the first-line maintenance setting

Bobbie J. Rimel [a], Dana M. Chase [b], Jessica Perhanidis [c], Armen A. Ghazarian [d,1], Ella Xiaoyan Du [e], Travis Wang [f], Jinlin Song [e], Amanda K. Golembesky [g], Jean A. Hurteau [h], Linda Kalilani [g,*], Ritu Salani [b], Bradley J. Monk [i]

[a] Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[b] Gynecologic Oncology Division, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[c] Value Evidence and Outcomes, GSK, Waltham, MA, USA
[d] Value Evidence and Outcomes, GSK, Rockville, MD, USA
[e] Analysis Group, Los Angeles, CA, USA
[f] Analysis Group, Boston, MA, USA
[g] Value Evidence and Outcomes, GSK, Durham, NC, USA
[h] US Medical Affairs, GSK, Waltham, MA, USA
[i] HonorHealth Research Institute, University of Arizona, Creighton University, Phoenix, AZ, USA

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ABSTRACT

Poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors (PARPi) are metabolized either via carboxylesterase (niraparib) or cytochrome P450 (CYP) enzymes (olaparib and rucaparib). Patients with advanced epithelial ovarian cancer (aOC) who receive concomitant medication metabolized by the CYP system may be at risk of drug-drug interactions impacting PARPi efficacy and tolerability. This study investigated CYP inhibitor/inducer treatment patterns in the first-line maintenance (1Lm) setting for patients with aOC.

This retrospective cohort study used de-identified databases of US patients with aOC. Eligible patients were aged ≥18 years, diagnosed with aOC between January 2015–March 2021, and received CYP inhibitors/inducers during 1Lm PARPi initiation or the eligibility window (90 days before to 120 days after first-line platinum-based therapy ended [index]). Patients were either prescribed 1Lm PARPi monotherapy (PARPi cohort) or were not prescribed any 1Lm therapy within 120 days post-index (PARPi-eligible cohort). Strong/moderate CYP inhibitors/inducers were defined as area under the plasma concentration–time curve ratio (AUCR) ≥2 or clearance ratio (CL) ≤0.5 (inhibitors), and AUCR ≤0.5 or CL ratio ≥2 (inducers).

Of 1411 patients (median age 63), 158 were prescribed PARPis and 1253 were PARPi-eligible. Among the PARPi cohort, 46.2%, 48.7%, and 5.1% were prescribed niraparib, olaparib, and rucaparib, respectively. For patients prescribed olaparib or rucaparib, 42.4% also received strong and/or moderate CYP inhibitors/inducers.

This real-world study indicated a considerable proportion of patients received strong and/or moderate CYP inhibitors/inducers and were prescribed PARPis metabolized by the CYP system. Understanding potential impacts of concomitant CYP inhibitors/inducers on PARPi efficacy and safety is warranted.

1. Introduction

Three poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor (PARPi) therapies have been approved in the United States and European Union for clinical use as maintenance therapies in advanced ovarian cancer (aOC): olaparib, rucaparib, and niraparib (DiSilvestro,

* Corresponding author.
E-mail address: linda.v.kalilani@gsk.com (L. Kalilani).
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2021). These PARPis have all shown improvements in progression-free survival for patients with aOC as first-line maintenance (1Lm) therapy versus placebo in Phase III trials (González-Martín, 2019; Moore, 2018; Monk, 2022). PARPi therapies share similar mechanisms of action by disrupting the DNA repair process in tumor cells (DiSilvestro, 2021); however, they are metabolized through different pathways (LaFargue, 2019). Niraparib is metabolized by carboxylesterase-catalyzed amide hydrolysis, primarily forming an inactive metabolite (GSK, 2023; GSK, 2022), whereas olaparib and rucaparib are metabolized via cytochrome P450 (CYP) enzymes (LaFargue, 2019). Due to these key metabolic differences, olaparib and rucaparib present a unique set of potential drug-drug interactions (DDIs) not shown for niraparib in vitro. For example, olaparib induces CYP2B6 and inhibits CYP3A (AstraZeneca, 2019; Friedlander, 2016), with CYP3A inhibitors known to increase olaparib exposure (AstraZeneca, 2019; Friedlander, 2016) with a high risk of adverse events (Velev, 2021). Consequently, concomitant use of strong CYP3A inhibitors should be avoided (AstraZeneca, 2019; Friedlander, 2016). Similarly, rucaparib is metabolized by CYP2D6, CYP1A2, and CYP3A4 in vitro and it is recommended that concomitant use with strong CYP3A4 inhibitors or inducers (inducer/inhibitor) (Clovis Oncology Inc, 2022) be pursued with caution. Moreover, the weak to moderate inhibition by rucaparib may require dose adjustments and/or monitoring if coadministered with medicines that are substrates for CYP1A2, CYP2C9, CYP3A, CYP2C19, and UGT1A1 (Clovis Oncology Inc, 2022). Niraparib, by contrast, has no contraindications for concomitant use with CYP inducer/inhibitor medications (GSK, 2023; GSK, 2022).

