Poly ADP-Ribose Polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value

Final Evidence Report

September 28, 2017

Prepared for

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The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

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Expert Review

In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input and feedback that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit this site.

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List of Acronyms Used in this Report

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine transaminase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
BID	Bis in die (twice a day)
BRCAm	BReast CAncer Mutation (somatic and germline)
BRCAwt	BReast CAncer wild-type
CADTH	Canadian Agency for Drugs and Technologies in Health
CR	Complete response
CTCAE	Common terminology criteria for adverse events
DCR	Disease control rate
DoR	Duration of response
ECOG PS	Eastern Coperative Oncology Group performance status
FACT-O	Functional Assessment of Cancer Therapy-Ovarian
FIGO	International Federation of Gynecology and Obstetrics
FOSI	FACT/NCCN Ovarian Symptom Index
gBRCAm	Germline BReast CAncer mutation
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
LOH	Loss of Heterozygosity
MDS	Myelodysplastic syndrome
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PAC+C	Paclitaxel with carboplatin
PARP	Poly ADP ribose polymerase
pCODR	Pan-Canadian Oncology Drug Review
PFI	Platinum-free interval
PFS	Progression-free survival
PLD (+C)	Pegylated liposomal doxorubicin (with carboplatin)
PO	Per os (orally)
PR	Partial reponse
QAPFS	Quality adjusted progression-free survival
QD	Quaque die (once a day)
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
sBRCAm	Somatic Breast Cancer mutation
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent treatment
TOI	Trial Outcome Index
TSST	Time to second subsequent treatment
TWiST	Time without symptoms of disease or toxicity
Tx	Treatment
USPSTF	US Preventive Services Task Force
VEGF-A	Vascular endothelial growth factor-specific angiogenesis

Executive Summary

Background

Ovarian cancer is the most common cause of gynecologic cancer death and fifth-leading cause of cancer death in women.[1,2] Due to the lack of early symptoms and absence of an accurate screening strategy, nearly 75% of women with ovarian cancer are diagnosed with advanced disease at presentation.[3,4] At this stage of disease, recurrence is common and prognosis is guarded; those who continue through three or more lines of therapy are likely to die or experience recurrence within six months.[5]

There are several options for patients when they experience recurrence, including several chemotherapy regimens and the vascular endothelial growth factor-specific angiogenesis (VEGF-A) inhibitor bevacizumab. Recently, ongoing trials have indicated promising results for a newer class of targeted oral agents, poly ADP-ribose polymerase (PARP) inhibitors. In ovarian cancer treatment, PARP inhibitors have primarily been studied in two populations: (1) as treatment for BRCA-mutated recurrent disease after multiple prior lines of chemotherapy; and (2) as maintenance therapy in patients with two or more prior lines of platinum-based chemotherapy who were in complete or partial response to their most recent regimen.

The Topic in Context

Epithelial ovarian cancers account for about 90% of all cancers of the ovaries. Most women with ovarian cancer are diagnosed at later stages, and those with multiple prior lines of treatment have a high likelihood of disease progression or death within six months.[5] High-grade serous tumors represent a particularly challenging subtype, with 5-year survival rates currently estimated at 35-40%.[6]

First-line therapy includes debulking cytoreductive surgery, in which the uterus, ovaries, and fallopian tubes are commonly removed, as well as neoadjuvant or postoperative/adjuvant therapy with a platinum (e.g., cisplatin, carboplatin) and a taxane agent (e.g., paclitaxel, docetaxel) or liposomal doxorubicin.[7-9] For recurrence, several chemotherapy regimens (e.g., docetaxel, paclitaxel, gemcitabine, liposomal doxorubicin, topotecan and etoposide) may be used, with or without the VEGF-A inhibitor bevacizumab.

Less than a decade ago, there was no evidence to support the use of maintenance therapy with platinum agents, liposomal doxorubicin, or paclitaxel to prevent recurrence.[10] However, two recent trials showed that the addition of bevacizumab to first-line carboplatin and paclitaxel, followed by bevacizumab monotherapy as maintenance therapy, prolonged progression-free survival (PFS) by approximately four months.[9,11] During this period, attention turned to subsets of patients with

genetic mutations affecting DNA repair. Identification of these mutations led to the development of poly ADP-ribose polymerase (PARP) inhibitors.

Poly ADP-ribose polymerase (PARP) Inhibitors

BReast CAncer (BRCA) genes *BRCA1* and *BRCA2* produce tumor suppressor proteins; mutations in either of these genes can cause improper repair of DNA, making an individual more susceptible to ovarian cancer.[12] BRCA mutations can either be inherited (i.e., germline BRCA mutations) or they can occur de novo in tumor tissue (i.e., somatic BRCA mutations). Mutations of *BRCA1* or *BRCA2* provide a target upon which to treat some ovarian cancers because they increase tumor sensitivity to DNA-damaging agents such as PARP inhibitors.[13]

Initially, PARP inhibitors were evaluated in patients with germline *BRCA1* and *BRCA2* mutations.[14-16] Two of the PARP inhibitors (rucaparib [Rubraca™; Clovis Oncology] and olaparib [Lynparza™; AstraZeneca]) were primarily tested in populations selected based on BRCA mutation status. Then, during late 2016, the NOVA trial of the PARP inhibitor niraparib (Zejula™; Tesaro) suggested that PARP inhibitors may be efficacious as maintenance therapy regardless of whether patients have germline BRCA mutations, albeit to varying degrees.[17] The table below (Table ES1) summarizes the PARP inhibitors that are FDA-approved for the treatment of advanced ovarian cancer.

Table ES1. PARP Inhibitors of Interest for the Evidence Review

PARP Inhibitor	Indication	Recommended Dose & Treatment Duration	Dosage Forms & Strengths	Date of FDA Approval	WAC per Month (USD)*
Olaparib (Lynparza™, AstraZeneca)[18]	1) Monotherapy for patients with deleterious or suspected deleterious germline BRCA-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy 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	300 mg BID (PO) tablets until disease progression or unacceptable toxicity	Tablets: 100 mg 150 mg	1) December 19, 2014 2) August 17, 2017	$13,679
Rucaparib (Rubraca®, Clovis Oncology)[19∞]	Monotherapy for patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic	600 mg BID (PO) until disease progression or unacceptable toxicity	Tablets: 200 mg 250 mg 300 mg	December 19, 2016	$13,940
Niraparib (Zejula™, Tesaro, Inc.)[20]	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	300 mg QD (PO) until disease progression or unacceptable adverse reaction	Capsules: 100 mg	March 27, 2017	$14,965

*Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed August 22, 2017), and is based on indicated dose; ∞ Rucaparib does not yet have a maintenance indication from the FDA but was included in the review of maintenance therapies for platinum-sensitive disease based on newly-published data.

Insights Gained from Discussions with Patients and Patient Groups

Our discussions with patient groups indicated that patients with recurrent ovarian cancer experience a great amount of anxiety about the low likelihood of cure and poor survival rates. Anxiety also comes from the non-specific nature of symptoms. For example, patients told us that because abdominal pain is both a toxicity of treatment and an indicator of disease progression, there is a hyper-awareness that occurs when those symptoms are present. Psychosocial support from nurses and physicians is considered critically important because of this.

Treatments, particularly the cytotoxic chemotherapies that are the historical standard of care, cause substantial toxicity and burden to patients and their families. PARP inhibitor side effects are generally considered tolerable compared to chemotherapy and can usually be managed through dose modifications.

Patients with ovarian cancer struggle with financial difficulties related to the costs of initial surgery and multiple lines of therapy. Patients who do not have a support system, partner, or family, have a more difficult time coping with the disease and treatment.

Comparative Clinical Effectiveness

We reviewed the clinical evidence of three Poly ADP-ribose Polymerase (PARP) inhibitors according to their current and/or anticipated indications. We assessed olaparib and rucaparib for patients who have a deleterious BRCA-mutation and who have relapsed after initial cytoreductive surgery and subsequent lines of chemotherapy (i.e., "recurrent, BRCA-mutated disease"). We considered bevacizumab in combination with standard chemotherapy and pegylated liposomal doxorubicin with carboplatin to be relevant comparators based on input from clinical experts.

We also reviewed olaparib, niraparib and rucaparib in platinum-sensitive women who have received at least two prior platinum-based chemotherapy regimens, were in complete or partial response to the most recent regimen, and were candidates for maintenance therapy (i.e., "maintenance therapy for platinum-sensitive disease"). We considered placebo (i.e., surveillance only) and bevacizumab as comparators of interest.

To inform our analysis, we abstracted evidence from available clinical studies of these agents, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents). The primary outcomes of interest included overall and progression-free survival, overall objective response, health-related quality of life, and harms.

The literature search identified six studies and a total of 15 references. Overall, we included four references focusing on treatment of BRCA-mutated recurrent disease and 11 references related to maintenance treatment of platinum-sensitive disease. After the publication of our evidence report, the results of an additional RCT relevant to the population of patients eligible for maintenance

treatment of platinum-sensitive disease were published (ARIEL3); although this study was not identified through our original literature search, we included its results in the current report.

In total, we identified four peer-reviewed published studies that included a control arm. Using criteria published by the US Preventive Services Task Force (USPSTF; see Appendix D), we rated one of these studies to be fair due to the potential loss of randomization after retrospective identification of BRCA mutation subgroups (see Study 19 of olaparib maintenance below) and the other three studies (NOVA trial of niraparib maintenance, ARIEL3 of rucaparib maintenance and SOLO2 trial of olaparib maintenance) to be of good quality. Single-arm studies and studies that were only available in grey literature sources were not assigned a quality rating.

Due to key differences in trial eligibility criteria, baseline characteristics of patient populations (e.g., BRCA mutation type/status, number of prior chemotherapies, platinum sensitivity), and evaluation protocols for tumor assessment (e.g., different intervals between scheduled measurements of response, assessment by investigator vs. blinded independent central review), we did not attempt to compare the PARP inhibitors to each other. Key differences across trials are summarized in Table ES2.

Table ES2. Comparability of Available Data Assessing PARP Inhibitors for Recurrent, BRCA-Mutated Disease and Maintenance Therapy for Platinum-Sensitive Disease

Comparison Variables for Evidence of Treatment of Recurrent, BRCA-Mutated Disease		
	Study 42 (Olaparib)	**ARIEL2 (Rucaparib)**
Platinum Sensitivity	Platinum-resistant/refractory patients made up 69% of analysis group; platinum-sensitive patients (29%) were deemed ineligible for further platinum-based therapy*	Results were stratified by platinum sensitive (immediate prior tx=platinum), platinum sensitive (immediate prior tx=non-platinum), and platinum resistant
# of Prior Chemotherapies	82% of patients had ≥3 prior chemotherapies	76% of patients had ≥3 prior chemotherapies
Deleterious BRCA Mutation	Included only patients with germline BRCA mutations	Included patients with BRCA mutations of germline, somatic, and uncertain origins
Outcome Measurement	Investigator-assessed tumor assessments using RECIST v1.1 occurred every 8 weeks for first 6 months, then every 12 weeks	Investigator-assessed tumor assessments using RECIST v1.1 occurred every 8 weeks for the first 4.5 months, then every 16 (±2) weeks

Comparison Variables for Evidence of Maintenance Therapy for Platinum-Sensitive Disease				
	Study 19 (Olaparib)	**SOLO2 (Olaparib)**	**ARIEL3 (Rucaparib)**	**NOVA (Niraparib)**
BRCA Mutation	All BRCA status (positive and negative) included. Retrospective BRCA mutation analysis included germline and somatic BRCA.	Any documented deleterious or suspected deleterious BRCA mutation for enrollment; confirmatory testing showed 97% gBRCA in each arm.	Study design included BRCAm (germline and somatic) and non-BRCAm (wildtype).	Study designed with two cohorts: germline BRCA mutation and non-germline BRCA mutation (included somatic and wild-type)
HRD Testing	None	None	Included	Included
Tumor Assessment Schedule	Every 12 weeks until week 60 and every 24 weeks thereafter	Every 12 weeks until week 72 then every 24 weeks until disease progression	Every 12 weeks until death, loss to follow-up, withdrawal of consent, or study closure	Every 8 weeks through cycle 14 (28-day continuous cycles), and then every 12 weeks until treatment discontinuation
Investigator vs. Blinded Independent Central Review (BICR) of PFS	Primary endpoint: Investigator-assessed PFS Sensitivity analysis: BICR PFS	Primary endpoint: Investigator-assessed PFS Sensitivity analysis: BICR PFS	Primary endpoint: Investigator assessed PFS Secondary endpoint: BICR PFS	Primary endpoint: BICR PFS Sensitivity analysis: Investigator-assessed PFS
RECIST Version	RECIST v 1.0	RECIST v 1.1	RECIST v 1.1	RECIST v 1.1
Quality of Life Instrument	FACT-O, FOSI and TOI	TOI	FOSI-18	FOSI and EQ-5D
Dosing/Formulation	400 mg BID/Capsules	300 mg BID/Tablets	600 mg BID/Tablets	300 mg QD/Capsules

Summary of recurrent, BRCA-mutated disease evidence based on Study 42 and ARIEL2 subgroup analyses;[21-23] *platinum status unknown in 2% of patients; tx=treatment; PFS=progression-free survival; BICR=blinded independent central review

Olaparib

Olaparib for Recurrent, BRCA-Mutated Disease

Data to inform our assessment of olaparib in patients with recurrent, BRCA-mutated disease were derived from a subgroup analysis of one single-arm trial (Study 42).[21,22] Median overall survival was 16.6 months and progression-free survival (PFS) was 6.7 months. While not a direct comparison, analyses of standard relapse therapies suggest an overall survival of 6-9 months and PFS of 4-6 months in similar patients.[5] Patients with platinum sensitivity had a longer median PFS (9.4 months) than platinum-resistant patients (5.5 months). Data on patient-reported outcomes such as health-related quality of life were not reported.

Olaparib for Maintenance Therapy in Platinum-Sensitive Disease

We identified two placebo-controlled RCTs of olaparib maintenance therapy: Study 19 and SOLO2.[24,25] Study 19 was a double-blind, placebo-controlled Phase II trial that enrolled women with platinum-sensitive ovarian cancer, irrespective of BRCA mutation (BRCAm) status. The second RCT of olaparib, SOLO2, was intended to replicate Study 19's trial design. However, a key difference between Study 19 and SOLO2 was the use of different dosing formulations of olaparib: in Study 19, patients received eight 50 mg capsules twice daily (400 mg BID), while SOLO2 patients received a new tablet formulation dosed at 300 mg BID. In addition, although SOLO2 allowed enrollment of any deleterious or suspected deleterious BRCA 1/2 mutations, a confirmatory BRCA test showed 97% of enrollees had a germline BRCA mutation.

Data from Study 19 showed no overall survival benefit with olaparib for either the entire study population or the subgroup with a BRCA mutation;[26] overall survival data in the SOLO2 trial are still immature but currently show no difference between groups.[25] Both RCTs indicate improved progression-free survival compared to placebo, especially in the presence of a deleterious BRCA mutation.[24,25,27] In the full Study 19 cohort, median progression-free survival was 8.4 months for olaparib and 4.8 months for placebo (hazard ratio 0.35; 95% CI 0.25 to 0.49).[24] In a subgroup analysis of patients with deleterious BRCA mutations (BRCAm), progression-free survival was 11.2 months in the olaparib arm and 4.3 months in the placebo arm (HR 0.18; 95% CI 0.10 to 0.31); benefits were less pronounced with wild-type BRCA mutations (7.4 months vs. 5.5 months; HR 0.54; 95% CI 0.34 to 0.85).[27] Data from the SOLO2 study showed a nearly 14-month progression-free survival benefit with olaparib for women with germline BRCA mutations (median 19.1 months vs. 5.5 months; hazard ratio 0.30; 95% CI 0.22 to 0.41).[25] A larger benefit was observed when PFS was assessed using blinded central review, but the investigators could not rule out the possibility that informed censoring contributed to the difference.

There were no significant differences in quality of life observed between olaparib and placebo.

Niraparib

Niraparib for Recurrent, BRCA-Mutated Disease

We found no studies of niraparib for the treatment of relapsed disease, but note that a relevant study (QUADRA trial; NCT02354586) is ongoing and is described in Appendix C.

Niraparib for Maintenance Therapy in Platinum-Sensitive Disease

We identified one good-quality randomized controlled trial for niraparib maintenance therapy (NOVA).[17] The NOVA trial was a double-blind Phase III trial of niraparib (300 mg QD) versus placebo that included platinum-sensitive patients from two independent cohorts based on the presence or absence of a germline BRCA mutation (gBRCAm). Mature overall survival data are not yet available from this trial. Median progression-free survival was significantly longer in those taking niraparib compared to placebo in patients with both germline (21.0 vs. 5.5 months; HR 0.27; 95% CI 0.17 to 0.41) and non-germline BRCA mutations (9.3 vs. 3.9 months; HR 0.45; 95% CI 0.34 to 0.61). There were no significant differences in quality of life observed between niraparib and placebo.

Rucaparib

Rucaparib for Recurrent, BRCA-Mutated Disease

To inform our assessment of rucaparib for recurrent, BRCA-mutated disease, we reviewed two subgroup analyses from the single-arm Phase II ARIEL2 trial.[23,28] Overall survival data for rucaparib are not yet available. Progression-free survival was approximately 10 months with rucaparib. Platinum-sensitive patients whose immediate prior treatment was a platinum therapy experienced a longer PFS (median 12.7 months; 95% CI 9.0 to 14.7). While not a direct comparison, analyses of standard ovarian cancer treatments suggest a median PFS of approximately 6 months in similar patients.[5] Patient-reported outcomes have not been reported.

Rucaparib for Maintenance Therapy in Platinum-Sensitive Disease

We found one study of rucaparib as maintenance therapy in platinum-sensitive disease (ARIEL3) published just prior to our public meeting on September 14, 2017.[29] These data were not discussed during the public meeting but are summarized in this final report. Overall survival data are not yet mature. Median progression-free survival was significantly longer in those taking rucaparib compared to placebo in patients with a BRCA mutation (16.6 vs. 5.4 months; HR 0.23; 95% CI 0.16 to 0.34), those with homologous recombinantion deficiency (13.6 vs. 5.4 months; HR 0.32; 95% CI 0.24 to 0.42), and in the intent-to-treat population (10.8 vs. 5.4 months; HR 0.36; 95% CI 0.30 to 0.45). There were no significant differences in quality of life observed between rucaparib and placebo.

Harms

Adverse event (AE) frequencies and rates of Grade 3-4 (severe and life-threatening) events are reported by regimen in Table ES3. The most common side effects of PARP inhibitors are nausea, vomiting, anemia, thrombocytopenia, and neutropenia. The most serious complications are myelodysplastic syndrome and acute myeloid leukemia, which have been reported in a small minority of patients (0-2%). Dose reduction due to toxicity appears to occur at a higher rate with niraparib (67%) than with the other two PARP inhibitors (22-25% and 49-55% with olaparib and rucaparib, respectively), and reported rates of both grade 3-4 neutropenia (20%) and thrombocytopenia (34%) were also considerably higher with niraparib. In most cases, dose reductions sufficiently addressed side effects. These harms appear to be less severe in general than those experienced with many chemotherapeutic agents.

Table ES3. Adverse Events of Olaparib, Niraparib, and Rucaparib

	Olaparib[21,24,25,27,30‡]	Niraparib*[17]	Rucaparib*[23,28,29,31]
Any Adverse Events	96-99%	100%	100%
Any Adverse Events Grade ≥3	32-55%	74%	48-61%
Any SAE	18-30%	30%	21-25%
Any Adverse Events Leading to Dose Reduction	22-25%	67%	49-55%
Any Adverse Events Leading to Discontinuation of Study Treatment	2-11%	15%	13%
Any Adverse Events with Outcome of Death	0.5-3%	0	1-2%
Grade ≥3 Adverse Events			
Abdominal Pain	2-8%	1%	0-2%
AST/ALT Increased	2%	NR	10-12%
Anemia	5-24%	25%	18-22%
Fatigue	4-7%	8%	7-9%
Hypertension	NR	8%	NR
MDS/AML	1-2%	1%	0-1%
Nausea	1-3%	3%	4%
Neutropenia	4-5%	20%	5-8%
Thrombocytopenia	0.7-1%	34%	2-3%
Vomiting	2-3%	2%	2-4%

‡Values for olaparib represent range of AEs reported in Study 42, Study 19, and SOLO2; *NOVA trial of niraparib and ARIEL2 and ARIEL3 trials of rucaparib reported treatment-emergent adverse events; AST/ALT=aspartate aminotransferase/alanine aminotransferase; NR=not reported; MDS/AML=myelodysplastic syndrome/acute myeloid leukemia

Comparator Evidence

There are currently no head-to-head studies of a PARP inhibitor versus later-line chemotherapy or maintenance bevacizumab. We did not perform full systematic reviews of comparator drugs but highlight the key outcomes from recent publications of bevacizumab maintenance therapy and pegylated liposomal doxorubicin for recurrent ovarian cancer (see Appendix D).

Controversies and Uncertainties

Multiple limitations in the body of evidence limit our ability to make judgments regarding the comparative net health benefits of the PARP inhibitors relative to each other or alternative therapies used in relapse and maintenance settings. First, final overall survival data demonstrating statistically-significant improvement over historical treatment options are not available. A trend in improved survival over time has meant that many patients receive multiple post-progression therapies, while obscuring the detection of a survival benefit in any individual treatment regimen or clinical trial.

In the maintenance setting, there is ongoing debate about the suitability of PFS to evaluate clinical benefit. Some clinical experts acknowledge that PFS may be a reasonable endpoint for trials of maintenance therapy, arguing that an extension of the interval of time between rounds of cytotoxic chemotherapy may be valuable.[32] Other clinicians are skeptical of the benefit of maintenance therapy, noting that the lack of a clear survival or quality of life benefit do not justify the additional toxicity patients must endure during a time when they would otherwise be appreciating a drug holiday.

There are also specific uncertainties regarding the evidence for individual PARP inhibitors. The benefit of olaparib maintenance therapy was questioned by FDA reviewers because of safety concerns, lack of overall survival data, and data quality (i.e., retrospective identification of BRCA mutation status). Although the SOLO2 trial was meant to be a confirmatory trial of Study 19, SOLO2 was focused exclusively on patients with a deleterious or suspected deleterious germline BRCA mutation and evaluated a different dose and formulation of the drug.[33]

The evidence base for patients with BRCA-mutated recurrent disease is currently limited to one single-arm trial for each of the two agents, and findings from the key single-arm trial of niraparib in this population are not yet available. More importantly, no comparator data are yet available, so the incremental gain in overall survival, progression-free survival, or quality of life compared to another therapy for recurrent ovarian cancer remain unknown.

Perhaps the greatest amount of uncertainty in comparative net health benefit lies in the inability to make comparisons between the PARP inhibitors themselves. The limited number of available studies, major differences in endpoint measurement, and the absence of data for certain key subgroups precluded even indirect comparison of the regimens in our review.

In addition, evidence from the key trials may have limited validity for the broader patient population in the U.S. Of note, patients with a deleterious BRCA mutation represent only a minority of patients, as do patients with the same degree of platinum sensitivity as those who participated in the PARP inhibitor maintenance trials. Several experts informed us that these therapies are being used off-label (e.g., as earlier-line treatment) in patients among whom the efficacy and safety are even less certain.

Finally, several important questions remain regarding the appropriate use of these agents in clinical practice. Future research should evaluate the optimal sequence of PARP inhibitors in the treatment pathway, whether they can safely be combined with other therapies, whether maintenance should be given indefinitely or for a fixed amount of time, whether it is better to use a PARP inhibitor as maintenance therapy or to reserve these agents for treatment at recurrence, what biomarkers are predictive of risk, and treatment after progression on a PARP inhibitor.

Summary

We reviewed data on PARP inhibitors for use in BRCA-mutated recurrent disease as well as for use as maintenance therapy in women with platinum-sensitive disease.

Table ES4. ICER Evidence Ratings

Population/PARP Inhibitor	ICER Evidence Rating
Recurrent, BRCA-Mutated Disease	
Olaparib	P/I
Rucaparib	P/I
Niraparib	I
Maintenance Therapy in Platinum-Sensitive Disease	
Olaparib	C+
Niraparib	C+
Rucaparib	C+

Summary and Evidence Ratings

Olaparib

Due to the lack of direct comparative evidence with other therapies used in recurrent, BRCA-mutated disease, we cannot be certain whether olaparib provides a survival benefit, is comparable, or possibly even inferior to alternative treatments. We believe that olaparib has a better safety profile than chemotherapy and may provide better quality of life, although patient-reported outcomes are not yet available. Because of this uncertainty, and because we cannot definitively rule out the possibility of net harm, we consider the evidence on olaparib in this population to be "promising but inconclusive" (P/I).

For women with platinum-sensitive disease who are candidates for maintenance therapy, we have moderate certainty that olaparib provides at least a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit when used as maintenance therapy relative to placebo (i.e., surveillance alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

Niraparib

The clinical study of niraparib that is relevant to the population of patients with BRCA-mutated recurrent disease has not yet released any data. We therefore consider the evidence for niraparib in this population to be "insufficient" (I).

In patients with platinum-sensitive ovarian cancer who are candidates for maintenance therapy, we have moderate certainty that niraparib provides at least a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit when used as maintenance therapy relative to placebo (i.e., surveillance alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

Rucaparib

Due to the lack of direct comparative evidence with other therapies used in recurrent, BRCA-mutated disease, we cannot be certain whether rucaparib provides a survival and/or quality of life benefit over alternative treatments, is comparable, or possibly even inferior. As with olaparib, we therefore deem the evidence for rucaparib in this population to be promising but inconclusive (P/I).

In patients with platinum-sensitive ovarian cancer who are candidates for maintenance therapy, we have moderate certainty that rucaparib provides at least a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit when used as maintenance therapy relative to placebo (i.e., surveillance alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

In all cases, documentation of an overall survival benefit would have likely changed the evidence assessment for these therapies.

Long-Term Cost Effectiveness

We estimated the cost-effectiveness of the PARP inhibitors (olaparib, niraparib, and rucaparib) in the treatment of adult women with ovarian cancer. Consistent with the issues of comparability highlighted in the evidence review, we did not attempt to conduct any explicit or implied comparisons across PARP inhibitors. We modeled two populations of interest, focusing on the actual or expected FDA indications based on published or otherwise publicly-available data:

- Treatment of recurrent, BRCA-mutated disease:
    - Olaparib (gBRCA only, 4th-line or later treatment) versus pegylated liposomal doxorubicin in combination with carboplatin (PLD+C)
    - Rucaparib (any deleterious BRCA mutation, 3rd-line or later treatment) versus PLD+C

- Maintenance treatment for platinum-sensitive disease:
    - Olaparib (gBRCA only) versus placebo (i.e., surveillance only)
    - Niraparib (gBRCA) versus placebo
    - Niraparib (non-gBRCA) versus placebo
    - Rucaparib (germline or somatic BRCA mutations) versus placebo

The model included three main health states: (a) progression-free (on treatment or off treatment); (b) progression (clinical evidence allowed for additional states, including first and second subsequent therapy, for some models); and (c) death from cancer or other causes. Patients who transitioned from the progression-free health states (on or off treatment) to progression state(s) remained there until they died from progressed cancer or from other causes. Statistical fitting methods allowed the extrapolation of survival results beyond the observed time-frame in clinical trials. Survival, quality-adjusted survival, and costs from the health-care system perspective were estimated for each model cycle and then summarized over a 15-year time horizon for each treatment option. All future costs and outcomes were discounted 3% per year.

Several key assumptions were made in the model (for a comprehensive list of model assumptions, along with the rationale for each, see Section 6 of the report):

- Trial-reported survival hazard ratios were assumed to remain constant beyond trial-reported follow-up time in extrapolated survival estimates.
- Discontinuation of treatment was assumed within the maintenance treatment populations for olaparib, niraparib, and rucaparib; rates of discontinuation were identical and were based on olaparib trial data.

- All patients who progress and go on to the next line of therapy post intervention failure were assumed to receive active chemotherapy rather than supportive care alone.
- Disease progression costs and utilities reflected a distribution of subsequent treatments and best supportive care.
- Where evidence was missing on overall survival (rucaparib and niraparib), we assumed the same likelihoods of overall survival from a PARP inhibitor with reported evidence within the same treatment population (i.e., olaparib for both treatment populations).

Model inputs were retrieved from published literature and from data provided by manufacturers. To calculate drug acquisition costs, we assumed a 10% discount from current WAC for the PARP inhibitors based on manufacturer input, as the PARP inhibitors do not have reliable estimates of net price available in the SSR Health database. We also assumed a 10% discount from current pricing for PLD+C. For the price of bevacizumab (used in budget impact only), we obtained data from SSR Health, LLC, that combines information on net US dollar sales through the first quarter of 2017 with information on unit sales to derive net pricing at the unit level across all payer types.[34] The derived discount for bevacizumab was 6%.

For regimens based on treat-to-progression, utilization and cost were applied to all patients who remained in the PFS health state over time. If trial evidence included patients who discontinued treatment but remained free of disease progression, then the model estimated the drug utilization (and cost) for only those patients that remained in the PFS state with active drug use.

We fit parametric survival curves to PFS and overall survival (OS) Kaplan-Meier data for each treatment and comparator utilizing the approach described by Guyot and colleagues.[35] (See Appendix E for further details on transition probability derivation.) The model included grade 3/4 adverse events, derived from key clinical trials and/or the drug's prescribing information, that occurred in ≥5% of patients in any of the treatment comparators (listed in Section 5, Table 5.2).

Health state utilities were derived from published literature that used validated patient-reported instruments mapped to generic health utility instruments from a healthy community of U.S. residents.[36] Specifically, data was collected from patients using the Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) instrument during Study 19 and then mapped to the EQ-5D.

Base-Case Results

Olaparib

In the recurrent BRCA-mutated population, olaparib had total discounted costs of approximately $158,000 with life-years gained and quality-adjusted life years (QALYs) of 2.11 and 1.26, respectively (Table ES5). At net prices, olaparib's estimated cost-effectiveness was approximately $146,000 per QALY gained and $80,500 per life-year gained compared to PLD+C in 4th line or later

use. The base-case findings in the recurrent BRCA-mutated population should be interpreted with caution, as there is no current evidence suggesting a relationship between progression-free and overall survival in this population for olaparib versus PLD+C or placebo, and overall survival evidence for PLD+C is derived from a source that combines BRCA-mutated and non-BRCA-mutated patients. The use of olaparib for maintenance therapy resulted in total discounted costs of approximately $247,600 with 3.75 life years and 2.67 QALYs gained. At estimated net prices, the cost-effectiveness of olaparib versus placebo was estimated to be approximately $324,000 per QALY and approximately $289,000 per life-year gained.

Table ES5. Discounted Costs, Outcomes, and Incremental Results for Olaparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Recurrent BRCA-Mutated Population					
Olaparib	$115,100	$43,032	$158,133	2.11	1.26
PLD + C (4th line or later use)	$20,040	$41,229	$61,269	0.91	0.59
Incremental Cost per Outcome				$80,258/LYG	$146,210/QALY
Maintenance Therapy for Platinum-Sensitive Disease					
Olaparib – gBRCAm	$194,475	$53,158	$247,633	3.75	2.67
Placebo (Olaparib) – gBRCAm	$9,050	$46,474	$55,524	3.09	2.08
Incremental Cost per Outcome				$288,538/LYG	$324,116/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs; §Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs; QALY: quality-adjusted life year; LYG: life-year gained

Table ES6 presents the results of the threshold analysis for olaparib in the recurrent BRCA-mutated population, and separately, the maintenance therapy population. For the recurrent BRCA-mutated population, discounts of 8% - 61% would be needed to meet thresholds of $50,000-$150,000 per QALY gained. Note that Olaparib's price could be slightly higher than the net price assumed in our base-case analysis for the BRCA-mutated population at a threshold of $150,000 per QALY gained. Discounts of 59% to 87% would be required to achieve thresholds of $50,000-$150,000 per QALY in the maintenance therapy population.

Table ES6. Threshold Analysis Results for Olaparib

	WAC per Unit	WAC per Month	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC to Reach Thresholds
Olaparib (Recurrent BRCA-Mutated)	$112.35	$13,679	$43.31	$73.35	$103.39	8% - 61%
Olaparib (Maintenance for Platinum-Sensitive)	$112.35	$13,679	$14.44	$30.24	$46.06	59% - 87%

QALY: quality-adjusted life year

Niraparib

In the gBRCA-mutated maintenance population, niraparib had total discounted costs of approximately $243,500, with discounted life-years and QALYs gained of 3.86 and 2.77, respectively (Table ES7). In the non-gBRCA-mutated maintenance population, niraparib had total discounted costs of approximately $175,300, with discounted life-years and QALYs of 2.59 and 1.84, respectively. In women with a gBRCA mutation, the cost-effectiveness of niraparib versus placebo is estimated at approximately $292,000 and $245,000 per QALY and per life-year gained, respectively. In women without a gBRCA mutation, the estimated cost-effectiveness was $1.9 million per QALY gained, due to a smaller incremental gain in progression-free survival. (Cost per life-year gained could not be calculated due to the lack of a statistical survival benefit.)

Table ES7. Discounted Costs, Outcomes, and Incremental Results for Niraparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Maintenance Therapy for Platinum-Sensitive Disease					
Niraparib – gBRCAm	$181,077	$62,348	$243,461	3.86	2.77
Placebo (Niraparib) – gBRCAm	$5,027	$46,474	$51,502	3.09	2.12
Incremental Cost per Outcome				$245,092/LYG	$291,454/QALY
Niraparib – non-gBRCAm	$122,106	$53,203	$175,310	2.59	1.84
Placebo (Niraparib) – non-gBRCAm	$5,200	$43,144	$48,344	2.59	1.77
Incremental Cost per Outcome				Not estimable	$1,908,822/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs

§Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs; QALY: quality-adjusted life year; LYG: life-year gained

Table ES8 presents the results of the threshold analysis for the niraparib gBRCA maintenance population. Discounts of 57% - 90% would be needed to meet thresholds of $50,000-$150,000 per QALY gained. In the non-gBRCA population, there is no price at which niraparib would meet these common thresholds, due to the high incremental cost relative to the small clinical benefit observed.

Table ES8. Threshold Analysis Results for Niraparib

	WAC per Unit	WAC per Month	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC Unit Price to Reach WTP Thresholds
Niraparib – gBRCA (Maintenance for Platinum-Sensitive)	$163.89	$14,965	$16.07	$43.28	$70.50	57% - 90%

QALY: quality-adjusted life year

Rucaparib

In the recurrent BRCA-mutated population, rucaparib (3rd line or later) had total discounted costs of approximately $247,000 with discounted life-years gained and QALYs of 2.11 and 1.41, respectively (Table ES9). Rucaparib's cost-effectiveness versus PLD+C is estimated to be $218,000 per life-year gained and $295,000 per QALY gained. The base-case findings in the recurrent BRCA-mutated population should be interpreted with caution, because there is no current evidence suggesting a relationship between progression-free and overall survival in the recurrent, BRCA-mutated population for rucaparib versus PLD+C or placebo, and overall survival evidence for PLD+C is derived from a source that combines BRCA-mutated and non-BRCA-mutated patients.

The use of rucaparib for maintenance therapy resulted in total discounted costs of approximately $229,500 with 3.64 life years and 2.60 QALYs gained. At estimated net prices, the cost-effectiveness of rucaparib versus placebo was estimated to be approximately $320,000 per life-year gained and $369,000 per QALY gained. Note that, while these results are similar in magnitude to those of olaparib and niraparib, the primary rucaparib maintenance population includes both germline and somatic BRCA mutations, while the relevant subgroup for the other PARP inhibitors is based on germline mutations only.

Table ES9. Discounted Costs, Outcomes, and Incremental Results for Rucaparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Recurrent BRCA-Mutated Population					
Rucaparib (3rd Line or Later Use)	$202,103	$45,031	$247,135	2.11	1.41
PLD + C (3rd Line or Later Use)	$23,144	$43,868	$67,012	1.28	0.80
Incremental Cost per Outcome				$217,738/LYG	$294,593/QALY
Maintenance Therapy for Platinum-Sensitive Disease					
Rucaparib – gBRCAm or sBRCAm	$174,761	$54,784	$229,546	3.64	2.60
Placebo (Rucaparib) – gBRCAm or sBRCAm	$4,988	$46,474	$51,463	3.09	2.11
Incremental Cost per Outcome				$320,236/LYG	$369,175/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs
§Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs; QALY: quality-adjusted life year; LYG: life-year gained

Table ES10 presents the results of the threshold analysis of the base-case for rucaparib in the recurrent BRCA-mutated and maintenance therapy populations. Discounts of 50% - 91% would be needed to meet cost-effectiveness thresholds of $50,000-$150,000 per QALY gained. Due to limitations of the evidence on survival in the recurrent population, we also estimated life-years gained and QALYs gained for rucaparib that would achieve the $150,000 per QALY cost-effectiveness threshold, assuming the same net price for rucaparib and PLD+C efficacy as in the base-case analysis (refer to Table 5.10 in Section 5 for more details). Estimated life-years gained with rucaparib would need to reach 4.41 (vs. 2.11 in the base-case), and estimated QALYs 2.72 (vs. 1.41 in the base-case), to result in rucaparib reaching the $150,000 per QALY threshold.

Table ES10. Threshold Analysis Results for Rucaparib

	WAC per Unit	WAC per Month	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC Unit Price to Reach WTP Thresholds
Rucaparib (Recurrent BRCA-Mutated)	$114.50	$13,940	$26.09	$41.82	$57.55	50% - 77%
Rucaparib (Maintenance for Platinum-Sensitive)	$114.50	$13,940	$10.60	$25.08	$39.57	65%-91%

QALY: quality-adjusted life year

Sensitivity Analysis Results

Major drivers of low and high incremental cost-effectiveness results for each comparison included utility values for progression and progression-free health states, cost per month of therapy, duration of treatment, and select adverse event costs. (Tornado diagrams and other results of scenario and sensitivity analyses are presented in Appendix E.) Combining gBRCA and non-gBRCA data for olaparib and niraparib in maintenance therapy resulted in higher cost-effectiveness estimates than in the base case (gBRCA only) populations for both PARP inhibitors. Use of the semi-Markov or partitioned survival method produced similar results (within 10% of our base-case findings) and the same general conclusions that other models have found (see Appendix Table E8).[37] In probabilistic sensitivity analysis (Appendix Table E10), for the majority of treatment comparisons, there was less than a 1% chance that a PARP inhibitor was cost-effective at a threshold of $150,000 per QALY. The exception was olaparib in the recurrent BRCA-mutated population, with an 52.5% chance of meeting a cost-effectiveness threshold of $150,000 per QALY.

Value-Based Benchmark Prices

Our value-based benchmark prices for olaparib, rucaparib, and niraparib are presented in Table ES11. The value-based benchmark prices for a drug are defined as the prices that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY gained. For the recurrent BRCA-mutated population, the assumed net price of olaparib (a 10% discount from WAC) would fall below the price required to achieve $150,000 per QALY gained (8% discount) but above the price required to achieve $100,000 per QALY (35% discount). The discounts required for rucaparib to meet the threshold prices are greater than the current assumed 10% discount from WAC. For the

population with maintenance therapy for platinum-sensitive disease, the discounts required to meet the threshold prices for olaparib (in the gBRCA subgroup), rucaparib (in the gBRCA+sBRCA subgroup) and niraparib (in the gBRCA and non-gBRCA subgroups) are also greater than the current assumed 10% discount from WAC.

Table ES11. Value-Based Benchmark Prices per Month of Ovarian Cancer Treatment, by Population

Drug Name	WAC per Month*	Net Price per Month†	Price to Achieve $100,000/QALY	Price to Achieve $150,000/QALY	Discount from WAC to Reach Thresholds
Recurrent BRCA-Mutated Population					
Olaparib	$13,679	$12,310	$8,930	$12,587	8% to 35%
Rucaparib	$13,940	$12,546	$5,091	$7,007	50% to 63%
Maintenance Therapy for Platinum-Sensitive Disease‡					
Olaparib	$13,679	$12,310	$3,682	$5,607	59% to 73%
Niraparib	$14,965	$13,468	$3,952	$6,437	57% to 74%
Rucaparib	$13,940	$12,546	$3,053	$4,817	65% to 78%

N/A: Not available; QALY: quality-adjusted life year, WAC: wholesale acquisition cost; *WAC as of August 23, 2017 † Assumed 10% discount from current WAC. ‡Based on findings for gBRCA subgroup for olaparib and niraparib, and both gBRCA and somatic BRCA subgroup for rucaparib

Potential Budget Impact

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of each drug for women with ovarian cancer. We used the WAC, an estimate of discounted WAC, and the three threshold prices for each drug in our estimates of budget impact.

Potential budget impact was defined as the total differential cost of using each therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. We assumed that olaparib and rucaparib would displace PLD+C in the recurrent BRCA-mutated population. In the population receiving maintenance therapy for platinum-sensitive disease, we assumed that olaparib, niraparib, and rucaparib would replace observation (i.e. placebo in the relevant trials) and bevacizumab. In the absence of data, we assumed this replacement would occur in the ratio of 75% for observation and 25% for bevacizumab in patients with BRCA mutation; for the non-BRCA patients, these proportions were assumed to be 67% for observation and 33% for bevacizumab. All costs were undiscounted and estimated over a five-year time horizon.

We estimated the size of the potential candidate populations for treatment using inputs for the US population size, ovarian cancer prevalence and treatment, and BRCA testing results. Ovarian cancer

prevalence was estimated to be 222,060 cases in 2014, based on the most recent SEER data.[8] SEER reports that approximately 60% of patients are diagnosed at advanced stages, representing 133,200 cases. We assumed that approximately 54% of these patients would receive third-line treatment,[38] and further assumed that 65% of those receiving third-line treatment would go on to receive fourth-line treatment. The estimated prevalence of gBRCA mutations (18%)[39] was used to calculate the estimated proportion of those patients who would be eligible for treatment with olaparib (8,423) or rucaparib (12,959). Assuming equal distribution over five years, this resulted in an estimate of 1,685 patients eligible for olaparib and 2,592 patients eligible for rucaparib in the recurrent BRCA-mutated population in the US per year.

Patients eligible for maintenance therapy had to have had recurrent ovarian cancer and response to their most recent platinum-containing regimen. This represented 4% of all prevalent cases of ovarian cancer in the US, of which 18% were assumed to have BRCA mutations. [39] [40] Applying these estimates to the US population, we estimated that there would be approximately 1,630 BRCA mutation and 7,440 non-BRCA mutation patients in this population, or 327 and 1,488 per year, respectively.

Tables ES12 illustrates the per-patient budget impact results for each drug. Note that the average annual budget impact of treatment over five years is well below the cost of drug treatment for one year, due to patients discontinuing treatment over time, and that the model was run separately for each drug and population being modeled, so that costs for comparator regimens will differ slightly across tables.

