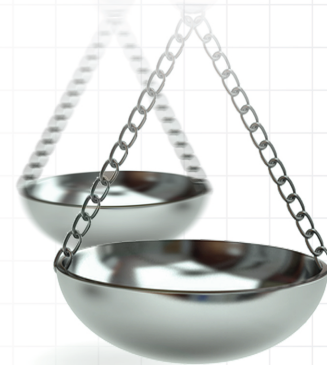




Budget impact of niraparib as maintenance treatment in recurrent ovarian cancer following platinum-based chemotherapy

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Aim: To estimate financial implications of adopting niraparib as maintenance treatment in recurrent ovarian cancer. **Materials & methods:** A model was developed to estimate the budget impact of treating patients with niraparib compared with alternative maintenance treatment options (olaparib, rucaparib, bevacizumab or 'watch and wait') over 3 years. **Results:** For a hypothetical plan with 1 million lives representative of US/Medicare-only populations, projected cost savings with niraparib were US\$78,721/\$293,723, \$276,671/\$1,009,729 and \$353,585/\$1,289,712 at years 1, 2 and 3, respectively. Sensitivity analyses showed prices of niraparib, rucaparib and olaparib to have the most significant impact on the budget. **Conclusion:** Factoring in all treatment-related costs, the use of niraparib could result in significant cost savings compared with other maintenance treatment options.

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Keywords: budget impact analysis • costs • economics • maintenance therapy • PARP inhibitors • recurrent ovarian cancer • USA

Ovarian cancer (OC), while rare, is the fifth most common cause of cancer death among women in the USA, resulting in over 14,000 deaths annually [1]. Although the incidence of OC is only a tenth that of breast cancer, the 5-year mortality is twice as high [2,3]. Most cases (79%) are diagnosed at an advanced stage, and almost three-quarters of patients (72%) diagnosed with advanced disease will die within 5 years of diagnosis [1]. The cornerstone of drug treatment in the first-line advanced disease setting is platinum-based chemotherapy plus a taxane; however, 85% of patients will experience disease recurrence after first-line treatment [4,5]. Recurrent OC is considered incurable.

Most patients with treatment recurrence are treated with repeated rounds of platinum-based chemotherapy. However, the effectiveness of this treatment diminishes over time, and the disease tends to recur more and more rapidly after completion of treatment, requiring further chemotherapy [4]. The duration of progression-free survival (PFS) decreases with each subsequent line of chemotherapy, while risk for cumulative toxicities increases [6,7]. Until recently, the standard of care for women who have responded to platinum-based chemotherapy in the USA was 'watchful waiting', which is generally associated with high levels of anxiety due to fear of recurrence [8].

Niraparib is an inhibitor of PARP 1 and 2, which aids in the repair of single-strand DNA breaks. PARP inhibition interferes with DNA repair, leading to the accumulation of single-strand breaks. Such single-strand breaks become double-strand breaks, the repair of which requires DNA reparation pathways that are often deficient in ovarian tumors. In these tumor cells, the inhibition of PARP leads to the persistence of double-strand breaks and subsequent programmed cell death [9]. Niraparib is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy, regardless of *BRCA* mutation status.

The ENGOT-OV16/NOVA trial evaluated the efficacy of niraparib versus placebo among patients with recurrent OC following complete or partial response to their most recent platinum-based regimen, including those with and

without a germline *BRCA* mutation (g*BRCA* cohort and non-g*BRCA* cohort), as reported previously [10]. Among patients in the g*BRCA* cohort, median PFS was 21.0 months with niraparib and 5.5 months with placebo (hazard ratio: 0.27; 95% CI: 0.17–0.41) [10]. Among patients in the non-g*BRCA* cohort, median PFS was 9.3 months with niraparib and 3.9 months with placebo (hazard ratio: 0.45; 95% CI: 0.34–0.61) [10]. Treatment-emergent adverse events (TEAEs) were manageable with dose modifications, and patients who required a dose reduction had similar efficacy to patients who continued treatment at the starting dose [11].

