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Cost-Effectiveness of Maintenance Therapy in Advanced Ovarian Cancer: Paclitaxel, Bevacizumab, Niraparib, Olaparib, Rucaparib, And Pembrolizumab

THESIS

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for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

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ABSTRACT OF THE THESIS

Cost-Effectiveness of Maintenance Therapy in Advanced Ovarian Cancer: Paclitaxel, Bevacizumab, Niraparib, Olaparib, Rucaparib, And Pembrolizumab

By

Juliet Elizabeth Wolford

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2018

Professor, Krishnansu Tewari, MD, Chair

Background: The greatest clinical obstacle in advanced ovarian cancer remains acquired drug resistance, indicative of the absence of effective maintenance therapies. We evaluated cost-effectiveness of available maintenance strategies for advanced ovarian cancer, adjusting for pre-treatment medication costs, infusion center charges, and costs of managing adverse events.

Methods: Toxicity and median PFS data were attained from the registration trials for a) paclitaxel (GOG 212); b) bevacizumab (GOG 218, ICON 7, OCEANS, GOG 213); c) niraparib (NOVA), olaparib (SOLO-2), rucaparib (ARIEL-3), and d) pembrolizumab. Since bevacizumab was investigated in different patient populations, each trial was modeled separately. Checkpoint inhibition phase III randomized trials in ovarian cancer are not mature, thus data for pembrolizumab (available via agnostic indication) was obtained from the phase IB ovarian cohort of KEYNOTE-028. Utilizing a Markov model, patients transitioned through health states of response, hematological and non-hematological

complications, progression, and death. Using Medicare data, the costs of pretreatment testing, infusions, and managing toxicities were estimated. To compare the therapies, incremental cost-effectiveness ratios (ICER) and quality of adjusted life-months gained were calculated.

Results: Seemingly, the most cost-effective was maintenance paclitaxel at $1,329 /PFS month. Expected costs of PARP inhibitors (PARPi(s)) prior to progression were approx. $510,387 (20.3x paclitaxel, 7.5x pembrolizumab, and 2.6-3.2x bevacizumab). Comparing pembrolizumab to PARPi(s) in BRCA-deficient patients, the immunotherapy maintenance therapy generated ICERs per month of life gained of $23,055 (niraparib), $25,622 (rucaparib), and $28,465 (olaparib).

Conclusion: Employing PFS as the benchmark, high costs of maintenance PARPi(s) are not abated by adjusting for the sequelae that occurs with maintenance chemotherapy and anti-angiogenic therapy. The current trend to study novel combinations is challenging when considering economic toxicity and the burden it places on our patients.

INTRODUCTION

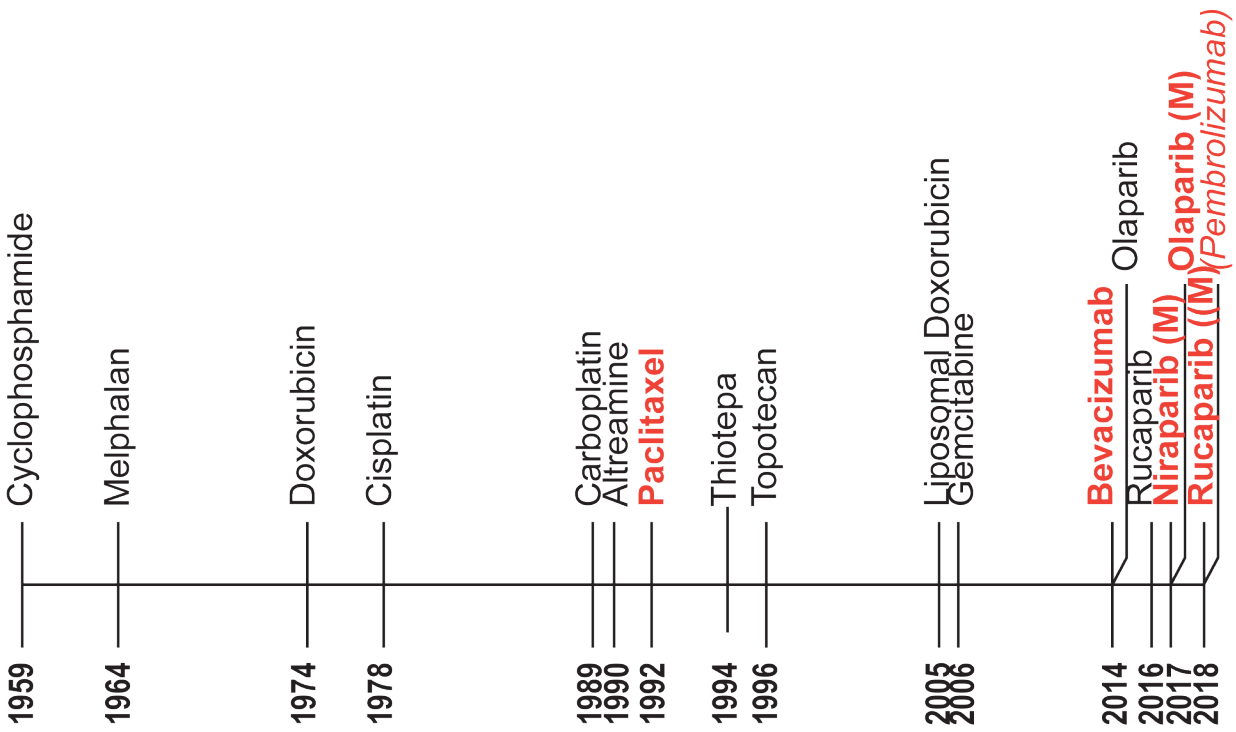
In the United States in 2018, there will be approximately 22,240 new cases diagnosed and 14,070 ovarian cancer deaths. Despite its low incidence, ovarian cancer is the eighth most common cause of cancer death among US women and the leading cause of death within the gynecologic cancer spectrum.[1] The lethality of ovarian cancer is multifactorial, mainly resultant of an absence of an effective screening tool for the general population and due to a lack of specific symptoms early in the disease course leading to the majority of women diagnosed with ovarian cancer at an advanced stage. The combination of cytoreductive surgery plus the platinum-based chemotherapy doublet has long been the widely accepted standard of care treatment of advanced ovarian cancer. Nevertheless, acquired drug resistance remains a critical issue for the treatment of advanced ovarian cancer, because even though 80% of women with advanced ovarian cancer are initially chemosensitive, 75% of those patients will ultimately relapse.[2]

