Biomarker Testing to Guide Cost Effective Use of PARPi in Patients with Newly Diagnosed Ovarian Cancer

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INTRODUCTION

- Each year, approximately 21,000 women in the United States (US) are diagnosed with ovarian cancer. While less common than some other cancers in women, it is among the most deadly. Currently, the average five-year survival rate is 48%; this rate varies from 92% when ovarian cancer is diagnosed and treated early to 29% when the cancer is diagnosed in more advanced stages.[1]
- Initial therapy for newly diagnosed ovarian cancer is typically surgery with adjuvant/neo-adjuvant chemotherapy. For many women however, the cancer recurs after standard first-line chemotherapy.[2]
- Lynparza (olaparib, MSD and AstraZeneca) is the first poly-ADP ribose polymerase (PARP) inhibitor to be approved as a first line maintenance therapy.
  - Its United States (US) approvals include for first line maintenance as monotherapy in patients with BRCA 1/2 mutations (BRCAm), supported by data from the SOLO-1 trial. In this trial, the hazard ratio (HR) for disease progression or death as assessed by investigators was 0.30 (95% CI 0.23 to 0.41).[3]
  - Lynparza has been found to be a cost-effective treatment in this setting (SOLO-1 CE model).[4]
  - Lynparza is also approved for first line maintenance treatment, in combination with bevacizumab, in cancers associated with homologous recombinant deficiency (HRD) positive status, supported by data from the PAOLA-1 trial.[5]
- In April 2020, Zejula (niraparib, GSK), also a PARP inhibitor, was approved as a first line maintenance treatment as monotherapy in patients irrespective of BRCA on the basis of results achieved in the PRIMA trial.[6,7]
  - The clinical benefit for niraparib was numerically greater for patients with BRCA mutations (PFS HR=0.40, 95% CI 0.27 to 0.76) than those without (overall population, PFS HR=0.62, 95% CI 0.50 to 0.76). PFS was measured by blinded central review.
- Consequently there are various treatment options for the first line maintenance setting, which may be guided by BRCA or HRD biomarker testing.
- This study evaluates the USA cost-effectiveness of BRCA biomarker testing and treatment with PARP inhibitor maintenance monotherapy in patients with advanced ovarian cancer after response to first-line platinum chemotherapy, following recommendations made by Gao et al[8].

METHODS

General

Table 1: Primary characteristics of the economic model

Target population	Patients with advanced OC at high risk for progression or death (as defined in PRIMA) eligible for first line maintenance monotherapy, more specifically: • Female, aged 18 years or over • Patients must have histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that is Stage III or IV according to FIGO criteria. • Surgical criteria per PRIMA • Patients with Stage III disease must have some visible residual disease after primary debulking surgery; addition • Patients must meet front-line therapy requirements that include: o Achieved complete or partial response to platinum-based regimen per RECIST • ECOG performance status 0-1
Subgroups of interest	Patients with BRCA 1/2 mutations (BRCAm) Patients without BRCA 1/2 mutations (BRCAwt)
Setting	United States
Perspective	Third party payer Drug acquisition costs are US Wholesale Acquisition Costs (WAC)
Time horizon	Lifetime
Model type	Three state partitioned survival (progression free, progressed disease, death)
Discounting	3% per year on costs and outcomes
Output / Outcomes	Cost, LYs, QALYs
Model technology	Microsoft Excel

Abbreviations: Eastern Cooperative Oncology Group (ECOG), International Federation of Gynecology and Obstetrics (FIGO), Response Evaluation Criteria in Solid Tumors (RECIST).

- Four strategies are evaluated in this cost-effectiveness model versus a strategy of no BRCA testing and Routine Surveillance (RS, strategy 0, Table 2).

Table 2: Strategies to be evaluated in the cost-effectiveness model

Strategy	BRCA testing	1L Maintenance treatment for BRCAm patients	1L Maintenance Treatment for BRCAwt patients
0	No	Routine Surveillance	
1	Yes	Olaparib	Routine Surveillance
2	Yes	Niraparib	Routine Surveillance
3	Yes	Olaparib	Niraparib
4	No	Niraparib	

- The outcomes associated with each strategy were calculated from individual pairwise CE models. Results from the pairwise models were combined to evaluate strategies 1-4 relative to strategy 0 (RS and no BRCA testing).This provided

the base case incremental analysis.

