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Abstract

Introduction

Approximately 5% of unselected breast cancer patients carry a germline mutation (gBRCAm) in the BRCA1 and BRCA2 genes that repair double-strand DNA breaks through homologous recombination. Olaparib, an oral poly ADP-ribose polymerase inhibitor (PARPi), incurs selective synthetic lethality in BRCA-deficient tumour cells by inhibiting single-strand DNA repair. In 2014, olaparib was approved in Europe and USA for the treatment of BRCA-mutated ovarian cancer. Olaparib is under evaluation as monotherapy for human epidermal growth factor receptor 2 (HER2)-negative, BRCA-mutated metastatic breast cancer (MBC) in phase III trials.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials. Furthermore, the magnitude of clinically meaningful benefit that can be expected from olaparib was evaluated based on, both the original and an adapted version of the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology.

Results of the OlympiAD trial

An intent-to-treat population of 302 patients with a confirmed gBRCAm and HER2-negative MBC, previously treated with fewer than three chemotherapy regimens, were randomly assigned to receive olaparib (n = 205) or physician's choice of chemotherapy (n = 97; capecitabine, eribulin, or vinorelbine in 21-day cycles). At 14-months follow-up, overall survival did not show a statistically significant difference between groups. Compared with chemotherapy, olaparib increased median progression-free survival (PFS) by 2.8 months by blinded independent central review (BICR), reduced the risk of disease progression and death by 42%, and reduced the risk of investigator-assessed second progression by 43%. BICR-assessed objective response rate was 59.9% for olaparib versus 28.8% for chemotherapy. At 15.3 months, chemotherapy improved disease-specific quality of life. Adverse events (AEs), primarily anaemia, caused a dose interruption, reduction or discontinuation in 50%, 27% and 5% of olaparib patients, respectively. Patients require monthly monitoring for haematological toxicity.

Conclusion

Overall, olaparib improves PFS and reduces the risk of progression in HER2-negative BRCA-mutated MBC relative to physician's choice chemotherapy. OlympiAD results hold limited internal and external validity, and follow-up may be insufficient to capture the risk of recurrence or second primary development. Not all patients respond to olaparib yet some sporadic triple negative breast cancer (TNBC) display a BRCAness phenotype without carrying a gBRCAm. While patients are selected based on a confirmed deleterious gBRCAm, there is currently no established biomarker for response to PARPi. Clinical utility of olaparib may be limited as three mechanisms of resistance have already been established, increasing use of platinum therapy in early TNBC may influence PARPi use, and the optimal PARPi-chemotherapy drug combination remains to be established.

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1 Research questions

EUnetHTA
HTA Core Model®

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

Element ID	Research question
Description of the technology	
B0001	What is the olaparib?
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A0007	What is the target population in this assessment?
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C0005	What are the susceptible patient groups that are more likely to be harmed through the use of olaparib?
A0021	What is the reimbursement status of olaparib?

2 Drug description

Generic/Brand name/ATC code:

Olaparib/Lynparza/AZD-2281/KU-59436

B0001: What is olaparib?

second generation PARPi

Olaparib, an oral poly(adenosine diphosphate-ribose-ribose) polymerase inhibitor (PARPi), traps PARP at sites of DNA damage, preventing the repair of single strand DNA breaks and causing double strand breaks (DSB). While homologous recombination (HR) is the most common means of repairing DSB, cells that are HR-deficient initiate more error-prone pathways such as non-homologous end joining or single strand annealing causing genomic instability and cell death. BRCA1 and BRCA2 (BReast CAncer gene 1 or 2) are tumour suppressor genes that encode proteins involved in the HR repair of DSB in DNA. The selective inhibition of PARP leads to synthetic lethality in tumour cells with deficiencies in HR repair such as germline mutations in BRCA1/2 that reduce the cell's ability to repair damaged DNA [2-4].

2 x 150 mg oral tablets twice/day

Olaparib is formulated as a 50 mg oral capsule and as 100 mg and 150 mg tablets [5-7]. The capsule formulation is approved for the treatment of BRCA-mutated advanced ovarian cancer at a dose of 400 mg twice daily in Europe and the United States (US) [6, 8]. The tablet formulation, recently approved in the US, was developed to reduce the dose units required and improve compliance [7]. However, the formulations are not bioequivalent [9]. A dose-finding study concluded that a 300 mg twice daily tablet dose (4 x 150 mg tablets per day) best matched the 400 mg twice daily capsule dose in terms of efficacy and tolerability [7, 10, 11]. In phase III olaparib monotherapy studies, olaparib is administered as two 150 mg tablets taken twice daily, an hour before or two hours after a meal, until disease progression or unacceptable toxicity [8, 12].

genetic testing for gBRCAm haematological monitoring

Myriad Genetics developed the companion diagnostic BRACAnalysis CDx™ to identify patients with deleterious or suspected deleterious germline BRCA mutations (gBRCAm) who may benefit from olaparib treatment [13]. Patients require baseline and monthly monitoring for haematological toxicity due to the risks for myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). Dose interruptions or reductions are recommended for individuals with adverse reactions or moderate renal impairment. Olaparib may be discontinued in patients with pneumonitis, MDS or AML. Concomitant use of strong CYP3A inhibitors or inducers should be avoided [7].

A0022: Who manufactures olaparib?

AstraZeneca

3 Indication

A0007: What is the target population in this assessment?

Olaparib (Lynparza™) is indicated as monotherapy for patients with BRCA-mutated, human epidermal growth factor 2 (HER2)-negative metastatic breast cancer (MBC).

BRCA-mutated, HER2-negative MBC

4 Current regulatory status

A0020: For which indications has olaparib received marketing authorisation?

On December 18, 2014, the first-in-class PARPi olaparib received market authorisation by the European Medicines Agency (EMA) for the maintenance treatment of adults with platinum-sensitive, relapsed, BRCA-mutated, high grade, serous epithelial ovarian, fallopian tube, or primary peritoneal cancer [14]. Initial approval was based on the results of the phase II trial, Study 19 [8, 15]. Europe implemented a risk management plan involving several trials to monitor safety [16].

EMA and FDA: authorised/approved for BRCA-mutated ovarian cancer in December 2014

On December 19, 2014, the US Food and Drug Administration (FDA) approved olaparib as monotherapy for patients with deleterious or suspected deleterious gBRCAm advanced ovarian cancer, as detected by BRACAnalysis CDx™, who were previously treated with three or more lines of chemotherapy [6, 13].

FDA approval for olaparib monotherapy in ovarian cancer

AstraZeneca plans to file a supplementary marketing application before the end of the year to expand the licensing indication to include BRCA-mutated MBC based on results of the OlympiAD trial [12, 17].

applying to expand licensed indication: BRCA-mutated MBC

5 Burden of disease

A0002: What is breast cancer?

