Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value

Draft Evidence Report

July 12, 2017

Prepared for

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About ICER

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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
HRR	Homologous recombination repair
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

An executive summary will be provided as part of the full Evidence Report.

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.[3] 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).[4,5]

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.[6]

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), 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.

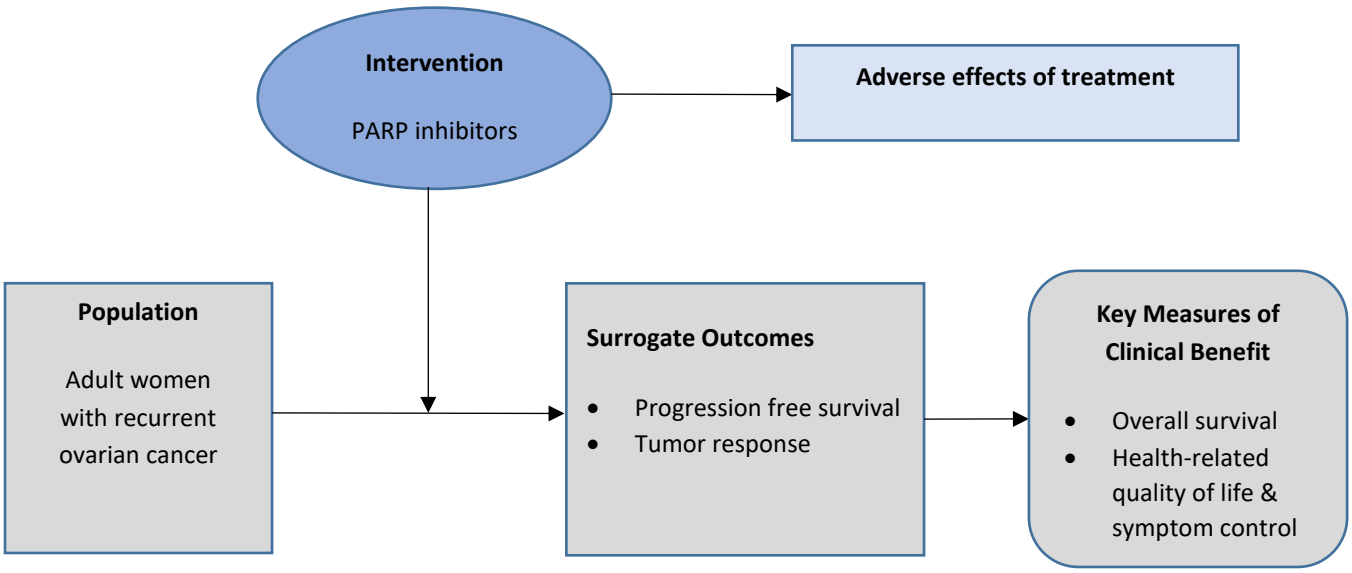
Scope of the Assessment

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.

Figure 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 BRCA mutation and who have relapsed after initial cytoreductive surgery and multiple subsequent lines of chemotherapy.

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.

Key Subpopulations

Recurrent, BReast CAncer gene (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 (4^{th}-line or later treatment, based on FDA indication)
- Rucaparib (3^{rd}-line or later treatment, based on FDA indication)

Maintenance therapy for platinum-sensitive disease:

- Olaparib
- Niraparib

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. In the maintenance population, the ARIEL3 trial of rucaparib has announced topline results, but at the time of this writing there are no published manuscripts or conference proceedings available.

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.[7] Treatment recommendations for epithelial ovarian cancer are also applied to fallopian tube cancer and primary peritoneal cancer.[7] 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).[8] 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.[6] High-grade serous tumors represent a particularly challenging subtype, with 5-year survival rates currently estimated at 35-40%.[9]

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, topotecan, pegylated liposomal doxorubicin, docetaxel).[3,10,11] Platinum-based agents, first cisplatin and later carboplatin, have been used to treat ovarian cancer since the 1970s.[12] In the 1990s, the addition of paclitaxel to the chemotherapy regimen was found to improve overall survival.[13] 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.[14]

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.[13,15] 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.[13,15]

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.[16] 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.[11,17] 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.[18] Several genetic mutations have been associated with HRD, including but not limited to, germline and somatic *BRCA1* and *BRCA2* mutations.[18] *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.[19] 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).[20] 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.[21]

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.[22] 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.[18] 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.[23] However with major repair pathways disabled, cancer cells cannot efficiently respond to damage, causing the cells to die.[24,25]

Initially, PARP inhibitors were evaluated in patients with germline *BRCA1* and *BRCA2* mutations.[26-28] 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.[18]

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 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 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)[29]	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	400 mg BID (PO) until disease progression or unacceptable toxicity	Capsules:ǂ 50 mg	December 19, 2014	$13,679
Rucaparib (Rubraca®, Clovis Oncology)[30]	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	$13,941
Niraparib (Zejula™, Tesaro, Inc.)[31]	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 June 8, 2017); ǂ a tablet formulation of olaparib is currently under evaluation in the SOLO2 trial*

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.[32] Olaparib has been combined with cediranib, a VEGF inhibitor.[32] 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.[33]

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.[18] 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.[18]

PARP inhibitors are also being studied as maintenance immediately following first-line therapy.[34,35] Researchers and patients are hopeful that introducing a PARP inhibitor earlier in the treatment pathway will improve chances of survival in recurrent ovarian cancer.[6,36]

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

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[37]

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[37]

Platinum-refractory – Ovarian cancer patients that experience persistent or progressive disease during initial platinum based therapy[38]

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[39]

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[39]

BRCA wild-type (BRCAwt) – A tumor which does not possess either a deleterious or suspected deleterious germline or a somatic BRCA mutation[39]

Homologous recombination deficiency (HRD) – Homologous recombination (HR) is a pathway that allows repair of double-stranded DNA breaks.[40] 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.[39]

Advanced Disease – Stage IIIC or Stage IV ovarian cancer[4,5]

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).[41]

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.[42]

Progression-free survival (PFS) – Time from a pre-defined date, such as randomization, to tumor progression or death.[42] The major trials of PARP inhibitors in a maintenance population designate PFS as the primary outcome.

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.

Recurrence/Relapse – Cancer that returns after a period of improvement and/or a time in which it could not be detected.[43]

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 bigger. 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.[43] In ovarian cancer, RECIST guidelines are often used to determine PFS endpoints.[44]

> **Measurable disease** – The presence of at least one measurable lesion (minimum size of 10mm by CT scan).[45]
>
> **Complete response** – The disappearance of all target lesions. Any pathological lymph nodes must have decreased to < 10 mm.[45] In ovarian cancer, the tumor marker CA-125 assists with determining complete or partial response.[45]
>
> **Partial response** – At least a 30% decrease in the sum of diameters of target lesions from baseline.[45]
>
> **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.[45]

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).[46-50] 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.[51] 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.[52] 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.[53]

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[8]

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 (in patients who have not received bevacizumab before), 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 (in patients who have not received bevacizumab prior); 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. NCCN specifically stated that it does not recommend olaparib as maintenance therapy.

European Society for Medical Oncology (ESMO) Guidelines[54]

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.[55]

National Institute for Health and Care Excellence (NICE) Guidelines[56]

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.[57]

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., "BRCA-mutated recurrent disease")

2. Olaparib and niraparib 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 treatment 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, results for key outcomes were stratified by line of therapy, BRCA mutation, 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 patients with a deleterious BRCA mutation who have had multiple prior lines of chemotherapy, 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 was 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.[58] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[59] 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

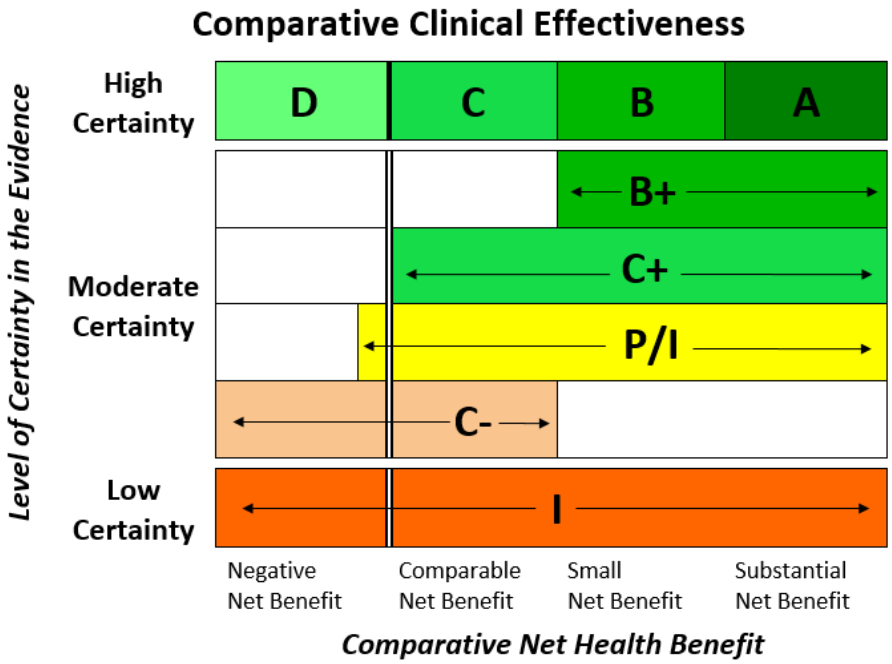
Data on relevant outcomes were summarized in evidence tables (see Appendix F) and are synthesized qualitatively in the text of the report. Differences in entry criteria, study populations, outcome measurements, and other factors precluded direct and indirect quantitative assessment of each PARP inhibitor's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

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) 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.[60]

Figure 2. 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).[61]

We included 11 references for maintenance treatment of platinum-sensitive disease; these references related to three placebo-controlled trials of olaparib and niraparib. Topline results from the ARIEL3 trial of rucaparib maintenance therapy were reported via a press release dated June 19, 2017; however, no publications or publicly-available presentations of ARIEL3 were identified by the time of report posting. While we summarized topline results from this study in Appendix D, these results do not currently have sufficient detail to be formally included in our evidence review.

