Cost-Effectiveness Analysis of Olaparib in Combination with Bevacizumab Compared with Bevacizumab Monotherapy for the First-Line Maintenance Treatment of Homologous Recombination Deficiency-Positive Advanced Ovarian Cancer

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Abstract

Background In the PAOLA-1 trial, olaparib plus bevacizumab demonstrated significant clinical benefit following partial or complete response to platinum-based chemotherapy in homologous recombination deficiency (HRD)-positive ovarian cancer. Our study evaluated the cost effectiveness of olaparib plus bevacizumab compared with bevacizumab alone as a maintenance treatment for women in this population.

Methods Our model was a cohort-level partitioned survival model with a lifetime horizon from a US healthcare system perspective. Its four health states were progression-free, post first progression, post second progression, and death, modeled using time to first progression (PFS1), second progression (PFS2), and overall survival (OS) from PAOLA-1. We modeled PFS1 through mixture survival modeling, and PFS2 and OS by fitting standard parametric models. Time-on-treatment was sourced directly from PAOLA-1, with treatment capped at 24 months for olaparib and 15 months for bevacizumab. Costs included drug acquisition and administration, adverse events, disease management, biomarker testing, and subsequent treatments. Deterministic and probabilistic sensitivity analyses tested the results.

Results Compared with bevacizumab alone, olaparib plus bevacizumab increased quality-adjusted life-years (QALYs; +2.89) and life-years (LYs; +3.43) at an incremental cost of $164,209, leading to an incremental cost-effectiveness ratio of $56,863 per QALY. Olaparib plus bevacizumab had a 97.0% probability of being cost effective compared with bevacizumab alone at a willingness-to-pay threshold of $100,000 per QALY.

Conclusion The addition of olaparib to bevacizumab led to clinically significant increases in progression-free survival, resulting in substantial predicted LYs and QALYs gained, while being cost effective in the maintenance treatment of advanced ovarian cancer with HRD in the US.

1 Introduction

Ovarian cancer is the fifth most common cause of death from cancer in women, with an estimated 22,530 new cases and 13,980 deaths in 2019 in the US [1, 2]. It is estimated the national expenditure for ovarian cancer care in the US was $6.4 billion in 2020 [3].

The introduction of poly-ADP ribose polymerase (PARP) inhibitors as frontline treatment presents new questions about the clinical and economic value of treatments for advanced ovarian cancers. The persistent clinical benefits of PARP inhibitors pose a welcome challenge for health economic modeling and demands quality reporting of PARP inhibitor models [4]. Biomarkers present an opportunity to optimize treatment for patient populations most likely to benefit from these therapies. Robust cost-effectiveness evidence can help determine the specific PARP inhibitors that provide the best value for money in these populations.

The standard treatment for newly diagnosed advanced ovarian cancer (stage III or IV) is surgery, followed by post-operative platinum-based chemotherapy primarily to delay disease progression and reduce the risk of recurrence and disease spread [5]. The addition of bevacizumab to first-line chemotherapy, and continuing with bevacizumab as

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Key Points for Decision Makers

- Olaparib plus bevacizumab provides significant clinical benefits and leads to substantial life-year and quality-adjusted life-year gain compared with bevacizumab among HRD-positive ovarian cancer patients.
- Olaparib plus bevacizumab achieves clinical benefits with reasonable cost and provides good economic value as it is cost effective, compared with bevacizumab, for HRD-positive ovarian cancer patients.
- Extrapolation methods accounting for long-term survivorship are important to capture the long-term clinical benefit associated with improved progression-free survival.
- A biomarker-guided approach leads to optimal clinical outcomes with good economic value.

maintenance therapy, improves progression-free survival (PFS) irrespective of disease stage and residual disease after surgery [6–8]. Maintenance therapy is intended to induce lasting remission or to prolong the disease-free interval by delaying relapse for as long as possible [9]. Both bevacizumab and PARP inhibitors have shown improved efficacy as maintenance therapies [10, 11].