Owing to the molecular pathogenesis of breast cancer, it is designated as a heterogeneous malignancy. It arises from the tissues of the breast and most commonly originates in the cells that line the ducts due to dysregulation of the cell cycle [18, 19]. BRCA-mutated breast cancer is associated with an earlier onset; a family history of several close relatives affected with breast, ovarian, prostate or pancreatic cancer; and ethnic populations with founder mutations [20, 21]. Approximately 5% of unselected breast cancer patients carry a germline mutation in the breast and ovarian cancer predisposition genes BRCA1 and BRCA2 involved in double-strand DNA repair by HR

5% have gBRCAm-breast cancer: early onset, family history, Ashkenazi Jewish descent

[22]. Up to 75% of women with BRCA1-mutated cancers, an estimated 180,000 women worldwide, have triple-negative breast cancer (TNBC) that lacks expression of the hormone oestrogen and progesterone receptors (HR-negative) and the absence of amplification of oncogene ERBB2 (HER2-negative) that encodes human epidermal growth factor receptor 2 [23]. Women with a BRCA2 mutation most often have tumours that express oestrogen receptors (ER-positive) [24].

A0004: What is the natural course of breast cancer?

TNM staging system

Breast cancer typically arises when epithelial cells lining the milk ducts and/or lobules undergo aberrant cell growth due to cell cycle dysregulation. Breast cancer is staged from I through IV based on tumour size, and presence or absence of lymph node involvement and metastases (TNM) [25]. The TNM staging system involves important tumour characteristics as well as survival data to support the estimation of outcomes. It classifies tumours on the basis of the primary tumour characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M). The TNM staging system is especially relevant for inflammatory and stage IV breast cancer [26].

staged I-IV by invasiveness

Ductal carcinoma, the most common type of breast cancer, originates in the cells of the ducts. In the early stages, atypical cells confined to the milk ducts are termed stage 0, ductal carcinoma in situ (DCIS). Breast cancer that spreads from its origin in the ducts or lobules to surrounding tissue is called invasive breast cancer. Approximately 70–80% of breast cancers are diagnosed as stage I (localized to one area) or stage II (early locally advanced, invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC). Stage III locally advanced breast cancer (LABC) includes tumours larger than 5 cm in diameter that involve the skin, underlying muscle, lymph nodes or inflammatory breast cancer (IBC). During stage IV, breast cancer cells travel through the blood or lymphatic system forming metastatic tumours in bone, liver, lungs and brain [25]. Cancer that has spread to distant parts of the body, referred to as metastatic breast cancer (MBC), has a five-year survival rate of less than 27% [27].

metastasize to bone, liver, lungs, brain; 5 year survival <27%

A0006: What are the consequences of breast cancer for society?

leading cause of cancer death in women worldwide

Globally, breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women worldwide. Approximately 30% of women diagnosed with early stage breast cancer develop advanced or MBC despite treatment [28]. Patients may progress or further metastasize causing significant cancer specific morbidity and mortality. In Austria, breast cancer is the 19th leading cause of disability adjusted life years and accounts for approximately 28,000 (2.6% of total) life lost due to premature mortality [29]. The incidence of breast cancer is highest for higher socioeconomic groups, whereas survival is lowest in lower socioeconomic groups [30]. Since increasing age is a risk factor for cancer, the incidence of breast cancer is likely to increase as the population ages.

incidence increases as population ages

A0023: How many people belong to the target population?

About 30% of all malignant neoplasm cases in Austria are due to breast cancer. It is the most common cause of death due to cancer in females. The age standardised incidence rate for the European Standard Population (2013) is 64.3 per 100,000 persons per year. In 2014, 5,454 persons were newly diagnosed with breast cancer in Austria, of whom approximately 98.0% were women. Moreover, around 86.0% of female breast cancer patients and 78.0% of male breast cancer patients (all stages are included) are alive at least five years after diagnosis [31].

incident rate based on European Standard Population: 64.3 per 100,000 persons/year

While the median age at diagnosis of breast cancer is 62 years (range 55 to 64 years) [27], most BRCA-mutated breast cancers are diagnosed before 50 years of age. Rates of BRCA-mutated breast cancers increase in early adulthood until age 30 or 40 years for women with BRCA1 mutations, and 40 to 50 years for those with BRCA2 mutations [20]. Women with mutations in BRCA1 or BRCA2 have an increased risk for contralateral breast cancer and metachronous ovarian cancer [22]. The ten year risk of ovarian cancer is 12.7% and 6.8% for women with BRCA1 and BRCA2 mutation-associated breast cancer, respectively [32]. Between 5.0% and 10.0% of the patients are primarily diagnosed with MBC that has spread to other parts of the body, e.g., bone, liver, lung and brain [33].

median age at diagnosis of BRCA-mutated breast cancer patients: <50 years

A0005: What are the symptoms and the burden of breast cancer?

Breast cancer is most commonly characterized by a hard, immovable, lump or mass in the breast with irregular borders [34-36]. Patients with LABC may experience swelling, dimpling or thickening of the skin, a change in shape or colour, nipple retraction or discharge, and pain in the breast or underarm. Symptoms of MBC include swollen lymph nodes, bone pain or fractures, headaches or seizures, shortness of breath or jaundice depending on the organs affected [25].

main symptoms: breast lump, thickening, pain

A0003: What are the known risk factors for breast cancer?

Approximately one in eight, or 12.4% of women will develop breast cancer at some point during their lifetime [27]. Risk factors for developing breast cancer include increasing age, female gender, a personal or family history of breast cancer, Caucasian race, obesity, increased breast density, alcohol consumption and cigarette smoking. Reproductive factors that increase risk of breast cancer include early menarche, nulliparity or older age at first birth, late menopause, and hormone replacement therapy. Up to 10% of breast cancers may be due to the inheritance of genetic alterations in BRCA1 and BRCA2. Inheritance of one mutated BRCA1 or BRCA2 allele confers a lifetime risk of breast cancer as high as 80% [20]. Up to age 80, breast cancer risk is 72% for women with a BRCA1 mutation and 69% for those with a BRCA2 mutation [20]. Genetic testing for BRCA1 and BRCA2 mutations helps identify unaffected high-risk women for prevention and surveillance.

main risk factors: increasing age, female gender, personal or family history of breast cancer, genetic alterations

gBRCAm: up to 80% lifetime risk of breast cancer

A0024: How is breast cancer currently diagnosed according to published guidelines and in practice?

diagnostics: mammography, biopsy, HR status, bone, CT, PET scans

Diagnostic mammography is an x-ray that uses small doses of radiation to make an image of the breast following abnormal results of a screening mammogram or clinical breast exam (CBE). A mammogram of both breasts is performed to define tumour size and assess whether the contralateral breast is affected. Breast magnetic resonance imaging (MRI) or ultrasound may also be performed to estimate tumour size and distinguish between a fluid-filled or solid mass. If breast cancer is suspected based on mammography, a biopsy is performed where a sample of breast cells or tissue from the lump is examined to determine the presence of cancer cells, and hormone receptor (HR) or HER2 protein expression. HR status is an important factor in planning clinical management. In later stages, bone scans, blood tests, x-rays, CT and PET scans may be conducted to determine whether breast cancer has spread to bone, liver, lungs or brain [25, 37].