Olaparib

Estimated results for olaparib in the recurrent BRCA-mutated population and the population receiving maintenance therapy for platinum-sensitive disease are shown in Table ES12. For the recurrent BRCA-mutated population, the average potential budgetary impact when using the WAC for olaparib was an additional cost of approximately $39,900 per patient, and approximately $34,700 using the discounted WAC, which was slightly less than the average potential budgetary impact ($35,800) using the unit price ($103.39) to achieve $150,000 per QALY. For the gBRCA-mutated maintenance therapy population, the average annual potential budgetary impact when using the WAC for olaparib was approximately $56,900, and approximately $49,600 using the discounted WAC.

Table ES12. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon

Net Average Annual Budget Impact					
	WAC	Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Recurrent BRCA-Mutated Population*					
Olaparib (4th Line or Later Use)	$39,904	$34,723	$35,773	$21,922	$8,071
Rucaparib (3rd Line or Later Use)	$67,013	$59,020	$27,257	$16,274	$5,290
Maintenance Therapy for Platinum-Sensitive Disease (BRCA mutations)†					
Olaparib	$56,901	$49,643	$14,077	$3,864	-$6,349§
Niraparib	$55,483	$48,804	$17,422	$6,330	-$4,763§
Rucaparib	$54,830	$46,703	$9,523	$1,041	-$7,441
Maintenance Therapy for Platinum-Sensitive Disease (non-gBRCA)‡					
Niraparib	$37,918	$32,634	-$14,477§	N/A	N/A

*Versus PLD+C using discounted WAC for PLD+C; †Versus observation and bevacizumab in the ratio 75:25; based on findings for gBRCA subgroup for olaparib and niraparib, and both gBRCA and somatic BRCA subgroup for rucaparib; ‡Versus observation and bevacizumab in the ratio 67:33; §Indicates cost-saving; QALY: quality-adjusted life year; WAC: wholesale acquisition cost

Niraparib

For the population with gBRCA mutations, the average annual potential budgetary impact when using the WAC for niraparib was approximately $55,500 per patient, decreasing to approximately $48,800 when using the discounted WAC (Table ES12). For the non-gBRCA population, the average annual potential budgetary impact when using the WAC for niraparib was approximately $37,900 per patient, decreasing to approximately $32,600 when using the discounted WAC.

Rucaparib

In the population with recurrent BRCA-mutated disease receiving 3rd line or later treatment, average potential budgetary impact when using the WAC for rucaparib was an additional per-

patient cost of approximately $67,000, and approximately $59,000 using the discounted WAC (Table ES12).

For the maintenance therapy population (germline and somatic BRCA mutations only), the average annual potential budgetary impact when using the WAC for rucaparib was approximately $54,800, and approximately $46,700 using the discounted WAC.

For each of the drugs and populations of interest, the annual potential budgetary impact of treating the entire eligible populations across all prices (WAC, discounted WAC, and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY) did not exceed the $915 million annual threshold. Overall, the greatest potential annual budget impact we estimated was for rucaparib in the recurrent BRCA-mutated population, reaching 42% of the $915 million threshold at the net price. This was largely due to the relatively small sizes of the specific ovarian cancer populations eligible for treatment in any given year.

Summary and Comment

The base-case findings from our analysis suggest that use of olaparib in recurrent, BRCA-mutated ovarian cancer provides clinical benefit in terms of longer time spent in PFS versus standard chemotherapy; this translates into cost-effectiveness estimates that meet commonly cited cost-effectiveness thresholds. However, the cost-effectiveness findings for BRCA-mutated disease are more uncertain due to a lack of direct comparative evidence. For maintenance therapy with olaparib, however, discounts from the current list price of 59%-87% would be required to meet thresholds of $50,000-$150,000 per QALY gained. While niraparib's clinical benefits in maintenance therapy are greater in women with gBRCA-mutated disease than without, cost-effectiveness estimates exceeded commonly-cited cost-effectiveness thresholds. Discounts of 57%-90% would be required to achieve these thresholds in the gBRCA population, while there is no price that would achieve these thresholds in women without the mutation. Finally, use of rucaparib for BRCA-mutated disease would require discounts of 50%-91% to achieve common cost-effectiveness thresholds.

Using discounted WAC for each of the drugs in the populations of interest, annual budget impact was estimated to range from approximately $32,600 per patient for niraparib in the non-gBRCA-mutated population receiving maintenance therapy for platinum-sensitive disease to approximately $59,000 per patient for rucaparib in the recurrent BRCA-mutated population. For each of the drugs and populations of interest, the annual potential budgetary impact of treating the entire eligible populations was not projected to exceed the $915 million threshold, with the greatest potential annual budget impact for rucaparib in the recurrent BRCA-mutated population reaching 42% of that threshold.

Important limitations of this analysis include limited evidence on overall survival (such as for niraparib and rucaparib in the maintenance population and rucaparib in the recurrent BRCA-mutated population) and the relation between progression-free and overall survival, lack of data on provider mark-ups associated with physician-administered drugs, and reliance on assumptions for fitting survival curves that may differ substantially between different parametric models. However, varying cost of PLD+C did not change our conclusions regarding cost-effectiveness. In addition, we ensured our assumptions did not lead to invalid models and nonsensical PFS or survival rates, such as the tail of the extrapolated progression-free survival curve crossing the tail of the overall survival curve. In sensitivity analyses, findings were sensitive to assumed net drug prices, treatment duration, assumptions regarding time spent on and off treatment, and utility values for progressive and progression-free health states.

In conclusion, the findings of our analysis suggest that the PARP inhibitors of focus for this review would provide gains in quality-adjusted and overall survival over alternative therapies, but are not currently priced in alignment with these benefits, with the exception of olaparib in recurrent, BRCA-mutated ovarian cancer.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits or contextual considerations offered by an intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the scientific evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits	Comment
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	Patients report low-grade adverse effects that are minor relative to what they experience with cytotoxic chemotherapy regimens and/or invasive surgeries. Dosing flexibility generally allows for management of side effects. However, it should be noted that improved tolerability has not translated into measured quality-of-life benefits in trials that report this information.
This intervention offers reduced complexity that will significantly improve patient outcomes.	PARP inhibitors are taken orally and may provide a benefit to individuals without convenient access to infusion centers. However, requisite BRCA testing for receipt of rucaparib and olaparib may introduce an element of complexity not present with alternative therapies. Regular monitoring for hematologic toxicity diminishes some of the convenience of an oral therapy.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	The possibility to take these regimens at home may improve access to care for those unable to seek treatment at major cancer centers. Conversely, PARP inhibitors are much more expensive than existing therapies and are taken until disease progression or unacceptable toxicity, allowing for the possibility of a long duration of time on a very costly medication. Only about a third of newly diagnosed patients receive *BRCA1/BRCA2* testing.[41] Thus, requisite BRCA testing for rucaparib and olaparib may exacerbate gaps in treatment, and the convenience offered by an oral therapy may be irrelevant for those without access to high-quality specialist care or genetic counselors.
This intervention will significantly reduce caregiver or broader family burden.	PARP inhibitors may reduce the number of trips caregivers make to accompany patients to major cancer treatment/infusion centers and/or their need to look after patient affairs during recovery from chemotherapy.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	PARP inhibitors offer a novel mechanism of action and are indicated for patients with recurrent disease (≥2 prior lines of therapy), a population in which few effective therapies exist.
This intervention will have a significant impact on improving return to work and/or overall productivity.	Data are lacking on the effect of PARP inhibitors on overall productivity, however a better side effect profile may prevent medical leaves of absence (and/or facilitate a faster return to work) for women who participate in the labor force.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	No additional benefits or disadvantages identified.

Potential Other Contextual Considerations	Comment
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	Less than half of patients with this level of advanced ovarian cancer survive five years from diagnosis.[8] Few effective treatment options exist for this level of disease progression.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	High rates of morbidity are associated with both ovarian cancer and its treatment (surgery, chemotherapy, etc.). The disease is also marked by multiple instances of recurrence and relapse, further adding to the burden on patients, families, and caregivers.
This intervention is the first to offer any improvement for patients with this condition.	Direct comparative evidence with alternative therapies is not available, although analyses of standard relapse therapies suggest a shorter duration of survival than that observed with PARP inhibitors in the setting of recurrent disease. PARP inhibitors offer a significant progression-free survival benefit in the maintenance setting, although it is uncertain whether the lack of a clear survival or quality of life benefit justify the additional toxicity patients must endure during a time when they would otherwise be experiencing a drug holiday (i.e., surveillance alone).
Compared to surveillance with no maintenance chemotherapy, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	Maintenance therapy with PARP inhibition introduces toxicity during a time when patients would otherwise experience a drug holiday with surveillance alone; the long-term safety of maintenance therapy remains uncertain.
Compared to surveillance with no maintenance chemotherapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	There is significant uncertainty about the long-term benefit of maintenance therapy with PARP inhibition compared to surveillance alone given the lack of data on the appropriate duration of maintenance therapy, the comparative benefits of maintenance therapy vs. treatment at recurrence, and overall survival attributable to maintenance therapy.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	Ovarian cancer treatment paradigms have not changed materially in the last 20 years.[42] PARP inhibitors represent innovative new therapies that provide additional treatment options for women who have received limited benefit from standard chemotherapy .

To make headroom for the anticipated costs of new technology, ICER has added a new section to our reports to identify potential cost savings. Queries from patients, clinicians, medical societies, and manufacturers identified three potential areas of low value care in ovarian cancer.

Screening asymptomatic or low to moderate risk women for ovarian cancer using biomarkers or imaging is not recommended due to high false positive rates in this rare disease. In addition, ongoing CA-125 and imaging to identify recurrent cancer provides little clinical value at a high cost.

Midwest CEPAC Voting Results

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on September 14 in St. Louis, Missouri. The results of the votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1) **In patients with recurrent BRCA-mutated disease, is the evidence adequate to demonstrate that the net health benefit of treatment with olaparib is greater than that of treatment with standard chemotherapy?**

Yes: 4 votes	**No: 5 votes**

2) **In patients with platinum-sensitive disease who are eligible for maintenance therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with olaparib is greater than that of surveillance alone?**

Yes: 7 votes	No: 2 votes

3) **In patients with recurrent platinum-sensitive, germline BRCA-mutated disease who are eligible for maintenance therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with niraparib is greater than that of surveillance alone?**

Yes: 8 votes	No: 1 votes

4) **In patients with recurrent platinum-sensitive disease who are eligible for maintenance therapy and do not have germline BRCA mutations, is the evidence adequate to demonstrate that the net health benefit of treatment with niraparib is greater than that of surveillance alone?**

Yes: 6 votes	No: 3 votes

5) **In patients with recurrent BRCA-mutated disease, is the evidence adequate to demonstrate that the net health benefit of treatment with rucaparib is greater than that of treatment with standard chemotherapy?**

Yes: 5 votes	No: 4 votes

Note for voting questions 6 through 8*: According to ICER's updated Value Assessment Framework, ICER will have the independent CEPAC voting panels vote on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.[43] At incremental cost-effectiveness ratios below $50,000 per QALY there will be a presumption of "high value"; at ratios above $175,000 the intervention will be deemed "low value" without formal voting by the committee. This included the other benefits and contextual consideration votes as well. As such, the only therapy and indication that fell within this range was olaparib for recurrent BRCA-mutated disease.*

6) **When compared to pegylated liposomal doxorubicin and carboplatin (PLD+C), does olaparib, for recurrent BRCA-mutated disease, offer one or more of the following "other benefits"? (select all that apply)**

This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	5/9
This intervention offers reduced complexity that will significantly improve patient outcomes.	7/9
This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	3/9
This intervention will significantly reduce caregiver or broader family burden.	8/9
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	7/9
This intervention will have a significant impact on improving return to work and/or overall productivity.	5/9

7) **Are any of the following contextual considerations important in assessing olaparib's long-term value for money in patients with recurrent BRCA-mutated disease? (select all that apply)**

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	8/9
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	6/9
This intervention is the first to offer any improvement for patients with this condition.	1/9
Compared to standard chemotherapy (or PLD+C) there is significant uncertainty about the long-term risk of serious side effects of this intervention.	2/9
Compared to standard chemotherapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	4/9

8) **Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, in patients with recurrent BRCA-mutated disease, what is the long-term value for money of olaparib compared with PLD+C?**

Low: 5 votes	Intermediate: 4 votes	High: 0 votes

Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on olaparib, niraparib, and rucaparib for recurrent ovarian cancer to policy and practice. The policy roundtable members included two patients, two clinical experts and a pharmacy benefits manager. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Payers and Manufacturers

- At current pricing, PARP inhibitors have the potential to be aligned with clinical benefit for treatment of recurrent disease, but will be challenged to meet common thresholds in maintenance therapy. Therefore, to align value and facilitate affordability as well as patient access, prices must be lowered accordingly.
- Both payers and manufacturers must work together to establish innovative payment mechanisms to seek the best affordability for patients, including outcomes based contracting and/or package discounting.

Researchers, Manufacturers, and Patient Groups

- Single-arm studies and surrogate endpoints do not provide the type of information that clinicians and patients need to make treatment decisions. Critical evidence gaps like these must be addressed in the design and execution of clinical research by researchers, manufacturers, and patients alike.
- The current evidence base is inadequate for any reasonable indirect comparison of the PARP inhibitors. Manufacturers and researchers should facilitate comparisons of the benefits and risks of the individual PARP inhibitors through standardization of research protocols and outcome measurement as well as post marketing head-to-head assessments, and patient groups should demand such standardization.
- Current evidence is inadequate to determine which patients would benefit most from maintenance therapy. Further research should be conducted to identify the patients who might benefit most from a maintenance regimen as well as those for whom surveillance remains a viable option.

Manufacturers

- Broaden eligibility criteria for patient assistance programs to counter the impact of financial toxicity.
- Price PARP inhibitors differentially by dosage strength, so that patients are not financially penalized when doses must be reduced to manage side effects.

Payers and Providers

- Eliminate methods of provider reimbursement that provide significant financial incentives favoring intravenous drugs over oral treatments. Such payment mechanisms can distort clinical decision-making to the detriment of good patient care.
- Health plans should work closely with clinicians to provide guideline-concordant testing for genetic mutations and consider adjustments to coverage policies based on the testing results.

Patient Advocacy Organizations

- Press researchers and manufacturers for an increased role in study design, so that comparisons and outcomes of most interest will be included.

1. Background

1.1 Introduction

Background

Ovarian cancer is the most common cause of gynecologic cancer death and fifth-leading cause of cancer death in women.[1,2] There are nearly 200,000 women currently living with ovarian cancer in the United States; each year over 22,000 new cases are diagnosed and there are approximately 14,000 deaths attributable to the disease.[8] Due to the lack of early symptoms and absence of an accurate screening strategy, nearly 75% of women with ovarian cancer are diagnosed with advanced disease at presentation (Stage IIIC or IV).[3,4]

At this stage of disease, recurrence is common and prognosis is guarded; those who continue through three or more lines of therapy are likely to die or experience recurrence within 6 months.[5]

There are several options for patients when they experience recurrence, including several chemotherapy regimens and the vascular endothelial growth factor-specific angiogenesis (VEGF-A) inhibitor bevacizumab. Recently, ongoing trials have indicated promising results for a newer class of targeted oral agents, poly ADP-ribose polymerase (PARP) inhibitors. FDA-approved PARP inhibitors include olaparib (Lynparza™; AstraZeneca; FDA approval on December 19, 2014 with expanded indication on August 17, 2018), rucaparib (Rubraca™; Clovis Oncology; FDA approval on December 19, 2016), and niraparib (Zejula™; Tesaro; FDA approval on March 27, 2017).

In ovarian cancer treatment, PARP inhibitors have primarily been studied in two populations: (1) as treatment for recurrent disease after multiple prior lines of chemotherapy; and (2) as maintenance therapy in patients with two or more prior lines of platinum-based chemotherapy who were in complete or partial response to their most recent regimen.

The introduction of PARP inhibitors is likely to trigger widespread changes in clinical practice, but the improvement in clinical outcomes may be heterogeneous across subpopulations. In addition, the costs of PARP inhibitor treatment are high relative to standard chemotherapy. This assessment will therefore focus on the available evidence for each of the PARP inhibitors in the two key populations of interest, with attention paid to clinical outcomes, the patient experience, costs, and cost-effectiveness.

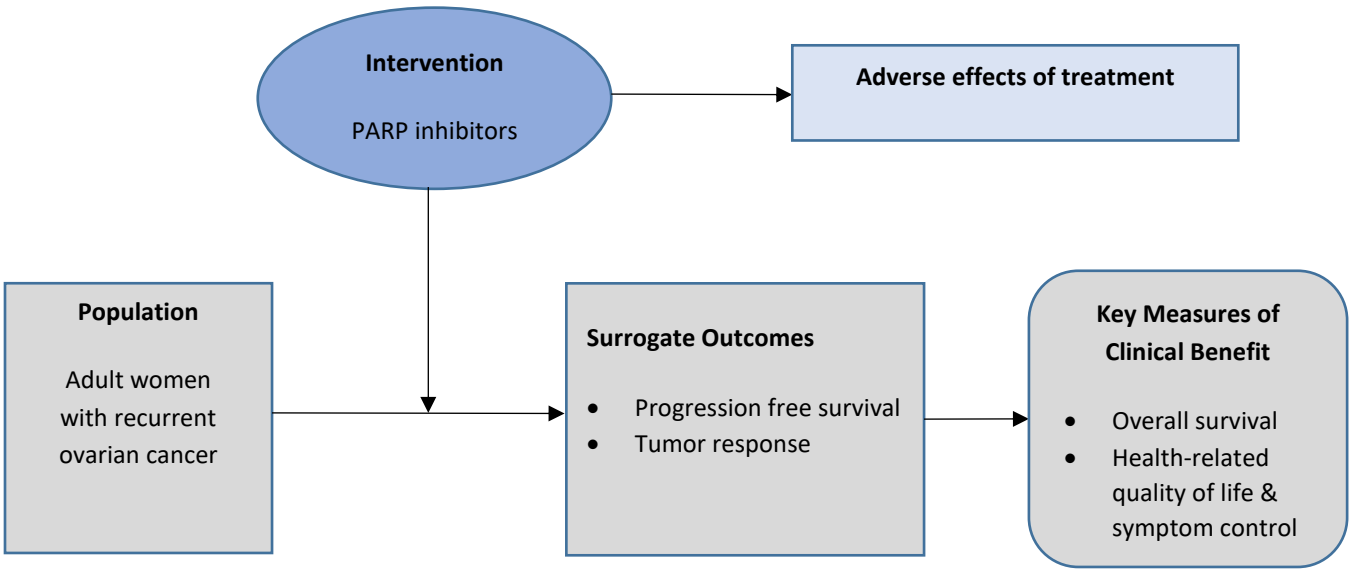
Scope of the Assessment

The proposed scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials, as well as high-quality systematic reviews. We did not restrict studies according to study duration or study setting; however, we did limit our review to those that included the specified populations and included the outcomes of interest. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers to the FDA, information provided by patient groups, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Management of Recurrent Ovarian Cancer



Population

The key populations of interest are described below and are intended to reflect current and/or anticipated indications for the three PARP inhibitors.

1) Adult women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous or mixed serous/endometrioid histology who have a deleterious BReast CAncer gene (BRCA) mutation and who have relapsed after initial cytoreductive surgery and multiple subsequent lines of chemotherapy ("Recurrent, BRCA-Mutated Disease").

2) Adult women with platinum-sensitive, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous or mixed serous/endometrioid histology who have received at least two prior platinum-based chemotherapy regimens, had a complete or partial response to the most recent regimen, and are candidates for maintenance therapy ("Maintenance Therapy for Platinum-Sensitive Disease").

<u>Key Subpopulations</u>

Recurrent, (BRCA)-mutated disease:

- Platinum sensitive
- Platinum resistant

Maintenance therapy for platinum-sensitive disease:

- Germline BRCA mutation
- Somatic BRCA mutation
- Wild-type BRCA mutation
- Homologous recombination deficiency (HRD) positive
- Homologous recombination deficiency (HRD) negative

Interventions

Recurrent, BRCA-mutated disease:

- Olaparib (4th-line or later treatment, based on FDA indication)
- Rucaparib (3rd-line or later treatment, based on FDA indication)

Maintenance therapy for platinum-sensitive disease:

- Olaparib
- Niraparib
- Rucaparib

We did not include niraparib as an intervention of interest in recurrent, BRCA-mutated disease because an ongoing study (QUADRA) will not be complete until late 2017.

Comparators

Relevant comparators were selected based on input from clinical experts and represent appropriate alternative therapies in each of the populations of focus.

Recurrent, BRCA-mutated disease:

- Bevacizumab in combination with standard chemotherapy for recurrent disease (e.g., gemcitabine + carboplatin)
- Pegylated liposomal doxorubicin in combination with carboplatin

Maintenance therapy for platinum-sensitive disease:

- Placebo (i.e., surveillance only)
- Bevacizumab

We did not attempt to compare the PARP inhibitors to each other through direct or indirect assessment, and therefore summarize the evidence for olaparib, rucaparib, and niraparb in each of the populations of interest separately (see Section 4).

Outcomes

This review examined key clinical outcomes of interest in these populations, including surrogate outcomes common to ovarian cancer trials. The primary outcomes of interest from clinical trials included overall and progression-free survival, rates of partial and complete response as well as overall objective response, and health-related quality of life. We also communicated with patients and clinical experts to ascertain which outcomes are of greatest importance to patients. We sought patient-reported outcomes to enrich the available data.

Other outcomes of interest included:

- Symptom control (e.g., Functional Assessment of Cancer Therapy [FACT]-Ovarian Symptom Index)
- Disease-specific health-related quality of life (e.g., TOI, FOSI, EQ-5D)
- Treatment-related adverse events
- Rates of Grade 3 or 4 adverse events
- Discontinuation due to adverse events
- Economic and functional impacts of specific adverse events (e.g., chronic, low-grade effects)
- Treatment-related deaths
- Costs and cost-effectiveness

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings.

2. The Topic in Context

Epithelial ovarian cancers account for about 90% of all cancers of the ovaries.[44] Treatment recommendations for epithelial ovarian cancer are also applied to fallopian tube cancer and primary peritoneal cancer.[44] This report refers to all of the above cancers collectively as "ovarian cancer."

The four main histologic subtypes of epithelial cancer include serous, endometrioid, mucinous, and clear cell, of which serous carcinomas are most common (constituting approximately 70% of the total).[45] As described previously, most women with ovarian cancer are diagnosed at later stages, and those with multiple prior lines of treatment have a high likelihood of disease progression or death within 6 months.[5] High-grade serous tumors represent a particularly challenging subtype, with 5-year survival rates currently estimated at 35-40%.[6]

2.1 Current Paradigm of Treatment

First-line therapy includes debulking cytoreductive surgery, in which the uterus, ovaries, and fallopian tubes are commonly removed, as well as neoadjuvant or postoperative/adjuvant therapy with a platinum (e.g., cisplatin, carboplatin) and a taxane agent (e.g., paclitaxel, docetaxel) or liposomal doxorubicin.[7-9] Platinum-based agents, first cisplatin and later carboplatin, have been used to treat ovarian cancer since the 1970s.[46] In the 1990s, the addition of paclitaxel to the chemotherapy regimen was found to improve overall survival.[47] There is evidence that many patients across the country may not be offered guideline-concordant care, particularly initial optimal cytoreductive surgery by a gynecologic oncologist.[48]

Approximately 75% of patients experience recurrence; subsequent treatment decisions are often guided by the duration of a patient's platinum-free interval (PFI), defined as the interval between the completion of last platinum-based treatment and relapse.[47,49] Although definitions have varied in clinical practice and clinical trials, patients are commonly characterized as platinum-sensitive (PFI ≥6 months), platinum-resistant (PFI <6 months), or platinum-refractory (progression while on platinum therapy or within 2 months). A longer PFI is thought to predict the probability of response to subsequent chemotherapy, although such intervals tend to become shorter with each recurrence and many patients eventually develop platinum-resistant disease.[47,49]

Several chemotherapy regimens (e.g., docetaxel, paclitaxel, gemcitabine, liposomal doxorubicin, topotecan and etoposide) or the VEGF-A inhibitor bevacizumab may be used when patients with ovarian cancer experience recurrence (see Clinical Guidelines section).

Less than a decade ago, there was no evidence to support the use of maintenance therapy with platinum agents, liposomal doxorubicin, or paclitaxel to prevent recurrence.[10] However, two recent

trials showed that the addition of bevacizumab to first-line carboplatin and paclitaxel, followed by bevacizumab monotherapy as maintenance therapy, prolonged progression-free survival (PFS) by about four months.[9,11] Around the same time, attention turned to subsets of patients with mutations affecting DNA repair. This finding brought forth a new class of agents, called Poly ADP-ribose polymerase (PARP) inhibitors, as treatment for recurrent ovarian cancer or as maintenance therapy.

2.2 Mutations Affecting DNA Repair and Poly ADP-Ribose Polymerase (PARP) Inhibitors

Some tumors have homologous recombination deficiency (HRD) and are unable to efficiently repair damage to DNA using the homologous recombination pathway.[50] Several genetic mutations have been associated with HRD, including but not limited to, germline and somatic *BRCA1* and *BRCA2* mutations.[50] *BRCA1* and *BRCA2* are genes that produce tumor suppressor proteins; mutations in either of these genes can cause improper repair of DNA, making an individual more susceptible to ovarian cancer.[12] BRCA mutations can either be inherited (i.e., germline BRCA mutations) or they can occur de novo in tumor tissue (i.e., somatic BRCA mutations).[51] In patients with high-grade serous tumors, 47% have tumor cells with HRD due to germline BRCA mutations, somatic/tumor BRCA mutations, epigenetic inactivation of *BRCA1*, or other defects of homologous DNA repair.[52]

HRD, and more specifically *BRCA1* and *BRCA2* mutations, provides a target upon which to treat some ovarian cancers because it increases tumor sensitivity to DNA-damaging agents such as PARP inhibitors.[13] PARPs are a family of proteins that include at least 17 enzymes; PARP-1 and PARP-2 enzymes are known to be involved in DNA damage repair by utilizing the base excision repair pathway to repair single-strand DNA breaks; PARP-3 is suspected to play a role in damage response as well.[50] When PARP enzymes are inhibited, different pathways, such as the homologous recombination pathway or non-homologous end joining pathway, must be utilized to repair DNA damage.[53] However with major repair pathways disabled, cancer cells cannot efficiently respond to damage, causing the cells to die.[54,55]

Initially, PARP inhibitors were evaluated in patients with germline *BRCA1* and *BRCA2* mutations.[14-16] Two of the PARP inhibitors (rucaparib [Rubraca™; Clovis Oncology] and olaparib [Lynparza™; AstraZeneca]) were primarily tested in populations selected based on BRCA mutation status or HRD mutation status. Then, during late 2016, the NOVA trial of the PARP inhibitor niraparib (Zejula™; Tesaro) suggested that PARP inhibitors may be efficacious as maintenance therapy regardless of whether patients have gBRCA mutations, albeit to varying degrees. Olaparib, rucaparib, and niraparib inhibit the PARP-1 and PARP-2 enzymes; in addition, rucaparib inhibits PARP-3, -4, -12, -15, -16 and tankyrase 1 and 2, although the clinical relevance of inhibiting these additional enzymes remains uncertain at this time.[50]

Interest in PARP inhibitors is high, in part because they appear to be well-tolerated, with mostly gastrointestinal and myelosuppressive effects. These types of adverse effects are considerably less severe than those typically observed with platinum-based chemotherapies and other chemotherapeutic agents used in later-line treatment.

The following table (Table 2.1) summarizes the PARP inhibitors that we included in the evidence review. Each agent is taken orally and has a separate dosing regimen, either once or twice per day.

Table 2.1. PARP Inhibitors of Interest for the Evidence Review

PARP Inhibitor	Indication	Recommended Dose & Treatment Duration	Dosage Forms & Strengths	Date of FDA Approval	WAC per Month (USD)*
Olaparib (Lynparza™, AstraZeneca)[18]	1) Monotherapy for patients with deleterious or suspected deleterious germline BRCA-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy 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	300 mg BID (PO) tablets until disease progression or unacceptable toxicity	Tablets: 100 mg 150 mg	1) December 19, 2014 2) August 17, 2017	$13,679
Rucaparib (Rubraca®, Clovis Oncology)[19∞]	Monotherapy for patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic	600 mg BID (PO) until disease progression or unacceptable toxicity	Tablets: 200 mg 250 mg 300 mg	December 19, 2016	$13,940
Niraparib (Zejula™, Tesaro, Inc.)[20]	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	300 mg QD (PO) until disease progression or unacceptable adverse reaction	Capsules: 100 mg	March 27, 2017	$14,965

* Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed August 22, 2017), and is based on indicated dose; ∞ Rucaparib does not yet have a maintenance indication from the FDA but was included in the review of maintenance therapies for platinum-sensitive disease based on newly-published data.

2.3 Future Directions

Additional studies of PARP inhibitors are ongoing for both treatment and maintenance indications (see Appendix C for details). Studies of PARP inhibitors in combination with chemotherapy or radiation are also ongoing.[56] Olaparib has been combined with cediranib, a VEGF inhibitor.[56] A single arm study of nirapirib with PD-1 inhibitor pembrolizumab (Keytruda®, Merck), will examine objective response rate and toxicity in women with high-grade recurrent serous ovarian cancer who have been previously treated with chemotherapy and who experienced a response lasting at least 6 months to first-line platinum-based therapy, but are currently considered platinum-resistant.[57]

Other PARP inhibitors are also under study. Talazoparib, a potent PARP inhibitor requiring only 1mg/day (as compared to 300-600 mg once or twice daily), is in development.[50] Currently, early-phase trials are underway to evaluate safety, pharmacokinetics and tumor markers. Veliparib is another PARP inhibitor currently being assessed in an ovarian cancer population. Veliparib has been reported to be the PARP inhibitor most likely to be combined with chemotherapy agents due to relatively low hematologic toxicity in early testing.[50]

PARP inhibitors are also being studied as maintenance immediately following first-line therapy.[58,59] Researchers and patients are hopeful that introducing a PARP inhibitor earlier in the treatment pathway will improve chances of survival in recurrent ovarian cancer.[5,23]

2.4 Insights Gained from Discussions with Patients and Patient Groups

Our discussions with patient groups indicated that patients with recurrent ovarian cancer experience a great amount of anxiety about the low likelihood of cure and poor survival rates. In addition, some physicians use the term “watchful waiting” to describe the observation approach historically used after treatment response; patients told us that this terminology causes them to focus excessively on when and how recurrence is likely to happen, and often refer to this period as “watch and worry”.

Anxiety also comes from the non-specific nature of symptoms and the clinical terminology employed. For example, patients told us that because abdominal pain is both a toxicity of treatment and an indicator of disease progression, there is a hyper-awareness that occurs when those symptoms are present. Psychosocial support from nurses and physicians is important. Treatments, particularly the cytotoxic chemotherapies that are the historical standard of care, cause substantial toxicity and burden to patients and their families. Since most patients are past the child-bearing phase, loss of fertility is not a major concern, though fertility remains a priority for younger patients.

PARP inhibitor side effects are generally tolerable. Patients report fatigue, dry mouth, headaches, mouth sores, nausea, loss of appetite, constipation, nausea, depression, and hair loss. The fatigue was reported to be less severe than with some other therapies. Patients reported their doses being

lowered when their blood counts fell. This reduction was reported to also reduce the side effects experienced at higher doses.

Patients with ovarian cancer struggle with financial difficulties related to the costs of initial surgery and multiple lines of therapy. While many of the patients that we spoke to have received the PARP inhibitors through clinical trials at no cost to them, the increasing use of these agents in clinical practice is likely to increase the financial burden. Patients who do not have a support system, partner, or family, have a very difficult time coping with the disease and treatment.

2.5 Definitions

Advanced Disease – Stage IIIC or Stage IV ovarian cancer[3,4]

Breast Cancer Mutation(s) - BRCA

> **Germline BRCA mutation (gBRCAm)** – An inherited deleterious mutation in either a *BRCA1* or *BRCA2* tumor suppressor gene which causes a defect in the repair of DNA[17]
>
> **Somatic BRCA mutation (sBRCAm)** – A deleterious or suspected deleterious alteration in the *BRCA1* or *BRCA2* genes that is acquired after conception (not hereditary). These mutations are not present in the germline and cannot be passed to offspring[17]
>
> **BRCA wild-type (BRCAwt)** – A tumor which does not possess either a deleterious or suspected deleterious germline or a somatic BRCA mutation[17]

Eastern Cooperative Oncology Group (ECOG) performance status – A measure of functional status and ability to perform activities of daily living on a 6-point scale: 0 (fully active); 1 (restricted only in strenuous activity); 2 (ambulatory and capable of self-care but unable to work); 3 (capable of only limited self-care, confined to bed or chair >50% of waking hours); 4 (completely disabled); 5 (dead).[60]

Homologous recombination deficiency (HRD) – Homologous recombination (HR) is a pathway that allows repair of double-stranded DNA breaks.[61] Dysregulation in the homologous recombination pathway due to genetic mutations or alterations leads to cellular genomic instability and an inability to efficiently repair damaged DNA. HRD-positive cells are thought to be more susceptible to the effects of DNA damaging agents such as platinum agents or PARP inhibitors.[17]

Loss of heterozygosity (LOH) – A change in genetic material from a heterozygous state in the germline DNA to a homozygous state in tumor DNA through loss or duplication of chromosomal regions.[61]

Objective response rate (ORR) – The proportion of patients with a confirmed complete response (CR) or partial response (PR) on subsequent tumor measurement a pre-specified length of time after first response documentation.

Overall survival (OS) – The length of time from the start of treatment for ovarian cancer until death. Can alternately be measured as length of time from diagnosis to death. Overall survival (OS) is the ideal endpoint to demonstrate clinical benefit of a new cancer therapy in a trial.[62]

Platinum-refractory – Ovarian cancer patients that experience persistent or progressive disease during initial platinum based therapy[63]

Platinum-resistant – Recurrent ovarian cancer patients with a platinum free interval (measured from last infusion of a platinum in primary treatment to documentation of recurrence) of less than 6 months[64]

Platinum-sensitive – Recurrent ovarian cancer patients with a platinum free interval (measured from last infusion of a platinum in primary treatment to documentation of recurrence) of 6 months or greater[64]

Progression-free survival (PFS) – Time from a pre-defined date, such as randomization, to tumor progression or death.[62] The major trials of PARP inhibitors in a maintenance population designate PFS as the primary outcome.

Recurrence/Relapse – Cancer that returns after a period of improvement and/or a time in which it could not be detected.[65]

Response Evaluation Criteria in Solid Tumors (RECIST) criteria – A standardized set of rules used to measure how well a cancer patient responds to treatment. The criteria are used to evaluate whether tumors shrink, stay the same, or get larger. Response is characterized as a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD). At least one solid tumor, measurable on x-rays, CT scans, or MRI scans, must be present to use RECIST criteria.[65] In ovarian cancer, RECIST guidelines are often used to determine PFS endpoints.[66]

- **Complete response** – The disappearance of all target lesions. Any pathological lymph nodes must have decreased to < 10 mm.[67] In ovarian cancer, the tumor marker CA-125 assists with determining complete or partial response.[67]
- **Measurable disease** – The presence of at least one measurable lesion (minimum size of 10mm by CT scan).[67]
- **Partial response** – At least a 30% decrease in the sum of diameters of target lesions from baseline.[67]

- **Progressive disease** – A minimum increase of 20% of the sum of diameters in the target lesion(s) and an absolute increase of at least 5mm or the appearance of one or more new lesions.[67]

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

To understand the insurance landscape for PARP inhibitors for advanced ovarian cancer, we reviewed publicly available 2017 coverage policies and formularies for Midwestern state Medicaid programs (Missouri), Centers for Medicare and Medicaid Services (CMS) policies, and major commercial plans in individual marketplaces across Missouri and other Midwestern states, including Anthem Blue Cross Blue Shield, Aetna, Blue Cross Blue Shield Kansas City, Cigna Missouri, and Cigna Part D.

We surveyed each plan's coverage policies for the three PARP inhibitors. Missouri Medicaid (MO HealthNet) covers all three PARP inhibitors without any prior authorization requirements. All private carriers tiered these drugs in the highest tier (tier 3 or 5 depending on the plan).[68-72] All of the plans listed olaparib on their formularies, most listed rucaparib, and only one plan listed niraparib, most likely due to its more recent FDA approval. Some plans required prior authorization for the PARP inhibitors, all of which aligned closely with the FDA labels for these agents. Prior authorization for olaparib required use of the drug as a monotherapy, a positive FDA-approved test for a germline BRCA mutation, and three or more lines of prior treatment.[73] Rucaparib prior authorization required use of the drug as a monotherapy, a positive FDA-approved test for a BRCA mutation, and two or more lines of prior therapy.[74] For niraparib, prior authorization required the use of the drug as a maintenance therapy (current partial or complete response to platinum-based chemotherapy) and two or more prior lines of platinum-based therapy.[75]

3.2 Clinical Guidelines

Many treatment guidelines differentiate between platinum-resistant/refractory disease and platinum-sensitive disease when determining the appropriate treatment for a patient experiencing relapsed ovarian cancer. The guidelines summarized below discuss treatment recommendations for both platinum-resistant and platinum-sensitive disease.

National Comprehensive Cancer Network (NCCN) Guidelines[45]

NCCN guidelines outline third- and fourth-line treatment options for persistent disease or recurrence, listing the following as preferred agents for platinum-sensitive disease: carboplatin; carboplatin in combination with: docetaxel, gemcitabine, gemcitabine+bevacizumab, liposomal doxorubicin, or paclitaxel; cisplatin; cisplatin in combination with gemcitabine. The guidelines also list bevacizumab and olaparib as single-agent targeted therapy options for platinum-sensitive

disease. For platinum-resistant disease, the guidelines recommend the following as preferred agents: docetaxel; oral etoposide, gemcitabine, pegylated liposomal doxorubicin as a single agent or in combination with bevacizumab); paclitaxel in combination with pazopanib or bevacizumab, and topotecan as a single agent or with bevacizumab. The guidelines also list bevacizumab and olaparib as single-agent targeted therapy options for platinum-resistant disease.

The NCCN guidelines also discuss recommended use for olaparib as a single agent, specifically recommending its use for patients with deleterious germline BRCA-mutated ovarian cancer having received three or more lines of therapy. As of the time of this writing, NCCN does not recommend olaparib as maintenance therapy due to insufficient data.

European Society for Medical Oncology (ESMO) Guidelines[76]

These ESMO guidelines defined platinum-resistant disease as progression during treatment or within 6 months of platinum-based therapy; platinum sensitive is defined as disease that progresses after 6-12 months. For those patients experiencing platinum-resistant disease, the guidelines recommend clinicians focus on quality of life and the control of symptoms when making treatment decisions. The guidelines recommend four treatment options: paclitaxel, topotecan, PLD and gemcitabine. Because none of these treatment options are superior to the other, clinicians should consider toxicity and administration preferences when selecting treatment. For patients experiencing platinum-sensitive disease, the guidelines recommend the use of platinum based doublets, again taking into consideration toxicity and administration convenience into account. For platinum-resistant disease in patients that have relapsed and have not been treated with bevacizumab previously, the guidelines recommend bevacizumab.

ESMO issued an update to their guidelines in 2016, recommending the use of olaparib as a maintenance therapy for patients with germline BRCA mutations after response to a platinum-based chemotherapy. They also recommend that patients be tested for germline BRCA mutations, and that clinicians consider testing tumors for somatic BRCA mutation as well.[77]

National Institute for Health and Care Excellence (NICE) Guidelines[78]

NICE recommends the use of paclitaxel in combination with platinum, or as a monotherapy, for treatment of recurrent ovarian cancer that is platinum-sensitive. In addition, it recommends pegylated liposomal doxorubicin (PLD) as a monotherapy or PLD in combination with platinum chemotherapy. NICE does not recommend the following treatment options for platinum-sensitive recurrent disease: gemcitabine combined with carboplatin; trabectedin with PLD, or topotecan. Topotecan was also not recommended for platinum-resistant disease.

NICE's guidelines recommend the use of olaparib as a maintenance therapy for relapsed platinum-sensitive ovarian cancer with BRCA mutations, specifically in patients who have already received

three or more courses of platinum-based chemotherapy; they also require that any drug costs incurred for patients on the drug longer than 15 months be paid by the manufacturer.

NICE was unable to make a recommendation on the use of bevacizumab due to the termination of its technology appraisal, citing a lack of data. In addition, NICE does not recommend the use of bevacizumab in combination with gemcitabine and carboplatin for use in patients with platinum-sensitive disease that have not been previously treated with bevacizumab.

Society for Gynecological Oncology (SGO)

The SGO released a clinical practice statement in October 2014 outlining their recommendations for genetic testing for patients with ovarian cancer. They established the need for women diagnosed with ovarian cancer, even without a family history, to receive genetic counseling and genetic testing. They also identify the development of new treatments like PARP inhibitors as an important consideration in their recommendation of offering genetic counseling and genetic testing to patients.[79]

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of PARP inhibitors in the treatment of ovarian cancer, we abstracted evidence from available clinical studies of these agents, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents).

Therapies of interest included:

1. Olaparib and rucaparib for patients who have a deleterious BRCA mutation and who have relapsed after initial cytoreductive surgery and subsequent lines of chemotherapy (i.e., "Recurrent, BRCA-mutated Disease")

2. Olaparib, niraparib and rucaparib for platinum-sensitive patients who have received at least two prior platinum-based chemotherapy regimens, were in complete or partial response to the most recent regimen, and are candidates for maintenance therapy (i.e., "Maintenance therapy for Platinum-sensitive Disease")

As mentioned in the Background section, comparators of interest included bevacizumab in combination with standard chemotherapy for recurrent disease (e.g., gemcitabine + carboplatin) and pegylated liposomal doxorubicin in combination with carboplatin for patients with a deleterious BRCA mutation and recurrent disease; in the population of platinum-sensitive patients eligible for maintenance therapy, we considered surveillance (i.e., placebo) or bevacizumab maintenance therapy to be relevant comparators. Due to key differences in study eligibility criteria, baseline characteristics of study populations, and outcome measurements, we did not attempt to compare the PARP inhibitors to each other through direct or indirect quantitative assessment. Our review focused on clinical benefits (i.e., overall and progression-free survival, objective response, and health-related quality of life), as well as potential harms (drug-related adverse events).

Where data were available, we summarized results for key outcomes by BRCA mutation status, homologous recombination deficiency (HRD) status, and sensitivity to prior platinum-based therapy.