Treating patients with bevacizumab plus chemotherapy, followed by bevacizumab monotherapy, demonstrated PFS benefit relative to chemotherapy alone in patients with newly diagnosed advanced epithelial ovarian cancer who had undergone debulking surgery [10]. Olaparib monotherapy demonstrated significant reduction in the risk of disease progression or death relative to routine surveillance in women with newly diagnosed advanced ovarian cancer with a breast cancer gene (BRCA) mutation [10]. Considering the success of these trials, PAOLA-1 evaluated the combination of olaparib and bevacizumab in women with newly diagnosed advanced ovarian cancer.

Olaparib plus bevacizumab was approved by the US FDA based on the results of PAOLA-1 (NCT02477644), a phase III, randomized, double-blind, placebo-controlled, multicenter study. It assessed the efficacy of olaparib with bevacizumab, relative to bevacizumab alone, as maintenance therapy in patients with high-grade serous or endometrioid advanced ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer) who had responded following first-line platinum/taxane-based chemotherapy plus bevacizumab concomitant with chemotherapy or had no evidence of disease after initial debulking surgery. Patients with homologous recombination deficiency (HRD)-positive tumors were a prespecified subgroup. Maintenance therapy with olaparib plus bevacizumab demonstrated a clinically significant benefit in PFS compared with bevacizumab monotherapy in patients with HRD-positive tumors (Genomic Instability Score ≥42), with a median PFS of 37.2 months versus 17.7 months (HR 0.33, 95% CI 0.25–0.45) [20].

As many as half of ovarian cancer patients have an HRD-positive tumor [13]. A large percentage of HRD-positive tumors are driven by mutations in the BRCA, but HRD can also be caused by other mutations to genes in the homologous recombination repair pathway or phenotypic changes leading to a loss of genomic instability [13]. Such mutations carry an increased risk of developing cancer compared with age-matched women in the general population [14]. Over 83% of patients already undergo BRCA testing and 62% undergo HRD testing before first-line treatment [15]. Early biomarker testing can guide oncologists and patients to select the optimal treatment strategies. Our economic model’s objective was to estimate the incremental cost effectiveness of olaparib plus bevacizumab relative to bevacizumab monotherapy as maintenance treatment among HRD-positive patients with advanced ovarian cancer.

2 Methods

2.1 Model Structure

The cost-effectiveness model was a partitioned survival model with four states: progression-free, post first progression, post second progression, and death (Fig. 1). Health state membership was modeled using first progression (PFS1), second progression (PFS2), and overall survival (OS) outcomes from the PAOLA-1 trial. Partitioned survival models are directly linked to trial outcomes such as OS and PFS and are one of the most common cost-effectiveness model structures for advanced cancers. The model structure has been used in recent health technology assessments of treatments for advanced ovarian cancers [16–18]. Progression was defined using the modified Response Evaluation Criteria in Solid Tumors 1.1 by investigators’ assessment, with PFS1 measuring the time from randomization to first progression or death, and PFS2 capturing the time from randomization to second progression or death. Health state membership was determined by PFS1, PFS2, and OS curves, which were used to directly estimate the proportion of patients occupying each state over time. The proportion of patients without progression were equal to the area under the PFS1 curve. The proportion of patients post first-progression was calculated as the difference in the areas under the PFS2 and PFS1 curves, while the proportion of patients post second-progression was the difference in the

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area under the OS curve and the PFS2 curve. The proportion of dead patients was calculated as 100% less the area under the OS curve. Electronic supplementary Fig. S1 illustrates the model structure. Patients incurred costs and accumulated quality-adjusted life-years (QALYs) based on membership in each health state.

