Cost-Effectiveness of Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

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ABSTRACT

Background: Maintenance therapy with the PARP inhibitor olaparib for metastatic pancreatic cancer (MPC) with a germline *BRCA1* or *BRCA2* mutation has been shown to be effective. We aimed to evaluate the cost-effectiveness of maintenance olaparib for MPC from the US payer perspective. **Materials and Methods:** A partitioned survival model was adopted to project the disease course of MPC. Efficacy and toxicity data were gathered from the Pancreas Cancer Olaparib Ongoing (POLO) trial. Transition probabilities were estimated from the reported survival probabilities in each POLO group. Cost and health preference data were derived from the literature. The incremental cost-utility ratio, incremental net-health benefit, and incremental monetary benefit were measured. Subgroup analysis, one-way analysis, and probabilistic sensitivity analysis were performed to explore the model uncertainties. **Results:** Maintenance olaparib had an incremental cost-utility ratio of \$191,596 per additional progression-free survival (PFS) quality-adjusted life-year (QALY) gained, with a high cost of \$132,287 and 0.691 PFS QALY gained, compared with results for a placebo. Subgroup analysis indicated that maintenance olaparib achieved at least a 16.8% probability of cost-effectiveness at the threshold of \$200,000/QALY. One-way sensitivity analyses revealed that the results were sensitive to the hazard ratio of PFS and the cost of olaparib. When overall survival was considered, maintenance olaparib had an incremental cost-utility ratio of \$265,290 per additional QALY gained, with a high cost of \$128,266 and 0.483 QALY gained, compared with results for a placebo. **Conclusions:** Maintenance olaparib is potentially cost-effective compared with placebo for patients with a germline *BRCA* mutation and MPC. Economic outcomes could be improved by tailoring treatment based on individual patient factors.

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Background

Pancreatic cancer is the seventh most common cause of cancer death worldwide, accounting for 3.88% of the disease burden from all neoplasms reported by the Global Burden of Disease Study 2017.¹ This abysmal statistic is partly attributed to the fact that nearly 50% of pancreatic cancers are diagnosed as metastatic and approximately 30% as locoregional disease, with a 5-year survival rate of 8%.² For more than a decade, the availability of new drugs and combinations, such as gemcitabine-based chemotherapy, has significantly improved the outcome of patients with metastatic pancreatic cancer (MPC), increasing median overall survival (OS) to 8 to 12 months.³ However, therapeutic options for MPC are still limited and the prognosis is poor.⁴

Due to the heterogeneous nature of pancreatic tumors, molecularly targeted therapies could offer physicians the opportunity to tailor a strategy to the unique properties of a patient's individual tumor.² Loss-of-function mutations in *BRCA1*, *BRCA2*, or both genes have been found in 4% to 7% of patients with pancreatic tumors.⁵ Cells with a *BRCA* mutation become sensitive to PARP inhibition through multiple mechanisms, including the trapping of PARP on DNA at sites of single-strand breaks.⁵ As an oral inhibitor of PARP, olaparib can bind the catalytic domain of PARP1, leading to a reduction of PARylation and therefore to a defect in DNA repair.⁶ Olaparib has already been used with success in breast and ovarian cancers.⁷ The Pancreas Cancer Olaparib Ongoing (POLO) trial reported the efficacy and safety of maintenance olaparib compared with placebo in patients with MPC with a germline *BRCA* mutation.⁸ Results revealed that maintenance olaparib notably prolonged median progression-free survival (PFS) compared with placebo (7.4 vs 3.8 months; hazard ratio [HR] for disease progression or death, 0.53; 95% CI, 0.35–0.82; *P* = .004), although no difference in OS between the olaparib and placebo groups was observed. Grade ≥ 3 adverse drug

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events were more frequently reported in the olaparib group than in the placebo group (40% vs 23%). Thus, the maintenance olaparib regimen seems to be an attractive option for the treatment of MPC with a germline *BRCA* mutation. However, considering cost-effectiveness in health decisions is crucial for clinicians and decision-makers to optimally allocate limited health resources. This analysis aimed to investigate the cost-effectiveness of maintenance olaparib for MPC with a germline *BRCA* mutation from the US payer perspective.

Materials and Methods

This study was based on a literature review and modeling techniques and did not require approval by an institutional research ethics board.

Analytic Overview

The hypothetical target population for this analysis was patients with MPC, a germline *BRCA1* or *BRCA2* mutation, and disease that had not progressed during first-line platinum-based chemotherapy (≥ 16 weeks of continuous first-line platinum-based chemotherapy), according to the patient characteristics of the POLO trial.⁸ A partitioned-survival model with 3 health states was constructed for an initial decision regarding therapy with maintenance olaparib or placebo.⁹ As shown in Figure 1, the 3 mutually exclusive states were progression-free disease (PFD), progressed disease (PD), and death. In these 3 states, the proportion of OS was partitioned into patients alive and with PFD and patients alive and with PD. The proportion of patients alive at cycle t (a 1-week cycle) was estimated by the area under the OS curve, and the proportion of patients alive and with PFD was estimated by the area under the PFS curve. The proportion of patients alive and with PD was estimated by the difference between the OS and PFS curves. The proportions of PFS and OS were based on the results of the POLO trial,⁸ which was validated by comparing predicted PFS and OS results with the observed data. Patients who initially received olaparib could stop treatment due to either

disease progression measure. Because the primary endpoint was PFS and the data maturity of OS was $<50\%$ in the POLO trial,⁸ the current analysis adopted the cost and health outcomes in the PFS state as the primary endpoints, and the cost and health outcomes in the whole disease course, including PFD, PD, and death, were used as the secondary endpoints.

