Olaparib as first line in BRCA-mutated advanced ovarian carcinoma: Is it cost-effective in Spain?

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HIGHLIGHTS

• Our results suggest that olaparib could delay disease progression and improve OS by 2 years vs. no maintenance treatment.
• Treatment with olaparib resulted in a gain of 2.00 QALYs vs. no maintenance treatment, at an ICER of 14,653.2/QALY.
• First-line maintenance with olaparib is cost-effective in advanced HGSO patients with BRCA mutations in Spain.

OBJECTIVE. To estimate the cost-effectiveness of olaparib after being funded by the Spanish National Health Service (SNHS) as first-line monotherapy maintenance treatment in patients with advanced high-grade serous ovarian carcinoma (HGSO) and BRCA mutations in Spain.

METHODS. A semi-Markov model with one-month cycles was adapted to the Spanish healthcare setting, using the perspective of the SNHS, and a time horizon of 50 years. Two scenarios were compared: receiving olaparib vs. no maintenance treatment. The model comprised four health states and included the clinical results of the SOLO1 study, along with the direct healthcare costs associated with the use of first-line and subsequent treatment resources (2020 €). A discount rate of 3% was applied for future cost and quality-of-life outcomes. A probabilistic sensitivity analysis (PSA) was also carried out and a cost-effectiveness threshold of €25,000 per quality adjusted life year (QALY) was considered.

RESULTS. The introduction of olaparib as a first-line maintenance treatment for advanced HGSO patients with BRCA mutations implied a cost of €131,614.98 compared to €102,369.54 without olaparib (difference: €29,245.44), with an improvement of 2.00 QALYs (5.56 and 3.57, respectively). Therefore, olaparib is cost-effective for advanced HGSO patients with BRCA mutations, with an incremental cost-effectiveness ratio of €14,653.2/QALY. The results from the PSA showed that 92.1% of the simulations fell below the €25,000/QALY threshold. The model showed that olaparib could improve the overall survival by 2 years, vs. no maintenance treatment.

CONCLUSIONS. Olaparib as first-line maintenance treatment is cost-effective in advanced HGSO patients with BRCA mutations in Spain.

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1. Introduction

Ovarian carcinoma (OC) has one of the highest mortalities of gynecologic cancer in women. In Spain, it is expected that 3645 incident patients will be diagnosed in 2020, showing a 2.7%-increase in comparison to those diagnosed last year. However, the 5-year prevalence is relatively low (10,236 patients), due to the high mortality associated with the disease (2106 cases) in 2020 [1]. Most OC cases have been thought to arise from epithelial cells (90%) and more than 70% of them are diagnosed with high-grade (HGOC), which typically presents at advanced stages (III and IV). This subtype grows aggressively, and generally responds to initial conventional chemotherapy [2–4]. In The Cancer Genome Atlas (TCGA) study, 20% of HGOC patients have BRCA1 or BRCA2 mutations: germline mutations have been recorded in 9% and 8% of the cases with BRCA1 and BRCA2 mutations, respectively; while somatic mutations have appeared in approximately 6% of the cases (3% BRCA1 and other 3% BRCA2) [5]. BRCA1/2 testing should be offered to all women diagnosed with high-grade epithelial non-mucinous ovarian cancer, regardless of family history [4]. Somatic testing has potential diagnostic, prognostic and predictive therapeutic implications, whereas germline testing also has preventive implications for their family members [6,7]. Although germline BRCA1/2 mutations are the most frequent, somatic BRCA1/2 are also predictive of response to targeted agents, and somatic testing would detect additional patients that can also benefit from the use of these therapies.

From the last 20 years, the first-line treatment of patients with advanced HGOC is contingent on the combination of cytoreductive surgery followed by first-line platinum-based chemotherapy [8,9], and it has been associated with a low rate of long-term survival. Although most BRCA-mutated patients have no evidence of disease after platinum-based chemotherapy, close to 80% will relapse within the first three years [10]. Relapsed patients tend to receive several treatment lines administered sequentially after each tumor progression, experiencing increasingly shorter progression-free periods on each subsequent line and developing cumulative toxicities (e.g., hypersensitivity, neurotoxicity and mielotoxicity) [11,12].

