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Bai, Jiaru
Moore, Kathleen
Kristeleit, Rebecca
et al.

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COST-EFFECTIVENESS OF NIRAPARIB, RUCAPARIB, AND OLAPARIB FOR TREATMENT OF PLATINUM-RESISTANT, RECURRENT OVARIAN CARCINOMA

JULIET E. WOLFORD, MD[1], **JIARU BAI, PhD**[2], **KATHLEEN N. MOORE, MD**[3], **REBECCA KRISTELEIT, MD, PhD**[4], **BRADLEY J. MONK, MD**[5], **KRISHNANSU S. TEWARI, MD**[1]

[1]Division of Gynecologic Oncology, University of California, Irvine, Orange, CA

[2]School of Business, Wake Forest University, Winston-Salem, NC, USA

[3]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK, USA

[4]University College London Cancer Institute, London, United Kingdom

[5]University of Arizona Cancer Center, Phoenix, AZ

Abstract

Background: Olaparib was approved on December 19, 2014 by the US FDA as 4th-line therapy (and beyond) for patients with germline *BRCA1/2* mutations; rucaparib was approved on December 19, 2016 as 3rd-line therapy (and beyond) for germline or somatic *BRCA1/2*-mutated recurrent disease. On June 24, 2019, niraparib was granted priority review for treatment of women

Corresponding Author: **JULIET E. WOLFORD, MD, MS-BATS, MArch, MLARP**, **Division of Gynecologic Oncology**, **University of California, Irvine**, Department of Obstetrics & Gynecology, The City Tower, 333 City Blvd, West - Suite 1400| Orange, CA 92868, Telephone: 714.456.8020 |Fax: 714.456.6632, jwolford@uci.edu.

Author Contributions:
Conceptualization: JW, BM, KT
Data Curation: JW, KT
Formal Analysis: JW, JB, KT
Methodology: JW, KT
Writing – original draft: JW, KT
Writing – Review & Editing: All Authors

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with damaging mutations in *BRCA1/2* or other homologous recombination repair genes who had been treated with three or more prior regimens. We compared the cost-effectiveness of PARPi(s) with intravenous regimens for platinum-resistant disease.

Methods: Median progression-free survival (PFS) and toxicity data from regulatory trials were incorporated in a model which transitioned patients through response, hematologic complications, non-hematologic complications, progression, and death. Using TreeAge Pro 2017, each PARPi(s) was compared separately to non-platinum-based and bevacizumab-containing regimens. Costs of IV drugs, managing toxicities, infusions, and supportive care were estimated using 2017 Medicare data. Incremental cost-effectiveness ratios (ICERs) were calculated and PFS was reported in quality adjusted life months for platinum-resistant populations.

Results: Non-platinum-based intravenous chemotherapy was most cost effective ($6,412/PFS-month) compared with bevacizumab-containing regimens ($12,187/PFS-month), niraparib ($18,970/PFS-month), olaparib ($16,327/PFS-month), and rucaparib ($16,637/PFS-month). ICERs for PARPi(s) were 3-3.5X times greater than intravenous non-platinum-based regimens.

Conclusion: High costs of orally administered PARPi(s) were not mitigated or balanced by costs of infusion and managing toxicities of intravenous regimens typically associated with lower response and shorter median PFS. Balancing modest clinical benefit with costs of novel therapies remains problematic and could widen disparities among those with limited access to care.

INTRODUCTION:

Ovarian carcinoma continues to represent the most lethal gynecologic malignancy. For 2019, the American Cancer Society estimates that there will be 22,530 new cases in the United States and 13,980 deaths due to disease.[1] The pairing of cytoreductive surgery with platinum-and-taxane-based combination chemotherapy can place the majority of women with newly diagnosed advanced epithelial ovarian cancer into complete clinical remission. Unfortunately, recurrence tends to be the rule with 10-year disease-specific survival rates under 10% reported in most studies.

Patients with ovarian carcinoma who relapse beyond six months are considered to have platinum-sensitive disease and are often re-treated with platinum-based combination therapy with or without the anti-angiogenesis drug, bevacizumab. Patients whose recurrence manifest within six months of completion of platinum-based therapy (as well as the refractory cases that do not respond to first-line platinum therapy) are considered to have platinum-resistant carcinoma and are typically treated with non-platinum-based single agents with or without bevacizumab, or are enrolled onto clinical trials studying novel drugs. Treatment in the recurrent setting is not curative, with response rates under 20% being reported for available salvage therapies. Most cytotoxic agents used in the recurrent setting, are administered intravenously.