6 Current treatment

A0025: How is breast cancer currently managed according to published guidelines and in practice?

factors for therapeutic decisions

Generally, breast cancer can be treated by surgery, adjuvant irradiation or systemic therapies [38]. To determine which treatment strategy is the most suitable for the patient, several factors are important [25, 38]:

- stage of cancer (AJCC TNM staging system)
- grade of disease
- tumour site
- menopausal status
- patient health
- HR and HER2 status
- proliferation rate estimated by means of a Ki67 test

curative treatment options for stage ≤3 breast cancer

The treatment of stage ≤3 breast cancer, where no distant metastases have been detected, has a curative intention and is dependent on the eligibility of a breast-conserving therapy (BCT) and whether it is a clinically node-negative breast cancer. For patients who are eligible for a BCT, the following treatment options in this sequence may be applied [38]:

- primary neoadjuvant systematic therapy (node-negative breast cancer)
- surgery (sentinel lymph node biopsy [SLNB])
- axillary node dissection
- adjuvant systematic therapy
- adjuvant radiation therapy

stage IV breast cancer treatment options with a palliative intent

For patients who are not eligible for a BCT and for locally ABC (stage IIB, IIIA/B) the previously mentioned treatment options can be applied as well. However, instead of a BCT, a mastectomy may be performed. In case of metastatic disease (stage IV), treatment with a palliative intent (systematic therapy, best supportive care, etc.) can be used [38].

treatment: surgery, chemotherapy, radiotherapy, no definitive regimen or treatment for BRCA-mutated breast cancer

For women with BRCA-mutated breast cancer, goals include preventing recurrence and second primary breast and ovarian cancer [21]. Both HR-positive and HER2-negative breast cancers are associated with a better prognosis than HR-negative and HER2-positive disease. TNBC often have worse outcomes than other breast cancer subtypes due to the lack of efficacy of hormone and HER2 targeted therapies [30]. More than 75% of tumours arising in women carrying a BRCA1 mutation are TNBC [32]. While BRCA-mutated breast cancer is treated using a combination of surgery, chemotherapy and radiotherapy, there is no definitive chemotherapy regimen or approved treatments specifically targeted for patients with a deleterious BRCA mutation [32, 39, 40]. However, the following treatment options are available for this patient population:

- Risk-reducing surgeries, including prophylactic mastectomy and salpingo-oophorectomy significantly reduce the risk of developing breast and/or ovarian cancer and improve overall survival in BRCA1 and BRCA2 mutation carriers [32, 41].
- Chemoprevention strategies, including the use of tamoxifen reduces the risk of contralateral breast cancer among BRCA1 and BRCA2 carriers after treatment for breast cancer [41].

TNBC treatment: adjuvant or neo-adjuvant anthracycline- and taxane-based chemotherapy

- Chemotherapy regimens for patients with HER2-negative breast cancer include anthracycline-based regimens followed or preceded by a taxane, and nonanthracycline-containing regimens. In addition to standard anthracycline- and taxane-based therapy, women may receive cyclophosphamide or gemcitabine or capecitabine with docetaxel followed by docetaxel [39].

BRCA1-mutated breast cancer: sensitive to platinums

- TNBC patients receive standard anthracycline- (doxorubicin or epirubicin) and taxane-based (docetaxel or paclitaxel) chemotherapy regimens as adjuvant or neoadjuvant treatment. Due to the involvement of BRCA genes in DNA repair, BRCA1-mutated breast cancer is more sensitive to platinums (cisplatin and carboplatin) compared to BRCA-proficient breast cancers. Neoadjuvant cisplatin treatment in BRCA1-mutated breast cancer demonstrated higher pathological complete response (PCR) compared to other chemotherapies. Higher PCR rates were also observed when carboplatin was added to anthracycline- and taxane-based neoadjuvant chemotherapy in TNBC [32, 39].

7 Evidence

systematic literature search in 5 databases: 160 hits

A literature search was conducted on 07 August 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “olaparib”, “lynparza”, “L01XX46”, “breast cancer”, “breast neoplasms”, “mamma carcinoma”, “metastatic” and “BRCA”. The manufacturer was also contacted and submitted six references (five of which had already been identified by systematic literature search, and a phase II study involving patients with various advanced cancers [42]). A manual search yielded three FDA reports [6, 7, 13], two EMA reports [14, 16], one clinical efficacy study [43], five clinical guidance documents [20, 25, 37, 39,

manual search: 14 additional references

41], three statistical documents [27, 29, 31], and a cost document [44]. Ongoing trials information was found on clinicaltrials.gov and EU Clinical Trials Register. Overall, 175 references were identified.

overall: 175 references included: 4 studies

Included in this reported are the following four studies to assess outcomes on clinical efficacy and safety:

- OlympiAD, phase III study [22, 45]
- ICEBERG 1, proof of concept, phase II study [46]
- Olaparib in patients with known BRCA mutation status and recurrent ovarian cancer or TNBC, phase II study [43]
- Olaparib monotherapy in advanced cancers with BRCA1 and BRCA2 mutations, phase II study [42]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [47]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "clinically meaningful benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [48]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [49]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Clinical efficacy and safety – Phase III studies

OlympiAD: olaparib versus chemotherapy in 302 patients with BRCA-mutated HER2-negative MBC

OlympiAD (NCT02000622) [12, 45] is an open-label, randomized, multicentre, phase III study involving 302 patients with a gBRCAm and HER2-negative MBC who had received no more than two previous chemotherapy regimens for metastatic disease. Efficacy data were analysed on an intention-to-treat (ITT) basis, and safety was assessed in all patients who received at least one dose of the assigned treatment.

ITT stratified by HR-status and previous chemotherapy

Study participants were adults with a deleterious gBRCAm and histologically or cytologically confirmed HER2-negative MBC; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; with adequate bone marrow, kidney and liver function; previously treated with no more than two chemotherapy regimens for metastatic disease. Prior platinum treatment was allowed provided at least 12 months had elapsed prior to study entry. HR-positive patients must have progressed on at least one endocrine therapy or have disease that is believed to be inappropriate for endocrine therapy. A deleterious or suspected deleterious gBRCAm was confirmed by central testing with BRACAnalysis (Myriad Genetics) in all but five cases. Patients who had previously received PARPi therapy, had untreated or uncontrolled brain metastases, HIV, or were pregnant or breast-feeding were excluded from study. Eligible patients were stratified according to previous use of chemotherapy for metastatic disease, HR-status (HR-positive versus TNBC), and previous use of platinum-based therapy.

olaparib 300 mg twice/day vs chemotherapy IV every 3 weeks; median follow-up 14 months

Patients were randomized 2:1 to receive olaparib tablets (300 mg twice daily) or 21-day cycles of physician's choice chemotherapy with capecitabine (2,500 mg/m^2 oral daily for 14 days), eribulin (1.4 mg/m^2 IV on days 1 and 8) or vinorelbine (30 mg/m^2 IV on days 1 and 8) until disease progression or unacceptable toxicity. The median total treatment duration was 8.2 months (range 0.5–28.7) in the olaparib group and 3.4 months (range 0.7–23.0) in the chemotherapy group. The median duration of follow-up was 14.5 months (range 2.1–29.5) for the olaparib group and 14.1 months (range 0.0–28.2) for the chemotherapy group.

primary endpoint: PFS secondary endpoints: OS, PFS2, ORR, HRQoL, and safety

The primary endpoint was progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to RECIST 1.1 or death due to any cause. At the time of data cut-off for the primary endpoint, 77.5% of patients had disease progression or had died. A pre-specified sensitivity analysis was based on investigator assessment. Secondary outcomes included overall survival (OS), time from randomization to second progression (PFS2), objective response rate (ORR), health related quality of life (HRQoL), and safety. HRQoL was assessed using the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30). Ranging from 0 to 100, higher QLQ-C30 scores indicate a better quality of life; where an increase or decrease of at least 10 points is considered a clinically meaningful change. Tumours were assessed at baseline, every 6 to 8 weeks for 6 months, then every 12 weeks up to 7 years.