4.2 Methods

Study Inclusion Criteria

We included evidence from all relevant clinical studies, irrespective of whether they used a comparative study design. We did not include studies that evaluated PARP inhibitors in combination with chemotherapy or other targeted agents, as labeled indications are currently for monotherapy only; we also excluded studies that did not meet a minimum sample size of 50 patients. For studies that included individuals with non-ovarian, fallopian tube, or primary peritoneal cancers (e.g., breast, pancreatic, prostate), we required that results be stratified by cancer type and that the ovarian cancer arm consist of at least 50 patients. For studies informing our analysis of recurrent, BRCA-mutated disease, we required at least 80% of study participants to have had at least two prior lines of chemotherapy for rucaparib, and at least three prior lines of chemotherapy for olaparib, in keeping with the FDA-labeled indications for these agents.

In recognition of the evolving evidence base for PARP inhibitors, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts that reported data also available in peer-reviewed publications. Where data were only available from a press release, we did not include the information in our review.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on PARP inhibitors for ovarian cancer followed established methods in systematic review research.[80] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[81] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

We searched MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE for relevant studies. We limited each search to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent peer-reviewed publications and public reports. Further details of the search algorithms, methods for study selection, and data extraction are available in Appendix A and Appendix D.

Data Synthesis and Statistical Analyses

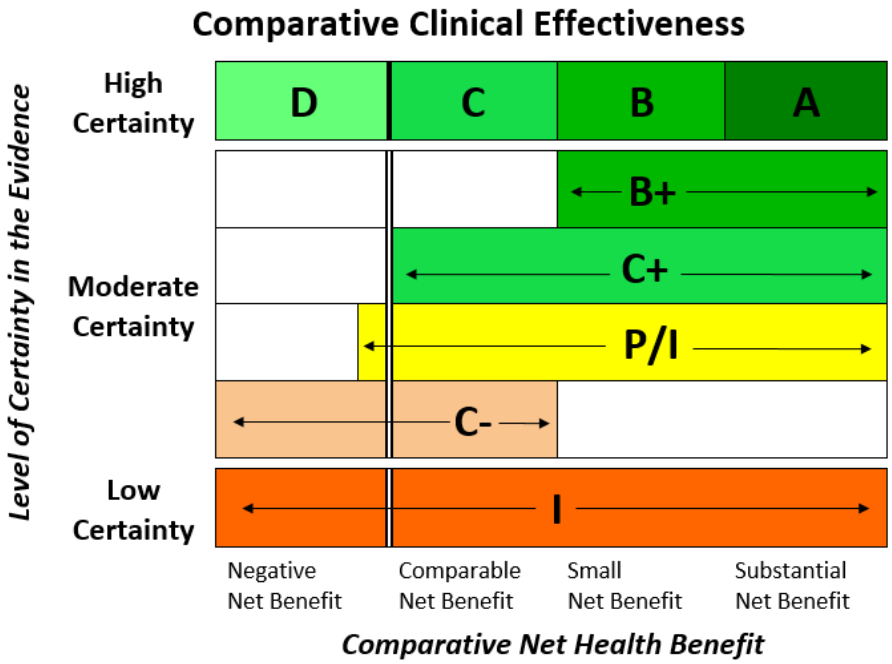
Data on relevant outcomes were summarized in evidence tables (see Appendix F) and are synthesized qualitatively in the text of the report. Differences in entry criteria, study populations, outcome measurements, and other factors precluded direct and indirect quantitative assessment of each PARP inhibitor's impact on selected outcomes.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 4.1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[82]

Figure 4.1 ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may have provided qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature. For this review, we did not find evidence of any completed studies that have not been published.

4.3 Results

Study Selection

Our literature search identified 392 potentially relevant references (see Appendix Figure A1), of which 15 met our inclusion criteria; these citations related to six individual studies. Primary reasons for study exclusion included use of a combination regimen not approved by the FDA, study population outside of our scope (e.g., patients with limited previous systemic therapy for ovarian cancer), and small sample sizes (n<50).

Overall, we included four references focusing on treatment of BRCA-mutated recurrent disease. We found no studies of niraparib in this population, but note that a relevant study is ongoing and is described in Appendix C. The studies of olaparib and rucaparib in this population were exclusively single arm designs. Although we identified one Phase II comparative trial of olaparib versus pegylated liposomal doxorubicin in patients with a *BRCA1* or *BRCA2* mutation and recurrent ovarian cancer, we excluded the study because more than a third of the study population had only received 1-2 prior chemotherapies, in contrast to the FDA indication for olaparib in this population (three or more prior lines).[83]

We included 11 references for maintenance therapy in platinum-sensitive disease; these references related to three placebo-controlled trials of olaparib and niraparib. Published results from the ARIEL3 trial of rucaparib maintenance therapy were reported after publication of the evidence report but prior to the public meeting. Data are included in this final report but were not available at the time of the systematic literature search and not counted in our PRISMA flow chart.

Details of all included studies are summarized in Appendix F and in the sections that follow.

Quality of Individual Studies

Much of our review drew upon data presented in single-arm clinical studies and grey literature (i.e., conference presentations and regulatory review documents). As noted above, we identified four references relevant to recurrent, BRCA-mutated disease, which consisted of subgroup analyses from three multicenter, single-arm, open-label trials; two of the four references were only available in unpublished conference presentations. Consequently, we did not assign quality ratings to individual references and instead highlight limitations, uncertainties, and gaps in the evidence in the Controversies and Uncertainties section.

In the maintenance population, we included 11 references from three placebo-controlled RCTs; of the eleven references selected for inclusion, four were conference abstracts and/or presentations. In total, we identified three peer-reviewed published studies that included a control arm. A fourth peer-reviewed publication was identified after posting of the evidence report (ARIEL3). Using criteria published by the US Preventive Services Task Force (USPSTF; see Appendix D), we rated one of these studies to be fair due to the potential loss of randomization after retrospective identification of BRCA mutation subgroups (see Study 19 of olaparib maintenance below) and the other studies (NOVA trial of niraparib, SOLO2 trial of olaparib, and ARIEL3 of rucaparib) to be of good quality. Studies that were only available in grey literature sources were not assigned a quality rating.

Comparability of Evidence Across PARP Inhibitors

We attempted to identify data on "overlapping" patient subgroups that might permit formal and even quantitative comparisons between PARP inhibitors. However, differences in trial eligibility criteria, endpoint measurement, and stratification of findings precluded these comparisons. Further detail is provided according to population of interest below.

Treatment of Recurrent, BRCA-mutated Ovarian Cancer

The key trial of olaparib in this population (Study 42) enrolled only patients with germline BRCA mutations, while the two rucaparib analyses focused on patients with any kind of BRCA mutation (germline, somatic, and mutations of uncertain origin). In addition, the patients categorized as platinum-sensitive in the olaparib trial (29%) were considered not suitable for further platinum therapy, while the same designation was not made in the key rucaparib study (ARIEL2); approximately half of the patients in this trial were platinum-sensitive (53%), and 75% were platinum-sensitive in a pooled analysis of this key study and an earlier one (Study 10). Finally, 100% of the patients included in the analysis of olaparib had received three or more prior chemotherapies, compared to 76% and 43% of patients included in the ARIEL2 and pooled rucaparib analyses, respectively. There were also differences in the schedule of investigator-assessed tumor assessments for progression in each trial: assessments occurred every eight weeks

in both the olaparib and rucaparib key trials, although after 4.5 months in the rucaparib trial, patients were assessed every 16 (±2) weeks, while in the olaparib study patients were assessed every 12 weeks following an initial 6 months of 8-week assessment periods. These differences are summarized in Table 4.1.

Table 4.1. Comparability of Available Data Assessing Olaparib Versus Rucaparib for Recurrent Ovarian Cancer with a Deleterious BRCA Mutation and Multiple Prior Lines of Therapy

	Study 42 (Olaparib)	ARIEL2 (Rucaparib)
Comparison Variables		
Platinum Sensitivity	Platinum-resistant/refractory patients made up 69% of analysis group; platinum-sensitive patients (29%) were deemed ineligible for further platinum-based therapy*	Results were stratified by platinum sensitive (immediate prior tx=platinum), platinum sensitive (immediate prior tx=non-platinum), and platinum resistant
# of Prior Chemotherapies	82% of patients had ≥3 prior chemotherapies	76% of patients had ≥3 prior chemotherapies
Deleterious BRCA Mutation	Included only patients with germline BRCA mutations	Included patients with BRCA mutations of germline, somatic, and uncertain origins
Outcome Measurement	Investigator-assessed tumor assessments using RECIST v1.1 occurred every 8 weeks for first 6 months, then every 12 weeks	Investigator-assessed tumor assessments using RECIST v1.1 occurred every 8 weeks for the first 4.5 months, then every 16 (±2) weeks

Summary based on Study 42 and ARIEL2 subgroup analyses;[21-23] *Platinum status unknown in 2% of patients; tx=treatment

Maintenance Therapy in Platinum-Sensitive Disease

Key differences were also noted in the major studies of olaparib, niraparib and rucaparib as maintenance therapy for platinum-sensitive disease. All studies were designed to measure improvement in progression-free survival (PFS) as the primary endpoint, with overall survival and quality of life as secondary endpoints. Although all studies recruited patients who had platinum-sensitive recurrent ovarian cancer, had received at least two prior lines of platinum therapy, and had at least a partial response to their most recent platinum therapy, trial populations, outcome measurement, and study design varied across trials.

The key trial of niraparib included two cohorts of patients: those with germline BRCA mutations and those with non-germline BRCA mutations. The ARIEL3 trial of rucaparib used a nested design of women with BRCA mutation (both germline or somatic) nested in a population of tumors exhibiting homologous recombination deficiency (HRD). ARIEL3 also analyzed the intent-to-treat population using a step-down statistical analysis plan. A Phase II maintenance trial of olaparib enrolled all women with platinum-sensitive ovarian cancer, irrespective of mutation status; patients were later analyzed according to whether they had a deleterious BRCA mutation or not, although identification of such mutations was found to be problematic by the FDA (see discussion below for further detail).

A confirmatory Phase III trial of olaparib restricted enrollment to patients with a documented deleterious or suspected deleterious BRCA mutation. All subjects received confirmatory testing using Myriad Genetics BRACAnalysis test after enrollment. Ninety-seven percent of women in both the olaparib and placebo arms had a confirmed germline BRCA1/2 mutation. Nine patients (3% in each arm) were found not to have a germline mutation. Four patients had variants of unknown significance, two were wildtype and three had missing tests.[30]

Analysis of progression-free survival (PFS) also differed across maintenance trials of the PARP inhibitors. Specifically, tumor assessments occurred at different intervals of time: whereas the trial of niraparib evaluated tumors every eight weeks through cycle 14 (28-day continuous cycles) and then every 12 weeks until treatment discontinuation, the two olaparib trials scheduled tumor assessments every 12 weeks for the first 60-72 weeks of the study and every 24 weeks thereafter. Rucaparib evaluated PFS at every 12 weeks until death, loss to follow-up, withdrawal of consent, or study closure. In addition, PFS was evaluated by blinded independent central review in the study of niraparib, while the olaparib and rucaparib trials used investigator-assessed PFS as the primary endpoint. The Phase II trial of olaparib also used an older version of the RECIST criteria, and it remains uncertain whether tumor response based on the older criteria aligns with that of the newer criteria when used in ovarian cancer. Finally, the two trials of olaparib maintenance therapy evaluated different formulations of the drug, limiting our ability to draw conclusions across studies about this agent. These differences are summarized in Table 4.2.

Table 4.2. Comparability of Available Data Assessing PARP Inhibitors as Maintenance Therapy for Platinum-Sensitive Disease

	Study 19 (Phase II Trial of Olaparib)	SOLO2 (Phase III Trial of Olaparib)	NOVA (Niraparib)	ARIEL3 (Rucaparib)
Comparison Variables				
BRCA Mutation	All BRCA status (positive and negative) included. Retrospective BRCA mutation analysis included germline and somatic BRCA.	Any documented deleterious or suspected deleterious BRCA mutation for enrollment; confirmatory testing showed 97% gBRCA in each arm.	Study designed with two cohorts: germline BRCA mutation and non-germline BRCA mutation (included somatic and wild-type)	Study design included BRCAm (germline and somatic) and non-BRCAm (wildtype).
HRD Testing	None	None	Included	Included
Tumor Assessment Schedule	Every 12 weeks until week 60 and every 24 weeks thereafter	Every 12 weeks until week 72 then every 24 weeks until disease progression	Every 8 weeks through cycle 14 (28-day continuous cycles), and then every 12 weeks until treatment discontinuation	Every 12 weeks until death, loss to follow-up, withdrawal of consent, or study closure
Investigator vs. Blinded Independent Central Review (BICR) of PFS	Primary endpoint: Investigator-assessed PFS Sensitivity analysis: BICR PFS	Primary endpoint: Investigator-assessed PFS Sensitivity analysis: BICR PFS	Primary endpoint: BICR PFS Sensitivity analysis: Investigator-assessed PFS	Primary endpoint: Investigator assessed PFS Secondary endpoint: BICR PFS
RECIST Version	RECIST v 1.0	RECIST v 1.1	RECIST v 1.1	RECIST v 1.1
Quality of Life Instrument	FACT-O, FOSI and TOI	TOI	FOSI and EQ-5D	FOSI-18
Dosing/Formulation	400 mg BID/Capsules	300 mg BID/Tablets	300 mg QD/Capsules	600 mg BID/Tablets

PFS=progression-free survival; BICR=blinded independent central review

Clinical Benefits of Olaparib

Olaparib for Recurrent, BRCA-Mutated Disease

Median overall survival with olaparib was 16.6 months and progression-free survival was approximately 7 months. While not a direct comparison, analyses of standard relapse regimens suggest a median overall survival of 6-9 months and PFS of 4-6 months in similar patients. Patients with platinum sensitivity had a longer PFS and higher response rate than platinum-resistant patients, although subgroup analyses were performed in only a small sample of patients. Quality of life data were not reported for olaparib in this population.

Data to inform our assessment of olaparib in patients with relapsed ovarian cancer, a deleterious BRCA mutation, and three or more prior lines of therapy were derived from a subgroup analysis of Study 42 (see Table 4.3).[21] Study 42 was a single-arm trial of olaparib in patients with a deleterious germline mutation in *BRCA1/2* and recurrent cancer, including those who had platinum-resistant ovarian cancer, breast cancer, pancreatic cancer, and prostate cancer.[22] The subgroup analysis focused on 137 patients with platinum-resistant (or platinum-sensitive disease but deemed unsuitable for further platinum therapy) epithelial ovarian, primary peritoneal, or fallopian tube cancer who had received at least three prior regimens of chemotherapy and had measurable disease at baseline. This analysis comprised the primary efficacy data upon which the FDA formed its decision to approve olaparib for fourth-line or later use.

Table 4.3. Clinical Outcome Summary of Olaparib in Recurrent Ovarian Cancer with a Deleterious BRCA Mutation

Key Study	Patient Characteristics	Outcomes
Study 42[21,22]	n=137 Median age: 58 gBRCAm: 100% Platinum sensitive: 28% Platinum resistant: 59% ≥3 prior chemotherapies: 100%	Median OS: 16.6 months Median PFS (overall): 6.7 months Median PFS (Platinum sensitive): 9.4 months Median PFS (Platinum resistant): 5.5 months ORR (Platinum sensitive): 46% ORR (Platinum resistant): 30% QoL: Not reported

Summary based on Study 42 subgroup analysis[21,22]

Overall Survival

Improving overall survival (OS) and quality of life (QoL) are generally considered the most important goals of cancer therapy.[84,85] Although OS was not reported for the subpopulation of focus from Study 42 (patients with ≥3 prior chemotherapies), evidence from a broader population of ovarian cancer patients who participated in the study (n=193; 18% had 1-2 prior chemotherapy regimens) showed a median OS of 16.6 months.[22]

As noted above, we did not identify any direct comparative data of olaparib versus other standard fourth-line therapies in ovarian cancer. However, an exploratory analysis from Hanker and colleagues followed patients who participated in three Phase III randomized controlled trials of primary taxane/platinum-based therapy through their sixth line of therapy.[5] Relapse therapies included chemotherapy, hormonal therapy, surgery, radiotherapy, and others. Across treatment modalities, median overall survival after the third relapse was 8.9 months (95% CI 7.8 to 9.9) and 6.2 months (95% CI 5.1 to 7.7) after the fourth relapse.[5]

Progression-free Survival

As described in the "Topic in Context" section, progression-free survival (PFS) is calculated from the time of the start of treatment to disease progression or death. Median PFS, which was assessed as a secondary endpoint in Study 42, was 6.7 months (95% CI 5.5 to 7.6) for patients with three or more prior regimens.[21] Patients with platinum-sensitive ovarian cancer experienced a longer median PFS than patients who had platinum resistance (9.4 months [95% CI 6.7 to 11. 4] versus 5.5 months [4.2 to 6.7]).[21] For context, in the study cited above by Hanker et al., median PFS across pooled treatment modalities after third and fourth relapse was 5.6 months (95% CI 4.8 to 6.2) and 4.4 months (95% CI 3.7 to 4.9), respectively.[5]

Objective Response

Objective response rate (ORR) quantifies the proportion of patients whose best response was either complete or partial using RECIST v1.1 criteria.[67] In Study 42 of olaparib, the overall ORR was 34% (95% CI 26% to 42%) for patients with a gBRCA mutation and at least three prior chemotherapy regimens.[21] The median duration of response, defined as the time from the date of first documented response to the date of documented progression or death, was 7.9 months. The ORR was higher for platinum-sensitive patients (46%; 95% CI 30% to 63%) than for patients with platinum-resistance (30% 95% CI 20% to 41%), although the median duration of response was similar in both populations (8.2 months vs. 8.0 months for platinum-sensitive and resistant groups, respectively).[21]

Quality of Life

We did not identify any patient-reported data related to symptom control or quality of life in patients treated with olaparib who had received three or more prior lines of therapy.

Olaparib for Maintenance Therapy in Platinum-Sensitive Disease

To date, there has been no overall survival benefit associated with olaparib for maintenance treatment. Progression-free survival was significantly longer in those taking olaparib compared to placebo, with the largest benefits observed in patients with a BRCA mutation. Patient-reported outcomes show no significant differences in quality of life with olaparib compared to placebo.

We identified two placebo-controlled RCTs of olaparib maintenance therapy: Study 19 and SOLO2. We also considered multiple supplemental manuscripts and abstracts from Study 19. Data from the two studies are summarized in Table 4.2.

Study 19 was a double-blind, placebo-controlled Phase II trial which enrolled women with platinum-sensitive ovarian cancer, irrespective of BRCA mutation (BRCAm) status. After an initial prespecified subgroup analysis of 97 patients with a known BRCAm status indicated that patients with deleterious BRCA mutations may derive a greater PFS benefit from olaparib, study investigators sought to retrospectively identify the BRCA status of all remaining trial participants. BRCA mutations were either reported on case report forms after local testing or were identified retrospectively through chart review, tumor tissue analysis or pre-randomization blood samples. The FDA expressed concern about the retrospective identification of the BRCAm population because it may have introduced potential bias into the analysis due to loss of randomization; we therefore rated this study to be of fair quality.

SOLO2 was the confirmatory Phase III trial of olaparib in a maintenance population based on Study 19's trial design. However, a key difference between Study 19 and SOLO2 is the use of different dosing formulations of olaparib: in Study 19, patients received eight 50 mg capsules twice daily (400 mg BID), which is the current FDA-approved dose, while SOLO2 patients received a new tablet formulation dosed at 300 mg BID. In addition, SOLO2 only includes patients with a documented deleterious or suspected deleterious BRCA mutation although confirmatory testing showed predominantly germline mutations. SOLO2's quality was rated as good.

Table 4.4. Clinical Outcome Summary of Olaparib Maintenance Therapy

Key Studies	Patient Characteristics		Treatment Outcomes	Comparator Outcomes	
Study 19 Median Follow-up: 71.0 m	Median age: 59 gBRCAm: 36% ≥3 PL: 54% TTP >12 m: 60%	Olaparib capsule BRCAm (n=74) PFS: 11.2 m OS: 34.9 m	Olaparib capsule BRCAwt (n=57) PFS: 7.4 m OS: 24.5 m	Placebo BRCAm (n=62) PFS: 4.3 m OS: 30.2 (26.6[±]) m	Placebo BRCAwt (n=61) PFS: 5.5 m OS: 26.6 m
SOLO2 Median Follow-up: 22.1 m	Median age: 56 gBRCAm: 97% Median prior chemo: NR ≥3 Prior platinum: 44%	Olaparib tablet (n=196) PFS: 19.1 m OS (immature): HR=0.80 (95% CI 0.50 to 1.31) p=0.43		Placebo (n=99) PFS: 5.5 m OS (immature): HR=0.80 (95% CI 0.50 to 1.31) p=0.43	

gBRCAm= germline BRCA; BRCAm=any *BRCA1/2* mutation (germline or somatic); BRCAwt= wild-type BRCA; OS=overall survival; PFS= progression-free survival; NR=not reported; ≥3 PL=3 or more prior lines of therapy; TTP=time to progression after penultimate platinum therapy

Overall Survival

Median overall survival for the entire study population of Study 19 was 29.8 and 27.8 months (nominal p-value=0.025) in the olaparib- and placebo-treated groups, respectively, which did not meet the required threshold for statistical significance of p<0.0095; differences in the BRCA mutation subgroup also did not reach statistical significance.[26] Matulonis et al. identified potential confounding in original OS findings for patients with BRCA mutations, as a small portion (n=14 [23%] of the gBRCA cohort plus 2 patients with BRCA of unknown origin) originally randomized to placebo were treated with PARP inhibitors after reaching their first progressive event. This occurrence may have masked potential differences between the two arms. An exploratory post hoc analysis was performed by removing all patients from sites where crossover occurred and re-analyzing median overall survival. The median overall survival in the cohort with deleterious BRCA mutations was 34.9 months for those who received olaparib compared to 26.6 months for those who received placebo (hazard ratio 0.52; 95% CI 0.28 to 0.97).[86] Findings were inconsistent, however, as a significant difference was seen in the overall BRCA mutation cohort (of both germline and somatic BRCA mutation) but not in the germline BRCA mutation cohort alone (hazard ratio 0.74; 95% CI 0.35 to 1.64). The authors could not explain this finding, given that a higher proportion of patients with germline BRCA mutation received a subsequent PARP inhibitor in the placebo arm.[87] Overall survival data from the SOLO2 study are not mature, although a preliminary analysis (24% of deaths reported) shows no significant difference between the olaparib and placebo arms.[25,30]

Progression-free Survival

Both RCTs of olaparib indicate improved progression-free survival compared to placebo, especially in the presence of a deleterious BRCA mutation.[24,25,27] In the full Study 19 cohort, median progression-free survival was 8.4 months for olaparib and 4.8 months for placebo (hazard ratio 0.35; 95% CI 0.25 to 0.49).[24] In the subgroup analysis of patients with deleterious BRCA mutations (BRCAm), progression-free survival was 11.2 months in the olaparib arm and 4.3 months in the placebo arm (HR 0.18; 95% CI 0.10 to 0.31); benefits were less pronounced with wild-type BRCA mutations (7.4 months vs. 5.5 months; HR 0.54; 95% CI 0.34 to 0.85).[27]

Data from the SOLO2 study showed a nearly 14-month progression-free survival benefit with olaparib for women with germline BRCA mutations (median 19.1 months vs. 5.5 months; hazard ratio 0.30; 95% CI 0.22 to 0.41) based on the primary endpoint of investigator-assessed events.[25] A planned secondary analysis of PFS based on blinded independent central review (BICR) showed even larger improvements in progression-free survival (median 30.2 months vs. 5.5 months; hazard ratio 0.25; 95% CI 0.18 to 0.41); however, concerns over the possibility of informative censoring (i.e., earlier detection of progression by investigator vs. blinded central assessment) led to a sensitivity analysis to intended to adjust for this potential bias. In the sensitivity analysis, PFS aligned more closely with investigator-assessed PFS (median 19.6 months vs. 5.5 months; hazard ratio 0.26; 95% CI 0.19 to 0.35).[30] These results differ from those in Study 19, most likely due to the inclusion of women with germline BRCA mutations only. Women with a BRCA mutation are thought to be more susceptible to PARP inhibition due to the deficiency in their DNA repair processes.

Objective Response

In a maintenance setting, objective response is considered a questionable outcome because many patients do not have measurable disease at the time of randomization. Nevertheless, objective response was measured in Study 19 and was 12% among those receiving olaparib and 4% for placebo (p=NS).[24]

Quality of Life

Patient-reported outcomes were measured in Study 19 using the Trial Outcome Index (TOI), the Functional Assessment of Cancer Therapy Ovarian (FACT-O) questionnaire, and the Functional Assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index (FOSI).[88] Study 19 showed no statistically significant or clinically relevant differences in health-related quality of life (HRQoL) between treatment arms on TOI, FACT-O, and FOSI assessments in the overall trial population, nor in the BRCAm or gBRCA subgroups.[88]

Data presented on the SOLO2 trial also identified no statistical difference in health-related quality of life using TOI between olaparib and placebo, although recently presented data on time without symptoms of disease or toxicity (TWiST) and quality-adjusted progression-free survival (QAPFS)

showed a potential benefit of olaparib over placebo (13.5 months vs. 7.2 months and 14.0 months vs. 7.3 months, respectively, p<0.0001 for both measures).[25,89]

Clinical Benefits of Niraparib

Niraparib for Recurrent, BRCA-Mutated Disease

We found no studies of niraparib for the treatment of relapsed disease, but note that a relevant study (QUADRA trial; NCT02354586) is ongoing and is described in Appendix C.

Niraparib for Maintenance Therapy in Platinum-Sensitive Disease

Mature overall survival data are not yet available for niraparib. Progression-free survival was significantly longer in those taking niraparib compared to placebo in patients with both germline and non-germline BRCA mutations. Patient-reported outcomes showed no significant differences in quality of life with niraparib compared to placebo.

We considered one good-quality randomized controlled trial for niraparib (NOVA). The NOVA trial was a double-blind Phase III trial of niraparib (300 mg QD) versus placebo that included patients from two independent cohorts based on the presence or absence of a germline BRCA mutation (gBRCAm). The primary endpoint was progression-free survival, which was assessed in a blinded fashion through computed tomography or magnetic resonance imaging using RECIST version 1.1 criteria every 8 weeks through cycle 14 (28-day continuous cycles), and then every 12 weeks until treatment discontinuation.

Table 4.5. Clinical Outcome Summary of Niraparib Maintenance Therapy

Key Study	Patient Characteristics	Treatment Outcomes		Comparator Outcomes	
NOVA **Median Follow-up: 16.9 m**	Median age: 61 gBRCAm: 37% ≥3 PL: 40% TTP ≥12 m: 61%	Niraparib gBRCAm (n=138) PFS: 21.0 m OS (immature): 16% died	Niraparib non-gBRCAm (n=234) PFS: 9.3 m OS (immature): 16% died	Placebo gBRCAm (n=65) PFS: 5.5 m OS (immature): 19% died	Placebo non-gBRCAm (n=116) PFS: 3.9 m OS (immature): 19% died

gBRCAm= germline BRCA; OS=overall survival; PFS= progression-free survival; ≥3 PL=3 or more prior lines of therapy; TTP= time to progression after penultimate platinum therapy

Overall Survival

Overall survival data from the NOVA trial of niraparib were not mature at the time of publication or FDA approval.[17] FDA review materials provide interim analyses showing no statistical significance in overall survival between niraparib and placebo in the full trial population (gBRCAm and non-gBRCAm combined; hazard ratio 0.73; 95% CI 0.48 to 1.11) but caution that no definitive conclusions could be made about overall survival with less than 20% of deaths reported at the time of FDA review.[17,90]

Progression-free Survival

Progression-free survival in the niraparib group was significantly longer than that in the placebo group across all populations studied ($p<0.001$).[17] From FDA documents, a pooled analysis in the intent to treat population showed a median PFS in the niraparib arm (n=372) was 11.3 months versus 4.7 months in the placebo arm (n=181), with an HR of 0.38 (95% CI 0.303 to 0.488).[90]

In the germline BRCA mutation cohort (gBRCA), the median duration of progression-free survival was 21.0 months with niraparib and 5.5 months with placebo (HR 0.27; 95% CI 0.17 to 0.41).[17] Across non-gBRCA patients, niraparib treatment also resulted in longer progression-free survival compared to placebo (median, 9.3 months vs. 3.9 months; HR 0.45; 95% CI 0.34 to 0.61). Within this group, those patients with HRD-positive typology (both somatic and wild-type) who received niraparib had significantly longer progression-free survival than those receiving placebo (median, 12.9 months vs. 3.8 months; HR 0.38; 95% CI 0.24 to 0.59). HRD-positive women with somatic BRCA mutation on niraparib had a median PFS of 20.9 months versus 11.0 months for placebo (HR 0.38; 95% CI 0.23 to 0.63).[91] HRD-positive women with wild-type BRCA mutation on niraparib had a median PFS of 9.3 months versus 3.7 months for placebo (HR 0.27; 95% CI 0.08 to 0.90).[91] Patients without gBRCA mutations and negative HRD typology also had a modest progression-free surivival benefit (median 6.9 vs. 3.8 months; HR 0.58; 95% CI 0.36 to 0.92).[17]

Objective Response

Objective response was not an endpoint in the NOVA trial.

Quality of Life

The NOVA trial measured patient-reported outcomes using the FOSI and the European Quality of Life-5 Dimensions (EQ-5D-5L) questionnaires. Patients reported similar changes in HrQoL across treatment groups. No statistically significant differences were found in either the FOSI or EQ-5D-5L between patients taking niraparib and placebo in both the gBRCA and non-gBRCA cohorts.[17]

Clinical Benefits of Rucaparib

Rucaparib for Recurrent, BRCA-Mutated Disease

Overall survival data for rucaparib are not yet available. Progression-free survival was approximately 10 months with rucaparib. While not a direct comparison, analyses of standard ovarian cancer treatments suggest a median PFS of approximately 6 months in similar patients. Patients with platinum sensitivity had a longer PFS and higher response rate than platinum-resistant patients. Quality of life data have not been reported for rucaparib in this population.

To inform our assessment of rucaparib, we reviewed two subgroup analyses from two single-arm trials. Both analyses included data from the Phase II ARIEL2 trial.[31,92] In Part 1 of ARIEL2, patients were recruited if they had high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal carcinoma, had received at least one previous platinum therapy, and were platinum-sensitive. Data from Part 1 have been published, but since more than half of the study population (58%) had received only one prior chemotherapy, efficacy results are excluded from our review.[31a] Part 2 of the study, which is still ongoing, limited recruitment to patients with 3-4 prior lines of chemotherapy, irrespective of platinum sensitivity. Results from Part 2 of the ARIEL2 trial are not yet published, although data from 93 (out of 287) patients participating in Part 2 have been pooled with data from 41 (out of 206) patients who participated in Part 1. The first subgroup analysis summarized below drew upon this pooled data.[23]

The second reference we identified for rucaparib was an analysis that was used to inform the FDA's review of the drug. The analysis pooled data from 106 patients who had a deleterious germline or somatic BRCA mutation, received at least two prior chemotherapies (including two or more platinum-based regimens), and had participated in an earlier study (Study 10) or ARIEL2.[28,31,92] Study 10 was a three-part, Phase I-II, open-label, single-arm study of rucaparib; Phase II of the study focused on 42 platinum-sensitive patients with germline BRCA mutations and 2-4 prior chemotherapies. Important study characteristics and inclusion criteria for the ARIEL2 trial, Study 10, (and corresponding subgroup analyses) are summarized in Appendix Table D1.[23,28,92]

[a]Safety data from part 1 of ARIEL2 are included in our review of harms.

Table 4.6. Clinical Outcome Summary of Rucaparib in Recurrent Ovarian Cancer with a Deleterious BRCA Mutation

Key Studies	Patient Characteristics	Outcomes
ARIEL2[23] (analysis of patients with BRCA mutations from Parts 1 & 2 of ARIEL2)	Median age: 60 gBRCAm: 58% sBRCAm: 17% BRCAm (origin uncertain): 25% Platinum sensitive: 53% Platinum resistant: 37% ≥3 prior chemotherapies: 76%	Rucaparib (n=134)* Median OS: Not reported Median PFS (overall): Not reported Median PFS (Platinum sensitive): 12.7 months Median PFS (Platinum resistant): 7.3 months ORR (Platinum sensitive): 52%† ORR (Platinum resistant): 25%† QoL: Not reported
Study 10/ARIEL2[28] (pooled analysis of patients BRCA mutations and ≥2 prior chemotherapies from Study 10 and ARIEL2)	Median age: 59 gBRCAm: 83% sBRCAm: 12% BRCA (origin uncertain): 5% Platinum sensitive: 75% Platinum resistant: 19% ≥3 prior chemotherapies: 61%	Rucaparib (n=106) Median OS: Not reported Median PFS: 10.0 months ORR (overall): 53.8% ORR (Platinum sensitive): 66% ORR (Platinum resistant): 25% QoL: Not reported

*Outcomes in patients with deleterious BRCA mutation; †ORR is for patients with ≥3 prior lines of chemotherapy; gBRCAm= germline BRCA; sBRCAm=somatic BRCA; OS=overall survival PFS=progression-free survival; ORR=objective response rate; QoL=quality of life

Overall Survival

Overall survival data are not yet available for patients being treated with rucaparib.

Progression-free Survival

PFS data were reported for a number of different subpopulations from ARIEL2.[23] Among those subpopulations, platinum-sensitive patients whose immediate prior treatment was a platinum therapy experienced the longest PFS (median 12.7 months; 95% CI 9.0 to 14.7). Platinum-sensitive patients whose immediate prior treatment was not a platinum regimen experienced a comparable PFS to that of platinum-resistant patients (7.4 months vs. 7.3 months, respectively).

As noted above, we did not identify any comparative data of rucaparib versus other standard third-line or later therapies in ovarian cancer. An exploratory analysis from Hanker and colleagues followed patients who participated in three Phase III randomized controlled trials of primary taxane/platinum-based therapy through their sixth line of therapy.[5] Relapse therapies included chemotherapy, hormonal therapy, surgery, radiotherapy, and others. Across treatment modalities, median PFS after the second relapse was 6.4 months (95% CI 5.9 to 7.0) and 5.6 months (95% CI 4.8 to 6.2) after the third relapse.[5]

Objective Response

The overall objective response rate in patients included in the pooled analysis of Study 10/ARIEL2 was 53.8% (95% CI 43.8% to 63.5%); in both analyses of rucaparib, levels of response were higher among platinum-sensitive patients (65.8-70.0%) versus platinum-resistant patients (25% in both analyses).[23,28] The median duration of response, which was only reported in the pooled Study10-ARIEL2 analysis, was 9.2 months (95% CI 6.6 to 11.7).[28]

Quality of Life

We did not identify any patient-reported data related to symptom control or quality of life in patients treated with rucaparib who had received two or more prior lines of therapy.

Rucaparib for Maintenance Therapy in Platinum-Sensitive Disease

Mature overall survival data are not yet available for rucaparib. Progression-free survival was significantly longer in those taking rucaparib compared to placebo. Patient-reported outcomes showed no significant differences in quality of life with rucaparib compared to placebo.

We considered one good-quality randomized controlled trial for rucaparib in the maintenance population (ARIEL3). ARIEL3 was a double-blind, placebo-controlled Phase III trial of rucaparib versus placebo in 564 platinum-sensitive ovarian cancer patients.[93] The trial enrolled women who had received at least two previous platinum-based chemotherapy regimens with complete or partial response.[29] Patients were randomized 2:1 to rucaparib using block randomization. Stratification was based on homologous recombination deficiency (HRD) status, progression-free interval and response following penultimate platinum-based regimen.[29] HRD status was assessed by gene mutations identified within tumor tissue. Subgroups included the presence of a deleterious germline or somatic mutation in *BRCA1* or *BRCA2* (BRCA mutant), a mutation in a non-BRCA gene associated with homologous recombination or no mutation in *BRCA1*, *BRCA2*, or other HRD associated genes.[29] HRD positive patients without a BRCA mutation (BRCA wildtype) were further stratified into those tumors with high genomic loss of heterozygosity (LOH), low genomic loss of heterozygosity or indeterminant levels of LOH.[29]

The primary outcome was investigator-assessed progression-free survival, with progression measured using RECIST version 1.1 every 12 weeks.[94] Secondary analyses included PFS assessed by blinded, independent central review (BICR), overall survival, and quality of life using the Cancer Therapy Ovarian Symptom Index 18 (FOSI-18).[94] Statistical analysis was performed using an ordered step-down procedure where the population with BRCA-mutated disease must reach statistical significance (one-sided α of 0.025) before additional subgroups are analyzed.

Table 4.7. Clinical Outcome Summary of Rucaparib Maintenance Therapy

Summary of Primary Efficacy Analyses and Selected Exploratory Endpoints for ARIEL3[29]			
	PFS by Investigator Review *(Primary Endpoint)*		
Primary Analyses			
	Hazard Ratio (95% CI)	**Median PFS (months) Rucaparib vs. Placebo**	
BRCAm (n=196)	0.23 (0.16–0.34)	16.6 vs. 5.4	
HRD-Positive (n=354)	0.32 (0.24–0.42)	13.6 vs. 5.4	
Intention-to-Treat (n=564)	0.36 (0.30–0.45)	10.8 vs. 5.4	
Exploratory Analyses			
BRCA^{wt} / HRD-Positive (n=158)	0.44 (0.29–0.66)	9.7 vs. 5.4	
BRCA^{wt} / HRD-Negative (n=161)	0.58 (0.40–0.85)	6.7 vs. 5.4	

BRCAm= germline or somatic BRCA mutation; BRCA^{wt}= BRCA wildtype; PFS=progression-free survival; HRD= homologous recombination deficiency

Overall Survival

Overall survival data from ARIEL3 are not yet mature.[29]

Progression-free Survival

In women with a *BRCA1* or *BRCA2* mutation (BRCAm), the median duration of progression-free survival assessed by the investigator was 16.6 months with rucaparib and 5.4 months with placebo (HR 0.23; 95% CI 0.16 to 0.34).[29] A secondary analysis performed by a blinded independent central review (BICR) showed a median progression-free survival of 26.8 months with rucaparib and 5.4 months with placebo (HR 0.20; 95% CI 0.13 to 0.32).[29]

Where the tumor showed a homologous recombination deficiency (HRD+) without a BRCA mutation, the median duration of progression-free survival assessed by the investigator was 13.6 months with rucaparib and 5.4 months with placebo (HR 0.32; 95% CI 0·24 to 0·42).[29] BICR-assessed median PFS was 22.9 months with rucaparib and 5.5 months with placebo (HR 0.34; 95% CI 0.24 to 0.47).[29]

Across all patients (intention-to-treat population), the median duration of progression-free survival assessed by the investigator was 10.8 months with rucaparib and 5.4 months with placebo (HR 0.36; 95% CI 0·30 to 0·45).[29] BICR-assessed median PFS was 13.7 months with rucaparib and 5.4 months with placebo (HR 0.35; 95% CI 0.28 to 0.45).[29]

An exploratory, pre-planned subgroup analysis of PFS in women with BRCA wildtype with both high and low loss of heterozygosity (LOH) showed benefit of rucaparib versus placebo. The median

progression-free survival in high-LOH assessed by the investigator was 9.7 months with rucaparib and 5.4 months with placebo (HR 0.44; 95% CI 0.29 to 0.66). [29] The BICR-assessed PFS in this subgroup was 11.1 months with rucaparib and 5.6 months with placebo (HR 0.55; 95% CI 0.35 to 0.89).[29] The median progression-free survival in low-LOH assessed by the investigator was 6.7 months with rucaparib and 5.4 months with placebo (HR 0.58; 95% CI 0.40 to 0.85) while the BICR assessment was 8.2 months with rucaparib and 5.3 months with placebo (HR 0.47; 95% CI 0.31 to 0.71).[29]

Objective Response

A prespecified exploratory analysis of objective response in women with measurable disease from partial response to penultimate platinum-based treatment was performed (207/554, 37%).[29]

For those with a BRCA mutation, objective response rates were 37.5% with rucaparib and 8.7% with placebo (95% CI 22.7% to 54.2% and 1.1% to 28.0%, respectively).[29] In women with HRD, ORR was 27.1% with rucaparib and 7.3% with placebo (95% CI 18.0% to 37.8% and 1.5% to 19.9%, respectively).[29] In the full intention-to-treat population, ORR was 18.4% with rucaparib and 7.6% with placebo (95% CI 12.4% to 25.8% and 2.5% to 16.8%, respectively).[29] Ten women who received rucaparib (7.1%) and one woman who received placebo (1.5%) experienced a complete response.[29]

Quality of Life

ARIEL3 measured time to worsening using the National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy Ovarian Symptom Index 18 (FOSI-18). No statistically significant differences were found in the BRCA mutation sub-group (HR 1.24 [95% CI 0.82–1.86); therefore, other subgroups were not evaluated.[29]

Harms

The most common side effects of PARP inhibitors are nausea, vomiting, anemia, thrombocytopenia, and neutropenia. Some risks appear to be severe across all therapies, including myelodysplastic syndrome/acute myeloid leukemia, but have been reported in a small minority of patients (0-2%).

Adverse event (AE) frequencies and rates of Grade 3-4 (severe and life-threatening) events are reported by regimen in Table 4.8. Note that these data are presented across study populations rather than individually for the recurrent, BRCA-mutated population and the maintenance therapy population. Detailed, drug-specific descriptions of safety data are presented in Appendix D. The most common AEs observed with the PARP inhibitors included gastrointestinal side effects (nausea, abdominal pain, vomiting) and hematologic toxicity (anemia, neutropenia, and thrombocytopenia).