Poly (ADP ribose) polymerase inhibitors (PARPi(s)) comprise a relatively new class of drugs available for treatment of ovarian carcinoma. The unique mechanism of action of these agents invokes the concept of synthetic lethality which was originally described in 1922 by the American geneticist, Calvin Bridges, during his studies of sex-linked traits in the fruit fly, *Drosophila melanogaster*. The phenomenon manifests when a nonlethal mutation is

induced to render the lethal phenotype through administration of a synthetic (i.e., pharmacologic) agent.[2] Treatment with PARPi(s) prevents repair by poly (ADP) ribose polymerase of single strand breaks in tumor DNA acquired through the effects of chemotherapy, replication errors, and cellular metabolism. Patients with germline *BRCA1/2* mutations (as well as those whose carcinomas harbor damaging somatic mutations in homologous recombination repair proteins, including *BRCA1/2*) are preferentially selective to PARPi(s) therapy as their carcinomas are unable to effectively repair the double strand breaks that arise as single strand breaks enter the DNA replication fork.[3-9] Currently three PARPi(s), olaparib, rucaparib, and niraparib, have been granted US FDA approval as maintenance therapies in the platinum-sensitive space for women who demonstrate a partial or complete response to retreatment with platinum-based chemotherapy.

Currently, two of the three PARPi(s) available as maintenance therapy for patients with platinum-sensitive recurrence,[3-6] also have treatment indications. Olaparib is approved as a 4th-line therapy (and beyond) for women with recurrent ovarian carcinoma harboring a germline *BRCA1/2* mutation,[3] and rucaparib is approved for 3rd-line therapy (and beyond) for tumors associated with either a germline or somatic *BRCA1*/2 mutation.[4,5] Niraparib is currently under priority review for its treatment indication for 4th-line and beyond for those patient with a germline or somatic *BRCA1*/2 mutation or have a homologous recombination deficiency.[6] PARPi(s) are relatively well-tolerated compared to traditional chemotherapy in general, with myelodysplastic syndrome (MDS) reported to manifest in 1-2% of patients treated. Because Medicare is not required to cover prescription medication, we evaluated the cost-effectiveness of PARPi(s) for treatment of recurrent disease. We hypothesized that the high drug costs of PARPi(s) would be balanced or possibly even offset by pre-treatment medication costs, infusion center charges, and the costs of managing adverse events of traditional non-platinum-based chemotherapy with or without bevacizumab.

METHODS:

Therapies were separated into three groups, with PARPi(s) being modeled separately so as not to compare the PARPi(s) directly to each other:

1. Non-platinum-based intravenous agents: pegylated liposomal doxorubicin (PLD) with or without trabectedin; topotecan, pemetrexed, paclitaxel, and nanoparticle albumin-bound paclitaxel (nab-paclitaxel).
2. Non-platinum-based intravenous drugs plus bevacizumab as reported in AURELIA[7] (i.e, bevacizumab combined with either PLD, topotecan, or paclitaxel)
3. PARPi(s): niraparib, olaparib, and rucaparib as reported in QUADRA[8], Study 42[3], and Study 10[4]/ARIEL-2 part 1[5], respectively.

Individual drug costs and infusion charges were obtained from the Center for Medicare Services Drug Payment Table and Physician Fee Schedule, utilizing the 2015 direct costs; billed charges and indirect costs were not included.[9] Outpatient medication costs were gathered from UptoDate.[10] Associated toxicity costs were determined by employing the common toxicity criteria (CTC) for grade 3 and above toxicities, established from the

registration trials for each treatment regimen.[11] Therefore, total costs per month were generated based on the cost of the drug, cost of pre-treatment testing, infusion costs, as well as associated toxicity costs that included the cost of treatment for the toxicity, associated testing costs, costs of office versus hospital visits, and outpatient medications (Table 1).