Many medications (including antifungals and antibiotics), which patients with aOC may be receiving, also interact with the CYP system (LaFargue, 2019). For these patients, potential DDIs can occur in the form of CYP inhibition or induction, either from these and/or PARPi medications themselves (LaFargue, 2019); the potential impact of DDIs on efficacy, safety, and tolerability of PARPi therapies when given concomitantly with CYP system inhibitors/inducers has been referenced previously by the group of authors (Rimel et al., 2023). Of note, DDIs were not evaluated in clinical studies of olaparib and rucaparib (DiSilvestro, 2021; Ledermann, 2020) and there is limited existing literature addressing the risk of DDIs for patients with aOC receiving PARPi maintenance therapy or who are under active surveillance.

The aim of this US-based real-world study was to quantify the proportion of patients with aOC who received CYP inhibitor/inducer medication and had either been prescribed or were eligible for PARPi therapy in the 1Lm setting.

2. Methods

2.1. Conceptualization and data source

This was a retrospective cohort study that used de-identified data from US patients with aOC from two real-world databases, Optum* Market Clarity Data and Optum* Enriched Oncology Data (Eden Prairie, MN), between January 1, 2007, and March 31, 2021. The Market Clarity database contains medical and pharmacy medication/prescription insurance claims and electronic health record (EHR) data from providers across the continuum of care. The Enriched Oncology database contains data elements including cancer stage, grade, histology, genetic mutations, biomarkers and measures of disease progression and drug response. The Optum* Enriched Oncology database also includes linked claims data via the Optum Market Clarity database, which consist of 60 million patients with EHR and medical and pharmacy claims data across payers.

The index date was defined as the date of the last dose of first-line (1L) platinum-based therapy. Patients were followed from index to the earliest occurrence of either the last clinical activity or enrollment date, the end of study period, or date of death.

The study complied with all applicable laws regarding patient privacy. No direct patient contact or primary collection of individual patient data occurred, and study results omitted patient identification; therefore, informed consent, ethics committee, and/or Institutional Review Board approval were not required.

2.2. Study population

Patients were included if they met the study eligibility criteria (full details in Table 1). In brief, eligible patients were aged ≥18 years at index and had aOC, defined as ≥1 inpatient or ≥2 outpatient diagnoses (at least 30 days apart) from claims or EHR as derived from International

Table 1
Patient population.

Selection step	Eligibility criteria	Eligible patients (n)
1*	Female patient with any diagnosis code for ovarian, fallopian tube, retroperitoneum/peritoneal or other unspecified female genital organ cancer diagnosis between January 2007 and March 2021	207,466
2*	≥1 inpatient or ≥2 outpatient claims/EHR (at least 30 days apart) for ovarian, fallopian tube, or peritoneal cancer diagnosis between Jan 2015 and Mar 2021†	97,904
3*	Evidence of advanced disease within 90 days of first diagnosis‡	34,447
4*	Evidence of epithelial tumor histology with 90 days of first diagnosis	33,854
5*	Healthcare activity in the EHR and/or continuous medical and pharmacy eligibility in the claims database for ≥12 months before and ≥3 months after first diagnosis, and no prior diagnosis of aOC in 12 months before initial OC diagnosis	5645
6*	No use of bleomycin between January 1, 2014 and March 31, 2021	5613
7§	Received 1L platinum-based therapy (regimen containing carboplatin, cisplatin, and/or oxaliplatin) completed on or after January 1, 2017; date of completion was defined as the index date	3198
8§	Aged ≥18 years at index date	3198
9§	≥1 EHR clinical encounter or activity in the claims data within 6 months before (baseline period) and after the index date	2895
10§	Pharmacy insurance eligibility in the received CYP i/i evaluation window (90 days before and 120 days after the end of 1L)	1854
11§	Alive or with nonmissing death date	1838
12§	Not pregnant at any time during baseline period	1827
13§	Prescribed or eligible for 1L PARPi monotherapy maintenance therapy	1459
	Prescribed PARPi monotherapy maintenance therapy	172
	Eligible for PARPi monotherapy maintenance therapy	1287
14§	Cohort selection	
	PARPi cohort: patients received CYP i/i	158
	PARPi eligible cohort: patients received CYP i/i	1253