The economic analysis was conducted from the US healthcare system perspective. Direct medical costs associated with disease management, treatment acquisition, adverse events (AEs), biomarker testing, and end-of-life care were included in the analysis. The model evaluated costs and outcomes over the lifetime of patients using a 50-year time horizon, which captured the full lifetime of patients, given an average starting age of 60.2 years. A 1-month model cycle was used with a half-cycle correction applied to all costs and outcomes. Both costs and outcomes were discounted at a rate of 3% per annum.

Consistent with the PAOLA-1 regimen, the intervention was 300 mg olaparib twice daily plus 15 mg/kg bevacizumab every 3 weeks; the comparator in this analysis was bevacizumab 15 mg/kg every 3 weeks.

### 2.2 Efficacy

Time-on-treatment, PFS1, PFS2, and OS were modeled using data from the HRD-positive population of PAOLA-1. Tumors were considered HRD-positive if a BRCA mutation or an HRD score of 42 or higher on the myChoice HRD Plus assay were identified [19]. There were 255 women with HRD-positive tumors in the olaparib plus bevacizumab arm and 132 in the bevacizumab arm of PAOLA-1. After the March 2019 data cut-off, there were 87 and 92 PFS events in the olaparib plus bevacizumab and bevacizumab arms, respectively. This represents approximately 46% of the total population and occurred after a median follow-up of 24.4 months.

PFS1, PFS2, and OS data were estimated using a parametric mixture cure model (PMM) for PFS1 and standard parametric curves for PFS2 and OS to extrapolate outcomes beyond the observed duration of the clinical trial. Time-on-treatment was modeled using Kaplan–Meier data directly, capped at 24 months for olaparib and 15 months for bevacizumab, in line with the trial protocol [20].

Evidence suggested that after initial diagnosis, approximately 15% of patients can survive for more than 10 years [20]. Therefore, the model assumed that women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer who were in complete response (CR) or partial response (PR) after completing first-line treatment were a mix of patients who are and are not long-term progression-free survivors [20]. Indeed, 20–25% of patients with stage III–IV epithelial ovarian cancer will remain progression-free for longer than 5 years following completion of first-line treatment, with relapse rare after 5 years progression-free; these patients are classified as long-term survivors [20]. They are expected to stay in remission and have mortality risks similar to those of the general population, matched by age and sex [21]. The use of olaparib combined with bevacizumab in the maintenance setting is expected to increase the proportion of patients who are considered long-term survivors, due to the statistical and clinically meaningful increase in PFS1 observed in the PAOLA-1 trial. Standard parametric models tend to poorly predict survivorship in cases where a plateau is observed or is to be expected; therefore, the
PMM approach was implemented to model PFS1. The PMM approach captured heterogeneity in susceptibility to relapse or disease progression among women with newly diagnosed ovarian cancer. PFS2 and OS were modeled with standard parametric models up to the point where the cumulative survival probabilities were predicted to be equal to or less than the cumulative survival of PFS1, at which point the curves followed the trajectory of PFS1 (Fig. 1). This reflected the long-term trend of survivorship and was a logical constraint in the model. The HRD-positive population was assumed to comprise a mixture of long-term survivors who would remain progression-free up to a landmark point and other patients whose survival would follow a parametric function ($S(t)$). The proportion of long-term survivors is denoted with $\pi$. The mathematical formulation of the PMM for progression-free survival function ($S(t)$) is shown in Eq. 1

$$S(t) = \pi \times 100\% + (1 - \pi) \times S(t)$$

Long-term survival in newly diagnosed advanced ovarian cancer varies across the literature and includes survival of beyond 5 years. It was assumed that to achieve long-term survival, patients must remain progression-free up to this landmark. Beyond the 5-year landmark point, patients who remained progression-free were additionally assumed to have the same survival rate as women of the same age in the general population [22].