Poly (ADP-ribose) polymerase inhibitors (PARPi) represent an important new class of oral personalized agents targeting cancers with defective DNA-damage repair. The administration of this inhibitors causes accumulation of DNA damage and death of tumor cells through the homologous recombination repair (HRR) system. BRCA mutations are the best example of the HRR system deficiency, being a marker with a high predictive response [9]. Olaparib was the first PARPi authorized by the European Medicines Agency (EMA) for the maintenance treatment of patients with platinum-sensitive relapsed HGOC with BRCA mutations [13].

SOLO1 double-blind, placebo-controlled, phase III trial analyzed the efficacy and safety of olaparib as maintenance treatment for two years, in patients with newly diagnosed advanced BRCA-mutated high grade serous (96.5% of patients) or endometrioid (5.4% of patients) ovarian cancer (HGOC) with clinical response after platinum-based chemotherapy. The study showed that treatment with olaparib tablets (300 mg twice daily) provided a substantial benefit, with a statistically meaningful 70%-reduction in the risk of disease progression or death in comparison to placebo with consistent and known adverse events profile [13]. As a result, olaparib was authorized by EMA in June 2019 and was recommended as first-line maintenance treatment in the National Comprehensive Cancer Network (NCCN) guidelines [14], and in the recent Spanish Medical Oncology Society (SEOM) guidelines [15]. In addition, its cost is predictable, because it has a flat-fixed dose and a maximum treatment duration of 24 months [16]. Primary results were supported by the 5-year follow-up results where the benefit derived from 2 years of maintenance olaparib was sustained beyond the end of treatment and after 5 years almost half of patients were progression-free versus 20% with placebo (HR 0.33; 95% CI 0.25–0.43) [17]. The aim of this study was to estimate the cost-effectiveness of olaparib from the perspective of the Spanish National Health Service (SNHS) as first-line monotherapy maintenance treatment in patients with advanced HGSC and BRCA mutations who are in response to first-line platinum-based chemotherapy after being commercialized.

2. Materials and methods

A partitioned survival model with one-month cycles was originally developed for the United Kingdom [18] using Microsoft Excel, and was subsequently adapted to the SNHS setting. Informed by the SOLO1 trial, the model considered two scenarios: receiving olaparib as first-line maintenance treatment in advanced HGSC BRCA-mutated patients vs. no maintenance treatment. The perspective was that of the SNHS and the time horizon was 50 years (covering lifetime of these patients). Future costs and quality-of-life outcomes were discounted at an annual rate of 3%, as reported by Spanish health technology assessment recommendations [19]. Model results were costs and quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) was estimated. According to the Spanish guidelines, a cost-effectiveness threshold between €25,000 - €60,000/ QALY was considered [20,21].

2.1. Data sources

Epidemiology data, utilization of healthcare resources and utilities were obtained from a literature review, including national and international references (the latter were used whenever national data were not available). Databases consulted were Medline/ Pubmed, Embase, Medes, and other official databases. All extracted data were contrasted and validated by a multidisciplinary expert group composed of clinical experts and pharmacoeconomic specialists. To validate the data, each expert first answered an online survey and then attended an in-person group meeting to reach a final consensus.

2.2. Model

The model included four health states (Fig. S1): progression-free state (PFS), first-progression state (PS1), second-progression state (PS2) and death. The simulation was initiated with patients in PFS who received a first-line platinum-based chemotherapy, and may suffer disease relapse, progress to s PS1 or die. PS1 patients may have another relapse (PS2) or die. As the progression of the disease is an irreversible process, patients in PS2 cannot return to PS1. Death is the absorbing state in the model.

2.3. Efficacy

Patients progression in PS1 and PS2 was informed by the first and second progression-free survivals (PFS) from SOLO1 trial [13]. The long-term survival of patients was estimated using Weibull distributions, fitted to the Kaplan-Meier curves from the clinical trial for first PFS, second PFS and overall survival (OS). Fig. 1 shows the predicted first and second PFS and OS curves.

