Utilization of poly(ADP-ribose) polymerase inhibitors in ovarian cancer: a retrospective cohort study of US healthcare claims data

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Supplementary material

Supplementary methods

Sensitivity analyses were performed to test the robustness of estimates; these included:

1. Analysis of incident clinical events of interest (CEIs) (ie for each CEI, patients with evidence of that CEI at baseline were excluded) for each poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) index regimen by starting dose, specifically below the indicated dose and at the highest indicated dose
2. A reduction of the permitted treatment gap from 90 days to 60 and 45 days in the calculation of persistence
3. Analysis of CEIs by index PARPi regimen for the subpopulation of patients who persisted with their PARPi regimen

Supplementary Table 1. US FDA approved indications and approval timelines of licensed PARPi

Drug	Indication	Year of approval
Olaparib [1]	Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy	2014
	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy	2017
	Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy	2018
	In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status (either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)	2020
Niraparib [2]	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	2017
	Treatment of adult patients with advanced ovarian, fallopian tube or primary peritoneal cancer who have been treated with ≥3 prior chemotherapy regimens and whose cancer is associated with HRD-positive status (a deleterious or suspected deleterious BRCA mutation, or genomic instability and with disease progression more than 6 months after response to the last platinum-based chemotherapy)	2019
	Maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy	2020
Rucaparib [3]	Treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube or primary peritoneal cancer who have been treated with ≥2 chemotherapies	2016
	Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	2018

Supplementary Table 2. ICD-9/10 code criteria for diagnosis of ovarian cancer

Code type	Code	Description
ICD-9-CM DX	1830	Malignant neoplasm of ovary
ICD-9-CM DX	1832	Malignant neoplasm of fallopian tube
ICD-9-CM DX	1580	Malignant neoplasm of retroperitoneum
ICD-9-CM DX	1588	Malignant neoplasm of specified parts of peritoneum
ICD-9-CM DX	1589	Malignant neoplasm of peritoneum, unspecified
ICD-10-CM DX	C561	Malignant neoplasm of right ovary
ICD-10-CM DX	C562	Malignant neoplasm of left ovary
ICD-10-CM DX	C569	Malignant neoplasm of unspecified ovary
ICD-10-CM DX	C5700	Malignant neoplasm of unspecified fallopian tube
ICD-10-CM DX	C5701	Malignant neoplasm of right fallopian tube
ICD-10-CM DX	C5702	Malignant neoplasm of left fallopian tube
ICD-10-CM DX	C480	Malignant neoplasm of retroperitoneum
ICD-10-CM DX	C481	Malignant neoplasm of specified parts of peritoneum
ICD-10-CM DX	C482	Malignant neoplasm of peritoneum, unspecified
ICD-10-CM DX	C488	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum

Supplementary Table 3. Prevalence of CEI during 6-month pre-index baseline period by index PARPi regimen