In the USA, the annual expenditure for the treatment of OC was estimated at US\$5.1 billion in 2010 [12]. To assist in estimating the financial implications of adoption and diffusion of niraparib in the USA, a budget impact analysis was performed that compared the three currently approved PARP inhibitors – niraparib, olaparib and rucaparib – for the maintenance treatment of adult patients with recurrent OC.

Materials & methods

Overview

A budget impact model (BIM) was developed in Microsoft Excel to estimate the financial consequences of the introduction of niraparib for patients with recurrent OC who are in complete or partial response to platinum-based chemotherapy. The outcomes of these analyses are presented as an incremental budget impact to US payers over 3 years.

The modeling approach and analytic framework of the BIM followed the guidance provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [13,14].

The model adopted the payer perspective and considered the following:

- Prevalence of the disease within the population;
- The dose and price of niraparib and alternative treatment options; and
- Costs and cost offsets associated with medical services.

Model structure

The BIM was constructed as a cost calculator in which drug costs per quarter were estimated as follows:

$$\text{Drug cost / quarter} = \text{Number of patients on treatment} \times \text{Cost per dose} \times \text{Average dose dispensed per patient / quarter}$$

The calculation began with estimating the number of patients eligible for treatment with a PARP inhibitor: adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. We estimated the number of patients on treatment in any given quarter as a function of the number of eligible patients, rate of uptake and rate of discontinuation.

To estimate the budget impact of the introduction of niraparib, the model compared two scenarios: scenario 1 corresponded to a situation where all PARP-treated patients receive niraparib, and scenario 2 corresponded to a situation where the PARP inhibitor share is evenly split between the other two approved PARP inhibitors. Market shares for bevacizumab and watch and wait remained the same in both scenarios. The financial consequence for payers was estimated by comparing the two scenarios for total costs, including the costs of drugs, monitoring, TEAEs and subsequent treatment. Incremental spending/saving was projected over 3 years.

Model inputs

Number of eligible patients

We used overall OC (epithelial and nonepithelial) epidemiology estimates as an approximation for the incidence/prevalence of epithelial ovarian, primary peritoneal and fallopian tube cancer, because the number of primary peritoneal and fallopian tube cancers [15,16] (incidence of 2000–4000) is approximately the same as that of nonepithelial OC ($\approx 10\%$ of all OC) [17].

The patient population eligible for niraparib consists of patients with recurrent OC who are in complete or partial response to platinum-based chemotherapy. The budget impact analysis was conducted for both a plan with the age distribution reflecting the overall US population and a plan with a Medicare-only population. The model assumed constant prevalence rates over the modeling period; results are presented per million lives covered.

To estimate the number of eligible patients in a hypothetical plan with 1 million members, we sourced estimates of the number of women with recurrent OC responsive to platinum therapy in the USA and therefore eligible for