Mortality rates due to HGSC and all causes were considered. The mortality risk in stable patients and those who had a remission period longer than 10 years [8], was that of the Spanish general population [22], adjusted for the potential excess mortality risk of having a BRCA1/2 mutation. The excess mortality risk was modeled using a hazard ratio (HR) for mortality of 1.26 (95% confidence interval [CI]: 0.00, 3.42), based on the excess mortality of female BRCA1/2 mutation carriers, aged 51–60 years and who have an absence of melanoma and breast, ovary or/and pancreas cancer [23].
2.4. Resource use

Healthcare resource use included first-line maintenance, second-line ± maintenance and subsequent lines of treatment, adverse events, oncology visits, follow-up tests and palliative care.

The model included those drugs used post-progression after first-line maintenance therapy in the SOLO1 trial (carboplatin, gemcitabine, paclitaxel, bevacizumab, trabectedin, pegylated liposomal doxorubicin [PLD], and olaparib [no maintenance treatment scenario], along with the combinations of these drugs usually used [13] (Table S1, S2

![Fig. 1. Comparison of first-progression (A), second-progression (B) free survival and overall survival (C) curves from the clinical trial (SOLO1) vs. the simulation results (model).](image-url)
and S3). It was considered that 56.8% of the relapsed patients received platinum-based chemotherapy for 6 cycles. The market shares of platinum and non-platinum-based chemotherapy are shown in Table S1 and S2. In the model, relapsed patients did not receive any PARPi in the olaparib scenario, because rechallenge is still being investigated [24]. However, as in the SOLO1, 39.2% of the relapsed patients received PARPi in the no maintenance treatment scenario (mainly olaparib) as a second-line maintenance treatment after platinum-based chemotherapy until the progression of the disease [25].

The model also considered the most frequent severe adverse events (grades 3 and 4) associated with olaparib and placebo in SOLO1: anemia, fatigue or asthenia, neutropenia and diarrhea (Table 1) [13].

In addition, our study included all oncology visits and follow-up tests required for patients in both scenarios (stable patients and those showing progression), based on the time interval since the administration of the first-line maintenance treatment (Table 2) [15]. Finally, it was assumed that palliative care is given to the patients in their last 48 days (terminal phase) [26].

### 2.5. Costs

Costs were expressed in 2020 Euros. Chemotherapy and bevacizumab costs were calculated using the list price [27] and were assessed as the minimum cost per mg of the marketed presentations for each drug. Olaparib and PLD costs were calculated using the confidential price by the SNHS. The first-line maintenance treatment with olaparib was assumed to last up to two years [28]. Since most of the relapsed patients received olaparib as PARPi, the cost of maintenance treatment was assumed to be the same as the olaparib treatment costs in the recurrence setting. Doses and market shares for each drug were also considered (Table S1, S2 and S3). It was considered that 56.8% of the relapsed patients received olaparib as PARPi, the cost of maintenance treatment was assumed to last up to two years [28]. Since most of the relapsed patients received olaparib as PARPi, the cost of maintenance treatment was assumed to be the same as the olaparib treatment costs in the recurrence setting. Doses and market shares for each drug were also considered (Table S1, S2 and S3). Doses were estimated considering the weight or body surface area of the patients, as indicated in the product labels (Table S3) [28]. Carboplatin dose was determined using the Calvert formula [29]. Du Bois et Du Bois formula was used to calculate the body surface area when necessary [30]. Patients’ height and weight were consulted in the Spanish National Health Survey according to the mean age at diagnosis of stages III and IV [22]. Simulated patients were 54 years old (SD: 10) [32] with a mean height of 161 cm (SD: 5.64) and weight of 67.51 kg (SD: 11.38) [22]. For intravenous drugs, the model also considered the non-optimization of vials and the cost of administration for each drug: cost of administration (€0.57 per min) and time of administration required for each administration in day hospital plus the cost of the 30-min preparation. The administration times were: gemcitabine and bevacizumab (60 min), carboplatin and PLD (90 min) and paclitaxel and trabectedin (210 min) [28].

Unit costs of oncology visits and follow-up tests reflected the median value of the unit costs for all Autonomous Communities in Spain [33]. Adverse events and palliative care costs came from scientific articles regarding the management of cancer (Table 1) [31]. A palliative care cost of € 3701.74 € was applied in the year of the patient’s death [26].

Since the costs of the oncology visits, follow-up tests and management of adverse events came from different years, they were updated to 2020 Euros using the medicine consumer price index [22].