Unfortunately, for those patients undergoing treatment for recurrent ovarian cancer, the 5-year survival rate is dismal as recurrent treatment strategies are not curative, with a 10-year disease specific survival of less than 10%.[3] This elucidates the need for therapies that will provide durable disease control after initial response. Therefore, recent developments in ovarian cancer therapy have shifted focus to maintenance therapy. Maintenance therapies are aimed at sustaining the initial chemosensitive response by increasing their time to recurrence. Accordingly, there has been a great investment of time and resources to study novel maintenance therapies in phase 3 randomized trials involving women with primary advanced and recurrent disease.

Following an 8-year drought, beginning in 2014 there have been several agents

added to our armamentarium of ovarian cancer treatments every 1-2 years affording us access to even more treatments for our patients with ovarian cancer. **(Figure 1).** These therapies not only include other chemotherapy agents, but additionally targeted therapies, such as poly (ADP ribose) polymerase inhibitors (PARPi), anti-angiogenics, and immunotherapy. Exploiting synthetic lethality, PARPi selectively target the tumor cells that are BRCA deficient and do not affect normal cells with intact homologous recombination mechanisms.[4] There have been three PARPi approved by the FDA thus far for the treatment of ovarian cancer, niraparib, rucaparib and olaparib, with varying indications based on germline or somatic mutational homologous recombination status, line of treatment, and for use as a treatment versus maintenance strategy. Anti-angiogenics, such as bevacizumab, target vascular endothelial growth factor (VEGF) and inhibit vessel growth, a key factor in the persistence of ovarian cancer.[5] Pembrolizumab, an immunotherapy, inhibits programmed cell death-1 (PD-1), a crucial component in the immune checkpoint pathway, blocking the binding of PD-1 to its ligand, PDL-1, which is overexpressed in ovarian cancer. In tumors, PD-L1 expression is upregulated to allow the cancer to evade the hosts immune response and allowing the tumor to grow uninhibited. Thus, by inhibiting this response, the host is able to recognize the tumor cells and mount a response.[6,7] These novel therapeutics have been investigated in numerous ovarian cancer clinical trials as treatment and maintenance strategies. It is unprecedented that there are potentially 6 targeted therapies that can be used as maintenance strategies for the treatment of advanced, recurrent ovarian cancer.

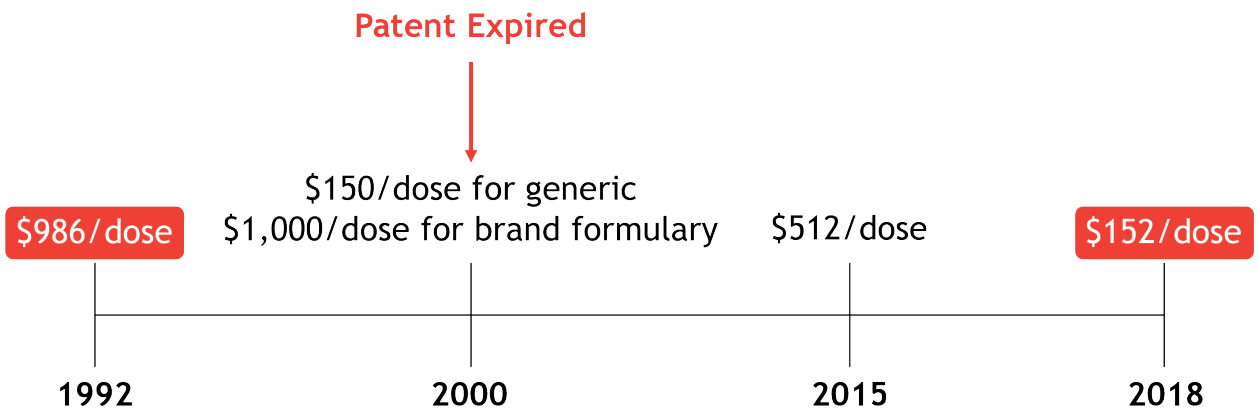
FIGURE1: Timeline of Clinical Research + US FDA Approvals