Presence of CEI, n (%)	Olaparib N=303	Niraparib N=348	Rucaparib N=162
Any	277 (91.4)	325 (93.4)	139 (85.8)
Hematologic	157 (51.8)	192 (55.2)	69 (42.6)
AML/MDS	0 (0)	2 (0.6)	0 (0)
AML	0 (0)	1 (0.3)	0 (0)
MDS	0 (0)	1 (0.3)	0 (0)
Anemia[a]	110 (36.3)	119 (34.2)	49 (30.2)
Leukopenia/neutropenia[b]	87 (28.7)	98 (28.2)	36 (22.2)
Thrombocytopenia or transfusion	66 (21.8)	91 (26.1)	35 (21.6)
Other	262 (86.5)	311 (89.4)	133 (82.1)
Acute kidney injury	15 (5.0)	23 (6.6)	16 (9.9)
Arthralgia	70 (23.1)	74 (21.3)	31 (19.1)
Constipation/diarrhea	58 (19.1)	72 (20.7)	34 (21.0)
Constipation	43 (14.2)	54 (15.5)	27 (16.7)
Diarrhea	21 (6.9)	29 (8.3)	9 (5.6)
Dermatitis/rash/photosensitivity	14 (4.6)	27 (7.8)	13 (8.0)
Dermatitis/rash	13 (4.3)	27 (7.8)	13 (8.0)
Photosensitivity	1 (0.3)	0 (0)	0 (0)
Fatigue	75 (24.8)	76 (21.8)	34 (21.0)
Hypertension	113 (37.3)	140 (40.2)	63 (38.9)
Infection	162 (53.5)	186 (53.4)	81 (50.0)
Insomnia	25 (8.3)	20 (5.7)	14 (8.6)
Nausea/vomiting	106 (35.0)	114 (32.8)	55 (34.0)
Nausea	99 (32.7)	109 (31.3)	55 (34.0)
Vomiting	14 (4.6)	14 (4.0)	7 (4.3)
Pneumonitis	1 (0.3)	1 (0.3)	0 (0)
Transaminitis	0 (0)	5 (1.4)	2 (1.2)

[a]CEI based on total claims comprising a diagnosis code only; [b]CEI based on total claims comprising a diagnosis code only, a procedure code only, or both a diagnosis and a procedure code

Supplementary Table 4. Association between PARPi treatment group and rate of any, hematologic, and other clinical events of interest

Pairwise comparison of PARPi treatment groups	Any CEI			Hematologic CEI			Other CEI		
	HR	LCL	UCL	HR	LCL	UCL	HR	LCL	UCL
Rucaparib versus olaparib	1.1604	0.9421	1.4291	1.2474	0.9528	1.6331	1.2151	0.9825	1.5028
Niraparib versus olaparib	1.3452	1.1375	1.5909	1.4756	1.1932	1.8249	1.2875	1.0845	1.5284
Niraparib versus rucaparib	1.1593	0.9502	1.4144	1.1829	0.9206	1.5200	1.0595	0.8661	1.2962

Analysis by multivariable Cox proportional hazards regression stratified by presence of a relevant CEI at baseline and adjusted for index PARPi regimen, CCI score, prior treatment with bevacizumab, and cancer-related surgery during the baseline period. Sample size: N=813; n=715 with any CEI; n=452 with hematologic CEI; n=679 with other CEI. LCL, 95% lower confidence limit; UCL, 95% upper confidence limit

Supplementary Table 5. Association between PARPi treatment group and time to discontinuation of the PARPi regimen

Pairwise comparison of PARPi treatment groups	Discontinuation		
	HR	LCL	UCL
Rucaparib versus olaparib	1.4154	1.1063	1.8107
Niraparib versus olaparib	1.5198	1.2428	1.8585
Niraparib versus rucaparib	1.0738	0.8577	1.3443

Analysis by multivariable Cox proportional hazards regression stratified by presence of a relevant CEI at baseline and adjusted for index PARP inhibitor regimen, CCI score, prior treatment with bevacizumab, and cancer-related surgery during the baseline period. Sample size: N=813; n=519 discontinued

Supplementary Table 6. All-cause healthcare-resource utilization and costs PPPM measured during the 6-month pre-index baseline period by index PARPi regimen