### 2.6. Utilities

Health state utility values were 0.82 in the PFSt, 0.77 in PS1 [13] and 0.68 in PS2 [34]. Health state utilities for advanced HGSOC patients with BRCA mutations were also age-adjusted along the time horizon to reflect the aging of the cohort. Mean utilities for the Spanish population were extracted from the Spanish National Health Survey [22] (Table S4).

Disutility associated to adverse events development was also considered in the model (Table 1). It was assumed that the effect of all adverse events on the patients’ quality of life lasted 7 days [35].

### 2.7. Sensitivity analyses

An univariate sensitivity analysis was carried out to examine the simulation’s robustness. Different assessments were made based on the possible variation of the most sensitive parameters: the distributions that best fit the Kaplan-Meier survival curves from the clinical trial, according to the Akaike information criterion (AIC) (generalized

### Table 1

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Frequency1</th>
<th>No maintenance treatment scenario</th>
<th>Unit cost2</th>
<th>Disutility4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>21.54%</td>
<td>1.54%</td>
<td>€947.43</td>
<td>−0.119 (SD = 0.01)3</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>3.85%</td>
<td>1.54%</td>
<td>€174.68</td>
<td>−0.073 (SD = 0.018)4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.46%</td>
<td>4.62%</td>
<td>€272.10</td>
<td>−0.090 (SD = 0.015)4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.08%</td>
<td>0.00%</td>
<td>€1546.37</td>
<td>−0.047 (SD = 0.016)4</td>
</tr>
</tbody>
</table>

Abbreviation: SD: standard deviation. References.

1. Moore, 2018 [13].
2. Idi, 2017 [31].
4. Nafees, 2008 [45].

### Table 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Stable patients</th>
<th>Patients showing progression</th>
<th>Unit costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
<td>Year 2</td>
<td>Years 3</td>
</tr>
<tr>
<td>Physical examination (Oncology visit)</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Biochemical analysis and hematology test</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Tumor markers (CA-125)</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Chest computed tomography</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

References: Autonomous Communities [33], Redondo, 2020 [15].
gamma distribution for first PFS and logistic regression for second PFS and OS), discount rate (0% and 6%), utility in the second-progression state (0.82 QALYs), remission period (7 and 13 years) and the excess mortality risk (0 and 3.42). A probabilistic sensitivity analysis (PSA) was also conducted, including one thousand simulations of the cohort. Most parameters were independently varied according to different distributions and point estimates were drawn using a Monte Carlo simulation (Table S5).

3. Results

3.1. Progression-free and overall survival

The results of the simulation showed that median time to first progression was 4.00 years in patients receiving first-line maintenance treatment with olaparib and 1.50 years in the no maintenance treatment scenario. The average patient receiving first-line maintenance treatment with olaparib had a longer mean average interval until first-progression (5.63 years) than those in the no maintenance treatment scenario (2.06 years). Olaparib patients improved their first-progression survival by 3.57 years in comparison to patients that did not receive maintenance treatment (Table 3).

The median OS in the simulation was 6.50 years and 4.67 years in the olaparib and no maintenance treatment groups, respectively. The model showed that, on average, olaparib patients had a 2.43-year increase in the OS, compared to the no maintenance treatment group (7.26 vs. 4.82, respectively). Therefore, our results suggest that olaparib decreased the mortality risk in more than 30% in advanced HGSOC patients with BRCA mutations (Table 3).

3.2. Quality adjusted life years

Treatment with Olaparib improved patients’ QALYs in the time interval until the first cancer relapse by 2.76 QALYs (4.43 vs. 1.67 QALYs).

Table 3 Cost-effectiveness results per HGSOC patient with BRCA mutations.