Our model was created from the perspective of the patient and the 3rd-party payer using a representative population with recurrent disease previously treated with chemotherapy prior to entering the model. Registration trial data were used to estimate transitions into the following health states:

A. Response

B. Hematologic complications (grade 3+)

C. Non-hematologic complications (grade 3+)

D. Progression – 'next-line' and onward

E. Death

All patients begin in the response health state and each month an individual patient may remain in that state or transition to a new one, incurring a cost of treatment each month as each health state is experienced. Patients who continue to respond to treatment (ie., partial response or stable disease) may remain in response or move to other health states in the next cycle. Hematologic toxicity included grade 3 or higher neutropenia, febrile neutropenia, thrombocytopenia, and anemia. Non-hematologic adverse events included hypertension, dermatologic conditions, abdominal pain, diarrhea/constipation, nausea/vomiting, arthralgia, neuralgias and gastrointestinal wall disruption (ie., fistula/bowel perforation). After one month, patients in a complication state may remain within the state and discontinue therapy, go back to response, or experience disease progression and receive next-line therapy. The probability of going from response to progression with next-line therapy and onward was determined by utilizing progression-free survival curves from the registration trials.

Several assumptions were incorporated into the design of the Markov decision tree:

A. Patients remain in each state for at least one month with all therapies scheduled on a 1-month cycle for ease of modeling.

B. Complications are mutually exclusive within the model indicating that a patient may only experience one complication overall in any given month.

C. Both treatment cost and the cost of managing an adverse event can be incurred by an individual patient in the same month, with the associated costs for toxicities requiring one month of treatment.

D. Patients in the next-line treatment state are assumed to have progressive disease even if it was an adverse event that necessitated institution of next-line line therapy.

E. Patients must transition to the progression state prior to entering the death state; therefore death from other causes (eg, grade 5 adverse events) is not accounted for in the Markov model. [3,7,12-21]

F. For many patients with recurrent ovarian carcinoma receiving multiple lines of therapy, survival is often reflected in months rather than years. For this reason, we calculated the quality of adjusted ovarian cancer life in months (QALmonth).

G. Although most patients treated with PARPi(s) in the 3rd-line setting and beyond have platinum-resistant recurrent disease, in the registration trials that secured the treatment indications for olaparib and rucaparib, there were patients with platinum-sensitive disease. For the comparison of cost-effectiveness of PARPi(s) with non-platinum-based intravenous therapies , we have modeled only patients with platinum-resistant disease.

Employing the complication data, the progression-free Kaplan-Meier curves from the trials, as well as the weighted probability of whether complications would lead to be taken out of treatment, an extracted probability estimation of time spent in one health state or another versus transitioning to the next-line or onward was determined. To compare cost-effectiveness between the therapies, we used Incremental Cost Effectiveness Ratios or ICERs. These were calculated by finding the difference in total cumulative cost between two drugs divided by the difference in effectiveness based on median PFS. Thus, the ICERs represented the average incremental cost associated for each month of life gained progression-free.

Health Utilities Values

Health utilities values were created to further clarify effectiveness of therapy, which is contingent on both the health state the patient is in and the quality of life (QoL) experienced in that state. From the response state (health utility value assignation ‘1’), there is a decrease in the healthy utility value if the patient transitions to another state due to perceived reduction in QoL. A hematologic complication has a health utility value of 0.75, while more severe non-hematologic complications as well as the next-line therapy health states are both valued at 0.5. The death state is valued at 0. The sum of the utilities over all months within the model in conjunction with the estimated PFS are a measure of quality of life in a given month (QAL_{month}), compared to the baseline of 1/month for those in the response state.[22,23].

Markov Chain:

A Markov model was developed (TreeAge Pro 2015) employing monthly transition probabilities that move patients in and out of different health states as described above. [23,24] The Markov chain was assembled from data collected from the chemotherapy registration trials, as well as the trials that prompted the FDA approval of rucaparib and olaparib (Figure 1). The model is comprised of two components: 1) current-line therapy which includes the health states of response, hematologic and non-hematologic complications; and 2) next-line therapy and onward, which includes death.

Employing the complication data, the progression-free Kaplan-Meier curves from the trials, as well as the weighted probability of whether complications would lead to be taken out of treatment, an extracted probability estimation of time spent in one health state or another versus transitioning to the next-line or onward, allowed construction of the Markov Decision Tree (Supplementary Tables 1-2, online only). Given that we are analyzing the costs of

regimens across trials instead of different regimens within a single trial, we did not model median PFS gains but rather the median PFS associated with the investigational arms of each trial in an effort to capture total costs associated with each of the investigational regimens from each trial.