- We assumed 30% of the target population (Table 1) had BRCA mutations, as observed in PRIMA.[7]
  - Strategy 1 vs 0 was evaluated by considering the incremental costs and effectiveness of BRCA testing in all, followed by olaparib in BRCAm patients.
  - Strategy 2 vs 0 was evaluated by considering the incremental costs and effectiveness of BRCA testing in all, followed by niraparib in BRCAm patients.
  - Strategy 3 vs 0 was evaluated by considering the incremental costs and effectiveness of BRCA testing in all, followed by olaparib in BRCAm and niraparib in BRCAwt patients.
  - Strategy 4 vs 0 was evaluated by considering the incremental costs and effectiveness of niraparib in all patients.
- The cost of BRCA testing was assumed to be $1337, on the basis of the cost of the test itself ($468, CMS HCPCS code 81163 [9]) plus the cost of genetic testing ($869 after inflation to 2020 [10]).

Comparison A: Niraparib vs RS in patients with BRCA mutations

The SOLO-1 CE model[4] was adapted to match to the higher-risk PRIMA population and evaluate niraparib rather than olaparib costs:

- The Progression-Free Survival (PFS) curves were modeled using the best-fitting PFS curve to each arm of the BRCAm subgroup of PRIMA.
- The scale parameters for the Overall Survival (OS) curves were adjusted such that the two year survival in that arm of the model matches the BRCAm subgroup of the placebo arm of PRIMA (85% and 91% respectively).[6]
- Niraparib was costed per recommended posology on the basis of treat to progression at the Wholesale Acquisition Cost (WAC) of $185.85 per 100 mg capsule[11] with an average daily dose of 180.7 mg.[6,7]

Comparison B: Olaparib vs RS in patients with BRCA mutations

The Comparison B model was derived from the Comparison A model as follows:

- A hazard ratio of 0.80 was applied to derive the olaparib PFS from the niraparib PFS, as derived from an indirect treatment comparison analysis involving data from SOLO-1 and the BRCAm subset of PRIMA.[12]
- The WAC drug acquisition cost of olaparib was updated to $78.70 per 100 mg tablet[11]; the average daily dose remained at 558.8 mg[3].

Comparison C: Niraparib vs RS in patients with or without BRCA mutations

The Comparison C model was derived from the Comparison A model as follows:

- The PFS curves were replaced by the best-fitting PFS curves of the ITT population of PRIMA.
- The scale parameter of the OS curves were adjusted such that the two year survival matches the ITT population of PRIMA (77% and 84% respectively).[6,7]
- The pattern of subsequent treatment was adjusted to match the similar patterns of treatment observed in both arms of PRIMA (40.9% and 51.2% of niraparib and placebo patients receiving subsequent second-line treatment respectively). [6,7]

Comparison D: Niraparib vs RS in patients without BRCA mutations

In the absence of PFS Kaplan-Meier curves for the BRCAwt subpopulation of PRIMA, results for this comparison were derived from model comparisons A and C assuming that 30.0% of the PRIMA population were observed to have BRCA mutations.

The cost in treatment arm *x* of comparison *D* was

$$Cost_{D,x} = \frac{Cost_{C,x} - 30\% \cdot Cost_{A,x}}{1 - 30\%}$$

and similar expressions were used for QALY and LY outcomes.

Probabilistic Sensitivity Analyses

- Probabilistic Sensitivity Analyses (PSAs) of the SOLO-1 CE model have been previously reported.[4] The same approach was used to provide simulated results for pairwise Comparisons A-D.
- The proportion of the Target Population with BRCA mutations was simulated according to a Beta distribution; the unit cost of a BRCA test was simulated according to a Lognormal distribution with standard error equal to 10% of the mean.

- Results were combined in the same manner as the base case incremental analysis.

RESULTS

Pairwise models, A-D

The results from the pairwise CE models A-D are shown in Table 3, excluding the costs of BRCA testing.