Clinical Data Inputs

PFS and OS for maintenance olaparib and placebo were informed by the results of the POLO trial⁸ (ie, the trial follow-up) and extrapolated over the model time horizon using standard statistical analyses described by Guyot et al.¹⁰ The GetData Graph Digitizer (version 2.26; <http://getdata-graph-digitizer.com>) was used to gather the data points from the PFS and OS curves, and these data points were then used to fit the following parametric survival functions: Weibull, log-normal, log-logistic, exponential, generalized gamma, Gompertz and Royston/Parma spline model, and parametric mixture and nonmixture cure models (see supplemental eTable 1, available with this article at JNCCN.org). The goodness of fit was based on Akaike information criterion. We determined that the Royston/Parma spline and log-normal model were the most reasonable functions for extrapolating PFS and OS in the placebo arm and that the log-logistic and Royston/Parma spline models were best for the maintenance olaparib arms. Virtual patient-level data comprised event and censor times and were equal in number to the initial number at risk, which was closely reproduced by digitized Kaplan-Meier curves. The PFS and OS plots created by using virtual patient-level data and the predicted curves created by using parametric survival models are shown in supplemental eFigures 1 and 2. The influences of the HR of PFS and OS between the maintenance olaparib and placebo groups were checked in sensitivity and subgroup analyses. After the disease progressed, the data of patients who received second-line active treatment were collected from the POLO trial.⁸ The key clinical inputs are summarized in Table 1.

Figure 1. Model structure for germline *BRCA*-mutated MPC.

Abbreviations: MPC, metastatic pancreatic cancer; P, partitioned survival model.

Table 1. Model Parameters: Baseline Values, Ranges, and Distributions for Sensitivity Analysis

Parameter	Expected Value	Range	Distribution	Reference
Clinical inputs ^a				8
Survival model of placebo				
Royston/Parmar spline model for PFS	Gamma0, −7.562 (SE, 1.202); gamma1, 2.879 (SE, 0.2915); gamma2, 0.315 (SE, 0.074)			
Log-normal model for OS	Meanlog, 4.355 (SE, 0.131); SDlog, 0.817 (SE, 0.109)			
Survival model of maintenance olaparib				
Log-logistic model for PFS	Shape, 1.9399 (SE, 0.2444); scale, 4.0412 (SE, 0.4932)			
Royston/Parmar spline model for OS	Gamma0, −8.3665 (SE, 1.8360); gamma1, 3.3842 (SE, 0.8936); gamma2, 0.5453 (SE, 0.2351)			
HR of PFS between maintenance olaparib and placebo	0.53	0.35–0.82	Log-normal: log-mean, −0.635; log-SD, 2.121	
HR of OS between maintenance olaparib and placebo	0.91	0.56–1.46	Log-normal: log-mean, −0.094; log-SD, 1.471	
Proportion of patients receiving subsequent treatment				
Placebo	0.74	0.557–0.928	Beta: α=4.1; β=1.4	
Maintenance olaparib and placebo	0.49	0.367–0.611	Beta: α=8.2; β=8.5	
Proportion of patients receiving subsequent PARP inhibitor treatment				
Placebo	0.15	0.109–0.181	Beta: α=13.7; β=80.7	
Maintenance olaparib and placebo	0.00	NA	NA	
Probability of AEs				
Any AEs in maintenance olaparib arm	0.56	0.42–0.7	Beta: α=7; β=5.5	
Grade ≥3 AEs in maintenance olaparib arm	0.40	0.3–0.5	Beta: α=9.6; β=14.4	
Any AEs in placebo arm	0.70	0.525–0.875	Beta: α=4.8; β=2.1	
Grade ≥3 AEs in placebo arm	0.23	0.173–0.288	Beta: α=12.3; β=41.2	
Grade ≥3 fatigue in maintenance olaparib arm	0.05	0.038–0.063	Beta: α=15.2; β=288.8	
Grade ≥3 anemia in maintenance olaparib arm	0.11	0.083–0.138	Beta: α=14.2; β=115.2	
Grade ≥3 fatigue in placebo arm	0.02	0.015–0.025	Beta: α=15.7; β=768.3	
Grade ≥3 anemia in placebo arm	0.03	0.023–0.038	Beta: α=15.5; β=501.8	
Utility inputs				
PFD	0.81	0.625–0.995	Beta: α=3.6; β=0.9	11
PD	0.58	0.396–0.764	Beta: α=4.2; β=3	12
Disutility due to grade 1–2 AEs	0.01	0.008–0.02	Beta: α=18; β=1283.2	13
Disutility due to grade ≥3 AEs	0.16	0.11–0.204	Beta: α=36; β=193	13
Cost inputs, USD				
Olaparib, 600 mg/d	\$244.52	\$122.26–\$244.52	Fixed	14
Salvage chemotherapy per month	\$19,379	\$17,626–\$21,132	Gamma: α=421,281; β=0.046	15
Supportive care per month	\$1,526	\$352–\$1,761	Gamma: α=811; β=1.882	16
Terminal care	\$15,308	\$11,481–\$19,135	Gamma: α=61,232; β= 0.25	17
Follow-up per month	\$245	\$184–\$307	Gamma: α=984; β=0.249	17
Managing anemia per event	\$858	\$729–\$986	Gamma: α=5,720; β=0.15	18–21
Managing fatigue per event	\$750	\$563–\$938	Gamma: α=2,988; β=0.251	18–21

Abbreviations: AE, adverse event; HR, hazard ratio; OS, overall survival; PD, progressed disease; PFD, progression-free disease; PFS, progression-free survival.

