

Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness, Value, and Value-Based Price Benchmarks

Background and Scope
April 4, 2017

Background

Ovarian cancer is the most common cause of gynecologic cancer death and fifth-leading cause of cancer death in women.¹ There are nearly 200,000 women currently living with ovarian cancer; each year over 22,000 new cases are diagnosed and there are approximately 14,000 deaths attributable to the disease.¹ The median age at diagnosis is 63 years.¹ 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).^{2,3} Of these women, those who continue through three or more lines of therapy are likely to die or have their disease progress within six months.⁴

Epithelial ovarian cancers account for about 90% of ovarian cancers and treatment recommendations for epithelial ovarian cancer are also applied to fallopian tube cancer and primary peritoneal cancer.⁵ Staging is recommended to differentiate histologic subgroups. Epithelial ovarian cancer has four histologic subtypes: serous, endometrioid, mucinous, and clear cell. About 70% of tumors have a serous histology.⁶ High-grade serous tumors represent a particularly challenging subtype, with 5-year survival rates currently estimated at only 35-40%.⁷

Cytoreductive surgery and postoperative/adjuvant therapy with a combination of a platinum and a taxane agent is considered first-line therapy.^{6,8} Some studies suggest a benefit of additional use of bevacizumab.⁹ The first line of therapy usually includes six cycles of chemotherapy in patients with stage II, III, or IV cancer.

Several chemotherapy combinations may be considered for patients when they experience recurrence. In addition, a newer class of targeted biologic agents known as poly ADP-ribose polymerase (PARP) inhibitors interfere with a pathway of DNA repair. As such, PARP inhibitors were originally evaluated for patients with germline mutations that affect DNA repair, such as mutations to BRCA1 or BRCA2. Initial study results indicated that patients with deleterious germline BRCA (gBRCA) mutations and recurrent ovarian cancer would respond to PARP inhibitors. Two of these PARP inhibitors (rucaparib [Rubraca™; Clovis Oncology] and olaparib [Lynparza™; AstraZeneca]) have been most widely tested in this group of patients. However, during late 2016, the NOVA trial of the PARP inhibitor niraparib (Zujela™; Tesaro)

suggested its use may be appropriate as maintenance therapy regardless of whether patients have gBRCA mutations.

This scoping document was developed with important input from ovarian cancer patients and patient organizations. Patients indicated that, beyond adverse events noted in clinical trials, depression and anxiety were critically important to consider as part of the patient experience. One specific example was the presence of abdominal pain, which is both a side effect of treatment and an indicator of relapse; this conceptual overlap is a common source of anxiety among women. Patient groups also noted the importance of considering “financial toxicity” and other financial burdens when evaluating the impact of treatment.

Report Aims

This report will focus on ovarian cancers with high-grade serous or mixed serous/endometrioid histology, which represent the population most likely to respond to current treatment options and are common entry criteria for clinical trials. We will evaluate the health outcomes and economic effects of the PARP inhibitors olaparib, rucaparib, and niraparib in the treatment of these patients.