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 BRCA-mutated recurrent 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, five were conference abstracts and/or presentations. In total, we identified only two 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 study (NOVA trial of niraparib maintenance) 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 analyses of rucaparib 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 2.

Table 2. Comparability of Available Data Assessing Olaparib vs. 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.[36,62,63]; *platinum status unknown in 2% of patients

Maintenance Therapy for Platinum-Sensitive Disease

Key differences were also noted in the major studies of olaparib and niraparib 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 with platinum-sensitive recurrent ovarian cancer, who 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. 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). An ongoing confirmatory trial of the phase II olaparib study has restricted enrollment to patients with germline BRCA mutations.

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. In addition, PFS was evaluated by blinded independent central review in the study of niraparib, while the olaparib 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 3.

Table 3. Comparability of Available Data Assessing Olaparib vs. Niraparib as Maintenance Therapy for Platinum-Sensitive Disease

	Study 19 (Phase II trial of Olaparib)	SOLO2 (Phase III trial of Olaparib)	NOVA (Niraparib)
Comparison Variables			
BRCA Mutation	All BRCA status (positive and negative) included. Retrospective BRCA mutation analysis included germline and somatic BRCA.	Only germline BRCA mutation included	Study designed with two cohorts: germline BRCA mutation and non-germline BRCA mutation (included somatic and wild-type)
HRD Testing	None	None	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
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
RECIST Version	RECIST v 1.0	RECIST v 1.1	RECIST v 1.1
Quality of Life Instrument	FACT-O, FOSI and TOI	TOI	FOSI and EQ-5D
Dosing/Formulation	400 mg BID/Capsules	300 mg BID/Tablets	300 mg QD/Capsules

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 therapies regimens suggest survival gains 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).[62] 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.[63] 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. Clinical Outcome Summary of Olaparib in Recurrent Ovarian Cancer with a Deleterious BRCA Mutation

Key Study	Patient Characteristics	Outcomes‡
Study 42[62,63]	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;[62,63]

Overall survival

Improving overall survival (OS) and quality of life (QoL) are generally considered the most important goals of cancer therapy.[64,65] 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.[63]

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.[6] 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.[6]

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.[62] 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]).[62] 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.[6]

Objective response

Objective response rate (ORR) quantifies the proportion of patients whose best response was either complete or partial using RECIST v1.1 criteria.[45] 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.[62] 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).[62]

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 maintenance studies of olaparib are summarized in Table 5.

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.

The second RCT of olaparib, SOLO2, is an ongoing confirmatory Phase III trial, which is intended to replicate 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 are receiving a new tablet formulation dosed at 300 mg BID. In addition, SOLO2 only includes patients with a germline BRCA mutation. SOLO2's quality was not rated, as the study has not yet been published in a peer-reviewed journal.

Table 5. 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 BRCAm: 100% Median prior chemo: NR ≥3 Prior platinum: 41%	Olaparib tablet (n=196) PFS: 30.2 m OS (immature): NR		Placebo (n=99) PFS: 5.5 m OS (immature): NR	

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.[66] 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).[67] 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.[68] Overall survival data are not yet available from the SOLO2 study.[69] Data are expected later this year.

Progression-free survival

Both RCTs of olaparib indicate improved progression-free survival compared to placebo, especially in the presence of a deleterious BRCA mutation.[69-71] 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).[70] 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).[71]

Data from a conference presentation on 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).[69] These results differ from those in Study 19, most likely due to the inclusion of women with germline BRCA mutations only.

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).[70]

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).[72] 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.[72]

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).[69,73]

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 6. 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.[39] 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.[39,74]

Progression-Free Survival

Progression-free survival in the niraparib group was significantly longer than that in the placebo group across all populations studied ($p<0.001$).[39] 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).[74]

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).[39] 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).[75] HRD-positive women with wild-type BRCA mutation on niraparib had a median PFS of 9.3 months 3.7 months for placebo (HR 0.27; 95% CI, 0.08 to 0.90).[75] 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).[39]

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.[39]

Clinical Benefits of Rucaparib

Rucaparib for Recurrent, BRCA-Mutated Disease

Overall survival data for rucaparib is not yet available. Progression-free survival was approximately 10 months with rucaparib. While not a direct comparison, analyses of standard ovarian cancer treatments suggest 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.[76,77] 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.[77a] 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.[36]

The second reference we identified for rucaparib was an analysis of 106 patients 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.[76-78] Study 10 was a three-part, phase 1-2, open-label, single-arm study of rucaparib; phase 2 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.[36,76,78]

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

Table 7. Clinical Outcome Summary of Rucaparib in Recurrent Ovarian Cancer with a Deleterious BRCA Mutation

Key Studies	Patient Characteristics	Outcomes
ARIEL2[36] (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%Δ ORR (Platinum resistant): 25%Δ QoL: Not reported
Study 10/ARIEL2[78] (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; Δ 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.[36] 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.[6] 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) the third relapse.[6]

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).[36,78] 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).[78]

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

As mentioned previously, the ARIEL3 study released topline data in a press release on June 19, 2017, which provided preliminary evidence for rucaparib in a maintenance population. ARIEL3 was a double-blind, placebo-controlled Phase III trial of rucaparib versus placebo in 564 platinum-sensitive, ovarian cancer patients.[79] The trial enrolled women with both germline and somatic BRCA mutations as well as those without a BRCA mutation.[80] The primary outcome was investigator-assessed disease progression (progression-free survival) measured using RECIST version 1.1 every 12 weeks.[80] Secondary analyses included PFS assessed by blinded, independent central review (BICR), overall survival, and quality of life.[80] Because the press release contained limited data, and there are currently no publications or other public presentations of information, it was not abstracted or included in our evaluation for maintenance therapy. See Appendix D for clinically-relevant data.

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 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.[81] 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.[81-83] 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.[84] When combined with chemotherapeutic agents such as gemcitabine and carboplatin, grade 3-5 thrombocytopenia (40%) may also occur.[85] Nausea (73%) and fatigue (82%) of any grade are also common with bevacizumab combination therapy.[84,85]

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 relative safety of the new 300 mg dose formulation of olaparib, currently under evaluation in the SOLO2 trial, remains uncertain; however, a recent abstract presented at ASCO showed adverse events to be manageable with supportive treatment and dose reductions.[86]

Niraparib

Niraparib has a different toxicity profile from that of the other PARP inhibitors.[18] Approximately two-thirds of patients treated with niraparib had an adverse event leading to a dose reduction and 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).[74] The current FDA prescribing information for niraparib includes warnings for MDS/AML, bone marrow suppression, and cardiovascular effects.[31]

Rucaparib

Rucaparib safety information is primarily informed by data from the ARIEL2 trial. Toxicities related to rucaparib were similar to those of olaparib, although nearly half of the patients who participated in ARIEL2 experienced a dose reduction related to a treatment-emergent adverse event (49%).[36] 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.

Table 8. Adverse Events of Olaparib, Niraparib, and Rucaparib

	Olaparib[62,69-71‡]	Niraparib*[39]	Rucaparib*[36,77,78]
Any AE	96-99%	100%	100%
Any AE grade ≥3	35-55%	74%	61%
Any SAE	18-30%	30%	25%
Any AE leading to dose reduction	22-25%	67%	49%
Any AE leading to discontinuation of study treatment	2-11%	15%	13%
Any AE with outcome of death	0.5-3%	0	2%
Grade ≥3 Adverse Events			
Abdominal pain	2-8%	1%	2%
AST/ALT increased	2%	NR	12%
Anemia	5-20%	25%	22%
Fatigue	4-7%	8%	9%
Hypertension	NR	8%	NR
MDS/AML	1-2%	1%	0%
Nausea	1-3%	3%	4%
Neutropenia	4-5%	20%	8%
Thrombocytopenia	0.7-1%	34%	2%
Vomiting	2-3%	2%	2%

‡ Values for olaparib represent range of AEs reported in Study 42, Study 19, and SOLO2; *NOVA trial of niraparib and ARIEL2 trial of rucaparib reported treatment-emergent adverse events; NR=not reported

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 and pegylated liposomal doxorubicin in recurrent ovarian cancer in 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.[85,87] 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.[85,88,89] 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.[90] 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."[91] 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.[39]

There are also specific uncertainties regarding the evidence for individual PARP inhibitors. 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 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 the confirmatory, ongoing SOLO2 trial are 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 is focused exclusively on patients with a deleterious or suspected deleterious germline BRCA mutation and is evaluating 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 are receiving 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.[91] Although there is insufficient evidence to determine if there is a dose-response relationship for efficacy, the incidence of anemia does appear to be related to dose. Therefore, the safety and tolerability of the new formulation is still uncertain, and it is currently unclear how much the SOLO2 trial will replicate the benefit-risk profile observed in Study 19.[91]

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 salvage therapy 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 salvage therapy in patients with recurrent ovarian cancer and a deleterious BRCA mutation 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 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	I

Summary and Evidence Ratings in Recurrent Ovarian Cancer with a Deleterious BRCA Mutation and Multiple Prior Chemotherapies

There are substantial uncertainties about the efficacy of olaparib and rucaparib as therapies for patients with recurrent ovarian cancer, a deleterious BRCA mutation, and multiple prior lines of therapy.

