COST-EFFECTIVENESS OF ADJUVANT OLAPARIB FOR PATIENTS WITH GERMLINE BRCA1/2-MUTATED, HIGH-RISK, HER2 NEGATIVE eBC IN PORTUGAL

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Background

- Breast Cancer (BC) is the most common cancer in females in Portugal, with a reported incidence of 7,425 new cases in 2020[1]. It is also the leading cause of cancer mortality in females in Portugal,with 1,785 deaths[2] annually, despite a relatively high survival rate (87% five-year global mortality rate).
- Approximately 5-10% of patients with BC carry germline BRCA gene mutations (gBRCAm)[3,4]. These women with gBRCAm have a risk of 45% to 65% of developing BC during their lives[5].
- The current treatment options for early-stage breast cancer (eBC) in Portugal mainly include (neo)adjuvant chemotherapy and endocrine therapy, followed by other therapeutic options depending on the disease setting. However, there are currently no recommended adjuvant therapy options specific to patients with human epidermal growth factor-2-negative (HER2 negative) BC and a germline BRCA1/2 mutation.
- In 2022, olaparib (Lynparza®), a poly(ADP)-ribose polymerase inhibitor (PARPi), was authorised for use in the European Union in monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk eBC previously treated with neo or adjuvant chemotherapy.

Objectives

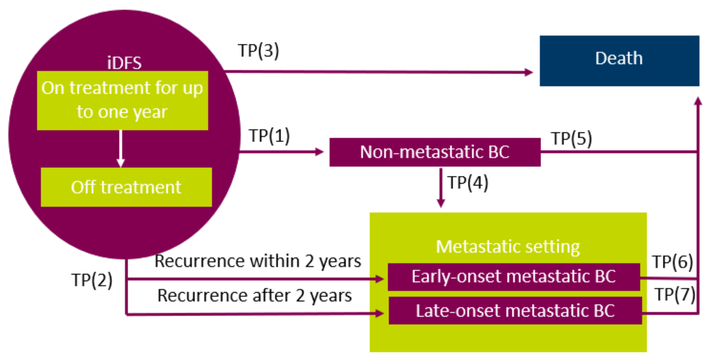
- The aim of this study was to evaluate the incremental cost-effectiveness ratio (ICER) of adjuvant olaparib for patients gBRCAm1/2, high-risk, HER2-negative eBC in the Portuguese setting.

Methods

Economic Model

- The analysis was conducted from the Portuguese National Health Service perspective assuming a 4% discount rate for costs and consequences (Quality-adjusted life years [QALY] and Life Years [LY]), assuming a lifetime horizon (57 years).
- The model was developed in monthly cycles (30.4 days) and a half-cycle correction was implemented.
- A semi-Markov state transition model was developed in Microsoft Excel® with five health states: iDFS (with distinction for patients on and off adjuvant treatment); non-metastatic BC, early-onset metastatic BC, late-onset metastatic BC, and death (Figure 1).
- One-way and probabilistic sensitivity analyses were used to assess uncertainty.

Figure 1. Model structure (Semi-Markov model with 1 – month cycle length)



Abbreviations: BC, breast cancer; iDFS, invasive disease-free survival; TP, transition probability

Clinical data

- Two subpopulations, HR+/HER2- and TNBC patients, were separately evaluated in accordance with the PICO (Population, Intervention, Comparator and Outcomes) framework defined by the Portuguese HTA agency. Selected comparator were also aligned with the PICO.
- Primary clinical data to inform the model was derived from the corresponding subgroups in the phase 3 OlympiA study, used to model outcomes for the HR+/HER2- and TNBC populations.
- Data informing comparator arm in the model was also derived from the placebo arm of OlympiA trial as a proxy for Watch and Wait (WaW). Patients with HR+/HER2- disease could also receive endocrine therapy alongside olaparib or WaW.

Methods (cont.)

- TNBC-specific iDFS data from the OlympiA trial were employed for the analysis of the TNBC subgroup during the iDFS assessments (TP1 and TP2) because the data was sufficiently mature. ITT data were utilized as a substitute for HR+/HER2- analysis due to the restricted number of iDFS events observed in this subgroup.
- The inclusion of two mBC health states enabled the model to capture differences in risk of death based on time of recurrence: patients with early recurrence (occurring within the first 2 years- TP6) typically have more aggressive disease than patients who experience late recurrence (occurring after 2 years – TP7)[6,7].
- The model assumed patients with TNBC who remain disease free for 5 years have no risk of recurrence thereafter. Literature data indicates that the risk of recurrence is higher within the initial 5 years following diagnosis, followed by a substantial decline and stabilization of the recurrence rate[8,9]. For the HR+/HER2- population BC events could occur throughout the lifetime horizon[9,10].
- Standard parametric models were fit to the clinical data informing each transition probability to extrapolate clinical outcomes beyond the trial period. All-cause mortality data were used to ensure death risks remained above the age/gender/BRCA-adjusted lifetable statistics[11].