Consideration of Niraparib for Platinum-Resistant Disease

Data for rucaparib and olaparib were obtained from 3rd-line and 4th-line registration trials, respectively.[3-5] Although niraparib currently does not have a treatment indication in recurrent ovarian cancer, data from the QUADRA study was compelling enough to secure it priority review with the US FDA on June 24, 2019. QUADRA is a phase II, single arm trial investigating safety and efficacy of niraparib for those with recurrent ovarian cancer who had received at least three prior lines of therapy. Of the 463 patients included in this trial, 58 (13%) had a germline *BRCA1*/2 mutation, 29 (6%) had a somatic *BRCA1*/2 mutation, and 135 (29%) were HRD-positive with *BRCA1*/2 wild-type or *BRCA1*/2 unknown. This trial elicited durable and meaningful responses in those patients with difficult to treat disease as a many had received niraparib as 6th line or greater (27%), as well as a majority were platinum resistant (33%) or refractory (35%). Niraparib was associated with an ORR of 27%, median duration of response of 9.2 mos, and an OS of 17.2mos in this difficult to treat population. [6]

Measuring Internal Validity

The validity of the Markov Model was determined by comparing the median PFS in months calculated by the model to the median PFS reported within the registration trials for each therapy.

RESULTS

Expected Cost and Cost Effectiveness:

By utilizing the Markov Model, the estimated total cost of therapy prior to progression for each patient, including toxicities, pretreatments, and infusion costs is $132,790 for niraparib with 4th line data, $114,289 for olaparib with 4th line data, $133,096 for rucaparib with the 3rd line data, $38,471 for the non-platinum-based intravenous therapies, and $85,309 for bevacizumab with chemotherapy. Costs associated with non-platinum therapies appear to be lowest, with 4th line olaparib data being associated with an estimated cost approximately 3 times more than the non-platinum-based group and 4th line niraparib and 3rd line rucaparib being 3.5 times costlier. Bevacizumab with chemotherapy is 2.2 times costlier than the non-platinum-based therapies. Stated alternatively, the use of olaparib and niraparib/rucaparib adds approximately $76,000 and $95,000, while bevacizumab with chemotherapy adds $46,838 to each patient treated prior to progression in comparison to the non-platinum-based group (Table 2).

Additionally, in calculating cost-effectiveness utilizing the average projected PFS for each group, the non-platinum-based group proved to be most cost-effective at $6,412 for each month of PFS gained, as compared with niraparib at $18,970 per month, rucaparib at $16,637 per month, and olaparib at $16,327 per month. The cost effectiveness chemotherapy plus bevacizumab was $12,187. The incremental cost-effectiveness ratio (ICER) for 4th-line

niraparib in comparison to non-platinum based intravenous regimens is $94,319 per 1.0-month gain in PFS. The ICER for 4th-line olaparib in comparison to the non-platinum-based therapies is $75,818 per 2.0-month gain in PFS. The ICER for 3rd-line rucaparib in comparison to non-platinum-based therapies is $47,787 per 1.0-month of life gained (Table 2, Figure 2A)

When utilizing the health utilities (eg., hematologic complication assigned 0.75, etc.) in conjunction with the simulated PFS, the QALmonth cost-effectiveness was $18,970 for niraparib, $16,637 for 3rd line rucaparib, $16,327 for 4th line olaparib, $6,883 for the non-platinum-based agents, $12,638 for the chemotherapy plus bevacizumab. (Table 3). There is no change noted for the PARPi(s) because the probability of transition to complications is so low that the median patient did not develop complications therefore, in this case, the PFS = QALmonth.

Internal Validity

For olaparib the simulated PFS was 7 months, which was equivalent to the 7 month PFS reported in Study 42 by Kaufman et al.[3] For niraparib, the simulated PFS was 7 months, which was similar to the 6.3 median PFS elicited by the QUADRA study.[8] For rucaparib the simulated PFS was 8 months in our model, and although the median PFS from the ARIEL-2/Study 10 trials was 10 months, the 2-month difference in the simulated PFS of 8 months lies within the confidence interval of the trials (95% CI, 7.3-12.5).[4] These data along with the simulated PFS for the other agents/regimens in the analysis appear in Supplementary Table 3 (online only).

Modeling Overall Survival

With a projected overall survival (OS) of 18 months for 4th line niraparib and 3rd line rucaparib, an overall estimated cost of $210,844 and $205,309 is incurred, respectively. For 17 months survival anticipated with 4th line olaparib, an estimated cost of $188,273 emerges. The 16 months of OS for non-platinum-based agents is associated with $147,390, while the 16 months of survival reported with chemotherapy plus bevacizumab corresponds to $203,553. (Table 4, Figure 2B). When considering the cost per month for each month survived, non-platinum-based therapies are the most cost-effective at $9,212, followed by 4th-line olaparib at $11,075, 3rd-line rucaparib at $11,406, 4th-line niraparib at $11,714, and finally chemotherapy plus bevacizumab at $12,722.