As described in the Topic in Context section, PARP inhibitors may be better tolerated than alternative relapse and/or maintenance therapies. For example, pegylated liposomal doxorubicin (PLD) has a black box FDA warning for cardiomyopathy and severe, life-threatening infusion-related reactions.[95] Hand-foot syndrome, a painful, blistering of the palms and soles of the feet, is also a reported side effect of doxorubicin, and when PLD is combined with a platinum agent such as carboplatin, grade 3-4 hematologic toxicities such as neutropenia (35.2%), and thrombocytopenia (16%) are common.[95-97] The side effect profile of bevacizumab, which is an FDA-approved relapse and maintenance therapy, carries an FDA black box warning for gastrointestinal perforation, surgery and wound healing complications, and hemorrhage.[98] When combined with chemotherapeutic agents such as gemcitabine and carboplatin, grade 3-5 thrombocytopenia (40%) may also occur.[99] Nausea (73%) and fatigue (82%) of any grade are also common with bevacizumab combination therapy.[98,99]

Olaparib

Although rates of severe and life-threatening side effects were relatively low for all PARP inhibitors, the FDA has expressed concern about the incidence of myelodysplastic syndrome and acute myeloid leukemia (MDS/AML) observed with olaparib, which occurred in approximately 2% of patients across trials. As the majority of these cases have proven fatal, the FDA has included warnings about MDS/AML in each of the PARP inhibitors' prescribing information and advised providers to regularly monitor patients for hematologic toxicity. The FDA label for olaparib also includes a warning about pneumonitis, which occurred in <1% of patients. The recently published SOLO2 study using the new formulation of olaparib (300 mg twice daily, tablets) showed low rates of grade 3 or higher adverse events (18% for olaparib; 8% for placebo).[30] Anemia was the most common serious adverse event for those on treatment (4%).[30] There was one treatment-related death attributed to AML.[30] Dose interruptions, reductions and discontinuations from adverse events occurred more frequently in the olaparib arm compared to placebo (45% vs. 18% for dose interruption; 25% vs. 3% for dose reduction; 11% vs 2% for discontinuation).[30]

Niraparib

Niraparib has a different toxicity profile from that of the other PARP inhibitors.[50] Approximately two-thirds of patients treated with niraparib had an adverse event leading to a dose reduction and reported rates of both grade 3-4 neutropenia (20%) and thrombocytopenia (34%) were considerably higher with niraparib than the other PARP inhibitors. Cardiovascular events were also of concern to the FDA. Grade 3-4 hypertension occurred in 9% of niraparib patients compared to 2% of placebo patients in the NOVA study (statistical significance was not reported).[90] The current FDA prescribing information for niraparib includes warnings for MDS/AML, bone marrow suppression, and cardiovascular effects.[20]

Rucaparib

Rucaparib safety information is primarily informed by data from the ARIEL2 and ARIEL3 trials. Toxicities related to rucaparib were similar to those of olaparib, although half of the patients who participated in ARIEL3 experienced a dose reduction related to a treatment-emergent adverse event (55%).[23] In addition, grade 3-4 increases in liver enzyme levels (aspartate aminotransferase [AST] and alanine transaminase [ALT]) were reported. As with olaparib and niraparib, the FDA prescribing information includes a warning to monitor patients for hematologic toxicity because of the possibility of MDS/AML. Two deaths were reported in ARIEL3 due to MDS/AML in the rucaparib arm (zero with placebo).

Table 4.8. Adverse Events of Olaparib, Niraparib, and Rucaparib

	Olaparib[21,24,25,27,30]*	Niraparib†[17]	Rucaparib†[23,28,29,31]
Any Adverse Events	96-99%	100%	100%
Any Adverse Events Grade ≥3	35-55%	74%	48-61%
Any SAE	18-30%	30%	21-25%
Any Adverse Events Leading to Dose Reduction	22-25%	67%	49-55%
Any Adverse Events Leading to Discontinuation of Study Treatment	2-11%	15%	13%
Any Adverse Events with Outcome of Death	0.5-3%	0	1-2%
Grade ≥3 Adverse Events			
Abdominal Pain	2-8%	1%	0-2%
AST/ALT Increased	2%	NR	10-12%
Anemia	5-24%	25%	19-22%
Fatigue	4-7%	8%	7-9%
Hypertension	NR	8%	NR
MDS/AML	1-2%	1%	0-1%
Nausea	1-3%	3%	4%
Neutropenia	4-5%	20%	5-7%
Thrombocytopenia	0.7-1%	34%	2-5%
Vomiting	2-3%	2%	2-4%

AST/ALT=Aspartate aminotransferase/Alanine transaminase; MDS/AML=Myelodysplastic syndrome/Acute myeloid leukemia; NR=not reported; *Values for olaparib represent range of AEs reported in Study 42, Study 19, and SOLO2; †NOVA trial of niraparib and ARIEL2 and ARIEL3 trials of rucaparib reported treatment-emergent adverse events

Comparator Evidence

There are currently no head-to-head studies of a PARP inhibitor versus later-line chemotherapy or maintenance bevacizumab.

We did not perform full systematic reviews of comparator drugs but highlight the key outcomes from recent publications of bevacizumab maintenance therapy and pegylated liposomal doxorubicin for recurrent ovarian cancer (see Appendix D).

Controversies and Uncertainties

Multiple limitations in the body of evidence limit our ability to make judgments regarding the comparative net health benefits of the PARP inhibitors relative to each other or alternative therapies used in relapse and maintenance settings. First, final overall survival data demonstrating statistically-significant improvement over historical treatment options are not available. Recent studies of other novel ovarian cancer therapies have shown statistical improvements in progression-free survival but not overall survival, despite a trend of improving survival over the past decade.[99,100] Although overall survival is generally regarded as the "gold-standard" endpoint in ovarian cancer, it has become increasingly difficult for clinical trials to demonstrate an OS benefit.[99,101,102] Improvement in the duration of survival is likely due to the cumulative benefit of multiple treatment regimens over time; such improvements have allowed patients to receive multiple post-progression therapies, while obscuring the detection of a survival benefit in any individual treatment regimen or clinical trial.

In the maintenance setting, there is ongoing debate about the suitability of PFS to evaluate clinical benefit. Some clinical experts acknowledge that PFS may be a reasonable endpoint for trials of maintenance therapy, arguing that an extension of the interval of time between rounds of cytotoxic chemotherapy may be valuable.[32] Other clinicians are skeptical of the benefit of maintenance therapy, noting that the lack of a clear survival or quality of life benefit do not justify the additional toxicity patients must endure during a time when they would otherwise be appreciating a drug holiday. As one member of the FDA Oncologic Drugs Advisory Committee (ODAC) stated, "if you're going to pay that penalty in terms of toxicity then you want a return on that, not just that your progression is delayed but that your overall survival was beneficial."[33] In addition, the question of who should receive maintenance therapy remains uncertain, as the PFS benefit observed in the NOVA trial of niraparib ranged from 15.5 months in patients with a germline BRCA mutation to 3.1 months among HRD negative patients with no deleterious BRCA mutation.[17] In the original pivotal trial of olaparib (Study 19) women with wild-type BRCA mutations received less than two months of progression-free survival benefit (n=118; 7.4 months vs. 5.5 months; HR 0.54; 95% CI 0.34 to 0.85).[27] Like physicians and regulators, patients value improvements in progression-free survival but are wary of taking on additional toxicity. However, each patient must individually weight their

personal potential benefit (given their genetic makeup, the history of their disease and their current clinical status) against the side effects they experience, which are highly individual.

There are also specific uncertainties regarding the evidence for individual PARP inhibitors. The benefit of olaparib maintenance therapy was questioned by FDA reviewers because of safety concerns, lack of clinically meaningful 6-month PFS improvement, lack of overall survival data and questions about data quality (i.e., retrospective identification of BRCA mutation status and unauthorized crossover to treatment in Study 19). Based on these concerns, the FDA ODAC voted 11-2 that marketing approval for olaparib should be delayed for the maintenance indication until data from SOLO2 was available. The FDA did subsequently approve olaparib for treatment in relapsed patients who had received three or more prior lines of therapy based on a subgroup analysis from Study 42; this subgroup represented more advanced, heavily pretreated patients, among whom olaparib had greater potential to serve an "unmet need" and the risk/benefit profile was more acceptable than the originally-proposed maintenance indication. Although the two studies have similar designs, SOLO2 enrolled predominantly patients with a deleterious or suspected deleterious germline BRCA mutation and evaluated a different dose and formulation of the drug; whereas patients participating in Study 19 received eight 50 mg capsules twice daily (400 mg BID), SOLO2 patients received a new tablet formulation dosed at 300 mg twice daily. The bioequivalence of this dose has not fully been established but is estimated to have approximately 1.5 times the relative bioavailability of the 400 mg capsules.[33] Data from the published SOLO2 trial confirmed the benefit-risk profile observed in Study 19 and led to FDA approval on August 17, 2017.[18,33]

The evidence base for patients with a deleterious BRCA mutation who have received multiple prior lines of therapy is currently limited to one single-arm trial for each of the two agents, and findings from the key single-arm trial of niraparib in this population are not yet available. These studies primarily looked at tumor response to inform the FDA's approval decision. We heard from clinical experts that this is a poor endpoint to use for assessing PARP inhibitor efficacy, since these agents "disrupt tumor machinery" while cytotoxic agents shrink the tumor. More importantly, no comparator data are yet available, so the incremental gain in PFS, OS, or quality of life compared to another therapy for recurrent cancer remain unknown.

Perhaps the greatest amount of uncertainty in comparative net health benefit lies in the lack of truly comparative data across trials. Given that many of these drugs were approved very recently, we do not expect there to be published head-to-head data available. However, the limited number of available studies, major differences in endpoint measurement, and the absence of data for certain key subgroups precluded even indirect comparison of the regimens in our review. For example, endpoints such as PFS varied in the increments of time between evaluation (8 weeks in NOVA and 12 weeks in Study 19) and used different versions of the RECIST criteria (1.0 in Study 19 vs. 1.1 in NOVA).

In addition, evidence from the key trials may have limited validity for the broader patient population in the U.S. Of note, patients with a deleterious BRCA mutation represent only a minority of patients, as do patients with the same degree of platinum sensitivity as those who participated in the PARP inhibitor maintenance trials. We heard from one leading gynecologic oncologist that patients similar to those who participated in trials of niraparib and olaparib account for less than a quarter of the patients she sees in practice. Several experts informed us that these therapies are being used off-label (e.g., as earlier-line treatment) in patients among whom the efficacy and safety are even less certain.

Finally, several important questions remain regarding the appropriate use of these agents in clinical practice. Future study should evaluate the optimal sequence of PARP inhibitors in the treatment pathway, whether they can safely be combined with other therapies, whether maintenance should be given indefinitely or for a fixed amount of time, whether it is better to use a PARP inhibitor as maintenance therapy or to reserve these agents for treatment at recurrence, what biomarkers are predictive of risk, and treatment after progression on a PARP inhibitor.

4.4 Summary

We reviewed data on PARP inhibitors for use as treatment for recurrent, BRCA-mutated ovarian cancer as well as for use as maintenance therapy in women with platinum-sensitive, recurrent ovarian cancer who have received at least two prior platinum-based chemotherapy regimens and were in response to the most recent regimen. Specifically, the PARP inhibitors olaparib, rucaparib, and niraparib were assessed and the evidence ratings below are evaluated independently.

Table 4.9. ICER Evidence Ratings

Population/PARP Inhibitor	ICER Evidence Rating
Recurrent, BRCA-Mutated Disease	
Olaparib	P/I
Rucaparib	P/I
Niraparib	I
Maintenance Therapy in Platinum-Sensitive Disease	
Olaparib	C+
Niraparib	C+
Rucaparib	C+

Olaparib

Olaparib for Recurrent, BRCA-Mutated Disease

- There are no comparative studies of 4th-line or later olaparib; it is uncertain if olaparib confers a clinical benefit over alternative chemotherapies in this population.
- Study 42 reported an overall survival of almost 17 months and progression-free survival of nearly 7 months; PFS was higher among patients with platinum sensitivity (9.4 months vs. 5.5 months in platinum-resistant patients).
- The tolerability of olaparib is relatively favorable compared to that of cytotoxic chemotherapy; it is likely that patients would experience better quality of life with olaparib than chemotherapy, although quality of life data have not yet been reported for patients treated with 4th-line or later olaparib.

Due to the lack of direct comparative evidence with other therapies used in recurrent, BRCA-mutated disease, we cannot be certain whether olaparib provides a survival benefit, is comparable, or possibly even inferior to alternative treatments. We believe that olaparib has a better safety profile than chemotherapy and may provide better quality of life, although patient-reported outcomes are not yet available. Because of this uncertainty, and because we cannot definitively rule out the possibility of net harm, we consider the evidence on olaparib in this population to be "promising but inconclusive" (P/I).

Olaparib for Maintenance Therapy in Platinum-Sensitive Disease

- Treatment with olaparib resulted in substantial improvements in progression-free survival compared to placebo for women with deleterious germline BRCA mutation. We are moderately confident that olaparib provides a small to substantial net health benefit for PFS in this population.
- Despite this potential benefit, overall surivival data from the Phase III study is immature. Therefore, we are currently uncertain whether olaparib will extend the life of ovarian cancer patients when used in a maintenance setting.
- Olaparib patients reported higher numbers of adverse events than placebo patients; however, many of these events were managed with dose reductions and dose interruptions. Currently-available data on quality of life do not indicate differences between olaparib and placebo.

For women with platinum-sensitive disease who are candidates for maintenance therapy, we have moderate certainty that olaparib provides at least a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit when used as maintenance therapy relative to placebo (i.e., surveillance alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

Niraparib

Niraparib for Recurrent, BRCA-Mutated Disease

The clinical study of niraparib that is relevant to the population of patients with BRCA-mutated recurrent disease has not yet released any data. We therefore consider the evidence for niraparib in this population to be "insufficient" (I).

Niraparib for Maintenance Therapy in Platinum-Sensitive Disease

- Treatment with niraparib resulted in substantial improvements in progression-free survival compared to placebo. Benefits were seen in both cohorts of the trial; however, patients with a deleterious or suspected deleterious germline BRCA mutation saw greater PFS benefit than those without (median PFS 21.0 m in gBRCAm vs. 9.3 m in non-gBRCAm). We are moderately confident that niraparib provides a substantial benefit in PFS in patients with deleterious or suspected deleterious germline BRCA mutation. We are moderately confident that niraparib provides a small to substantial benefit in PFS in patients without such a mutation. We are less certain of the size of the benefit in patients without deleterious BRCA mutations because the median incremental benefit (5.4 months vs. placebo) is less than that described as a clinically-important difference during FDA advisory committee discussions (six months).[33]
- Despite the PFS benefits described above, there have been no published data on overall survival. We therefore currently lack certainty that niraparib will extend the life of ovarian cancer patients when used in a maintenance setting.
- Niraparib patients reported higher numbers of adverse events than placebo patients; however, many of these events were managed with dose reductions and dose interruptions. Reported rates of certain events (e.g., neutropenia) were higher than with the other PARP inhibitors. Currently-available data on quality of life do not indicate differences between niraparib and placebo.

In patients with platinum-sensitive ovarian cancer who are candidates for maintenance therapy, we have moderate certainty that niraparib provides at least a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit when used as maintenance therapy relative to placebo (i.e., surveillance alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

Rucaparib

Rucaparib for Recurrent, BRCA-Mutated Disease

- There are no comparative studies of 3rd-line or later rucaparib; it is uncertain if rucaparib confers a clinical benefit over alternative therapies in this population.
- Overall survival data are not yet available for rucaparib. The median duration of PFS was 12.7 months for platinum-sensitive patients and 7.3 months for platinum-resistant patients.
- Rucaparib has a relatively favorable safety profile compared to that of chemotherapy; it is likely that patients would experience better quality of life with rucaparib, although data are not yet available.

Due to the lack of direct comparative evidence with other therapies used in recurrent, BRCA-mutated disease, we cannot be certain whether rucaparib provides a survival and/or quality of life benefit over alternative treatments, is comparable, or possibly even inferior. As with olaparib, we therefore deem the evidence for rucaparib in this population to be promising but inconclusive (P/I).

Rucaparib for Maintenance Therapy in Platinum-Sensitive Disease

- Treatment with rucaparib resulted in substantial improvements in progression-free survival compared to placebo. We are moderately confident that rucaparib provides a small to substantial net health benefit for PFS in this population.
- An objective response to rucaparib was seen in women with measurable disease following partial response to platinum-based therapy; however, statistical significance was not reported in this exploratory analysis.
- Despite this potential benefit, overall surivival data from the Phase III study are still immature. Therefore, we are currently uncertain whether rucaparib will extend the life of ovarian cancer patients when used in a maintenance setting.
- Rucaparib patients reported higher numbers of adverse events than placebo patients; however, many of these events were managed with dose reductions and dose interruptions.
- Currently-available data on quality of life do not indicate a difference between rucaparib and placebo.

For women with platinum-sensitive disease who are candidates for maintenance therapy, we have moderate certainty that rucaparib provides at least a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit when used as maintenance therapy relative to placebo (i.e., surveillance alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

5. Economic Analyses

5.1 Long-Term Cost Effectiveness

Overview

The aim of this analysis was to estimate the cost-effectiveness of the PARP inhibitors (olaparib, niraparib, and rucaparib) in the treatment of adult women with ovarian cancer. Model parameters were estimated from published literature and from information received from the manufacturers. The primary outcomes of the model included discounted total payer costs, life years, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios, using a health-care system perspective over a 15-year time horizon. Uncertainty in the data inputs and assumptions were evaluated using sensitivity and scenario analyses.

The model was structured as a "semi-Markov" model (i.e., one that allows for additional health states beyond progression-free, progression, and death). We modeled the two populations of interest for this review as listed below, focusing on the actual FDA indications or primary analytic cohorts from clinical trials based on published or otherwise publicly-available data:

- Treatment of recurrent, BRCA-mutated disease:
    - Olaparib (gBRCA only, 4th-line or later treatment) versus pegylated liposomal doxorubicin in combination with carboplatin (PLD+C)
    - Rucaparib (any deleterious BRCA mutation, 3rd-line or later treatment) versus PLD+C

- Maintenance treatment for platinum-sensitive disease:
    - Olaparib (gBRCA only) versus placebo (i.e., observation only)
    - Niraparib (gBRCA) versus placebo
    - Niraparib (non-gBRCA) versus placebo
    - Rucaparib (germline or somatic BRCA mutations) versus placebo

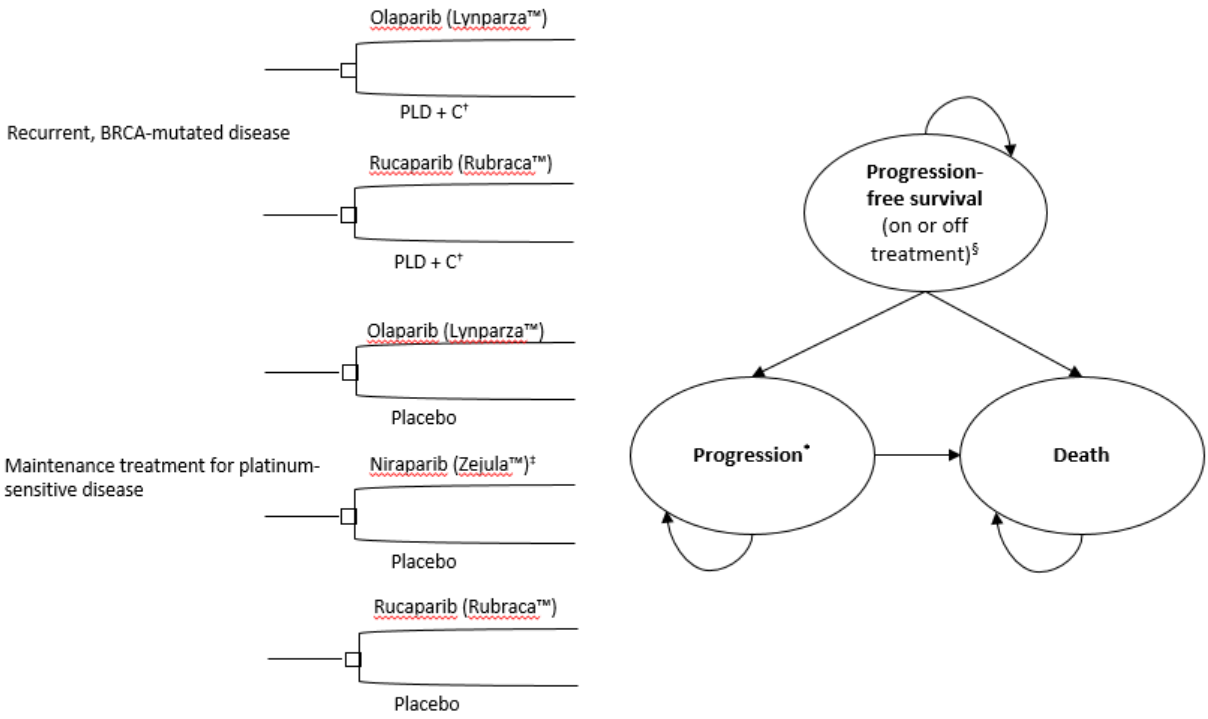
Importantly, given the issues of data incompatibility across drugs and studies highlighted in Section 4, we did not attempt to conduct any explicit or implied comparisons across PARP inhibitors. For this reason, our findings are organized by PARP inhibitor rather than population in the sections that follow.

Cost-Effectiveness Model: Methods

Model Structure

We developed a semi-Markov model with time-dependency (Figure 3). The model included three main health states with inputs dependent on the intervention and population modeled. The health states included: (a) progression-free (on treatment or off treatment); (b) progression (clinical evidence allowed for additional states, including first and second subsequent therapy, for some models); and (c) death from cancer or other causes. Patients who transitioned from the progression-free health states (on or off treatment) to progression state(s) remained there until they died from progressed cancer or from other causes. The semi-Markov approach was chosen because of its flexibility to model additional health states beyond progression-free, progression, and death (i.e., on- and off-treatment sub-states). This approach has been shown to have greater flexibility than other cancer modeling techniques such as partitioned survival.[36] The transition probabilities were calculated based on survival functions derived from Kaplan-Meier curves from trial data, referenced in the sub-sections below. Statistical fitting methods allowed the extrapolation of the survival results beyond the observed time frame in clinical trials.

Figure 5.1. Model Structure



§ Separate utility and cost inputs were incorporated for on or off treatment
*The semi-Markov approach allows for modeling of progression defined by multiple subsequent lines of treatment (data dependent)
†Pegylated liposomal doxorubicin + carboplatin
‡Nirparib was evaluated for both gBRCAmut and non-gBRCAmut subpopulations whereas olaparib was evaluated within a gBRCAmut sub-cohort only and rucaparib was evaluated within a somatic or gBRCAmut population for base-case findings

Survival, quality-adjusted survival, and costs from the health-care system perspective were estimated for each model cycle of one month and then summarized over a 15-year time horizon for each treatment option. The 15-year time horizon represents the shortened life-span often observed in advanced ovarian cancer and is reflective of previous modeling analyses. The model was developed in Microsoft Excel (Office 2016; Microsoft Corporation, Redmond, WA).

Model Parameters

The economic evaluation was primarily from a health-system perspective, and thus focused on direct medical and pharmacy costs. For a more detailed description of the types of impacts included in this analysis from a health care sector perspective, refer to the impact inventory in Appendix Table E1. All future costs and outcomes were discounted at 3% per year. The model was informed by several assumptions, which are detailed below in Table 5.1.

Table 5.1. Model Assumptions and Rationale

Assumption	Rationale
The model utilized multiple clinical trials to derive PFS and survival estimates for each drug regimen.	Given lack of head-to-head comparisons and overlap between trials and subpopulations, we did not utilize any indirect treatment comparison methods.
Parametric curve functions were fit separately for each population/treatment setting and used to extrapolate the data to a lifetime horizon. (See Population and Intervention Sections, below.)	Between the five comparisons modeled, there was no single uniform baseline comparator used across treatments/populations.
Trial-reported survival hazard ratios were assumed to remain constant beyond trial-reported follow-up time in extrapolated survival estimates.	We fit multiple survival functions and selected the most appropriate function based on AIC criteria.[37] The same survival distribution was used within each comparison to reduce the risk of intra-comparison survival differences being explained solely by parametric assumptions.
Discontinuation of treatment was assumed within the maintenance populations for olaparib, niraparib, and rucaparib. Rates of discontinuation were identical and were based on olaparib trial data. The PFS survival curves remained unique to niraparib and olaparib.	Discontinuation allowed for on and off treatment modeling within the PFS health state. Treatment cost was not applied to the proportion of patients in PFS who have discontinued treatment. The only available evidence on discontinuation was from olaparib trial data.[103]
Subsequent treatment following discontinuation reflected onset of symptomatic disease progression.	Trial evidence included subsequent treatment lines as a marker for disease progression.
All patients who progress to the next line of therapy were assumed to receive active chemotherapy.	Trial data on subsequent treatment suggest that most women receive active therapy rather than supportive care alone.
Disease progression costs and utilities reflected a distribution of subsequent treatments and best supportive care. The cost per month and utility while in disease progression was consistent within each comparison.	Assuming uniform costs and utilities in the progressed state allows any differences between treatments to be driven by the time spent in the state.
The model included severe adverse events (grade 3 or 4) only.	Less severe events are not expected to significantly impact patient health or costs.
Where evidence was missing on overall survival (rucaparib and niraparib), we assumed the same likelihoods of overall survival from a PARP inhibitor with reported evidence within the same treatment population (i.e., olaparib for both treatment populations).	Overall survival is required for estimating life years and quality-adjusted life years. Given weak evidence on the correlation between PFS and overall survival in ovarian cancer, relying on PARP inhibitor evidence within the same treatment population was a reasonable proxy rather than assuming no survival benefit without evidence.

Target Population

The key populations of interest are described below.

1. Recurrent BRCA-mutated disease
2. Maintenance therapy for platinum-sensitive disease

Interventions

The interventions of interest included three PARP inhibitors, olaparib, rucaparib, and niraparib. The interventions of interest and selected comparators are listed below.

Recurrent BRCA-mutated disease:

- Olaparib compared to pegylated liposomal doxorubicin + carboplatin (PLD + C)
- Rucaparib compared to pegylated liposomal doxorubicin + carboplatin (PLD + C)

Maintenance therapy for platinum-sensitive disease:

- Olaparib gBRCAm compared to placebo
- Niraparib gBRCAm compared to placebo
- Niraparib non-gBRCAm compared to placebo
- Rucaparib BRCAm (germline or somatic) compared to placebo

Niraparib was not included as an intervention for the recurrent BRCA-mutated population because detailed published or otherwise publicly-available data were not yet available from ongoing RCTs.

We also considered bevacizumab as a possible comparator for the maintenance population but could not identify any comparable data (i.e., treatment following at least two prior lines of platinum-based chemotherapy among women who were in response to their most recent regimen). We have nevertheless calculated bevacizumab treatment costs for the purposes of the budget impact analysis (see Section 6.4), as clinical expert input suggested that bevacizumab is a key alternative treatment for the maintenance population. Given the lack of comparable data, the non-intervention costs for bevacizumab in the maintenance population were assumed to be the same as for the PARP inhibitors, so that any budget impact differences were driven by differences in drug acquisition cost alone.

Model Inputs

Model inputs were retrieved from published literature and from data provided by manufacturers. The inputs that informed the model are described below, separated into cost and clinical inputs.

Clinical Inputs

Transition Probabilities

We fit parametric survival curves to progression-free survival (PFS) and overall survival (OS) Kaplan-Meier data for each treatment and comparator utilizing the approach described by Guyot and colleagues.[35] We tested a variety of distributions to estimate survival functions. The base-case function was selected based on best model fit using AIC values and visual comparison. Transition probabilities were derived monthly using the survival function with the best model fit. This allowed us to extrapolate survival beyond the observed trial evidence. See Appendix E for further details on transition probability derivation.

Given limitations in available clinical trial evidence such as immature survival data and surrogate endpoints, the evidence summarized in Appendix Table E4 represents the most recent and best-available evidence given each sub-population comparison's decision problem.

Adverse Events

The model included grade 3/4 adverse events derived from key clinical trials and/or the drug's prescribing information. The model included any grade 3/4 adverse event that occurred in ≥5% of patients in any of the treatments or comparators, as listed in Table 5.2.

Table 5.2. Grade 3/4 Adverse Events

	Olaparib (BRCA-mutated)[18]	Olaparib (Maintenance)[18]	Rucaparib (BRCA-mutated)[19]	Rucaparib (Maintenance)[2 9]	Niraparib (Maintenance)[20†]	PLD + C[97]
Abdominal Pain	8%	0%	3%	*	2%	*
Anemia	18%	4%	25%	19%	25%	7.9%
Fatigue	8%	6%	11%	7%	8%	7%
Hand-Foot Syndrome	*	*	*	*	*	24%
Hypertension	*	*	*	*	9%	*
Thrombocytopenia	3%	6%	5%	5%	35%	15.9%
Leukopenia	*	*	*	*	7%	*
Nausea	3%	2%	5%	4%	3%	5%
Neutropenia	7%	8%	5%	7%	21%	35.2%
Proteinuria	*	*	*	*	*	*
Rash	*	0%	0.3%	*	0.5%	4.2%
Stomatitis	*	*	*	*	0.5%	8%
Vomiting	4%	4%	4%	4%	2%	8%

*Not reported (assumed 0%); †Evidence for women with germline or somatic BRCA mutations only

Utilities

Health state utilities were derived from published literature that used validated patient-reported instruments mapped to generic health utility instruments from a healthy community of U.S. residents.[36] Specifically, data was collected from patients using the Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) instrument during Study 19 and then mapped to the EQ-5D.[103] Health state utilities were applied to the disease states of progression-free, progressed disease, and, if included, first and second subsequent therapies (Table 5.3). In the absence of comparable utility data, and due to a lack of conclusive evidence on utility differences for orally-administered versus infused products, on-treatment utility with PLD+C was assumed to be equivalent to that of the PARP inhibitors. We assumed that health state utility values did not vary across the treatments after patients had progressed in the model. In the maintenance population, patients treated with olaparib had different utility values in first and second subsequent states based on clinical trial evidence, whereas niraparib and rucaparib were assumed to have a single utility value upon progression due to a lack of evidence on therapy transitions post-progression. Further, we applied

a regimen-weighted disutility for experiencing any Grade 3/4 adverse event. The disutilities for each adverse event are detailed in Appendix E.

Table 5.3. Health State Utilities

Recurrent BRCA-Mutated Population	Base Case	Lower Range	Upper Range	Std. Error	Distribution	Source/Notes
Progression-Free Disease (on Treatment) [Olaparib]	0.77	0.72	0.82	0.024	Beta	Olaparib NICE HTA Submission[103]
Progression-Free Disease (on Treatment) [Rucaparib]	0.77	0.72	0.82	0.024	Beta	Olaparib NICE HTA Submission[103]
Progression-Free Disease (on Treatment) [PLD+C]	0.7977	0.7572	0.8382	0.024	Beta	Olaparib NICE HTA Submission[103]Havrilesky et al.[104]
Progressed Disease	0.50	0.37	0.63	0.065	Beta	Mehta et al.[105]
Maintenance Therapy for Platinum-Sensitive Disease	**Base Case**	**Lower Range**	**Upper Range**	**Std. Error**	**Distribution**	**Source/Notes**
Progression-Free Disease (on Treatment) [Olaparib]	0.77	0.73	0.808	0.024	Beta	Olaparib NICE HTA Submission[103]
Progression-Free Disease (on Treatment) [Niraparib]	0.77	0.73	0.808	0.024	Beta	Olaparib NICE HTA Submission[103]
Progression-Free Disease (on Treatment) [Rucaparib]	0.77	0.73	0.808	0.024	Beta	Olaparib NICE HTA Submission[103]
Progression-Free (off Treatment) [Olaparib]	0.71	0.66	0.76	0.024	Beta	Olaparib NICE HTA Submission[103]
Progression-Free (off Treatment) [Niraparib]	0.71	0.66	0.76	0.024	Beta	Olaparib NICE HTA Submission[103]
Progression-Free (off Treatment) [Rucaparib]	0.71	0.66	0.76	0.024	Beta	Olaparib NICE HTA Submission[103]
Progressed Disease [Niraparib]	0.68	0.55	0.80	0.065	Beta	Olaparib NICE HTA Submission,[103] assumed average of 1st & 2nd subsequent treatments
Progressed Disease [Rucaparib]	0.68	0.55	0.80	0.065	Beta	Olaparib NICE HTA Submission,[103] assumed average of 1st & 2nd subsequent treatments
First Subsequent Therapy [Olaparib]	0.72	0.58	0.84	0.065	Beta	Olaparib NICE HTA Submission[103]
Second Subsequent Therapy [Olaparib]	0.65	0.52	0.77	0.065	Beta	Olaparib NICE HTA Submission[103]

Cost Inputs

Drug Acquisition Costs

Where available, we obtained net pricing estimates from SSR Health, LLC, which combine data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs, to derive a net price. We estimated net prices by comparing the four-quarter rolling averages (i.e., second quarter of 2016 through first quarter of 2017) of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the most recent WAC (August 2017) to arrive at an estimated net price per unit.[34] For the PARP inhibitors, due to a lack of data in the SSR database, we calculated net price from the most recent WAC by assuming a 10% discount, based on manufacturer input. We also assumed a 10% discount from current pricing for PLD+C. For bevacizumab, the derived discount from the SSR database was 6%, which when applied to the WAC resulted in a net price of $7.13 per unit (Table 5.4).

Table 5.4. Drug Wholesale Acquisition Parameters

Drug Cost Parameters	WAC per Unit	WAC per Month	Net Price per Unit	Net Price per Month	Reference
Olaparib 100/150mg BID	$112.35	$13,679	$101.12	$12,311	Assumed 10% off WAC
Niraparib 100mg QD	$163.89	$14,965	$147.50	$13,469	Assumed 10% off WAC
Rucaparib 200/250/300mg BID	$114.50	$13,940	$103.05	$12,546	Assumed 10% off WAC
PLD + C per mg	$55.51	$3,610	$49.95	$3,249	Assumed 10% off WAC
Bevacizumab per mg (Budget Impact Only)	$7.59	$11,396	$7.13	$10,712	SSR Health[34]

* Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed August 23, 2017)

Drug Utilization

To model drug utilization and associated costs, information was needed on the number of treatment cycles for each regimen, number of doses per cycle for each drug in each regimen, dosage for each indication (fixed, by weight, or by body surface area), dose intensity, and dose adjustments over time. Dose intensity was based on a weighted average calculation using dose adjustment guidance from product labels or FDA clinical reviews[106-108] as well as rates of discontinuation from Study 19 of olaparib in the maintenance population;[103] the only study in our set that reported detailed discontinuation rates over the duration of the trial. For model comparisons in the maintenance population, those that discontinued and stayed in the progression

free state did not incur treatment costs from that point forward. See Appendix E for a more detailed discussion of dose adjustments.

For PLD+C we used prior evidence on average weight (69.1 kg) and serum creatinine levels (0.76 mg/dL) in a representative sample of ovarian cancer patients to calculate treatment dosing,[109,110] and used the same average weight to calculate treatment dosing for bevacizumab (used in budget impact only).

Administration and Monitoring Costs

There are no reported administration costs associated with PARP inhibitors. Supportive care costs include a monthly office visit and CT scans for all surviving patients on PARP inhibitors, and PLD+C. There was an additional cost for a monthly blood test for patients on PARP inhibitor treatment. For administration and monitoring cost inputs please see Appendix E.

Adverse Event Costs

Consistent with prior economic evaluation, grade 3 or 4 adverse events were assumed to require hospitalization, the costs of which were estimated based on data from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUPnet).[111,112] Adverse events reported from FDA labels and clinical trials from the interventions are listed in the Clinical Inputs section. Please see Appendix E for all adverse event cost inputs used in the model. These costs were varied in sensitivity analyses; the range employed for each event is also presented in Appendix E.

Threshold Analyses

A threshold analysis was conducted to estimate the maximum drug prices that would correspond to commonly cited willingness-to-pay thresholds. Specifically, we estimated the drug price (not including administration or monitoring costs) needed to achieve cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained.

Sensitivity Analyses

The model programming allowed for flexible and comprehensive sensitivity analyses. One-way sensitivity analyses used the low and high bounds from 95% confidence intervals for key model inputs where available. For inputs where 95% confidence intervals were not available, uncertainty estimates were based on plausible values from the published literature. Tornado diagrams were used to display the results of the one-way sensitivity analyses. Additionally, a probabilistic sensitivity analysis was conducted to vary parameter estimates across their plausible range simultaneously. Finally, we conducted a structural sensitivity analysis using a partitioned survival approach for olaparib in the recurrent BRCA-mutated population. Recent evidence has indicated little difference between survival probabilities between the semi-Markov approach and the

partitioned survival approach.[37] Given that previous cost-effectiveness analyses have used both approaches, a structural sensitivity analysis was relevant for comparisons to other analyses in ovarian cancer and for validation purposes.

Scenario Analyses

We conducted the scenario analyses using different assumptions on populations and health state utilities. Specifically, we used combined BRCA and non-BRCA data to generate cost-effectiveness estimates for olaparib, niraparib, and rucaparib in the maintenance therapy population. We also conducted a scenario analysis on BRCA investigator-assessed PFS (rather than the blinded central review estimates used in the base case) for olaparib in the maintenance therapy population. For a more detailed description of the curves used and distributional assumptions, please refer to Appendix Table E4. We also conducted a life-years gained analysis in which any survival gains were weighted at full health. Such an approach is considered important in evaluating life-extending treatments for severe diseases, and is now a consistent scenario in the revised ICER value framework.[43] Finally, given the typically advanced age and severity of disease in ovarian cancer patients, there was limited evidence on indirect costs, employment levels, and time missed at work. Therefore, we did not perform a societal analysis incorporating lost productivity. For a more detailed description of the types of impacts from a societal perspective that were not included in this analysis, refer to the impact inventory in Appendix Table E1.

Cost-Effectiveness Model: Results

Base-Case Results

Olaparib

In the recurrent BRCA-mutated population, olaparib had total discounted costs of approximately $158,000 with life-years gained and QALYs of 2.11 and 1.26, respectively (Table 5.5). At net prices, olaparib's estimated cost-effectiveness was approximately $80,500 per life-year gained and $146,000 per QALY gained compared to PLD+C in 4th line or later use. The base-case findings in the recurrent BRCA-mutated population should be interpreted with caution. There is no current evidence suggesting a relationship between progression-free and overall survival in the recurrent, BRCA-mutated population for olaparib versus PLD+C or placebo. Furthermore, overall survival evidence for PLD+C is derived from a source that combines BRCA-mutated and non-BRCA-mutated patients. Therefore, estimates in the BRCA-mutated population are preliminary and require further evidence. Please see section 6.4 for a detailed discussion of these limitations.

The use of olaparib for maintenance therapy resulted in total discounted costs of approximately $247,600 with 3.75 life years and 2.67 QALYs gained. The higher cost of olaparib in this population

is due to two specific reasons: (1) a longer progression-free interval than for treatment of recurrent, BRCA-mutated disease; and (2) the drug's price does not vary with initial dose reduction adjustments. At estimated net prices, the cost-effectiveness of olaparib versus placebo was estimated to be approximately $289,000 per life-year gained and $324,000 per QALY gained.

Table 5.5. Discounted Costs, Outcomes, and Incremental Results for Olaparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Recurrent BRCA-Mutated Population					
Olaparib	$115,100	$43,032	$158,133	2.11	1.26
PLD + C (4th line or later use)	$20,040	$41,229	$61,269	0.91	0.59
Incremental Cost per Outcome				$80,258/LYG	$146,210/QALY
Maintenance Therapy for Platinum-Sensitive Disease					
Olaparib – gBRCAm	$194,475	$53,158	$247,633	3.75	2.67
Placebo (Olaparib) – gBRCAm	$9,050	$46,474	$55,519	3.09	2.08
Incremental Cost per Outcome				$288,538/LYG	$324,116/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs

§Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs; QALY: Quality-Adjusted Life Year; LYG: Life-Year Gained

Threshold Analysis Results for Olaparib

Table 5.6 presents the results of the threshold analysis of the base-case using a 15-year time horizon and health care system perspective for olaparib in the recurrent BRCA-mutated population, and separately, the maintenance therapy population. The table presents the unit price and discount needed to obtain the commonly cited value thresholds of $50,000, $100,000, and $150,000 per QALY gained. For the recurrent BRCA-mutated population, discounts of 8% - 61% would be needed to meet thresholds of $50,000-$150,000 per QALY gained. Note that Olaparib's price could be slightly higher than the net price assumed in our base-case analysis (8% discount vs. assumed 10% discount off WAC in the base-case analysis) and still meet a threshold of $150,000 per QALY gained. Discounts of 59% to 87% would be required to achieve thresholds of $50,000-$150,000 per QALY in the maintenance therapy population.

Table 5.6. Threshold Analysis Results for Olaparib

	WAC per Unit	WAC per Month	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC to Reach Thresholds
Olaparib (Recurrent BRCA-mutated)	$112.35	$13,679	$43.31	$73.35	$103.39	8% - 61%
Olaparib (Maintenance for Platinum-Sensitive)	$112.35	$13,679	$14.44	$30.24	$46.06	59% - 87%

QALY: Quality-Adjusted Life Year

Niraparib

In the gBRCA-mutated maintenance population, niraparib had total discounted costs of approximately $243,500 with discounted life-years gained and QALYs of 3.86 and 2.77, respectively (Table 5.7). In the non-gBRCA-mutated maintenance population, niraparib had total discounted costs of approximately $175,300 with discounted life-years gained and QALYs of 2.59 and 1.84, respectively. The lower level of clinical benefit in the non-gBRCA-mutated population translates to shorter time spent in the progression-free state, and correspondingly lower costs in comparison to the gBRCA population.

The cost-effectiveness of niraparib for maintenance treatment differs markedly by the presence of a gBRCA mutation. In women with this mutation, the cost-effectiveness of niraparib versus placebo is estimated at approximately $245,000 and $292,000 per life-year gained and per QALY gained, respectively. In women without a gBRCA mutation, the estimated cost-effectiveness is $1.9 million per QALY gained (a cost per life-year gained could not be calculated due to the lack of a statistical survival benefit).

Table 5.7. Discounted Costs, Outcomes, and Incremental Results for Niraparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Maintenance Therapy for Platinum-Sensitive Disease					
Niraparib – gBRCAm	$181,077	$62,348	$243,461	3.86	2.77
Placebo (Niraparib) – gBRCAm	$5,027	$46,474	$51,502	3.09	2.12
Incremental Cost per Outcome				$245,092/LYG	$291,454/QALY
Niraparib – Non-gBRCAm	$122,106	$53,203	$175,310	2.59	1.84
Placebo (Niraparib) – Non-gBRCAm	$5,200	$43,144	$48,344	2.59	1.77
Incremental Cost per Outcome				Not estimable	$1,907,822/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs

§Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs; QALY: quality-adjusted life year; LYG: life-year gained

Threshold Analysis Results for Niraparib

Table 5.8 presents the results of the threshold analysis of the base-case using a 15-year time horizon and health care system perspective for the niraparib gBRCA maintenance population. The table presents the unit price and discount needed to obtain the commonly cited value thresholds of $50,000, $100,000, and $150,000 per QALY gained. Discounts of 57% - 90% would be needed to meet thresholds of $50,000-$150,000 per QALY gained. In the non-gBRCA population, there is no price at which niraparib would meet these common thresholds, due to the high incremental cost relative to the small clinical benefit observed.