Most agents approved for the treatment of ovarian cancer, such as the cytotoxic therapies, immunotherapies and antiangiogenic agents are administered intravenously and have the associated costs of receiving an infusion, unlike the PARPi which are given orally. Additionally, the PARPi and immunotherapies are unique by virtue of being relatively well-tolerated in comparison to traditional cytotoxic chemotherapy and the spectrum of anti-angiogenic-associated toxicology. Moreover, even though the novel targeted therapies have shown great promise in the treatment of ovarian cancer, the unfortunate nature is that they are often cost-prohibitive secondary to their associated high developmental costs. Although, it is important to recognize that while clinical benefit will always be relevant, by contrast, drug costs are fluid. Anything concerning costs discussed in this paper as it is

being written may not be applicable tomorrow. For example, during the mid-1990s when the Gynecologic Oncology Group introduced the world to paclitaxel through GOG protocol 111, drug cost was approximately $6000 for 6 cycles. Today, it is off patent and commercially synthesized and only costs approximately $1000 for 6 cycles. (**Figure 2**)

FIGURE 2: Cost of Paclitaxel through Time



Typically, the benchmark for cost-effectiveness studies include $50,000 per quality-adjusted life year (QALY) with reported range between 20,000 and 100,000.[8] Although, critics of cost-effectiveness studies are quick to point out that the $50,000 QALY threshold benchmark is unrealistic, not generalizable and not supported by scientific evidence. Diamond et al. adequately describes the threshold as a "gross oversimplication of a complex process."[9] Nevertheless, cost-effectiveness studies are useful, especially in the setting of identifying causes of economic toxicity, but it is essential to be aware that by invoking thresholds, cost-effectiveness studies have built-in clinical endpoints which permit predetermined limits to be established. To date there are very few studies

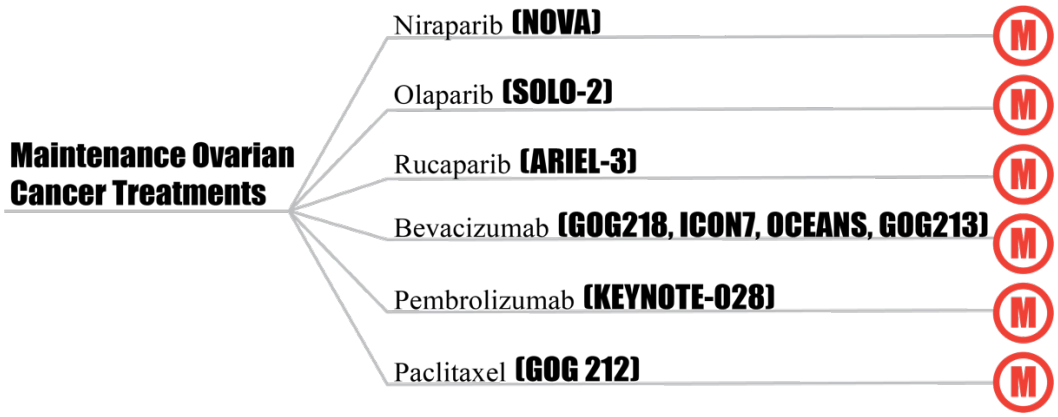
investigating the cost-effectiveness of ovarian cancer treatments, and there have been no previous studies examining the cost-effectiveness of the various maintenance therapies for the treatment of ovarian cancer. In our study, we sought to evaluate and compare the cost-effectiveness of actual and potential maintenance strategies in advanced/recurrent ovarian cancer. Therefore, we evaluated the cost-effectiveness of available maintenance strategies for the treatment of advanced ovarian cancer, paclitaxel, niraparib, rucaparib, olaparib, bevacizumab, pembrolizumab, and paclitaxel, adjusting for pre-treatment medication costs, infusion center charges, and costs of managing adverse events.

METHODS

Determining the Costs

For the therapies included in this analysis, United States registration trials were used to obtain data on the frequency and severity of adverse events and on the primary endpoint, which was progression-free survival (PFS) in most of the studies. Although ICON7 was run outside of the U.S., this study also provided important data for maintenance bevacizumab for our model.[10] Because anti-angiogenesis therapy was studied in different patient populations, each trial, GOG 218, ICON7, OCEANS, and GOG 213, was modeled separately.[10–13] Importantly, the phase 3 randomized trial of bevacizumab in the platinum-resistant population, AURELIA, was not included in our model as patients in that study were treated to progression without a maintenance component.[14] Although phase III randomized trials involving checkpoint inhibition in ovarian cancer have not matured, data for pembrolizumab (available via agnostic indication) were obtained from the phase IB ovarian cohort of KEYNOTE-028.[15] Finally, GOG protocol 212 was modeled to study paclitaxel, and NOVA, SOLO-2, and ARIEL-3, and allowed us to incorporate the PARPi(s) niraparib, olaparib, and rucaparib in our analyses, respectively.[16–19] **(Figure 3)** Drug trials were only compared to trials studying drugs of a different class. For example, none of the PARPi(s) were compared with one another, and bevacizumab was only compared to trials studying PARPi(s), chemotherapy, and pembrolizumab.