In exploiting the same health utilities as provided for the PFS evaluation of QALmonth, the cost effectiveness of OS as determined by the QALmonth were $13,433 for non-platinum-based agents, $16, 786 for 4th-line niraparib, $15,719 for 4th-line olaparib, $15,917 for 3rd-line rucaparib, and $17,070 for chemotherapy plus bevacizumab (Supplementary Table 5).

DISCUSSION:

PARPi(s) comprise a new class of generally well-tolerated, orally administered targeted drugs. When compared with alternative treatments for recurrent ovarian carcinoma we had hypothesized that the high drug costs of PARPi(s) would have been offset by the costs associated with intravenous administration and management of clinically significant adverse

events. However, this premise is not supported by our data. The cost-effectiveness model suggests that the primary expense lies in the high developmental cost of the drugs, rather than the costs of infusions and the complications associated with their use.

An interesting, albeit not unexpected, phenomenon we observed in our analyses was that with the relatively higher response rates and/or duration of response associated with PARPi(s) treatment, higher drug costs are incurred. In the recurrent setting where complete responses are uncommon, most patients are treated with salvage therapy until disease progression. The longer patients remain progression-free, the longer they remain on treatment and accumulate treatment-related cost. While the ICERs of PARPi(s) are similar to bevacizumab-containing regimens, we found a three-fold difference in ICERs of PARPi(s) relative to non-platinum-based intravenous chemotherapy. Similarly, when extrapolating the health utilities of QAL_{months}, the cost-effectiveness when modeling OS for PARPi(s) is approximately 1.3 times that of non-platinum-based intravenous chemotherapy. This may in part be due to relatively lower efficacy of chemotherapy and shorter duration of treatment resulting in lower cost.

According to many models, minimal reductions in cost should have a strong impact on the cost-effectiveness of new therapies. Such reductions to improve the affordability of many novel molecules can be achieved through mechanisms which result in more widespread use and increased awareness and accessibility of the targeted agent in clinical practice. It has been estimated that when considering germline *BRCA1/2* mutation rates, the occurrence of somatic *BRCA1/2* mutations, as well as the homologous recombination deficiency (HRD) phenotype, that nearly 50% of patients with ovarian carcinoma are candidates for PARPi(s). Studies to expand the label of PARPi(s) to other *BRCA1/2* mutated cancers as well as to those cancers containing evidence of HRD are ongoing, with olaparib having been granted a label for metastatic germline *BRCA1/2*-mutated HER2-negative breast cancer on June 12, 2018.

With both treatment *and* maintenance indications, it is unclear where rucaparib, and olaparib (and possibly niraparib) are best positioned in the spectrum for ovarian cancer. Because in many cases the disease retains chemosensitivity for extended periods of time, there are several opportunities where intervention with PARPi(s) may have a clinically meaningful impact. Importantly, access at different points along the disease spectrum broadens accessibility of novel agents. Cost-effectiveness studies such as the one contained in our model may contribute to the discussion. At present, data is lacking on re-treatment with PARPi(s) treatment (the same PARPi(s) or different PARPi(s)) making it difficult to determine whether sequencing this drug class represents a viable strategy from both the standpoint of treatment efficacy and/or the cumulative incidence of MDS. It should be noted, however, that MDS has been reported to occur at similar rates in the placebo arms of randomized trials. Though, should we find that the sequencing of PARPi to be effective and safe, this would further drive down the cost as indications would include multiple PARPi rather than the selection of a specific PARPi per patient population increasingly widening access to the drug class. Finally, acquired resistance to PARPi(s) is also not well understood. The prevalence of secondary somatic mutations that restore *RAD51C* and *RAD51D* is unknown[31] as are the clinical effects of *BRCA1/2* reversion mutations.[32]

Using a drug earlier in the disease course is another example through which cost-effectiveness can be improved. On December 19, 2018, olaparib received FDA approval as front-line maintenance therapy after the results of SOLO-1 showed a significantly delayed disease progression among women with newly diagnosed *BRCA1/2*-mutated advanced ovarian carcinoma.[25] On June 13, 2018, bevacizumab was approved as a frontline treatment and maintenance therapy for newly diagnosed advanced ovarian cancer. [26,27] Accordingly, women with newly diagnosed ovarian cancer who undergo primary cytoreduction may commence adjuvant platinum-and-taxane-based chemotherapy with bevacizumab, and if found to have a germline or somatic *BRCA1/2* mutation, can be counseled to switch maintenance therapy from bevacizumab to olaparib after six cycles of platinum-and-taxane based chemotherapy.