Table 5.8. Threshold Analysis Results for Niraparib

	WAC per Unit	WAC per Month	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC Unit Price to Reach WTP Thresholds
Niraparib – gBRCA (Maintenance for Platinum-Sensitive)	$163.89	$14,965	$16.07	$43.28	$70.50	57% - 90%

QALY: quality-adjusted life year

Rucaparib

In the recurrent BRCA-mutated population, rucaparib (used as 3rd line or later treatment) had total discounted costs of approximately $247,000 with discounted life-years gained and QALYs of 2.11 and 1.41, respectively (Table 5.9). The treatment costs for rucaparib were high for two specific reasons: (1) rucaparib price does not vary with initial dose reduction adjustments; and (2) rucaparib is indicated for 3rd line or later use, lengthening the time in the progression-free state (and therefore the time on treatment). Rucaparib's cost-effectiveness versus PLD+C is estimated to be $218,000 per life-year gained and $295,000 per QALY gained. The base-case findings in the recurrent BRCA-mutated population should be interpreted with caution. There is no current evidence suggesting a relationship between progression-free and overall survival in the recurrent, BRCA-mutated population for rucaparib versus PLD+C or placebo. Furthermore, overall survival evidence for PLD+C is derived from a source that combines BRCA-mutated and non-BRCA-mutated patients. Given that the base-case finding was greater than $150,000/QALY, and the lack of overall survival data for rucaparib, we also provide survival benchmark values for rucaparib to meet the $150,000 per QALY threshold below. Additionally, please see section 6.4 for a detailed discussion of these limitations.

The use of rucaparib for maintenance therapy resulted in total discounted costs of approximately $229,500 with 3.64 life years and 2.60 QALYs gained. At estimated net prices, the cost-effectiveness of rucaparib versus placebo was estimated to be approximately $369,000 per QALY gained and $320,000 per life-year gained. Note that, while these results are similar in magnitude to those of olaparib and niraparib, the primary rucaparib maintenance population includes both germline and somatic BRCA mutations, while the relevant subgroup for the other PARP inhibitors is based on germline mutations only.

Table 5.9. Discounted Costs, Outcomes, and Incremental Results for Rucaparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Recurrent BRCA-Mutated Population					
Rucaparib (3rd Line or Later Use)	$202,103	$45,031	$247,135	2.11	1.41
PLD + C (3rd Line or Later Use)	$23,144	$43,868	$67,012	1.28	0.80
Incremental Cost per Outcome				$217,738/LYG	$294,593/QALY
Maintenance Therapy for Platinum-Sensitive Disease					
Rucaparib – BRCAm	$174,761	$54,784	$229,546	3.64	2.60
Placebo (Rucaparib) – BRCAm	$4,988	$46,474	$51,463	3.09	2.11
Incremental Cost per Outcome				$320,236/LYG	$369,175/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs §Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs; QALY: quality-adjusted life year; LYG: life-year gained. NOTE: Data for maintenance therapy reflect women with germline or somatic BRCA mutations receiving rucaparib or placebo

Threshold Analysis Results for Rucaparib

Table 5.10 presents the results of the threshold analysis of the base-case using a 15-year time horizon and health care system perspective for rucaparib in the recurrent BRCA-mutated population and, separately, the maintenance for platinum-sensitive disease population. Table 5.10 presents the unit price and discount needed to obtain the commonly cited cost-effectiveness value thresholds of $50,000, $100,000, and $150,000 per QALY gained. For the recurrent BRCA-mutated population, discounts of 50% - 77% would be needed to meet cost-effectiveness thresholds of $50,000-$150,000 per QALY gained. Discounts of 65% to 91% would be required to achieve thresholds of $50,000-$150,000 per QALY in the maintenance therapy population.

Table 5.10. Threshold Analysis Results for Rucaparib

	WAC per Unit	WAC per Month	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Discount from WAC Unit Price to Reach WTP Thresholds
Rucaparib (Recurrent BRCA-Mutated)	$114.50	$13,940	$26.09	$41.82	$57.55	50% - 77%
Rucaparib (Maintenance for Platinum-Sensitive)	$114.50	$13,940	$10.60	$25.08	$39.57	65% to 91%

QALY: quality-adjusted life year

Table 5.11. presents a separate survival benchmark scenario to address the limitations described in the base-case findings within the recurrent BRCA-mutated population only (Table 5.10 does not include the maintenance population). Specifically, we estimated life-years gained and QALYs gained for rucaparib that would achieve the $150,000 per QALY cost-effectiveness threshold, assuming the same net price for rucaparib and PLD+C efficacy as in the base-case analysis. Estimated life-years gained with rucaparib would need to reach 4.41 (vs. 2.11 in the base-case), and estimated QALYs 2.72 (vs. 1.41 in the base-case), to result in rucaparib reaching the $150,000 per QALY threshold.

Table 5.11. Benchmark Survival Analysis Results to Achieve $150,000 per QALY

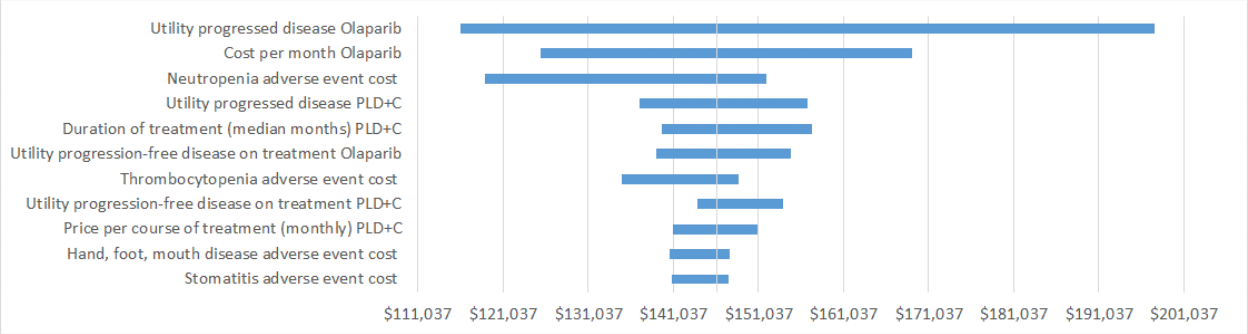
Intervention	LYG	QALYs
Recurrent BRCA-Mutated Population		
PLD + C (3rd Line or Later Use)	1.28	0.80
Rucaparib (Recurrent BRCA-Mutated)	4.41	2.72

QALY: quality-adjusted life year; LYG: life-year gained

One-Way Sensitivity Analysis Results

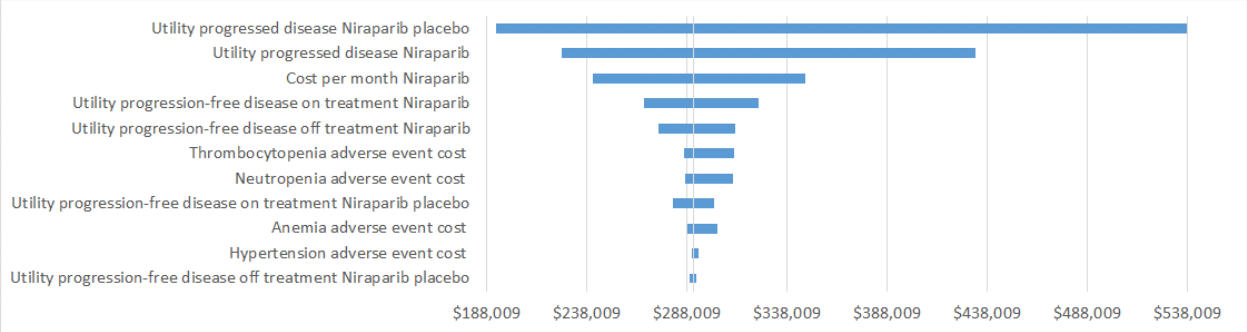
Illustrative one-way sensitivity analyses are presented in tornado diagrams (Figures 5.2-5.3) with tables to accompany the estimates. Major drivers of low and high incremental cost-effectiveness results for each comparison include utility values for progression and progression-free health states, cost per month of therapy, duration of treatment, and select adverse event costs. All other tornado diagrams are included in Appendix E.

Figure 5.2. Olaparib versus PLD+C (4th line or later use) in Recurrent BRCA-Mutated Population



Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility Progressed Disease Olaparib	$116,037	$197,590	0.37	0.63
Cost per Month Olaparib	$125,464	$169,064	$10,015	$14,837
Neutropenia Adverse Event Cost	$118,857	$152,013	$1.48	$77,892
Utility Progressed Disease PLD+C	$137,006	$156,741	0.37	0.63
Duration of Treatment (Median Months) PLD+C	$139,655	$157,358	2.10	10.76
Utility Progression-free Disease on Treatment Olaparib	$139,032	$154,791	0.72	0.82
Thrombocytopenia Adverse Event Cost	$135,032	$148,756	$3.39	$57,182
Utility Progression-Free Disease on Treatment PLD+C	$143,803	$153,942	0.75	0.83
Price per Course of Treatment (monthly) PLD+C	$140,985	$150,955	$2,643	$3,915
Hand, Foot, Mouth Disease Adverse Event Cost	$140,614	$147,669	$6.85	$19,482
Stomatitis Adverse Event Cost	$140,854	$147,513	$8.26	$55,153

Figure 5.3. Niraparib versus Placebo in Maintenance Therapy for Platinum-Sensitive Disease (gBRCAm)



Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility Progressed Disease Niraparib Placebo	$193,009	$538,196	0.55	0.80
Utility Progressed Disease Niraparib	$225,429	$432,333	0.55	0.80
Cost per Month Niraparib	$240,956	$347,083	$10,958	$16,232
Utility Progression-Free Disease on Treatment Niraparib	$266,565	$323,928	0.72	0.82
Utility Progression-Free Disease off Treatment Niraparib	$274,188	$312,063	0.66	0.76
Thrombocytopenia Adverse Event Cost	$286,786	$311,963	$3.39	$57,182
Neutropenia Adverse Event Cost	$287,316	$310,968	$1.48	$77,892
Utility Progression-Free Disease on Treatment Niraparib Placebo	$281,412	$301,723	0.66	0.76
Anemia Adverse Event Cost	$288,597	$303,335	$5.02	$38,830
Hypertension Adverse Event Cost	$290,529	$294,145	$125	$26,587
Utility Progression-Free Disease off Treatment Niraparib Placebo	$289,755	$293,095	0.66	0.76

Scenario and Sensitivity Analysis Results

Results of scenario and sensitivity analyses are presented in Appendix Tables E8-E9. Combining gBRCA and non-gBRCA data for olaparib, niraparib, and rucaparib in maintenance therapy resulted in higher cost-effectiveness estimates than in the base case (BRCA mutation only) populations for both PARP inhibitors. Conversely, cost-effectiveness estimates were lower when using BICR PFS curves for olaparib and placebo. Use of the semi-Markov or partitioned survival method produced similar results (within 10% of our base-case findings) and the same general conclusions that other modelers have found (see Appendix Table E8).[37]

The probabilistic sensitivity analysis results are described in Appendix Table E10. For the majority of treatment comparisons, there was less than a 1% chance that a PARP inhibitor was cost-effective at $150,000 per QALY. The exception was olaparib in the recurrent BRCA-mutated population, with a 52.5% chance of meeting a cost-effectiveness threshold of $150,000 per QALY. All scenario and sensitivity analysis results are available in Appendix Tables E8, E9, and E10.

Model Validation and Prior Published Evidence on Costs and Cost-Effectiveness

Model validation followed standard practices in the field. The modeling team undertook internal model validation to test the mathematical functions in the model and ensure that these were consistent with the report (and supplemental Appendix materials). The modeling team also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, two independent modelers tested the mathematical functions in the model, as well as the PARP inhibitor-specific inputs and corresponding outputs. Model validation procedures were conducted to ensure similar median PFS and OS estimates with observed clinical trial estimates. The comparison between model estimates and trial-based evidence is shown in Appendix Table E5. In all circumstances, model-generated medians were within one month of those presented in the trial publications or other documentation.

We also compared the ICER model to previously published models. We searched the literature to identify models that were similar to our own, with comparable populations, settings, perspective, and treatments.

Smith et al. (2015) conducted a US-based cost-effectiveness analysis of olaparib as maintenance therapy for patients with platinum-sensitive recurrent ovarian cancer in comparison to observation alone, using two models: one for patients with gBRCA mutation, and one for patients with wild-type BRCA.[113] They estimated ICERs of approximately $259,000 and $600,000 per progression-free life-year saved in gBRCA patients and wild-type BRCA patients, respectively. They reported that the cost of olaparib would need to be reduced to $2,500 or less per month to achieve ICERs less than $50,000 per progression-free life-year saved. Their analysis used a cost per month for olaparib of $13,440 (based on the 2014-2015 WAC) which was similar to our WAC estimate of $13,679 per month, and slightly higher than our net price of $12,311 per month. One major difference from our analysis was the use of progression-free life-years saved rather than QALYs or life-years gained as the outcome measure. However, as all three measures produced similar incremental gains (of just over 6 months), our results in the gBRCA population (in the range of $260,000-$270,000) were very similar to the relevant findings from this study.

Tappenden and colleagues (2015) performed a technology appraisal of olaparib maintenance treatment of BRCA-mutated platinum-sensitive recurrent ovarian cancer in the UK, reviewing a manufacturer-developed cost-effectiveness analysis of olaparib compared to routine surveillance.[114] The base case analysis reported an estimated cost-effectiveness ratio of £79,953 (approximately $117,400) per QALY. One major difference from our analysis was the assumption of a much lower drug price, with a cost per month of £3,628 (approximately $5,300). In addition, the review group had concerns that the assumptions used in the company's model (including the exclusion of outcomes relating to time from randomization to death and PFS, and methods for modelling time-to-event outcomes that led to discordance between model predictions and

observed study data) may have overestimated the incremental health gains for olaparib versus routine surveillance.

The cost-effectiveness of different treatment strategies for patients with platinum-sensitive recurrent ovarian cancer was examined by Secord and colleagues (2013), including: surveillance, general treatment with olaparib, and BRCA mutation testing followed by olaparib treatment if positive.[115] They estimated that BRCA testing followed by treatment would cost approximately $193,000 per progression-free life-year saved compared to observation. The incremental cost-effectiveness of olaparib treatment for all patients compared to BRCA testing and treatment was estimated to be approximately $234,000 per progression-free life-year saved. In addition to using a different outcome measure (progression-free life-years saved) than our analysis, this study also used a lower estimated cost for olaparib ($6,356 per month), as the drug was not yet FDA-approved.

Finally, Hettle, Posnett, and Borrill (2015) explored the feasibility of developing a semi-Markov model using times to first and second subsequent treatments from a Phase II clinical trial[24,27] of olaparib maintenance therapy in patients with BRCA-mutated platinum-sensitive recurrent ovarian cancer.[36] They reported that survival estimates projected by their model were generally similar to the clinical trial outcomes, but did not include costs or calculate measures of cost-effectiveness as this was not an objective of this study. Based in part on this study, our modeling approach took a similar form.

5.2 Value-Based Benchmark Prices

Our value-based benchmark prices for olaparib, rucaparib, and niraparib are presented in Table 5.12. As noted in the initial ICER methods document (http://icer-review.org/wpcontent/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINALcorrected-8-22-1.pdf), the value-based benchmark prices for a drug are defined as the prices that would achieve incremental cost-effectiveness ratios of $100,000 and $150,000 per QALY gained.

For the recurrent BRCA-mutated population, the assumed net price of olaparib (a 10% discount from WAC) would fall below the price required to achieve $150,000 per QALY gained (8% discount) but above the price required to achieve $100,000 per QALY (35% discount). The discounts required for rucaparib to meet the threshold prices are greater than the current assumed 10% discount from WAC. For the population with maintenance therapy for platinum-sensitive disease, the discounts required to meet the threshold prices for olaparib, niraparib, and rucaparib (in the subgroups with BRCA mutations) are also greater than the current assumed 10% discount from WAC. In the non-

gBRCA population, there was no price at which niraparib would meet these common thresholds, due to the high incremental cost relative to the small clinical benefit observed.

Table 5.12. Value-Based Benchmark Prices per Month of Ovarian Cancer Treatment, by Population

Drug Name	WAC per Month*	Net Price per Month†	Price to Achieve $100,000/QALY	Price to Achieve $150,000/QALY	Discount from WAC to Reach Thresholds
Recurrent BRCA-Mutated Population					
Olaparib	$13,679	$12,310	$8,930	$12,587	8% to 35%
Rucaparib	$13,940	$12,546	$5,091	$7,007	50% to 63%
Maintenance Therapy for Platinum-Sensitive Disease‡					
Olaparib	$13,679	$12,310	$3,682	$5,607	59% to 73%
Niraparib	$14,965	$13,468	$3,952	$6,437	57% to 74%
Rucaparib	$13,940	$12,546	$3,053	$4,817	65% to 78%

N/A: Not available; QALY: quality-adjusted life year, WAC: wholesale acquisition cost; *WAC as of August 23, 2017 † Assumed 10% discount from current WAC. ‡Based on findings for gBRCA subgroup for olaparib and niraparib, and both gBRCA and somatic BRCA subgroup for rucaparib

5.3 Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of each drug for women with ovarian cancer in the recurrent BRCA-mutated population and the population receiving maintenance therapy for platinum-sensitive disease. We used the WAC, an estimate of discounted WAC, and the three threshold prices for each drug in our estimates of budget impact. Olaparib was included in this analysis despite its presence in the market since 2014 due to its recent expansion to maintenance therapy.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the two candidate populations eligible for treatment: the recurrent BRCA-mutated population, and the population receiving maintenance therapy for platinum-sensitive disease. To estimate the size of the potential candidate populations for

treatment, we used inputs for the US population size, ovarian cancer incidence, prevalence and treatment, and BRCA testing results.

Ovarian cancer prevalence was estimated to be 222,060 cases in 2014, based on the most recent SEER data.[8] SEER reports that approximately 60% of patients are diagnosed at advanced stages, which would correspond to 133,200 cases. Inputs for treatment initiation and progression were based on Clovis Oncology data on file. We assumed that approximately 54% of these patients would be treated with at least two prior lines of chemotherapy and would go on to receive third-line treatment, [38] and further assumed that 65% of those receiving third-line treatment would go on to receive fourth-line treatment. Finally, the estimated prevalence of gBRCA mutations (18%)[39] was used to calculate the estimated proportion of those patients who would be eligible for treatment with olaparib (8,423) or rucaparib (12,959). Assuming equal distribution over five years, this resulted in an estimate of 1,685 patients eligible for olaparib and 2,592 patients eligible for rucaparib in the recurrent BRCA-mutated population in the US per year.

To be potentially eligible for maintenance treatment, patients had to have had recurrent ovarian cancer and response to their most recent platinum-containing regimen. This population is estimated to represent approximately 4% of prevalent ovarian cancer patients, or approximately 9,000 patients in the US.[40] Assuming that 18% of these patients would have BRCA mutations,[39] we estimated that there would be approximately 1,630 BRCA mutation and 7,440 non-BRCA mutation patients in this population, or 327 and 1,488 per year, respectively.

ICER's methods for estimating potential budget impact are described in detail and have recently been updated (http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf). The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we calculate the potential budget impact associated with completely displacing use of existing therapies with the new intervention. In this case, we assumed that olaparib and rucaparib would displace PLD+C as a treatment in the eligible recurrent BRCA-mutated population. In the population eligible to receive maintenance therapy for platinum-sensitive disease, we assumed that olaparib, niraparib, and rucaparib would replace observation (i.e. placebo in the relevant trials) and bevacizumab. In the absence of data, we assumed this replacement would occur in the ratio of 75% for observation and 25% for bevacizumab in patients with BRCA mutation; for the non-BRCA mutation patients, these proportions were assumed to be 67% for observation and 33% for bevacizumab. While bevacizumab was not included in the cost-effectiveness analysis because of a lack of efficacy data in a comparable population, we did include it in the budget impact analysis because of input from clinical experts that bevacizumab is used in comparable populations. To include bevacizumab in the budget impact analysis, we applied costs for bevacizumab treatment while assuming the same efficacy, safety, and discontinuation as for olaparib.

We tested the potential budget impact of each drug by assuming different unit price points (WAC, discounted WAC, and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY) and comparing costs against the base case costs for the comparator in each population. Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 5.13

For 2017-19, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 5.13. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	33.5	FDA, 2016
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

Potential Budget Impact Model: Results

Tables 5.13 and 5.14 illustrate details of the per-patient budget impact results for each drug. Costs for each drug were calculated using that drug's WAC, discounted WAC, and threshold prices. The base case net costs of PLD+C, bevacizumab, and usual care were used to calculate costs for those treatments in the relevant populations. Note that in all cases, the average annual budget impact of treatment over five years is well below the cost of drug treatment for one year, due to patients discontinuing treatment over time. Also note that the model was run separately for each drug and population being modeled, so that costs for comparator regimens will differ slightly across tables.

Olaparib

The estimated results for olaparib in the recurrent BRCA-mutated population and the population receiving maintenance therapy for platinum-sensitive disease are shown in Table 5.14. For the recurrent BRCA-mutated population, the average potential budgetary impact when using the WAC for olaparib was an additional per-patient cost of approximately $39,900, and approximately $34,700 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $35,800 per patient using the unit price ($103.39) to achieve $150,000 per QALY to approximately $8,100 using the unit price ($43.31) to achieve a $50,000 per QALY cost-effectiveness threshold.

For maintenance therapy population (gBRCA-mutated only for olaparib), the average annual potential budgetary impact when using the WAC for olaparib was approximately $56,900, and approximately $49,600 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $14,100 per patient using the unit price ($46.06) to achieve $150,000 per QALY to a cost savings of approximately $6,300 per patient using the unit price ($14.44) to achieve a $50,000 per QALY cost-effectiveness threshold.

Table 5.14. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Olaparib

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Recurrent BRCA-Mutated Population					
Olaparib (4th Line or Later Use)	$65,845	$60,664	$61,714	$47,863	$34,012
PLD+C (Discounted WAC Only)			$25,941		
Difference	$39,904	$34,723	$35,773	$21,922	$8,071
Maintenance Therapy for Platinum-Sensitive Disease (gBRCA)					
Olaparib	$84,182	$76,924	$41,358	$31,145	$20,932
Usual Care (75%)/ Bevacizumab (25%, Discounted WAC Only)			$27,281		
Difference	$56,901	$49,643	$14,077	$3,864	-$6,349*

*Indicates cost-saving; QALY=quality-adjusted life year, WAC=wholesale acquisition cost

Niraparib

The estimated results for niraparib in the population receiving maintenance therapy for platinum-sensitive disease are shown in Table 5.15. Data are available for populations with and without gBRCA mutations. Note that comparator costs differ between the two populations, due to different assumptions about the relative mix of usual care and bevacizumab treatments.

For the population with gBRCA mutations, the average annual potential budgetary impact when using the WAC for niraparib was approximately $55,500 per patient, decreasing to approximately $48,800 when using the discounted WAC. Average potential budgetary impact at the cost-effectiveness threshold prices for the drug ranged from approximately $17,400 per patient using the unit price ($70.50) to achieve $150,000 per QALY to approximately $6,300 per patient using the unit price ($43.28) to achieve $100,000 per QALY. The unit price ($16.07) to achieve a $50,000 per QALY cost-effectiveness threshold was low enough that we estimated a cost savings of approximately $4,800 per patient compared to the mix of usual care/bevacizumab.

For the non-gBRCA population, the average annual per-patient potential budgetary impact when using the WAC for niraparib was approximately $37,900, and approximately $32,600 using the discounted WAC. The unit price ($1.39) required to achieve a $150,000 per QALY cost-effectiveness threshold is so low that it would decrease treatment costs to the point that niraparib was estimated to save approximately $14,500 per patient. Budget impact was not calculated for the other two thresholds, because there was no positive drug price for niraparib in the non-gBRCA group that would achieve ICERs of $100,000 or $50,000 per QALY gained.

As noted in the evidence review, published or otherwise publicly-available data on niraparib for treatment of recurrent, BRCA-mutated disease are not yet available.

Table 5.15. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Niraparib

Average Annual Per Patient Budget Impact					
	WAC	Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Maintenance Therapy for Platinum-Sensitive Disease (gBRCA)					
Niraparib	$81.726	$75,046	$43,664	$32,572	$21,480
Usual Care (75%)/ Bevacizumab (25%, Discounted WAC Only)			$26,242		
Difference	$55,483	$48,804	$17,422	$6,330	-$4.763†
Maintenance Therapy for Platinum-Sensitive Disease (non-gBRCA)					
Niraparib	$69,081	$63,796	$16,685	N/A	N/A
Usual Care (67%)/ Bevacizumab (33%, Discounted WAC Only)			$31,162		
Difference	$37,918	$32,634	-$14,477*	N/A	N/A

*Indicates cost-saving; N/A=not available, QALY=quality-adjusted life year, WAC= wholesale acquisition cost

Rucaparib

The estimated results for rucaparib (3rd line or later) in the population with recurrent BRCA-mutated disease and the population receiving maintenance therapy for platinum-sensitive disease are shown in Table 5.16. For rucaparib in the recurrent BRCA-mutated population, the average potential budgetary impact when using the WAC for rucaparib was an additional per-patient cost of approximately $67,000, and approximately $59,000 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $27,300 per patient using the unit price ($57.55) to achieve $150,000 per QALY to approximately $5,300 using the unit price ($26.09) to achieve a $50,000 per QALY cost-effectiveness threshold.

For maintenance therapy population (in women with germline or somatic BRCA mutations), the average annual potential budgetary impact when using the WAC for rucaparib was approximately

$54,800, and approximately $46,700 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $9,500 per patient using the unit price ($39.57) to achieve $150,000 per QALY to a cost savings of approximately $7,400 per patient using the unit price ($10.60) to achieve a $50,000 per QALY cost-effectiveness threshold.

Table 5.16. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Rucaparib

Average Annual Per Patient Budget Impact					
	WAC	Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Recurrent BRCA-Mutated Population					
Rucaparib (3rd Line or Later Use)	$93,841	$85,847	$54,084	$43,101	$32,117
PLD+C (Discounted WAC Only)	$26,827				
Difference	$67,013	$59,020	$27,257	$16,274	$5,290
Maintenance Therapy for Platinum-Sensitive Disease (gBRCA)					
Rucaparib	$81,045	$72,918	$35,738	$27,256	$18,774
Usual Care (75%)/ Bevacizumab (25%, Discounted WAC Only)	$26,215				
Difference	$54,830	$46,703	$9,523	$1,041	-$7,441*

*Indicates cost-saving, QALY=quality-adjusted life year, WAC=wholesale acquisition cost

For each of the drugs and populations of interest, the annual potential budgetary impact of treating the entire eligible populations across all prices (WAC, discounted WAC, and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY) did not exceed the $915 million threshold. The annual potential budgetary impacts of treating the entire eligible populations using net prices (discounted WAC) are compared to the $915 million threshold in Table 5.17. Overall, the greatest potential annual budget impact we estimated was for rucaparib (3rd line or later) in the recurrent BRCA-mutated population, reaching 42% of the $915 million threshold at the net price. This was largely due to the relatively small sizes of the specific ovarian cancer populations eligible for treatment in any given year.

Table 5.17. Estimated Total Potential Budget Impact (BI) of Ovarian Cancer Treatment Using Net Prices Over a Five-year Time Horizon

	Eligible Population	N Treated per Year	Annual BI per Patient	Total BI (Millions)	Percent of Threshold
Recurrent BRCA-Mutated Population					
Olaparib	8,423	1,685	$34,723	$141.6	15%
Rucaparib	12,959	2,592	$59,020	$387.1	42%
Maintenance Therapy for Platinum-Sensitive Disease (BRCA mutations)					
Olaparib	1,633	327	$49,643	$40.4	4%
Niraparib	1,633	327	$48,804	$39.1	4%
Rucaparib	1,633	327	$46,702	$37.3	4%
Maintenance Therapy for Platinum-Sensitive Disease (non-gBRCA)					
Niraparib	7,441	1,488	$32,634	$109.4	12%

5.4 Summary and Comment: Long-Term Cost Effectiveness and Potential Budget Impact

The base-case findings from our analysis suggest that use of olaparib in recurrent, BRCA-mutated ovarian cancer provides clinical benefit in terms of longer time spent in PFS versus standard chemotherapy; this translates into cost-effectiveness estimates that meet commonly cited cost-effectiveness thresholds. However, the cost-effectiveness findings for BRCA-mutated disease are more uncertain due to a lack of direct comparative evidence. For maintenance therapy with olaparib, however, discounts from the current list price of approximately 60-90% would be required to meet thresholds of $50,000-$150,000 per QALY gained.

While niraparib's clinical benefits in maintenance therapy are greater in women with gBRCA-mutated disease than without, cost-effectiveness estimates exceeded commonly-cited thresholds. Discounts of 57%-90% would be required to achieve these thresholds in the gBRCA population, while there is no price that would achieve these thresholds in women without the mutation. Finally, use of rucaparib for BRCA-mutated disease may also provide clinical benefit; however, a lack of direct comparative evidence generated cost-effectiveness findings that were uncertain and above commonly cited cost-effectiveness thresholds. Discounts of 50%-77% for rucaparib would be required to achieve common cost-effectiveness thresholds in the BRCA-mutated (3rd line or later) disease population. Discounts of 65%-91% for rucaparib would be required to achieve common cost-effectiveness thresholds when used as maintenance therapy for platinum-sensitive disease.

Multiple sensitivity analyses, scenario analyses, and structural sensitivity analyses were conducted to assess the impact of certain model assumptions and parameters on the results and conclusions.

Base-case findings were sensitive to assumed net drug prices, treatment duration, assumptions regarding time spent on and off treatment, and utility values for progressive and progression-free health states. The impact of these variables was assessed in one-way sensitivity analyses and the probabilistic sensitivity analysis. However, cost-effectiveness estimates did not approach $150,000 per QALY gained even when varying these parameters over wide ranges, except for olaparib in recurrent, BRCA-mutated ovarian cancer. Scenario and structural sensitivity analyses using different sources of survival evidence and different modeling methods found similar, if not higher, cost-effectiveness estimates.

Using the discounted WAC for each of the drugs in the populations of interest, annual budget impact was estimated to range from approximately $32,600 per patient for niraparib in the non-gBRCA-mutated population receiving maintenance therapy for platinum-sensitive disease to approximately $59,000 per patient for rucaparib in the recurrent BRCA-mutated population. For each of the drugs and populations of interest, the annual potential budgetary impact of treating the entire eligible populations was not projected to exceed the $915 million threshold. Overall, the greatest potential annual budget impact we estimated was for rucaparib (as 3rd line or later treatment) in the recurrent BRCA-mutated population, reaching 42% of the $915 million threshold at the net price.

Limitations

Our analysis has important assumptions and limitations. Major limitations result from the limited evidence on overall survival. In some cases, such as for niraparib in the maintenance population and rucaparib in the recurrent BRCA-mutated and maintenance populations, overall survival from olaparib was applied in order to estimate life-year and QALY outcomes. Further, there was limited comparative evidence on the relationship between progression-free survival and overall survival for niraparib versus placebo in the maintenance population.

The best available comparative evidence on the relationship between progression-free survival and overall survival for PARP inhibitors was reported in Study 19.[26] In the BRCA-mutated maintenance sub-population, the gain in median time to first subsequent treatment (i.e., proxy for symptomatic disease progression[116]) was 9.4 months versus placebo, which translated into a gain in median overall survival of 4.7 months versus placebo. Therefore, for every one-month gain in progression-free survival, a 0.5-month gain in overall survival was observed within this sub-population. To address this limitation, we calibrated the model in certain scenarios to reflect this proportionate gain in overall survival from progression-free survival reported in Study 19. For example, the gain in investigator-assessed progression-free survival from SOLO-2 was approximately 19.1 months versus placebo of 5.5 months, for a difference of 13.6 months of progression-free survival time. Using the proportionate gain in overall survival to progression-free survival from Study 19, we calibrated the

model to report a gain in overall survival of 13.6*0.5 = 6.8 months of overall survival. This calibration procedure mainly impacted estimates within the maintenance therapy BRCA-mutated sub-population.

We were not able to conduct similar calibrations in the recurrent, BRCA-mutated population because comparative progression-free and overall survival estimates versus placebo were not estimated in clinical trials. Additionally, evidence used to generate life-year and QALY estimates for PLD+C are derived from a source with mixed BRCA- and non-BRCA-mutated patients. Previous studies have shown extended survival in patients with BRCA-mutation versus patients without BRCA-mutation.[117] To our knowledge, however, there is no published evidence in BRCA-mutated populations that separates survival by line of therapy (which is a significant predictor as well as necessary factor in approximating the FDA indications for olaparib and rucaparib). To address these limitations in the recurrent, BRCA-mutated population, we conducted a scenario analysis for rucaparib to identify the absolute overall survival gains needed to achieve a cost-effectiveness threshold of $150,000 per QALY when compared to PLD+C for third-line or later use.
Due to differences in trial design and population, comparable clinical data were not available for bevacizumab in the populations of interest. We therefore included bevacizumab (in the budget impact analysis only) by assuming the same efficacy, safety, and discontinuation inputs as that for olaparib.

We also note that comparator agents such as PLD+C or bevacizumab (for budget impact modeling only) require physician administration, and additional costs from significant provider mark-ups or infusion fees may be associated with these physician-administered drugs. This information is frequently proprietary and varies substantially by payer-provider contract, making a generalizable estimate problematic. However, we varied the cost of PLD+C from 81% to 120% of the base-case estimates, and our conclusions regarding cost-effectiveness remained the same in all circumstances.

Further, survival curve fitting relies on assumptions that may differ substantially between different parametric models. We ensured our assumptions did not lead to invalid models and unrealistic PFS or survival rates, such as the tail of the extrapolated progression-free survival curve crossing the tail of the overall survival curve. Our model structure limited our ability to generate uncertainty estimates around transition probabilities. This was in part addressed through the partitioned survival structural sensitivity analysis.

Conclusion

In conclusion, the findings of our analysis suggest that the PARP inhibitors of focus for this review would provide gains in quality-adjusted and overall survival over alternative therapies, but are not

currently priced in alignment with these benefits, with the possible exception of olaparib in recurrent, BRCA-mutated ovarian cancer.

6. Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits or contextual considerations offered by an intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the scientific evidence on comparative clinical effectiveness. These elements are listed in the table below.

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to surveillance with no maintenance chemotherapy, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to surveillance with no maintenance chemotherapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

Although substantial uncertainty remains about the impact of PARP inhibitors on overall survival and quality of life, these agents appear to provide additional benefit over existing ovarian cancer therapies that may not be adequately captured in the clinical literature. For example, patients report low-grade adverse effects, such as fatigue, loss of appetite, and mouth sores, but state that these effects are minor relative to what they experience with cytotoxic chemotherapy regimens and the long-term sequelae of invasive surgeries. Moreover, dosing flexibility allows patients and their providers to manage such symptoms. One patient appreciated that niraparib is taken once daily,

which allows her to take the drug before bed to reduce any adverse effects she feels from the medication. Though data are lacking on the effect of PARP inhibitors on overall productivity, a better side effect profile may prevent medical leaves of absence (and/or facilitate a faster return to work) for those women who participate in the labor force.

Because the PARP inhibitors are taken orally, they may provide a benefit to individuals without convenient access to infusion centers. We heard from several patients that they had to travel long distances to major cancer centers to receive their chemotherapy treatments, many of whom acknowledged would not have been feasible without the financial means to afford regular overnight stays in a city, caregiver support to accompany them on such trips or look after their affairs while they recovered, and pricier insurance policies that allowed them to access specialist care. The relative simplicity of an oral regimen may therefore reduce caregiver burden as well as disparities in access to care for those who are unable to seek treatment at major cancer centers.

Conversely, these agents are much more expensive than existing therapies. Unlike standard chemotherapy, which is typically given for a fixed number of cycles, PARP inhibitors are taken until disease progression or unacceptable toxicity, allowing for the possibility of a long duration of time on a very costly medication. Treatment with PARP inhibitors requires regular monitoring for hematologic toxicity, which adds to their cost and diminishes some of the convenience of an oral therapy.

It is expected that PARP inhibitors will be covered by most insurance companies when prescribed based on medical necessity and in accordance with FDA labeling; however, for patients who do not qualify for clinical trials or payment assistance programs, these regimens may be out of reach financially. A recent review of individual expenses for Medicare Part D enrollees reported that for on-formulary, specialty cancer drugs, the median annual out-of-pocket costs range from $7,227 (Zytiga) to $11,538 (Revlimid) in 2016.[118] PARP inhibitors were not included in the report. Using Medicare's Plan Finder tool, the estimated annual range for beneficiary Part D out of pocket cost for Lynparza® ranged from $6,265 to $7,114.[119b]

Research has shown that only 37% of patients receive the standard of care (i.e., care that adheres to NCCN guidelines); women who are treated in low-volume hospitals by a low-volume physician tend to receive non-guideline-adherent care and survive a shorter duration of time.[48] Patients may not have access to initial optimal surgery because there is a severe shortage of gynecologic oncologists in the United States, particularly in areas where there is no major cancer center. In addition, an analysis from Herzog and colleagues indicates that only about a third of newly diagnosed patients who are eligible for *BRCA1/BRCA2* testing according to NCCN guidelines actually receive such testing, with large disparities observed across states (rates range from 9% in

[b] Estimates assume original Medicare, zip code=02115, and no financial assistance; costs do not account for other medications consumed by subscriber

Mississippi to 44% in Rhode Island).[41] Testing rates are positively correlated with higher incomes, advanced education, and the number of physicians per 100,000 in the population.[41] In addition, there is a shortage of genetic counselors given the increased frequency of testing. Thus, requisite BRCA testing for receipt of rucaparib and olaparib may exacerbate gaps in treatment, and the convenience offered by an oral therapy may be irrelevant for those without access to high-quality specialist care.

Finally, the need for better, more effective therapies for individuals with ovarian cancer must not be underestimated. Mortality from ovarian cancer is high, with less than half of patients surviving five years from diagnosis.[8] Few effective treatment options exist in this space and treatment paradigms have not changed materially in the last 20 years.[42] Although there is uncertainty around the long-term benefit and safety of PARP inhibition, these agents offer a novel mechanism of action and add an additional tool for the treatment armamentarium. The potential of PARP inhibitors to improve upon existing therapeutic paradigms, and the fact that they provide additional options to patients and their providers cannot be overlooked.

Potential Cost-Saving Measures in Ovarian Cancer

This report marks the debut of a new section devoted to identification of areas of waste and low-value care in ovarian cancer that could be reduced to make headroom in health care budgets for new innovations. We reached out to clinicians, patients and patient groups, manufacturers, and other payers for input on potential targets for waste reduction. The following areas were highlighted by stakeholders:

- Eliminate cancer antigen (CA)-125 test as a routine screen for ovarian cancer diagnosis in average-risk women and as a marker for disease progression in women with the disease—no evidence-based recommendations for these uses

- Routine use of CT scans for follow-up during periods of remission—no published data suggesting routine follow-up imaging provides benefit

Several of these recommendations have been echoed by clinical societies. The American Board of Internal Medicine's Choosing Wisely® campaign, which encourages specialty societies to identify areas of low-value care that could be reduced or eliminated, [120] lists recommendations from both SGO and ACOG not to screen asymptomatic and/or low to average risk women for ovarian cancer using the CA-125 biomarker or ultrasound given the disease's relative rarity and the possibility of false positives requiring invasive testing.[121,122] SGO also recommends not delaying palliative care for women with advanced or relapsed cancer due to its potential for reductions in unnecessary treatment and associated cost savings.[121]

The United States Preventative Services Task Force (USPSTF) also reviewed the evidence for screening asymptomatic women without specific risk factors for ovarian cancer (such as BRCA mutations) in 2012. They gave the evidence a "D" rating, citing "moderate certainty that the harms of screening for ovarian cancer outweigh the benefits".[123] An update to this recommendation is currently underway.

7. Summary of the Votes and Considerations for Policy

7.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the September 14, 2017 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of PARP inhibitors for recurrent ovarian cancer. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at 1:38:40), the Midwest CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and other benefits and contextual considerations related to olaparib, niraparib, and rucaparib. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure X below):

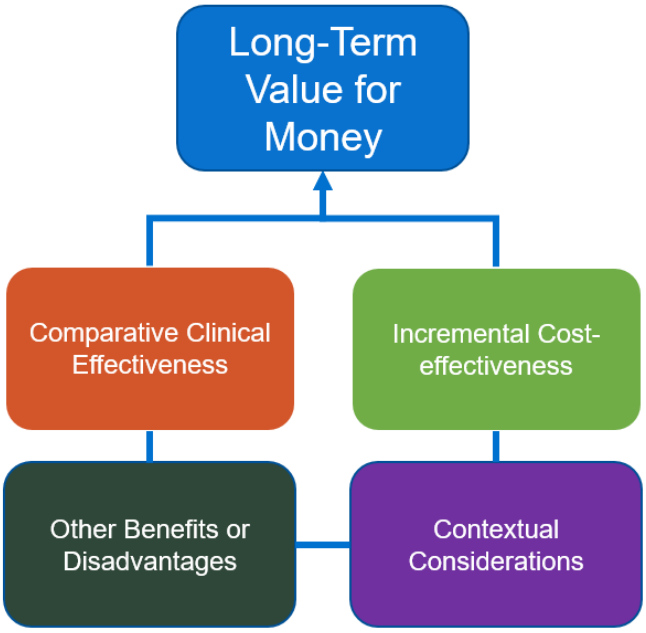
1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 7.1. Conceptual Structure of Long-Term Value for Money



7.2 Voting Results

1) **In patients with recurrent BRCA-mutated disease, is the evidence adequate to demonstrate that the net health benefit of treatment with olaparib is greater than that of treatment with standard chemotherapy?**

Yes: 4 votes	**No: 5 votes**

Comment: One panel member mentioned that the nature of available data (i.e., single-arm studies only) made it difficult to vote yes on a comparative question.

2) **In patients with platinum-sensitive disease who are eligible for maintenance therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with olaparib is greater than that of surveillance alone?**

Yes: 7 votes	No: 2 votes

Comment: For this question, members of the panel noted the clear distinction between the strength of evidence available for each subpopulation, given the differing performance of the drug in gBRCA and non-gBRCA populations. Several panel members also indicated that the presence of randomized controlled trials in the body of evidence impacted their vote in this case.

3) **In patients with recurrent platinum-sensitive, germline BRCA-mutated disease who are eligible for maintenance therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with niraparib is greater than that of surveillance alone?**

Yes: 8 votes	No: 1 votes

Comment: One panel member noted that while the available evidence did not demonstrate a quality of life benefit, it also did not show a decline as compared to placebo in the maintenance population, an important consideration. One panel member noted the large progression-free survival benefit as a justification for their yes vote.

4) **In patients with recurrent platinum-sensitive disease who are eligible for maintenance therapy and do not have germline BRCA mutations, is the evidence adequate to demonstrate that the net health benefit of treatment with niraparib is greater than that of surveillance alone?**

Yes: 6 votes	No: 3 votes

Comment: The panel discussed the risks of some of the adverse events, particularly acute myeloid leukemia and myelodysplastic syndrome, as they considered this vote. Panel members identified that the reduced benefit in progression-free survival seen in this subgroup as the reason for changing their vote from previous questions.