Olaparib

- There are no comparative studies of 4th-line or later olaparib; it is uncertain if olaparib confers an efficacy 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.

For patients with a deleterious BRCA mutation, we have low certainty of the net health benefit provided by 4th-line or later olaparib. Due to the lack of direct comparative evidence with other salvage therapies, we cannot be certain whether olaparib provides a survival benefit over alternative treatments, is comparable, or possibly even inferior. We believe that olaparib has a better safety profile than chemotherapy and may provide better quality of life, although HrQoL evidence is not yet available. We therefore consider the evidence on olaparib in this population to be "promising but inconclusive" (P/I).

Rucaparib

- There are no comparative studies of 3rd-line or later rucaparib; it is uncertain if rucaparib confers an efficacy 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.

For patients with a deleterious BRCA mutation and either platinum sensitivity or platinum-resistance, we have low certainty that 3rd-line or later rucaparib confers a net health benefit over alternative therapeutic regimens. Due to the lack of direct comparative evidence with other salvage therapies, we cannot be certain whether rucaparib provides a survival and/or quality of life benefit over alternative treatments, is comparable, or possibly even inferior. We therefore deem the evidence for rucaparib in this population also to be promising but inconclusive (P/I).

Niraparib

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

Summary and Evidence Ratings in the Maintenance Therapy Population

There are some uncertainties about the safety and efficacy of olaparib and niraparib as maintenance therapy for platinum-sensitive patients with recurrent ovarian cancer with or without a deleterious or suspected deleterious BRCA mutation.

Olaparib

- 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.
- Overall surivival data from the Phase III study is anticipated later this year. Therefore, we are currently a 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. Quality of life reports for active medication were no worse than for placebo.

For women with platinum-sensitive recurrent ovarian cancer treated with more than two lines of chemotherapy and with a deleterious or suspected deleterious germline BRCA mutation, 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., observation alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

Niraparib

- Treatment with niraprib resulted in substantial improvements in progression-free survival compared to placebo. Benefits were seen in both arms 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 benefit in PFS in patients without such a mutation.
- Because there have been no published data on overall survival, we lack confidence 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. Quality of life reports for active medication were no worse than for placebo.

In patients with platinum-sensitive recurrent ovarian cancer treated with more than two lines of chemotherapy, 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., observation alone). Therefore, we assess the evidence to be "comparable or better" ("C+").

Rucaparib

The clinical study of rucaparib that is relevant to the maintenance population (ARIEL3) has only released topline data in a press release. We therefore consider the evidence for rucaparib in this population to be "insufficient" (I).

In all cases, overall survival benefits would have changed the evidence assessment for these therapies.

5. 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.[92] 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.[93b]

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.[14] 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

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

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 Mississippi to 44% in Rhode Island).[94] Testing rates are positively correlated with higher incomes, advanced education, and the number of physicians per 100,000 in the population.[94] 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.[3] Few effective treatment options exist in this space and treatment paradigms have not changed materially in the last 20 years.[95] 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.

6. Economic Analyses

6.1 Long-Term Cost Effectiveness

Overview

The aim of this analysis was to estimate the cost-effectiveness of the PARP inhibitors (olaparib, rucaparib, and niraparib) 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, progression-free survival time, life years, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios, using a payer/health-system perspective. 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, progressive, and death). We modeled the two populations of interest for this review as listed below, 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., observation only)
    - Niraparib (gBRCA) versus placebo
    - Niraparib (non-gBRCA) versus placebo

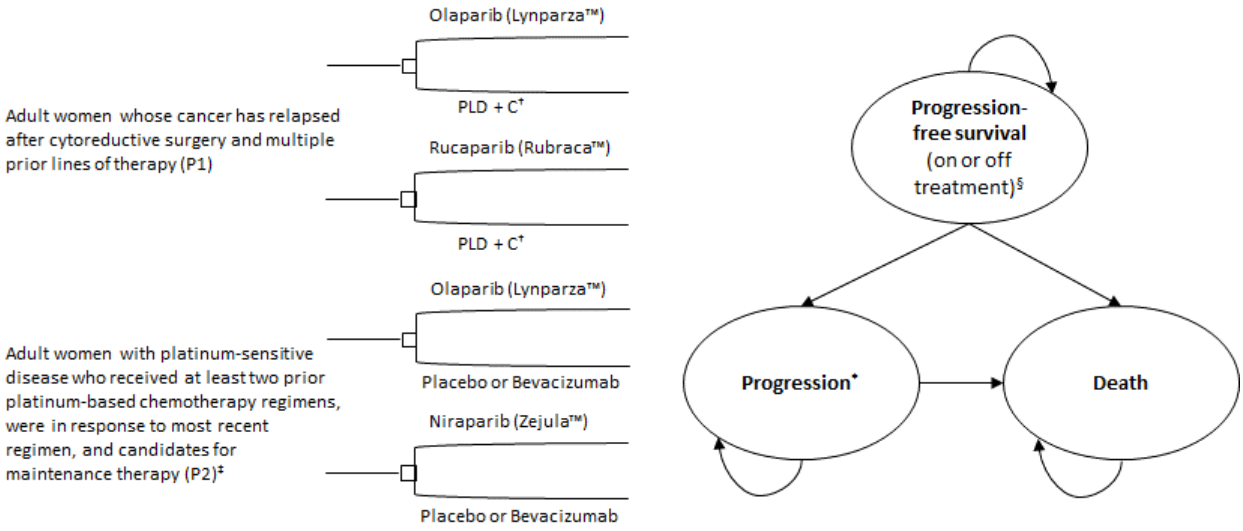
Importantly, given the issues of data incompatibility across drugs and studies highlighted in Section 4, we did not attempt to conduct any explicit or implied comparisons across PARP inhibitors. For this reason, our findings are organized by PARP inhibitor rather than population in the sections that 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, progressive, 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.[96] The transition probabilities were calculated based on survival functions derived from Kaplan-Meier curves. Statistical fitting methods allowed the extrapolation of the survival results beyond the observed time frame in clinical trials.

Figure 3. 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
‡ Niraparib was evaluated for both gBRCAmut and non-gBRCAmut subpopulations whereas olaparib was evaluated within a gBRCAmut sub-cohort only

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. The 15-year time horizon represents the shortened life-span observed in advanced ovarian cancer and is reflective of previous modeling analyses. The model was developed in Microsoft Excel.

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, see the impact inventory in Appendix Table E1. All future costs and outcomes were discounted 3% per year. The model was informed by several assumptions, which are detailed below in Table 10.

Table 10. 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 four populations 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. 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 and niraparib. Rates of discontinuation were identical and were based on olaparib trial data. The PFS survival curves remained unique to niraparib and olaparib.**	Discontinuation allows for on and off treatment modeling within the PFS health state. Cost is not applied to the proportion of patients in PFS who have discontinued treatment. The only available evidence on discontinuation was from olaparib trial data.
• **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

Niraparib and rucaparib were not included as interventions for the recurrent BRCA-mutated and maintenance populations respectively, because detailed published or otherwise publicly-available data were not yet available from ongoing RCTs. As noted in Section 4, top-line findings from the ARIEL3 trial of rucaparib for maintenance treatment are currently available only in press release form.

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 line of therapy). 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 and effectiveness defined by PFS.

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.

Cost Inputs

Drug Acquisition Costs

To calculate drug acquisition costs, we assumed a 10% discount from current WAC for the PARP inhibitors based on manufacturer input, as two of the PARP inhibitors are new to market and hence do not have reliable estimates of net price from the SSR database. We also assumed a 10% discount from current WAC for PLD+C, as PLD+C also did not have reliable estimates of net price in the SSR database (Table 11). The model utilized the lowest cost combination of tablets or capsules for each regimen. The range in dose was modeled based on observed trial utilization that incorporated any modifications to dosing based on adverse events.

For the price of bevacizumab, 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.[97] 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 WAC as of June 2017 to arrive at an estimated net price per unit. The derived discount for bevacizumab was 7%, which was then applied to the WAC for a net price of $6.90 per unit.

Table 11. Drug Wholesale Acquisition Parameters

Drug Cost Parameters	WAC per unit	WAC per month	Net price per unit	Net price per month	Reference
Olaparib price	$28.09	$13,679	$25.28	$12,311	Assumed 10% off WAC
Niraparib price	$163.89	$14,965	$147.50	$13,469	Assumed 10% off WAC
Rucaparib price	$114.50	$13,940	$103.05	$12,546	Assumed 10% off WAC
PLD + C price	$55.51	$3,610	$49.95	$3,249	Assumed 10% off WAC
Bevacizumab price (budget impact only)	$7.42	$11,145	$6.90	$10,365	SSR Health

** Price reflects the wholesale acquisition price listed on Red Book Online (Greenwood Village, CO: Truven Health Analytics. http://www.micromedexsolutions.com/. Accessed June 8, 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. 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. 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.[98,99] and used the same average weight to calculate treatment dosing for bevacizumab.