FIGURE 3: Maintenance Ovarian Cancer Treatments



The MediCare Services Drug Payment Table and Physician Fee Schedule were used to determine direct costs of individual drugs and infusion charges.[20] Billed charges and indirect costs were not modeled. Outpatient medication costs were collected from UptoDate.[21] Registration trial data were used to model Common Toxicity Criteria version 4 for grade 3 and above adverse events for each treatment regimen.[22] We included the costs of germline/somatic BRCA testing for the PARPi(s), and for pembrolizumab we modeled unique immune-mediated adverse events, including endocrinopathies. Adjustments were made for pre-treatment medication costs such as anti-emetics and steroids, specialized testing including genetic testing, infusion center charges, and the costs of managing adverse events. Although germline mutation is not required to prescribe any of the PARPi(s), we included the costs in our model because mutational analysis informs patients of their prognosis, their personal risk of breast cancer, the magnitude of benefit conferred by PARPi(s), and potentially affected family members. **(Table 1)**

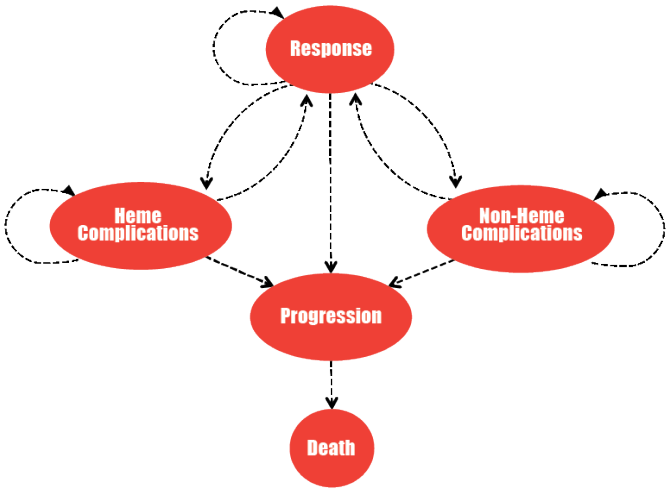
TABLE 1: Determining the Costs

Estimated Cost Breakdown									
	Drug	Study	Dose	Drug Cost	Pre-Tx Cost	Infusion Cost	Heme Tox Cost	Non-Heme Tox	Combined Cost per Drug
PARPi	Niraparib	***NOVA***	300mg QD	17,700.00	3351.85	0.00	1187.52	5572.83	**$27,812.21**
	Olaparib	***SOLO 2***	300mg BID	16,178.40	3351.85	0.00	925.04	2033.28	**$22,488.57**
	Rucaparib	***ARIEL 3***	600mg BID	16,488.00	3048.85	0.00	965.58	5896.68	**$26,399.10**
Anti-Angio	Bevacizumab	***GOG 218***	15mg/kg q 3 weeks	9,557.63	197.11	568.13	1478.66	3173.13	**$14,974.66**
	Bevacizumab	***ICON 7***	7.5mg/kg q 3 weeks	4,778.82	197.11	568.13	1511.69	5998.73	**$13,054.48**
	Bevacizumab	***OCEANS***	15mg/kg q 3 weeks	9,557.63	197.11	568.13	2981.77	2845.84	**$16,150.48**
	Bevacizumab	***GOG 213***	15mg/kg q 3 weeks	9,557.63	197.11	568.13	1518.85	4952.85	**$16,794.57**
Immuno	Pembrolizumab	***KEYNOTE 028***	200mg q 3 weeks	10,994.20	1266.65	568.13	0.00	2820.83	**$15,649.81**
Chemo	Taxol	***GOG 212***	175mg/m2 q monthly	152.76	94.81	568.13	577.50	3524.81	**$4,918.01**

The Markov Model

As executed in most cost-effectiveness studies involving making medical decisions we utilized a Markov Model to perform our study. Markov models are a form of predictive modeling that allow patients to transition between different health states by employing monthly transition probabilities. This type of decision tree permits varying clinical scenarios to exist within one model.[23–25] Our Markov model was created using a population with recurrent or advanced ovarian cancer previously treated with chemotherapy prior to entering the model. The chain consisted of different nodes that patients can transition to, including Response, Hematologic Complications, Non-Hematologic Complications, Progression, and Death. **(Figure 4)** Registration trial data was used to estimate the transition probabilities between the different health states.

FIGURE 4: The Markov Model



With our model all patients began in Markov chain node, or the health state of "response." With each subsequent month an individual patient remained in that state as they continued to respond to treatment or transitioned into a new health state node in the chain. Each month a cost of treatment for each month is incurred as each health state is experienced. Within the "hematologic complications" node, toxicities included grade 3 or higher neutropenia, thrombocytopenia, and anemia. While within the "non-hematologic complications" node, adverse events included hypertension, dermatologic conditions, abdominal pain, diarrhea/constipation, nausea/vomiting, arthralgia, neuralgias and gastrointestinal wall disruption (i.e., fistula/bowel perforation). In any given month, patients could only remain or transition into one of these health states. Patients who experience complications may transition back into "response" if the complications were successfully treated. Therefore, after one month, patients in a complication or toxicity state may remain within the health state and discontinue therapy, go back to response, or

experience disease progression and receive next-line therapy. The likelihood of progressing from response to progression with the next-line therapy and onward was determined by utilizing the Kaplan Meier PFS curves from their registration trials.

As with all Markov models, several assumptions were incorporated into the design of the Markov decision tree for ease of modeling:

A. All therapies were scheduled on a 1-month cycle and patients remain in each health state for one month.
B. An individual patient can only experience one complication in any given month as the complications are mutually exclusive within the model.
C. Within the same month, individual patients can accumulate the cost of managing an adverse event and the cost of the treatment.
D. Even if it was a complication that determined advancement on to next-line line therapy, patients are assumed to have progressive disease when they are within the next-line therapy or "progression" state.
E. Before entering the "death" state patients must transition through the progression state; therefore, death from other causes, such as grade 5 adverse events, is not accounted for in the Markov model.