<table>
<thead>
<tr>
<th>Survival(years)</th>
<th>Olaparib scenario</th>
<th>No maintenance treatment scenario</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period until first progression</td>
<td>5.63</td>
<td>2.06</td>
<td>3.57</td>
</tr>
<tr>
<td>Period until second progression</td>
<td>0.67</td>
<td>1.65</td>
<td>−0.98</td>
</tr>
<tr>
<td>Overall survival</td>
<td>7.26</td>
<td>4.82</td>
<td>2.43</td>
</tr>
<tr>
<td>QALYs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period until first progression</td>
<td>4.43</td>
<td>1.67</td>
<td>2.76</td>
</tr>
<tr>
<td>Period until second progression</td>
<td>0.51</td>
<td>1.17</td>
<td>−0.66</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>5.56</td>
<td>3.57</td>
<td>2.00</td>
</tr>
<tr>
<td>Costs (€)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olaparib (first line)</td>
<td>71,489.08</td>
<td>0.00</td>
<td>71,489.08</td>
</tr>
<tr>
<td>Olaparib (second and subsequent lines)</td>
<td>0.00</td>
<td>31,673.88</td>
<td>−31,673.88</td>
</tr>
<tr>
<td>Platinum-based chemotherapy</td>
<td>23,745.15</td>
<td>28,639.15</td>
<td>−4894.0</td>
</tr>
<tr>
<td>Non-platinum-based chemotherapy</td>
<td>27,199.73</td>
<td>32,805.74</td>
<td>−5606.01</td>
</tr>
<tr>
<td>Total treatment costs</td>
<td>122,433.97</td>
<td>93,118.77</td>
<td>29,315.20</td>
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<tr>
<td>Other healthcare costs</td>
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</tr>
<tr>
<td>Period until first progression</td>
<td>3709.75</td>
<td>2198.22</td>
<td>1511.52</td>
</tr>
<tr>
<td>Period until second progression</td>
<td>956.83</td>
<td>2197.28</td>
<td>−1240.45</td>
</tr>
<tr>
<td>Progression of the disease</td>
<td>1367.08</td>
<td>1591.17</td>
<td>−224.09</td>
</tr>
<tr>
<td>Adverse events</td>
<td>184.46</td>
<td>22.90</td>
<td>161.56</td>
</tr>
<tr>
<td>Terminal phase</td>
<td>2962.90</td>
<td>3241.20</td>
<td>−278.30</td>
</tr>
<tr>
<td>Total other healthcare costs</td>
<td>9181.02</td>
<td>9250.77</td>
<td>−69.75</td>
</tr>
<tr>
<td>Total costs</td>
<td>129,320.07</td>
<td>99,601.64</td>
<td>29,718.43</td>
</tr>
<tr>
<td>ICER</td>
<td>14,853.20</td>
<td>€</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PARPi: inhibitor of the poly ADP ribose polymerase; QALYs: quality-adjusted life-years.

These results were in line with the survival results previously registered (Table 3).

In the simulated lifetime of patients, the use of olaparib as a first-line maintenance treatment improved QALYs by 2.00 (5.56 vs. 3.57 QALYs) (Table 3).

3.3. Costs

Treatment costs were higher in patients that received olaparib (€122,433.97) than in the no maintenance treatment scenario (€93,118.77). However, olaparib implied a cost saving in the platinum-based (€4894) and non-platinum-based chemotherapy (€5606.01) administered in the recurrence setting (Table 3).

Regarding other healthcare resources, most of the costs in the olaparib scenario were associated to the period up to the PS1 (40.4%), followed by the terminal phase (32.3%) and the progression of the disease (14.9%). However, the distribution of the costs was different in patients without maintenance treatment, as most of the costs were associated to the terminal phase (35%), followed by the time interval up to the first relapse (23.8%), and the period up to the second relapse (23.8%). As shown in Table 3, the first-line maintenance treatment with olaparib reduced costs associated to the time interval until second progression (€1240.45), the progression disease period (€224.09) and the terminal phase (€278.30) vs. the no maintenance treatment scenario. Therefore, the administration of olaparib to newly diagnosed patients with advanced HGSC and BRCA mutations results in health care cost savings of €69.75 per patient, in comparison to the no maintenance treatment scenario (Table 3).

3.4. Incremental cost-effectiveness

Our results showed that, as first-line maintenance treatment, olaparib would lead to an increase of 2.43 years free of disease progression and of €29,245.44 and per patient (Table 3). Therefore, the incremental cost-effectiveness ratio (ICER) was €12,020.67 per free-progression year saved.

Olaparib also implied an improvement in 2.00 QALYS per patient compared to the no maintenance treatment scenario, so the ICER was €14,653.2/QALY. Thus, the administration of olaparib as first-line maintenance treatment is cost-effective, taking into account the cost-effective threshold between €25,000 - €60,000/QALY considered in Spain [20,21].