The PMM, using Weibull, Gompertz, and generalized gamma distributions, produced long-term PFS1 estimates that were in line with expectations from clinical practice and evidence from the literature (Table 1) for the placebo plus bevacizumab arm. Exponential, log-normal and log-logistic distributions produced estimates below those in the literature. The Weibull model had the lowest Akaike information criterion (AIC)/Bayesian information criterion (BIC) for the bevacizumab treatment arm and was within 2 points of the lowest AIC/BIC for olaparib plus bevacizumab. Combined with a clinically plausible 5-year PFS extrapolation and close fit to Kaplan–Meier data in the bevacizumab monotherapy arm, the PMM approach with Weibull distribution was preferred for modeling PFS1. Weibull was selected to model the first progression in both treatment arms, as long-term survival data are not available for olaparib plus bevacizumab.

**AIC** Akaike information criterion, **BIC** Bayesian information criterion, **PFS1** first progression-free survival, **RWE** real-world evidence, **HRD** homologous recombination deficiency

PFS2 was modeled in both treatment arms using log-normal parametric curves fit independently. Log-normal was selected based on statistical fit, had the lowest AIC/BIC in the olaparib plus bevacizumab arm, and was within 2 points of the lowest AIC/BIC in the bevacizumab arm. OS was modeled in both treatment arms using log-normal parametric curves fit independently. Log-normal was selected based on statistical fit as it had the lowest BIC and second lowest AIC in the olaparib plus bevacizumab arm, and the lowest AIC/BIC in the bevacizumab arm.

We compared our modeled OS long-term estimation for the bevacizumab arm with real-world evidence (Table 2) and other plausible parametric curves. Takaya et al. obtained data from The Cancer Genome Atlas and investigated different subtypes of high-grade serous ovarian carcinoma. PAOLA-1 used a cut-off of 42 to determine HRD status, and the modeled OS falls below the estimates that Takaya et al. found for patients with HRD scores of between 42 and 62 and those with an HRD score of ≥63 [30]. Norquist et al. evaluated long-term survival in patients who received chemotherapy plus bevacizumab as primary treatment and then received bevacizumab as maintenance therapy and found the 5-year OS rates were approximately 53%. Kehoe et al., Gadducci et al., and Vergote et al. evaluated survival among women with stage III or IV ovarian cancer after primary debulking surgery plus chemotherapy or neoadjuvant chemotherapy and found the 5-year OS was approximately 31–42% [23, 25, 27]. In general, our model resulted in long-term survival estimates that are in line with external empirical evidence.

Figure 1 presents the PFS1, PFS2, and OS curves used in the model; each individual curve is compared with the relevant Kaplan–Meier data in Figs. 2, 3 and 4.

### 2.3 Resource Use and Costs

Model cost year was 2020 US dollars (US$) and all costs valued before 2020 were inflation-adjusted to 2020 US$ using the medical care component of the Bureau of Labor Statistics’ Consumer Price Index [32]. Drug wholesale acquisition costs were sourced from Red Book, with olaparib costing $7082.79 per pack of 60 × 150 mg tablets and bevacizumab costing $796.94 per 100 mg vial and $3187.76 per 400 mg vial [33]. Relative dose intensity, which captured both dose reductions and dose interruptions, was applied to the cost per model cycle. The mean relative dose intensities for bevacizumab were 91.2% and 90.5% in the olaparib plus bevacizumab arm and bevacizumab monotherapy arms, respectively. The mean relative dose intensity for olaparib was 86.7% in the safety analysis set population [1]. As bevacizumab has weight-based dosing, the model calculated an average dose based on the weight distribution observed in PAOLA-1 using the method of moments approach. All treatments incurred costs based on the number of full vials used in order to account for wastage. Intravenous administration costs were sourced for bevacizumab from the Centers for Medicare & Medicaid Services (CMS) Physician Fee
Schedule [34]; oral drugs were assumed to have no administration cost.

The costs of treatment-related AEs were included for grade 3 or higher AEs with incidences >2% for either treatment arm in the intention-to-treat population of PAOLA-1. AE costs and durations were sourced from the Healthcare Cost and Utilization Project, assuming that all grade 3 or higher AEs resulted in hospitalization [35].