^aClinical inputs were all collected from the POLO trial.⁸

Cost and Utility Inputs

Only direct medical costs were considered and reported in 2018 US dollars, including the drug acquisition costs, costs attributed to the patient's health state, costs for the management of adverse events (AEs), and costs of

end-of-life care (Table 1). The costs associated with healthcare services were inflated to 2018 values according to the US Consumer Price Index.¹¹

Based on the POLO trial,⁸ olaparib was prescribed at a dose of 300 mg twice daily until disease progression.

The prices of olaparib in the United States (average wholesale price) were collected from public databases and the literature.¹² In the United States, the price of olaparib was discounted at 17% to account for contract pricing.¹³ Because the median relative dose intensity of olaparib was 99.3% (range of dose intensity, 45%–100%),⁸ drug wastage cost was not assumed for olaparib in this analysis because whenever a patient with AEs needs to reduce the dose during the treatment cycle, a new drug package must be purchased. After disease progressed, 48.9% of patients in the olaparib arm and 74.2% of patients in the placebo arm received subsequent active therapy; 14.5% of patients in the placebo arm received PARP inhibitor treatment in subsequent therapy.⁸ The cost of salvage chemotherapy was \$19,379 per patient per month—this cost was derived from a retrospective study including 345 US patients with MPC.¹⁴ The cost of PARP inhibitor treatment in subsequent therapy was estimated based on the cost of olaparib. The cost of supportive care was \$1,526 per month.¹⁵ The costs of follow-up and terminal care were \$245 and \$15,308 per month, which were collected from an economic study on advanced pancreatic cancer.¹⁶

The analysis included costs related to fatigue and anemia—grade 3/4 AEs for which patients in the POLO trial had notably different probabilities.⁸ The unit costs of managing fatigue and anemia were derived from the literature.^{17–20}

Each health state was assigned a health utility preference on a scale of 0 (death) to 1 (perfect health). Because the POLO trial⁸ showed that EORTC Core Quality of Life Questionnaire (QLQ-C30) scores were similar between patients receiving maintenance olaparib and those receiving a placebo, we assumed that the health utility preference was only associated with the disease status. The utility preferences of PFD and PD states related to MPC were 0.81 and 0.58, respectively, which were derived from the EuroQol 5 Dimensions-3 level (EQ-5D-3L) values related to MPC in a Canadian study.²¹ The health utility preference for patients with stable MPC at 8 weeks was adopted for PFD because it was representative of the patients in our analysis.²² The disutility values due to grade 1/2 and 3/4 AEs were included in this analysis.²³ All AEs were assumed to be incurred in the first cycle. The duration-adjusted disutility was subtracted from the baseline PFS utility.

Analysis

In the base-case analysis, the incremental cost-effectiveness ratio (ICER) and incremental cost-utility ratio (ICUR) were calculated as the incremental cost per additional life-year gained and the additional quality-adjusted life-year (QALY) gained for patients taking maintenance olaparib and those taking a placebo, respectively. When

the ICUR was lower than the prespecified willingness-to-pay (WTP) threshold (\$200,000 per additional QALY gained), cost-effectiveness was assumed according to the recommendation.²⁴ Cost and QALYs were discounted at an annual rate of 3%.²⁵ We also estimated the incremental net-health benefit (INHB) and incremental monetary benefit (INMB) based on the following formulas:

$$\text{INHB}(\lambda) = (\mu_{E1} - \mu_{E0}) - (\mu_{C1} - \mu_{C0})/\lambda = \Delta E - \Delta C/\lambda \text{ and}$$

$$\text{INMB}(\lambda) = (\mu_{E1} - \mu_{E0}) \times \lambda - (\mu_{C1} - \mu_{C0}) = \Delta E \times \lambda - \Delta C,$$

where μ_{Ci} and μ_{Ei} were the cost and effectiveness of maintenance olaparib ($i=1$) or placebo ($i=0$), respectively, and λ was the WTP threshold (\$200,000 per additional QALY gained)^{26,27}

Subgroup analysis was performed in the prespecified subgroup as reported in the POLO trial by varying the HRs of PFS.⁸ The model and statistical analyses were implemented in R software (R Foundation for Statistical Computing, version 3.5.2). The data used in this analysis are anonymous and therefore no informed consent was needed.

To evaluate the robustness of the base-case result, 1-way and probabilistic sensitivity analyses were conducted. One-way sensitivity analyses were conducted for all parameters, and the estimated range of each parameter was either based on the reported or estimated 95% confidence intervals in the referenced studies or determined by assuming a 25% change from the base-case value (Table 1). In the probabilistic sensitivity analyses, a Monte Carlo simulation of 1,000 iterations was generated by simultaneously sampling the key model parameters from the prespecified distributions. Gamma distribution was selected for the cost parameters, log-normal distribution was used for HRs, and beta distribution was used for probability, proportion, and preference value parameters. Based on the data from the 1,000 iterations, a cost-effectiveness acceptability curve was created to represent the likelihood that maintenance olaparib would be considered cost-effective at various WTP levels for health gains (QALYs).