Table 3: Discounted cost and health outcome results from pairwise cost-effectiveness analyses

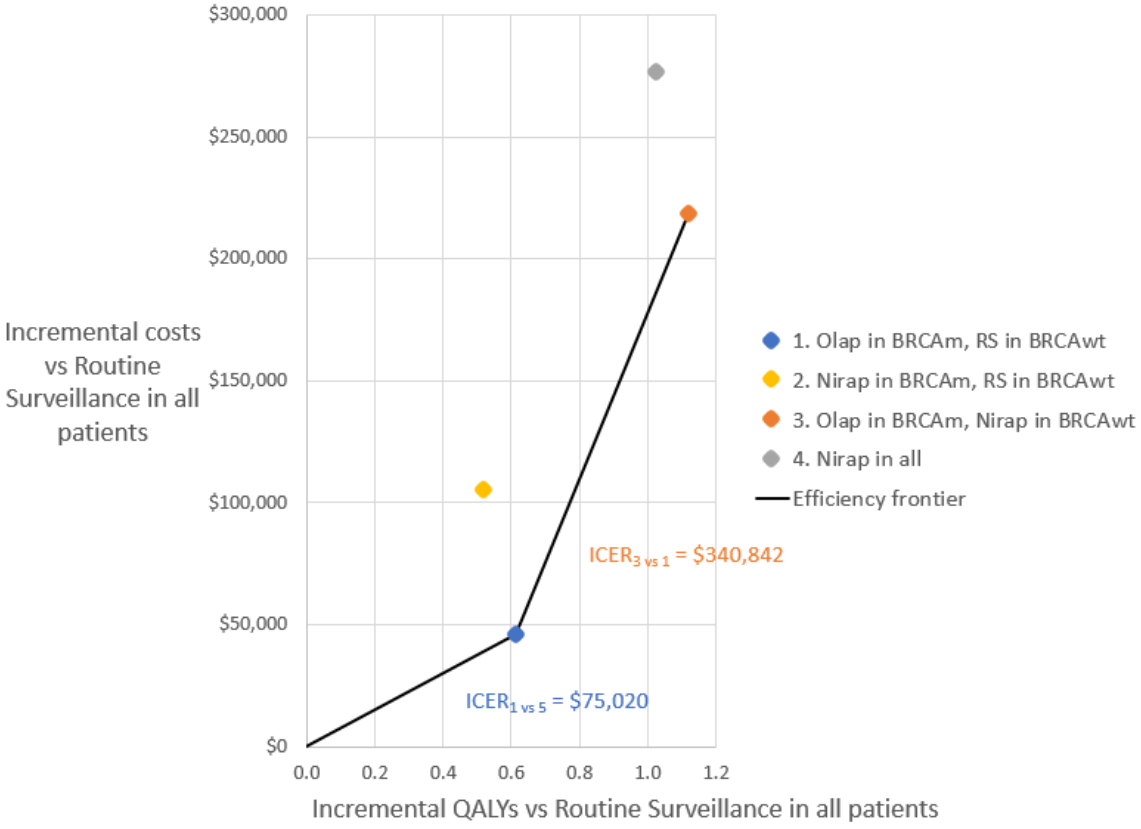
Model	Population	Treatment arm	Costs (US$)			Health outcomes	
			1L PARP maintenance treatment	Other	Total	LYs	QALYs
A	BRCAm	Niraparib	$461,751	$229,362	$691,113	7.472	6.059
		Routine Surveillance	$0	$345,073	$345,073	5.342	4.331
B	BRCAm	Olaparib	$265,087	$228,458	$493,546	7.847	6.370
		Routine Surveillance	$0	$345,073	$345,073	5.342	4.331
C	All	Niraparib	$281,142	$125,474	$406,616	5.321	4.320
		Routine Surveillance	$0	$129,930	$129,930	4.055	3.294
D	BRCAwt	Niraparib	$203,738	$80,950	$284,688	4.399	3.575
		Routine Surveillance	$0	$37,726	$37,726	3.504	2.850

Abbreviations: Life Year (LY), Quality adjusted life year (QALY)