Healthcare resource use included office visits, blood count, and computed tomography (CT) scans, with different
resource use rates for progression-free while on treatment, progression-free off treatment, and progressed disease to reflect clinical practice (electronic supplementary Table S1). Resource use rates were determined based on guidelines, and costs were sourced from the CMS Physician Fee Schedule [34, 36].

The cost of testing for HRD status was accounted for as a one-off cost for patients receiving olaparib. The unit cost of the HRD test was $4040 [37]. In PAOLA-1, 48% of patients were HRD-positive [19]. The cost of testing to identify one HRD-positive woman was therefore $8414.

Subsequent treatments included a mix of platinum and non-platinum chemotherapy, as well as PARP inhibitors, and reflected the treatments received in PAOLA-1. We assumed no subsequent PARP inhibitor use among patients in the olaparib with bevacizumab arm. Ninety-five percent of patients received second-line treatment, 52% received third-line treatment, and 34% received fourth-line or later treatment. Electronic supplementary Table S2 shows the proportion of patients receiving platinum chemotherapy, non-platinum chemotherapy, and a PARP inhibitor at second-line, third-line, fourth-line and later for both arms [38].

Fig. 2 Modeled PFS1 and Kaplan–Meier curves. *PFS1* first progression-free survival, *KM* Kaplan–Meier

Fig. 3 Modeled PFS2 and Kaplan–Meier curves. *PFS2* second progression-free survival, *KM* Kaplan–Meier
Subsequent treatment costs were sourced from Red Book and are presented in electronic supplementary Table S3 [33]. Most patients receiving subsequent platinum treatment received carboplatin (93.7%), while the remainder were assumed to receive cisplatin (6.3%). Non-platinum chemotherapy consisted of doxorubicin hydrochloride liposome (47.3%), paclitaxel (21.3%), gemcitabine (21.1%), topoisomerase inhibitor (6.7%), and trabectedin (3.7%) []. All patients receiving a subsequent PARP inhibitor were assumed to receive olaparib.

End-of-life costs of $48,142, based on a recent systematic review, were applied to the 51.3% of patients assumed to require terminal care [39].

2.4 Health-Related Quality of Life

The PAOLA-1 trial collected EQ-5D-5L data, a questionnaire used to determine patients’ quality of life across disease areas, from randomization through to secondary progression. The Pickard US tariff was applied to the EQ-5D-5L data to calculate utility values relevant to the US population [40], with downwards adjustment for age to avoid utility values larger than the general population [41].

Health state utility values were estimated using linear mixed-effect models fit to observed data in the HRD-positive population. A variety of specifications were explored, including coefficients for progression, on treatment, and for specific treatments, as well as interactions between them. Based on AIC and BIC goodness-of-fit statistics, the best fitting model included only time-varying covariates for progression status and whether on bevacizumab treatment, without any treatment, or interaction effects.

Before their first progression, patients being treated with bevacizumab had a utility value of 0.779, while not receiving bevacizumab had a 0.816 utility value. After their first progression, patients had a utility value of 0.753 and 0.679 after their second progression [42].

2.5 Sensitivity Analyses

Sensitivity analyses were conducted to identify the most influential parameters and to test the robustness of results. One-way sensitivity analysis was performed to deterministically investigate the impact of varying each parameter in isolation between its lower and upper bound. Lower and upper bound values for parameters were taken from 95% CIs of the assigned distribution. Probabilistic sensitivity analysis was conducted to assess the uncertainty in model inputs associated with the base-case model results. A probabilistic sensitivity analysis simultaneously sets all variables in the model to a value randomly sampled from the appropriate distribution. Parameters bounded by 0 and 1, such as proportions and utility values, were assigned a beta distribution; a Dirichlet distribution was used for multivariate proportions. The multivariate normal was used to account for uncertainty in coefficients from regression models, and normal distribution was used for all other parameters. When uncertainty data were not reported, the standard error was assumed to be 10% of the mean.
3 Results