ITT: median age 44 years, 50% had TNBC, 71% had prior chemotherapy, 28% had prior platinum therapy

The ITT population (n = 302; 205 olaparib vs 97 chemotherapy) had a median age of 44 years, 2.3% were male, 65.2% were Caucasian, 50% had TNBC, 77% had two or more metastatic sites, 71% had prior chemotherapy for MBC and 28% had prior platinum-based therapy in the neoadjuvant, adjuvant, or metastatic setting. Mean QLQ-C30 (±SD) scores at baseline were 63.2±21.0 in the olaparib group and 63.3±21.2 in the chemotherapy group. Of the 97 patients assigned to chemotherapy, six patients declined treatment due to treatment allocation. While these patients were included in the efficacy analysis, they were excluded from the safety analysis. Detailed patient characteristics, including inclusion and exclusion criteria are reported in Table 4 and study quality is described in Table 5 of the appendix, respectively. Clinical efficacy data are presented in Table 1 and adverse events (AEs) are listed in Table 2.

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of olaparib on mortality?

OS did not differ between groups

median time to death: 19.3 months for olaparib vs 19.6 months for chemotherapy

At the time of analysis, December 9, 2016, a total of 94 (45.9% of) olaparib recipients and 46 (47.4% of) chemotherapy recipients had died. The median time to death was 19.3 months in the olaparib group and 19.6 months in the chemotherapy group. OS did not show a statistically significant difference between groups (hazard ratio [HR] for death 0.90, 95% CI 0.63–1.29; p = 0.57). However, after the first progression event, more chemotherapy recipients than olaparib recipients received treatment with a PARPi, platinum-based therapy or other cytotoxic chemotherapy.

D0006: How does olaparib affect progression (or recurrence) of breast cancer?

median BICR-assessed PFS: 7.0 months for olaparib vs 4.2 months for chemotherapy

median investigator-assessed PFS2: 13.2 months for olaparib vs 9.3 months for chemotherapy

Olaparib patients had a median PFS of 7.0 months compared to 4.2 months for chemotherapy recipients. Compared to standard chemotherapy with capecitabine, eribulin or vinorelbine, olaparib statistically significantly improved PFS, as assessed by BICR (HR 0.58, 95% CI 0.43–0.80; p < 0.001). At 12 months, 25.9% of olaparib patients and 15.0% of chemotherapy patients were free from progression or death. At the time of analysis, when 77% of data were mature, 52% of all patients had a second progression event or had died after a first progression event. The median time to PFS2 or death after a first progression event was 13.2 months in the olaparib group and 9.3 months in the chemotherapy group. Compared to chemotherapy, olaparib improved investigator-assessed PFS2 (HR 0.57, 95% CI 0.40–0.83; p = 0.003).

D0005: How does olaparib affect symptoms and findings (severity, frequency) of breast cancer?

ORR: 59.9% for olaparib vs 28.8% for chemotherapy

median DOR: 6.4 months for olaparib vs 7.1 months for chemotherapy

Based on BICR, an objective response to treatment occurred in 100 of 167 patients with measurable disease in the olaparib group (ORR 59.9%, 95% CI 52.0–67.4) and 19 of 66 patients in the chemotherapy group (ORR 28.8%, 95% CI 18.3–41.3). A complete response was seen in 9.0% of patients with measurable disease in the olaparib group and 1.5% of chemotherapy recipients. The median DOR was 6.4 months (interquartile range [IQR] 2.8–9.7) in the olaparib group and 7.1 months (IQR 3.2–12.2) in the standard chemotherapy group; median time to onset was 47 days and 45 days, respectively.

D0011: What is the effect of olaparib on patients' body functions?

increased risk of haematological toxicity, monitor monthly

pneumonitis requiring discontinuation

The most common laboratory abnormalities associated with olaparib use were anaemia (40%), neutropenia (27%), decreased white-cell count (16%), increased alanine aminotransferase (11%) and increased aspartate aminotransferase levels (9%). MDS/AML causing death occurred in less than 1.5% of patients exposed to olaparib monotherapy. Monthly haematological monitoring is recommended [7]. Less than 1% of patients developed pneumonitis requiring discontinuation of treatment [7].

D0012: What is the effect of olaparib on generic health-related quality of life?

D0013: What is the effect of olaparib on disease-specific quality of life?

median time to a clinically meaningful improvement in QoL was not reached for olaparib and was 15.3 months for chemotherapy

Among the 264 patients who completed the HRQoL QLQ-C30 questionnaire, at baseline and at least once thereafter, the adjusted mean (±SE) change from baseline across all time points was 3.9±1.2 in the olaparib group and -3.6±2.2 in the chemotherapy group (estimated difference 7.5, 95% CI 2.5–12.4; p = 0.004). The median time to a clinically meaningful decrease in QLQ-C30 score (≥10 points) was not reached in the olaparib group and was 15.3 months in the chemotherapy group (HR 0.44, 95% CI 0.25–0.77; p = 0.004).

Table 1: Efficacy results of OlympiAD [22, 45]

Descriptive statistics and estimate variability	**Treatment group**	**Olaparib**	**Chemotherapy**
	Number of subjects	205	97
	PFS events, n (%) PFS events at 12 months, n (%) Median PFS, months	163/205 (79.5) 53/205 (25.9) 7.0	71/97 (73.2) 15/97(15.0) 4.2
	OS, n (%) Death, n (%) Median time to death, months	111/205 (54.1) 94/205 (45.9) 19.3	51/97 (52.6) 46/97 (47.4) 19.6
	PFS2 events, n (%)	157/302 (52)	
	Median PFS2, months	13.2	9.3
	ORR, n (%) CR, n (%) Median DOR, months (IQR) Median time to response, days	100/167 (59.9) 15/167(9) 6.4 (2.8–9.7) 47	19/66 (28.8) 1/66 (1.5) 7.1 (3.2–12.2) 45
	HRQoL, n QLQ-C30 change from BL, ±SD	191 3.9±1.2	73 -3.6±2.2
	Time to QLQ-C30 ≥10 points	NR	15.3
Effect estimate per comparison	***Comparison groups***		*Olaparib versus chemotherapy*
	PFS by BICR[1]	HR	0.58
		95% CI	0.43–0.80
		Log-rank test p-value	<0.001
	OS[1]	HR	0.90
		95% CI	0.63–1.29
		Log-rank test p-value	0.57
	PFS2[1]	HR	0.57
		95% CI	0.40–0.83
		Log-rank test p-value	0.003
	QoL (n = 264)	ED	7.5
		95% CI	2.5–12.4
		Log-rank test p-value	0.004
	Time to QLQ-C30 ≥10 points (n = 264)	HR	0.44
		95% CI	0.25–0.77
		Log-rank test p-value	0.004

Abbreviations: BL = baseline, BICR = blinded independent central review, CI = confidence interval, CR = complete response, DOR = duration of response, ED = estimated difference, HR = hazard ratio, HRQoL = health related quality of life, IQR = interquartile range, NR = not reached, ORR = objective response rate, PFS = progression-free survival, PFS2 = time from randomization to second progression or death, , SD = standard deviation, QLQ-C30 = 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, [1] = intention-to-treat population (n = 302)

7.1.2 Safety

C0008: How safe is olaparib in relation to the comparator(s)?