Results

Base-Case Analysis and Subgroup Analyses

In the PFS disease phase, maintenance olaparib provided an additional 0.691 PFS QALYs (approximately 8.3 quality-adjusted life-months) and 0.938 PFS life-years (approximately 11.3 life-months) with an incremental cost of \$132,287 compared with placebo, which resulted in an ICUR of \$191,596 per additional PFS QALY gained and an

ICER of \$141,003 per additional PFS life-year gained. The INHB in the PFS state was 0.029 QALYs, and the INMB was \$5,803 at the threshold of \$200,000 per additional QALY gained (Table 2).

In the whole disease course, maintenance olaparib provided an additional 0.483 QALYs (~5.8 quality-adjusted life-months) and 0.579 overall life-years (~6.9 life-months), with an incremental cost of \$128,266 compared with placebo, which resulted in an ICUR of \$265,290 per additional QALY gained and an ICER of \$221,789 per additional life-year gained. The INHB was -0.158 QALYs, and the INMB was -\$31,567 at the threshold of \$200,000 per additional QALY gained in the whole disease course (Table 2).

Subgroup analysis by varying the HRs of PFS found that maintenance olaparib presented a positive trend of gaining an INHB in all the subgroups at the threshold of \$200,000 per additional QALY (Figure 2). The INHBs in the subgroups with respect to the health benefit varied from -0.30 (range, -0.57 to 0.11; probability of cost-effectiveness, 16.8%) in patients aged ≥ 65 years to 0.24 (range, -0.13 to 0.54; probability of cost-effectiveness, 80.3%) in those with a duration of first-line treatment before randomization of >6 months.

Sensitivity Analyses

The 1-way sensitivity analyses revealed that the HR of PFS played a vital role in model outcomes (Figure 3). When its lower (HR, 0.35) and upper boundaries (HR, 0.82) were adopted, the ICURs of maintenance olaparib versus placebo increased from \$155,913 per additional

PFS QALY gained to \$353,480 per additional PFS QALY gained. If the daily cost of olaparib were halved, the ICUR would be less than \$100,000 per additional PFS QALY. When the utility score of PFD was set at 1, the ICUR was close to \$150,000 per additional PFS QALY. Other parameters, such as the cost and utility related to AEs, had only a small impact on the outcome.

The Monte Carlo simulation of 1,000 patients showed that the cost and effectiveness in the PFS disease phase were $\$3,124 \pm \$1,534$ and 0.905 ± 0.449 QALY for placebo and $\$139,563 \pm \$33,046$ and 1.544 ± 0.408 QALY for maintenance olaparib. The cost-effectiveness acceptability curve showed a nearly 54% probability of maintenance olaparib and 46% probability of placebo being a cost-effective strategy at the threshold of \$200,000 per additional QALY gained (Figure 4).

Discussion

Although oncologists and patients are interested in the clinical benefit from maintenance olaparib treatment noted in the POLO trial due to the increasing incidence of pancreatic cancer,⁸ the high price of an anticancer drug can be a barrier to its access. Health policymakers and payers assess the clinical value of a drug to ensure that patients can access it and that it will be sustainable for national healthcare and reimbursement systems and pharmaceutical companies.²⁸ Our study addresses the unmet need for the economic assessment of maintenance olaparib use.²⁹ Based on the results of the POLO trial,⁸ our analysis showed that maintenance olaparib

Table 2. Summary of Cost and Outcome Results in Base-Case Analysis

	Placebo	Maintenance Olaparib
Progression-free cost, USD	\$2,665	\$134,952
Overall cost, USD	\$10,141	\$138,407
Progression-free LYs	0.950	1.888
Overall LYs	2.094	2.673
Progression-free QALYs	0.726	1.417
QALYs	1.380	1.863
ICER (USD per additional PFS LY gained) ^a		\$141,003
ICER (USD per additional LY gained) ^a		\$221,789
ICUR (USD per additional PFS QALY gained) ^a		\$191,596
ICUR (USD per additional QALY gained) ^a		\$265,290
PFS-based INHB (QALY gained) ^a		0.029
PFS-based INMB (USD, money gained) ^a		\$5,803
Overall INHB (QALY gained) ^a		-0.158
Overall INMB (USD, money gained) ^a		-\$31,567

Abbreviations: ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; INHB, incremental net-health benefit; INMB, incremental monetary benefit; LY, life-year; PFS, progression-free survival; QALY, quality-adjusted life-year.

^aCompared with placebo.

Figure 2. Subgroup analysis of INHB and probabilities of cost-effectiveness by varying HRs of PFS. The vertical line indicates the point of no effect (INHB = 0), the red circle indicates the median INHB, and the green bar indicates the ranges of INHB adjusted by HRs.

Abbreviations: HR, hazard ratio; INHB, incremental net-health benefit; NED, no evidence of disease; PFS, progression-free survival; QALY, quality-adjusted life-year; WTP, willingness to pay.

^aDetermined by BRACAnalysis CDx (Myriad Genetics, Inc).

treatment of MPC harboring a *BRCA1* or *BRCA2* mutation could be optimal for WTP thresholds <\$200,000 per additional QALY when only the health benefits in the PFS disease phase were considered. Nearly half of the subgroups favored maintenance olaparib treatment because of its positive trend of gaining an INHB compared with placebo.