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

In an exploratory analysis to evaluate quality of life we recognized that for women with ovarian cancer, progression is measured in months. Our data was therefore reported in quality-adjusted life months (QALmonth) rather than the quality-adjusted life year (QALyear) that is typically used in cost-effectiveness studies. Therefore, we quantified the health utilities within the model by assigning scores to each of the health states in our model – the response state was assigned a score of 1, the hematologic complications group was assigned 0.75, the non-hematologic complications were scored at 0.5 because they are not often as easily corrected as hematologic adverse events; progression was also scored at 0.5 and death was a zero. Within our Markov model, cost-effectiveness associated with QALmonth was determined by applying these health utilities scores with the median PFS reported in a given trial. This adjustment indicates a decrease in quality of life if the patient transitions out of the health state of response.

Measuring Internal Validity

By comparing the median PFS simulated within the model to the median PFS reported within the registration trials for each therapy, we were able to determine the validity of the Markov Model. The actual PFS and simulated PFS values are shown in **Table 2** below. While there were very minimal differences between the values for a majority of

the treatments, the largest difference between the actual and simulated PFS values was noted to be within the niraparib and the pembrolizumab data. This difference is accounted for within the methodology of the creation of the Markov model. In order to unify the scale of the treatment effects across the registration trials, the Kaplan-Meier PFS curves were used to reconstruct individual patient data within the model to determine the transition probabilities. Thus, the shape of the PFS curves themselves can have an impact on the simulation. In the NOVA and Keynote-028 studies because of the large variance in response for those patients included in the study, this lead to a PFS curve that has the appearance of being less exponential or flatter appearing, which can slightly skew the simulated PFS in either direction. Since a majority of the values were so close and the actual PFS values are the most widely reported and recognized by those who treat ovarian cancer, for the purposes of the cost-effectiveness analyses included in the results section we utilized the actual median PFS obtained from the registration trials. However, in order to elucidate the nuances after assigning the health utility values for the QALmonth calculations, we included the simulated median PFS values with their quantified health value.

TABLE 2: Measuring Internal Validity

	ACTUAL Progression-Free Survival	SIMULATED Progression-Free Survival	SIMULATED QALmonth before Progress
Treatment	***PFS***	***PFS***	***PFS***
Niraparib with mutation	21.0	17.0	16.8
Olaparib	19.1	19.0	19.0
Rucaparib with mutation	16.6	16.0	16.0
Bevacizumab (GOG218)	14.1	13.0	12.3
Bevacizumab (ICON7)	19.8	22.0	21.8
Bevacizumab (OCEANS)	12.4	12.0	11.8
Bevacizumab (GOG213)	13.8	15.0	14.0
Paclitaxel	18.9	19.0	19.0
Pembrolizumab	1.9	5.0	4.0

RESULTS

Expected Cost Prior to Progression and Cost-Effectiveness

Comparing the cost-effectiveness, defined as the expected cost before progression divided by the PFS, with the longest PFS and lowest cost, maintenance paclitaxel clearly dominated. Even when adjusting for costs of infusion and managing adverse events, as seen in **Table 2** below, maintenance paclitaxel appeared to be the most cost-effective at $1,329 per month gained progression-free, while pembrolizumab was the least cost effective with a cost of $39, 397 per month gained progression-free. The costs prior to progression, including the drug costs, managing adverse events, infusion costs, physician costs, and the costs of pre-treatment testing, were highest for the PARPi(s), ranging between $451,499 for rucaparib, $515,211 for niraparib, and $564, 451 for olaparib. Ultimately, in comparison to the other therapies the cost of PARPi(s) prior to progression were approximately 20.3 times more than paclitaxel, 7.5 times more than pembrolizumab, and 2.6-3.2 times more than bevacizumab. We believe the estimated costs before progression were highest for the PARPi(s) for two reasons:

1. Cost is incurred daily based on the oral drug intake schedule, and
2. For the PARPi trials we knew mutational status and those patients with germline BRCA mutations tend to have a more favorable prognosis as evidenced by response to platinum and manifestation of platinum sensitive disease at recurrence. Therefore, they incur more cost because they typically live longer

Even though pembrolizumab was noted to be the least cost-effective because of its short PFS, when calculating the ICERs because pembrolizumab is administered only once per month keeping its cost prior to progression low, when compared to each of the

PARPi(s) in BRCA-deficient populations, the ICERs make the anti-PD-1 therapy appear relatively cost-effective. The anti-PD-1 maintenance yielded ICERs per month of life gained of $23,055 in comparison to niraparib, $25,622 to rucaparib, and $28,465 to olaparib. This phenomenon of apparent cost-effectiveness of pembrolizumab despite a dismal PFS was even more apparent in the ICERs associated with the bevacizumab trials, with ICERs ranging between $5,632 and $12,019 per month of life gained.