The most common AEs of any grade associated with olaparib use were anaemia (40%), nausea (58%), vomiting (30%), fatigue (29%), neutropenia (27%), and diarrhoea (21%). Neutropenia (50%), palmar-plantar erythrodysesthesia (21%), and increased liver function enzymes (17%) of any grade occurred more frequently in the chemotherapy group. AEs of any grade were

most common AEs: anaemia, nausea, vomiting, fatigue, neutropenia and diarrhoea

experienced by 97% of patients in both groups (199/205 olaparib and 88/91 chemotherapy patients). The rates of grades 3, 4, and 5 AEs were 37%, 3% and 0% for olaparib versus 51%, 12% and 1% for chemotherapy, respectively. Other grade 3 or higher AEs occurring in at least 2% of patients in either group were leukopenia (2% vs 3%), dyspnoea (1% vs 3%), and decreased platelet count (2% vs 1%) of olaparib versus chemotherapy patients, respectively. A case of sepsis in an olaparib recipient and dyspnoea with disease progression in a chemotherapy recipient occurred both resulted in death. One new primary cancer, melanoma in situ, developed in an olaparib recipient with known medical history of skin melanoma.

C0002: Are the harms related to dosage or frequency of applying olaparib?

27% and 5% olaparib vs 31% and 8% of chemotherapy patients, respectively, required dose reduction or discontinuation due to anaemia

The median relative dose intensity, defined as the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation was 99.5% (IQR 89.5–100.0; mean 92.3%) for olaparib patients and 92.4% (IQR 77.4–99.0; mean 89.3%) for chemotherapy patients. Approximately 50% (102/205) of olaparib patients had a dose interruption, 27% (55/205) had a reduction in dose and 5% (10/205) discontinued treatment due to AEs. In the chemotherapy group, 31% (28/91) had a dose reduction due to AE, 28% (25/91) experienced a delay in treatment, and 8% (7/91) discontinued treatment.

dose reductions in the olaparib group mostly due to anaemia

Dose reduction was primarily due to anaemia (14% of patients) in the olaparib group and to palmar-plantar erythrodysesthesia (8% of patients) in the chemotherapy group. Other AEs causing dose reductions in two or more olaparib recipients include neutropenia (5%), fatigue (2%), leukopenia (2%), increased alanine aminotransferase (2%), decreased platelet count (2%), thrombocytopenia (2%), increased aspartate aminotransferase (1%), nausea (1%), decreased neutrophil count (2%), and decreased white blood cell count (1%).

in both groups 2% of patients discontinued therapy due to anaemia

While 2% of patients in both groups discontinued treatment due to anaemia, olaparib recipients also discontinued due to decreased platelet count, increased intracranial pressure, abdominal pain, dyspnea, erythma nodosum, and thrombocytopenia (0.5% for all). Chemotherapy patients also discontinued due to neutropenia, leukopenia, decreased neutrophil count, radiation skin injury, plamer-plantar erythrodysesthesia, peripheral moter neuropathy and vomiting (1% for all).

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of olaparib?

dose reduction for patients with renal impairment

Patients with moderate renal impairment (CLcr 31–50 ml/min) are at increased exposure and should receive a reduced dose of 200 mg (2 x 100 mg tablets) twice daily, for a total daily dose of 400 mg. No statistically significant difference in safety was noted for patients above versus below 65 years of age. However, there is no evidence regarding the use of olaparib in patients over 85 years or those with moderate or severe hepatic impairment.

olaparib may cause genotoxicity and foetal harm

Females are advised to use effective contraception during olaparib treatment and for 6 months following completion of therapy based on the potential for foetal toxicity. Women are also advised not to breastfeed during treatment and for one month following their last dose [7].

Table 2: Most frequent adverse events of OlympiAD [22, 45]

Adverse Event (according to CTCAE version 4.0)	**Olaparib** (n = 205)		**Chemotherapy** (n = 91)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Any AE	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anaemia	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0 (0)	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0 (0)	14 (15.4)	1 (1.1)
Diarrhoea	42 (20.5)	1 (0.5)	20 (22.0)	0 (0)
Decreased appetite	33 (16.1)	0 (0)	11 (12.1)	0 (0)
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0 (0)	16 (17.6)	0 (0)
Cough	35 (17.1)	0 (0)	6 (6.6)	0 (0)
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0 (0)
Palmar-plantar erythrodysesthesia	1 (0.5)	0 (0)	19 (20.9)	2 (2.2)
Dose reduction due to AE	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay due to AE	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation due to AE	10 (4.9)	NA	7 (7.7)	NA

Abbreviations: AE = adverse event, CTCAE = Common Terminology for Cancer Adverse Events, NA = not applicable

7.2 Clinical effectiveness and safety – further studies

ICEBERG 1: 54 BRCA-mutated advanced breast cancer patients receive maximum vs lower dose olaparib

ICEBERG 1 (NCT00494234) is a multicentre, open-label, sequential cohort, proof of concept phase II trial investigating the efficacy, safety and tolerability of olaparib monotherapy assigned to 54 women with BRCA-mutated advanced breast cancer previously treated with chemotherapy. The first cohort (n = 27) received continuous oral olaparib at the maximum tolerated dose (400 mg twice daily) and the second cohort (n = 27) received a lower dose (100 mg twice daily) for 168 days. The median number of prior chemotherapy regimens was three (range 1–5 for cohort 1, 2–4 for cohort 2) [46].

ORR: 41% for maximum vs 22% for lower dose

common treatment-related AEs: fatigue, nausea, vomiting, and anaemia at maximal dosage

Patients receiving the maximum dose (400 mg twice daily) had an ORR of 41% (11/27, 95% CI 25–59) and patients receiving 100 mg twice daily had an ORR of 22% (6/27, 95% CI 11–41). The median duration of objective response was 144 days (range 92–393) in cohort 1 and 141 days (55–175) in cohort 2. The median PFS was 5.7 months (95% CI 4.6–7.4) for cohort 1 and 3.8 months (95% CI 1.9–5.5) for cohort 2. PFS events were reported in 96% (26/27) of patients in cohort 1 and 78% (21/27) patients in cohort 2. The most common treatment-related AEs in the maximum dose cohort were fatigue (grade 1 or 2, 11 [41%]; grade 3 or 4, 4 [15%]), nausea (grade 1 or 2, 11 [41%]; grade 3 or 4, 4 [15%]), vomiting (grade 1 or 2, 3 [11%]; grade 3 or 4, 3 [11%]), and anaemia (grade 1 or 2, 1 [4%]; grade 3 or 4, 3 [11%]). The most frequent causally related AEs in the lower dose cohort were nausea (grade 1 or 2, 11 [41%]; none grade 3 or 4) and fatigue (grade 1 or 2, 7 [26%]; grade 3 or 4, 1 [4%]) [46].

phase II: olaparib for ovarian, breast and TNBCs (n = 26) with known BRCA status

Olaparib was investigated in 91 patients with advanced ovarian (n = 65), breast or TNBC (n = 26) with known BRCA mutation status (NCT00679783) in a multicentre, open-label, non-randomized, correlative phase II study [43]. The study was designed to evaluate the ORR, assess early markers of activity and to identify markers that correlate with a response. Patients received olaparib (400 mg twice daily) until disease progression and were stratified according to BRCA mutation status. In the breast cancer cohorts, one (7%) of 15 women with TNBC had a BRCA mutation. Of the 11 patients initially recruited into the mutation-positive cohort, four (36%) had TNBC, five (45%) had non-TNBC and two (19%) were reclassified as BRCA-negative after central screening favoured genetic variants rather than mutations. Median exposure to treatment in the breast cancer cohort was 56 days (range 20–288 days).