1L, first-line; CYP i/i, cytochrome P450 inhibiting/inducing medications; EHR, electronic health record; OC, ovarian cancer; PARPi, poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor.

* Criteria used to select patients for line of therapy assessment.

† 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.

‡ Defined as ≥1 of the following criteria: Stage III or IV OC from enriched oncology data; "T3" extent of ovarian tumor spread via American Joint Committee on Cancer (AJCC) Classification of Malignant Tumours (TNM) staging system from enriched oncology data; "M1" presence of metastasis from OC via AJCC TNM staging system from enriched oncology; ≥1 diagnosis code (ICD-9-CM or ICD-10-CM) for secondary malignancy on or after the initial OC diagnosis from health claims or EHR data; ≥1 physician note on metastatic OC from enriched oncology data.

§ Criteria implemented per study protocol.

Classification of Diseases codes (defined in Table 1) between January 1, 2015 and March 31, 2021. Patients were required to have epithelial histology and have ≥1 clinical encounter (EHR data) or activity (claims data) within 6 months on both sides of index. In addition, patients were required to have received 1L platinum-based therapy with the last dose on/after January 1, 2017 with no prior instances of aOC during the 12 months before the initial OC diagnosis. Finally, patients needed to have a confirmed use (defined as ≥1 pharmacy or service claim) of a CYP medication within the pharmacy insurance eligibility window (90 days before and 120 days after the end of 1L therapy) and were PARPi-eligible or initiated PARPi monotherapy as 1Lm. Ineligible patients included those who were pregnant within 6 months prior to the index date, those treated with bleomycin between January 1, 2014 and March 31, 2021 (to avoid including patients with germ cell tumors, where this agent is standard of care), and those flagged as deceased with a missing death date.

Eligible patients were split into two cohorts:

- PARPi cohort: Patients who were prescribed 1Lm PARPi monotherapy (olaparib, rucaparib, or niraparib).
- PARPi-eligible cohort: Patients who were not prescribed any 1Lm therapy within 120 days after index and did not initiate second-line therapy within 60 days of index date given this may have indicated quick disease progression or a lack of a complete/partial response to 1Lm therapy.

2.3. Data analysis

Summary statistics were used to describe patient demographics, clinical characteristics, PARPi prescriptions, and CYP inhibitor/inducer medications. This study was a purely descriptive analysis with no statistical or hypothesis testing.

Lines of therapy were defined using a rules-based algorithm derived from US treatment guidelines and knowledge of routine clinical practice. 1Lm therapy was defined as PARPi and/or bevacizumab continued after the index date or initiated within 120 days after the index date.

Confirmed CYP inhibitor/inducer medications (including weak, moderate, and strong inducers/inhibitors) were defined using National Drug Codes and Healthcare Common Procedure Coding System procedure codes present on at least one pharmacy or service claim within 90 days before and 120 days after index. Using EMA and FDA guidelines (US Food and Drug Administration, Center for Drug Evaluation and Research, 2020; EMA, 2012), strong and/or 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 and strong and/or moderate CYP inducers were defined as therapies with AUCR ≤ 0.5 or CL ratio ≥2.

The top four strong and/or moderate CYP inhibitor/inducer medication classes were selected based on the total number of patients in the PARPi cohort who were prescribed olaparib or rucaparib.

3. Results

3.1. Patient population

Of a total of 207,466 patients with OC initially considered, 1411 met eligibility criteria and were included in the study (PARPi cohort N = 158; PARPi-eligible cohort N = 1253) (Table 1).