Olaparib plus bevacizumab was more costly but led to greater life-years (LYs) and QALYs than bevacizumab monotherapy (Table 3). Drug acquisition costs accounted for the majority of incremental costs ($265,831 increase) but were partially offset by savings in subsequent treatment costs ($108,570 reduction), primarily due to use of subsequent PARP inhibitors in the bevacizumab arm. Biomarker testing and other cost categories did not have a large impact on incremental costs. Patients on olaparib plus bevacizumab lived 9.55 years compared with 6.12 years for those on bevacizumab after starting maintenance therapy; they accumulated more PFS time, with an increase of 4.80 progression-free LYs and 3.88 progression-free QALYs. They spent less time in the progressed health states (decrease of 1.37 LYs and 0.99 QALYs). Over a 50-year time horizon, olaparib plus bevacizumab generated an additional 3.43 LYs and 2.89 QALYs at an incremental cost of $164,209 relative to bevacizumab monotherapy. This results in an incremental cost-effectiveness ratio (ICER) of $56,863 per QALY and $47,910 per LY.

Figure 2 illustrates the importance of PFS1 and subsequent treatments received to the final ICER. The proportion of patients who were long-term survivors was the most influential parameter, followed by the proportion of patients receiving a PARP inhibitor as second-line maintenance treatment (Fig. 5).

Probabilistic sensitivity analysis, using 10,000 iterations, generated an ICER of $56,502 per QALY with a 95% credible interval (CrI) of $30,486–$82,517 per QALY, a result that supports the deterministic results. Notably, the upper limit of the 95% CrI was below common willingness-to-pay (WTP) thresholds. At a WTP of $100,000 and $150,000 per QALY gained, olaparib plus bevacizumab had a 97.0% and 99.5% chance of being cost effective versus bevacizumab maintenance, respectively, as illustrated in electronic supplementary Fig. S2.

Scenario analyses were conducted to test structural assumptions made in the model (Table 4). Scenario analysis evaluating different curve fit distributional choices, model settings, and alternative assumptions all resulted in ICERs below the $100,000 per QALY threshold. Using a log-normal PMM for PFS1 resulted in an ICER of $66,453, while using Weibull distributions for PFS2 and OS resulted in ICERs of $56,431 and $51,899, respectively. Changing long-term survivors to have general population mortality, rather than no risk of death, before the landmark point led to essentially no change in ICER. Using a landmark of 7 years versus 5 years in the base-case for PMM also led to minimal change in the ICER. In scenarios exploring different time horizons, as the time horizon decreased the ICER increased due to most costs being incurred during the first 2 years of treatment and benefits persisting over the patient’s lifetime.

4 Discussion

The introduction of PARP inhibitors has rapidly changed the ovarian cancer treatment landscape. With the approval of olaparib, niraparib, and olaparib with bevacizumab, newly diagnosed ovarian cancer patients now have several treatment options for first-line maintenance treatment.

A recent systematic review of cost-effectiveness models for PARP inhibitors in advanced ovarian cancer identified
numerous issues with the reporting of models in this disease area and provided recommendations for future work [4]. Issues include unclear model structures, unvalidated projections, and cost-effectiveness conclusions drawn from surrogate outcomes, such as cost per progression-free life-year, which have no established WTP threshold and cannot be compared across disease areas [43, 44]. We have followed the best practices for modeling and reporting identified in this study.