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, bevacizumab 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). [100,101] 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.

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.[102] 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 treatment comparators, as listed in Table 12.

Table 12. Grade 3/4 Adverse Events

	Olaparib (BRCA-mutated)[29]	Olaparib (maintenance)[29]	Rucaparib[30]	Niraparib[31†]	PLD + C[83]
Abdominal pain	8%	0%	3%	2%	*
Anemia	18%	4%	25%	25%	7.9%
Fatigue	8%	6%	11%	8%	7%
Hand-foot syndrome	*	*	*	*	24%
Hypertension	*	*	*	9%	*
Thrombocytopenia	3%	6%	5%	35%	15.9%
Leukopenia	*	*	*	7%	*
Nausea	3%	2%	5%	3%	5%
Neutropenia	7%	8%	5%	21%	35.2%
Proteinuria	*	*	*	*	*
Rash	*	0%	0.3%	0.5%	4.2%
Stomatitis	*	*	*	0.5%	8%
Vomiting	4%	4%	4%	2%	8%

*Not reported; †Evidence not split by gBRCA and non-gBRCA

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.[96] 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. Health state utilities were applied to the disease states of progression-free, progressed disease, and, if included, first and second subsequent therapies (Table 13). We assumed that health state utility values did not vary across the treatments after patients had progressed in the model. 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 13. 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]	0.79	0.75	0.83	0.024	Beta	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 (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]
Progressed disease [Niraparib]	0.68	0.55	0.80	0.065	Beta	Olaparib NICE HTA Submission[103] assumed avg of 1st & 2nd subsequent trtmt
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]

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.[106] 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 and niraparib 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 see 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.[107] 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, see 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 $139,114 with life-years gained and QALYs of 2.11 and 1.26, respectively (Table 14). At net prices, olaparib's estimated cost-effectiveness is $119,500 per QALY gained and $64,500 per life-year gained compared to PLD+C in 4th line or later use.

The use of olaparib for maintenance therapy resulted in total discounted costs of $205,470 with 3.64 life years and 2.64 QALYs gained. The higher cost of olaparib in this population is reflective of a longer progression-free interval than for treatment of recurrent, BRCA-mutated disease. At estimated net prices, the cost-effectiveness of olaparib versus placebo is estimated to be approximately $270,000 per life-year or QALY gained.

Table 14. Discounted Costs, Outcomes, and Incremental Results for Olaparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Recurrent BRCA-mutated population					
Olaparib	$96,082	$43,032	$139,114	2.11	1.26
PLD + C (4th line or later use)	$20,040	$41,229	$61,269	0.91	0.61
Incremental cost per outcome				$64,500/LYG	$119,500/QALY
Maintenance therapy for platinum-sensitive disease					
Olaparib – gBRCAm	$153,038	$52,432	$205,470	3.64	2.64
Placebo (Olaparib) – gBRCAm	$9,050	$46,474	$55,524	3.09	2.08
Incremental cost per outcome				$269,500/LYG	$267,000/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

Threshold analysis results for olaparib

Table 15 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. Discounts of 22% - 54% would be needed to meet thresholds of $50,000-$100,000 per QALY gained. Olaparib's price could be a premium on the current WAC for the BRCA-mutated population at a threshold of $150,000 per QALY gained, while a 49% discount would be required to achieve this threshold in the maintenance therapy population.

Table 15. Threshold Analysis Results

	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
Olaparib (recurrent BRCA-mutated)	$28.09	$13,679	$12.90	$21.81	$30.71	+9% (increase) - 54%
Olaparib (maintenance for platinum-sensitive)	$28.09	$13,679	$4.92	$9.60	$14.29	49% - 82%

Rucaparib

In the recurrent BRCA-mutated population, rucaparib had total discounted costs of $247,135 with discounted life-years gained and QALYs of 2.11 and 1.41, respectively (Table 16). 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 in 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 $301,000 per QALY gained respectively.

Table 16. Discounted Costs, Outcomes, and Incremental Results for Rucaparib

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	LYG	QALYs
Recurrent BRCA-mutated population					
Rucaparib	$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	0.81
Incremental cost per outcome				$218,000/LYG	$301,000/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

Threshold analysis results for rucaparib

Table 17 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. 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 51% - 77% would be needed to meet cost-effectiveness thresholds of $50,000-$150,000 per QALY gained.

Table 17. Threshold Analysis Results

	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	$13,679	$25.77	$41.18	$56.59	51% - 77%

Niraparib

In the gBRCA-mutated maintenance population, niraparib had total discounted costs of $144,130 with discounted life-years gained and QALYs of 3.64 and 2.60, respectively (Table 18). In the non-gBRCA-mutated maintenance population, niraparib had total discounted costs of $124,388 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 $316,000 and $275,000 per QALY and per LY 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 18. 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	$144,130	$60,479	$204,610	3.64	2.60
Placebo (Niraparib) – gBRCAm	$5,027	$46,474	$51,502	3.09	2.12
Incremental cost per outcome				$275,000/LYG	$316,500/QALY
Niraparib – non-gBRCAm	$124,388	$53,203	$177,592	2.59	1.84
Placebo (Niraparib) – non-gBRCAm	$5,200	$43,144	$48,344	2.59	1.77
Incremental cost per outcome				Not estimable	$1,942,000/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

Threshold analysis results for niraparib

Table 19 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 61% - 92% 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.

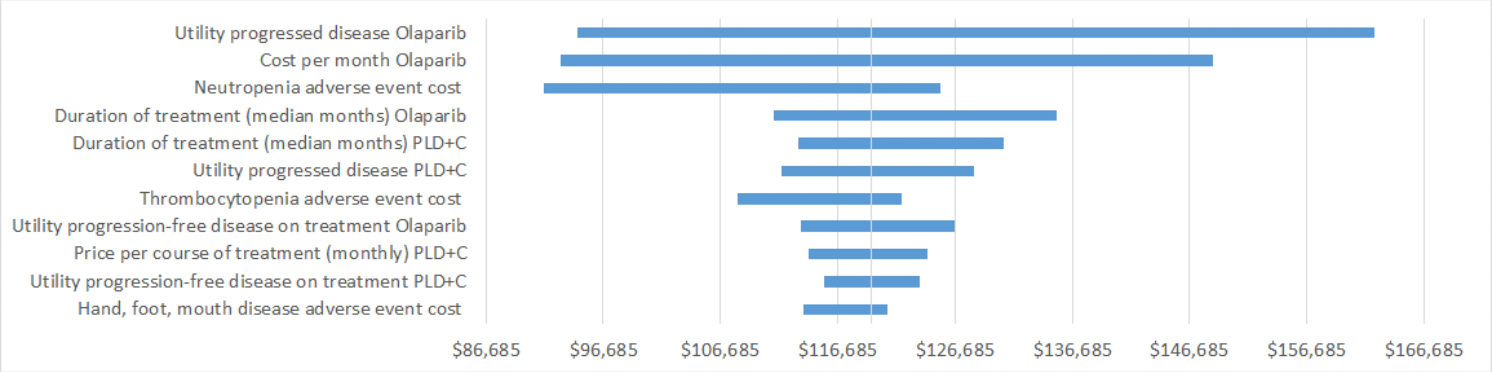
Table 19. Threshold Analysis Results

	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	$13.21	$38.41	$63.62	61% - 92%

One-Way Sensitivity Analysis Results

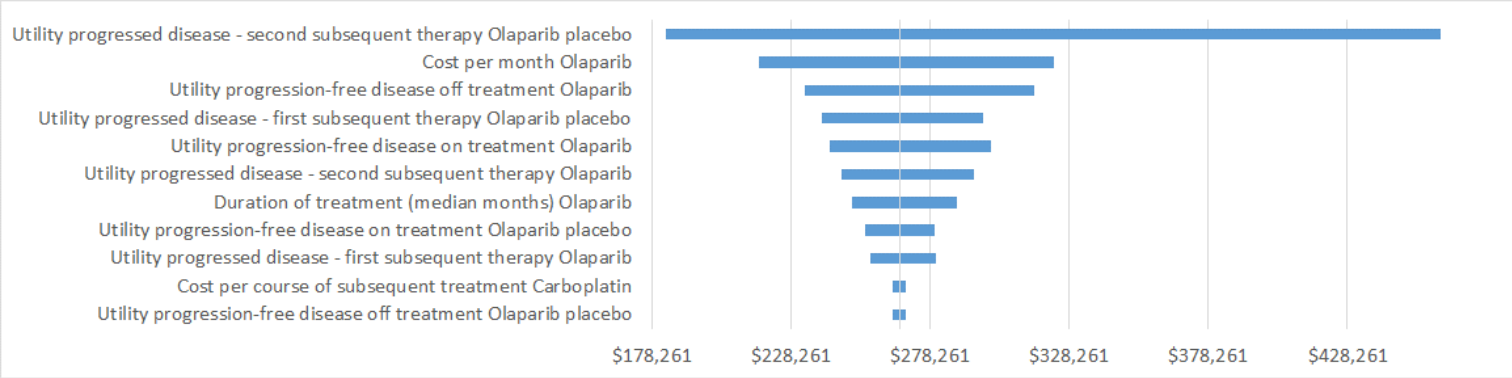
Illustrative one-way sensitivity analyses are presented in tornado diagrams (Figures 4 – 5) with tables to accompany the estimates. Major drivers of low and high ICER results for each comparison include utility values for progression and progression-free health states, cost per month of therapy, duration of treatment, and select adverse event costs. All other tornado diagrams are included in Appendix E.

