FORCE Response to Institute for Clinical and Economic Review (ICER) draft report, "Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value"

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Facing Our Risk of Cancer Empowered (FORCE) is the only national nonprofit organization serving all individuals affected by hereditary breast, ovarian, and related cancers (HBOC), and families with a BRCA or other inherited mutation that increases risk for these cancers. The following is FORCE's response to the Institute for Clinical and Economic Review (ICER) draft report, "Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness and Value."

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, nonprofit foundations, health plans, provider groups, and health industry manufacturers.

ICER states that their review focuses on clinical outcomes, patient experience, costs, and cost-effectiveness. FORCE has concerns regarding the conclusions drawn by this report as there are significant differences in the patient populations used for comparative data and significant gaps in the costs used for value analysis. Additionally, the design of the analysis does not adequately represent the interests of patients, clinicians, and the hereditary cancer community.

We respectfully submit that this analysis of Poly ADP-ribose polymerase (PARP) Inhibitors for Ovarian Cancer: Effectiveness & Value is premature and could be potentially harmful to patients since it may be used to drive practice as well as coverage decisions.

Concerns with the Comparators used for Effectiveness Analysis:

The first population of focus in the report is stated as "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.

However, the studies chosen as comparators for this population include women receiving only a 2nd line of treatment and are not stratified for BRCA mutation status.

The second population of focus in the report is stated as "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."

Again the populations included in the comparator studies are not equivalent to the PARP patient populations in terms of number of prior treatments, platinum sensitivity or BRCA mutation status.

Concerns Regarding the Economic Analysis:

We question some of the underlying assumptions used in the development of the cost models and therefore question the veracity of the resulting value conclusions.

1. A significant percentage of patients will have a platinum reaction which can result in additional costs in order to continue treatment (e.g. desensitization protocols) or result in the need to use another agent altogether in the 2+ line of treatment. There is no accounting for these additional costs in the Pegylated liposomal doxorubicin in combination with carboplatin (PLD + C) cost inputs.
2. The cost inputs also do not appear to include the cost of managing any side effects outside of grade 3 or 4 Adverse Events (AE's). The costs of managing side effects can include additional office visits, medications, additional blood tests, imaging and other functional tests, physical therapy, the use of compression garments, and so on.
3. The assumptions regarding costs associated with grade 3 or 4 AE's are not complex enough to accurately compare costs between the groups. The report uses estimated costs that are "an aggregate of emergency department and hospital costs associated with each adverse event". But this assumes that all grade 3 or 4 AE's require equal intervention and does not have a mechanism for calculating the cost of multiple episodes of an AE over the course of a treatment regimen vs. a single episode of an AE.
4. For bevacizumab adverse events, there is a 3-5% risk of bowel perforation and arterial thrombotic events (such as myocardial infarction or stroke) that needs to be included in order to accurately reflect the cost of that treatment. These events can be fatal and the costs associated with these AE's are extremely high.
5. The costs attributed to (PLD + C) and Bevacizumab treatments do not appear to fully include the cost of the infusion administration in addition to the drug cost even though the report acknowledges that the infusions require physician administration, travel, time away from work, etc., and attempts to account for it by using 120% of drug cost. We question if that accurately captures the costs associated with infusion administration – particularly for hospital based infusions.

PARP Inhibitors and the Hereditary Cancer Community

FORCE was introduced to early PARP inhibitor research in 2005, when phase 1 studies were conducted for people with solid tumors. We recognized the importance of these agents as the first targeted therapies to be developed to exploit the weaknesses in cancers caused by BRCA mutations; we then began educating the HBOC community about this early research and opportunities to participate in clinical trials. At the time, options were limited for people with advanced cancers due to a BRCA mutation. Our community was key to participation in, and completion of these clinical trials to open the possibility of new treatments for hereditary cancer.

Since that time, we have followed the research, educated our community about these agents, generated excitement about the research focus on HBOC, and facilitated clinical trial enrollment. For the HBOC community and the more than 1 million people in the U.S. that FORCE represents, a drug targeted against BRCA-associated cancers meant HOPE.