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Transition probability (TP)	Source	Risk by treatment arm
TP1 and TP2: iDFS to disease recurrence	OlympiA trial DCO2[12,13]	Same
TP3: iDFS to death	Portuguese lifetables [11] Adjustment for the excess mortality associated with gBRCA 1/2 mutations [14]	Same
TP4: Non-mBC to metastatic BC	OlympiA trial DCO2[12,13]	Same
TP5: Non-mBC death	OlympiA trial DCO2[12,13]	Same
TP6: EOM BC to death (recurrence ≤ 2 years)	OlympiA trial DCO2[12,13]	Different based on data from OlympiA trial
TP7: LOM BC to death (recurrence > 2 years)	OlympiAD[15] and RWE data from Collins *et al* [16]	Same

Abbreviations: BC, breast cancer; DCO, data cutoff; EOM, early-onset metastatic; gBRCA, germline BRCA gene; iDFS, invasive disease-free survival; LOM, late-onset metastatic; TP, transition probability.

Adverse Events

- Grade ≥ 3 adverse event (AE), reported in at least 3% of patients in the OlympiA trial were considered in the model using disutility values sourced from literature [17,18].
- AEs costs were obtained from Portuguese databases and literature.

Utilities

- Utility values for the iDFS and non-metastatic health states were derived by mapping data from OlympiA to the EQ-5D-5L[19]. Portuguese tariffs were used for utility calculation[20]. Utility value for non-mBC was assumed to be the same as iDFS[21-23].
- Early and late-onset mBC utility values were informed by published literature[24] and were further adjusted for age using the Ara and Brazier [25] equation from.

Costs

- Modelled costs included drug acquisition (including up to one year of olaparib) and administration, subsequent therapies, adverse events, hospitalization, and physician visits. Unit costs were based on Portuguese official sources[26-28].

Results

- In TNBC patients olaparib increases average life expectancy by 1.3LY or 1.1 QALY when compared with WaW. Economic analysis shows that these benefits in terms of LY and QALY gained are accompanied by an increase in costs of €42,801. The resulting ICER was €38,917 per QALY gained vs. WaW.

Results (cont.)

- In HR+/HER2- patients olaparib increases average life expectancy by 1.1LY or 1.0 QALY when compared with WaW. Economic analysis shows that these benefits in terms of LY and QALY gained are accompanied by an increase in costs of € 46,426. The resulting ICER was €48,408 per QALY gained vs. WaW.
- Deterministic results were consistent with probabilistic results: €38,355 per QALY in the TNBC and €45,416 per QALY in the HR+/HER2- populations.
- Analyses based on olaparib list price; additional confidential discounts may apply, reducing the ICE.

Figure 2. iDFS extrapolation and Kaplan-Meier curves

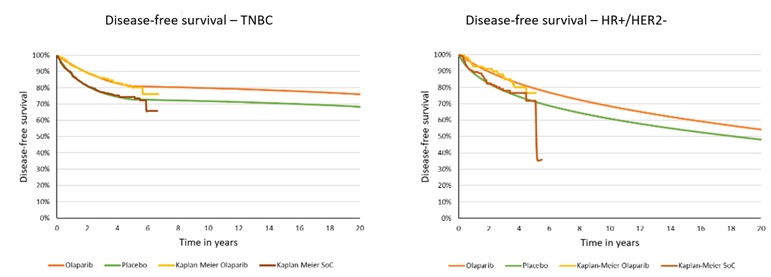
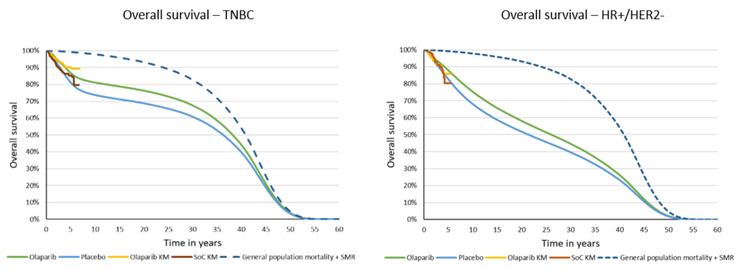


Figure 3. OS extrapolation and Kaplan-Meier curves

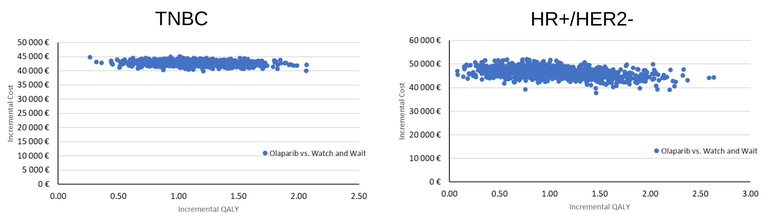


Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; QALY, quality-adjusted life year; TNBC, triple-negative breast cancer.

Sensitivity analysis

- In the deterministic sensitivity analysis, the ICER was most sensitive to changes in the time horizon, discount rates, and selected parametric models for the iDFS stage.
- Probabilistic sensitivity analysis was conducted (1,000 simulations), also showing that results are robust (Figure 4). For TNBC population ICER ranged between €28,310 per QALY (percentile 25) and €46,507 per QALY (percentile 75). For HR+/HER2- population ICER ranged between € 32,893 per QALY (percentile 25) and €70,116 per QALY (percentile 75).

Figure 4. Cost-effectiveness planes



Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; QALY, quality-adjusted life year; TNBC, triple-negative breast cancer.

Conclusions

- In the Portuguese setting treatment with olaparib increased LY and QALY in patients with gBRCAm1/2, high-risk, HER2-negative eBC at a generally acceptable incremental cost.
- This cost-effectiveness analysis was considered valid to support a reimbursement decision in Portugal.

Disclosure

- All authors are employees of AstraZeneca and may or may not own stock options.

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