	Olaparib N=303	Niraparib N=348	Rucaparib N=162
Inpatient			
Patients with an admission, n (%)	94 (31.0)	98 (28.2)	54 (33.3)
Number of inpatient admissions			
Mean (SD)	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)
Median [IQR]	0.0 [1.0]	0.0 [1.0]	0.0 [1.0]
Length of stay, days			
Mean (SD)	1.6 (2.9)	1.4 (2.7)	1.6 (2.8)
Median [IQR]	0.0 [3.0]	0.0 [2.0]	0.0 [3.0]
Outpatient ER visits			
Patients with an ER visit, n (%)	88 (29.0)	96 (27.6)	35 (21.6)
Number of ER visits			
Mean (SD)	0.6 (1.8)	0.4 (1.1)	0.3 (0.8)
Median [IQR]	0.0 [1.0]	0.0 [1.0]	0.0 [0.0]
Outpatient office visits			
Patients with an office visit, n (%)	300 (99.0)	348 (100.0)***	160 (98.8)†
Number of office visits			
Mean (SD)	11.1 (5.0)	11.3 (5.9)	10.0 (5.3)*†
Median [IQR]	11.0 [6.0]	10.0 [7.0]	9.0 [5.0]
Other outpatient services			
Patients with another outpatient service, n (%)	303 (100.0)	348 (100.0)***	161 (99.4)***
Number of services			
Mean (SD)	23.8 (13.4)	24.2 (12.3)	22.7 (13.4)
Median [IQR]	22.0 [17.0]	22.0 [14.0]	20.0 [12.0]
Outpatient pharmacy			
Patients with a prescription, n (%)	297 (98.0)	344 (98.9)	160 (98.8)
Number of prescriptions			
Mean (SD)	18.3 (14.0)	18.3 (13.1)	18.1 (13.6)
Median [IQR]	15.0 [15.0]	15.0 [15.5]	15.0 [16.0]
Mean monthly inpatient costs (SD)[a]	$13,706 ($28,329)	$12,890 ($32,991)	$12,081 ($26,938)
Mean monthly outpatient costs (SD)[a]	$63,889 ($57,504)	$80,083 ($78,470)**	$67,961 ($66,585)
ER visits	$1265 ($5197)	$696 ($2154)	$393 ($1129)*

Outpatient office visits Other outpatient services costs	$1994 ($1453) $60,630 ($56,748)	$1888 ($1576) $77,498 ($77,904)**	$1753 ($1479) $65,815 ($66,271)
Mean monthly outpatient pharmacy costs (SD)[a]	$2677 ($5952)	$2330 ($5002)	$2139 ($6027)
Mean monthly total medical costs, excluding pharmacy (SD)[a]	$77,595 ($68,159)	$92,973 ($88,694)*	$80,042 ($72,704)
Mean monthly total costs (SD)[a]	$80,272 ($68,465)	$95,304 ($88,942)*	$82,181 ($73,025)

*P<0.05 versus olaparib; **P<0.01 versus olaparib; ***P<0.001 versus olaparib; †P<0.05 versus niraparib; statistical comparisons were performed using chi-squared or Fisher's exact tests for categorical variables and t-tests for continuous variables. [a]All dollar estimates are reported PPPM to account for variation in duration of the index PARP inhibitor regimen and were adjusted for inflation using the Medical Care Component of the Consumer Price Index and standardized to the value of the US dollar in 2018. In addition to costs, rows representing number of services have also been standardized to PPPM

Supplementary Table 7. Prevalence of incident CEIs during the follow-up period by index PARPi regimen, based on starting dose

Below highest indicated dose			
Presence of incident[a] CEI, n (%)	**Olaparib N=31**	**Niraparib N=107**	**Rucaparib N=9**
Any	19 (61.3)	78 (72.9)	NC
Hematologic	11 (35.5)	39 (36.4)	NC
Other	18 (58.1)	70 (65.4)	NC
Highest indicated dose[b]			
Presence of incident[a] CEI, n (%)	**Olaparib N=271**	**Niraparib N=241**	**Rucaparib N=151**
Any	163 (60.1)	192 (79.9)***	110 (72.8)**
Hematologic	66 (24.4)	107 (44.4)***	53 (35.1)*
Other	143 (52.8)	155 (64.3)**	103 (68.2)**