The nature of olaparib in preventing disease progression was a major driver of economic outcomes. Findings of the one-way sensitivity analysis showed that the HR of PFS is the most sensitive parameter. This result indicated that maintenance olaparib would become more cost-effective in patients with a more favorable HR of PFS, such as those harboring a *BRCA1* mutation and receiving >6 months of chemotherapy before initiating olaparib treatment. However, in some patients with a more unfavorable HR of PFS with a high risk of progression, such as those aged ≥65 years, maintenance olaparib may be less cost-effective.

Because there was no statistical difference in OS between patients treated with olaparib and versus a placebo, maintenance olaparib treatment during the whole disease course was not cost-effective because its ICUR was higher than the threshold of \$200,000 per additional QALY. This lack of cost-effectiveness can be

partly explained by the fact that longer duration of olaparib treatment and higher cost associated with the PD state in the olaparib arm could more substantially compensate for the high cost of olaparib treatment in the PFS state compared with the placebo arm. However, the compensation was not substantial in the current analysis because of the short duration of the PD state in the olaparib arm. The cost of olaparib was also found to be an important influential factor. When the daily cost of olaparib decreased by 50%, the ICUR for maintenance olaparib decreased to a level lower than \$200,000/QALY. Recently, the US government has proposed indexing the prices that Medicare pays for drugs to those paid by health systems in other developed countries to help reduce the relatively high prices paid by US patients.³⁰ Once this proposal is enacted or implemented, the initiative may lead to a reduction in the price of olaparib and to achieving more favorable economic outcomes.

The strengths of this study are worth highlighting. To our knowledge, this is the first analysis to simultaneously evaluate the economic outcomes of olaparib for the maintenance treatment of MPC harboring a germline *BRCA* mutation by synthesizing the latest evidence through an economic modeling approach. Maintenance treatment is a new concept in MPC, although maintenance

Figure 3. Tornado diagram of one-way sensitivity analyses of maintenance olaparib versus placebo.

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PFD, progression-free disease; PFS, progression-free survival; QALY, quality-adjusted life-year.

capecitabine and fluorouracil have shown promising results in early trials.^{31,32} However, there is a dearth of information regarding the economic outcome of maintenance treatments for MPC. Although 2 previous economic analyses have shown that a chemotherapy regimen containing nab-paclitaxel was cost-effective in the United States and United Kingdom,^{20,33,34} these analyses included treatment-naïve patients with MPC. The target populations in those studies were different from ours in that the patients we studied had received at least 16 weeks of continuous first-line platinum-based chemotherapy. Second, the current analysis examined the economic outcomes of 19 subgroups prespecified by the POLO trial.⁸ The information about subgroup economic analysis would be helpful for physicians and patients.

Several weaknesses in the analysis should be noted. First, because of the lack of data, we did not include other PARP inhibitors and chemotherapeutic agents as maintenance treatment. New PARP inhibitors such as niraparib have shown favorable economic outcomes as maintenance treatment in other cancers with germline *BRCA* mutations.³⁵ The current analysis needs to be updated when evidence is available. Second, we explored the health benefits beyond the observation time of the POLO trial through the fitting of parametric distributions to the

reported survival data. Because the data maturity of OS was lower than 46%, the current analysis needs to be updated when the data become mature. Third, we did

Figure 4. Cost-effectiveness acceptability curves of maintenance olaparib versus placebo.

Abbreviations: PFS, progression-free survival; QALY, quality-adjusted life-year; WTP, willingness to pay.

not measure the budget impact of maintenance olaparib on society. A long-lasting prescription of olaparib may raise the financial burden extremely high. Because approximately one-half of the 56,770 patients newly diagnosed with pancreatic cancer each year will be diagnosed with advanced disease with a 7.5% prevalence of a germline *BRCA* mutation,^{8,36} we estimated that nearly 1,700 patients would be eligible for maintenance olaparib treatment after 4 months of first-line chemotherapy. Fourth, the current analysis adopted a pre-specified WTP threshold of \$200,000 per additional QALY gained because an ICER of \$200,000 per additional QALY gained, or <3 times the annual gross domestic product per capita, are commonly used thresholds to determine the cost-effectiveness of cancer treatment. However, note that there is no official WTP threshold recognized in the United States. When a threshold of <\$100,000 per additional QALY gained is adopted, maintenance olaparib will become not cost-effective. Thus, the final conclusions should be carefully explained and referenced. Finally, the costs of grade 1/2 AEs were excluded from the evaluation, which may overestimate the economic results of maintenance olaparib. This weakness may not be a major one, as implied by the findings in the 1-way sensitivity analysis, which indicated that the costs related to AEs had only a small impact. However, because the results of this evaluation reflect the general clinical conditions of

managing MPC, this finding may be a valuable reference for physicians and policymakers.

Conclusions

Our estimates show that maintenance olaparib is potentially a cost-effective option for patients with MPC harboring a germline *BRCA* mutation from a US payer perspective. Economic outcomes could be improved by tailoring treatment based on individual patient factors. These findings may help clinicians make optimal treatment decisions for patients with MPC. Because of the methodological flaws in the present study, more quality clinical and economic real-world data are needed in this area; we believe that this focus will provide more sound evidence as a framework for determining the value of different therapeutic alternatives in oncology.

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Bin Wu, PhD, and Lizheng Shi, PhD

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eFigure 1: Replicated Kaplan-Meier PFS Curves of Maintenance Olaparib and Placebo in the POLO Trial

eFigure 2: Replicated Kaplan-Meier OS Curves of Maintenance Olaparib and Placebo in the POLO Trial

eFigure 3: Probabilistic Results of the Incremental Cost-Effectiveness Difference for Maintenance Olaparib Versus Placebo

eTable 1: Estimated Parameters and Akaike Information Criterion Values From Each Survival Model

eFigure 1. Replicated Kaplan-Meier PFS curves of maintenance olaparib and placebo in the POLO trial, based on distribution information shown in Table 1. The solid smooth line indicates the predicted PFS (mean), and the dotted and dashed lines indicate the 95% upper and lower predicted PFS.