Reconciliation of incremental clinical benefits with exponentially rising costs remains problematic. Cost-prohibitive therapies widen the economic disparities among vulnerable patients coming from marginalized populations. However, it should be recognized that ICERs are driven by drug costs, and drug costs themselves are fluid. While clinical benefit as reported in high-quality prospective phase I-III clinical trials is long-lasting, what is discussed today concerning costs may be not be applicable tomorrow. During the mid-1990s, the Gynecologic Oncology Group introduced the world to paclitaxel through GOG protocol-0111 during a time when an old-growth Pacific Yew tree had to be cut down to treat one patient and the cost for six cycles of therapy exceeded $10,000. Today, paclitaxel is synthesized and off patent, and six cycles (175 mg/m^2 body surface area administered intravenously on a 21-day schedule) costs approximately $1,000.00.[28] Importantly, paclitaxel is now used as part of primary therapy for many solid tumors. Similarly, PARPi(s) have had their first indication in ovarian carcinoma. PARPi(s) are now also approved in two subtypes of metastatic breast cancer and are likely to be used in other cancer types during the upcoming years. This should have a positive impact on the ICERs and increase accessibility to these novel, effective, and tolerable therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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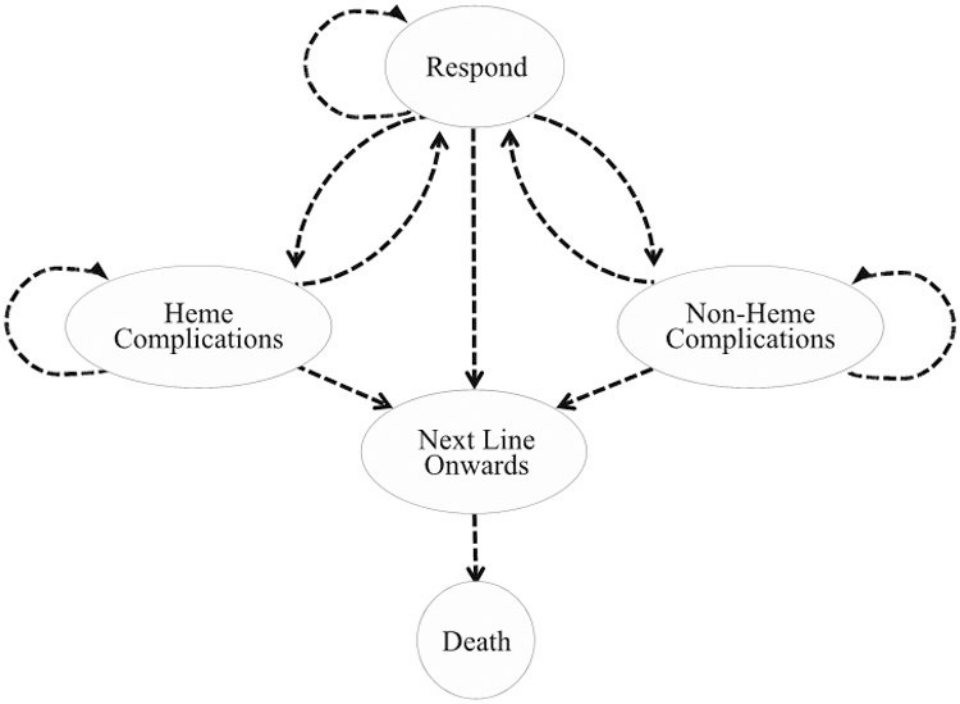

Figure 1: Development of the Markov Model:

The Markov tree developed depicts the health states of Response, Hematologic Toxicity, Non-Hematologic Toxicity, Progression, and Death. This model allows patients to transition to different nodes in the chain.