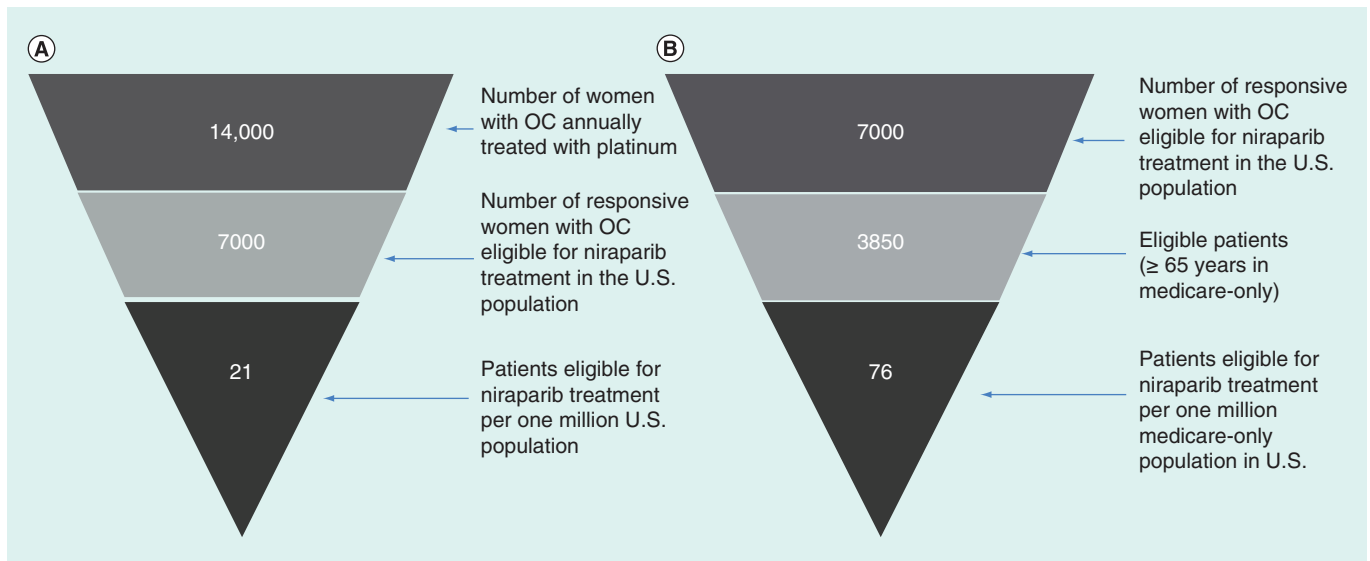


Figure 1. Number of patients eligible for niraparib. (A) Population representative of the USA; (B) Medicare-only patients. OC: Ovarian cancer.

PARP inhibitor treatment. We used this estimate to calculate the proportion of such women in a population of 1 million covered members, either in the general US population or those over 65 years of age.

Approximately 14,000 patients with recurrent OC are treated with platinum therapy every year in the USA [18]. Of these patients, 50% are estimated to be responsive [17,19–27], yielding an estimated 7000 patients eligible for treatment. Using this to define a proportion of eligible patients in the US population ($n = 326$ million [28]) yielded an estimate of 21 patients eligible for a PARP inhibitor in a population of 1 million US patients (Figure 1A).

Among the 7000 patients with recurrent OC eligible for treatment, an estimated 45% [1] to 59% [29] are over 65 years of age. Using a conservative estimate beyond the midpoint of this range (55%) yielded 3850 eligible cases among the Medicare population. Given the estimated 51 million persons over 65 years of age in the USA [28], and therefore eligible for Medicare, an estimated 76 patients are eligible for PARP inhibitor treatment among every 1 million Medicare members (Figure 1B).

Uptake assumptions

Niraparib, olaparib and rucaparib are approved for all patients regardless of *BRCA* mutation status and were included in the model along with bevacizumab and watch and wait. In this model, we estimated the cost to payers for treating all patients receiving PARP inhibitors with niraparib versus splitting PARP inhibitor use evenly between olaparib and rucaparib.

The number of patients on each treatment regimen was derived by multiplying the number of eligible patients by the expected market shares for each treatment. Table 1A provides the proportion of patients receiving alternate therapies for the two scenarios (with and without niraparib).

Treatment costs

The model included the costs of drugs, routine monitoring, managing TEAEs and subsequent treatment following discontinuation of maintenance treatment.

Drug costs were derived from the wholesale acquisition cost and the average monthly dose. No drug costs were allocated for watch and wait. For all three PARP inhibitors, adverse events can be managed through dose modification (reduction). Since all olaparib and rucaparib tablet strengths are priced the same, the first two dose reductions do not result in a lower cost. For rucaparib, however, a third dose reduction results in a 50% reduction in costs compared with higher doses; yet, it is not clear how many patients required such a dose reduction. In contrast, the cost of niraparib is proportional to the dose administered, and costs are two-thirds and a third that of the starting dose for the first and second dose reduction, respectively. The average dose in the ENGOT-OV16/NOVA trial was 195.6 mg, which is similar to the dose observed in real-world oncology practice (202 mg) [40]. Drug costs per month

Table 1. Model inputs of (A) market shares of investigated interventions; (B) frequency of TEAEs (grade ≥ 3 with $>10\%$ frequency); and (C) cost of TEAE (per event).