Baseline demographic and clinical characteristics for PARPi and PARPi-eligible cohorts are shown in Table 2. In brief, most patients were non-Hispanic White (PARPi cohort 68.4%, n = 108; PARPi-eligible cohort 59.1%, n = 740) and median age was 63.0 (quartile 1 [Q1], quartile 3 [Q3]: 56.0, 71.8) and 64.0 (Q1, Q3: 56.0, 73.0) years for the PARPi and PARPi-eligible cohorts, respectively. Clinical characteristics including breast cancer gene (*BRCA)* mutation status, Eastern Cooperative Oncology Group (ECOG) performance status, epithelial histology subtype, and disease stage had high levels of missingness and stratified analyses by these variables could not be performed. The median (Q1, Q3) follow-up time was 11.9 months (7.3, 18.4) and 20.1 months (10.1, 32.1) for the PARPi and PARPi-eligible cohort respectively.

Table 2
Patient baseline demographic and clinical characteristics.

	PARPi cohort (n = 158)	PARPi-eligible cohort (n = 1253)
Age (years), 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)
Follow-up (months), median (Q1, Q3)	11.9 (7.3, 18.4)	20.1 (10.1, 32.1)

FIGO, International Federation of Gynecology and Obstetrics; NR, not reported; OC, ovarian cancer; PARPi, poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors; Q1/3, quartile 1/3; US, United States.

* n < 5, thus not reported to maintain patient confidentiality.

† Due to rounding of values, percentages may not add up to 100%.

‡ Patients whose geographical region was unavailable or could not be mapped into one of the US Census Regions (e.g., if the patient lived outside the US).

§ Defined using the nonmissing stage reported during the 6 months period before or 90 days after the initial OC diagnosis based on the following hierarchy: enriched oncology stage value; enriched oncology Classification of Malignant Tumours (TNM) value; enriched oncology physician note on metastatic disease (patient classified as stage IV); presence of a secondary malignancy diagnosis code from claims or electronic health record (patient classified as stage IV). Due to the limitations of the database, FIGO staging at diagnosis was not available.

3.2. Treatment patterns

In the PARPi cohort, 46.2% (n = 73) of patients were prescribed niraparib, 48.7% (n = 77) were prescribed olaparib, and 5.1% (n = 8) were prescribed rucaparib. In total, 38.0% (n = 60) of the PARPi cohort and 33.0% (n = 414) of the PARPi-eligible cohort received strong and/or moderate CYP inhibitor/inducer medications (Fig. 1). Among patients who were prescribed PARPi metabolized by the CYP system (olaparib or rucaparib), 42.4% (n = 36) received strong and/or moderate CYP inhibitor/inducer medications. Antiemetics (substance P/neurokinin 1 receptor antagonists) were the most commonly used strong and/or moderate CYP inhibitor/inducer medication class in both the PARPi and PARPi-eligible cohort (48.3% [n = 29] and 40.8% [n = 169], respectively), followed by antibiotics (fluoroquinolones; 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 (calcium channel blockers; 11.7% [n = 7]; 6.8% [n = 28]). Of note, imidazole-related antifungals excluded topical formulations and therefore were likely to be systemic.