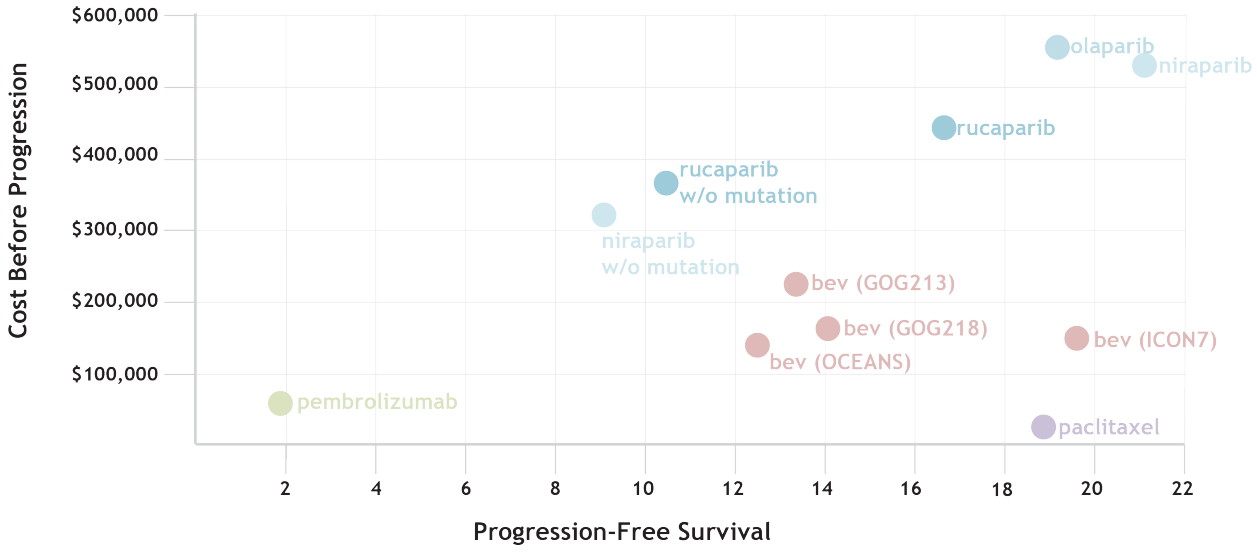
TABLE 3: Cost Effectiveness → Cost vs PFS

	Costs: (Expected cost)	Progression-Free Survival (Expected Months)	Cost-Effectiveness	ICER of Niraparib with mutation	ICER of Olaparib	ICER of Rucaparib with mutation	ICER of Bevacizumab (OCEANS)	ICER of Taxol	ICER of Pembrolizumab
Treatment	*Cost before next line*	*PFS*	*vs PFS*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*
Niraparib with mutation	$515,211	21.0	$24,534				$39,821	dominated by Taxol	$23,055
Olaparib	$564,451	19.1	$29,552				$58,462	dominated by Taxol	$28,465
Rucaparib with mutation	$451,499	16.6	$27,199				$66,368	dominated by Taxol	$25,622
Bev (GOG218)	$177,750	14.1	$12,606	$48,907	$77,340	$109,500		dominated by Taxol	$8,434
Bev (ICON7)	$175,660	19.8	$8,872	dominated by Bev (ICON7)	dominated by Bev (ICON7)	dominated by Bev (ICON7)		dominated by Taxol	$5,632
Bev (OCEANS)	$172,752	12.4	$13,932	$39,821	$58,462	$66,368		dominated by Taxol	$9,324
Bev (GOG213)	$217,882	13.8	$15,789	$41,296	$65,390	$83,435		dominated by Taxol	$12,019
Taxol	$25,123	18.9	$1,329	dominated by Taxol	dominated by Taxol	dominated by Taxol	dominated by Taxol		dominated by Taxol
Pembrolizumab	$74,853	1.9	$39,397	$23,055	$28,465	$25,622	$9,324	dominated by Taxol	

Exploiting the same data but in a different format for ease of comprehension, in Figure 5 below, we depict cost prior to progression alongside median PFS. The PARPi(s) cluster towards the top-right of the figure as these patients are on therapy longer due to an extended PFS, however they are costlier, particularly among the favorable prognosis group with germline BRCA mutation patients. When comparing the mutation positive to mutation negative patient population, the estimated cost before progression for mutation-positive

niraparib is $515,211 as compared to $316,488 without mutation. A similar phenomenon occurs with rucaparib with and without mutation. SOLO-2 only recruited mutation-positive patients and therefore we do not have a mutation-negative comparator for olaparib. All four bevacizumab studies congregate just to the right of center of the figure demonstrating the cost-effectiveness of bevacizumab in comparison to the PARPi . Pembrolizumab and paclitaxel are seen towards the bottom of the figure because of their low expected costs prior to progression. It should be noted though that the relatively short PFS associated with pembrolizumab reflects the poor prognosis of heavily pretreated phase I patients in KEYNOTE-028 from which our data are derived since to date we do not have phase III data available. By contrast, paclitaxel was studied as a first-line maintenance therapy among a population of women with newly diagnosed disease who responded favorably enough to primary therapy to be randomized to GOG 212. For this reason, they enjoyed a healthier, cost-effective PFS.

FIGURE 5: Cost Effectiveness → Cost vs PFS



Modifying for Quality of Life

Below in Table 3 is our exploratory analysis where we assigned quantified health utility scores to the different health states to further evaluate the quality of life as measured in months (QALmonth) for the different therapies. For this evaluation we used the simulated PFS from the model in addition to the health utility scores. As evidenced below, even when assigning scores to each of the health care states in our model, the months of quality adjusted life gained progression-free are very similar to what we observed earlier without using the modifiers indicative that maintenance therapies as a whole are generally well tolerated, and it again demonstrates that paclitaxel maintenance therapy was the most cost effective.