Previous studies have demonstrated the clinical benefit of olaparib first-line maintenance treatment and showed that in BRCA-mutated populations, olaparib monotherapy is cost effective compared with routine surveillance [45]. Our modeling expands the cost-effectiveness analysis of adding olaparib to bevacizumab among the HRD-positive population. This study produced a similar ICER as a US cost-effectiveness model based on the SOLO1 trial. In that model, treatment with olaparib monotherapy led to incremental costs of $152,545, a 3.63 increase in LYs and 2.93 additional QALYs, for an overall ICER of $51,986 per QALY gained [45]. The small difference in ICERs shows the combination of olaparib plus bevacizumab in the HRD-positive

Table 3 Deterministic cost-effectiveness results

|                         | Olaparib plus bevacizumab | Bevacizumab | Increment  |
|-------------------------|---------------------------|-------------|------------|
| Costs US$               |                           |             |            |
| Drug acquisition and administration | 355,999                  | 90,167      | 265,831    |
| Healthcare resource use | 12,144                    | 4655        | 7490       |
| Subsequent treatment    | 12,007                    | 120,577     | −108,570   |
| Terminal care           | 17,659                    | 20,155      | −2496      |
| Adverse event           | 4954                      | 3000        | 1954       |
| Total                   | 402,763                   | 238,554     | 164,209    |

LYs
Progression-free 8.80 4.00 4.80
First progression 0.27 1.12 −0.84
Second progression 0.48 1.01 −0.53
Total 9.55 6.12 3.43

QALYs
Progression-free 7.08 3.20 3.88
First progression 0.21 0.84 −0.63
Second progression 0.32 0.68 −0.36
Total 7.61 4.72 2.89

ICER ($/LY) 47,910
ICER ($/QALY) 56,863

Table 4 Scenario analyses

| Scenario                                          | Incremental costs ($) | Incremental QALYs | ICER ($/QALY) |
|---------------------------------------------------|-----------------------|-------------------|---------------|
| PFS1 modeled with a log-normal PMM                | 151,563               | 2.28              | 66,453        |
| PFS2 modeled with a Weibull distribution          | 163,844               | 2.90              | 56,431        |
| OS modeled with a Weibull distribution            | 165,057               | 3.18              | 51,899        |
| Long-term survivors have general population mortality before landmark | 164,214               | 2.89              | 56,900        |
| 7-year landmark point for PMM                     | 164,240               | 2.90              | 56,587        |
| 40-year time horizon                              | 164,221               | 2.89              | 56,848        |
| 30-year time horizon                              | 163,369               | 2.76              | 59,162        |
| 20-year time horizon                              | 162,060               | 2.16              | 75,199        |
| Patients can receive multiple PARP inhibitors     | 192,303               | 2.89              | 66,591        |

ICER incremental cost-effectiveness ratio, LYs life-years, QALYs quality-adjusted life-years.
population can be as cost effective as olaparib monotherapy in BRCA patients. Despite different reference treatments (placebo maintenance in SOLO-1 vs. bevacizumab maintenance in PAOLA-1), both analyses are based on the addition of olaparib to treatment, leading to comparable incremental costs. Similarity in LYS and QALYS gained from SOLO-1 and PAOLA-1 demonstrated the consistent added benefits of olaparib regardless of whether patients received bevacizumab maintenance treatment or not. In SOLO-1, the HR for disease progression or death in the BRCA-mutated population was 0.30 (95% CI 0.23–0.41) after a median follow-up of 41 months [10], while the HR for disease progression or death observed in the HRD-positive population of PAOLA-1 was 0.33 (95% CI 0.25–0.45) after a median follow-up of 24.4 months [19].

As biomarker testing becomes more widespread, patients will increasingly have the option of receiving targeted therapies. Understanding the cost effectiveness of olaparib plus bevacizumab in the HRD-positive population is therefore important for payers and healthcare decision makers. There are several factors contributing to the robust cost effectiveness of olaparib plus bevacizumab compared with bevacizumab alone. Over a lifetime horizon, olaparib plus bevacizumab produced a large clinical benefit relative to bevacizumab alone, with benefits concentrated in progression-free LYS. Despite treatment with olaparib being capping at 2 years, many patients continued to have benefit beyond this point. The upfront drug cost of olaparib was offset by long-term patient benefit and subsequent treatment due to PARP use after progression with bevacizumab monotherapy.