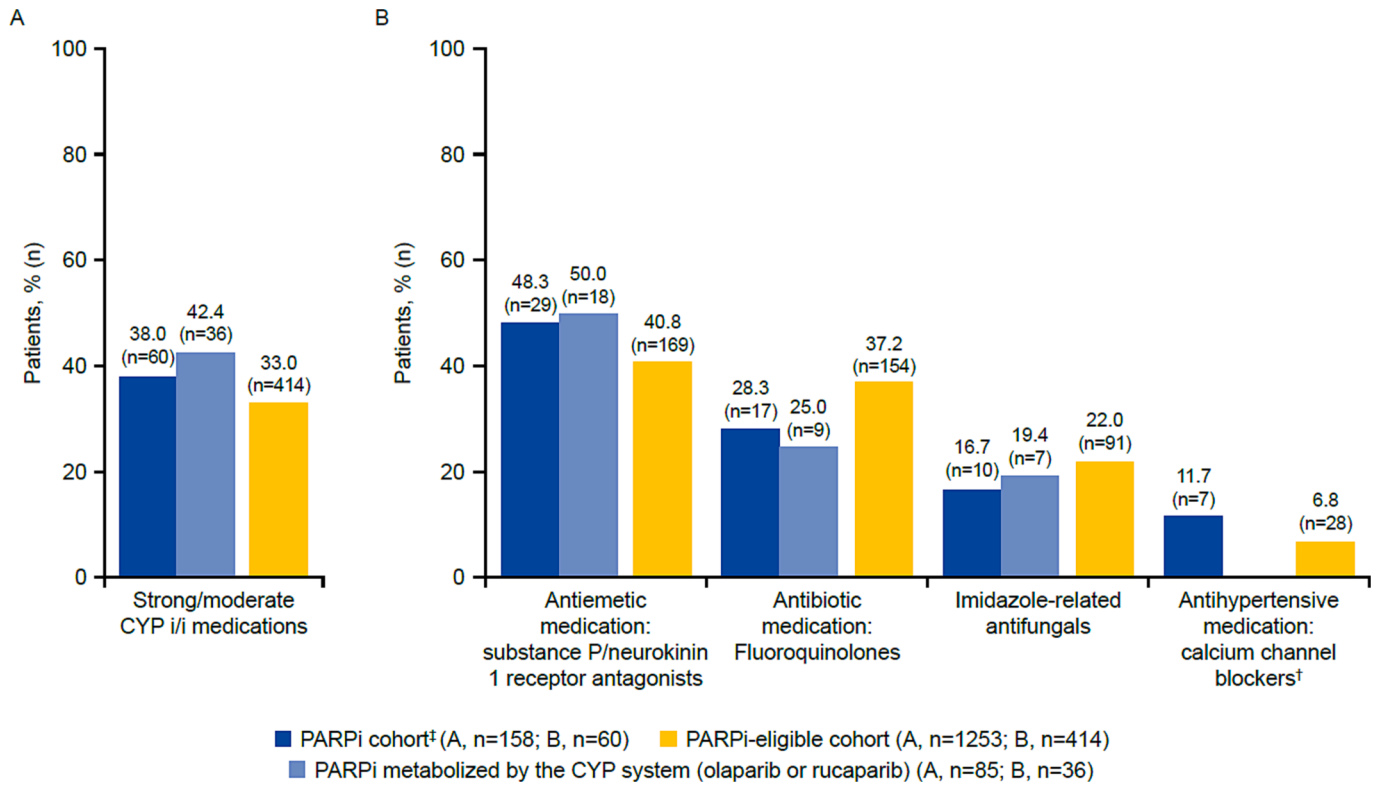

Fig. 1. Strong and/or moderate CYP inhibitor/inducer medications* received in PARPi and PARPi-eligible cohorts. The number of patients in the PARPi metabolized by the CYP system cohort who received topical antifungals was the same as those who received antihypertensive medication (ie, both were listed as the fourth most frequently used strong and/or moderate CYP i/i medication); however, these data are not reported here to maintain patient confidentiality. †n<5 patients in the PARPi metabolized by the CYP system (olaparib and rucaparib), thus not reported to maintain patient confidentiality. ‡Includes olaparib, rucaparib, and niraparib. CYP i/i medications, cytochrome P450 inhibiting/inducing medications; PARPi, poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitor.

4. Discussion

To our knowledge, this is the first real-world study that has assessed treatment patterns among US patients with aOC prescribed or eligible for PARPis in the 1Lm setting. While niraparib has no known interactions with CYP inhibitor/inducer medications or DDIs (GSK, 2023; GSK, 2022); in vitro and ex-vivo studies have shown olaparib and rucaparib interactions with CYP enzymes and DDIs between these PARPis and CYP inhibitor/inducer medications (Friedlander, 2016; AstraZeneca, 2019; Clovis Oncology Inc, 2022). These interactions were not evaluated in clinical studies of olaparib and rucaparib (DiSilvestro, 2021; Ledermann, 2020), and assessments in the real-world setting are limited.

