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

Background and Scope

March 6, 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.[2] Due to the lack of early symptoms and absence of an accurate screening strategy, nearly 75% of women with ovarian cancer are diagnosed with advanced disease at presentation (Stage IIIC or IV).[3] Only 40% of women are cured.[2] For patients who present with Stage III cancer, the median overall survival is less than two years.[4] Of these women, those who continue through three or more lines of therapy have a median survival without evidence of disease progression ("progression-free survival") of less than six months.[5]

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.[6] Staging is recommended to differentiate histologic subgroups. Epithelial ovarian cancer has four histologic subtypes: serous, endometroid, mucinous, and clear cell. About 70% of tumors have a serous histology. This report will focus on tumors with high-grade serous or endometroid histology, which represent the population most likely to respond to current treatment options and are common entry criteria for clinical trials.

Cytoreductive surgery and postoperative/adjuvant therapy with a combination of a platinum and a taxane agent are considered first line therapy.[7,8] Some studies suggest a benefit of additional use of bevacizumab.[9] Six cycles of chemotherapy are commonly given to patients with stage II, III, or IV cancer. There is not much available evidence to support maintenance therapy for those who experience remission after first-line treatment, but this may include paclitaxel, pazopanib, or bevacizumab (if part of the initial regimen). Those who either do not experience remission for more than six months or experience disease progression have a poorer prognosis.

Those who experience remission for greater than six months are considered to be "platinum sensitive." Several therapies may be considered for patients when they experience recurrence, including a newer class of biologic agents known as Poly ADP-ribose polymerase (PARP) inhibitors. Patients with mutations to BRCA are at increased risk for ovarian cancer and have a worse

prognosis. PARP inhibitors interfere with a pathway of DNA repair. As such, PARP inhibitors were initially evaluated for patients with germline mutations that affect DNA repair, such as mutations to BRCA1 or BRCA2. Patients with BRCA mutations who have recurrent platinum-sensitive ovarian cancer appear to 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.

In addition, during late 2016, the NOVA trial showed that the PARP inhibitor niraparib (investigational; [Tesaro]) may be appropriate as maintenance therapy regardless of whether patients have germline BRCA (gBRCA) mutations. Niraparib was shown to have a positive effect on progression-free survival in patients with gBRCA mutations, patients without gBRCA mutations, and the subset of non-gBRCA patients who were positive for homologous recombination DNA repair deficiency (HRD).

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 evaluate the health outcomes and economic effects of the PARP inhibitors olaparib, rucaparib, and niraparib in the treatment of ovarian cancer patients with and without germline BRCA mutations.

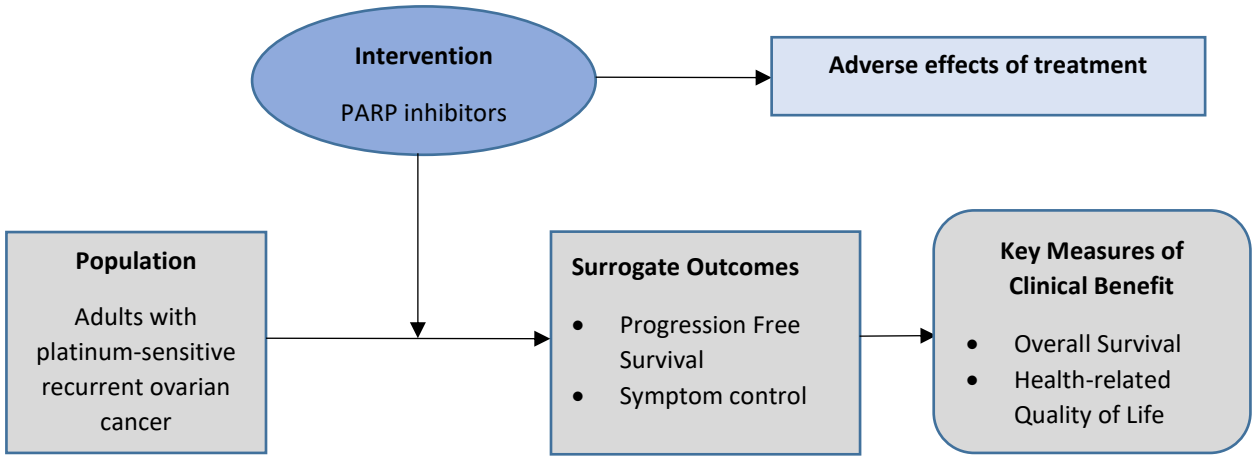
Scope of Review

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 below.