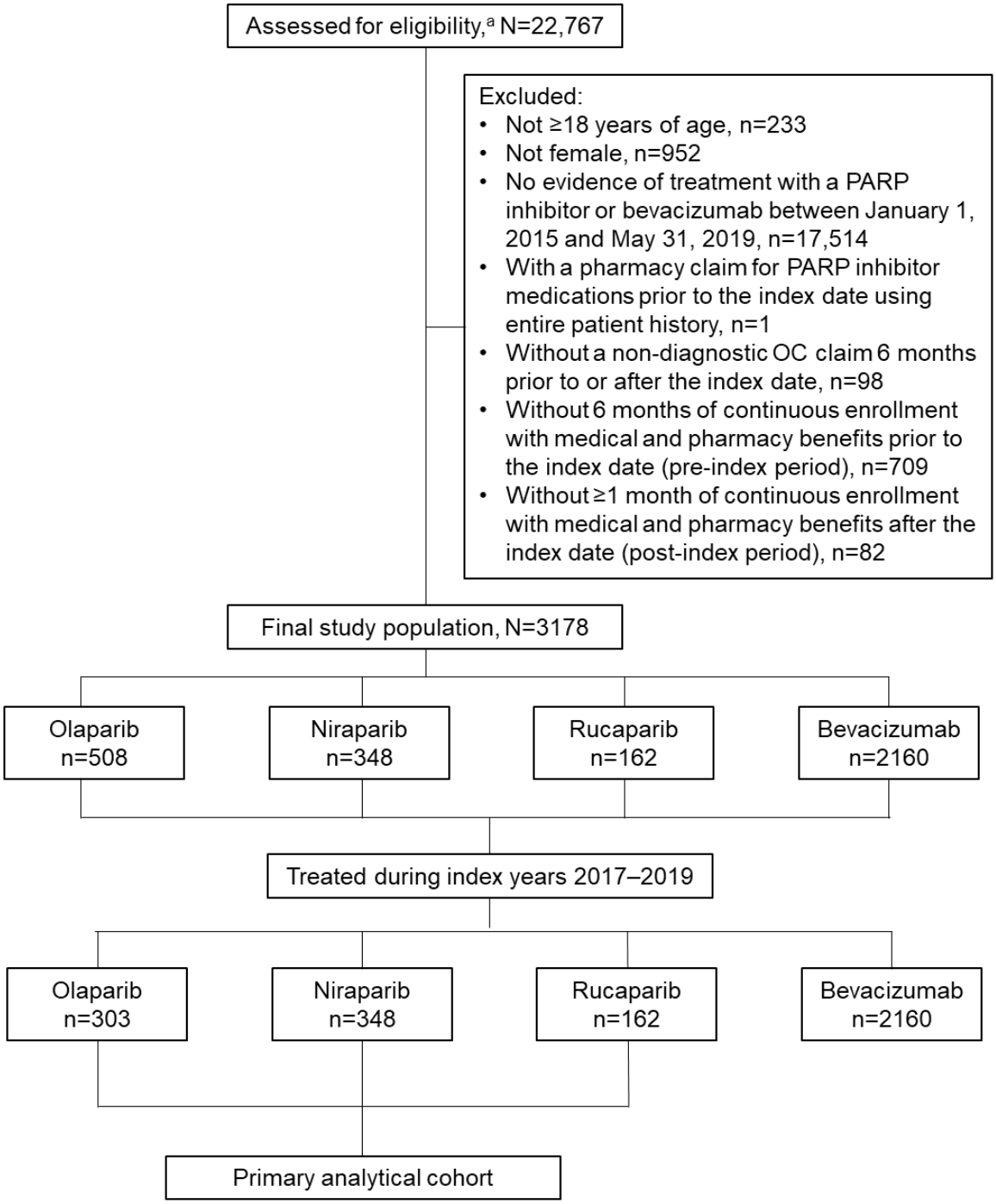
*P<0.05 versus olaparib; **P<0.01 versus olaparib; ***P<0.001 versus olaparib; statistical comparisons were performed using chi-squared or Fisher's exact tests for categorical variables. [a]Patients with evidence of a relevant CEI at baseline were excluded; [b]Highest indicated doses were taken from the prescribing information for each PARPi as 600, 800, 300, and 1200 mg/day for olaparib tablets, olaparib capsules, niraparib capsules, and rucaparib tablets, respectively. NC, not calculable