Abbreviation: PFS, progression-free survival.

eFigure 2. Replicated Kaplan-Meier OS curves of maintenance olaparib and placebo in the POLO trial, based on distribution information shown in Table 1. The solid smooth line indicates the predicted OS (mean), and the dotted and dashed lines indicate the 95% upper and lower predicted OS.

Abbreviation: OS, overall survival.

eFigure 3. Probabilistic results of the incremental cost-effectiveness difference for maintenance olaparib versus placebo. The y axis represents the incremental costs, whereas the x axis represents the incremental QALYs gained. The red ellipses surround 95% of the estimates. Abbreviations: PFS, progression-free survival; QALY, quality-adjusted life-year.

eTable 1. Estimated Parameters and AIC Values From Each Survival Model

Strategies	Distribution	Parameter	PFS					OS				
			Est	L95%	U95%	SE	AIC	Est	L95%	U95%	SE	AIC
Placebo	Weibull	shape	0.9200	0.7538	1.1229	0.0935	420.64	1.2401	0.9674	1.5897	0.1571	365.46
		scale	13.4944	10.1961	17.8598	1.9297		28.1682	21.6247	36.6916	3.7993	
	Gamma	shape	0.9810	0.7270	1.3239	0.1500	421.32	1.4136	0.9919	2.0145	0.2555	364.67
		rate	0.0726	0.0455	0.1159	0.0173		0.0531	0.0306	0.0920	0.0149	
	Exponential	rate	0.0744	0.0575	0.0963	0.0098	419.34	0.0321	0.0236	0.0436	0.0050	366.07
	Log-logistic	shape	1.3575	1.1012	1.6733	0.1449	408.50	1.5604	1.2100	2.0122	0.2025	362.77
		scale	7.4637	5.6041	9.9402	1.0912		19.8907	15.0544	26.2809	2.8272	
	Log-normal	meanlog	2.0621	1.7826	2.3416	0.1426	405.04	3.0155	2.7068	3.3242	0.1575	362.99
		SDlog	1.2210	1.0092	1.4772	0.1187		1.1509	0.9164	1.4453	0.1338	
	Gompertz	shape	-0.0527	-0.0935	-0.0119	0.0208	413.21	0.0081	-0.0260	0.0421	0.0174	367.86
		rate	0.1092	0.0767	0.1556	0.0197		0.0294	0.0181	0.0477	0.0073	
	Royston/Parma spline model (0 knot)	gamma0	-2.3941	-2.9221	-1.8661	0.2694	420.64	-4.1421	-5.1034	-3.1808	0.4905	365.46
		gamma1	0.9200	0.7367	1.1034	0.0935		1.2408	0.9327	1.5490	0.1572	
	Royston/Parma spline model (1 knot)	gamma0	-3.4324	-4.2928	-2.5720	0.4390	401.88	-4.9572	-6.7122	-3.2021	0.8954	365.83
		gamma1	2.0762	1.4300	2.7224	0.3297		1.8112	0.7898	2.8327	0.5211	
		gamma2	0.1981	0.1052	0.2910	0.0474		0.1200	-0.0750	0.3151	0.0995	
	Royston/Parma spline model (2 knot)	gamma0	-4.0499	-5.2464	-2.8533	0.6105	399.35	-4.7662	-6.5469	-2.9855	0.9085	367.49
		gamma1	3.3322	1.7946	4.8698	0.7845		1.5833	0.3621	2.8045	0.6231	
		gamma2	0.9515	0.1209	1.7820	0.4237		-0.1801	-1.0246	0.6644	0.4309	
		gamma3	-0.4427	-0.9684	0.0830	0.2682		0.4377	-0.8172	1.6927	0.6403	
	Mixture cure model (Weibull)	theta	0.1915	0.1024	0.3297	NA	411.54	0.1915	0.1024	0.3297	NA	411.54
		shape	1.2040	0.9804	1.4784	0.1262		1.2040	0.9804	1.4784	0.1262	
		scale	7.9517	6.1178	10.3353	1.0637		7.9517	6.1178	10.3353	1.0637	
	Mixture cure model (gamma)	theta	0.1959	0.1065	0.3326	NA	409.46	0.1959	0.1065	0.3326	NA	409.46
		shape	1.4893	1.0629	2.0866	0.2563		1.4893	1.0629	2.0866	0.2563	
		rate	0.2034	0.1254	0.3299	0.0502		0.2034	0.1254	0.3299	0.0502	
	Mixture cure model (exp)	theta	0.1718	0.0814	0.3268	NA	412.26	0.1718	0.0814	0.3268	NA	412.26
		rate	0.1210	0.0859	0.1703	0.0211		0.1210	0.0859	0.1703	0.0211	
	Mixture cure model (log-logistic)	theta	0.1724	0.0763	0.3442	NA	405.01	0.1724	0.0763	0.3442	NA	405.01
		shape	1.7314	1.3388	2.2391	0.2272		1.7314	1.3388	2.2391	0.2272	
		scale	5.2705	3.8663	7.1848	0.8332		5.2705	3.8663	7.1848	0.8332	
	Mixture cure model (log-normal)	theta	0.1786	0.0831	0.3429	NA	401.39	0.1786	0.0831	0.3429	NA	401.39
		meanlog	1.6728	1.3750	1.9707	0.1520		1.6728	1.3750	1.9707	0.1520	
		SDlog	0.9449	0.7483	1.1932	0.1125		0.9449	0.7483	1.1932	0.1125	
	Mixture cure model (Gompertz)	theta	0.1776	0.0835	0.3387	NA	414.22	0.1776	0.0835	0.3387	NA	414.22
		shape	0.0071	-0.0577	0.0720	0.0331		0.0071	-0.0577	0.0720	0.0331	
		rate	0.1184	0.0795	0.1763	0.0241		0.1184	0.0795	0.1763	0.0241	
	Nonmixture cure model (Weibull)	theta	0.1871	0.0989	0.3255	NA	408.92	0.1871	0.0989	0.3255	NA	408.92
		shape	1.3565	1.1035	1.6675	0.1429		1.3565	1.1035	1.6675	0.1429	
		scale	11.6445	7.9977	16.9542	2.2320		11.6445	7.9977	16.9542	2.2320	
	Nonmixture cure model (gamma)	theta	0.1935	0.1039	0.3317	NA	406.88	0.1935	0.1039	0.3317	NA	406.88
		shape	1.6561	1.2046	2.2768	0.2690		1.6561	1.2046	2.2768	0.2690	
		rate	0.1587	0.0843	0.2986	0.0512		0.1587	0.0843	0.2986	0.0512	
	Nonmixture cure model (exp)	theta	0.1257	0.0342	0.3687	NA	413.21	0.1257	0.0342	0.3687	NA	413.21
		rate	0.0527	0.0243	0.1143	0.0208		0.0527	0.0243	0.1143	0.0208	