Figure 1. Analytic Framework: Management of Recurrent Epithelial 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. For example, rucaparib is approved for use in patients with two or more prior lines of chemotherapy, so we will access appropriate fourth-line subgroup data for between-agent comparisons.

P1) Adults with platinum-sensitive, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous or endometrioid histology who have a germline BRCA mutation and who have relapsed after cytoreductive surgery and three or more prior lines of chemotherapy

P2) Adults with platinum-sensitive, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer of high-grade serous or 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

Interventions

P1) Olaparib, rucaparib, or niraparib as fourth line or later treatment

P2) Olaparib, rucaparib, or niraparib as maintenance therapy

We note that 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. Further, olaparib's maintenance data will be restricted to BRCA-mutated patients only. 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.

Comparator

P1) Other fourth line therapies (e.g., docetaxel, paclitaxel, gemcitabine)

P2) Watchful waiting

Outcomes

This review will examine key clinical outcomes that occur 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 as compared with other cancer patients. 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. Clinical expert guidance indicated that measures of tumor response may not represent a fair comparison, given different methods of action for targeted vs. cytotoxic therapies; in addition, response measures are likely to be less sensitive in populations that have shown response to their most recent treatment. Data on 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-Ovarian Symptom Index)
- Health-related quality of life (e.g., EQ-5D-5L)
- Treatment-related adverse events
- Rates of Grade 3 or 4 adverse events
- Discontinuation due to adverse events
- Treatment-related deaths
- Costs and cost-effectiveness

Evidence tables will be developed for each outcome. In addition, to the extent feasible, techniques of network meta-analysis will be used to generate indirect comparisons across therapies. As described above, the focus of attention in these analyses will be on common populations and/or subpopulations from clinical trials, as well as on general considerations of population homogeneity and coherence of direct and indirect evidence.

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 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 platinum-sensitive recurrent ovarian cancer who: P1) have previously been treated with at least three lines of platinum-based therapy, and P2) are candidates for maintenance treatment after receipt of at least two lines of platinum-based chemotherapy and are in response to their most recent regimen. 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 subject to presentation and/or publication of all available data, proposed regimens for each population of interest include:

- P1: Recurrent disease, 3+ prior lines of chemotherapy
  - Olaparib
  - Niraparib
  - Rucaparib
  - Chemotherapy comparator (e.g., docetaxel, paclitaxel)

- P2: Recurrent disease, in response to most recent platinum-based chemotherapy, candidates for maintenance treatment
  - gBRCA mutation: olaparib, niraparib, rucaparib, watchful waiting
  - non-gBRCA mutation, overall: niraparib, rucaparib, watchful waiting
  - non-gBRCA mutation, subset with HRD positivity: niraparib, rucaparib, watchful waiting

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 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 product uptake and calculating value-based price benchmarks can be found on ICER's website.

References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Ovarian Cancer. https://seer.cancer.gov/statfacts/html/ovary.html. Accessed February 2017.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA: a cancer journal for clinicians.* 2016;66(1):7-30.
3. Wright AA, Bohlke K, Armstrong DK, et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2016;34(28):3460-3473.
4. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2003;21(17):3194-3200.
5. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2012;23(10):2605-2612.
6. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds. *WHO Classification of Tumours of the Female Reproductive Organs.* 4th ed. Lyon2014; No. 6.
7. National Comprehensive Cancer Network. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 1.2016). https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed February, 2017.
8. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *The New England journal of medicine.* 2011;365(26):2484-2496.
9. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *The New England journal of medicine.* 2011;365(26):2473-2483.