TABLE 4: Cost Effectiveness → Cost vs PFS with QALmonth modifiers

	Costs: (Expected cost)	QALmonth before progress(Expected Months)	Cost-Effectiveness	ICER of Niraparib with mutation	ICER of Olaparib	ICER of Rucaparib with no mutation	ICER of Bevacizumab (OCEANS)	ICER of Taxol	ICER of Pembrolizumab
Treatment	*Cost before next line*	*PFS*	*vs PFS*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*	*$/pfs month*
Niraparib with mutation	$515,211	16.8	$30,759				$30,759	dominated by Taxol	$34,538
Olaparib	$564,451	19.0	$29,708				$29,708	dominated by Taxol	$32,640
Rucaparib with mutation	$451,499	16.0	$28,219				$28,219	dominated by Taxol	$31,387
Bev (GOG218)	$177,750	12.3	$14,510	$74,991	$57,289	$73,000		dominated by Taxol	$12,472
Bev (ICON7)	$175,660	21.8	$8,076	dominated by Bev (ICON7)	dominated by Bev (ICON7)	dominated by Bev (ICON7)		$54,741	$5,679
Bev (OCEANS)	$172,752	11.8	$14,702	$68,492	$54,027	$65,587		dominated by Taxol	$12,632
Bev (GOG213)	$217,882	14.0	$15,563	$108,120	$69,314	$116,809		dominated by Taxol	$14,303
Taxol	$25,123	19.0	$1,322	dominated by Taxol	dominated by Taxol	dominated by Taxol	dominated by Taxol		dominated by Taxol
Pembrolizumab	$74,853	4.0	$18,713	$34,538	$32,640	$31,387	$18,713	dominated by Taxol	

Sensitivity Analysis

With comparable PFS curves and better tolerability to the other maintenance therapies, the limiting factor for the PARPi therapies becoming cost-effective appears to be the cost of the drug itself. Therefore, a sensitivity analysis was performed to assess the "cost-effectiveness cost" at which the PARPi would become cost-effective to the other therapies. Additionally, for pembrolizumab, while being mid-range for cost prior to progression, it had the lowest PFS secondary to the trial the data was acquired from. Thus, since this is immature data and has a very small sample size, we believed this could be confounding the results, resulting in a misleadingly low PFS. Subsequently, for this sensitivity analysis we asked two questions. Firstly, since the PARPi(s) appeared to not be cost-effective, we wanted to determine at what level of reduction in cost would the PARPi(s) become cost-neutral in comparison to the other drugs in our model. And secondly, because pembrolizumab was associated with the short PFS given the high-risk phase I population in which it was studied, we sought to determine what the benchmark PFS would need to be for it then to become cost-neutral to the other drugs in the model. Furthermore, with the recent US FDA approval of maintenance bevacizumab this past June for advanced ovarian cancer based on the GOG-218 study included in this analysis, we were particularly interested in controlling for the anti-VEGF therapy. [26] As seen in **Table 4**, taking an example from the PARPi(s), to be seen as cost-neutral with anti-VEGF therapy, niraparib would require a 68% reduction in cost. Although to be fair, we modeled niraparib using the label's dose of 300 mg, when in the real world, we should acknowledge that most patients are treated at a daily dose of 200 mg. For pembrolizumab, in comparison to bevacizumab, the gain in median PFS would need to increase from 1.9 month to between at least 5-8

months. With paclitaxel dominating pembrolizumab in cost-effectiveness, pembrolizumab would need to have an PFS of over 56 months to compete with paclitaxel.

TABLE 5: Sensitivity Analysis

	Costs: (Expected cost)	Progression-Free Survival (Expected Months)	Cost-Effectiveness	Cost-Effective Cost for Niraparib	Cost-Effective Cost for Olaparib	Cost-Effective Cost for Rucaparib	Cost-Effective PFS for Pembrolizumab
Treatment	*Cost before next line*	*PFS*	*vs PFS*	*$*	*$*	*$*	*pfs month*
Niraparib with mutation	$515,211	21.0	$24,534				3
Olaparib	$564,451	19.1	$29,552				3
Rucaparib with mutation	$451,499	16.6	$27,199				3
Bev (GOG218)	$177,750	14.1	$12,606	$11,927	$16,946	$14,592	6
Bev (ICON7)	$175,660	19.8	$8,872	$15,662	$20,681	$18,327	8
Bev (OCEANS)	$172,752	12.4	$13,932	$10,602	$15,621	$13,267	5
Bev (GOG213)	$217,882	13.8	$15,789	$8,745	$13,764	$11,410	5
Taxol	$25,123	18.9	$1,329	$23,205	$28,223	$25,869	56
Pembrolizumab	$74,853	1.9	$39,397	-$14,863	-$9,844	-$12,198	

CONCLUSION

In conclusion, we recognized several phenomena from our model. One is that the high starting costs of PARPi(s) together with daily dosing and longer median PFS associated with germline BRCA mutation carriers make the PARPi(s) the least cost-effective of potential maintenance therapies in advanced ovarian carcinoma. In other words, the favorable prognosis associated with BRCA-deficiency means that patients live longer progression-free and therefore receive more drug. Secondly, even though the targeted therapies such as PARPi (s) and immunotherapy are overall considerably better tolerated, assigning scores to health utility states to account for toxicology does very little to mitigate the high costs associated with these novel targeted therapies. Thirdly, to become cost-neutral with anti-VEGF therapy, PARPi(s) would require a significant (i.e., >50%) reduction in initial drug cost. Lastly, the upcoming onco-immunology maintenance trials in the recurrent/advanced ovarian cancer disease space need the median PFS benchmark to range between at least 5 to 8 months to become cost-effective in comparison to the other maintenance strategies.