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eTable 1. Estimated Parameters and AIC Values From Each Survival Model (cont.)

Strategies	Distribution	Parameter	PFS					OS				
			Est	L95%	U95%	SE	AIC	Est	L95%	U95%	SE	AIC
Placebo (cont.)	Nonmixture cure model (log-logistic)	theta	0.1813	0.0860	0.3425	NA	405.70	0.1813	0.0860	0.3425	NA	405.70
		shape	1.6707	1.2793	2.1819	0.2276		1.6707	1.2793	2.1819	0.2276	
		scale	8.5199	5.1686	14.0440	2.1726		8.5199	5.1686	14.0440	2.1726	
	Nonmixture cure model (log-normal)	theta	0.1746	0.0759	0.3527	NA	401.08	0.1746	0.0759	0.3527	NA	401.08
		meanlog	2.1736	1.5952	2.7519	0.2951		2.1736	1.5952	2.7519	0.2951	
		SDlog	1.0317	0.7738	1.3756	0.1514		1.0317	0.7738	1.3756	0.1514	
	Nonmixture cure model (Gompertz)	theta	0.1783	0.0884	0.3268	NA	414.24	0.1783	0.0884	0.3268	NA	414.24
		shape	0.0417	-0.0195	0.1028	0.0312		0.0417	-0.0195	0.1028	0.0312	
		rate	0.0564	0.0333	0.0952	0.0151		0.0564	0.0333	0.0952	0.0151	
Maintenance olaparib	Weibull	shape	1.0856	0.8786	1.3413	0.1172	253.52	1.5373	1.1675	2.0242	0.2158	256.86
		scale	6.7873	5.1476	8.9493	0.9576		24.4556	19.2737	31.0308	2.9712	
	Gamma	shape	1.3729	0.9567	1.9701	0.2530	251.34	2.1173	1.3708	3.2701	0.4696	254.71
		rate	0.2157	0.1326	0.3510	0.0536		0.0960	0.0535	0.1720	0.0286	
	Exponential	rate	0.1484	0.1101	0.2001	0.0226	252.07	0.0354	0.0248	0.0506	0.0065	262.44
	Log-logistic	shape	1.9399	1.5154	2.4833	0.2444	232.39	2.0892	1.5679	2.7837	0.3059	252.59
		scale	4.0412	3.1815	5.1332	0.4932		17.5577	13.6596	22.5682	2.2490	
	Log-normal	meanlog	1.4487	1.1979	1.6995	0.1280	237.93	2.8832	2.6265	3.1399	0.1310	251.28
		SDlog	0.9159	0.7389	1.1354	0.1004		0.8169	0.6293	1.0604	0.1087	
	Gompertz	shape	-0.0514	-0.1165	0.0138	0.0332	251.16	0.0288	-0.0084	0.0659	0.0189	262.32
		rate	0.1869	0.1266	0.2759	0.0371		0.0257	0.0144	0.0460	0.0076	
	Royston/Parma spline model (0 knot)	gamma0	-2.0793	-2.6344	-1.5243	0.2832	253.52	-4.9147	-6.2391	-3.5903	0.6757	256.86
		gamma1	1.0858	0.8561	1.3155	0.1172		1.5374	1.1143	1.9604	0.2158	
	Royston/Parma spline model (1 knot)	gamma0	-3.3244	-4.3063	-2.3424	0.5010	234.45	-8.3665	-11.9649	-4.7680	1.8360	232.26
		gamma1	2.8794	1.9142	3.8445	0.4925		3.3842	1.6327	5.1356	0.8936	
		gamma2	0.3150	0.1700	0.4601	0.0740		0.5453	0.0845	1.0061	0.2351	
	Royston/Parma spline model (2 knot)	gamma0	-3.2913	-4.3279	-2.2548	0.5289	235.96	-9.0772	-14.4905	-3.6639	2.7619	254.27
		gamma1	2.7541	0.8662	4.6421	0.9633		3.8360	0.7951	6.8769	1.5515	
		gamma2	-0.0291	-1.0954	1.0373	0.5441		0.8583	-1.6571	3.3736	1.2834	
		gamma3	0.3327	-0.4419	1.1072	0.3952		-0.2791	-2.7751	2.2169	1.2735	
	Mixture cure model (Weibull)	theta	0.1063	0.0398	0.2544	NA	239.11	0.1063	0.0398	0.2544	NA	239.11
		shape	1.5208	1.2295	1.8809	0.1649		1.5208	1.2295	1.8809	0.1649	
		scale	4.8227	3.8940	5.9729	0.5263		4.8227	3.8940	5.9729	0.5263	
	Mixture cure model (gamma)	theta	0.1086	0.0411	0.2573	NA	235.47	0.1086	0.0411	0.2573	NA	235.47
		shape	2.3418	1.5856	3.4586	0.4659		2.3418	1.5856	3.4586	0.4659	
		rate	0.5480	0.3408	0.8812	0.1328		0.5480	0.3408	0.8812	0.1328	
	Mixture cure model (Exp)	theta	0.0890	0.0263	0.2614	NA	248.22	0.0890	0.0263	0.2614	NA	248.22
		rate	0.2037	0.1442	0.2878	0.0359		0.2037	0.1442	0.2878	0.0359	
	Mixture cure model (Log-logistic)	theta	0.0962	0.0306	0.2646	NA	233.43	0.0962	0.0306	0.2646	NA	233.43
		shape	2.3880	1.8267	3.1216	0.3264		2.3880	1.8267	3.1216	0.3264	
		scale	3.5246	2.8298	4.3900	0.3948		3.5246	2.8298	4.3900	0.3948	
	Mixture cure model (Log-normal)	theta	0.1023	0.0353	0.2620	NA	232.69	0.1023	0.0353	0.2620	NA	232.69
		meanlog	1.2396	1.0180	1.4612	0.1131		1.2396	1.0180	1.4612	0.1131	
		sdlog	0.7169	0.5688	0.9035	0.0846		0.7169	0.5688	0.9035	0.0846	
	Mixture cure model (Gompertz)	theta	0.1011	0.0360	0.2533	NA	247.62	0.1011	0.0360	0.2533	NA	247.62
		shape	0.0753	-0.0053	0.1558	0.0411		0.0753	-0.0053	0.1558	0.0411	
		rate	0.1654	0.1075	0.2545	0.0364		0.1654	0.1075	0.2545	0.0364	