5) **In patients with recurrent BRCA-mutated disease, is the evidence adequate to demonstrate that the net health benefit of treatment with rucaparib is greater than that of treatment with standard chemotherapy?**

Yes: 5 votes	No: 4 votes

Comment: As with olaparib in this population, panel members noted that they found the evidence difficult to evaluate due to the single arm design of the studies. Without a comparator, it was difficult to ascertain the true impact of the therapy.

Note for voting questions 6 through 8*: According to ICER's updated Value Assessment Framework, ICER will have the independent CEPAC voting panels vote on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.[43] At incremental cost-effectiveness ratios below $50,000 per QALY there will be a presumption of "high value"; at ratios above $175,000 the intervention will be deemed "low value" without formal voting by the committee. This included the other benefits and contextual consideration votes as well. As such, the only therapy and indication that fell within this range was olaparib for recurrent BRCA-mutated disease.*

6) When compared to pegylated liposomal doxorubicin and carboplatin (PLD+C), does olaparib, for recurrent BRCA-mutated disease, offer one or more of the following "other benefits"? (select all that apply)

This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	5/9
This intervention offers reduced complexity that will significantly improve patient outcomes.	7/9
This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.	3/9
This intervention will significantly reduce caregiver or broader family burden.	8/9
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	7/9
This intervention will have a significant impact on improving return to work and/or overall productivity.	5/9

Comment: One of the clinical experts noted that discussing other benefits compared to another treatment strategy was not quite the correct framing. Instead, the panel should consider that patients will most likely use both a PARP inhibitor as well as any major alternative treatments during the course of their diseases, and instead consider the other benefits of a treatment paradigm that includes PARP inhibitors versus one without.

Discussion touched on the issue of disparities, both racial disparities and geographic disparities. One of the patient representatives stated that she was from a rural area, making it particularly challenging to access high quality specialized care.

One panel member noted that the oral administration of PARP inhibitors represented a potential benefit, simplifying administration of the therapy over infused chemotherapy. The

panel also discussed that this benefit similarly impacted caregiver burden; patients needing chemotherapy infusions would usually rely on family or caregivers to drive them to and from their appointments; whereas, they were far more independent on PARPs, able to drive themselves to pick up their prescriptions and attend their appointments.

Panel members also noted that by definition, the PARP inhibitors did represent a new mechanism of action, and as such represented an additional benefit. Patient public comment earlier in the meeting also indicated that these drugs did in fact impact their work and productivity levels, allowing them to work and participate in life events more comfortably than on chemo.

One panel member also noted the value of potential long duration responders may not be captured by the QALY, and that it is important to consider how this factors into the value of the therapy.

7) **Are any of the following contextual considerations important in assessing olaparib's long-term value for money in patients with recurrent BRCA-mutated disease? (select all that apply)**

This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	8/9
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	6/9
This intervention is the first to offer any improvement for patients with this condition.	1/9
Compared to standard chemotherapy (or PLD+C) there is significant uncertainty about the long-term risk of serious side effects of this intervention.	2/9
Compared to standard chemotherapy, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	4/9

Comment: In addition to the contextual considerations listed, panel members discussed the importance of the impact of financial toxicity. One panel member noted that in addition to the severity of the disease itself, the diagnosis brings with it stigma and anxiety that should also be considered.

8) **Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits and contextual considerations, in patients with recurrent BRCA-mutated disease, what is the long-term value for money of olaparib compared with PLD+C?**

Low: 5 votes	Intermediate: 4 votes	High: 0 votes

Comment: The panel discussed the balance of uncertainty in the data quite openly. One panel member, voting low value, noted that for an incremental cost-effectiveness ratio of $146,000 per QALY gained, she would expect better certainty for what we are paying for. Another panel member, voting intermediate value, discussed the potential "value" of this therapy moving forward and felt certain that there is important clinical value, even if conclusions on that value are currently limited due to the nature of the evidence.

7.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on olaparib, niraparib, and rucaparib for recurrent ovarian cancer to policy and practice. The policy roundtable members included two patients, two clinical experts and a pharmacy benefits manager. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix H.

Table 7.1. Policy Roundtable Members

Name	Title and Affiliation
Harold Carter, Pharm.D.	Senior Director of Clinical Solutions, Express Scripts
Susan Leighton	Co-Founder, Lilies of the Valley
Betsy Neisner	Board of Directors, Ovarian Cancer Survivor Foundation
Matthew Powell, MD	Director, Gynecologic Oncology Department, Washington University at St. Louis
Andrea Wahner Hendrickson, MD	Assistant Professor, Mayo Clinic

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers and Manufacturers

At current pricing, PARP inhibitors have the potential to be aligned with clinical benefit for treatment of recurrent disease, but will be challenged to meet common thresholds in maintenance therapy. Therefore, to align value and facilitate affordability as well as patient access, prices must be lowered accordingly.

Findings from ICER's long-term cost-effectiveness analyses indicated that the additional costs of PARP inhibitor therapy were at or near common value thresholds. This was not the case in maintenance therapy, however, as the common comparator is surveillance only, and treatment duration is longer in this less severely-ill population. Manufacturers must lower prices to achieve this alignment, and should also consider indication-specific pricing given the divergent findings for recurrent disease and maintenance therapy.

Both payers and manufacturers must work together to establish innovative payment mechanisms to seek the best affordability for patients, including outcomes based contracting and/or package discounting.

Available evidence is insufficient to distinguish between PARP inhibitors. However, payers are often reluctant or statutorily prohibited from excluding oncology drugs from formularies, even when such data exist. There is therefore little opportunity for payers to insert leverage into their negotiations through single-source contracting, for example. To address affordability concerns, payers should develop alternative payment methods, such as outcomes-based or performance-based contracting. While these arrangements are not yet common in oncology, we note that the manufacturer of chimeric antigen receptor T-cell (CAR-T) therapy for blood and lymphatic cancers has publicized agreements that tie payment to the achievement of a treatment response; on its face, there appears to be no reason why arrangements tied to treatment response or a clinically-meaningful period of time without progression cannot be made for PARP inhibitors.

In addition, with forthcoming studies evaluating PARP inhibitors in combination with immunotherapies or anti-angiogenics, among other treatments, costs of treatment for advanced ovarian cancer are anticipated to grow exponentially. The advent of combination therapy will require multiple manufacturers to cooperate in offering a "package discount" to payers in order to ensure an even playing field for negotiations.

Researchers, Manufacturers, and Patient Groups

Single-arm studies and surrogate endpoints do not provide the type of information that clinicians and patients need to make treatment decisions. Critical evidence gaps like these must be addressed in the design and execution of clinical research by researchers, manufacturers, and patients alike.

Drug development is dominated by the goal of getting new, effective drugs onto the market as quickly and efficiently as possible. This approach is particularly common in oncology, with approvals increasingly based on single-arm studies and surrogate endpoints like progression-free survival, both of which were features in the evidence base for PARP inhibitors. The clinical research community should design studies with active control arms to better understand the clinical effectiveness of the PARP inhibitors relative to other common relapse regimens. Further, there is a dearth of data comparing different approaches to sequencing treatment for patients with recurrent disease. Sequencing trials may also help to answer important questions surrounding the use of PARP inhibitors as maintenance therapy versus reserving these agents for recurrence. Overall survival (OS) still remains an important outcome and we eagerly await these results.

The current evidence base is inadequate for any reasonable indirect comparison of the PARP inhibitors. Manufacturers and researchers should facilitate comparisons of the benefits and risks of the individual PARP inhibitors through standardization of research protocols and outcome measurement as well as post marketing head-to-head assessments, and patient groups should demand such standardization.

As all three of the PARP inhibitors have been introduced relatively recently, there are no head-to-head comparisons of these agents. This represents an opportunity for integrated health systems or research networks such as those managed by the Patient-Centered Outcomes Research Institute (PCORI) to conduct rigorous observational studies and/or pragmatic clinical trials to address this need. In addition, differences in trial design, timing and method for outcome measurement, and patient entry criteria preclude even formal indirect comparisons of the PARP inhibitors. While some differences may have been related to the evolution of the clinical community's understanding of ovarian cancer treatment and monitoring, others, such as timing and method for assessment of disease progression, are easily standardized across trials and interventions.

Current evidence is inadequate to determine which patients would benefit most from maintenance therapy. Further research should be conducted to identify the patients who might benefit most from a maintenance regimen as well as those for whom surveillance remains a viable option.

The broader research community should investigate which patients are appropriate candidates for maintenance therapy. The clinical expert roundtable participants noted emerging evidence suggesting that the level of response to prior platinum-based chemotherapy may affect the benefits seen from maintenance therapy. For example, patients with residual disease (partial response) may continue to see improvement in tumor response by switching to a PARP inhibitor for maintenance therapy; conversely, it is currently unclear whether those in remission (i.e., with a complete response to prior treatment) will receive sufficient incremental benefit over surveillance alone to merit the additional toxicity of maintenance therapy. Further studies should focus on response level as a possible determinant of the need for maintenance therapy.

Manufacturers

Broaden eligibility criteria for patient assistance programs to counter the impact of financial toxicity.

Financial toxicity is a real and devastating phenomenon for patients diagnosed with cancer. Manufacturers have addressed this issue in part through the creation of patient assistance programs that allow patients to receive PARP inhibitors at a reduced or no cost. Unfortunately, as several roundtable participants noted, the income eligibility thresholds to qualify for such programs force many low-to-moderate income families to impoverish themselves in order to become eligible for manufacturer or government assistance.

Price PARP inhibitors differentially by dosage strength, so that patients are not financially penalized when doses must be reduced to manage side effects.

As described during the meeting, dose reductions for PARP inhibitors were commonly observed in clinical trials in order to manage side effects and continue treatment. However, two of the three PARP inhibitors have prices that do not differ by dosage strength, so the cost to patients and payers does not decline when dosage is reduced. Each PARP inhibitor manufacturer includes a "dosage adjustment guide" for such situations in the product labeling; product pricing should reflect these adjustments accordingly.

Payers and Providers

Eliminate methods of provider reimbursement that provide significant financial incentives favoring intravenous drugs over oral treatments. Such payment mechanisms can distort clinical decision-making to the detriment of good patient care.

Clinicians stand to financially benefit when treatment is administered intravenously or otherwise requires facility-based administration, and therefore little incentive to recommend an oral agent. Payers should ensure that inappropriate financial incentives do not obstruct patient access to PARP inhibitors or negatively influence clinical decision-making. Payers may want to consider bundled payment programs specifically for ovarian cancer. Building treatment paradigms into these bundles with disease-specific considerations (e.g., presence of a deleterious BRCA mutation) may be beneficial to ensure access and manage cost. Private payers can emulate this model and include drug cost negotiations as part of the bundle.

Health plans should work closely with clinicians to provide guideline-concordant testing for genetic mutations and consider adjustments to coverage policies based on the testing results.

Although genetic testing is currently considered the standard of care in newly diagnosed ovarian cancer, rates of testing vary widely in practice and next-generation sequencing tests to assess mutations in the tumor are still considered investigational. Given variations in the level of benefit derived from PARP inhibitors among patients with and without deleterious BRCA mutations, payers should work closely with clinicians to ensure that accurate testing occurs and develop procedures for when how and when to test. Plans should consult with clinicians to consider whether adjustments to coverage policies, such as tiering, based on the results of testing (i.e., evidence of greater effectiveness in BRCAm and HRD positive subpopulations) are appropriate.

Patient Advocacy Organizations

Press researchers and manufacturers for an increased role in study design, so that comparisons and outcomes of most interest will be included.

At the public meeting, patients and patient advocacy groups described several potential advantages of PARP inhibitors, such as faster return to work and/or normal daily activities as well as reduced caregiver burden, but also noted that the current evidence base lacks any information on these outcomes. Patients and their advocates should use their position as those who know best what living with ovarian cancer is like to push for an increased role in the design of major clinical studies, so that the measures of most importance to them are included and the potential advantages of new innovations in treatment are fully elucidated.

7.4 Recommendations from Policy Roundtable Participants on Methods for Prioritizing Innovation

As noted in Section 6 of the report, ICER has solicited feedback from all stakeholders on areas of lower-value or wasteful care for ovarian cancer that could be reduced or eliminated to make additional headroom in health-system budgets for higher-value services. This question was also posed to Policy Roundtable participants at the public meeting; responses are summarized below.

Limit screening in asymptomatic women.

Clinical experts acknowledged that screening and/or monitoring asymptomatic women with frequent imaging and CA-125 biomarkers may be overutilized, with no evidence that such services improve treatment outcomes relative to clinical diagnosis based on symptoms. Patient representatives did note that disease monitoring with CA-125 biomarkers gave them peace of mind and helped them to be more proactive in managing their cancer, however. Specialty societies can help to clarify the situations in which these services are clearly not necessary, and those in which patient preferences play a key role.

Centralize care at centers of excellence.

Clinical experts also identified that centralizing care at "Ovarian Cancer Centers of Excellence" for the initial diagnosis and surgical management of the disease can improve outcomes for patients. This recommendation was twofold. First, these centers perform more surgery than smaller hospitals, and prognosis is driven, in large part, by optimal surgical debulking. Second, these centers are more likely to offer a multitude of clinical trials. While the experts agreed that diagnosis, surgical care, and trial management are best accommodated at centers of excellence, they believed that medical oncology and pharmaceutical treatment could be performed by a wider network of providers, especially given the convenience to patients from receipt of care as close to home as possible.

Use integrative therapies to manage side effects of treatment.

Having insurers consider providing coverage for integrative care treatments such as reflexology for managing side effects was thought to represent the potential for clinical benefit and cost savings over current management options (e.g., anti-emetics for nausea). Payers may consider broadening benefits to help ovarian cancer patients manage their symptoms outside of conventional medical therapies.

Educate nurses and nurse practitioners on efficient care management.

Roundtable participants also noted the opportunity for greater education of nurses and nurse practitioners on appropriate referral paths and care coordination for women with ovarian cancer, in particular because many women are receiving ongoing care at multiple sites.

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This is the first Midwest CEPAC review of PARP inhibitors for ovarian cancer.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of Bias Across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.
From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097		

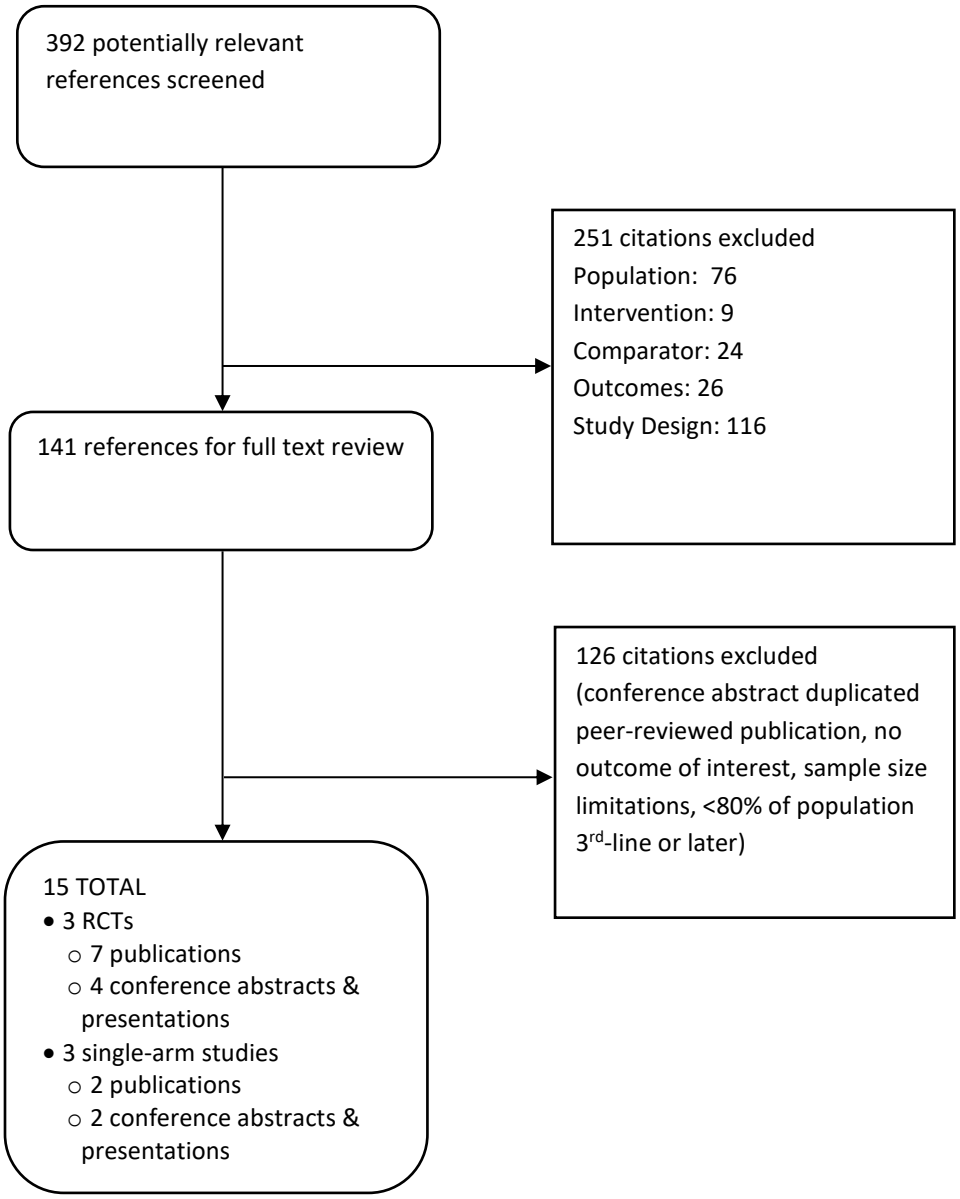
Table A2. Search Strategies of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials

1	**exp ovarian neoplasms/**
2	exp ovary/
3	ovar*.mp.
4	exp fallopian tube neoplasms/
5	exp peritoneal neoplasms/
6	or/1-5
7	olaparib.mp.
8	niraparib.mp.
9	rucaparib.mp.
10	or/7-9
11	6 and 10
12	(animals not (humans and animals)).sh.
13	11 not 12
14	limit 13 to english language
15	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase i or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt
16	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.
17	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
18	16 or 17
19	14 not 15
20	18 and 19

Table A3. Embase Search Strategy

#1	**'ovary cancer'/exp**
#2	'ovary'/exp
#3	ovar*.mp
#4	#1 OR #2 OR #3
#5	'peritoneum cancer'/exp
#6	'uterine tube carcinoma'/exp
#7	#4 OR #5 OR #6
#8	'olaparib':de OR 'olaparib':ab,ti
#9	'niraparib':de OR 'niraparib':ab,ti
#10	'rucaparib':de OR 'rucaparib':ab,ti
#11	#8 OR #9 OR #10
#12	#11 AND #7
#13	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#14	'human'/exp
#15	#13 AND #14
#16	#13 NOT #15
#17	#12 NOT #16
#18	#17 AND [english]/lim
#19	#18 AND [medline]/lim
#20	#18 NOT #19
#21	#20 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#22	#20 NOT #21

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Ovarian Cancer



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified two completed technology assessments on olaparib, one from the National Institute for Health and Care Excellence (NICE) in the UK and another from the Canadian Agency for Drugs and Technologies in Health (CADTH). These reviews are summarized below. Of note, NICE expects to publish a final appraisal document on niraparib maintenance treatment in March 2018.

Technology Assessments

NICE Technology Assessment Report: Olaparib For Maintenance Treatment Of Relapsed, Platinum-Sensitive, BRCA Mutation-Positive Ovarian, Fallopian Tube And Peritoneal Cancer After Response To Second-Line Or Subsequent Platinum-Based Chemotherapy [ID735] (January 27, 2016)

https://www.nice.org.uk/guidance/ta381

NICE recommended olaparib as an option for treating adults with relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer who have *BRCA1* or *BRCA2* mutations if they have received three or more courses of platinum-based chemotherapy and the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.

NICE: Niraparib As Maintenance Treatment Of Recurrent, Platinum-Sensitive Ovarian, Fallopian Tube, And Peritoneal Cancer That Has Responded To Platinum-Based Chemotherapy (March 2018)

https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/proposed-technology-appraisals/ovarian-cancer-niraparib-draft-scope-1.pdf

NICE is currently appraising the clinical and cost effectiveness of niraparib as maintenance treatment for recurrent, platinum-sensitive ovarian, fallopian tube, and peritoneal cancer that has responded to platinum-based chemotherapy, with expected publication in March 2018.

CADTH: Pan-Canadian Oncology Drug Review (pCODR) Final Clinical Guidance Report: Olaparib (Lynparza) for Ovarian Cancer (September 29, 2016)

https://www.cadth.ca/sites/default/files/pcodr/pcodr_olaparib_lynparza_oc_fn_cgr.pdf

The pCODR Clinical Guidance Panel identified one clinical trial of olaparib, Study 19, that met the eligibility criteria of their review. The panel concluded that there may be a clinical benefit to maintenance olaparib therapy in the treatment of recurrent, platinum-sensitive high grade ovarian, fallopian tube, or peritoneal cancer, defined by the presence of a deleterious BRCA mutation. This conclusion was based on the results of a pre-planned subgroup analysis of 136 BRCAm carriers enrolled in Study 19 (see Appendix Table F2). This trial demonstrated a clinically significant PFS [HR 0.18; 95% CI 0.1 to 0.310; p<0.0001] with olaparib relative to placebo; OS did not meet the required

threshold for statistical significance of p<0.0095 [HR 0.62; 95% CI 0.41 to 0.94; p=0.02480]. Although a greater percentage of BRCAm patients experienced grade ≥3 adverse events with olaparib (38% vs. 18% with placebo), changes in quality of life were not statistically different between groups.

Previous Systematic Reviews

We identified one systematic review on olaparib maintenance therapy for advanced ovarian cancer. This review is summarized below.

Wiggans AJ, Cass GKS, Bryant A, Lawrie TA, Morrison J. Poly(ADP-Ribose) Polymerase (PARP) Inhibitors For The Treatment Of Ovarian Cancer. *Cochrane Database of Systematic Reviews.* 2015; (5):1-3

Wiggans et al. identified four randomized trials published between 1990 and April 2015 of PARP inhibitors versus other treatments or placebo. The four completed studies included 599 women with recurrent epithelial ovarian cancer. Three studies evaluated olaparib and one study (n=75) assessed veliparib. A meta-analysis of two studies in women with platinum-sensitive disease found an improvement in PFS when olaparib (alongside conventional treatment and/or when used as maintenance treatment) was compared to a placebo or no further treatment (HR 0.42; 95% CI 0.29 to 0.60). The included studies were not powered for OS, however individual study results and meta-analysis showed no differences between PARP inhibitors and control groups (HR 1.05; 95% CI 0.79 to 1.39). There was a small difference in objective response favoring the PARP inhibitors; pooled data from four studies showed that patients were only slightly less likely to show no response with a PARP inhibitor versus placebo (RR 0.90; 95% CI 0.82 to 0.99). Adverse events of any severity were common with both a PARP inhibitor (veliparib and olaparib) and placebo. However, serious adverse events were more common with olaparib when given as maintenance treatment after a course of chemotherapy. The most common serious adverse events were anemia and fatigue. Quality of life data were insufficient for meta-analysis.

Appendix C. Ongoing Studies

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Olaparib					
A Study to Examine Olaparib Maintenance Retreatment in Patients with Epithelial Ovarian Cancer (OReO) AstraZeneca NCT03106987	Phase IIIb RCT Double-blind Estimated Enrollment: 416	1. Olaparib 300mg tablets taken twice daily 2. Placebo 300mg tablets taken twice daily	Inclusion Criteria • Female patients ≥18 years of age • Documented *BRCA1/2* status • ≥ 1 Lesion • ≥ 1 PARPi therapy received prior to inclusion in this study • ECOG performance status 0-1 Exclusion Criteria • Immunocompromised patients • Patients with current or previous myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) • Persistent toxicities (CTCAE grade 2 or higher) caused by previous cancer therapy • Participation in another clinical study • Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection.	Primary Outcome Measures • PFS [evaluated at randomization visit and every 12 weeks until objective radiological disease progression or other discontinuation criteria met] Secondary Outcome Measures • OS • TFST • TSST • HRQoL • AEs and SAEs	November 8, 2020

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
A Study to Assess the Efficacy and Safety of Olaparib Maintenance Monotherapy in the Treatment of Ovarian Cancer (ORZORA) AstraZeneca NCT02476968	Phase 4 Open Label Single Arm Estimated Enrollment: 275	1. Olaparib 400 mg capsules taken twice daily	Inclusion Criteria • ≥ 18 years of age • Platinum-sensitive relapsed high grade epithelial ovarian cancers • 2 previous lines of platinum containing therapy • Postmenopausal or non-childbearing status • Deleterious germline or somatic mutation in *BRCA1* or *BRCA2* genes or tumor BRCAwt status and qualifying mutation in any of 13 genes involved in the HRR pathway Exclusion Criteria • Participation in another clinical study with an investigational product • Patients with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) • Immuno-compromised patients • Patients at high medical risk due to a serious, uncontrolled medical disorder, systemic disease, or active, uncontrolled infection • Persistent toxicities (CTCAE grade 2) caused by previous cancer therapy	Primary Outcome Measures • PFS [Evaluated every 12 weeks] Secondary Outcome Measures • OS • TFST • TSST • HRQoL • AEs	January 2, 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Olaparib Maintenance Monotherapy in Patients with BRCA Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy (SOLO1). AstraZeneca NCT01844986	Phase 3 Double-blind RCT Estimated Enrollment: 397	1. Olaparib tablets 300mg twice daily for up to 3 years or until disease progression. 2. Placebo tablets 300mg twice daily for up to 3 years or until disease progression	Inclusion Criteria • Deleterious/suspected deleterious mutation in *BRCA1* or *BRCA2* • Completed first line platinum containing therapy • Female patients with high risk advanced (FIGO stage III - IV) BRCA-mutated high grade serous or endometrioid ovarian cancer • Randomized within 8 weeks of their last dose of chemotherapy Exclusion Criteria • Non-detrimental *BRCA1* and/or *BRCA2* mutations • Patients with early stage disease (FIGO Stage I, IIA, IIB or IIC) • Previously diagnosed and treated for earlier stage ovarian, fallopian tube or primary peritoneal cancer • Previously received chemotherapy for any abdominal or pelvic tumor, including treatment for prior diagnosis at an earlier stage for their ovarian, fallopian tube or primary peritoneal cancer	Primary Outcome Measures • PFS by review of investigator-reported RECIST data [~10 years] Secondary Outcome Measures • HRQoL • OS • PFS • TFST • TSST • AEs	March 29, 2023

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Niraparib					
A Study of Niraparib in Patients with Ovarian Cancer Who Have Received Three or Four Previous Chemotherapy Regimens (QUADRA) Tesaro, Inc. NCT02354586	Phase II Open-label Single arm Estimated Enrollment: 400	1. Niraparib administered once daily continuously during a 28-day cycle	Inclusion Criteria • 3 or 4 previous chemotherapy regimens • Measurable disease according to RECIST • Histologically diagnosed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease, and previously treated with chemotherapy experiencing a response lasting at least 6 months to first-line platinum based therapy • Agree to undergo tumor HRD testing and blood gBRCAm status testing Exclusion Criteria • No known history or current diagnosis of MDS or AML • Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease or active, uncontrolled infection • No transfusion within 4 weeks of the first dose of study treatment • No pelvic radiotherapy as treatment for primary or recurrent disease within 1 year of the first dose of study treatment	Primary Outcome Measures • Antitumor activity of niraparib [6 months] Secondary Outcome Measures • Disease Control Rate (DCR) • PFS • OS • Antitumor activity of niraparib in HRD+ and gBRCAm	October 2017

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Niraparib vs. Niraparib-bevacizumab Combination in Women with Platinum-sensitive Epithelial Ovarian Cancer (AVANOVA) Nordic Society for Gynecologic Oncology NCT02354131	Phase 1/2 Open-label Dose-escalation RCT Estimated Enrollment: 108	1. Niraparib monotherapy until progression 2. Niraparib-bevacizumab combination therapy until progression	<u>Inclusion Criteria</u> • Recurrent platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer • ECOG performance status 0-2 • Disease that is measurable according to RECIST • ≥18 years of age • Patients must have received platinum-containing therapy for primary disease <u>Exclusion Criteria</u> • Active infections or other serious underlying significant medical illness, abnormal laboratory finding or psychiatric illness/social situation • Persistence of clinically relevant therapy related toxicity from previous chemotherapy • Concurrent treatment with an investigational agent or participation in another clinical trial • Patients must not have any known history of MDS • Known uncontrolled hypersensitivity to the investigational drugs	<u>Primary Outcome Measures</u> • PFS [30 months] <u>Secondary Outcome Measures</u> • DCR	November 2018

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
A Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy Tesaro, Inc. NCT02655016	Phase 3 Double-blind RCT Estimated Enrollment: 330	1. Niraparib-Administered once daily continuously during a 28-day cycle 2. Placebo-Administered once daily continuously over a 28-day cycle	Inclusion Criteria • Advanced (Stage III or IV) high-grade serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have completed first line platinum based chemotherapy • Complete response or partial response following completion of chemotherapy course • Agree to undergo tumor HRD testing • Randomized within 12 weeks of the first day of the last cycle of chemotherapy Exclusion Criteria • Received bevacizumab with first-line platinum based therapy • Had prior treatment with a known PARP inhibitor • Has mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer • Has undergone more than 2 debulking surgeries	Primary Outcome Measures • PFS [~15 months] Secondary Outcome Measures • OS • Patient Reported Outcomes • Time to progression on the next anticancer therapy • TEAEs	August 2019

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
Rucaparib					
ARIEL4: A Study of Rucaparib vs. Chemotherapy BRCA Mutant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients Clovis Oncology, Inc. NCT02855944	Phase 3 RCT Estimated Enrollment: 345	1. Chemotherapy per local standard of care and regulations. (Specific comparator depends on platinum status and investigator decision) 2. Tablets of rucaparib, at a dose of 600 mg, taken orally twice daily	Inclusion Criteria • ≥18 years of age • Histologically confirmed Grade 2 or Grade 3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer • Received ≥ 2 prior chemotherapy regimens and have relapsed or progressive disease • Biopsiable and evaluable disease • Sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue available for planned analyses Exclusion Criteria • Prior treatment with any PARPi • Symptomatic and/or untreated central nervous system metastases • Hospitalization for bowel obstruction within 3 months prior to enrollment • History of prior cancers except for those that have been curatively treated, with no evidence of cancer currently	Primary Outcome Measures • PFS for rucaparib vs. chemotherapy [evaluated from randomization until date of first documented progression or date of death, for the duration of the study, ~4 years] Secondary Outcome Measures • OS • AEs	June 2022

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

Additional Comparative Clinical Effectiveness Methods

Screening for Study Inclusion

We performed screening at both the abstract and full-text level. Two investigators screened abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study; a third investigator resolved any discrepancies in selection as necessary.

We also included FDA documents related to the agents of interest. These included manufacturer submissions to the agency, internal FDA review documents, package inserts, and transcripts of Advisory committee deliberations and discussions.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs, using the categories "good," "fair," or "poor".[124] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat or modified intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid*

measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat analysis is lacking.

Data Extraction

Two reviewers extracted key information from the full set of accepted studies. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance. Summary tables of extracted data are available in Appendix F.

Additional Comparative Clinical Effectiveness Results

Clinical benefits

Recurrent BRCA-Mutated Disease: Additional Evidence

Table D1. Study Design and Participant Inclusion Criteria for Studies of Rucaparib

Study 10[92]	ARIEL2[31]	Pooled Analysis of Study 10/ARIEL2[28]	Subgroup Analysis of Parts 1 & 2 of ARIEL2
Study Characteristics • Three-part study • Phase 1-2 • Open-label Patient Inclusion Criteria *(Part 2A phase 2 expansion)* • Platinum-sensitive • Germline BRCA • 2-4 prior chemotherapies • N=42	Study Characteristics • Two-part • Phase II • Open-label • Single-arm study Patient Inclusion Criteria *Part 1* • Platinum-sensitive • ≥1 prior platinum therapy • N=206 *Part 2 (ongoing)* • Platinum-sensitive or platinum-resistant • 3-4 prior chemotherapies • N=286	• Germline or somatic BRCA • ≥2 prior chemotherapies, including ≥2 platinum-based regimens • Study 10 (n=42) + ARIEL2 (n=64) • N=106	• Germline or somatic BRCA • ARIEL2 Part 1 (n=41) + Part2 (n=93) • N=134

Harms

Rucaparib

The FDA's safety review of rucaparib pooled 409 patients from three clinical trials. The three single-arm trials were Study 10, ARIEL2, and RUCAPANC, which included ovarian cancer patients as well as patients with other tumors. The majority of the safety review only considered the ovarian cancer patient population (n=378).[125]

Treatment-emergent AEs (TEAEs) led to 14/409 (3.4%) deaths in the safety population, which included 5/144 (3.5%) deaths in the population of patients with a BRCA mutation. Amongst all reported TEAEs to result in death, malignant neoplasm progression occurred with the greatest frequency (10 patients, 2.4%).[125] In addition, one fatal event of AML in two cases was reported in the FDA prescribing information.[19]

Serious adverse events (SAEs) occurred in 28% of patients with ovarian cancer. The following SAEs were the most frequently reported: intestinal obstruction (6.1%), malignant neoplasm progression (5.0%), and anemia (4.8%). There were no discernible safety differences between patients with and without a deleterious BRCA mutation.[125]

Discontinuation due to TEAEs was reported in 17% of ovarian cancer patients and 63.8% experienced a TEAE which led to a dose reduction or interruption. The TEAEs that were present in ≥5% of patients which led to reduction or interruption included the following: combined terms of anemia/hemoglobin (21.2%), combined terms of asthenia/fatigue (19.8%), nausea (17.2%), vomiting (11.4%), increase in ALT (9.8%), combined terms of thrombocytopenia/decrease in platelets (9.8%), increase in AST (6.6%), and combined terms of neutropenia/decrease in ANC (6.3%).[125]

ARIEL3, a published, controlled study, looked at rucaparib versus placebo as a maintenance therapy in women with complete or partial response to last platinum-based chemotherapy after two or more lines of platinum. Safety results mirror those in the single arm studies; however, dose discontinuation rates were higher at 55% in the rucaparib arm vs. 4% in the placebo arm.[29] Additionally, three cases of AML/MDS were reported in the rucaparib arm with two cases leading to death (no reported cases in the placebo arm).[29]

Olaparib

In Study-19, adverse events of all grades occurred in at least 10% of both arms. Of all grades, 130 (95.6%) patients in the olaparib arm had at least one adverse event compared to 116 (90.6%) in the placebo arm. The most frequent adverse events of any grade were nausea (68.4% olaparib vs.

35.2% placebo), fatigue (48.5% olaparib vs. 37.5% placebo), vomiting (31.6% olaparib vs. 14.1% placebo) and diarrhea (22.8% olaparib vs. 22.7% placebo).

Table D2. Grade ≥ 3 Adverse Events with Olaparib

Adverse Events Grade ≥ 3 (%) for Olaparib					
	Study 19[24]		SOLO2[25]		Study 42[21,22]
	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=195)	Placebo (n=99)	Olaparib (n=154)
Hematologic					
Anemia	5.1	0.8	18	2.0	20.1
Neutropenia	NR	NR	4	3.0	1.3*
Thrombocytopenia	NR	NR	1.0	1.0	1.3*
AML/MDS	NR	NR	2.0	4.0	1.3
Non-hematologic					
Nausea	2.2	0	3.0	0	0.6
Fatigue/Asthenia	6.6	3.1	4.0	2.0	6.5
Vomiting	2.2	0.8	3.0	1.0	2.6
Diarrhea	2.2	2.3	1.0	0	1.3
Headache	0	0.8	1.0	0	0
Abdominal Pain	1.5	3.1	3.0	3.0	8.4

*Reported as serious adverse events. Grade ≥3 not reported; NR=not reported

Data on frequency of event in both Study 19 and SOLO2 can be found in the table below.

Table D3. Supplemental Adverse Event Data: Olaparib

Adverse Event Frequency in Study 19 and SOLO2 Adverse Events Frequency				
	Study 19[24]		SOLO2[25]	
Characteristic, n (%)	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=195)	Placebo (n=99)
Any Adverse Event	130 (95.6)	116 (90.6)	192 (98.5)	94 (94.9)
Any Adverse Event grade ≥3	48 (35.3)	26 (20.3)	71 (36.4)	18 (18.2)
Any SAE	30 (22)	11 (9)	35 (18.0)	8 (8.1)
Any Adverse Event Leading to Dose Reduction	34 (25)	5 (4)	49 (25.0)	3 (3.0)
Any Adverse Event Leading to Discontinuation of Study Treatment	8 (6)	2 (2)	21 (11.0)	2 (2.0)
Any Adverse Event with Outcome of Death	3	0	1 (1.0)	0

In addition, elevated ALT was found in 10 (5.1%) patients in the olaparib group versus 4 (4.0%) in the placebo group and elevated AST was found in 4 (2.1%) patients in the olaparib group versus 4 (4.0%) in the placebo group.[25]

Pneumonitis is listed as a potential side effect in the olaparib FDA label. Pneumonitis occurred in <1% of patients, although some cases were fatal.[18]

Review of the FDA Oncologic Drugs Advisory Committee (ODAC) transcripts reveal four cases of AML/MDS with olaparib in 2010. Three of these were confirmed (2 olaparib, 1 placebo) and one was unconfirmed (olaparib).[126] SOLO2 reported that 2.0% of patients in the olaparib arm and 4.0% of patients in the placebo arm were diagnosed with AML/MDS (including one CMML who received olaparib).[25] AML was listed as the cause of death in one patient receiving olaparib.[30]

ODAC transcripts from 2012 outlined that most of the deaths in Study 19 were due to progressive ovarian cancer. Seven deaths were reviewed, four in the olaparib arm and three in the placebo arm. Causes of death included unknown (2 olaparib, 1 placebo), septic shock (1 olaparib, 1 placebo), pulmonary embolism (placebo) and cerebrovascular disorder (olaparib).[126]

Deaths related to adverse events from treatment included a hemorrhagic stroke, cholestatic jaundice (ruled progressive disease as final diagnosis) and AML/MDS.[30,126]

Niraparib

In the NOVA trial, all patients receiving niraparib reported at least one treatment-emergent adverse event (TEAE). Over 95% of placebo patients also reported at least one TEAE.[17]

Most commonly reported adverse events (greater than 50% patients) included nausea (73.6%), thrombocytopenia (61.3%), fatigue (59.4%) and anemia (50.1%). Most of these were deemed lower than a grade 3.[17] Dose reductions or interruptions due to adverse reactions occurred in 69% of patients receiving niraparib, most frequently from thrombocytopenia (41%) and anemia (20%). The permanent discontinuation rate due to adverse reactions was 15%.[90]

Hematologic events of grade 3 and 4 occurred in 10% of patients and at a higher rate in the niraparib group.[17] In the NOVA study, AML and MDS occurred in 5 out of 367 (1.4%) patients who received niraparib and in 2 out of 179 (1.1%) patients who received placebo. In the niraparib full safety database, AML/MDS was 0.9% (n=751). This was reported to be similar to olaparib (0.8%).[90]

Cardiovascular events were also of concern. Mean greatest increases from baseline in pulse rate on treatment were 24.1 and 15.8 beats/min in the niraparib and placebo arms, respectively. Grade 3-4 hypertension occurred in 9% of niraparib-treated patients compared to 2% of placebo-treated patients in the NOVA study.[90] The current FDA label for niraparib includes warnings for

myelodysplastic syndrome/acute myeloid leukemia, bone marrow suppression and cardiovascular effects.[20]

Within the NOVA trial, there were no reported adverse events that led to death in 30 days.[90]

Comparator Evidence

Bevacizumab

Bevacizumab is a vascular endothelial growth factor-specific angiogenesis (VEGF-A) inhibitor approved by the FDA as part of a combination regimen with carboplatin/gemcitabine or carboplatin/paclitaxel for women with platinum-sensitive recurrent ovarian cancer, followed by bevacizumab as a single agent until disease progression.[98] Bevacizumab is also approved for use in platinum-resistant recurrent ovarian cancer in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan.[98]

We reviewed three randomized controlled trials of bevacizumab in recurrent ovarian cancer: OCEANS, AURELIA, and GOG 0213. In three studies, bevacizumab plus chemotherapy was shown to provide statistically significant benefits in progression-free survival in both platinum-sensitive and platinum-resistant ovarian cancer.[100,127,128] Studies did not show a statistically significant survival benefit (OS) and when quality of life was measured, no statistically significant differences were identified.[100,127,128] See table D5 below for details on patient characteristics, outcomes and harms.

The side effect profile of bevacizumab includes different harms than those experienced with PARP inhibitors, some of which may be considered more severe (bevacizumab carries an FDA black box warning for GI perforation, surgery and wound healing complications, and hemorrhage).[98]

Table D4. Key Trials for Bevacizumab

Key Trials	Patient Characteristics	Treatment Outcomes	Comparator Outcomes	Harms (Bevacizumab arm)
OCEANS[99,100] **N=484** **Median Follow-up: 24 m**	Median age: 61 ECOG: 0=75.8%; 1=24%; 2=0.2% Serous adeno-carcinoma: >80% Cytoreductive disease: 11% Time to recurrence since last plat. tx, months: 6-12=42%; >12=58% Chemotherapy tx: 2nd line Platinum sensitive: 100%	Gemcitabine + carboplatin with bevacizumab (n=242) PFS: 12.3 m ORR: 78.5 OS (immature): 33.6	Gemcitabine + carboplatin with placebo (n=242) PFS: 8.6 m ORR: 57.4 OS (immature): 32.9	D/C due to AEs: 22.3% Grade ≥3: 90% Serious AE: 36.4%
AURELIA[127] **N=361** **Median Follow-up: 13.9 m**	Median age: 61 ECOG: 0=57%; 1=35%; 2=6% Serous adeno-carcinoma: >85% Chemotherapy tx: 2nd line Platinum resistant: 100%	Chemotherapy of choice (PLD, paclitaxel or topotecan) + bevacizumab (n=179) PFS: 6.7 m OS: 16.6 m	Chemotherapy alone (n=182) PFS: 3.4 m OS: 13.3 m	5 deaths in each arm (2.8%) Hypertension (grade ≥2): 7% GI perforation (grade ≥2): 2%
GOG 0213[128] **N=674** **Median Follow-up: 49.6 m**	Median age: 60 Previous tx-free intervals: 6-12 m (31%) Previous plat-free interval: 6-12 m (27%)	Paclitaxel+ carboplatin + bevacizumab (n=330) PFS: 13.8 m OS: 42.2 m	Paclitaxel + carboplatin alone (n=327) PFS: 10.4 m OS: 37.3 m	Serious AEs: 15% Tx related death: 3% (9 deaths) D/C due to AEs: 25% Neutropenia (grade ≥3): 7% Hypertension (grade 3): 12% Proteinuria (grade ≥3): 8%

*outcomes are presented for patients undergoing bevacizumab initiation (cycles 2-6 only) and bevacizumab throughout (cycles 2-22); ± reported IRC-assessed PFS; PFS=progression-free survival; OS=overall survival; D/C=discontinuation; AE=adverse event

Pegylated liposomal doxorubicin (PLD)

Pegylated liposomal doxorubicin with carboplatin (PLD+C) was chosen as our primary comparator for recurrent, BRCA-mutated disease based on clinical expert input.