Base case incremental analysis, strategies 0-4

- The least costly PARP strategy was olaparib in BRCA only (1), which had an incremental cost-effectiveness ratio (ICER) of $75,020 per QALY vs RS (Figure 1).
  - A similar result held for LYs instead of QALYs, with an ICER of $61,057 per LY.
- This strategy was both less costly and more effective than niraparib in BRCA only, such that Strategy 1 dominated Strategy 2.
- The use of niraparib in non-BRCA alongside olaparib in BRCA (3) led to increased costs and QALYs vs Strategy 1, with an ICER of $340,842 per QALY gained.
  - A similar result held for LYs instead of QALYs, with an ICER of $275,913 per LY.
- The most expensive PARP strategy of niraparib in all patients (4) was less effective than olaparib in BRCA and niraparib in BRCAwt (3), such that Strategy 3 dominated Strategy 4.

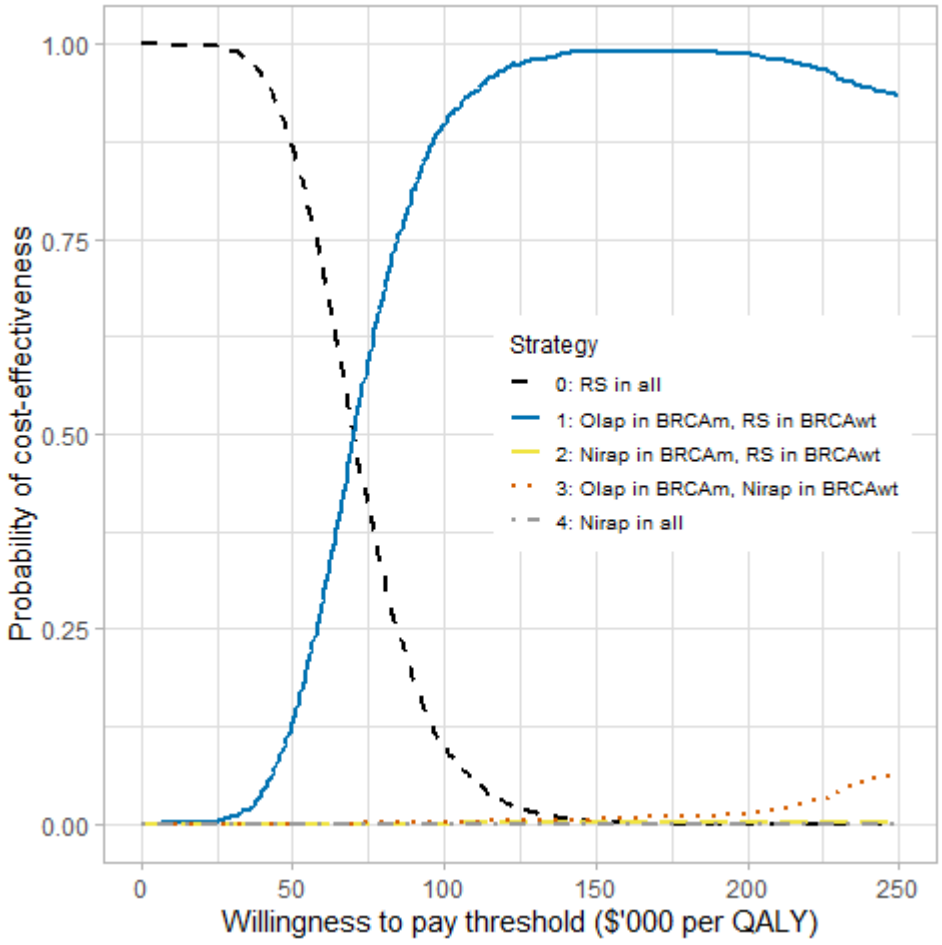
Figure 1: Cost-effectiveness plane (effectiveness measured as QALYs)



Probabilistic Sensitivity Analysis

- A cost-effectiveness acceptability curve is shown in Figure 2.
- Probabilities that Strategy 1 was the most cost-effective strategy were:
  - 89.8% and 99.7% at willingness to pay (WTP) values of $100,000 or $150,000 per QALY respectively; and
  - 97.8% and 99.9% at WTP values of $100,000 or $150,000 per LY respectively