ORR: no confirmed objective response in breast cancer cohorts

common AEs: fatigue, nausea, vomiting, decreased appetite

None of the breast cancer patients had an objective response. At 8 weeks, the disease control rate was 38% (95% CI 22–57; 10/26); 70% (40–89; 7/10) in the BRCA1 or BRCA2 positive cohort and 19% (7–43; 3/16) in mutation-negative cohorts. While target lesions in five (50%) patients with BRCA1 or BRCA2 mutations were reduced in size by more than 30%, they were not confirmed objective responders as assessed by RECIST). PFS in patients with BRCA mutations was 109 days (range 95% CI 53–168 days), BRCA-negative was 54 days (range 49–54 days), and in all those with breast cancer 54 days (range 51-106 days). The most common treatment-related AEs in breast cancer patients were fatigue (50%), nausea (62%), vomiting (35%), and decreased appetite (27%) [43].

phase II: olaparib monotherapy for advanced cancers with gBRCAm (n = 63 breast cancer)

The efficacy and safety of olaparib monotherapy in advanced cancers with gBRCAm was investigated in 298 patients in a multicentre, non-randomised, phase II study (NCT01078662). Patients with platinum-resistant ovarian cancer (n = 193), breast cancer previously treated with more than three lines of chemotherapy for metastatic disease (n = 62), pancreatic cancer with prior gemcitabine treatment (n = 23), prostate cancer with progression following hormonal and systemic therapy (n = 8), or other solid tumours (n = 12) were treated with olaparib (400 mg twice daily). Of the 63 patients with breast cancer, the mean number of prior chemotherapy courses for metastatic disease was 4.6 (SD 2; range 3–11), 68% had received prior platinum, more than 75% had received prior cyclophosphamide, doxorubicin or paclitaxel, and more than 45% had received fluorouracil, capecitabine, docetaxel or gemcitabine.

The tumour response rate was 26.2% (78/298, 95% CI 21.3–31.6) overall and 12.9% (8/62, 95% CI 5.7–23.9) for breast cancer, respectively. Stable disease ≥ 8 weeks was observed in 42% of patients (95% CI 36.0–47.4), including 47% (95% CI 34.0–59.9) of those with breast cancer, respectively. Overall median DOR was 204 days for breast cancer and time to onset of response was 54.5 days. Of the 32 patients with ER-positive breast cancer, 4 (12.5%, 95% CI 3.5–29.0) had a tumour response to olaparib, compared with four of 30 (13.3%, 95% CI 3.8–30.7) of those with ER-negative breast cancer. OS was 11 months; 44.7% of breast cancer patients were alive at 12 months. Overall, the most common AEs were fatigue (48%), nausea (53%), and vomiting (34%). Serious AEs (grade ≥3) were reported in 25.8% of breast cancer patients, primarily due to anaemia (15%) [42].

RR: 12.9% for breast cancer

median DOR: 204 days

OS: 11 months; 12-month survival: 45%

AEs: fatigue, nausea, vomiting, anaemia

8 Estimated costs

A0021: What is the reimbursement status of olaparib?

In Austria, olaparib is available as 50 mg hard capsules in packages of 448 pieces. One package of 448 50 mg capsules is available for € 5,059.29 (ex-factory price). At the recommended dose of 300 mg tablets twice daily (equivalent dose of 400 mg capsules twice daily), the cost for olaparib treatment would be € 3,794.47 per 21-day cycle [7, 10, 11, 44]. A median duration of 14.5 months (range, 2.1–29.5 months) of olaparib treatment would cost approximately € 75,889.40. Patients may be selected for therapy based on an FDA-approved companion diagnostic BRACAnalysis CDx™ for olaparib. Myriad Genetics have made an agreement with AstraZeneca to provide companion diagnostic BRCA testing for the olaparib phase III trial programme [8].

€ 3,797.47 per 21-day cycle

€ 75,889.40 per 14.5 months of olaparib treatment

9 Ongoing research

Several studies are ongoing to investigate olaparib as monotherapy for advanced or metastatic HER2-negative gBRCAm-positive breast cancer or TNBC following pre-treatment with chemotherapy, and in combination with immune checkpoint inhibitors or anticancer agents. In September 2017, a search of clinicaltrials.gov using search terms “olaparib” and “breast cancer” yielded 26 registered studies (three phase III, one phase 2/3, seven phase II, four phase I/II, eleven phase I). A search of the EU Clinical Trials Register yielded 13 studies (eleven were already identified in clinicltrials.gov; three phase III, one phase II/III, four phase II, and five phase I/II). Most studies are industry-sponsored or conducted in collaboration with industry.

26 registered trials; 3 industry-sponsored phase III studies

Selected ongoing phase III, II and I/II studies investigating olaparib for BRCA-mutated breast cancer patients:

- NCT02681562: A phase II, randomized, controlled, open-label, study in patients with locally advanced HR-negative and HER2-negative TNBC and locally advanced gBRCAm-positive breast cancer to correlate baseline gene expression and clinical response. Estimated primary completion date is January 2018.
- NCT02789332: A phase II, prospective, randomized, open-label study evaluating the efficacy and safety of paclitaxel and olaparib compared to paclitaxel with carboplatin followed by epirubicin and cyclophosphamide as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and a deleterious gBRCAm. Estimated primary completion date is November 2018.
- NCT02484404: A phase I/II, dose-escalation study investigating the anti-programmed death ligand-1 antibody (PD-L1) MEDI4736 in combination with olaparib and/or cediranib for advanced solid tumours and/or recurrent ovarian, TNB, lung and colorectal cancers. Estimated primary completion date is December 2018.
- NCT03167619: A phase II, randomized trial to assess the efficacy of olaparib in combination with durvalumab in platinum-treated metastatic TNBC. Estimated primary completion date is October 2019.
- NCT02032823: A phase III, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with gBRCA1/2 mutations and high risk HER2-negative primary breast cancer who have completed local treatment and neoadjuvant or adjuvant chemotherapy. Estimated primary completion date is March 2020.
- NCT03150576: A phase III, randomized, open-label neoadjuvant study to evaluate the safety and efficacy of concurrent platinum-based chemotherapy with olaparib for TNBC in patients with a gBRCAm. Estimated primary completion date is January 2022.