The main source of evidence came from a systematic review of pegylated liposomal doxorubicin in relapsed ovarian cancer. Efficacy and safety of PLD with carboplatin (PLD+C) and paclitaxel with carboplatin (PAC+C) were compared. The study authors concluded that PLD+C is more effective than PAC+C and is better tolerated.[96] Table D6 below highlights the comparative efficacy and harms between the therapies.

As described in the Topic in Context section, PARP inhibitors may be better tolerated than platinum-based chemotherapy. For example, PLD+C has a black box FDA warning for cardiomyopathy and severe, life-threatening infusion-related reactions.[95] Hand-foot syndrome, a painful, blistering of the palms and soles of the feet, is also a reported side effect of doxorubicin.[95,96]

Table D5. Summary of Outcome from Systematic Review (PLD/Carboplatin)[96]

Outcome	Comparative Risks/Rates (95% CI for Relative Risk)		Relative Effect (95% CI)	Number of Participants	Quality of Evidence (Grade)
	PLD/carboplatin*	PAC/carboplatin*			
Median Progression-Free Survival (PFS)	11 months	9 months	HR 0.85 (0.74 to 0.97)	1164	High
Overall Survival	31 months	33 months	HR 1.01 (0.88 to 1.17)	1164	Moderate
SAE: Hand-foot Syndrome (grade 3)	13 per 1000 (3 to 60)	3 per 1000	RR 4.30 (0.92 to 20.15)	1140	Moderate
SAE: Hair Loss (grade 2)	76 per 1000 (50 to 126)	840 per 1000	RR 0.09 (0.06 to 0.15)	1140	High
Discontinuation due to Toxicity	55 per 1000 (37 to 82)	144 per 1000	RR 0.38 (0.26 to 0.57)	1150	High

Arms assessed pegylated liposomal doxorubicin * (PLD)/carboplatin and paclitaxel (PAC)/carboplatin.

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory (adapted from Sanders et al., JAMA. 2016;316(10):1093-1103)

Sector	Type of Impact	Included in This Analysis from… Perspective?		Notes on Sources
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	✓	☐	
	Health-related quality of life effects	✓	☐	
	Adverse events	✓	☐	
Medical Costs	Paid by third-party payers	✓	☐	
	Paid by patients out-of-pocket	✓	☐	
	Future related medical costs	✓	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	☐	
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA=not applicable

Model Parameters

Administration and Monitoring Costs

Resource use associated with administration, monitoring, and follow-up are shown in Appendix Table E2. There are no reported (or assumed) administration costs associated with PARP inhibitors. Supportive care costs include a monthly office visit and CT scans for all surviving patients, and a monthly blood test for patients on PARP inhibitor treatment.

To incorporate costs in the progression health state, we applied 6 cycles of subsequent chemotherapy and chemotherapy pre-medications to the proportion of patients entering the progression health state.

End of life costs were assumed the same across treatments using an average, inflated-adjusted cost from a previous systematic review in ovarian cancer.[129] These costs represent the weighted average cost for the last 6 months of life ($48,142 in 2017 US dollars) across two different patient groups: neoadjuvant chemotherapy and primary debulking surgery.

Table E2. Administration and Monitoring Costs (Inflated to 2017 Dollars)

Resource Component	Model Input	Source
Subsequent Chemotherapy per Course of Treatment (6 cycles applied)	$4,941	Redbook (WAC)
Cost of Chemotherapy Pre-Medication	$426	Medicare reimbursement rates from Smith et al.[130]
Office Visit	$111	Medicare reimbursement rates from Smith et al.[130]
CT Scan Abdomen and Pelvis	$532	Medicare reimbursement rates from Smith et al.[130]
Blood Test	$124	Medicare reimbursement rates from Smith et al.[130]
End of Life Costs	$49,182	Poonawalla et al.[129]
Proportion Requiring End of Life Costs	0.51	Poonawalla et al.[129]

Drug Utilization

Dose intensity was based on a weighted average calculation using dose adjustment guidance from product labels or FDA clinical reviews[18-20,90,106-108,125] as well as rates of discontinuation from Study 19 of olaparib in the maintenance population;[103] the only study in our set that reported detailed discontinuation rates over the duration of the trial. For model comparisons in the maintenance population, those that discontinued and stayed in the progression free state did not incur treatment costs from that point forward. For example, for niraparib, we used the FDA clinical review data, which reported the percent of patients reducing from 300mg dose to 200mg dose as well as to 100mg dose over the course of the trial; these increments of dose reduction are also reflected in the product label. The model begins by starting all patients on the 300mg dose, and over time patients who are on treatment and do not discontinue receive a decreasing dose until median discontinuation of 11 months (i.e., discontinuation observed in Study 19). Once patients reach the 11-month point, all patients who are still on treatment and did not discontinue are assumed to receive a weighted average of 220mg of niraparib. Those that discontinued and stayed in the progression-free state did not incur treatment costs from that point forward. A similar strategy was used for olaparib and rucaparib in the maintenance population.[107] In the recurrent, BRCA-mutated population for rucaparib and olaparib, we also used a similar weighted average calculation to decrease dose intensity over the model time horizon, but discontinuation evidence

was not available in this population. Therefore, treatment costs based on the weighted average dose was applied to all patients remaining in the progression-free state.

For PLD+C we used prior evidence on average weight (69.1 kg) and serum creatinine levels (0.76 mg/dL) in a representative sample of ovarian cancer patients to calculate treatment dosing,[109,110] and used the same average weight to calculate treatment dosing for bevacizumab (used in budget impact only).

Adverse Event Costs

Adverse event costs were derived from treatment assumptions used in previous analyses[111] and the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUPnet).[112] Adverse events reported from FDA labels and clinical trials from the interventions are listed in the Clinical Inputs section. The estimated cost represents an aggregate of emergency department and hospital costs associated with each adverse event ICD-9-CM code. HCUPnet uses a hospital-wide cost-to-charge ratio to estimate cost. Estimates are inflated to 2017 US dollars using the medical care component of the U.S. Consumer Price Index (Appendix Table E3).

Table E3. Adverse Event Costs

Grade 3/4 Adverse Events (ICD-9-CM)	Base-Case	SE	Lower	Upper	Distribution
Anemia (285.3)	$7,533	$10,958	$5	$38,830	Gamma
Fatigue (780.71)	*	*	*	*	*
Hypertension (401)	$6,903	$7,256	$125	$26,587	Gamma
Thrombocytopenia (287.5)	$10,607	$16,207	$3	$57,183	Gamma
Leukopenia (288.5)	$8,705	$12,202	$10	$43,381	Gamma
Nausea (787.01)	$7,007	$9,370	$14	$33,455	Gamma
Neutropenia (288)	$13,633	$22,203	$1	$77,893	Gamma
Hand, Foot, and Mouth Disease (074.3)	$4,032	$5,463	$7	$19,482	Gamma
Stomatitis (528)	$10,796	$15,551	$8	$55,154	Gamma
Rash (782.1)	$5,359	$7,306	$8	$26,040	Gamma

*Not estimated in HCUPnet, assumed to be $0

Transition Probabilities

Base case survival was derived from parametric fits to each intervention's available PFS and OS Kaplan-Meier data. Transition probabilities were derived monthly using the survival function with the best model fit. Median PFS and OS time from the trial evidence was compared to the median PFS and OS time generated from the model. In cases where the model produced median time estimates that varied by more than +/- 2 months, we used a calibration multiplier to ensure that the median PFS or OS was within +/- 2 months of what was reported in the trial.

Given limitations in available clinical trial evidence such as immature survival data and surrogate endpoints, the evidence summarized in Appendix Table E4 represents the most recent and best-available evidence given each sub-population comparison's decision problem. For example, in the case of olaparib in platinum-sensitive disease eligible for maintenance therapy, evidence on the benefits of maintenance treatment with olaparib included delaying progression within sub-states on and off treatment, and transitioning to two additional subsequent chemotherapy lines of treatment. In order to model this decision problem, we relied on multiple sources of evidence including evidence from the olaparib single HTA submission,[103] along with the most recent evidence on PFS (2017 presentation SOLO2 PFS BICR curve) and OS.[26] Conversely, evidence from niraparib included PFS subdivided by gBRCA and non-gBRCA status with OS data immature at the point of completing this analysis.

Given this limited comparative evidence on the relationship between progression-free survival and overall survival for PARP inhibitors versus placebo in the maintenance population, we calibrated the model to reflect a proportional gain in overall survival from progression-free survival in Study 19.[26] For example, in the BRCA mutated maintenance sub-population, the gain in median time to first subsequent treatment (i.e., proxy for symptomatic disease progression[116]) was 9.4 months versus

placebo which translated into a gain in median overall survival of 4.7 months versus placebo. Therefore, for every 1-month gain in progression-free survival, a 0.5-month gain in overall survival was observed within this sub-population. The model, however, currently uses the most recent and best available evidence on progression-free survival with key overall survival evidence not available yet from trials. In order to address this limitation, we calibrated the model in certain scenarios to reflect this proportionate gain in overall survival from progression-free survival reported in Study 19. For example, the gain in investigator-assessed progression-free survival from, SOLO-2 was approximately 19.1 months versus placebo of 5.5 months, for a difference of 13.6 months of progression-free survival time. Using the proportionate gain in overall survival from gains in progression-free survival from Study 19, we calibrated the model to report a gain in overall survival of 13.6*0.5 = 6.8 months of overall survival instead of assuming a gain of 4.7 months of overall survival from Study 19. This calibration procedure mainly impacted estimates within the maintenance therapy BRCA-mutated sub-population comparisons.

We were not able to conduct similar calibrations in the recurrent, BRCA-mutated population because comparative progression-free and overall survival estimates versus placebo were not estimated in clinical trials. Additionally, evidence used to generate life-year and QALY estimates for PLD+C are derived from a source with mixed BRCA- and non-BRCA-mutated patients. Previous studies have shown extended survival in patients with BRCA-mutation versus patients without BRCA-mutation. To our knowledge, there is no known evidence in BRCA-mutated populations that separate survival by line of therapy which is also a significant predictor as well as necessary factor in approximating the FDA-indicated uses of olaparib and rucaparib. Therefore, given these limitations in the recurrent, BRCA-mutated population, life-year and QALY estimates are preliminary and require further evidence. To address these limitations in the recurrent, BRCA-mutated population, we conducted a scenario analysis for rucaparib in particular to identify absolute overall survival gains needed to achieve a cost-effectiveness threshold of $150,000/QALY when compared to PLD+C for third-line or later use. We did not conduct a similar exercise in olaparib given the base-case estimate of olaparib meets the $150,000/QALY threshold given a survival gain of 8 months over PLD+C in 4th line or later use.

Table E4 a. Evidence to Generate Transition Probabilities for Recurrent BRCA Mutated Population

Recurrent BRCA-Mutated Population			
Transition Probabilities	**Olaparib**	**PLD+C**	**Notes**
Progression-Free to Progressive	Kaufman et al. 2015 J Clin Oncol[22] Figure 1	Pujade-Lauraine et al.[97] and Hanker et al.[5] Figure 2A 3rd relapse	Evidence not split into multiple lines of therapy. PLD+C evidence from combination of BRCA-mutated and non-BRCA-mutated population.
Overall Survival	Kaufman et al. 2015 J Clin Oncol[22] Figure 2	Pujade-Lauraine et al.[97] and Hanker et al.[5] Figure 2B 3rd relapse	
	Rucaparib	**PLD+C**	**Notes**
Progression-Free to Progressive	Konecny et al.[23] 2017 presentation Slide 14	Pujade-Lauraine et al.[97] and Hanker et al.[5] Figure 2A 2nd relapse	Evidence not split into multiple lines of therapy. Overall survival from olaparib recurrent BRCA-mutated evidence. PLD+C evidence from combination of BRCA-mutated and non-BRCA-mutated population.
Overall Survival	Kaufman et al.[23] 2015 J Clin Oncol[22] Figure 2	Pujade-Lauraine et al.[97] and Hanker et al.[5] Figure 2B 2nd relapse	

PLD+C pegylated liposomal doxorubicin + carboplatin

Table E4 b. Evidence to Generate Transition Probabilities for Maintenance Therapy for Platinum-Sensitive Disease

Maintenance Therapy for Platinum-Sensitive Disease		
Transition Probabilities	**Olaparib And Placebo Arms**	**Notes**
Progression-Free to Progressive	Pujade-Lauraine et al.[25] 2017 presentation SOLO2 PFS IA curve	Evidence split into multiple lines of therapy for olaparib only.
Overall Survival	Ledermann 2016[26] Figure 2B	
Progression-Free to Discontinuation	Single HTA submission olaparib maintenance Figure 5[103]	
Progressive Subsequent Therapy 1 to Subsequent Therapy 2	Single HTA submission olaparib maintenance Figure 13[103]	
	Niraparib gBRCAm and Placebo Arms	**Notes**
Progression-Free to Progressive	Mirza et al.[17] NEJM Figure 2A	Evidence not split into multiple lines of therapy. Overall survival and discontinuation rates from olaparib applied.
Overall Survival	Ledermann 2016[26] Figure 2B	
Progression-Free to Discontinuation	Single HTA submission olaparib maintenance Figure 5[103]	
	Niraparib non-gBRCAm and Placebo Arms	**Notes**
Progression-Free to Progressive	Mirza et al.[17] NEJM Figure 2C	Evidence not split into multiple lines of therapy. Discontinuation rates from olaparib applied. Overall survival from olaparib placebo arm was applied to both arms of niraparib OS non-gBRCAm as there was no statistically significant difference between OS.
Overall Survival	Ledermann 2016 Figure 2C [26]	
Progression-Free to Discontinuation	Single HTA submission olaparib maintenance Figure 5 [103]	
	Rucaparib gBRCAm and Placebo Arms	**Notes**
Progression-Free to Progressive	Coleman et al. Lancet Oncol Figure 3A[29]	Evidence not split into multiple lines of therapy. Overall survival and discontinuation rates from olaparib applied.
Overall Survival	Ledermann 2016[26] Figure 2B	
Progression-Free to Discontinuation	Ledermann 2016[26] Figure 2B Single HTA submission olaparib maintenance Figure 5[103]	

Appendix Table E5 displays the comparison of the median progression-free survival and median overall survival of the model and the trial evidence. We also present any values that were calibrated for proportional gains in overall survival from gains in progression-free survival.

Table E5. Comparison of Model and Trial-Based Evidence

Arm	Population	Outcome	Model Output	Trial Evidence	Source
Olaparib – gBRCAm	Maintenance	Median Survival	37	34.9	Calibrated for proportionate gain in PFS to OS vs. placebo from Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS on and off treatment	20	19.1	SOLO2 PFS investigator assessed Curve - Pujade-Lauraine 2017
		Median Discontinuation	11	11	Single HTA submission olaparib maintenance Figure 5
		Median time to second subsequent treatment	24	23.8	Single HTA submission olaparib maintenance Figure 13
Olaparib Placebo – gBRCAm	Maintenance	Median Survival	30	30.2	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS on and off treatment	6	5.5	SOLO2 PFS investigator assessed curve - Pujade-Lauraine 2017
		Median Discontinuation	6	4.6	Single HTA submission olaparib maintenance Figure 5
		Median time to second subsequent treatment	12	15	Single HTA submission olaparib maintenance Figure 13

Arm	Population	Outcome	Model Output	Trial Evidence	Source
Niraparib – gBRCAm	Maintenance	Median Survival	38	34.9	Calibrated for proportionate gain in PFS to OS vs. placebo from Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS	21	21	Figure 2A - NEJM Mirza 2016
		Median Discontinuation	11	11	Single HTA submission olaparib maintenance Figure 5
Niraparib Placebo – gBRCAm	Maintenance	Median Survival	30	30.2	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS	6	5.5	Figure 2A - NEJM Mirza 2016
		Median Discontinuation	6	4.6	Single HTA submission olaparib maintenance Figure 5
Niraparib – Non-gBRCAm	Maintenance	Median Survival	27	26.6	Figure 2C - Lancet Oncology Ledermann 2016
		Median PFS	10	9.3	Figure 2C - NEJM Mirza 2016
		Median Discontinuation	11	11	Single HTA submission olaparib maintenance Figure 5
Niraparib Placebo – Non-gBRCAm	Maintenance	Median Survival	27	26.6	Figure 2C - Lancet Oncology Ledermann 2016
		Median PFS	4	3.9	Figure 2C - NEJM Mirza 2016

Arm	Population	Outcome	Model Output	Trial Evidence	Source
		Median Discontinuation	6	4.6	Single HTA submission olaparib maintenance Figure 5
Rucaparib – gBRCAm	Maintenance	Median Survival	36	34.9	Calibrated for proportionate gain in PFS to OS vs. placebo from Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS	17	16.6	Figure 3A – Lancet Oncology 2017
		Median Discontinuation	11	11	Single HTA submission olaparib maintenance Figure 5
Rucaparib Placebo – gBRCAm	Maintenance	Median Survival	30	30.2	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS	5	5.4	Figure 3A – Lancet Oncology 2017
		Median Discontinuation	6	4.6	Single HTA submission olaparib maintenance Figure 5
Rucaparib	Recurrent BRCA-mutated	Median Survival	17	16.6	Figure 2 - J of Clin Oncol Kaufman 2015
		Median PFS	13	12.7	ARIEL2 Slide 14 - Konecny 2017
PLD + C Comparison to Rucaparib	Recurrent BRCA-mutated	Median Survival	12	11.3	Hanker Annals of Clin Oncol 2012 (Figure 2B - 2nd Relapse)*
		Median PFS	7	6.4	J of Clin Oncol Pujade-Lauraine 2010 and Hanker Annals of Clin Oncol 2012 (Figure 2A - 2nd Relapse)*

Arm	Population	Outcome	Model Output	Trial Evidence	Source
Olaparib	Recurrent BRCA-mutated	Median Survival	17	16.6	Figure 2 - J of Clin Oncol Kaufman 2015
		Median PFS	7	7	Figure 1 - J of Clin Oncol Kaufman 2015
PLD + C Comparison to Olaparib	Recurrent BRCA-mutated	Median Survival	9	8.9	Hanker Annals of Clin Oncol 2012 (Figure 2B - 3rd Relapse)*
		Median PFS	6	5.6	J of Clin Oncol Pujade-Lauraine 2010 and Hanker Annals of Clin Oncol 2012 (Figure 2A 3rd Relapse)*

*Hanker et al. survival estimates based on mixed population of BRCA-mutated and non-BRCA-mutated patients

Appendix Table E6 presents the final distributions chosen for the model based on the lowest Akaike information criterion (AIC). The shape and scale parameters were used to generate time-dependent transition probabilities for each curve over a 15-year time horizon. As described previously, calibration efforts were used to ensure median survival time estimates were within +/- 2 months of what was reported in the trial. Additional calibration efforts were used to extend overall survival time as a proportion of gains in progression-free survival in certain scenarios as described in Table E5.

Table E6. Survival Curve Fit, Shape, and Scale Parameters for Final Model

Arm	Population	Outcome (Distribution Chosen)	AIC	Shape	Scale	Source
Olaparib - Gbrcam	**Maintenance**	Overall Survival (Log-Normal)	450.79	3.73325328	0.873203828	Figure 2B - Lancet Oncology Ledermann 2016
		PFS On And Off Treatment (Log-Logistic)	813.36	1.81761426	15.09023115	SOLO2 PFS IA Curve - Pujade-Lauraine 2017
		Discontinuation (Log-Logistic)	445.62	1.34409275	11.71640879	Single HTA submission olaparib maintenance Figure 5
		Time From First To Second Subsequent Treatment s(Log-Logistic)	196.96	2.20642898	6.24486773	Single HTA submission olaparib maintenance Figure 13
Olaparib Placebo - Gbrcam	**Maintenance**	Overall Survival (Log-Normal)	406.87	3.27633624	0.72686854	Figure 2B - Lancet Oncology Ledermann 2016
		PFS On And Off Treatment (Log-Logistic)	371.60	2.53179574	5.54507239	SOLO2 PFS IA Curve - Pujade-Lauraine 2017
		Discontinuation (Log-Logistic)	278.02	2.15070479	4.8284887	Single HTA submission olaparib maintenance Figure 5
		Time From First To Second Subsequent Treatment (Log-Normal)	277.39	2.6314707	8.33485133	Single HTA submission olaparib maintenance Figure 13
Niraparib - Gbrcam	**Maintenance**	Median Survival (Log-Normal)	450.79	3.73325328	0.873203828	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS (Log-Normal)	439.6	2.8604668	1.02437545	Figure 2A - NEJM Mirza 2016
		Discontinuation (Log-Logistic)	445.62	1.34409275	11.71640879	Single HTA submission olaparib maintenance Figure 5

Arm	Population	Outcome (Distribution Chosen)	AIC	Shape	Scale	Source
Niraparib Placebo - Gbrcam	**Maintenance**	Median Survival (Log-Normal)	406.87	3.27633624	0.72686854	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS (Log-Normal)	225.98	1.68673628	0.64685316	Figure 2A - NEJM Mirza 2016
		Discontinuation (Log-Logistic)	278.02	2.15070479	4.8284887	Single HTA submission olaparib maintenance Figure 5
Niraparib - Non Gbrcam	**Maintenance**	Median Survival (Log-Normal)	383.03	3.38669957	0.76328639	Figure 2C - Lancet Oncology Ledermann 2016
		Median PFS (Log-Normal)	777.43	2.20930923	0.91461013	Figure 2C - NEJM Mirza 2016
		Discontinuation (Log-Logistic)	445.62	1.34409275	11.71640879	Single HTA submission olaparib maintenance Figure 5
Niraparib Placebo – Non-Gbrcam	**Maintenance**	Median Survival (Log-Normal)	469.18	3.29805989	0.66075784	Figure 2C - Lancet Oncology Ledermann 2016
		Median PFS (Log-Normal)	362.67	1.68108524	0.72885076	Figure 2C - NEJM Mirza 2016
		Discontinuation (Log-Logistic)	278.02	2.15070479	4.8284887	Single HTA submission olaparib maintenance Figure 5
Rucaparib - Gbrcam	**Maintenance**	Median Survival (Log-Normal)	406.87	3.27633624	0.72686854	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS (Log-Normal)	489.24	1.613342	17.87622	Figure 3A – Lancet Oncology Coleman 2017
		Discontinuation (Log-Logistic)	278.02	2.15070479	4.8284887	Single HTA submission olaparib maintenance Figure 5
	Maintenance	Median Survival (Log-Normal)	406.87	3.27633624	0.72686854	Figure 2B - Lancet Oncology Ledermann 2016

Arm	Population	Outcome (Distribution Chosen)	AIC	Shape	Scale	Source
Rucaparib Placebo - Gbrcam		Median PFS (Log-Normal)	314.49	1.506978	0.88699	Figure 3A - Lancet Oncology Coleman 2017
		Discontinuation (Log-Logistic)	278.02	2.15070479	4.8284887	Single HTA submission olaparib maintenance Figure 5
Rucaparib	**Recurrent BRCA Mutated**	Median Survival (Log-Logistic)	1283.53	1.76868707	16.66539575	Figure 2 - J of Clin Oncol Kaufman 2015
		Median PFS (Log-Normal)	257.87	2.58904738	0.73227516	ARIEL2 Slide 14 - Konecny 2017
PLD + C Comparison to Rucaparib	**Recurrent BRCA Mutated**	Median Survival (Log-Logistic)	1283.53	1.76868707	16.66539575	Hanker Annals of Clin Oncol 2012 (Figure 2B - 2nd Relapse)
		Median PFS (Log-Normal)	2320.649	2.5117674	0.54421827	J of Clin Oncol Pujade-Lauraine 2010 and calibrated to Hanker Annals of Clin Oncol 2012 (Figure 2A - 2nd Relapse)
Olaparib	**Recurrent BRCA Mutated**	Median Survival (Log-Logistic)	1283.53	1.76868707	16.66539575	Figure 2 - J of Clin Oncol Kaufman 2015
		Median PFS (Log-Logistic)	2162.39	1.99046362	6.78371336	Figure 1 - J of Clin Oncol Kaufman 2015
PLD + C Comparison to Olaparib	**Recurrent BRCA Mutated**	Median Survival (Log-Logistic)	1283.53	1.76868707	16.66539575	Hanker Annals of Clin Oncol 2012 (Figure 2B - 3rd Relapse)
		Median PFS (Log-Logistic)	2286.141	3.4549378	12.43594645	J of Clin Oncol Pujade-Lauraine 2010 and calibrated to Hanker Annals of Clin Oncol 2012 (Figure 2A 3rd Relapse)

Disutilities

We applied a regimen-weighted disutility for experiencing any Grade 3/4 adverse event (Appendix Table E7); the total percentage of patients who experienced any Grade 3/4 adverse event for each regimen was multiplied by the adverse event disutility and then subtracted from each month of PFS for each regimen. We assumed that the total time with a Grade 3/4 adverse event for patients experiencing any Grade 3/4 adverse event was three months.

Table E7. Disutilities for Grade 3/4 Adverse Events

Adverse Event (ICD-9-CM)	Base Case Disutility	SE	Lower	Upper	Distribution	Source
Anemia (285.9)	-0.022	0.0171	-0.002	-0.066	Beta	Tesaro data on file(non-gBRCAm overall)
Fatigue (780.71)	-0.0204	0.0161	-0.002	-0.062	Beta	Olaparib NICE HTA Submission [103] for any grade 3/4vs. no grade ¾
Hypertension (401)	-0.0204	0.0161	-0.002	-0.062	Beta	Olaparib NICE HTA Submission [103] for any grade 3/4vs. no grade 3/4
Thrombocytopenia (287.5)	-0.015	0.0116	-0.001	-0.045	Beta	Tesaro data on file (non-gBRCAm overall)
Leukopenia (288.5)	-0.0204	0.0161	-0.002	-0.062	Beta	Olaparib NICE HTA Submission [103] for any grade 3/4 vs. no grade 3/4
Nausea (787.01)	-0.0204	0.0161	-0.002	-0.062	Beta	Olaparib NICE HTA Submission [103] for any grade 3/4vs. no grade 3/4
Neutropenia (288)	-0.014	0.0137	-0.0004	-0.051	Beta	Tesaro data on file (non-gBRCAm overall)
Hand, Foot, and Mouth Disease (074.3)	-0.0204	0.0161	-0.002	-0.062	Beta	Olaparib NICE HTA Submission [103] for any grade 3/4vs. no grade 3/4
Stomatitis (528)	-0.0204	0.0161	-0.002	-0.062	Beta	Olaparib NICE HTA Submission [103] for any grade 3/4vs. no grade 3/4
Rash (782.1)	-0.0204	0.0161	-0.002	-0.062	Beta	Olaparib NICE HTA Submission [103] for any grade3/4 vs. no grade 3/4

Scenario and Sensitivity Analysis Results

Olaparib

Appendix Table E8 includes scenario and sensitivity analysis results described in Section 6. In the recurrent BRCA-mutated population, using a partitioned survival approach, similar results to the base-case estimates were produced. Other results include combined BRCA and non-BRCA evidence and BICR PFS evidence in the maintenance therapy for platinum-sensitive population.

Table E8. Discounted Costs, Outcomes, and Incremental Results for Olaparib from Model for Scenario and Sensitivity Analyses

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Recurrent BRCA-Mutated Population					
Olaparib (Partitioned Survival Sensitivity Analysis)	$128,153	$43,147	$171,300	2.11	1.28
PLD+ C (Partitioned Survival Sensitivity Analysis) (4th Line or Later Use)	$25,016	$41,229	$66,245	0.91	0.60
Incremental Cost per Outcome				$87,046/LYG	$154,148/QALY
Maintenance Therapy for Platinum-Sensitive Disease					
Olaparib – Combined gBRCAm and Non- gBRCAm	$229,589	$48,756	$180,832	3.11	2.21
Placebo (Olaparib) – Combined gBRCAm and Non- gBRCAm	$8,729	$44,469	$53,198	2.79	1.89
Incremental Cost per Outcome				$541,606/LYG	$542,937/QALY
Olaparib – BICR PFS in gBRCAm	$257,756	$56,545	$201,210	4.27	3.07
Placebo (Olaparib) – BICR PFS in gBRCAm	$9,042	$46,474	$55,516	3.09	2.08
Incremental Cost per Outcome				$170,087/LYG	$204,830/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs

§Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs

Niraparib

Appendix Table E9 includes scenario analysis results described in Section 6. In the maintenance for platinum-sensitive disease population, combined BRCA and non-BRCA evidence for niraparib was used to generate additional cost-effectiveness estimates.

Table E9. Discounted Costs, Outcomes, and Incremental Results for Niraparib from Model for Scenario and Sensitivity Analyses

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Maintenance Therapy for Platinum-Sensitive Disease					
Niraparib – Combined gBRCAm and Non-gBRCAm	$137,235	$56,867	$194,102	3.11	2.21
Placebo (Niraparib) – Combined gBRCAm and Non- gBRCAm	$5,190	$44,469	$49,659	2.79	1.91
Incremental Cost per Outcome				$443,511/LYG	$481,555/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs
§Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs

Rucaparib

Appendix Table E10 includes scenario analysis results described in Section 6. In the maintenance for platinum-sensitive disease population, combined BRCA and non-BRCA evidence (i.e., intention-to-treat) for rucaparib was used to generate additional cost-effectiveness estimates.

Table E10. Discounted Costs, Outcomes, and Incremental Results for Rucaparib from Model for Scenario and Sensitivity Analyses

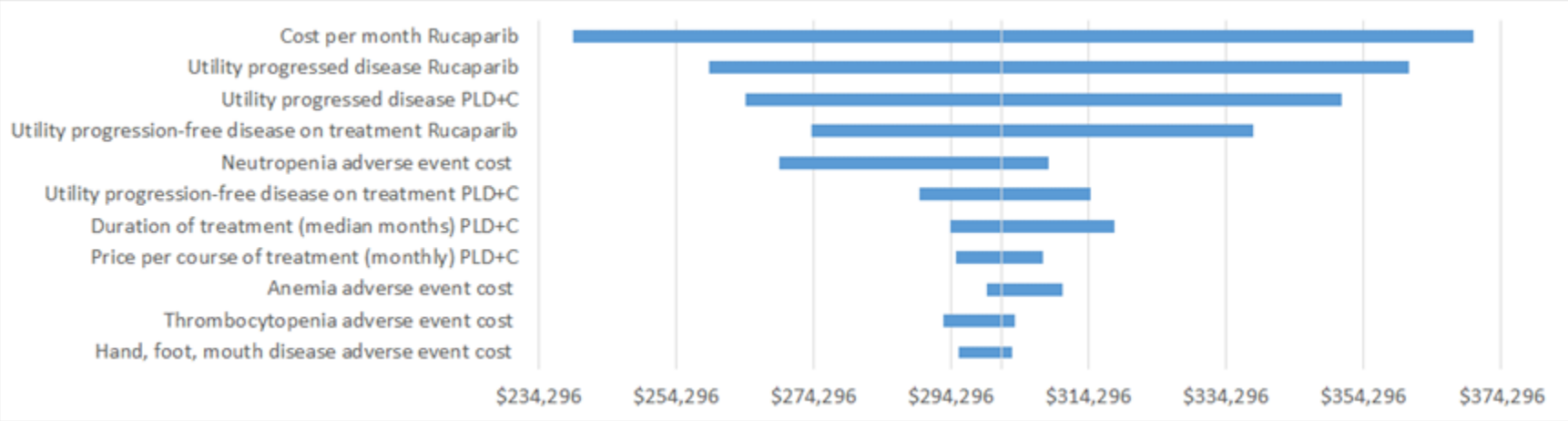
Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Maintenance Therapy for Platinum-Sensitive Disease					
Rucaparib – Combined gBRCAm and Non-gBRCAm	$148,314	$50,968	$199,282	3.11	2.21
Placebo (Rucaparib) – Combined gBRCAm and Non- gBRCAm	$5,020	$44,469	$49,489	2.79	1.91
Incremental Cost per Outcome				$459,938/LYG	$504,851/QALY

*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs
§Non-intervention costs include supportive care costs (office visit, CT scan, blood test), adverse event costs, and end of life costs

One-Way Sensitivity Analysis Results

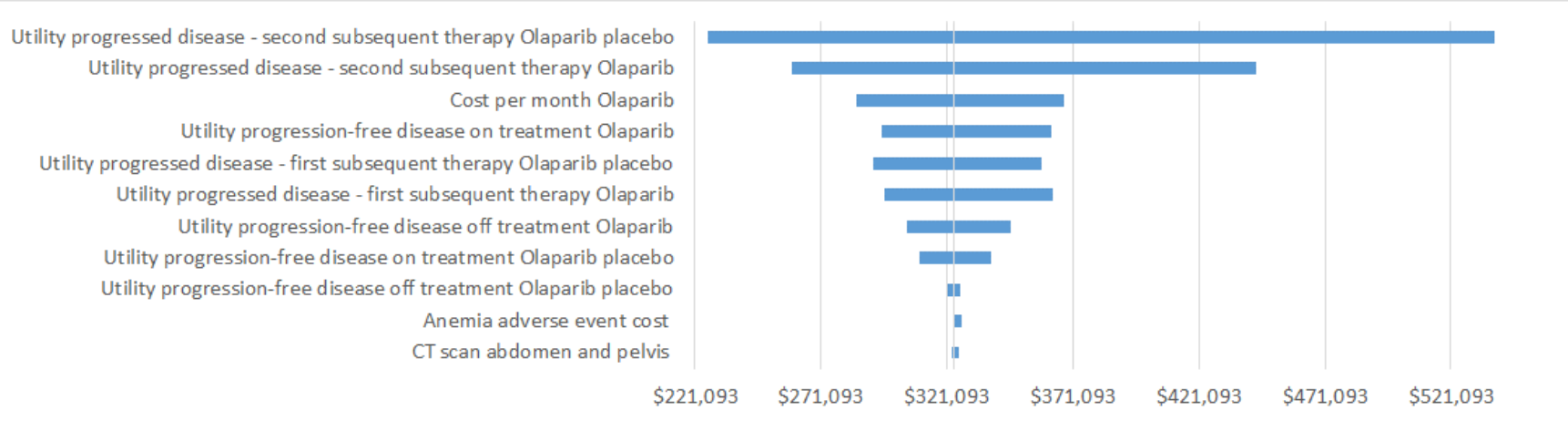
Tornado diagrams not shown in Section 6 are shown in Figures E1-E3. For the non-gBRCA niraparib comparison, the tornado diagram is not shown given no variation in estimates produced a cost-effectiveness estimate of less than $500,000/QALY.

Figure E1. Rucaparib Versus PLD+C (3rd line or later use) in Recurrent BRCA-Mutated Population



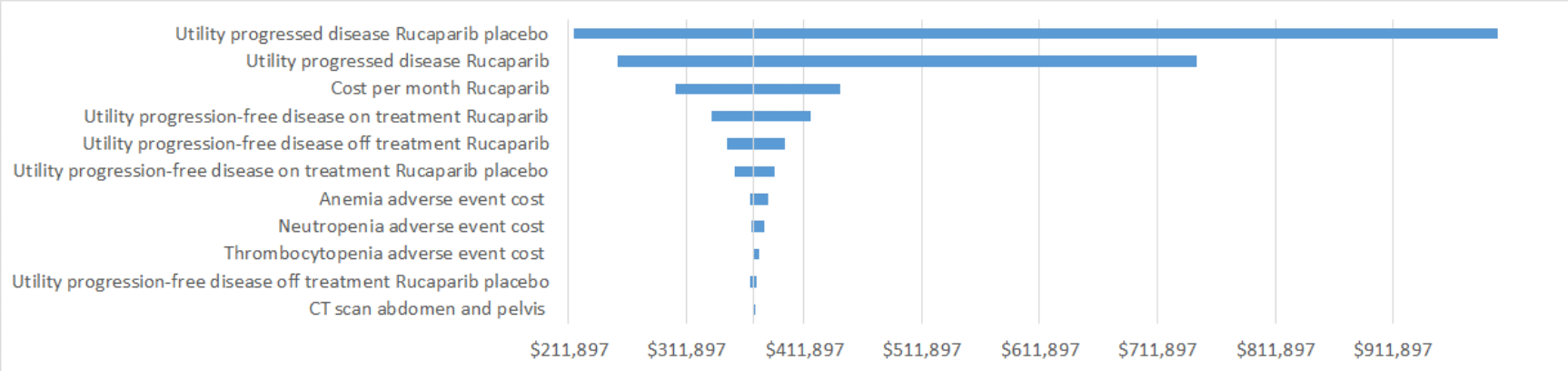
Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Cost per Month Rucaparib	$233,562	$361,823	$10,207	$15,121
Utility Progressed Disease Rucaparib	$253,735	$351,135	0.37	0.62
Utility Progressed Disease PLD+C	$258,863	$341,766	0.37	0.62
Utility Progression-Free Disease on Treatment Rucaparib	$268,045	$329,647	0.72	0.82
Neutropenia Adverse Event Cost	$262,854	$301,326	$1.48	$77,892
Utility Progression-Free Disease on Treatment PLD+Cs	$288,738	$313,675	0.75	0.83
Duration Of Treatment (Median Months) PLD+C	$287,420	$310,725	2.41	12.30
Price per Course of Treatment (Monthly) PLD+C	$288,071	$300,514	$2,643	$3,915
Anemia Adverse Event Cost	$292,488	$303,346	$5.02	$38,830
Thrombocytopenia Adverse Event Cost	$286,290	$296,483	$3.39	$57,182
Hand, Foot, Mouth Disease Adverse Event Cost	$288,529	$296,173	$6.85	$19,482

Figure E2. Olaparib – gBRCAm Versus Placebo in Maintenance Therapy for Platinum-Sensitive Disease



Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility Progressed Disease - Second Subsequent Therapy Olaparib Placebo	$226,093	$538,641	0.52	0.77
Utility Progressed Disease - Second Subsequent Therapy Olaparib	$259,709	$443,977	0.52	0.77
Cost per Month Olaparib	$284,913	$367,302	$10,015	$14,837
Utility Progression-Free Disease on Treatment Olaparib	$295,162	$362,271	0.72	0.82
Utility Progressed Disease - First Subsequent Therapy Olaparib Placebo	$291,926	$358,440	0.58	0.84
Utility Progressed Disease - First Subsequent Therapy Olaparib	$296,539	$362,987	0.58	0.84
Utility Progression-Free Disease off Treatment Olaparib	$305,454	$346,304	0.66	0.76
Utility Progression-Free Disease on Treatment Olaparib Placebo	$309,992	$338,838	0.66	0.76
Utility Progression-Free Disease off Treatment Olaparib Placebo	$321,565	$326,587	0.66	0.76
Anemia Adverse Event Cost	$323,481	$326,756	$5	$38,830
CT Scan Abdomen and Pelvis	$322,778	$325,590	$433	$642.1541

Figure E3. Rucaparib – gBRCAm Versus Placebo in Maintenance Therapy for Platinum-Sensitive Disease



Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility Progressed Disease Rucaparib Placebo	$216,897	$1,000,613	0.55	0.80
Utility Progressed Disease Rucaparib	$253,990	$745,123	0.55	0.80
Cost per Month Rucaparib	$302,876	$442,209	$10,207	$15,121
Utility Progression-Free Disease on Treatment Rucaparib	$333,334	$417,356	0.72	0.82
Utility Progression-Free Disease off Treatment Rucaparib	$346,940	$395,775	0.66	0.76
Utility Progression-Free Disease on Treatment Rucaparib Placebo	$352,574	$386,531	0.66	0.76
Anemia Adverse Event Cost	$366,210	$381,503	$5.02	$38,830
Neutropenia Adverse Event Cost	$367,197	$378,500	$1.49	$77,892
Thrombocytopenia Adverse Event Cost	$368,076	$374,003	$3.40	$57,182
Utility Progression-Free Disease off Treatment Rucaparib Placebo	$366,387	$371,874	0.66	0.76
CT Scan Abdomen and Pelvis Cost	$367,802	$370,688	$433.49	$642.15

Probabilistic Sensitivity Analysis Results

A multivariate probabilistic sensitivity analysis was conducted to assess the impact of varying multiple inputs on the model outputs. Appendix Table E11 describes the percentage of simulations that were cost-effective at different willingness-to-pay thresholds.