(A) Market shares of investigated interventions						
Scenario for gBRCAmut						
	With niraparib on the market			Without niraparib on the market		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Niraparib	48%	74%	75%	–	–	–
Olaparib	0%	0%	0%	24%	37%	37.5%
Rucaparib	0%	0%	0%	24%	37%	37.5%
Bevacizumab [†]	20%	19%	18%	20%	19%	18%
Watch and wait [†]	32%	7%	7%	32%	7%	7%
Sum	100%	100%	100%	100%	100%	100%
Scenario for non-gBRCAmut						
	With niraparib on the market			Without niraparib on the market		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Niraparib	37%	68%	72%	–	–	–
Olaparib	0%	0%	0%	18.5%	34%	36%
Rucaparib	0%	0%	0%	18.5%	34%	36%
Bevacizumab [†]	23%	14%	2%	23%	14%	12%
Watch and wait [†]	40%	18%	16%	40%	18%	16%
Sum	100%	100%	100%	100%	100%	100%
(B) Frequency of TEAEs (grade ≥3 with >10% frequency)						
gBRCAmut subpopulation						
	Niraparib [‡] [10,30]	Olaparib [31,32]	Rucaparib [33]		Bevacizumab [34]	Watch and wait
	Grade 3–4	Grade 3–4	Grade 3	Grade 4	Grade 3–5	Grade 3–4
Anemia	25.3%	5.4%	18%	1%	0%	0%
Neutropenia	19.6%	4.1%	5%	2%	0%	1.5%
Thrombo-cytopenia	33.8%	0%	3%	2%	0%	1.5%
Hypertension	8.2%	NR	0%	0%	11.3%	1.5%
Non-gBRCAmut subpopulation						
	Niraparib [‡]	Olaparib	Rucaparib		Bevacizumab	Watch and wait
	Grade 3–4	Grade 3–4	Grade 3	Grade 4	Grade 3–5	Grade 3–4
Anemia	25.3%	4.8%	18%	1%	0%	0%
Neutropenia	19.6%	3.2%	5%	2%	0%	0%
Thrombo-cytopenia	33.8%	0%	3%	2%	0%	0%
Hypertension	8.2%	NR	0%	0%	11.3%	0%
(C) Cost of TEAEs (per event)						
	Non-medicare		Medicare		Ref.	
	Unit cost (US\$)		Unit cost (US\$)			
Anemia [¶]	765 [§]		437		[35]	
Neutropenia [¶]	162 [§]		93		[35]	
Thrombocytopenia [¶]	741 [§]		423		[35]	
Hypertension [¶]	217 [§]		124		[36]	
[†] The market shares are based on market forecasts.						
[‡] Results for niraparib combine both gBRCA and non-gBRCA subpopulations.						
[§] Medicare costs were multiplied by 1.75, representing an average cost proportion of non-Medicare and Medicare services to estimate the cost for the overall population [37].						
[¶] To convert costs from earlier years to the year 2018, an average inflation rate of 3% was applied [38,39].						
gBRCAmut: Germline BRCA mutation; NR: Not reported; TEAE: Treatment-emergent adverse event.						

based on the average dose administered were US\$13,168, US\$13,886, US\$15,922 and US\$13,662 for niraparib (200 mg/d), olaparib (600 mg/d), rucaparib (1200 mg/d) and bevacizumab (1200 mg/cycle), respectively [41]. To estimate the total expenditure for payers, the costs per treated patient were multiplied by the number of patients receiving each treatment regimen and summed in both scenarios.

The costs of routine monitoring were based on the annual frequency of resource consumption (e.g., physician visits, monitoring and blood tests) for each patient, which were multiplied by the unit costs of each service based on Current Procedural Terminology codes (i.e., US\$74 per physician visit, US\$512 per magnetic resonance imaging/computed tomography monitoring and US\$10 per blood count) [42–45]. These costs were multiplied by a factor (i.e., 1.75) representing an average cost proportion of non-Medicare and Medicare services to estimate the cost for the overall population [37].

The number of patients receiving niraparib treatment in any given quarter is a function of the number of eligible patients, uptake, attrition and drop off. Data from the ENGOT-OV16/NOVA trial were used to model the attrition and drop off after each quarter for all PARP inhibitors. The attrition and drop-off rate for bevacizumab were derived from a clinical trial [46].