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eTable 1. Estimated Parameters and AIC Values From Each Survival Model (cont.)

Strategies	Distribution	Parameter	PFS					OS				
			Est	L95%	U95%	SE	AIC	Est	L95%	U95%	SE	AIC
Maintenance olaparib (cont.)	Nonmixture cure model (Weibull)	theta	0.0925	0.0331	0.2331	NA	235.84	0.0925	0.0331	0.2331	NA	235.84
		shape	1.7922	1.4463	2.2206	0.1960		1.7922	1.4463	2.2206	0.1960	
		scale	7.3573	5.5111	9.8219	1.0846		7.3573	5.5111	9.8219	1.0846	
	Nonmixture cure model (Gamma)	theta	0.1011	0.0367	0.2494	NA	233.65	0.1011	0.0367	0.2494	NA	233.65
		shape	2.5088	1.7480	3.6007	0.4625		2.5088	1.7480	3.6007	0.4625	
		rate	0.3858	0.2090	0.7121	0.1206		0.3858	0.2090	0.7121	0.1206	
	Nonmixture cure model (Exp)	theta	0.0263	0.0005	0.5873	NA	251.16	0.0263	0.0005	0.5873	NA	251.16
		rate	0.0514	0.0145	0.1825	0.0332		0.0514	0.0145	0.1825	0.0332	
	Nonmixture cure model (Log-logistic)	theta	0.0960	0.0319	0.2550	NA	233.25	0.0960	0.0319	0.2550	NA	233.25
		shape	2.2614	1.7095	2.9915	0.3228		2.2614	1.7095	2.9915	0.3228	
		scale	5.6846	3.9389	8.2039	1.0640		5.6846	3.9389	8.2039	1.0640	
	Nonmixture cure model (Log-normal)	theta	0.0892	0.0245	0.2762	NA	233.01	0.0892	0.0245	0.2762	NA	233.01
		meanlog	1.8009	1.3050	2.2969	0.2531		1.8009	1.3050	2.2969	0.2531	
		sdlog	0.8309	0.6184	1.1164	0.1252		0.8309	0.6184	1.1164	0.1252	
	Nonmixture cure model (Gompertz)	theta	0.0840	0.0273	0.2306	NA	247.07	0.0840	0.0273	0.2306	NA	247.07
		shape	0.1487	0.0623	0.2352	0.0441		0.1487	0.0623	0.2352	0.0441	
		rate	0.0557	0.0296	0.1048	0.0180		0.0557	0.0296	0.1048	0.0180	

Abbreviations: AIC, Akaike information criterion; Est, point estimation; L95%, lower boundary of 95% confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival; U95%, upper boundary of 95% confidence interval.