Figure 4. Olaparib vs. 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	$94,510	$162,470	0.37	0.63
Cost per month Olaparib	$93,046	$148,650	$10,015	$14,837
Neutropenia adverse event cost	$91,685	$125,405	$2	$77,892
Duration of treatment (median months) Olaparib	$111,244	$135,414	3	24
Duration of treatment (median months) PLD+C	$113,309	$130,841	3	10
Utility progressed disease PLD+C	$111,861	$128,269	0.37	0.63
Thrombocytopenia adverse event cost	$108,135	$122,092	$3	$57,182
Utility progression-free disease on treatment Olaparib	$113,542	$126,644	0.72	0.82
Price per course of treatment (monthly) PLD+C	$114,189	$124,329	$2,643	$3,915
Utility progression-free disease on treatment PLD+C	$115,569	$123,717	0.75	0.83
Hand, foot, mouth disease adverse event cost	$113,812	$120,987	$7	$19,482

Figure 5. Olaparib vs. 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	$183,261	$461,747	0.52	0.77
Cost per month Olaparib	$217,010	$322,656	$10,015	$14,837
Utility progression-free disease off treatment Olaparib	$233,142	$315,765	0.66	0.76
Utility progressed disease - first subsequent therapy Olaparib placebo	$239,368	$297,395	0.58	0.84
Utility progression-free disease on treatment Olaparib	$242,410	$300,366	0.72	0.82
Utility progressed disease - second subsequent therapy Olaparib	$246,747	$293,904	0.52	0.77
Duration of treatment (median months) Olaparib	$250,523	$288,101	3	24
Utility progression-free disease on treatment Olaparib placebo	$255,004	$280,140	0.66	0.76
Utility progressed disease - first subsequent therapy Olaparib	$256,677	$280,628	0.58	0.84
Cost per course of subsequent treatment Carboplatin	$264,807	$269,525	$4,020	$5,956
Utility progression-free disease off treatment Olaparib placebo	$265,106	$269,387	0.66	0.76

Scenario and sensitivity analysis results

Results of scenario and sensitivity analyses are presented in Appendix E, Tables E6-E7. Combining gBRCA and non-gBRCA data for olaparib and niraparib in maintenance therapy resulted in higher cost-effectiveness estimates than in the base case for both PARP inhibitors. Similar results were found when using investigator-assessed PFS curves for olaparib and placebo. Use of the semi-Markov or partitioned survival method produced similar results (within 10%) and the same conclusion that other modelers have found (see Appendix Table E5).[106]

The probabilistic sensitivity analysis results are described in Appendix Table E9. For the majority of the thresholds, 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 an 87.3% chance of meeting a cost-effective threshold of $150,000 per QALY. All scenario and sensitivity analysis results are available in Appendix E, tables E6, E7, and E8.

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

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.[108] 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.[109] The base case analysis reported an estimated cost-effectiveness ratio of £79,953 ($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 ($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.[110] 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 2 clinical trial[70,71] of olaparib maintenance therapy in patients with BRCA-mutated platinum-sensitive recurrent ovarian cancer.[96] 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.

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 E, Table E4. In all circumstances, model-generated medians were within one month of those presented in the trial publications or other documentation.

6.2 Value-based Benchmark Prices

Value-based benchmark prices will be released in the revised Evidence Report, which will be released on or about August 30, 2017.

6.3 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 planned 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.[3] 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 (71,995) would be treated with at least two prior lines of chemotherapy and would go on to receive third-line treatment.[111] The estimated prevalence of gBRCA mutations (18%)[112] was used to calculate the estimated proportion of those patients who would be eligible for treatment with olaparib or rucaparib (12,959). Assuming equal distribution over five years, this resulted in an estimate of 2,592 eligible patients in the recurrent BRCA-mutated population in the US per year.

To estimate the number of patients potentially eligible for maintenance treatment, we used the prevalence of ovarian cancer in the US in 2014, which was estimated to be 222,060 cases.[3] To qualify for this population, 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.[113] Assuming that 18% of these patients would have gBRCA mutations,[112] we estimated that there would be approximately 1,630 gBRCA mutation and 7,440 non-gBRCA 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 displacing use of existing therapies with the new intervention. In this case, we assumed that olaparib and rucaparib would displace PLD+C as a common alterative treatment in the recurrent BRCA-mutated population. In the population receiving maintenance therapy for platinum-sensitive disease, we assumed that olaparib and niraparib 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 gBRCA mutation; for the non-gBRCA patients, these

proportions were assumed to be 67% for observation and 33% for bevacizumab. 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 20.

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 20. 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 22-24 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 15. 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 $31,600, and approximately $27,300 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $35,700 per patient using the unit price ($30.71) to achieve $150,000 per QALY to approximately $8,100 using the unit price ($12.90) 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 $44,600, and approximately $38,600 using the discounted WAC. Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $15,000 per patient using the unit price ($14.29) to achieve $150,000 per QALY to a cost savings of approximately $5,100 per patient using the unit price ($4.92) to achieve a $50,000 per QALY cost-effectiveness threshold.

Table 21. 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	$57,553	$53,202	$61,614	$47,822	$34,031
PLD+C (Discounted WAC Only)	$25,941				
Difference	$31,612	$27,261	$35,673	$21,881	$8,090
Maintenance Therapy for Platinum-Sensitive Disease (gBRCA)					
Olaparib	$71,126	$65,093	$41,503	$31,434	$21,364
Usual Care (75%)/ Bevacizumab (25%, Discounted WAC Only)	$26,512				
Difference	$44,614	$38,581	$14,991	$4,922	-$5,148†

†Indicates cost-saving; QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Rucaparib

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 (Table 22). Average potential budgetary impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $26,600 per patient using the unit price ($56.59) to achieve $150,000 per QALY to approximately $5,100 using the unit price ($25.77) to achieve a $50,000 per QALY cost-effectiveness threshold. As noted in the evidence review, published or otherwise publicly-available data on rucaparib for maintenance therapy are not yet available.

Table 22. 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	$93,841	$85,847	$53,416	$42,655	$31,895
PLD+C (Discounted WAC Only)	$26,827				
Difference	$67,013	$59,020	$26,589	$15,828	$5,067

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 23. 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 per-patient potential budgetary impact when using the WAC for niraparib was approximately $49,700, decreasing to approximately $43,700 when using the discounted WAC. Average potential budgetary impact at the cost-effectiveness threshold prices for the drug ranged from approximately $23,000 per patient using the unit price ($63.62) to achieve $150,000 per QALY to approximately $10,300 per patient using the unit price ($38.41) to achieve $100,000 per QALY. The unit price ($13.21) to achieve a $50,000 per QALY cost-effectiveness threshold was low enough that we estimated a cost savings of approximately $2,300 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 $40,000, and approximately $34,600 using the discounted WAC. The unit price ($1.37) 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 $13,500 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 23. 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	$75,225	$69,199	$48,509	$35,856	$23,203
Usual Care (75%)/ Bevacizumab (25%, Discounted WAC Only)	$25,527				
Difference	$49,698	$43,671	$22,982	$10,329	-$2,324†
Maintenance Therapy for Platinum-Sensitive Disease (non-gBRCA)					
Niraparib	$70,254	$64,852	$16,686	N/A	N/A
Usual Care (67%)/ Bevacizumab (33%, Discounted WAC Only)	$30,210				
Difference	$40,044	$34,642	-$13,523†	N/A	N/A

†Indicates cost-saving

N/A: not available, 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 24. 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.

Table 24. 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	12,959	2,592	$27,261	$171.7	19%
Rucaparib	12,959	2,592	$59,020	$387.1	42%
Maintenance Therapy for Platinum-Sensitive Disease (gBRCA)					
Olaparib	1,633	327	$38,581	$30.7	3%
Niraparib	1,633	327	$43,671	$33.5	4%
Maintenance Therapy for Platinum-Sensitive Disease (non-gBRCA)					
Niraparib	7,441	1,488	$34,642	$116.6	13%

6.4 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. This is not the case for maintenance therapy with olaparib, however, where discounts from the current list price of approximately 50-80% would be required to meet thresholds of $50,000-$150,000 per QALY gained.

Use of rucaparib for BRCA-mutated disease also provides substantial clinical benefit; however, costs were high for this PARP inhibitor, as initial dose reductions do not reduce cost because of level pricing across dosage strengths. Discounts of 50-75% for rucaparib would be required to achieve common cost-effectiveness thresholds. Finally, while niraparib's clinical benefits in maintenance therapy are greater in women with gBRCA-mutated disease than without, cost-effectiveness estimates still exceeded common thresholds. Discounts of 60-90% would be required to achieve these thresholds in the gBRCA population, while there is no price that would achieve the thresholds in women without the mutation.