During the first quarter following the discontinuation of initial treatment, patients were assumed to incur the costs associated with chemotherapy. An average monthly cost for postprogression chemotherapy of US\$6433 per month [47] was applied to this quarter (converted to the year 2018 cost, based on an average inflation rate of 3%) [38,39].

TEAE rates & TEAE-related costs

Grade 3 and 4 TEAEs with rates greater than 10% reported in published clinical trials were included in the model for each drug regimen. Grade 3 and 4 TEAEs generally occurred in the first quarter after treatment initiation. Therefore, the occurrence rates of TEAEs were multiplied by TEAE-specific costs found in the literature and applied to the first quarter after treatment initiation (Table 1B & C) [33–36,48].

Analysis

Costs were estimated for a plan with an age distribution representative of the overall US population as well as for a Medicare-only plan. Both plans were assumed to cover 1 million lives.

For each scenario, the results were presented as total cost and by type of cost (i.e., drug costs, physician visits and monitoring, TEAEs and subsequent treatment).

A one-way sensitivity analysis was performed by varying each input parameter by $\pm 10\%$. We also explored range of uptake of niraparib as a proportion of the overall use of PARP inhibitors in the sensitivity analysis.

The potential impact of a third dose reduction in patients treated with rucaparib was tested in a scenario analysis.

Results

Full age distribution

For a hypothetical health plan with an age distribution representative of the US population, the model projected 21 patients per year that are newly eligible for niraparib, olaparib, rucaparib, bevacizumab or watch and wait. Adding newly eligible patients to patients continuing treatment for years 2 and 3 brought the total to 30 and 36 patients, respectively.

Total annual costs (pharmacy and medical) with and without niraparib were calculated. These included costs of monitoring, managing TEAEs, subsequent chemotherapy upon progression and costs associated with bevacizumab treatment.

The difference between the two scenarios, with and without niraparib, was a net cost savings, including both pharmacy and medical costs, of US\$78,721, US\$276,671 and US\$353,585 at years 1, 2 and 3, respectively (Table 2A).

Medicare plan

For a hypothetical health plan with 1 million Medicare-only (aged ≥ 65 years) covered lives, the model projected 76 patients eligible per year, growing to 111 patients at year 2 and 130 patients at year 3. The cost savings with niraparib in this population ranged from US\$293,723 (year 1) to US\$1,289,712 (year 3; Table 2B).

Sensitivity/scenario analysis

One-way sensitivity analysis showed that the prices for niraparib, rucaparib and olaparib and the prevalence of OC in the population were parameters that mainly influenced the outcomes of the budget impact analysis (Figure 2).

Given the lower cost of niraparib at its average dose, switching from either rucaparib or olaparib to niraparib will result in savings to the healthcare budget.

Table 2. Costs and budget impact per year in (A) population representative of the USA and (B) Medicare-only population.

Costs (US\$)	Year 1			Year 2			Year 3		
	With niraparib	Without niraparib	Δ	With niraparib	Without niraparib	Δ	With niraparib	Without niraparib	Δ
(A) Population representative of the USA									
Drug cost	859,704	941,456	-81,752	2,371,952	2,647,756	-275,804	2,956,796	3,309,483	-352,687
Niraparib	620,039	0	620,039	2,091,800	0	2,091,800	2,674,915	0	2,674,915
Olaparib	0	326,933	-326,933	0	1,102,961	-1,102,961	0	1,410,424	-1,410,424
Rucaparib	0	374,858	-374,858	0	1,264,643	-1,264,643	0	1,617,178	-1,617,178
Bevacizumab	239,666	239,666	0	280,152	280,152	0	281,881	281,881	0
Monitoring cost	44,857	44,727	130	93,822	93,383	439	115,827	115,266	561
TEAE cost	3909	1008	2901	6628	1615	5012	6909	1667	5231
Subsequent treatment	125,934	125,934	0	186,534	192,853	-6,318	234,011	240,701	-6,690
Total	1,034,405	1,113,125	-78,721	2,658,936	2,935,607	-276,671	3,313,543	3,667,128	-353,585
(B) Medicare-only population									
Drug cost	3,127,862	3,425,300	-297,439	8,629,875	9,633,332	-1,003,457	10,757,711	12,040,894	-1,283,183
Niraparib	2,255,887	0	2,255,887	7,610,598	0	7,610,598	9,732,143	0	9,732,143
Olaparib	0	1,189,480	-1,189,480	0	4,012,903	-4,012,903	0	5,131,547	-5,131,547
Rucaparib	0	1,363,845	-1,363,845	0	4,601,152	-4,601,152	0	5,883,778	-5,883,778
Bevacizumab	871,975	871,975	0	1,019,277	1,019,277	0	1,025,568	1,025,568	0
Monitoring cost	93,259	92,989	270	195,058	194,146	912	240,808	239,642	1166
TEAE cost	4643	1197	3445	7871	1919	5952	8205	1992	6212
Subsequent treatment	261,821	261,821	0	387,810	400,946	-13,136	486,516	500,424	-13,909
Total	3,487,585	3,781,307	-293,723	9,220,614	10,230,343	-1,009,729	11,493,240	12,782,952	-1,289,712