10 Discussion

EMA authorised /FDA-approved for BRCA-mutated ovarian cancer

On December 18, 2014, olaparib received market authorisation in Europe and the US for the maintenance treatment of adults with platinum-sensitive, relapsed, BRCA-mutated advanced ovarian, fallopian tube or primary peritoneal cancer [14]. While initial approval was based on the results of the phase II trial, Study 19 [15], a risk management plan was implemented to monitor safety [16]. In December 2014, The FDA also approved olaparib as monotherapy for patients with deleterious gBRCAm advanced ovarian cancer, as detected by BRACAnalysis CDx™, previously treated with three or more lines of chemotherapy [6, 27]. Based on the results of the OlympiAD trial, the manufacturer plans to file a supplementary marketing application to expand the licensing indication to include BRCA-mutated MBC before the end of the year [12].

AstraZeneca filing expansion for BRCA-mutated MBC

OlympiAD: no statistically significant difference in OS, increased PFS (+2.8 months), reduced risk of progression

OlympiAD, a randomized, open-label, phase III study compared the safety and efficacy of olaparib (300 mg twice daily) versus chemotherapy (capecitabine, eribulin, or vinorelbine in 21-day cycles) in 302 patients with a gBRCAm and HER2-negative MBC who were previously treated with fewer than three chemotherapy regimens [12]. At a median follow-up of 14 months, OS did not show a statistically significant difference between groups. Compared with chemotherapy, olaparib increased BICR-assessed median PFS by 2.8 months, reduced the risk of disease progression and death by 42%, and reduced the risk of investigator-assessed second progression by 43% in the ITT population. BICR-assessed ORR was 59.9% for olaparib versus 28.8% for chemotherapy, where olaparib conferred a shorter DOR (6.4 vs 7.1 months) and longer time of onset (47 vs 45 days) than chemotherapy. The median time to achieve an improvement in disease-specific quality of life, based on a clinically meaningful decrease in QLQ-C30 of ≥10 points, was not reached in the olaparib group and was 15.3 months in the chemotherapy group [12, 45].

AEs requiring dose interruption were more common in the olaparib group

The most common AEs were anaemia, nausea, vomiting, fatigue, neutropenia and diarrhoea. Approximately 50% of olaparib patients had a dose interruption, 27% had a dose reduction and 5% discontinued treatment due to AEs compared to 31%, 28%, and 8% for chemotherapy patients, respectively. Regardless, fewer AEs of grade 3 or higher were reported in the olaparib group compared to chemotherapy. Anaemia was the primary cause of dose reduction (14%) and treatment discontinuation (2%) in the olaparib group. Other AEs resulting in dose adjustment or discontinuation include neutropenia, fatigue, leukopenia, increased liver enzymes, decreased platelet count, decreased neutrophils and white blood cell count.

inconsistency in OR compared to one former phase II study

The clinical efficacy and safety results of OlympiAD are consistent with phase II data from ICEBERG 1 and a study (NCT01078662) that investigated olaparib monotherapy for advanced cancers with gBRCAm [42, 46] where olaparib monotherapy resulted in an objective response and prolonged median PFS for women with BRCA-mutated advanced breast cancer previously treated with chemotherapy. However, the efficacy results of OlympiAD differ from those of a phase II study that investigated olaparib monotherapy in 26 breast or TNBC patients of known BRCA mutation status where none of the breast cancer patients had an objective response to treatment [43]. While target lesions in 50% of patients with BRCA mutations were reduced in size by ≥30%, they were not confirmed objective responders as assessed by RECIST. Differences in objective response may be due to chance based on the small sample size of Gelmon et al. the heavily pre-treated characteristics of these patients, and the fact that TNBC comprises a heterogeneous group where representation of a PARPi-sensitive BRCAness subgroup may be low in a small unselected population [43]. While the median time to a clinically meaningful decrease in QLQ-30 was not reached in the OlympiAD trial, olaparib prolonged quality–adjusted PFS and the duration without symptoms of disease or treatment toxicity for ovarian cancer patients compared to placebo [31]. Anaemia, fatigue, nausea, and vomiting were also the most commonly reported AEs in phase II trials [42, 43, 46].

common AEs: anaemia, fatigue, nausea, and vomiting

high risk of bias: unclear allocation concealment, open-label study

Several methodological limitations of the OlympiAD compromise internal and external validity. While patients were randomized 2:1 olaparib versus chemotherapy via a centralized interactive voice/web response system that generated a random allocation sequence, allocation concealment was not maintained and may influence how participants were assigned to a given group. Internal validity may be compromised in an open-label study where

patients and treating physicians are aware of treatment allocation, and the physician chooses the chemotherapeutic comparator.

ESMO-MCBS original: 3 adapted: 3

Given the non-curative setting of olaparib and the statistically significant primary endpoint PFS we applied form 2b of the ESMO-MCBS in order to assess whether olaparib satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). Both the original as well as the adapted version of the MCBS were applied [48, 49]. The application of the ESMO-MCBS to the OlympiAD study resulted in a grade 3 in the original as well as in the adapted version of the ESMO-MCBS, respectively. Therefore, olaparib does not lead to a meaningful clinical benefit in both scales.

limitations: insufficient power to assess OS, confounded by treatments following first progression

Results of the OlympiAD trial hold several limitations. While OS did not show a statically significant difference between groups, the study was not powered to assess differences in OS and OS could be confounded as more patients in the chemotherapy group than in the olaparib group received treatment with PARPi, platinum-based therapy, or other cytotoxic chemotherapy following a first progression event [12]. While anthracycline- and taxane-based chemotherapy regimens are considered standard treatment, because there is no definitive chemotherapeutic regimen for BRCA-mutated MBC, the addition of a platinum may also have served as an appropriate comparator [39]. Higher PCR rates have been observed when carboplatin was added to anthracycline- and taxane-based neoadjuvant chemotherapy in TNBC, and BRCA1-mutated breast cancers are more sensitive to cisplatin than BCRA-proficient breast cancers [32]. Approximately 50% of olaparib patients had a dose interruption due to AEs, primarily due to anaemia. For patients with moderate renal impairment, preference for treatment may lie with therapeutic options that pose less risk for haematological toxicities, MDS and AML.

phase III trials of niraparib or talazoparib versus physician's choice chemotherapy for patients with gBRCAm MBC; most exclude patients previously treated with platinum

veliparib combinations better tolerated than olaparib with topotecan

Other PARPis have shown some synthetic lethal activity in BRCA-mutant patients, including talazoparib (Biomarin), niraparib (Merck/Tesaro), rucaparib, (Clovis) and veliparib (Abbvie). Most trials exclude patients who were previously treated with platinums and investigate PARPi monotherapy compared to standard chemotherapy or PARPi in combination with chemotherapy in advanced disease and neoadjuvant therapy settings. Similar to OlympiAD, two phase III trials BRAVO (niraparib, NCT01905592) and EMBRACA (talazoparib, NCT02000622) are evaluating PARPi monotherapy versus physician's choice chemotherapy in patients with gBRCAm MBC. Another phase III study (NCT02163694) will investigate veliparib versus placebo in combination with carboplatin and paclitaxel in HER2-negative BRCA-mutated MBC. A phase II study is assessing rucaparib as adjuvant treatment for TNBC or HER2-negative BRCA-mutated breast cancers following preoperative chemotherapy (NCT01074970). The addition of veliparib and carboplatin to standard neoadjuvant therapy for TNBC resulted in an estimated 52% PCR rate compared to 26% for standard therapy. While combination topotecan and olaparib resulted in dose-limiting haematological AEs at sub-therapeutic doses, veliparib combinations have been better tolerated. The length of follow-up for most studies is insufficient to predict the risk of developing new primary malignancies, a major concern regarding drugs that inhibit DNA damage repair mechanisms [2, 4, 50].