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. Scenario and structural sensitivity analyses using different sources of survival evidence or 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 $27,300 per patient for olaparib in the recurrent BRCA-mutated population to approximately $59,000 per patient for rucaparib in the same 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 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. A major limitation results 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 population, overall survival from olaparib was applied in order to estimate life-year and QALY outcomes.

In addition, comparator agents such as PLD+C or bevacizumab (for budget impact modeling only) require physician administration. Additional costs from significant provider mark-ups 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 also varied the cost of PLD+C from 81% to 120% of the basecase estimates, and our conclusions regarding cost-effectiveness remained the same in all circumstances.

Survival curve fitting relied on assumptions that may differ substantially between different parametric models. 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. 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.

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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

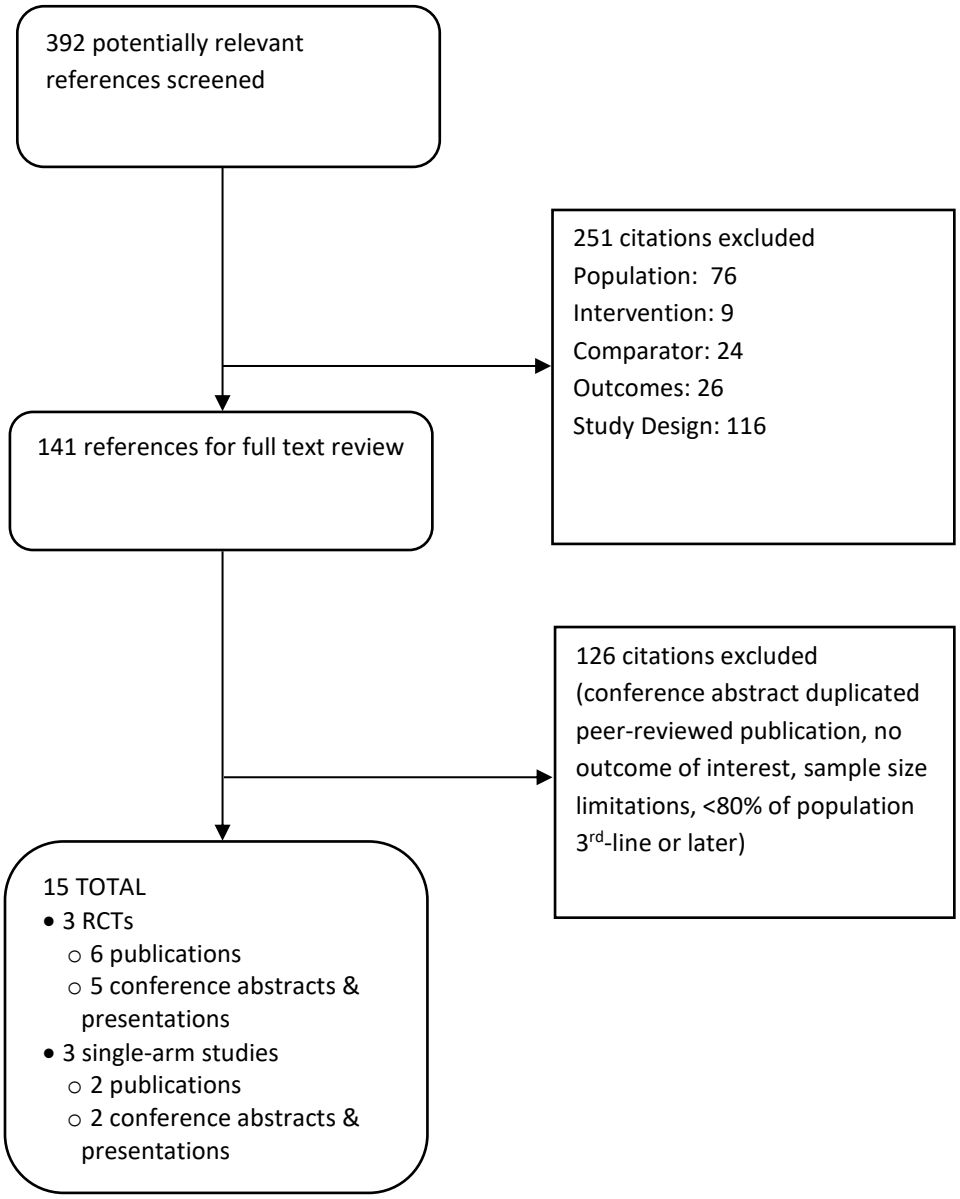
Table A2. Search Strategies of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled trials

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 0.1-0.310); p<0.0001] and OS benefit [HR 0.62 (95% CI 0.41-0.94); p=0.02480] with olaparib relative to placebo. 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 and 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 ORR 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 2 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 versus 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					
A Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer (ARIEL3) Clovis Oncology, Inc. NCT01968213	Phase 3 Double-blind RCT Estimated Enrollment: 540	1. Rucaparib - Oral tablets twice daily; 28-day cycles of treatment 2. Placebo - Oral tablets twice daily; 28-day cycles of treatment	Inclusion Criteria • Confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer • Received ≥2 prior platinum-based treatment regimens • Must have had at least a 6-month disease-free period following prior treatment with the penultimate platinum-based chemotherapy and achieved a response • Received no more than 1 non-platinum chemotherapy regimen Exclusion Criteria • Untreated or symptomatic central nervous system metastases • Prior treatment with any PARP inhibitor • History of prior cancer except for non-melanoma skin cancer, breast cancer curatively > 3 years ago, curatively treated solid tumor (>5 years ago without evidence of recurrence), and synchronous endometrial cancer (Stage 1A) with ovarian cancer.	Primary Outcome Measures • PFS in molecularly defined subgroups [~3 years.] Secondary Outcome Measures • OS • AEs • Individual model parameter estimates of rucaparib and covariates identification • FOSI-18	March 2017

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Completion Date
ARIEL4: A Study of Rucaparib Versus 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 pre-market RCTs, using the categories "good," "fair," or "poor".[114] 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 Ovarian Cancer with a Deleterious BRCA Mutation: Additional Evidence

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

Study 10[76]	ARIEL2[77]	Pooled Analysis of Study 10/ARIEL2[78]	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 2 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

Rucaparib- ARIEL3

The following table was presented by Clovis Oncology in a June 19, 2017 press release. While not part of the formal review, the data is included due to its relevance for the maintenance population.

Table D2. Topline Primary Efficacy for ARIEL3 Reported in June 19, 2017 Press Release

Summary of Primary Efficacy Analyses and Selected Exploratory Endpoints for ARIEL3				
	PFS by Investigator Review *(Primary Endpoint)*		PFS by BICR *(Secondary Endpoint)*	
Primary Analyses				
	Hazard Ratio	**Median PFS (months) Rucaparib vs. Placebo**	**Hazard Ratio**	**Median PFS (months) Rucaparib vs. Placebo**
BRCAm (n=196)	0.23; p<0.0001	16.6 vs. 5.4	0.20; p<0.0001	26.8 vs. 5.4
HRD-positive (n=354)	0.32; p<0.0001	13.6 vs. 5.4	0.34; p<0.0001	22.9 vs. 5.5
Intent-to-Treat (n=564)	0.36; p<0.0001	10.8 vs. 5.4	0.35; p<0.0001	13.7 vs. 5.4
Exploratory Analyses				
BRCA^{wt} / HRD-positive (n=158)	0.44; p<0.0001	9.7 vs. 5.4	0.55; p=0.0135	11.1 vs. 5.6
BRCA^{wt} / HRD-negative (n=161)	0.58; p=0.0049	6.7 vs. 5.4	0.47; p=0.0003	8.2 vs. 5.3

PFS: progression-free survival; BRCAm: tumor BRCA mutant which includes germline and somatic mutations; HRD: homologous recombination deficiency; BRCAwt: BRCA wild-type

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).[115]

Treatment-emergent AEs 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%).[115] In addition, one fatal event of AML in two cases was reported in the FDA prescribing information.[30]

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.[115]

Discontinuation due to treatment-emergent adverse events (TEAEs) were 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%).[115]

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 D3. Grade ≥ 3 Adverse Events with Olaparib

Adverse Events Grade ≥ 3 (%) for Olaparib					
	Study 19[70]		SOLO2[696969696969]		Study 42[62,63]
	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=195)	Placebo (n=99)	Olaparib (n=154)
Hematologic					
Anemia	5.1	0.8	19.5	2.0	20.1
Neutropenia	NR	NR	5.1	4.0	1.3*
Thrombocytopenia	NR	NR	1.0	1.0	1.3*
AML/MDS	NR	NR	2.1	4.0	1.3
Non-hematologic					
Nausea	2.2	0	2.6	0	0.6
Fatigue/asthenia	6.6	3.1	4.1	2.0	6.5
Vomiting	2.2	0.8	2.6	1.0	2.6
Diarrhea	2.2	2.3	1.0	0	1.3
Headache	0	0.8	0.5	0	0
Abdominal pain	1.5	3.1	2.6	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 D4. Grade ≥ 3 Adverse Event Type and Frequency with Olaparib

Adverse Event Frequency in Study 19 and SOLO2 Adverse Events Frequency				
	Study 19[70]		SOLO2[69]	
Characteristic, n (%)	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=195)	Placebo (n=99)
Any AE	130 (95.6)	116 (90.6)	192 (98.5)	94 (94.9)
Any AE grade ≥3	48 (35.3)	26 (20.3)	72 (36.9)	18 (18.2)
Any SAE	30 (22)	11 (9)	35 (17.9)	8 (8.1)
Any AE leading to dose reduction	34 (25)	5 (4)	49 (25.1)	3 (3.0)
Any AE leading to discontinuation of study treatment	8 (6)	2 (2)	21 (10.8)	2 (2.0)
Any AE with outcome of death	3	0	1 (0.5)	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.[69]

Pneumonitis is listed as a potential side effect in the olaparib FDA label. Pneumonitis occurred in <1% of patients although some cases were fatal.[29]

Review of the FDA panel 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).[116] SOLO2 reported that 2.1% 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).[69]

Review of the FDA panel transcripts in 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).