3.5. Sensitivity analyses

The results of the univariate deterministic analysis showed that the most influential parameters on the cost per QALY gained were the remission period (−44.02%; 38.11%); the discount rate (−35.32%; 40.69%) and the excess mortality risk (−17.88%; 13.80%). The assumed survival distributions (fitting the model according to the AIC) and the variation of the health-state utility in PS2 had a lower impact of cost per QALY gained (9.07% and 1.11%, respectively) (Fig. 2A).

The PSA showed that most of the simulations were located in the upper-right quadrant of the cost-effectiveness plane (Fig. 2B). The ICER ranged from €-9546.19/QALY (dominant) to €51,978.64/QALY. The willingness-to-pay curve is shown in Fig. 2C. The results of the sensitivity analysis showed that 92.1% of the simulations fell below the €25,000/QALY threshold, and 100% were below the €60,000/QALY threshold (Fig. 2C).

4. Discussion

Treatment with olaparib substantially improving the first PFS (3.57 years), OS (2.43 years) and QALYS (2.00 QALYS) of an average simulated patient with advanced HGSC and BRCA mutation for the first-line maintenance treatment. Furthermore, olaparib is cost-effective
Fig. 2. Sensitivity analyses: tornado diagram (A), cost-effectiveness plane (B) and willingness-to-pay curve (C).
Abbreviations: AIC: Akaike information criterion; PS2: second-progression state; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life-years.
(ICER €14,653.2/QALY), taking into account the cost-effective threshold between €25,000 - €60,000/QALY considered in Spain. Our simulation showed that the median first PFS in patients without maintenance treatment was 1.50 years, compared to 4.00 years in the olaparib group, increasing progression free survival by 2.5 years. These results are in line and slightly more conservative than those in the 5-year follow-up from SOLO1 trial, as the median time to first PFS was 13.8 months (1.15 years) and 56 months (4.67 years) in the placebo and olaparib group, respectively [13,17]. In addition, the simulation showed that patients in the no maintenance treatment scenario had a 5-year OS rate of 45%, which is in line with previous clinical evidence [36]. Therefore, our results clearly show that the maintenance treatment with olaparib improves the long-term OS and QALYs of these patients.

To our knowledge, this is one of the first published studies that estimates the cost-effectiveness of olaparib as first-line maintenance treatment in Europe. Several economic evaluations were carried out in the United States, regarding the cost-effectiveness of olaparib for the treatment of OC. However, the majority of these evaluations included patients with platinum-sensitive recurrent OC [37–39].

Regarding the recent indication of olaparib in first-line treatment, two economic evaluations analyzed the cost-effectiveness of olaparib; one developed in Italy [40] and the other in Singapore [41]. The Italian economic evaluation analyzed the cost-effectiveness of olaparib maintenance therapy compared with no maintenance therapy, according the SOLO1 trial results, from the Italian National Health Service perspective. This study determined that olaparib is cost-effective (€11,345/QALY) as maintenance monotherapy for patients with advanced BRCA1/2-mutated HGSOC who are in response (complete or partial) to first-line platinum-based chemotherapy. A PSA was also developed, which results demonstrated that olaparib was associated with a 97.6% probability of being cost-effective, considering a threshold of €16,372/QALY [40]. Our results are in line with these conclusions, as 92.41% of the simulations from our probabilistic sensitivity analysis fell below the €25,000/QALY threshold, which is considered cost-effective as per the Spanish guidelines [20,21].

The economic evaluation developed in Singapore analyzed the cost-effectiveness of olaparib maintenance therapy versus routine surveillance, according to the results from the SOLO1 trial. This study was developed from the healthcare payer perspective, using similar conditions to the ones we considered in our study. It showed that olaparib maintenance vs. routine surveillance resulted in an ICER of SGD17,326/QALY (around €11,500/QALY). The researchers also developed a PSA, which demonstrated that olaparib was associated with an 81% probability of being cost-effective, considering a threshold of SGD50,000/QALY (around €33,000/QALY). In addition, their results were most sensitive to variations in the discount rate and mortality risk in long-term survivors [41]. These conclusions are in agreement with our results [20,21]. It should be noted that researchers considered a remission period of 7 years, while we assumed 10 years in the base case. A 7-year remission period was included in our sensitivity analysis, resulting in an ICER of €9202.35/QALY, lower than our base case results, and closer to the ICER in Singapore. In addition, it should be stressed that the two last studies simulated patients over a three-state model; however, we considered four states, based on the first-progression and second-progression free survival from the SOLO1 trial. We estimate that our four-state model is more accurate to simulate the outcomes of the olaparib treatment in these patients.