DISCUSSION

The strengths of this study are that it is a comprehensive assessment of the total cost of the therapies, not only limited to just the drug cost, but also including administration of the drug, physician costs, costs of managing adverse events, and the costs of pre-treatment testing, including molecular and genetic testing. In addition, the use of the Markov model based on the registration trial data allows for a more accurate predictive model of acquired costs associated with the therapies studied, accommodating for an evaluation of cost and clinical outcomes concurrently. Another strength of this study is that there is a need for additional cost-effectiveness studies in the ovarian cancer treatment arena. As maintenance therapies are further being developed and investigated, it is important to perform cost-effectiveness analyses in order to understand where the primary expense of these therapies is arising from. Financial toxicity can place an unnecessary burden on our ovarian cancer patients and their families as they navigate through their treatment course, demonstrating the need for studies such as this one.

As with all cost-effectiveness studies the limitations of the study are that the analysis had to include multiple assumptions. Though the analysis is based on randomized controlled clinical trials, it is still a simulation model, and thus in order to provide comparisons, those assumptions must be incorporated into the model. Furthermore, there are differences in the registration trial populations included in this study that the model was unable to account for. Therefore, when discussing patient care, it is important to note that cost-effectiveness analyses can inform decisions, but they should never be utilized to make clinical decisions independent of the additional, relevant clinical information, especially with the knowledge that costs fluctuate over time. Lastly, a limitation was that

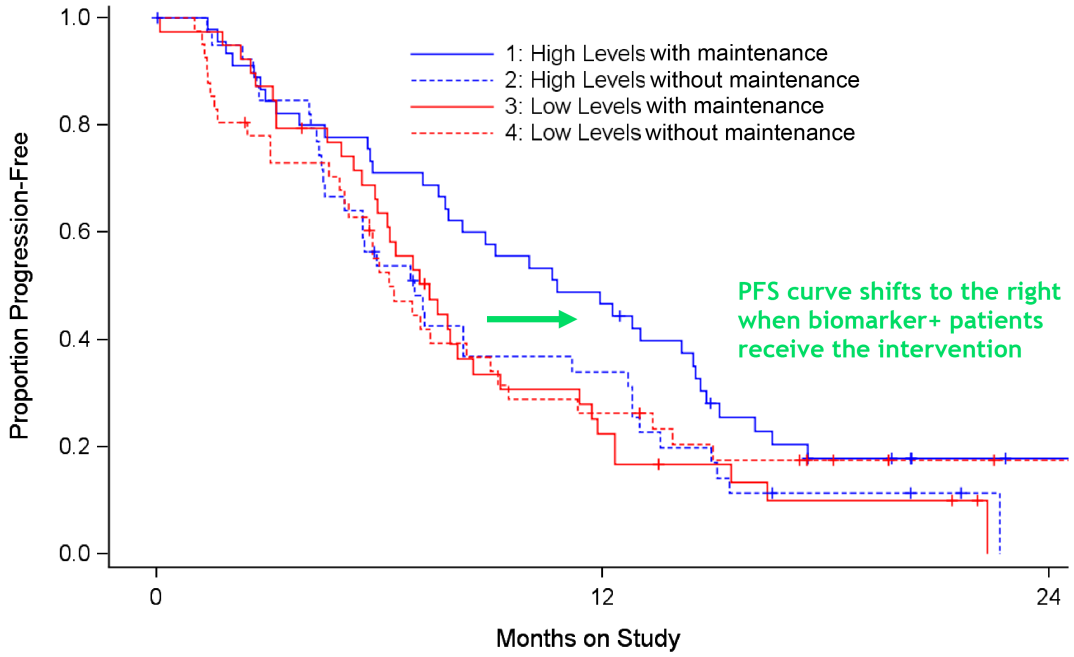
for the purposes of this study the clinical outcome employed was PFS. Mature overall survival (OS) data are still lacking for PARPi(s) and will need to be modeled once available. Likewise, immuno-oncology phase III trials in this disease will start reporting in the next 1-2 years and that data will also needed to be modeled when available.

While the data on the efficacy of PARPi(s) is promising, the unfortunate nature of new novel therapies is their inherent associated high costs reflecting the high costs of development. As seen in this study, the primary expense of novel targeted therapies lies in the high cost of the drug, rather than the complications associated with its use. Reconciling the often incremental clinical benefit with exponentially rising costs for novel therapeutics remains challenging. As with most cost-effectiveness studies of new therapies, minimal reductions in cost should have a great benefit in the cost effectiveness of the medications. Thus, to make these novel drugs more cost-effective, several strategies can be employed, including identifying lower dosages that do not compromise on efficacy, reformulating the oral medications to allow for use of a reduced number of tablets or for slower release of the therapy in order to increase time between dosing, using the drugs earlier in the disease course, expanding the label to include other tumor types, and development of active and tolerable generics and/or biosimilars.

In our study, by using PFS as the benchmark, the high costs of novel therapeutics, are not mitigated by adjusting for the sequelae that may manifest with maintenance chemotherapy and anti-angiogenic therapy. This is especially apparent in the setting of maintenance therapies, where patients remain on the therapies for an increased length of time, where the expense can preclude them from being a viable option in patients who could potentially benefit. This is extremely disheartening in an era where the development

and combination of novel therapeutics will likely serve an essential role in overcoming acquired drug resistance, which is the crucial obstacle that we must cross in order to overcome the lethality of this deadly disease. When considering economic toxicity, the current trend to study novel combinations is problematic and once again the critical issue is the absence of validated predictive biomarkers through which unnecessary toxicity and cost can potentially be mitigated. **(FIGURE 6)**

FIGURE 6: A Need for Predictive Biomarkers



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