A key consideration in this cost-effectiveness model was the long-term extrapolation of survival outcomes. For PFS1 extrapolation, we compared the standard parametric approach, PMM, and real-world evidence at different time points for the bevacizumab arm. The real world 5-year PFS rate lies between 11% and 25% (Table 1); all standard parametric models predicted PFS well below the real-world evidence. Due to the poor prediction of 5-year PFS of the standard parametric models, a mixture cure model was selected. The Weibull, Gompertz, and generalized gamma PMMs all produced plausible estimates of 5 year survival, ranging from 16.9% to 20.6%. The PMM approach was preferred based on similarity to 5-year PFS of the standard parametric models and plausible proportions of long-term survivors.

Olaparib plus bevacizumab was found to be cost effective, largely due to the initial improvement and ongoing persistence of survival benefits over the lifetime horizon, while increased costs were incurred during the first 2 years when patients received active treatment. The long-term survival benefits were driven by the improved PFS and represent the main source of uncertainty in the model.

The main limitation of the analysis is that the PFS2 and OS data from the PAOLA-1 study are still immature. Although current extrapolations are based on the best available evidence and show good consistency with historical data, the ICER estimates are subject to uncertainty with further survival readouts from the trial. The model also does not consider broader societal benefits resulting from reduced caregiving costs, increased productivity, value based on patient risk preference, option values, or the insurance value to non-patients. Inclusion of societal benefits would capture more benefits of olaparib plus bevacizumab and increase its cost effectiveness [46].

Routine surveillance and bevacizumab have been the standard of care for maintenance treatment of ovarian cancer. PARP inhibitors, such as olaparib, delay disease progression and help manage the disease after primary therapy. The combination of olaparib plus bevacizumab provides good value for money as a maintenance therapy for women with advanced ovarian cancer and HRD-positive tumors.

5 Conclusion

This cost-effectiveness model was developed to assess the economic value of olaparib in combination with bevacizumab versus bevacizumab alone for the first-line maintenance treatment of ovarian cancer for patients with HRD-positive tumors. Olaparib plus bevacizumab significantly increased patients’ PFS compared with bevacizumab monotherapy. This benefit persisted after patients finished first-line maintenance treatment with olaparib, resulting in significant improvement in LYS and QALYS.

The key challenges of the model were associated with the extrapolation of immature data for PFS2 and OS. At data cut-off, the median PFS2 was only reached by patients in the placebo plus bevacizumab arm, while neither arm reached the median for OS. The PMM approach to modeling PFS shows good agreement with historical data (Tables 1, 2) but is an extrapolation based on data collected during PAOLA-1.

The ICER for olaparib plus bevacizumab compared with bevacizumab monotherapy for maintenance therapy of women with advanced HRD-positive ovarian cancer was substantially below the $100,000–$150,000 per quality WTP thresholds used by the Institute for Clinical and Economic Review [47]. Relative to bevacizumab monotherapy, olaparib plus bevacizumab is cost effective from the perspective of a third-party payer in the US.

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Declarations

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Consent to participate Not applicable.

Consent for publication (from patients/participants) Not applicable.

Availability of data and material Model inputs are described in the manuscript, electronic supplementary material, and references. No further data and material are available.

Code availability The Excel model is not available. Note, the Excel model was made available to the journal during the peer review process.

Author contributions DE performed the analysis and interpretation of the data, drafted the manuscript, approved the final version, and agrees to be accountable for all aspects of the work. LF, AM, DS, MM, and DM reviewed the analysis and interpretation of the data, critically revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work. FEM performed the analysis and interpretation of the data, critically revised the manuscript, approved the final version, and agrees to be accountable for all aspects of the work.

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