Deaths related to adverse events from treatment included a hemorrhagic stroke, cholestatic jaundice (ruled progressive disease as final diagnosis) and MDS.[116]

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.[39]

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. [39] 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%.[74]

Hematologic events of grade 3 and 4 occurred in 10% of patients and at a higher rate in the niraparib group.[39] In the NOVA study, AML and MDS occurred in 5 out of 367 (1.4%) of 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%).[74]

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 NOVA study.[74] The current FDA label for niraparib includes warnings for myelodysplastic syndrome/acute myeloid leukemia, bone marrow suppression and cardiovascular effects.[31]

Within the NOVA trial, there were no reported adverse events that led to death in 30 days.[74]

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.[84] Bevacizumab is also approved for use in platinum-resistant recurrent ovarian cancer in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan.[84]

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.[87,117,118] Studies did not show a statistically significant survival benefit (OS) and when quality of life was measured, no statistically significant differences were identified.[87,117,118] 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).[84]

Table D5. Key Trials for Bevacizumab

Key Trials	Patient Characteristics	Treatment Outcomes	Comparator Outcomes	Harms (Bevacizumab arm)
OCEANS[85,87] **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[117] **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[118] **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.[82] Table D6 below highlights the comparative effects and relative risks 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.[81] Hand-foot syndrome, a painful, blistering of the palms and soles of the feet, is also a reported side effect of doxorubicin.[81,82]

Table D6. Summary of Outcome from Systematic Review (PLD/Carboplatin)[82]

Outcome	Comparative Risks/Rates (95% CI for Relative Risk)		Relative Effect (95% CI)	Number of Participants	Quality of Evidence (Grade)
	PLD/carbo*	PAC/carbo*			
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

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.[119] 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.[120]
Office visit	$111	Medicare reimbursement rates from Smith et al.[120]
CT scan abdomen and pelvis	$532	Medicare reimbursement rates from Smith et al.[120]
Blood test	$124	Medicare reimbursement rates from Smith et al.[120]
End of life costs	$49,182	Poonawalla et al.[119]
Proportion requiring end of life costs	0.51	Poonawalla et al.[119]

Adverse Event Costs

Adverse event costs were derived from treatment assumptions used in previous analyses[100] and the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUPnet).[101] 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.[66] Conversely, evidence from niraparib included PFS subdivided by gBRCA and non-gBRCA status with OS data immature at the point of completing this analysis. Therefore, we applied the OS curves and discontinuation rates from olaparib to the niraparib sub-population comparisons in order to estimate LYG and QALYs. Including this olaparib evidence allowed us to include an off treatment sub-state within PFS.

Table E4 a. Comparison of Model and Trial-Based Evidence 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[63] Figure 1	Pujade-Lauraine et al.[83] and Hanker et al.[6] Figure 2A 3rd relapse	Evidence not split into multiple lines of therapy. Lognormal and log-logistic distributions chosen for PFS and OS, respectively, for both arms.
Overall Survival	Kaufman et al. 2015 J Clin Oncol[63] Figure 2	Pujade-Lauraine et al.[83] and Hanker et al.[6] Figure 2B 3rd relapse	
	Rucaparib	**PLD+C**	**Notes**
Progression-free to progressive	Konecny et al.[36] 2017 presentation Slide 14	Pujade-Lauraine et al.[83] and Hanker et al.[6] Figure 2A 2nd relapse	Evidence not split into multiple lines of therapy. Overall survival from olaparib recurrent BRCA-mutated evidence. Lognormal and log-logistic distributions chosen for PFS and OS, respectively, for both arms.
Overall Survival	Kaufman et al.[36] 2015 J Clin Oncol[63] Figure 2	Pujade-Lauraine et al.[83] and Hanker et al.[6] Figure 2B 2nd relapse	
Overall Survival	Ledermann 2016[66] Figure 2C		
Progression-free to discontinuation	Single HTA submission olaparib maintenance Figure 5[103]		

PLD+C pegylated liposomal doxorubicin + carboplatin

Table E4 b. Comparison of Model and Trial-Based Evidence 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.[69] 2017 presentation SOLO2 PFS BICR curve	Evidence split into multiple lines of therapy for olaparib only. Log-logistic and lognormal distributions chosen for PFS and OS, respectively, for both arms. Log-logistic best fit for discontinuation for both arms. Log-logistic chosen for progression to 2nd subsequent therapy for olaparib and lognormal chosen for placebo arm.
Overall Survival	Ledermann 2016[66] 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.[39] NEJM Figure 2A	Evidence not split into multiple lines of therapy. Overall survival and discontinuation rates from olaparib applied. Lognormal distributions chosen for PFS and OS, respectively, for both arms. Log-logistic chosen for discontinuation for both arms. Log-logistic chosen for progression to 2nd subsequent therapy for olaparib and lognormal for placebo arm.
Overall Survival	Ledermann 2016[66] 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.[39] 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. Lognormal distributions best fit for PFS and OS, respectively, for both arms. Log-logistic best fit for discontinuation for both arms. Loglogistic for progression to 2nd subsequent therapy for olaparib and lognormal for placebo arm.

Appendix Table E5 displays the comparison of the median progression-free survival and median overall survival of the model and the trial evidence.

Table E5. Comparison of Model and Trial-Based Evidence

Arm	Population	Outcome	Model Output	Trial Evidence	Source
Olaparib - gBRCAm	Maintenance	Median Survival	36	34.9	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS on and off treatment	30	30.2	SOLO2 PFS BICR Curve - Pujade-Lauraine 2017
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 BICR Curve - Pujade-Lauraine 2017
Niraparib - gBRCAm	Maintenance	Median Survival	36	34.9	Figure 2B - Lancet Oncology Ledermann 2016
		Median PFS	21	21	Figure 2A - NEJM Mirza 2016
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
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
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
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)

Disutilities

We applied a regimen-weighted disutility for experiencing any Grade 3/4 adverse event (Appendix Table E6); 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 E6. 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 request (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 request (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 request (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 E7 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 investigator-assessed PFS evidence in the maintenance therapy for platinum-sensitive population.

Table E7. 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)	$109,003	$43,147	$152,150	2.11	1.28
PLD + C (Partitioned Survival Sensitivity Analysis) (4th line or later use)	$25,016	$41,229	$66,245	0.91	0.61
Incremental cost per outcome				$71,100/LYG	$128,000/QALY
Maintenance therapy for platinum-sensitive disease					
Olaparib – combined gBRCAm and non-gBRCAm	$148,009	$48,756	$196,766	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				$441,000/LYG	$442,000/QALY
Olaparib – investigator assessed PFS in gBRCAm	$156,278	$52,431	$208,709	3.64	2.60
Placebo (Olaparib) – investigator assessed PFS in gBRCAm	$9,048	$46,474	$55,522	3.09	2.08
Incremental cost per outcome				$275,500/LYG	$296,500/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 E8 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 E8. 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	$139,769	$56,867	$196,637	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				$451,000/LYG	$490,000/QALY

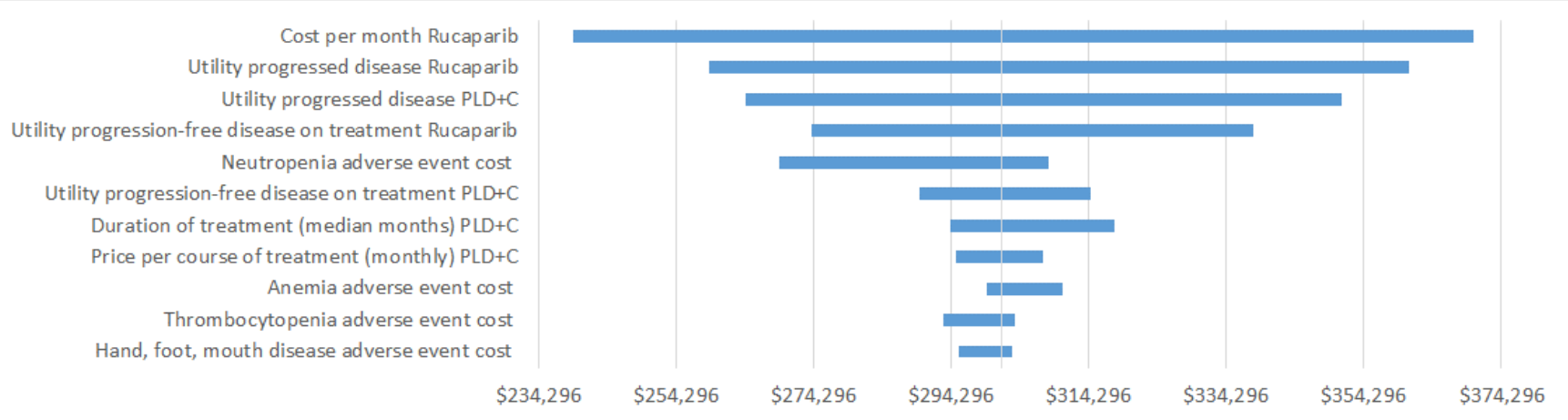
*Intervention costs include cost of PARP or comparator (exception placebo) and subsequent chemotherapy costs