Assumptions of the model are as follows:

- Patients remain in each state for at least one month with all therapies scheduled on a 1-month cycle for ease of modeling.
- Complications are mutually exclusive within the model indicating that a patient may only experience one complication in any given month.
- Both treatment cost and the cost of managing an adverse event can be incurred by an individual patient in the same month.
- Patients in the Next Line Onwards state are assumed to have progressive disease even if it was an adverse event that necessitated institution of next line therapy.
- Patients must transition to the progression state prior to entering the death state; therefore death from other causes (eg, grade 5 adverse events) is not accounted for in the Markov model

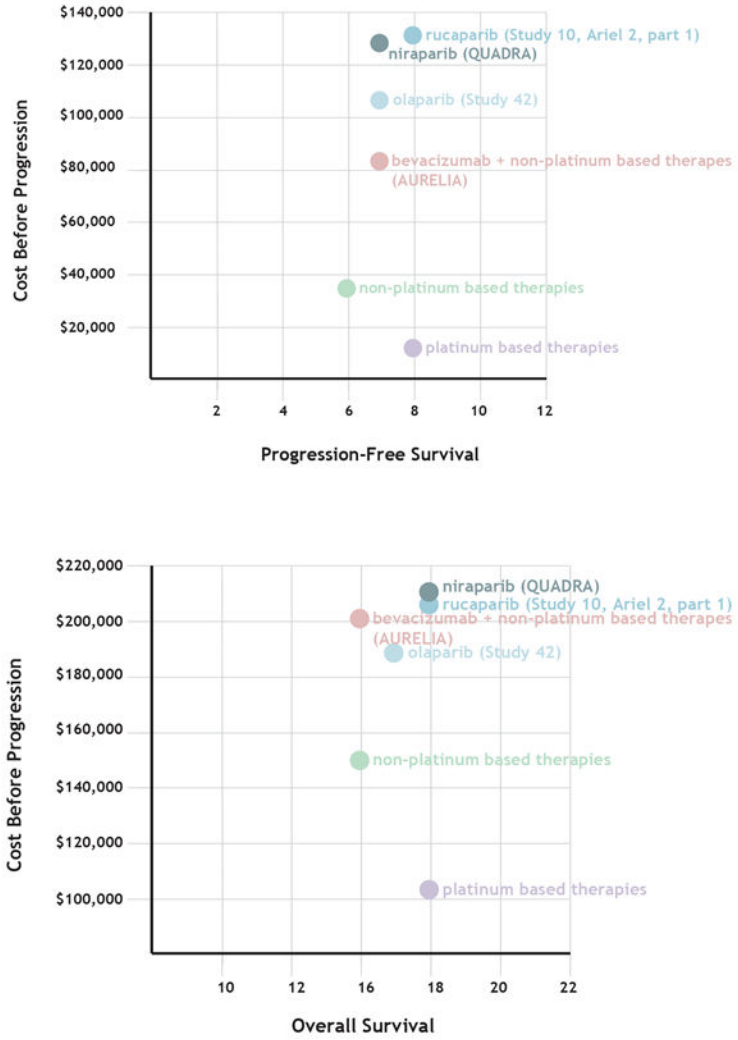

Figure 2:

Panel A: Cost Effectiveness → Cost vs PFS

Cost as a Function of Median Progression-Free Survival

Panel B: Cost Effectiveness → Cost vs OS

Cost as a Function of Median Overall Survival

Table 1:

Estimated cost breakdown for drugs/regimens used to treat recurrent ovarian carcinoma

Estimated Cost Breakdown								
	Drug	**Dose**	**Drug Cost**	**Infusion Cost**	**Pre-Tx Cost**	**Heme Tox Cost**	**Non-Heme Tox Cost**	**Total Combined Cost per Drug**
PARPi	Niraparib	300mg QD PO	17700.00	0.00	148.85	1012.97	7846.93	**$26,708.75**
	Rucaparib	600mg BID PO	16488.00	0.00	148.85	1066.63	5820.52	**$23,523.99**
	Olaparib	400mg BID PO	16178.40	0.00	148.85	1365.41	4709.68	**$22,402.34**
Non-platinum Based Therapies	Pegylated Liposomal Doxorubicin	50 mg/m2 BSA for 1hr QM	4287.40	477.67	616.16	1124.99	5240.32	**$11,746.54**
	Topotecan	1.5 mg/m2 BSA QD for 5d Q3W	282.84	1370.07	148.85	1094.11	6108.08	**$9,003.95**
	Pemetrexed	900 mg/m2 BSA for 10 min Q3W	9559.62	477.67	148.85	1115.40	5113.53	**$16,415.07**
	Abraxane	100 mg/m2 BSA days 1,8,15 QM	5079.38	477.67	148.85	1096.36	4655.18	**$11,457.44**
	Trabectedin/ Pegylated Liposomal Doxorubicin	PLD 30 mg/m2 BSA + 3hr trabectedin 1.1 mg/m2 BSA Q3W	6820.57	624.63	616.16	1134.53	9218.68	**$18,414.57**
Bevacizumab + Non-Platinum Based Therapies	Bevacizumab/ Paclitaxel	Paclitaxel 80 mg/m2 BSA on days 1, 8, 15, 22 QM + Bevacizumab 10 mg/kg Q2W	9607.64	1104.85	197.11	1616.17 *	7202.12 *	**$19,727.88**
	Bevacizumab/ Pegylated Liposomal Doxorubicin	PLD 40 mg/m2 BSA for 1hr QM + Bevacizumab 10 mg/kg Q2W	12935.64	791.23	664.42	1616.17 *	7202.12 *	**$23,209.57**
	Bevacizumab/ Topotecan	Topotecan 4 mg/m2 BSA on days 1, 8, 15 QM + Bevacizumab 10 mg/kg Q2W	9958.27	1104.85	197.11	1616.17 *	7202.12 *	**$20,078.51**