It took almost a decade of research before the first PARP inhibitor was approved. The approval of Lynparza marked the first new treatment for ovarian cancer in six years. The investment made in this personalized approach to cancer was extraordinary: a decade of research, and the participation of thousands of cancer patients enrolling in PARP inhibitor clinical trials to advance science for themselves, but also for their families. During this period of research, people who didn't qualify or who couldn't participate in a clinical trial regularly contacted FORCE, begging us to help them get access to PARP inhibitors. Many women who could not access PARP inhibitors died of ovarian cancer while waiting for these studies to be completed. For these women, the research wasn't quick enough. Many more will die if these agents are restricted. In the interim, while research has continued on these promising agents, how many other drugs have failed clinical trials? How many people have sacrificed health and life for all the research studies to test these agents?

The last few years have seen the approval of two additional PARP inhibitors for ovarian cancer, each with different indications and profiles. Some are approved for people with BRCA mutations but others are approved for a wider patient population. Each agent is different, and important to cancer survivors. It is critical that oncologists are not limited in their ability to match the right patient to the best individualized therapy for them.

The ICER value framework misses the perspective of patients affected by ovarian cancer and importantly, the value to communities such as the HBOC community; where use and continued investment into research of these agents in additional settings have the potential to improve and save even more lives than the comparative treatments. Since approval of PARP inhibitors, we have heard from the women with ovarian cancer who are living longer without chemotherapy on these agents. It does not capture the value to families and society; especially in the hereditary ovarian cancer community, where cancer tends to strike at a younger age, at the time of diagnosis these women are more likely to be working or raising young children. The median age of patients included in the PARP studies ranged from 57-62 years old which means that more than half of the patients were younger and likely still working or caring for children under the age of 18. Anecdotal data from ovarian cancer

patients strongly points to fewer interruptions of activities of daily living for PARP inhibitor treatment as compared to chemotherapy treatment and higher quality of life. ICER chose not to perform a societal analysis (page 51: *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).* These are real costs that are borne by patients and their families and should have equal consideration to the cost borne by insurers in the calculations of value and cost-effectiveness.

By it's very nature, personalized medicine means fewer people may benefit from a new agent. As a society, we must decide if we want to continue to invest in progress to assure that the right patient gets the right drug with the most benefit and the least side effects or turn back the clocks to a one-size-fits-all approach. On an individual scale, these agents appear costly, but the savings in productivity, quality-of-life, and the ability to keep patients from wasting precious time on agents that won't work for them is the large-scale societal benefit of this approach. For personalized medicine to succeed, it is critical that these agents, upon FDA-approval, are accessible to patients and incorporated into clinical practice.

In 1998, Herceptin was approved for metastatic Her2neu-positive, metastatic breast cancer—a small subset of women with a very aggressive type of breast cancer. It took another 8 years before Herceptin was approved in an adjuvant, maintenance setting. Her2neu-positive breast cancer is particularly aggressive and cruel, and in the past when women (and men) were diagnosed, even at an early stage, they died. And now, almost 2 decades later, many are being cured. Women with ovarian cancer deserve the chance to access new therapies and the same opportunity for better outcomes. **The hereditary cancer community deserves access to these agents in earlier settings now, given the current evidence that these drugs improve outcomes, and the potential for tremendous community benefit from additional research.**

ICER states that they received input from multiple stakeholders – including patients – in developing this report. Yet, this draft appears to mainly represent and serve the interest of the health insurance industry. The cost effectiveness threshold applied in this report, represented as cost-per-quality-of-life-years, belies the fact that these life-years belong to actual people. The head-to-head PARP inhibitor studies that ICER calls for, will, (if they happen at all) cost us many more years, lives, and dollars. The ongoing studies will take many more years for the data to mature, in part as a result of the fact that so many women are doing well on these agents. **In the meantime, restricting coverage and reimbursement for these agents for women who may benefit from them will set back progress and send a discouraging message to scientists, patients, families, biotech companies and society.**

FORCE believes that discussions about cancer treatment value frameworks must include open and continued dialog between all stakeholders, including patients. The review process and resulting frameworks must focus on improving patient outcomes by maximizing patient benefit and equitable access to the best care, minimizing patient harm, and incentivizing continued research and development of more effective, less toxic therapies.