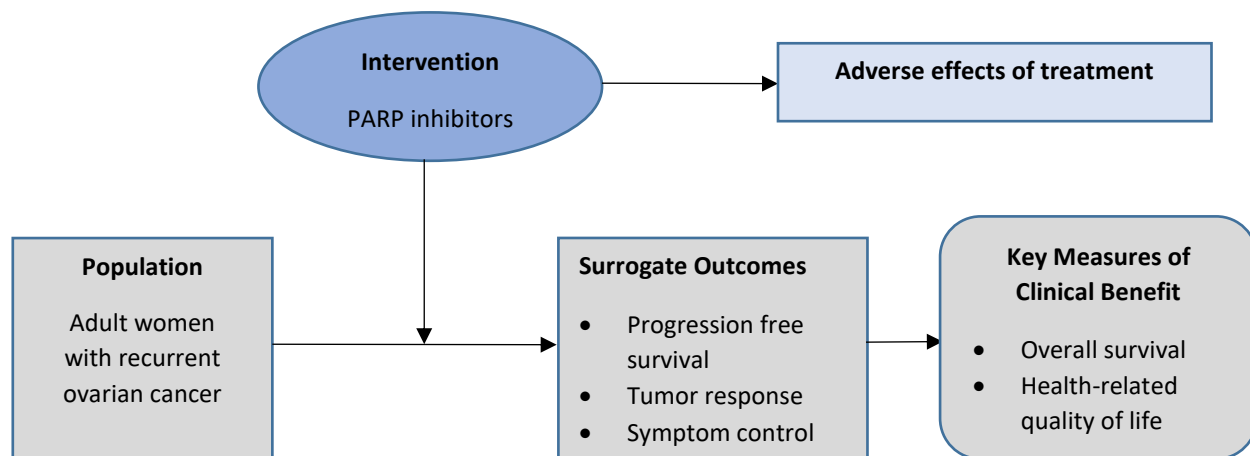
Scope of Review

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

Analytic Framework:

The general analytic framework for assessment of all the interventions is depicted in Figure 1 on the following page.

Figure 1. Analytic Framework: Management of Recurrent Ovarian Cancer



Population

The key populations of interest are described below. Note that these are defined to provide a basis for comparison of the three PARP inhibitors, and do not necessarily reflect their FDA-indicated uses. Some proposed comparisons may require evaluation of subgroup data presented in publications, conference proceedings, and/or submissions to the FDA.

P1) 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 cytoreductive surgery and multiple prior lines of chemotherapy.

P2) 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, were in response to the most recent regimen, and are candidates for maintenance treatment.

Key Subpopulations

Subpopulations of interest will be determined in large part by the availability of data for each PARP inhibitor. For example, for population P1, key studies of olaparib and rucaparib were conducted in different populations (4th-line or later use vs. 3rd-line or later use respectively); it is unclear whether data are currently available to make direct 4th-line or later comparisons between the two agents. In addition, for population P2, the pivotal trial of niraparib was conducted in patients with and without gBRCA mutations, with results stratified by mutation status, while the major trial of olaparib was restricted to gBRCA patients only. The literature suggests that BRCA mutation plays an important role risk stratifying patients. In the serous subtype, analyses adjusted for age at diagnosis, tumor grade, and clinical stage show improved five-year survival for patients with either gBRCA1 or gBRCA2 compared to those with no gBRCA mutation.¹⁰

Another population of interest involves patients whose tumors were positive for homologous recombination DNA repair deficiency (HRD). For example, the NOVA trial of niraparib presents data on progression-free survival in patients with gBRCA mutations, patients without gBRCA mutations, and the subset of non-gBRCA patients who were positive for HRD.

In addition, the response to prior platinum-based therapy is an important factor. Those who experience remission for greater than six months after completing platinum-based chemotherapy are considered to be “platinum sensitive.” We will examine outcomes for both platinum-sensitive and platinum-resistant subpopulations whenever possible.

Interventions

P1) Olaparib (4th-line or later treatment)

Rucaparib (3rd-line or later treatment)

*The manufacturer has advised us that data from the trial of niraparib in this population are unlikely to be available during the project timeline

P2) Olaparib

Niraparib

*The manufacturer has advised us that data from the trial of rucaparib in this population are unlikely to be available during the project timeline

As noted above, some data to support use of the PARP inhibitors in these populations is currently emerging. For example, an ongoing study of niraparib in fourth-line or later use is expected in the second half of 2017. In addition, trials of olaparib and rucaparib for maintenance treatment have recently been completed or are nearing completion. Final determinations of the comparability of the clinical data across the PARP therapies will be made based on the timing and detail of available data for both primary trial populations and subgroups of interest.

Comparators

P1) Other third- or fourth-line therapies (e.g., docetaxel, paclitaxel, gemcitabine, bevacizumab)

P2) Placebo or bevacizumab

Outcomes

This review will examine key clinical outcomes of interest in this population, including surrogate outcomes common to cancer trials. We will also engage with patient groups and clinical experts to ascertain which outcomes are of greatest importance to patients and seek patient-reported outcomes or other evidence sources to enrich the available data. Initial discussions with patient groups indicate that patients with recurrent ovarian cancer have anxiety over the low likelihood of cure. Treatments, particularly the cytotoxic treatments which are standard of care, cause substantial toxicity and burden to patients and their families.

