Poster PS5-11-03

The Value of Innovation in Breast Cancer Treatment: Real Option Value of Olaparib for First-Line Treatment of gBRCA1,2 Pathogenic Mutation HR+/HER2-negative and Triple Negative Metastatic Breast Cancer

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Objective

- To estimate the potential increase in survival due to the real option value (ROV) of first-line (1L) olaparib vs. chemotherapy treatment of physician's choice (TPC) for the treatment of hormone receptor-positive (HR+)/HER2-negative metastatic breast cancer (mBC) and triple negative metastatic breast cancer (TNBC) with germline BRCA1,2 pathogenic mutations.

Conclusions

- In a modeled patient population, 1L olaparib was associated with an increase in ROV among patients with HR+/HER2-negative and triple negative mBC, quantifying additional benefits attributable to future innovation.
- A treatment that extends progression-free and overall survival may increase patients' opportunity to benefit from subsequent innovations, informing patient-clinician discussions treatment selection.
- Future studies could apply the ROV framework to understand the broader impact of treatments due to innovation, beyond conventional measures of effectiveness.

Plain language summary

Why did we perform this research?
To evaluate how olaparib extends survival, enabling patients to access future FDA-approved innovations that may provide additional survival benefits.

How did we perform this research?
We used a computer model to estimate how much extra potential survival benefit hypothetical patients might gain from taking olaparib if doing so allows them to live long enough to receive future innovative therapies.

- This study looked at patients with breast cancer that had spread from its original site (metastatic), had an inherited mutation in the BRCA1 or BRCA2 genes (gBRCAm), and a low level of a protein called HER2.
- The model compared overall survival for patients receiving olaparib versus standard chemotherapy, both with and without access to future innovative treatments.
- The difference between these scenarios represents the hypothetical additional survival benefit patients may gain due to future innovation. We also adjusted these estimates to account for patients' quality of life.

What were the findings of this research?
When the potential impact of future innovative therapies was included, olaparib increased expected survival compared to chemotherapy by 1.6% to 10.3%, depending on the model inputs used, in a modelled patient population.

What are the implications of this research?
These results suggest that future treatment advances could enhance the long-term benefits of olaparib. This information may help guide discussions between patients and clinicians about using olaparib earlier to maximize opportunities to benefit from future innovations.

Poster | Plain language summary infographic

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Introduction

- Pathogenic germline mutations in the genes *BRCA1* or *BRCA2* (gBRCAm) present a more aggressive phenotype of metastatic breast cancer (mBC) among those who have HR+/HER2-negative and triple negative mBC.[1,2]
- Olaparib is an oral poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor approved for HER2-negative, gBRCAm mBC receiving <2 prior therapies, demonstrating a numerically longer median overall survival (OS) in the OlympiAD trial of 19.3 months vs. 17.1 months s (hazard ratio [HR]=0.90, 95% CI 0.63-1.29) for treatment of physician's choice (TPC, consisting of capecitabine, vinorelbine, and eribulin).[3]
- In the OlympiAD extended follow-up trial published in January 2023, the subgroup of first-line (1L) olaparib patients (n=87) had a median OS of 22.6 vs. 14.7 months (HR=0.55, 95% CI 0.33-0.95) and 3-year survival of 40.8% vs. 12.8% for TPC.[4]
- **Real option value (ROV)** is the hypothetical added value a drug provides due to prolonging survival and enabling the patient to receive future, yet to be developed innovative treatments.[5]
- Recent ROV studies have shown that the magnitude of ROV ranges from a 5-20% increase in modeled survival in various cancers, but no such studies have yet been conducted in mBC.
- Since the OlympiAD results in January 2023, novel drug classes (e.g. ADCs, AKT inhibitors, and oral SERDs) were approved and became available, which may provide additional survival benefits supporting the ROV hypothesis

Methods

- ROV was estimated by comparing outcomes in a modelled patient population with and without access to future innovative treatments (Figure 1) using an *ex-ante* pipeline forward-looking approach, based on the 1L OS reported in the OlympiAD extended follow-up trial.
- We developed a Markov model with time-varying transition probabilities between the health states of progression-free (PF), progressed disease (PD), and death, comparing 1L olaparib to TPC among gBRCAm patients over a lifetime horizon from a US healthcare perspective.
  - The population was weighted between HR+/HER2-negative and triple negative mBC according to the OlympiAD trial (53.4% and 46.6% respectively).[4]
  - Treatment-specific health utilities from the literature were assigned for PF disease: 0.841 for olaparib and 0.793 for TPC.[3] Upon progression, both arms were assigned a utility of 0.521.[6]
- A low, middle, and high value was chosen for each of the four ROV parameters due to uncertainty around each (Table 1).
- Future innovation included drugs known to be in development as of Jan 2023: sacituzumab govitecan, capivasertib, elacestrant, trastuzumab deruxtecan, and datopotomab deruxtecan for HR+/HER-, and sacituzumab govitecan, trastuzumab deruxtecan, and toripalimab for TNBC.
- HR+/HER2-negative mBC and TNBC were differentiated through their 2L+ innovation impacts.