Our study has some limitations. First, due to the lack of information about the real-world outcomes of the OC treatment in Spanish patients with advanced HGSOC and BRCA mutation, the model included the results from the SOLO1 trial (efficacy and utilities) which are selected patients that were required to accomplish several criteria of inclusion. Second, based on data from SOLO1, the simulation did not include either the antiangiogenic therapy (bevacizumab) as first-line maintenance treatment nor the treatment with other PARPi for recurrent HGSOC. It should be noted that the Italian study collected these treatments obtaining results similar to ours [40]. Third, although the efficacy results available from SOLO1 were still immature, our model considered those for the assessments, including the OS (data maturity, 21%). Four, we took into account the burden associated to all severe adverse events (grades 3 and 4) registered in the SOLO1 trial, in terms of impact on health status and costs. Even if we assume that most of the burden is indeed associated to severe adverse events, those graded 1 and 2 may be also relevant in the determination of quality of life and costs, and our model may be underestimating the total burden. Moreover, we did not consider the development of adverse events due to the second and subsequent lines of treatment. Finally, costs and disutilities associated to adverse events came from studies developed in other cancers. However, the variations in base-case values, including the duration of the adverse events, were analyzed in the PSA. Finally, although the resources use (oncology visits and follow-up tests) was agreed by a multidisciplinary expert group, the real-world practice in some Spanish hospitals may be different (e.g., pelvic ultrasound may also be included in the follow-up procedures). Therefore, these possible variations were evaluated in the PSA, and the corresponding results were compared to the cost–utility threshold.

Despite its limitations, the main contribution of this study is the economic evaluation of olaparib for the maintenance therapy of newly diagnosed patients with advanced HGSOC and BRCA mutation in Spain. Our results confirm that the incremental cost associated with olaparib monotherapy administered to patients in response after first-line platinum-based chemotherapy is associated with increased overall survival and QALYs, and is a cost-effective treatment option in Spain. These results are in line with recent studies, concluding that maintenance treatment with targeted therapies in advanced OC patients can be cost-effective [42]. In conclusion, our results support the strong recommendation of SEOM guidelines [15] about the use of olaparib as first-line maintenance treatment in patients with advanced HGSOC BRCA mutated- with a cost-effective ICER of €14,653.2/QALY, according to the cost-effectiveness threshold considered in Spain [20,21].

Conflict of interest statement

VGB reports personal fees from Astra Zeneca, during the conduct of the study and personal fees from GSK, outside the present study. MPBG reports fees from GlaxoSmithKline, Clovis Oncology, Pharmamar, AstraZeneca, MSD, and Roche for consulting or advisory functions and travel support from GlaxoSmithKline, PharmaMar, Astra Zeneca, MSD, and Roche, outside the present study. JAPF reports personal fees from AstraZeneca, Clovis, Roche, Abily Pharma and Pharmamar for speaker bureau or advisory functions and grants and personal fees from GSK for speaker bureau, advisory functions and research grant, outside the present study. AR reports grants and personal fees from Pharmamar and Roche for research funding, travel expenses and advisory functions, personal fees from Agena, Astra Zeneca, GSK and Clovis for advisory functions, travel expenses or speakers bureau, and grants from Eisai for research funding, outside the present study. CMA is an AstraZeneca employee. AGD and YIM work at Weber, company that received fees from AstraZeneca, during the conduct of the study.

Author contribution

CMA and AGD conceived and designed this study. All authors contributed to the acquisition of the data. AGD contribute to analysis of the data. All authors contributed to interpretation of the data. AGD and YIM contributed to the development of the drafts of this manuscript. CMA, VGB, MPBG, JAPF and AR critically revised the manuscript. All authors approved the submitted version of the manuscript.