Supplementary Table 8. Persistence among patients with at least 6 months of continuous enrollment by index PARPi regimen

	Olaparib N=172	**Niraparib N=251**	**Rucaparib N=117**
Persistence[a] (no treatment gaps of >45 days) with the index PARPi regimen, n (%)	99 (57.6)	74 (29.5)***	54 (46.2)
Persistence[a] (no treatment gaps of >60 days) with the index PARPi regimen, n (%)	103 (59.9)	85 (33.9)***	55 (47.0)*

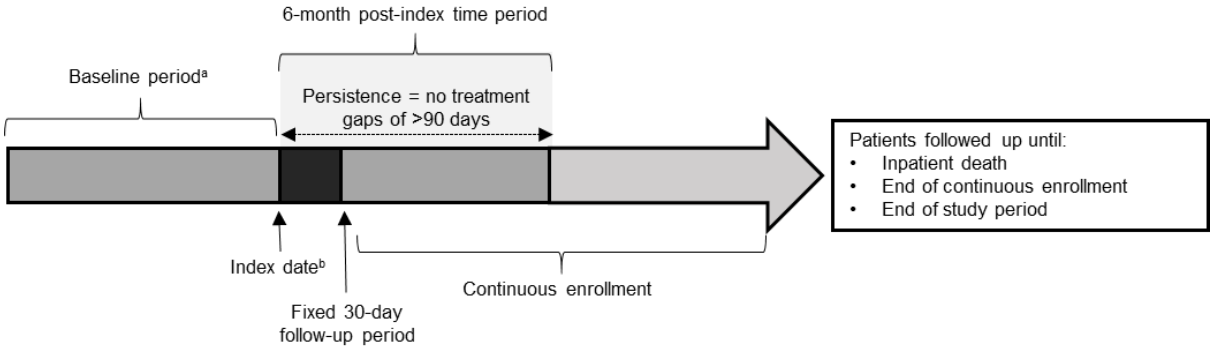
*P<0.05 versus olaparib; ***P<0.001 versus olaparib; statistical comparisons were performed using chi-squared or Fisher's exact tests for categorical variables. [a]Persistence was determined among the subset of patients who had at least 6 months of follow-up and was indicated by no treatment gaps of >45 or >60 days during the 6-month post-index period