In this study, 33.0% of patients with aOC who were eligible to receive PARPi therapies and 42.4% of patients who were prescribed olaparib or rucaparib, also received a strong and/or moderate CYP inhibitor/inducer medication, despite recommendations for clinicians who treat patients receiving olaparib or rucaparib to avoid strong CYP inhibitor/inducer medications and to exercise caution when using moderate CYP inhibitor/inducer medications (AstraZeneca, 2019; Clovis Oncology Inc, 2022). These results demonstrate that a considerable proportion of US patients prescribed 1Lm PARPis metabolized via CYP system enzymes are at risk of potential DDIs. Therefore, when selecting PARPi therapy, care providers need to be aware of potential interactions with concomitant medication, and refer to recommendations on interaction management and prevention as appropriate (US Food and Drug Administration, Center for Drug Evaluation and Research, 2020; EMA, 2012). Moreover, these data highlight the need for studies to assess the potential impact of DDIs on the efficacy, safety, and tolerability of PARPi therapies, to help educate patients and care providers on concomitant medication use.

The study has some limitations. Firstly, while 1411 patients were included in the study, only 11% of these were prescribed PARPis, with a smaller subset of these being prescribed a PARPi with the potential for a DDI. Moreover, DDIs for these PARPis are poorly understood in both clinical and real-world settings. In addition, although observational cohort studies provide the potential to look across the continuum of care and not just data from hospital settings, using claims and EHR data has the potential for misclassification bias due to coding inaccuracies and missingness in diagnosis, procedure, drug codes, and physician notation (Saesen, 2022). Furthermore, there was a high level of missingness in the enriched oncology real-world database, limiting the data available on some clinical characteristics (eg, *BRCA* mutation status and ECOG performance status), and responses to 1L therapy were not in the scope of the study. The study also implemented the clinical activity requirement before and after index to ensure patients had clinical activity following aOC diagnosis, which could lead to potential patient selection bias by excluding those treated outside the specified window. As the eligibility window started 90 days before the last dose of 1L therapy, it is possible that patients received CYP inhibitor/inducer medications during 1L therapy, rather than concomitantly with PARPi. Information on medication adherence was not captured for this analysis; thus, the degree of overlap and/or temporal relationship between PARPi and CYP inhibitor/inducer medications could not be determined. Finally, although the real-world database includes routine health data from a large cohort (~60 million patients), the patient population selected from the database may not be fully representative of the aOC patient population in the United States, thus limiting the generalizability of the findings.

In conclusion, in this real-world study population, more than 40% of patients with aOC who were prescribed 1Lm olaparib or rucaparib also received strong and/or moderate CYP inhibitors/inducers and thus may have been exposed to potential DDIs during their treatment. These

findings warrant further study to understand the potential impact of concomitant CYP inhibitor/inducer use on the efficacy, safety, and tolerability of PARPi therapies.

Data availability

The deidentified data used were licensed from Optum and are not publicly available but may be made available upon request subject to contracting with Optum. Any such requests or general questions can be submitted using Optum's website: https://www.optum.com/business/insights/life-sciences/page.hub.contact-life-sciences.html.

Footnote

Trademarks are the property of their respective owners.

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CRediT authorship contribution statement

Bobbie J. Rimel: Conceptualization, Methodology, Writing – review & editing. **Dana M. Chase:** Conceptualization, Methodology, Writing – review & editing. **Jessica Perhanidis:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Armen A. Ghazarian:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Ella Xiaoyan Du:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Travis Wang:** Conceptualization, Formal analysis, Methodology, Software, Writing – review & editing. **Jinlin Song:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Amanda K. Golembesky:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Jean A. Hurteau:** Conceptualization, Methodology, Writing – review & editing. **Linda Kalilani:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Ritu Salani:** Conceptualization, Methodology, Writing – review & editing. **Bradley J. Monk:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **BJR** has received consulting or advisory fees from Deep6AI, AstraZeneca, and Tesaro, a GSK company; **DMC** 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**, **JAH**, and **LK** 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 from Amgen, Aravive AstraZeneca, Clovis, GOG Foundation, Gradalis ImmunoGen Laekna Health Care, Merck, Mersana Myriad, Nucana Oncomed Oncoquest Pfizer, Roche/Genentech, GSK), speakers' bureau fees (Clovis, Merck, Roche/Genentech, GSK), honoraria (Amgen, Aravive AstraZeneca, Clovis, GOG Foundation, Gradalis ImmunoGen Laekna Health Care, Merck, Mersana Myriad, Nucana Oncomed Oncoquest Pfizer, Roche/Genentech, GSK).

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