The primary outcomes of interest from clinical trials will include overall and progression-free survival, rates of partial and complete response as well as overall objective response, and health-related quality

of life. Clinical expert guidance indicated that measures of tumor response may not represent a fair comparison, given different methods of action for targeted versus cytotoxic therapies. Data on partial, complete, and overall objective response rate will nevertheless be captured, as this measure is often a primary or co-primary endpoint in many cancer trials.

Other outcomes of interest will include:

- Symptom control (e.g., Functional Assessment of Cancer Therapy[FACT]-Ovarian Symptom Index)
- Disease-specific health-related quality of life (e.g., EORTC QLQ-C30, FACT-G)
- 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

Evidence tables will be developed for each outcome. Analyses are expected to be descriptive in nature only, as differences in entry criteria, study populations, outcome measurements, and other factors are likely to preclude formal quantitative indirect comparisons between the PARP inhibitors. As described above, the focus of attention in these analyses will be on common populations and/or subpopulations from clinical trials, as available.

Timing

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

Settings

All relevant settings will be considered, including inpatient, clinic, and outpatient settings.

Simulation Models Focusing on Comparative Value

As a complement to the evidence review, we will develop a simulation model to assess the cost-effectiveness of the regimens of interest relative to standard treatments. The model structure will take the form of a semi-Markov model with time in each state tabulated from the time since entry into that state. The model will include at least three health states informed by PARP inhibitor clinical evidence: (1) progression-free survival, (2) progression, and (3) death. A model structure will be developed to evaluate ovarian cancer treatments from a health-system perspective over a lifetime horizon. The model structure and inputs will be informed by prior published economic evaluations, clinical trials, and observational studies in ovarian cancer treatment. The model will focus attention on regimens most likely to be used for 3rd- or 4th-line and maintenance treatment, respectively; key model estimates will differ to reflect differences in disease severity and quality of life for patients receiving treatment.

The populations of focus for the model will be adult women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous or mixed serous/endometrioid histology who meet the population definitions as defined previously:

P1) Treatment in women whose cancer has relapsed after cytoreductive surgery and multiple prior lines of chemotherapy.

P2) Women with platinum-sensitive disease who have received at least two prior platinum-based chemotherapy regimens, were in response to the most recent regimen, and are candidates for maintenance treatment.

Effectiveness will be estimated based on the clinical review of progression-free and/or overall survival. Based on input from clinical experts as well as listed FDA indications and/or clinical trial entry criteria, and based on current expectations regarding available data, proposed comparisons of interest include:

- P1: Olaparib vs. comparator chemotherapy for 4th line or later treatment
- P1: Rucaparib vs. comparator chemotherapy in 3rd line or later treatment
- P2: Olaparib vs. bevacizumab or placebo in maintenance treatment
- P2: Niraparib vs. bevacizumab or placebo in maintenance treatment

Key model inputs will include rates of disease progression, treatment-related adverse event rates, costs, and the health-related quality-of life associated with different disease states and serious adverse events. Outcomes are dependent on available clinical review evidence but may include the following: time to treatment discontinuation; time to first subsequent therapy; time from first to second subsequent therapy; and time from second subsequent therapy to death. Costs will include those of current and subsequent treatment, management of adverse events, and ongoing cancer-related care. Results from the model will include estimated life expectancy, quality-adjusted life expectancy, health care costs, the incremental cost per life-year gained and incremental cost per quality-adjusted life year (QALY) gained.

We will also assess the potential budgetary impact of each regimen over a 5-year time horizon, utilizing information on treatment costs and cost offsets from the model described above. Potential budget impact analyses will calculate the percentage of patients that could be treated at selected prices without crossing a budget impact threshold over the 5-year period. Finally, we will develop a “value-based price benchmark” for each regimen reflecting prices aligned with long-term cost-effectiveness thresholds. More information on ICER’s methods for estimating potential budget impact and calculating value-based price benchmarks can be found on [ICER’s website](#).

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