Table E11. Probabilistic Sensitivity Analysis Results

Intervention	% Cost-Effective at $50,000/QALY	% Cost-Effective at $100,000/QALY	% Cost-Effective at $150,000/QALY	% Cost-Effective at $200,000/QALY	% Cost-Effective at $250,000/QALY
Recurrent BRCA-Mutated Population					
Olaparib vs PLD + C (4th Line)	0.10%	1.70%	52.50%	93.70%	99.30%
Rucaparib vs PLD + C (3rd Line)	0.00%	0.00%	0.00%	0.40%	13.00%
Maintenance Therapy for Platinum-Sensitive Disease					
Olaparib (gBRCA) vs Olaparib Control (gBRCA)	0.00%	0.00%	0.00%	1.70%	12.80%
Niraparib (gBRCA) vs Niraparib Control (gBRCA)	0.00%	0.00%	0.20%	8.00%	30.80%
Niraparib (non-gBRCA) vs Niraparib Control (Non-gBRCA)	0.00%	0.00%	0.00%	0.00%	0.50%
Rucaparib (gBRCA) vs. Rucaparib Control (gBRCA)	0.00%	0.00%	0.10%	2.60%	15.00%

Appendix F. Evidence Tables

Table F1. Recurrent Ovarian Cancer with a Deleterious BRCA Mutation

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Olaparib						
Domcheck SM Gynecol Oncol. 2016 (Study 42) Not rated for quality	Multicenter Non-Randomized Phase II	Olaparib (n=193) Oral Olaparib at 400mg bid (capsule formation) monotherapy until disease progression or other Olaparib discontinuation were met; dose reductions (to 200 or 100 mg bid) were allowed if toxicity occurred	Patients with ovarian cancer with documented progressive or recurrent disease according to RECIST v1.1 or Gynecologic Cancer Intergroup CA 125 criteria, either during or within 6 months of completion of their most recent platinum-based chemotherapy regimen; patients could also be platinum sensitive but considered not suitable for further platinum therapy	*Patients with ≥3 prior lines of chemotherapy (n=137)* **Median age, yr (range)** 58 (35-79) **ECOG PS=1, n (%)** 52 (38.0) **gBRCA mutation status, n (%)** *BRCA1*: 106 (77.4) *BRCA2*: 30 (21.9) Both: 1 (0.7) **Prior chemotherapy regimens, n (%)** 3 Lines: 41 (29.9) 4 Lines: 26 (19.0) 5 Lines: 24 (17.5) ≥6 Lines: 46 (33.6) Platinum sensitive: 39 Platinum resistant: 81 Platinum refractory: 14	*Patients with ≥3 prior lines of chemotherapy (n=137)* **Median PFS, m** 6.7 Platinum Sensitive - 9.4 Platinum Resistant - 5.5 **ORR, n (%)** 46 (34) Platinum Sensitive/Resistant: 18 (46) / 24 (30) **Median DoR, m (95% CI)** 7.9 (5.6–9.6) Platinum Sensitive/Resistant: 8.2 (5.6–13.5) / 8.0 (4.8–14.8	*Patients with ≥3 prior lines of chemotherapy (n=137)* **AEs ≥3, n (%)** Fatigue: 10 (7) Anemia: 31 (20) Abdominal pain: 13 (8) Dyspnea: 6 (4) *Gamma-glutamyltransferase: 16 (9) **Treatment-related Death (overall population):** 6 (3) **Discontinuation due to AE (overall population):** 9 (5)

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Kaufman B J Clin Oncol. 2015[22] (Study 42) Not rated for quality	Multicenter Non-Randomized Phase II Patients were enrolled and treated between February 21, 2010, and July 31, 2012	Olaparib (n=298) Oral Olaparib at 400mg bid (capsule formation) monotherapy until disease progression; dose reductions (to 200 or 100 mg bid) and dose interruptions were permitted if toxicity occurred	Age ≥18 years; g*BRCA1*/2m; ≥1 measurable or evaluable lesion according to RECIST; ECOG PS 0 to 2; ovarian cancer resistant to prior platinum; breast cancer with ≥3 chemo regimens for metastatic disease; pancreatic cancer with prior gemcitabine treatment; or prostate cancer with progression on hormonal and one systemic therapy	*Patients with ovarian cancer (n=193)* **Median age, yr (range)** 57 (29-79) **ECOG PS=1/2, n (%)** 69 (35.8)/10 (5.2) **gBRCA mutation status, n (%)** *BRCA1*: 148 (76.7) *BRCA2:* 44 (22.8) Both: 1 (0.5) **Mean Prior chemotherapy regimens** 4.3 **Measurable disease at baseline, n (%)** 167 (86.5)	*Patients with ovarian cancer (n=193)* **Median PFS, m** *7.0* **Median OS, m** *16.6* **Tumor Response Rate, n (%) (95% CI)** 60 (31.1) (24.6-38.1*)* **CR, n (%)** 6 (3) **PR, n (%)** 54 (38) **Median DoR, days** 225	*Patients with ovarian cancer (n=193)* **AEs ≥3, n (%)** Anemia: 36 (18.7) Abdominal Pain: 14 (7.3) Fatigue: 12 (6.2) Vomiting: 5 (2.6) *Overall Population (n=298)* **Treatment-related Death, n** 2 **Discontinuation due to AE, n (%)** 11 (3.7)

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Rucaparib						
Kristeleit SR ESMO 2016[28] (Study 10 and ARIEL2) ***CONFERENCE PRESENTATION*** Not rated for quality	**ARIEL2** RCT Phase II Open Label **Study 10** Non-Randomized Phase I/II Open Label RCT	Rucaparib (n=106) ≥1 dose of oral rucaparib 600 mg twice daily until disease progression or discontinuation	Received ≥2 prior chemotherapies, including ≥2 platinum-based regimens; deleterious germline BRCA or somatic BRCA mutation *Pooled data from ARIEL2 (n=64) and Study 10 (n=42) analyzed as Efficacy Population.	**Age, median (range)** 59 (33–84) **ECOG PS, n (%)** 0: 65 (61.3) 1: 41 (38.7) **BRCA mutation, n (%)** Germline: 88 (83.0) Somatic: 13 (12.3) Origin Uncertain: 5 (4.7) **BRCA, n (%)** 1: 67 (63.2) 2: 39 (36.8) **Platinum response, n (%)** Sensitive: 79 (74.5) Resistant: 20 (18.9) **Prior lines of chemotherapy, n (%)** 2 therapies: 41 (38.7) ≥3 therapies: 65 (61.3)	**Median PFS, m (95% CI)** Efficacy Population: 10.0 (7.3–12.5) **ORR, n (%)** Efficacy population: 57 (53.8) ARIEL2: 32 (50.0) Study 10: 25 (59.5) **CR, n (%)** Efficacy Population: 9 (8.5) ARIEL2: 5 (7.8) Study 10: 4 (9.5) **PR, n (%)** Efficacy Population: 48 (45.3) ARIEL2: 27 (42.2) Study 10: 21 (50.0) **Median DoR, m, (95% CI)** Efficacy Population: 9.2 (6.6-11.7)	*AE ≥3, n (%) 229 (60.7) **TEAE ≥3, n (%)** 177 (46.9) **Discontinuation, n (%)** d/t AEs: 50 (13.3 d/t TAE: 30 (8.0) **TEAEs ≥3, n (%)** Nausea: 19 (5.0) Asthenia/fatigue: 41 (10.9) Increased ALT/AST: 41 (10.9) Anemia: 94 (24.9) Thrombocytopenia: 17 (4.5) **AE leading to death:** 9 (2.4) AEs reported for safety population (n=377) consisted of all ovarian cancer patients who received 600 mg BID

ORR	n(%)	95% CI
≥2 prior Plat	53.8	(43.8–63.5)
Plat Sens	65.8	(54.3–76.1)
Plat Resistant	25.0	(8.7–49.1)

<table>
<tr><th>Author & Year of Publication (Trial Name) Quality Rating</th><th>Study Design and Duration of Follow-up</th><th>Interventions (n) & Dosing Schedule</th><th>Major Inclusion & Exclusion Criteria</th><th>Patient Characteristics</th><th>Key Outcomes</th><th>Harms</th></tr>
<tr>
<td>Konecny EG SGO 2017[23]

(ARIEL2)

CONFERENCE PRESENTATION

Not rated for quality</td>
<td>RCT
Phase II
Open Label</td>
<td>1) Rucaparib (n=134)

≥1 dose of oral rucaparib 600 mg twice daily until disease progression or discontinuation</td>
<td>Diagnosis of ovarian cancer (inclusive of primary peritoneal and fallopian tube cancer);
ECOG PS 0–1

Analysis of subpopulation of Part 1 (n=41) and Part 2 (n=93) of ARIEL2 consisting of patients with germline/somatic BRCA mutations</td>
<td>Age, median (range)
60 (33–82)

ECOG PS, n (%)
0: 68 (50.7)
1: 66 (49.3)

BRCA mutation, n (%)
Germline: 78 (58.2)
Somatic: 23 (17.2)

BRCA, n (%)
1: 86 (64.2)
2: 48 (35.8)

Platinum response, n (%)
Sensitive (No Intervening tx): 57 (42.5)
Sensitive (Intervening tx): 14 (10.4)
Resistant: 49 (36.6)

Prior chemotherapies, n (%)
2 therapies: 14 (10.4)
≥3 therapies: 102 (76.1)</td>
<td>Median PFS, m (95% CI)
Plat Sensitive (immediate prior tx=plat):
12.7 (9.0–14.7)
Plat Sensitive (immediate prior tx=non-plat):
7.4 (3.7–11.4)
Plat Resistant:
7.3(5.5–7.7)

<table>
<tr><th colspan="2">ORR, %</th></tr>
<tr><td>Overall/Plat Sens</td><td>70</td></tr>
<tr><td>2 Prior Lines/Plat Sens</td><td>86</td></tr>
<tr><td colspan="2">≥3 prior lines</td></tr>
<tr><td>Plat Sensitive (immediate prior tx-plat)</td><td>52</td></tr>
<tr><td>Plat Sensitive (immediate prior tx=non-plat)</td><td>43</td></tr>
<tr><td>Plat Resistant</td><td>25</td></tr>
</table>

<table>
<tr><th colspan="2">Median PFS in Plat Sensitive Subgroup, m</th></tr>
<tr><td>PFI ≥18mo</td><td>25.1</td></tr>
<tr><td>PFI ≥12mo</td><td>16.9</td></tr>
<tr><td>gBRCA</td><td>12.8</td></tr>
<tr><td>sBRCA</td><td>12.7</td></tr>
</table>
</td>
<td>AEs ≥3, (%)
Nausea: 5
Vomiting: 5
Anemia: 29
Asthenia/fatigue: 10
ALT/AST increased: 10
Thrombocytopenia: 7

Treatment-emergent discontinuation d/t AEs, %
13

Treatment-emergent AEs led to dose reductions, %
49</td>
</tr>
</table>

Table F2. Maintenance Therapy for Platinum-Sensitive Disease

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Niraparib						
Mirza MR N Engl J Med 2016 (ENGOT-OV16/NOVA)[91] (NOVA) Good quality	RCT Double-blind Phase III Median duration of follow-up at data cutoff: 16.9 m	1) Niraparib gBRCA QD (n=138) 2) Niraparib Non gBRCA QD (n=234) 3) Placebo gBRCA (n=65) 4) Placebo Non gBRCA (n=116) Niraparib (300 mg QD) or placebo once daily in 28-day cycles	Age ≥18 years; Histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer; platinum sensitive; ≥2 prior lines of platinum therapy; CR or PR to most recent platinum therapy	**Age, median (range)** 1) 57 (36–83) 2) 63 (33–84) 3) 58 (38–73) 4) 61 (34–82) **ECOG PS= 0/1, n (%)** 1) 91 (65.9)/47 (34.1) 2) 160 (68.4)/74 (31.6) 3) 48 (73.8)/17 (26.2) 4) 78 (67.2)/38 (32.8) **≥ 3 Prior chemotherapy regimens, n (%)** 1) 67 (48.6) 2) 79 (33.8) 3) 35 (53.8) 4) 38 (32.8) ***BRCA1/BRCA2*, %** 1) 61.6/37.0 2) 66.2/27.7 3 &4) NA	**Median PFS, m** 1) 21.0 2) 9.3 3) 5.5 4) 3.9 1 & 3) HR=0.27; 95% CI 0.17-0.41 2 & 4) HR=0.45; 95% CI, 0.34- 0.61 **Median TFST, m** 1) 21.0 2) 11.8 3) 8.4 4) 7.2 **Median PFS, m** Niraparib HRD+/wBRCA: 9.3 Placebo HRD+/wBRCA: 3.7 HR= 0.38; 95% CI, 0.23-0.63 Niraparib HRD+/Somatic BRCAm: 20.9 Placebo HRD+/Somatic BRCAm: 11.0 HR=0.27; 95% CI, 0.08 -0.90	*AEs ≥3, n (%)* **Thrombocytopenia** Niraparib: 124 (33.8) Placebo: 1 (0.6) **Anemia** Niraparib: 93 (25.3) Placebo: 0 **Neutropenia** Niraparib: 72 (19.6) Placebo: 3 (1.7) **Fatigue** Niraparib: 30 (8.2) Placebo: 1 (0.6) **Hypertension** Niraparib: 30 (8.2) Placebo: 4 (2.2) **Discontinuation d/t AEs, n** 1) 17 2) 33 3) 1 4) 2

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Olaparib						
Ledermann J N Engl J Med 2012[24] (Study 19) Fair quality	RCT Double-blind Phase II	1) Olaparib, 400 mg BID (n=136) 2) Placebo (n=129) Olaparib was administered twice daily or matching placebo within 8 weeks after completion of last dose of platinum-based chemotherapy Patients continued assigned treatment until objective disease progression, as defined by RECIST guidelines, provided they did not need to discontinue (any grade 3 or 4 adverse event for >28 d)	Inclusion: ≥18 yrs of age; recurrent ovarian or fallopian tube cancer or primary peritoneal cancer with high grade (2 or 3) serous features/component; platinum-sensitive (defined by an objective response to a previous platinum - based therapy for >6 months); completed ≥2 courses of platinum-based chemotherapy; most recent regimen induced an objective response as defined by the RECIST guidelines; *BRCA1/2* mutation not required	**Median age, yrs (range)** 1) 58.0 (21-89) 2) 59.0 (33-84) **Primary tumor location, n (%)** *Ovary* 1) 119 (87.5) 2) 109 (85.4) **Median previous chemo regimens, n (range)** 1) 3 (0-11) 2) 3 (2-8) **Median previous platinum-based chemo regimens, n (range)** 1) 2 (0-7) 2) 2 (2-8) **gBRCA (1 or 2), n (%)** 1) 31 (22.8) 2) 28 (21.7) **Negative BRCA, n (%)** 1) 18 (13.2) 2) 20 (15.5)	**Median PFS, months** 1) 8.4 2) 4.8 *Hazard ratio: 0.35; 95% CI (0.25-0.49); p<0.001* **Median time to progression, months** 1) 8.3 2) 3.7 *Hazard ratio: 0.35; 95% CI (0.25-0.47); p<0.001* **ORR, n (%)** 1) 7/57 (12) 2) 2/48 (4) OR: 3.36; 95% CI (0.75-23.71); p=0.12 **Median OS, months** 1) 29.7 2) 29.9 *HR: 0.94; 95% CI (0.63-1.39)* *P=0.75*	**Incidence of Grade 3/4 AEs, %** 1) 35.3 2) 20.3 **Grade 3/4 AEs, n (≥5%)** *Nausea* 2) 8 (6.3) *Fatigue* 1) 9 (6.6) 2) 8 (6.3) *Anemia* 1) 7 (5.1) **Dose interruptions due to AEs, %** 1) 27.9 2) 8.6 **Dose reductions due to AEs, %** 1) 22.8 2) 4.7 **Discontinuations due to AEs, n** 1) 3 2) 1

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Ledermann J Lancet Oncol 2014[27] (Study 19) Fair quality	*See Ledermann J N Engl J Med 2012 (Study 19)* Data cutoff: Nov 26, 2012 (85% overall survival data maturity)	1) Olaparib, 400 mg BID (n=136) 2) Placebo (n=129) Olaparib was administered twice daily or matching placebo within 8 weeks after completion of last dose of platinum-based chemotherapy Patients continued assigned treatment until objective disease progression, as defined by RECIST guidelines, provided they did not need to discontinue (any grade 3 or 4 adverse event for >28 d)	*See Ledermann J N Engl J Med 2012 (Study 19)*	*See Ledermann J N Engl J Med 2012 (Study 19)* **Patients with BRCA mutation** Olaparib: n=74 Placebo: n=62 **Patients with wild-type BRCA** Olaparib: n=57 Placebo: n=61	*All patients* **Median OS, mo (95% CI)** 1) 29.8 (27.2-35.7) 2) 27.8 (24.4-34.0) *HR: 0.88 (95% CI, 0.64-1.21); p=0.44* *Patients with BRCA mutation* **Median PFS, mo (95% CI)** 1) 11.2 (8.3-NC) 2) 4.3 (3.0-5.4) *Hazard ratio: 0.18; 95% CI, 0.10-0.31; p<0.0001* **Median OS, mo (95% CI)** 1) 34.9 (29.2-NC) 2) 31.9 (23.1-40.7) *Hazard ratio: 0.73; 95% CI, 0.45-1.17; p=0.19* *Patients with wild-type BRCA mutation* **Median PFS, mo (95% CI)** 1) 7.4 (5.5-10.3) 2) 5.5 (3.7-5.6) *HR: 0.54; 95% CI, 0.34-0.85; p=0.0075* **Median OS, mo (95%CI)** 1) 24.5 (19.8-35.0) 2) 26.2 (22.6-33.7) *HR:0.99; 95% CI, 0.63-1.55; p=0.96*	*Patients with BRCA mutation* **Patients with any Grade ≥3 AE, n (%)** 1) 28 (38) 2) 11 (18) **Grade ≥3 AEs, n (%)** *Fatigue* 1) 5 (7) *Anemia* 1) 4 (5)

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Ledermann JA Lancet Oncol 2016[26] (Study 19) Fair quality	*See Ledermann J N Engl J Med 2012 (Study 19)* Data cutoff: Sep 30 2015 (77% overall survival data maturity)	1) Olaparib, 400 mg BID (n=136) 2) Placebo (n=129) Olaparib was administered twice daily or matching placebo within 8 weeks after completion of last dose of platinum-based chemotherapy Patients continued assigned treatment until objective disease progression, as defined by RECIST guidelines, provided they did not need to discontinue (any grade 3 or 4 adverse event for >28 d)	*See Ledermann J N Engl J Med 2012 (Study 19)*	*See Ledermann J N Engl J Med 2012 (Study 19)*	*Total population* **Median OS, months (95% CI)** 1) 29.8 (26.9-35.7) 2) 27.8 (24.9-33.7) *HR: 0.73 (95% CI 0.55-0.96); p=0.025* **TFST, HR (95% CI)** *0.39; 95% CI (0.29-0.51)* *p<0.0001* **Median TSST, HR (95% CI)** *0.52; (95% CI 0.39-0.68); p<0.0001* *Patients with BRCAm* **Median OS, months (95% CI)** 1) 34.9 (29.2-54.6) 2) 30.2 (23.1-40.7) *HR: 0.62 (95% CI, 0.41-0.94); p=0.025* **TFST, HR (95% CI)** *0.32; 95% CI (0.22-0.48); p<0.0001* **TSST, HR (95% CI)** *0.41; 95% CI (0.28-0.62); p<0.0001* *Patients with BRCAwt* **Median OS, months (95% CI)** 1) 24.5 (19.8-35.0) 2) 26.6 (23.1-32.5) *HR: 0.83 (95% CI, 0.55-1.24); p=0.37* **TFST, HR (95% CI)** *0.45 (95% CI, 0.30-0.66); p<0.0001* **TSST, HR (95% CI)** 0.63 (95% CI, 0.43-0.94); p=0.023	*See Ledermann J N Engl J Med 2012 (Study 19)* **Discontinuation due to AEs, n (%)** 1) 8 (6) 2) 2 (2) **Grade ≥3 AE, n (≥5%)** *Fatigue* 1) 11 (8) *Anemia* 1) 8 (6) **Dose reductions due to AEs, n (%)** 1) 34 (25) 2) 5 (4)

<table>
<tr><th>Author & Year of Publication (Trial Name) Quality Rating</th><th>Study Design and Duration of Follow-up</th><th>Interventions (n) & Dosing Schedule</th><th>Major Inclusion & Exclusion Criteria</th><th>Patient Characteristics</th><th>Key Outcomes</th><th>Harms</th></tr>
<tr>
<td>Ledermann JA
Br J Cancer 2016[88]

(Study 19)

Fair quality</td>
<td>See Ledermann J N Engl J Med 2012 (Study 19)

Data cutoff: June 30 2010</td>
<td>1) Olaparib, 400 mg BID (n=136)
2) Placebo (n=129)

Olaparib was administered twice daily or matching placebo within 8 weeks after completion of last dose of platinum-based chemotherapy

Patients continued assigned treatment until objective disease progression, as defined by RECIST guidelines, provided they did not need to discontinue (any grade 3 or 4 adverse event for >28 d)</td>
<td>See Ledermann J N Engl J Med 2012 (Study 19)</td>
<td>See Ledermann J N Engl J Med 2012 (Study 19)

BRCAm, n
1) 64
2) 53

gBRCAm, n
1) 45
2) 37</td>
<td>
<table>
<tr><td>Overall</td><td>BRCAm</td><td>gBRCAm</td></tr>
<tr><td colspan="3">TOI, n (%)</td></tr>
<tr><td colspan="3">Improved</td></tr>
<tr><td>1)23 (20)
2)20 (18)</td><td>1)16 (25)
2)10(18.9)</td><td>1)12(26.7)
2)3 (8.1)</td></tr>
<tr><td colspan="3">Worsened</td></tr>
<tr><td>1)16(13.9)
2)20 (18)</td><td>1)7 (10.9)
2)10(18.9)</td><td>1)4 (8.9)
2)9(24.3)</td></tr>
<tr><td colspan="3">No change</td></tr>
<tr><td>1)72(62.6)
2)67(60.4)</td><td>1)38(59.4)
2)30(56.6)</td><td>1)27 (60)
2)22(59.5)</td></tr>
<tr><td colspan="3">FOSI, n (%)</td></tr>
<tr><td colspan="3">Improved</td></tr>
<tr><td>1)20(17.1)
2)17(14.8)</td><td>1)14(21.2)
2)9 (16.1)</td><td>1)12(26.1)
2)5 (12.8)</td></tr>
<tr><td colspan="3">Worsened</td></tr>
<tr><td>1)20(17.1)
2)21(18.3)</td><td>1)11(16.7)
2)9 (16.1)</td><td>1)6 (13)
2) 9 (23.1)</td></tr>
<tr><td colspan="3">No change</td></tr>
<tr><td>1)74(63.2)
2)74(64.3)</td><td>1)39(59.1)
2)36(64.3)</td><td>1)26(56.5)
2)23(59.0)</td></tr>
<tr><td colspan="3">FACT-O, n (%)</td></tr>
<tr><td colspan="3">Improved</td></tr>
<tr><td>1)24(21.1)
2)21(18.9)</td><td>1)17 (27)
2)11(20.8)</td><td>1)13(28.9)
2)4 (10.8)</td></tr>
<tr><td colspan="3">Worsened</td></tr>
<tr><td>1)20(17.5)
2)24(21.6)</td><td>1)10(15.9)
2)14(26.4)</td><td>1)6 (13.3)
2)12(32.4)</td></tr>
<tr><td colspan="3">No change</td></tr>
<tr><td>1)68(59.6)
2)63(56.8)</td><td>1)35(55.6)
2)26(49.1)</td><td>1)25(55.6)
2)19(51.4)</td></tr>
</table>
In this study, there were no statistically significant or clinically relevant differences in HRQol b/w treatment arms on TOI, FACT-O, and FOSI assessments
</td>
<td>See Ledermann J N Engl J Med 2012 (Study 19)</td>
</tr>
</table>

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Matulonis UA Gynec Oncol 2015[87] (Study 19) ***CONFERENCE ABSTRACT*** Not rated for quality	*See Ledermann J N Engl J Med 2012 (Study 19)*	1) Olaparib, 400 mg BID (n=136) 2) Placebo (n=129) Olaparib was administered twice daily or matching placebo within 8 weeks after completion of last dose of platinum-based chemotherapy Patients continued assigned treatment until objective disease progression, as defined by RECIST guidelines, provided they did not need to discontinue (any grade 3 or 4 adverse event for >28 d)	*See Ledermann J N Engl J Med 2012 (Study 19)* Given maintenance treatment with the oral PARPi inhibitor led to a significant improvement in PFS was proven, this study sets out to prove the hypothesis that the treatment of PARPi after disease progression confounded the OS results. Therefore, this study was an additional analysis of OS that didn't include patients from sites where at least one patient received post-progression treatment with a PARPi	*See Ledermann J N Engl J Med 2012 (Study 19)* *PARPi sites excluded (additional analysis)* **Overall Population** Olaparib: 103 Placebo: 95 **gBRCAm Population** Olaparib: 41 Placebo: 24	*Overall Population* **Events** 1) 58 2) 59 **Median, months** 1) 29.8 2) 26.6 *HR (95% CI)* *0.80 (0.55-1.16)* *P=0.243* *gBRCAm Population* **Events** 1) 21 2) 11 **Median, months** 1) 32.9 2) 30.2 *HR (95% CI)* *0.74 (0.35-1.64)* *P=0.444*	*See Ledermann J N Engl J Med 2012 (Study 19)*

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Matulonis U Cancer 2016[86] (Study 19) Fair quality	*See Ledermann J N Engl J Med 2012 (Study 19)*	1) Olaparib, 400 mg BID (n=74) 2) Placebo (n=62)	*See Ledermann J N Engl J Med 2012 (Study 19)* To investigate whether the OS results from Study 19 may have been confounded by the post progression use of PARP inhibitors, we conducted an exploratory post hoc analysis of OS that, to control for treatment switching, excluded all patients from the sites where at least 1 patient received post progression treatment with a PARP inhibitor with the RPSFT approach.	*See Ledermann J N Engl J Med 2012 (Study 19)* *PARPi sites excluded (additional analysis)* **Total gBRCAm Population** n=97 **gBRCAm Population** Olaparib: 57 Placebo: 40	*PARPi excluded after progression BRCAm* **Median OS, m** Olaparib: 34.9 Placebo: 26.6 HR=0.52; 95% CI 0.28-0.97 **Deaths, total patients (%)** Olaparib: 28:57 (49.1) Placebo: 22:40 (55.0)	*See Ledermann J N Engl J Med 2012 (Study 19)*

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Hodgson EJOC 2015[131] (Study 19) ***CONFERENCE ABSTRACT*** Not rated for quality	*See Ledermann J N Engl J Med 2012 (Study 19)*	1) Olaparib, 400 mg BID (n=136) 2) Placebo (n=129) Olaparib was administered twice daily or matching placebo within 8 wks after completion of last dose of platinum-based chemotherapy Patients continued assigned treatment until objective disease progression, as defined by RECIST guidelines, provided they did not need to discontinue (any grade 3 or 4 adverse event for >28 d)	*See Ledermann J N Engl J Med 2012 (Study 19)*	*See Ledermann J N Engl J Med 2012 (Study 19)*	*Progression Free Survival HR (95% CI)* **BRCAwt**: 0.48 (0.18-1.27) p=0.14 for Olaparib vs placebo in 36 patients with BRCAwt HRD tumors **BRCAwt with no detectable loss-of-function mutations in DNA repair genes**: 0.71 (0.37-1.35) p=0.30	*See Ledermann J N Engl J Med 2012 (Study 19)*

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Pujade-Lauraine Lancet Oncol 2017[30] (SOLO2) Good quality	RCT Double-blind Phase III	1) Olaparib, 300 mg BID (n=196) 2) Placebo (n=99) Olaparib tablets were taken orally twice daily until disease progression or until investigator deemed patient no longer benefiting from tx; dose reduction to 250 mg and 200 mg was permitted if toxicity occurred	*BRCA1/2* mutation; platinum-sensitive relapsed ovarian cancer; ≥2 prior lines of platinum therapy; CR or PR to most recent platinum therapy	**Median age, yr (IQR)** 1) 56 (51-63) 2) 56 (49-63) **Primary tumor location, n (%)** *Ovarian* 1) 164 (84) 2) 86 (87) **Prior platinum regimens, n (%)** *2 lines* 1) 110 (56.1) 2) 62 (63) *3 lines* 1) 60 (31) 2) 20 (20) *≥4 lines* 1) 25 (12.8) 2) 17 (17.2)	*By investigator assessment* **Median PFS, months (95% CI)** 1) 19.1 (16.3-25.7) 2) 5.5 (5.2-5.8) *HR: 0.30; 95% CI (0.22-0.41)* *p<0.0001* *Sensitivity analysis using BICR* **Median PFS, months (95% CI)** 1) 30.2 (19.8-not calculable) 2) 5.5 (4.8-5.6) *HR: 0.25; 95% CI (0.18-0.35)* *p<0.0001* **Overall Survival (24% maturity)** *HR: 0.80; 95% CI (0.50-1.31)* *P=0.43* TOI over first 12 months ***Change from baseline, adjusted mean (95% CI)*** 1) -2.90 (-4.13 to -1.67) 2) -2.87 (-4.64 to –1.10) ***Estimated difference in adjusted means****= -0.03; 95% CI (-2.19 to 2.13)* *p=0.98* **Median TFST, HR (95% CI)** *0.28; 95% CI (0.21-0.38), p<0.0001* **Median TSST, HR (95% CI)** 0.37; 95% CI (0.26-0.53), p<0.0001	**Any AE grade≥3, n (%)** 1) 71 (36) 2) 18 (18) **Any AE leading to dose reduction, n (%)** 1) 49 (25) 2) 3 (3) **Discontinuation due to AEs, n (%)** 1) 21 (11) 2) 2 (2) **Any AE w/outcome of death** 1) 1 (0.5) 2) 0 **MDS/AML events, n** 1) 4 2) 4 *Grade ≥3* **Anemia, n (%)** 1) 38 (19) 2) 2 (2) **Thrombocytopenia, n (%)** 1) 2 (10) 2) 1 (1)

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Friedlander J Clin Oncol 2017[89] (SOLO2) ***CONFERENCE ABSTRACT*** Not rated for quality	RCT Double-blind Phase III	1) Olaparib, 300 mg (n=196) 2) Placebo (n=99) Tablets were taken orally twice daily until objective radiological disease progression (per RECIST) as assessed by the investigator; dose reduction to 250mg and 200mg is permitted if toxicity occurred	See Pujade-Lauraine SGO 2017[25]	See Pujade-Lauraine SGO 2017[25]	*From baseline to 12 months* **HQROL in TOI score** 1) -3.1 2) -2.9 95% CI: -2.4, 2.1 p=0.88 **Time without symptoms of disease or toxicity, months** 1) 13.5 2) 7.2 95% CI: 2.9, 8.6 p<0.001 **Quality-adjusted PFS, mean months** 1) 14.0 2) 7.3 95% CI: 5.0, 8.5 p<0.0001	See Pujade-Lauraine SGO 2017[25]

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Ledermann J Clin Oncol 2017[132] (SOLO2) ***CONFERENCE ABSTRACT*** Not rated for quality	RCT Double-blind Phase III	1) Olaparib, 300 mg (n=196) 2) Placebo (n=99) Tablets were taken orally twice daily until objective radiological disease progression (per RECIST) as assessed by the investigator; dose reduction to 250mg and 200mg is permitted if toxicity occurred	See Pujade-Lauraine SGO 2017[25]	See Pujade-Lauraine SGO 2017[25]	See Pujade-Lauraine SGO 2017[25]	**Grade 3-4 AEs, n (%)** **Nausea:** 1) 5 (3) **Vomiting**: 1) 5 (3) 2) 1 (1) **Fatigue/asthenia:** 1) 8 (4) 2) 2 (2) **Anemia:** 1) 38 (19) 2) 2 (2) **Neutropenia:** 1) 10 (5) 2) 4 (4) **Discontinuation, n (%)** **Nausea:** 1) 1 (1) **Anemia:** 1) 6 (3) **Neutropenia:** 1) 3 (2) **Dose interruptions, %** 1) 45 2) 18 **Dose reductions, %** 1) 25 2) 3

Author & Year of Publication (Trial Name) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Rucaparib						
Coleman Lancet 2017[29] (ARIEL3) Good quality	RCT Double-blind Phase III	1) Rucaparib, 600 mg (n=375) 2) Placebo (n=189) 600 mg BID oral rucaparib or placebo until disease progression, death, or other reason for discontinuation. Dose reductions (decrements of 120 mg) for ≥grade 3 or persistent grade 2 AE. Discontinuation for toxicity-related treatment interruption >14 consecutive days	Age ≥18 years; platinum-sensitive; high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma; ≥2 previous platinum-based regimens; CR or PR to last platinum-based regimen; CA125 < upper limit of normal; ECOG PS=0-1; adequate organ function. Exclusion for symptomatic or untreated central nervous system metastases, anticancer therapy ≤14 days of starting study, previous PARP inhibitor.	**Median age, yr (IQR)** 1) 61.0 (53.0-67.0) 2) 62.0 (53.0-68.0) **Diagnosis, n (%)** *Epithelial ovarian* 1) 312 (83%) 2) 159 (84%) **Prior platinum regimens, n (%)** *2 lines* 1) 236 (63%) 2) 126 (67%) **BRCA, n (%)** *Germline* 1) 82 (22) 2) 48 (25) *Somatic* 1) 40 (11) 2) 16 (8) *Wild-type/LOH high* 1) 245 (65)/106 (28) 2) 123 (65)/52 (28)	*By investigator assessment* **Median PFS, months (95% CI)** ***BRCAm*** 1) 16.6 (13.4-22.9) 2) 5.4 (3.4-6.7) *HR: 0.23; 95% CI (0.16-0.34)* *p <0.0001* ***HRD*** 1) 13.6 (10.9-16.2) 2) 5.4 (5.1-5.6) *HR: 0.32; 95% CI (0.24-0.42)* *p<0.0001* ***Intention-to-treat*** 1) 10.8 (8.3-11.4) 2) 5.4 (5.3-5.5) *HR: 0.36; 95% CI (0.30-0.45)* *p<0.0001* *See also: sensitivity analyses using BICR* **Time to worsening FOSI-18, BRCAm** *HR: 1.24 95% CI (0.8-1.86)* **ORR (ITT) in patients with measurable disease at baseline, n (%)** 1) 26 (18) 2) 5 (8)	**Any AE grade≥3, n (%)** 1) 209 (56) 2) 28 (15) **Any AE leading to dose reduction, n (%)** 1) 203 (55) 2) 8 (4) **Discontinuation due to AEs, n (%)** 1) 50 (13) 2) 3 (2) **Any AE w/outcome of death** 1) 6 (2) 2) 2 (1) **MDS/AML, n (%)** 1) 3 (1) 2) 0 *Grade ≥3, n (%)* **Anemia** 1) 70 (19) 2) 1 (1) **Neutropenia** 1) 25 (7) 2) 2 (1)

Appendix G. Public Comments

This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on September 14, 2017 in St. Louis, MO. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. A video recording of all comments can be found here, beginning at minute 1:38:40.

Josefa Briceno, MD, AstraZeneca
Medical Director for Ovarian Cancer

Josefa Briceno, a physician trained in surgical oncology who currently holds the position of Medical Director, US Medical Affairs for Ovarian Cancer, spoke on behalf of AstraZeneca.

AstraZeneca supports patient-centric value assessments, but notes they should be constructed to ensure they do not limit appropriate therapeutic options for patients. Given that women have advanced disease and poor prognosis at the time of diagnosis, providing therapeutic options for patients is important. PARP inhibitors are meaningful to women affected by ovarian cancer, and it is important that patients continue to have access to FDA-approved therapies that can provide significant clinical benefit.

From a clinical perspective, just two years ago, women diagnosed with ovarian cancer had limited treatment options. PARP inhibitors as a class represent major innovation in ovarian cancer. Recent FDA approvals of new indications for PARP inhibitors, including maintenance therapy, have given women in earlier disease settings additional treatment options, and shown the value of these therapies.

At AstraZeneca, we appreciate and understand that we are called to continually demonstrate the value of our products, and that is why we participated in the public meeting. We note the meaningfulness of the current evaluation will likely be limited since new data will emerge in the near future. Finally, we ask each member of the voting panel to consider all implications of their votes, which could include and impact patient access to FDA-approved drugs and patient treatment options.

Mohan Bala, Tesaro
Vice President, Health Economics Outcomes Research

TESARO is a biopharmaceutical company devoted to providing transformative therapies to people bravely facing cancer. In the Phase 3 NOVA trial, patients treated with niraparib had significantly longer progression free survival compared to control regardless of germline BRCA mutation status. This represents a meaningful benefit to patients when the consequence of progression is another round of chemotherapy.

We have significant concerns regarding the cost-effectiveness modeling that forms the basis of ICER's value assessment. The results of the cost-effectiveness assessment conducted by ICER are almost entirely dependent on assumptions made regarding overall survival data. Further, ICER seems to have applied a ratio of medians to extrapolate OS data from a different drug to niraparib. However, cost-effectiveness modeling requires use of means rather than medians. When TESARO applied the ratio of means to calibrate, the cost effectiveness ratios for niraparib versus surveillance fell within acceptable thresholds. The fact is that we will not know the true cost-effectiveness ratio as calculated using ICER's approach until the OS data mature.

TESARO believes that this is a fundamental limitation of the analytical approach. Many new promising oncology therapies are on the horizon which, like niraparib, have the potential to transform the treatment paradigm of many cancers. Many of them will be approved based on PFS or ORR with immature survival data. We believe that to advance the value conversation a fundamentally new approach is needed to appropriately value endpoints such as PFS and ORR in cancer that is not overly reliant on uncertain assumptions.

Lisa Schlager, FORCE
Vice President Community Affairs & Public Policy

FORCE has grave concerns about ICER's report. There are significant differences in the study populations. The comparative studies are not equivalent to the stated PARP patient populations in regard to number of prior treatments, platinum sensitivity, or gBRCA status.

The economic analysis has key gaps. Certain cost models and resulting value conclusions are questionable, including: inadequate cost estimates for grade 3/4 adverse events, managing side effects beyond the worst adverse events, platinum regimen reactions, infusion administration, and Avastin related bowel perforation and thrombotic events. The analysis also fails to account for lost productivity due to side effects from traditional therapies.

ICER neglects to capture the value of PARPis to patients, families and society; especially in the

BRCAm community. The PARPi study participants' median age suggests that over half were younger, working and/or caring for children. Women on PARPis note fewer interruptions of daily living activities and higher quality-of-life versus chemotherapy. PARPis may seem costly but offer important benefits given the development investment, productivity savings, improved quality-of-life, promise of new, non-chemotherapy treatment options, and potential for improvement. These costs should have equal weight to those borne by payers.

We believe this report is premature. The conclusions are misleading and will likely result in limiting use, coverage and reimbursement. This will set back progress and send a discouraging message to all involved. Head-to-head studies will cost many more years, lives, and dollars. In the interim, ovarian cancer patients need continued PARPi access.

Seana Roubinek
Ovarian Cancer Survivor and Advocate

I carry the BRCA1 gene mutation. In 2011, I had a prophylactic oophorectomy to reduce my risk but the surgery revealed ovarian cancer instead.

I drove 2 hours each way for weekly treatment for 18 straight weeks. I felt like **time** was slipping away and **life** was passing me by during those 4 1/2 months of weekly treatment.

Many women travel this journey of one chemotherapy after another and when one stops working, another is introduced until there are no more available drugs. During my 2nd recurrence, IV chemotherapy had stopped working so I was then eligible for olaparib.

Ovarian cancer survival statistics showed that I likely would not live long enough to see my son graduate from high school. In my mind, taking olaparib might let me see his graduation day.

Taking olaparib at home allowed me to continue with my daily routine. This new therapy was a game-changer for me.

My cancer initially responded very well but it eventually progressed after several months. Olaparib allowed me to witness and participate in life events that I would not have seen had I not tried it.

The financial cost of PARP inhibitors is high but there is **no way** to put a price on the hope that they bring to women like me. We need to have as many treatment options as possible. I ask you to strongly consider the quality of our lives in the setting of a disease that robs us of so much.

Chad Ramsey, OCRFA
Vice President, Policy

OCRFA seeks to ensure that patients are able to access medications when they and their physicians feel they are appropriate, and that innovation in drug development can thrive. To that end, we have some concerns about this report that can be delineated as follows: the analysis is premature, it could chill innovation, and threaten treatment availability.

Patients and clinical experts have spoken clearly: this report is premature. PARP inhibitors represent a new class of medicine for patients, many of whom face multiple recurrences and have few effective therapeutic options. PARP trials are ongoing and research has yet to be completed. No overall survival data yet exist, and the report undervalues the importance of progression-free survival among patients. This endpoint is especially relevant with PARP inhibitors, which offer most patients good quality of life. Data in this report could be used by payers to deny patients access to these medicines.

The financial strain of treatment can be significant for patients, yet research and development done by the companies that developed PARP inhibitors is considerable. PARP inhibitors hold great promise for ovarian cancer patients, and continued investment by industry is essential to realizing this promise. This report could lead to a devaluation of this breakthrough class of drugs, and could have a chilling effect on innovation.

It is essential that patients and physicians have access to all of the PARP inhibitors reviewed in this report. As more data comes available, we strongly urge ICER to consider updating this assessment in the future.

Jill Holdren
Ovarian Cancer Survivor

As a BRCA1 mutation carrier and survivor of ovarian cancer, I have grave concerns about ICER's final report on PARP inhibitors (PARPis).

Throughout the report, ICER emphasizes the difficulty of assessing PARPis for value and cost-effectiveness because of a lack of both outcomes and comparator data. But despite that deficit, ICER finalized a report that will likely restrict women's access to these important therapies.

Despite hearing to the contrary directly from patients, ICER appears to dismiss Progression-Free Survival (PFS) as an important outcome for patients. PFS is the most important clinical outcome to many women with advanced ovarian cancer.

ICER's decision to forgo a societal analysis of lost productivity due to "the typically advanced age" of ovarian cancer patients seriously undervalues the impact of PARPis. In women with gBRCA mutations, ovarian cancer frequently occurs in women in their 30s and 40s, when we are immersed in careers, civic engagement, and parenting. The decades of productivity lost when young women do not have effective treatment options has a meaningful impact on society that must be considered.

ICER's "final" report is incomplete and premature. Its analysis is based on inadequate data and mischaracterizes key points that impact the value assessment. It lacks meaningful patient input – input that should be integrated into the analysis and change the value calculus. This report will adversely impact the ability of very ill women to access critical drugs and the ability of scientists to further study, understand, and improve on their function and value.

Appendix H. Conflict of Interest Disclosures

Table H1 through H3 contain conflict of interest (COI) disclosures for all participants at the September 14, 2017 public meeting of the Midwest CEPAC.

Table H1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosure
Jonathan Campbell, PhD	University of Colorado	None
Geri Cramer, BSN, MBA	ICER	None
Sonya Khan, MPH	ICER	None
R. Brett McQueen, PhD	University of Colorado	None
Molly Morgan	ICER	None
Daniel Ollendorf, PhD	ICER	None
Steve Pearson, MD, MSc	ICER	None
Lipika Samal, MD	Harvard Medical School	None
Patricia Synnott, MALD, MS	ICER	None

Table H2. Midwest CEPAC Panel Member COI Disclosures

Name	Organization	Disclosure
Eric Armbrecht, PhD	St Louis University Center for Health Outcomes Research	*
Ryan Barker, MSW, MPPA	Missouri Foundation for Health	*
Donald Casey, MD, MPH, MBA	Medecision; IPO4Health; Jefferson College of Population Health; Rush Medical College	*
Rena Conti, PhD	University of Chicago	*
Jill Johnson, Pharm. D.	University of Arkansas for Medical Sciences	*
Bill Moore, PhD	REACH Healthcare Foundation	*
Scott Micek, Pharm. D.	St. Louis College of Pharmacy	*
Rachel Sachs, JD, MPH	Washington University in St. Louis	*
Shumei Yun, MD, PhD	MO Department of Health and Senior Services	*

*No conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from relevant health care manufacturers or insurers.

Table H3. Policy Roundtable Participant Disclosures

Name	Affiliation	Disclosure
Harold Carter	Express Scripts	Express Scripts employee
Susan Leighton	Ovarian Cancer Survivor	None
Betsy Neisner	Ovarian Cancer Survivor	None
Matthew Powell, MD	Washington University at St. Louis	Research grants from Clovis, Tesaro and AstraZeneca
Andrea Wahner Hendrickson, MD	Mayo Clinic	None