TEAE: Treatment-emergent adverse event.

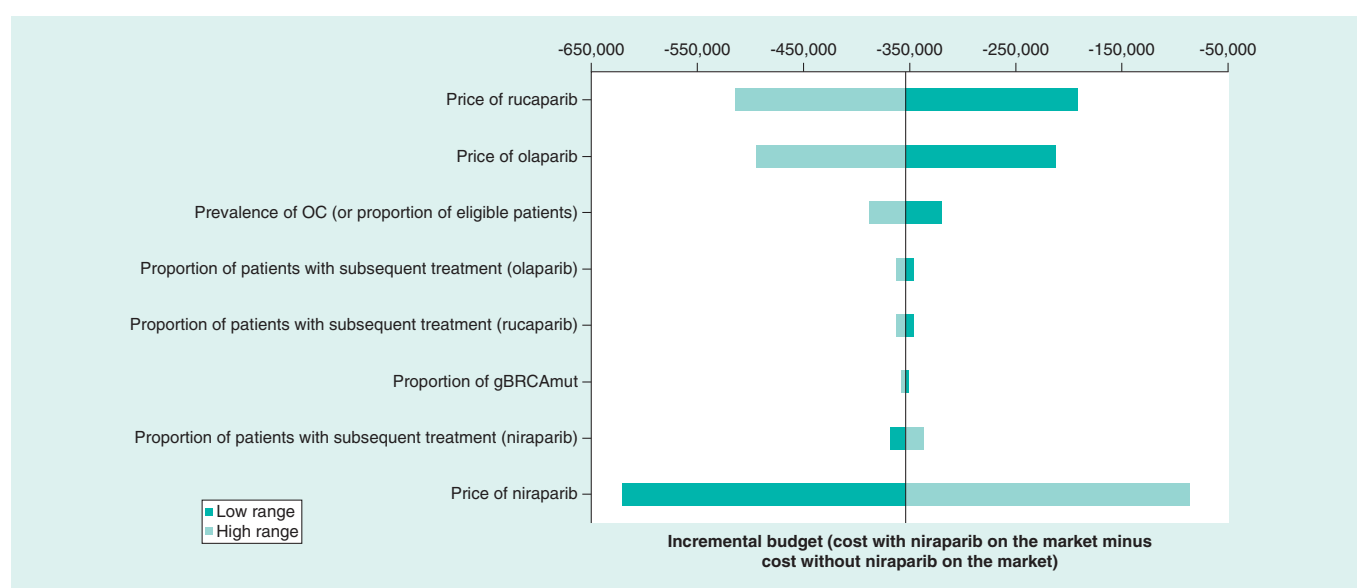


Figure 2. Impact of input parameters on the budget (population representative of the USA; same parameters were identified in the Medicare-only population).