§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

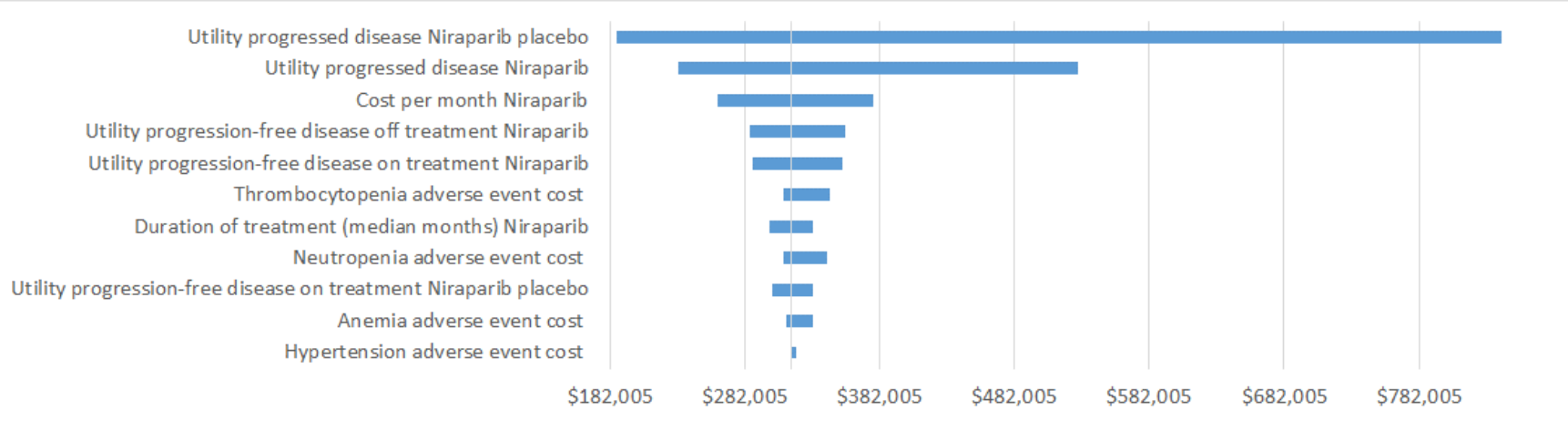
Tornado diagrams not shown in Section 6 are shown in Figures E1 and E2. For the non-gBRCA niraparib comparison, the tornado diagram is not shown given no variation in estimates produced a cost-effectiveness estimate of less than $500,000/QALY.

Figure E1. Rucaparib vs. 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	$239,296	$370,212	$10,207	$15,121
Utility progressed disease Rucaparib	$259,018	$360,909	0.37	0.63
Utility progressed disease PLD+C	$264,348	$351,047	0.37	0.63
Utility progression-free disease on treatment Rucaparib	$273,901	$338,310	0.72	0.82
Neutropenia adverse event cost	$269,194	$308,463	$1.50	$77,892
Utility progression-free disease on treatment PLD+C	$289,602	$314,614	0.75	0.83
Duration of treatment (median months) PLD+C	$294,269	$318,057	2	12
Price per course of treatment (monthly) PLD+C	$294,934	$307,634	$2,643	$3,915
Anemia adverse event cost	$299,442	$310,525	$5	$38,830
Thrombocytopenia adverse event cost	$293,116	$303,520	$3	$57,182
Hand, foot, mouth disease adverse event cost	$295,401	$303,204	$7	$19,482

Figure E2. Niraparib – gBRCAm vs. Placebo in Maintenance Therapy for Platinum-Sensitive Disease



Input Name	Lower ICER	Upper ICER	Lower Input	Upper Input
Utility progressed disease Niraparib placebo	$187,005	$842,759	0.55	0.80
Utility progressed disease Niraparib	$232,760	$529,724	0.55	0.80
Cost per month Niraparib	$262,302	$376,915	$10,958	$16,232
Utility progression-free disease off treatment Niraparib	$286,206	$356,895	0.66	0.76
Utility progression-free disease on treatment Niraparib	$288,317	$354,489	0.72	0.82
Thrombocytopenia adverse event cost	$310,484	$344,754	$3	$57,182
Duration of treatment (median months) Niraparib	$299,985	$333,125	3.7	19.2
Neutropenia adverse event cost	$311,204	$343,400	$2	$77,892
Utility progression-free disease on treatment Niraparib placebo	$302,123	$332,272	0.66	0.76
Anemia adverse event cost	$312,949	$333,009	$5	$38,830
Hypertension adverse event cost	$315,578	$320,500	$125	$26,587

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 E9 describes the percentage of simulations that were cost-effective at different willingness-to-pay thresholds.

Table E9. 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)	0.0%	17.4%	87.3%	98.9%	99.8%
Rucaparib vs PLD + C (3rd line)	0.0%	0.0%	0.0%	0.8%	9.4%
Maintenance therapy for platinum-sensitive disease					
Olaparib (gBRCA) vs Olaparib Control (gBRCA)	0.0%	0.0%	0.4%	10.4%	39.4%
Niraparib (non-gBRCA) vs Niraparib Control (non-gBRCA)	0.0%	0.0%	0.0%	0.1%	0.7%
Niraparib (gBRCA) vs Niraparib Control (gBRCA)	0.0%	0.0%	0.6%	9.3%	25.4%

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[63] (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)

<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 colspan="7">Rucaparib</td></tr>
<tr><td>Kristeleit SR ESMO 2016[78]

(Study 10 and ARIEL2)

CONFERENCE PRESENTATION

Not rated for quality</td><td>ARIEL2
RCT
Phase II
Open Label

Study 10
Non-Randomized
Phase I/II
Open Label
RCT</td><td>1) Rucaparib (n=106)

≥1 dose of oral rucaparib 600 mg twice daily until disease progression or discontinuation</td><td>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.</td><td>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)</td><td>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)
<table><tr><th>ORR</th><th>n(%)</th><th>95% CI</th></tr><tr><td>≥2 prior Plat</td><td>53.8</td><td>(43.8–63.5)</td></tr><tr><td>Plat Sens</td><td>65.8</td><td>(54.3–76.1)</td></tr><tr><td>Plat Resistant</td><td>25.0</td><td>(8.7–49.1)</td></tr></table>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)</td><td>*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</td></tr>
</table>

<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[36]

(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)[75] (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[70] (Study 19) Fair quality	RCT, double-blind, placebo-controlled, phase II study	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[71] (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[66] (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[72]

(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[68] (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[67] (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[121] (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 SGO 2017[69] (SOLO2) ***CONFERENCE PRESENTATION*** Not rated for quality	Phase III, RCT, double-blind, placebo-controlled, multicenter study	1) Olaparib, 300 mg BID (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	*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 (range)** 1) 56 (26-83) 2) 56 (39-78) **Primary tumor type, n (%)** *Ovarian* 1) 162 (82.7) 2) 86 (86.9) **Prior platinum regimens, n (%)** *2 lines* 1) 110 (56.1) 2) 2 (62.6) *3 lines* 1) 60 (30.6) 2) 20 (20.2) *≥4 lines* 1) 25 (12.8) 2) 17 (17.2)	*By investigator assessment* **Median PFS, months** 1) 19.1 2) 5.5 **Events (%)** 1) 107 (54.6) 2) 80 (80.8) *HR: 0.30; 95% CI (0.22-0.410)* *p<0.0001* *Sensitivity analysis using BICR* **Median PFS, months** 1) 30.2 2) 5.5 **Events (%)** 1) 81 (41.3) 2) 70 (70.7) *HR: 0.25; 95% CI (0.18-0.35)* *p<0.0001* TOI over first 12 months ***Change from baseline, adjusted mean*** 1) -2.90 2) -2.87 ***Estimated difference in adjusted means****= -0.03; 95% CI (-2.19-2.13)* *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) 72 (36.9) 2) 18 (18.2) **Any AE leading to dose reduction, n (%)** 1) 49 (25.1) 2) 3 (3.0) **Discontinuation due to AEs, n (%)** 1) 21 (10.8) 2) 2 (2.0) **Any AE w/outcome of death** 1) 1 (0.5) 2) 0 **MDS/AML events, n (%)** 1) 4 (2.1) 2) 0 *Grade ≥3* **Anemia, n (%)** 1) 38 (19.5) 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[73] (SOLO2) ***CONFERENCE ABSTRACT*** Not rated for quality	Phase III Randomized, double-blind, placebo-controlled trial	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[69]	See Pujade-Lauraine SGO 2017[69]	*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[69]

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[86] (SOLO2) ***CONFERENCE ABSTRACT*** Not rated for quality	Phase III Randomized, double-blind, placebo-controlled trial	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[69]	*See* Pujade-Lauraine SGO 2017[69]	*See* Pujade-Lauraine SGO 2017[69]	**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