PO: oral; IV: intravenous; PLD: Pegylated Liposomal Doxorubicin; QD: daily; BID: twice daily; Q2W: every 3 weeks ;Q3W: every 3 weeks; QM: monthly; BSA: body surface area

* For Bevacizumab + Non-Platinum Based Therapies, the rate of adverse events was reported for all patients on trial and not parsed out for specific therapy therefore the costs of managing the toxicities are the same.

Table 2:

Incremental cost effectiveness ratios (ICERs) for niraparib, rucaparib and olaparib modeled using median progression-free survival (PFS).

	Costs: (Expected cost)	**Progression-Free Survival (Expected Months)**	**Cost-Effectiveness**	**ICER of Niraparib**	**ICER of Rucaparib**	**ICER of Olaparib**
Treatment	***Cost before next line***	***PFS***	***vs PFS***	***$/pfs month***	***$/pfs month***	***$/pfs month***
Niraparib	$132,790	7.0	$18,970			
Rucaparib	$133,096	8.0	$16,637			
Olaparib	$114,289	7.0	$16,327			
Non-Platinum Based Therapies	$38,471	6.0	$6,412	$94,319	$47,313	$75,818
Bevacizumab + Non-Platinum Based Therapies (AURELIA)	$85,309	7.0	$12,187	Bevacizumab based therapies more cost-effective than Niraparib	$47,787	Bevacizumab based therapies more cost-effective than Olaparib

ICER: Difference between Expected Costs between two drugs divided by the difference in Median PFS of the two drugs.

Table 3:

Incremental cost-effectiveness ratios (ICERs) of niraparib, rucaparib and olaparib modeled using quality of adjusted life-months (QALmonth).

	Costs: (Expected cost)	QALmonth before progress (Expected Months)	Cost-Effectiveness	ICER of Niraparib	ICER of Rucaparib	ICER of Olaparib
Treatment	***Cost before fifth line***	***QALmonth***	***vs QALmonth***	***$/QALmonth***	***$/QALmonth***	***$/QALmonth***
Niraparib	$132,790	7.0	$18,970			
Rucaparib	$133,096	8.0	$16,637			
Olaparib	$114,289	7.0	$16,327			
Non-Platinum Based Therapies	$39,579	5.8	$6,883	$74,569	$41,563	$59,768
Bevacizumab + Non-Platinum Based Therapies (Aurelia)	$85,309	6.8	$12,638	$189,924	$38,230	$115,920

ICER: Difference between Expected Costs between two drugs divided by the difference in Median PFS of the two drugs.

Table 4:

Incremental cost-effectiveness ratios for niraparib, rucaparib and olaparib modeled using median overall survival (OS).

	Costs: (Expected cost)	Overall Survival (Expected Months)	Cost-Effectiveness	ICER of Niraparib	ICER of Rucaparib	ICER of Olaparib
Treatment	***Cost over lifetime***	***OS***	***vs OS***	**$/QALmonth**	**$/QALmonth**	**$/QALmonth**
Niraparib	$210,844	18.0	$11,714			
Rucaparib	$205,309	18.0	$11,406			
Olaparib	$188,273	17.0	$11,075			
Non-Platinum Based Therapies	$147,390	16.0	$9,212	$31,727	$28,960	$40,883
Bevacizumab + Non-Platinum Based Therapies (Aurelia)	$203,553	16.0	$12,722	$3,646	$878	Olaparib is more cost-effective than Bevacizumab based therapies

ICER: Difference between Expected Costs between two drugs divided by the difference in Median OS of the two drugs.