Supplementary Figure 1. Patient attrition and selection



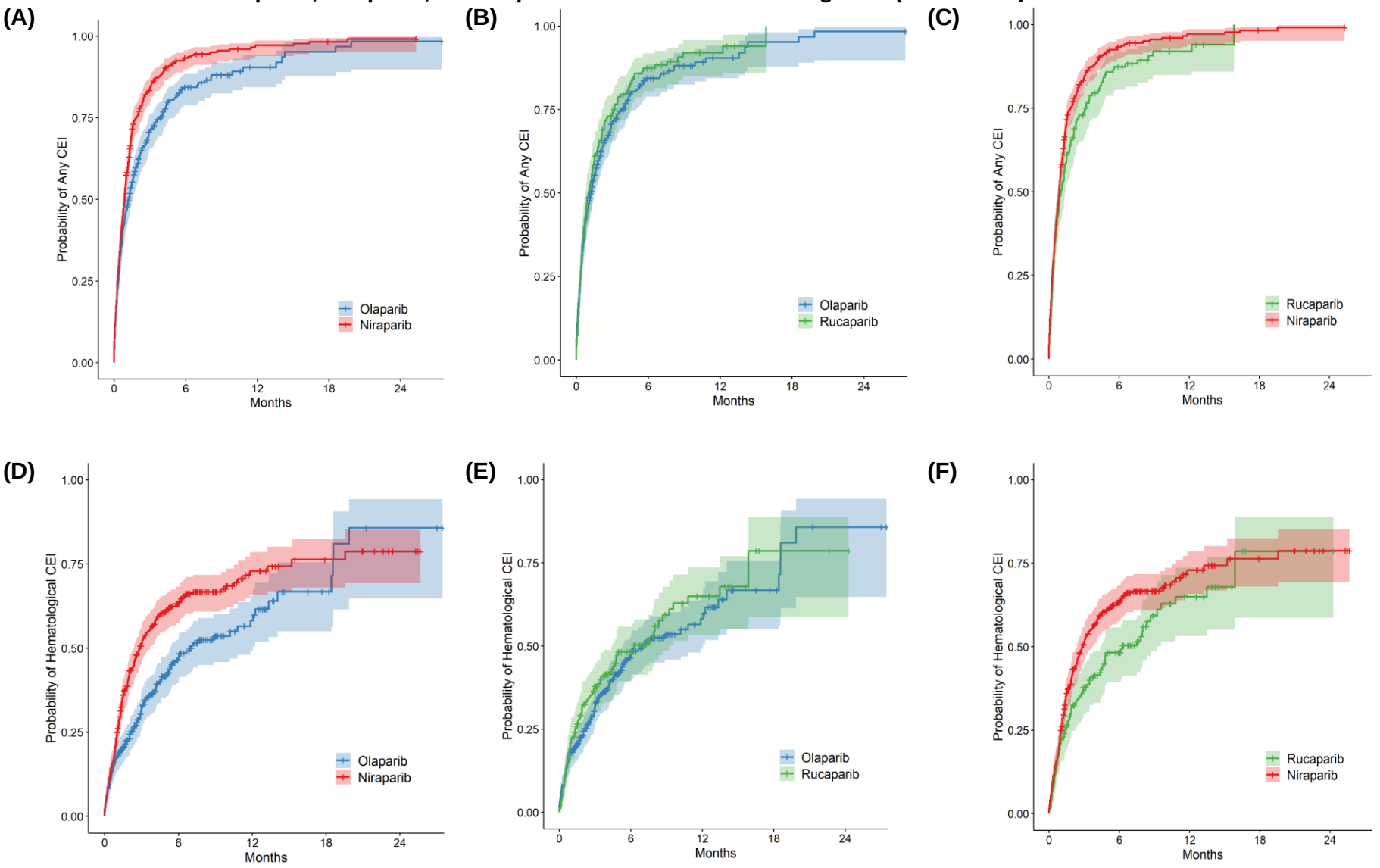
[a]Patients in the MarketScan® Commercial or Medicare Supplemental Databases with an ICD-9-CM or ICD-10-CM diagnosis code on one inpatient claim in any position or two non-diagnostic outpatient claims for epithelial ovarian, fallopian tube, or primary peritoneal cancer 30–365 days apart between January 1, 2015 and May 31, 2019 (first ovarian cancer diagnosis during the patient selection period = index date)

Supplementary Figure 2. Diagram illustrating definition of persistence with PARPi index regimen



[a]At least 6 months of continuous enrollment in medical and pharmacy benefits and no prior PARPiclaims in the patient history before the index date; [b]Date of first PARPi treatment

Supplementary Figure 3. Kaplan–Meier curves showing time to (A–C) any and (D–F) hematologic CEIs in women with ovarian cancer treated with olaparib, niraparib, or rucaparib as the index PARPi regimen (2017–2019)



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1. AstraZeneca. Lynparza® (olaparib) tablets, for oral use. US prescribing information. 2019.
2. Tesaro. Zejula (niraparib) capsules, for oral use. US prescribing information. 2020.
3. Clovis Oncology. Rubraca® (rucaparib) tablets, for oral use. US prescribing information. 2020.