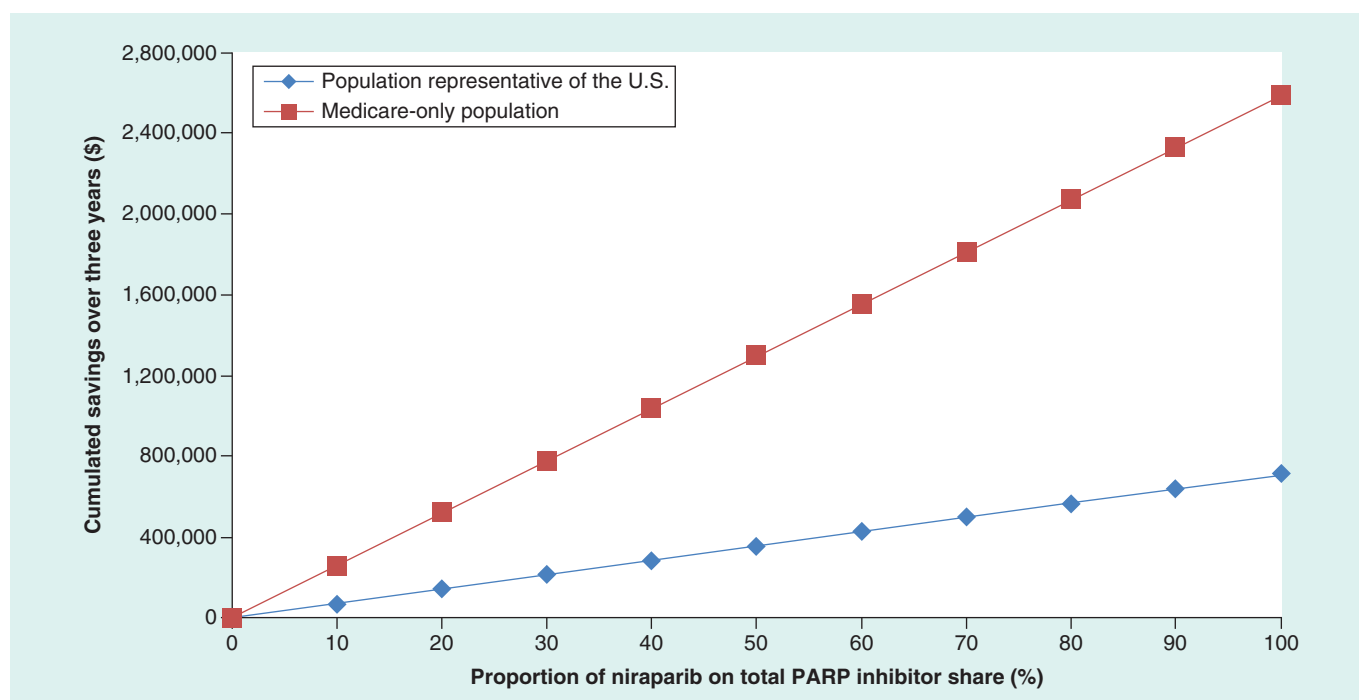


Figure 3. Sensitivity analysis of the switch from rucaparib and olaparib to niraparib.

A further sensitivity analysis assessed the degree of projected cost savings as the PARP inhibitor market share varies (Figure 3). The savings were correlated linearly with the market share of niraparib.

In addition, a scenario analysis was performed by taking into account that 15% of all rucaparib-treated patients required a third dose reduction. The ARIEL3 Trial [33] indicated that 54.6% of the population had dose reductions; however, it remains unclear how many of these patients had a third dose modification, as cost reduction is only applicable in those patients. Furthermore, ≥ 1 serious TEAE was reported in 21% of patients in the rucaparib group. Taking into consideration these findings and other recorded grade 3/4 TEAEs, we assumed that 15% would be a realistic approximation. Upon applying adjusted drug costs (50% lower drug cost) in 15% of rucaparib-treated patients, the total average drug cost per month decreased from US\$15,922 to US\$14,728 (85% with US\$15,922 and 15% with US\$7961). With this analysis, the cost savings with niraparib in the population representative of the USA decreased for all 3 years from US\$78,721 to US\$50,606 at year 1 and from US\$353,585 to US\$232,297 at year 3. For the Medicare-only population, the net savings decreased from US\$293,723 to US\$191,434 at year 1 and US\$1,289,712 to US\$848,429 at year 3.

Discussion

This budget impact analysis was undertaken to understand the financial consequences to health plans for the market entrance of niraparib in the treatment of patients with recurrent OC following complete or partial response to platinum-based chemotherapy. The analysis considered two scenarios, with and without niraparib on the market, and included the costs of drugs, treating drug-specific TEAEs, and subsequent chemotherapy following discontinuation over 3 years.