Figure 1. Model Framework

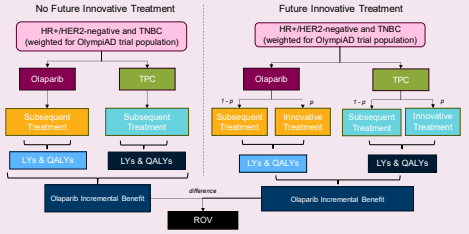


Table 1. ROV Model Parameters for Low, Mid, and High Scenarios

	HR+/HER2-negative			TNBC			Data Sources and Assumptions
	Low	Mid	High	Low	Mid	High	
Probability of approval	40%	60%	80%	40%	60%	80%	Based on 3 studies[7-9] that estimated approval rates for oncology drugs; probability = 48.5% from Phase 3 to approval for lead indications.[7]
Rate of Uptake	50%	70%	80%	50%	70%	80%	Based on a rate of 75% used in a previously published ROV model in NSCLC.[10]
Timing of Innovation	4 months	6 months	8 months	1 month	4 months	6 months	Estimated using drugs previously approved for mBC; calculated as the duration between study primary completion date and known FDA approval date (median time to approval = 7.4 months).
Effect Size (OS HR)	0.65	0.75	0.85	0.40	0.60	0.70	Based on published literature and company press releases for completed Phase 2 trials as of January 2023

KEY: HR – hazard ratio; HR+ - hormone receptor positive; mBC – metastatic breast cancer; LY – life years; NSCLC – non-small cell lung cancer; OS – overall survival; QALY – quality adjusted life year; ROV – real option value; TNBC – triple negative breast cancer

Results and Interpretation

Primary Outcomes

- In the aggregate (HR+/HER2-negative and TNBC) population, ROV yielded an increase in survival of 0.139, 0.069, and 0.022 life years (LYs) in the high, mid, and low scenarios, a relative increase of 10.3%, 5.1%, and 1.6%, respectively (Figure 2).
- The ROV primarily resulted from innovation in the HR+/HER2-negative subpopulation. For example, 0.115 LYs were due to HR+ innovation, and 0.028 LYs due to TNBC innovation in the high scenario.

When only HR+/HER2-negative innovation is considered, ROV yielded an increase of 0.139, 0.079, and 0.022 LYs in the high, mid, and low scenarios respectively.

This translates into a relative increase in survival of 8.5%, 3.8%, and 1.1%.

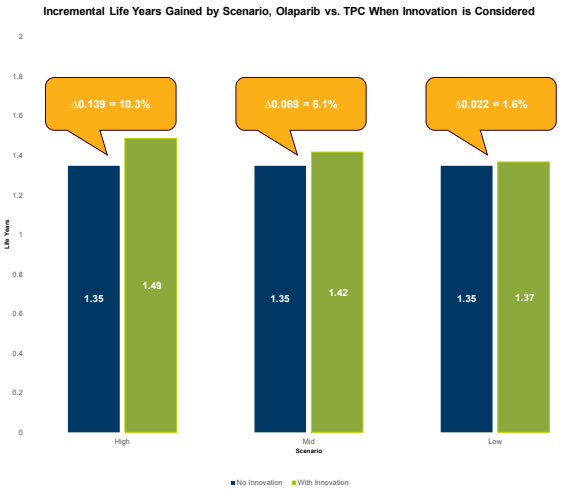
When only TNBC innovation is considered, ROV yielded an increase of 0.115, 0.051, and 0.014 LYs in the high, mid, and low scenarios respectively.

This translates into a relative increase in survival of 2.1%, 1.3%, and 0.6%.

Differences are driven by lower survival among TNBC patients and fewer TNBC patients in the overall population.

- **One-way sensitivity analysis:** The PD to death transition probabilities for TPC, and the effect size for innovation were the two largest drivers of the model (Figure 3).
- **Two-way sensitivity analysis:** Simultaneously varying the probability of success and innovation efficacy, illustrates a hypothetical range of increase in LY ROV.
  - Example: A 75% success rate and an OS HR of 0.65 yields an approximately 7.5-10% increase in LY ROV. This increases to nearly 15%, assuming an innovation hazard ratio of 0.6 and probability of success of 100%.

Figure 2. Modeled Incremental Survival by Scenario, No Innovation vs. Innovation



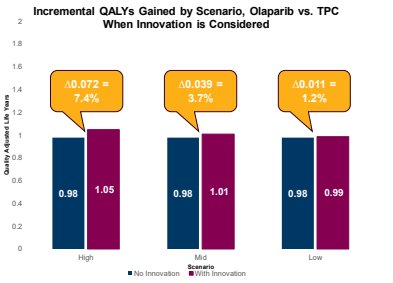
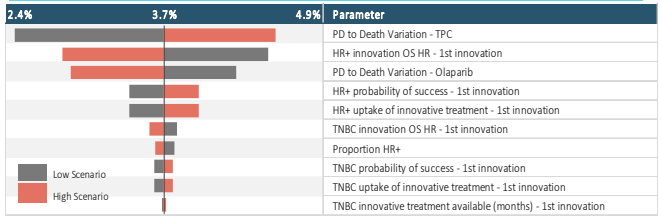


Figure 3. One-Way Sensitivity Analyses: % Increase in Survival Due to ROV



Limitations

- This is a modeling study, with results dependent on model assumptions rather than observed real-world outcomes.
- Future innovations are projected rather than observed, introducing uncertainty in success rates, effect sizes, and clinical uptake. This required the use of wide parameter ranges due to limited and evolving evidence.
- Comparators were limited by available trial data (e.g., exclusion of CDK4/6 inhibitors in 1L), which may affect estimated ROV.

Disclosures

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