Figure 2: Cost-effectiveness acceptability curve (effectiveness measured as QALYs)


1.00
0.75
0.50
0.25
0.00
Probability of cost-effectiveness
0
50
100
150
200
250
Willingness to pay threshold ($'000 per QALY)
Strategy
0: RS in all
1: Olap in BRCAm, RS in BRCAwt
2: Nirap in BRCAm, RS in BRCAwt
3: Olap in BRCAm, Nirap in BRCAwt
4: Nirap in all

CONCLUSIONS AND DISCUSSION

Conclusions

- At thresholds of $75,020-$340,842 per QALY gained, the optimal cost-effective strategy was BRCA testing followed by olaparib in BRCAm and RS in BRCAwt (Strategy 1).
- At thresholds of $61,057-$275,913 per LY gained, the same strategy (1) was cost-effective.
- Strategies involving niraparib were either dominated (Strategies 2 and 4) or cost-ineffective (Strategy 3).

Discussion

- This analysis provides a fuller evaluation of testing and treatment strategies than prior economic models, which have focused on examining the cost-effectiveness of treatment in biomarker-specific subgroups of patients.[4,8]
- A fully incremental analysis was performed in a homogeneous population of interest, thereby avoiding the flaws seen elsewhere where costs and outcomes from one population have been compared with costs and outcomes in another.[8]
- These are suitable WTP ranges to consider in the US, given that the Institute of Clinical and Economic Review reports results at $100,000 and $150,000 per QALY.[13]
- Biomarker guided treatment is essential to the cost-effective use of PARP inhibitors in this setting.
  - This is consistent with the recent finding by Gonzalez et al that treating all newly diagnosed advanced stage ovarian cancer patients with PARP inhibitors according to a targeted, biomarker-directed approach is cost-effective compared to treating all patients with those agents.[14]

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DISCLOSURES

This study was supported by funding from AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

DM, LF and MM are employees of Merck & Co., Inc.; RH and KM are employees of AstraZeneca.

ABSTRACT

Objectives

Evaluate the USA cost-effectiveness of BRCA biomarker testing and treatment with PARP inhibitor maintenance monotherapy in patients with advanced ovarian cancer after response to first-line platinum chemotherapy.

Methods

A 3-state partitioned survival model was developed to assess the cost-effectiveness of biomarker test and treat with olaparib in BRCA only (1), niraparib in BRCA only (2), olaparib in BRCA and niraparib in non-BRCA (3), and a test-free strategy of niraparib in all patients (4), versus routine surveillance (RS). Progression-free survival, overall survival and BRCA prevalence were modelled on data from PRIMA and SOLO1 trials, the latter adjusted to the higher-risk PRIMA population. A 50-year horizon was adopted, with costs and effects discounted at 3.0%.

Results

Compared to RS, the per patient incremental costs of each strategy was $45,879 (1), $105,149 (2), $218,753 (3), and $276,686 (4) with incremental QALYs of 0.61 (1), 0.52 (2), 1.12 (3), 1.03 (4). The least costly PARP strategy was olaparib in BRCA only (1), which had an incremental costeffectiveness ratio (ICER) of $75,020 per QALY vs RS. This strategy was both less costly and more effective than niraparib in BRCA only, such that (1) dominated (2). The use of niraparib in non-BRCA alongside olaparib in BRCA (3) led to increased costs and QALYs vs (1), with an ICER of $340,842 per QALY gained. The most expensive PARP strategy of niraparib in all patients (4) was less effective than olaparib in BRCA and niraparib in non-BRCA (3), such that (3) dominated (4).

Conclusions

At thresholds of $75,020-$340,842 per QALY gained, the optimal cost-effective strategy was testing followed by olaparib in BRCA and RS in non-BRCA (1). Strategies involving niraparib were either dominated (2, 4) or cost-ineffective (3). Biomarker guided treatment is essential to the cost-effective use of PARP inhibitors in this setting.