This model-based analysis of both a population representative of the USA as a whole and a Medicare-only population showed that the greater the use of niraparib relative to other PARP inhibitors (olaparib and rucaparib) the larger the cost savings. The analyses estimated an annual savings of US\$78,721 to US\$353,585 per million lives covered for a plan with a population representative of the USA and of US\$293,723 to US\$1,289,712 in the Medicare-only population. When the findings for the Medicare-only population are projected out to all US patients on Medicare, the overall estimated savings to Medicare were US\$15, US\$51 and US\$65 million at years 1, 2 and 3, respectively.

The results of the one-way sensitivity analyses showed that drug price is the main parameter that influences the overall cost. However, the observed cost savings in scenario 1 occur over a wide niraparib price range. The

break-even point (i.e., where the total annual costs in scenario 1 and 2 are equal) is at a monthly niraparib cost of US\$14,900, which is well above the US\$13,168 used in the main analysis.

Continually increasing healthcare expenditures represent a growing burden for societies globally. To allocate resources efficiently, it is increasingly important to analyze the consequences of the launch of new products based on available information. As an option to assess the economic consequences, BIMs have proven to be a valuable analysis tool. Based on the currently available data and plausible assumptions, these models allow an estimation of the expected consequences.

In order to check the certainty of the results obtained, the underlying assumptions were compared with another economic analysis with a comparable patient population [49]. The population size, distribution of *gBRCA* and non-*gBRCA* patients and total costs were found to be within a plausible range.

Findings from the underlying analysis show that the adoption of niraparib can lead to cost savings compared with other PARP inhibitors, which are reliable over a wide range of underlying assumptions.

Limitations

The projected uptake of niraparib, as well as the market share of other products, is a key driver of the model results and could vary from plan to plan. Medical management costs are based on Medicare reimbursement rates and were used to calculate the corresponding costs for commercially insured patients by applying a factor that represented an average of various commercial insurers.

Summary points

- Ovarian cancer (OC) is often diagnosed at an advanced stage, associated with a high recurrence rate following first-line treatment and decreasing progression-free survival following each subsequent treatment.
- There is a high unmet need for a medication that enables women with recurrent OC to live well for a longer period without disease progression.
- PARP inhibitors provide significant clinical benefit to patients with recurrent OC who are in response (partial or complete) to platinum-based chemotherapy.
- This budget impact analysis aimed to estimate the financial consequences of the introduction of niraparib, comparing a scenario where all PARP-treated patients receive niraparib versus a scenario where these patients receive one of the other two approved PARP inhibitors.
- For a hypothetical health plan of 1 million lives, the model projects that using niraparib instead of other PARP inhibitors would result in cost savings of US\$78,721, US\$276,671 and US\$353,585 at years 1, 2 and 3, respectively.
- For 1 million lives in a Medicare-only population, the net estimated savings from exclusive niraparib use would be US\$293,723, US\$1,009,729 and US\$1,289,712 at years 1, 2 and 3, respectively.
- When the findings for the Medicare-only population are projected out to all US Medicare patients, the overall estimated savings would range from US\$15 to US\$65 million from year 1 to year 3.
- The results of the one-way sensitivity analyses showed that the price of PARP inhibitors is the main parameter with an impact on the overall cost. A scenario analysis that took into account a significant dose and cost reduction in a portion of patients treated with rucaparib has shown that the niraparib-related cost savings are valid over a wide range.
- Findings from the underlying analysis show that the adoption of niraparib can lead to cost savings compared with other PARP inhibitors, which are reliable over a wide range of underlying assumptions.

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Author contributions

Study concept and design of the analysis were contributed by K Neeser, B Harrow, L Stern and WM O'Neil. Data collection, data preparation and data interpretation were conducted by B Harrow, K Travers and K Neeser. Writing of the manuscript was performed by K Neeser and B Harrow. All authors were involved in the revision of the manuscript.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

All data used to perform this budget impact analysis were derived from published scientific literature, publicly accessible databases or market analysis.

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