€ 3,794.47 per 21-day cycle; € 75,889.40 per 14.5 months of treatment

The cost of one package of 448 50 mg olaparib capsules is € 5,059.29 (ex-factory price). At the recommended dose of 300 mg tablets twice daily (400 mg capsules twice daily), the cost of olaparib treatment would be € 3,794.47 per 21-day cycle [44]. A median duration of 14.5 months (range, 2.1–29.5

months) of olaparib treatment would cost approximately € 75,889.40. Patients may be selected for therapy based on an FDA-approved companion diagnostic BRACAnalysis CDx™ for olaparib. Myriad Genetics have made an agreement with AstraZeneca to provide companion diagnostic BRCA testing for the olaparib phase III trial programme [8].

olaparib improves PFS and reduces risk of progression

Overall, the OlympiAD phase III randomized, open-label study reports that olaparib improves PFS and reduces the risk of progression in patients with HER2-negative BRCA-mutated MBC relative to physician's choice chemotherapy following prior chemotherapy for metastatic disease. Not all patients with BRCA-associated breast cancer or TNBC respond to PARPi; however, some sporadic TNBC display a BRCAness phenotype without carrying a gBRCAm. Patients are selected for treatment based on a confirmed deleterious BRCA mutation and homologous recombination deficiency scores may identify those with HR deficiency; however, there is currently no established biomarker for response to PARPi. The length of follow-up may be insufficient to capture the risk of recurrence or the development of a second primary cancer.

not all patients respond and some without gBRCAm respond; no established biomarker for response or resistance screening

mechanisms of resistance

The clinical utility of PARPi may be limited. Three mechanisms of resistance to PARPi have already been established where the development of a secondary mutation restores BRCA functionality, drug efflux is increased by overexpression of P-glycoprotein, and a loss of p53 binding protein 1 reduces sensitivity to PARPi. Increasing the use of platinum in early TNBC may also influence PARPi use given the overlapping mechanisms of action and resistance [4]. Veliparib exhibits a cytotoxic effect by suppressing PARPs' catalytic activity while olaparib, talazoparib, rucaparib, and niraparib are effective in trapping PARPs to DNA. PARP trapping is synergistic in combination with alkylating agents and PARP catalytic inhibition synergizes with topoisomerase inhibitors. Despite synergism between PARP inhibition and cytotoxic agents under investigation, the optimal PARPi-chemotherapy combination for evaluation in TNBC remains to be established.

optimal PARPi-chemotherapy combination remains to be established

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [48, 49]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	Olaparib	breast cancer	NC	PFS	2b	≤6 months	+2.8	0.58 0.43–0.80	HR ≤0.65 AND Gain ≥1.5 months	3	-13.9% grade 3–4 AEs, dose reductions +19%	ND	x	**3**
Original ESMO-MCBS	Olaparib	breast cancer	NC	PFS	2b	≤6 months	+2.8	0.58 0.43–0.80	HR ≤0.65 AND Gain ≥1.5 months	3	x	ND	x	**3**

Abbreviations: AJ = Adjustments, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

11 References

[1] European Network for Health Technology Assessment (eunethta). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals Version 3.0. 2013 [Cited 2017-08-16];Available from: http://meka.thl.fi/htacore/model/HTA%20core%20model%20for%20rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] Lord CJ, Tutt AN, Ashworth A. Synthetic lethality and cancer therapy: lessons learned from the development of PARP inhibitors. Annu Rev Med. 2015;66:455-70.

[3] Liang H, Tan AR. PARP inhibitors. Current Reports. 2011;3(1):44-54.

[4] Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: Current data and future prospects. BMC Medicine. 2015;13(1).

[5] Plummer R, Swaisland H, Leunen K, Herpen CM, Jerusalem G, Grève J, et al. Olaparib tablet formulation: effect of food on the pharmacokinetics after oral dosing in patients with advanced solid tumours. Cancer chemotherapy and pharmacology [Internet]. 2015; (4):[723-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/393/CN-01096393/frame.html.

[6] U.S. Food and Drug Administration Drugs@FDA. Lynparza™Label Information. 2017 [Cited 2017-08-10];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206162lbl.pdf.

[7] U.S. Food and Drug Administration Drugs@FDA. Lynparza™(olaparib tablet) Label Information. 2017 [Cited 2017-08-23];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208558s000lbl.pdf.

[8] Deeks ED. Olaparib: first global approval. Drugs. 2015;75(2):231-40.

[9] Molife R, Kaye S, Forster M, Ransom M, Greystoke A, Middleton MR, et al. A phase I study to determine the comparative bioavailability of two different oral formulations of the PARP inhibitor, olaparib (AZD2281), in patients with advanced solid tumours. J Clin Oncol. 2010;28(7S);abst 2599.

[10] Mateo J, Friedlander M, Sessa C, Leunen K, Nicum S, Gourley C, et al. Administration of continuous/intermittent olaparib in ovarian cancer patients with a germline BRCA1/2 mutation to determine an optimal dosing schedule for the tablet formulation. Eur J Cancer. 2013;49(Suppl):abst 801.

[11] Molife LR, Mateo J, McGoldrick T, Krebs MG, Drew Y, Banerjee S, et al. Safety and efficacy results from two randomized expansions of a phase I study of a tablet formulation of the PARP inhibitor, olaparib, in ovarian and breast cancer patients with BRCA1/2 mutations. J Clin Oncol. 2012;30(15S):abst 3048.

[12] Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017.

[13] U.S. Food and Drug Administration Medical Devices (PMA) BRACAnalysis CDx™ Premarket Approval Information. 2017 [Cited 2017-08-22];Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=p140020.

[14] European Medicine Agency. Lynparza™: EPAR-Product Information. Cited [2017-08-24];Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Summary_for_the_public/human/003726/WC500180153.pdf.

[15] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366 (15):1382-92.

[16] European Medicine Agency. Summary of the risk management plan (RMP) for Lynmparza™ (olaparib). Cited [2017-08-24];Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Risk-management-plan_summary/human/003726/WC500176260.pdf.

[17] Cancer Discovery. Olaparib Keeps Hereditary Breast Tumors in Check. Cancer Discov. 2017;7(8):OF10.

[18] Liedtke C, Kiesel L. Breast cancer molecular subtypes - Modern therapeutic concepts for targeted therapy of a heterogeneous entity. Maturitas. 2012;73(4):288-94.

[19] Di Cosimo S, Baselga J. Management of breast cancer with targeted agents: Importance of heterogenicity. Nature Reviews Clinical Oncology. 2010;7(3):139-47.

[20] BREASTCANCER.ORG. Study estimates breast cancer risk by age for women with BRCA mutations. . 2017 [2017-08-29];Available from: http://www.breastcancer.org/research-news/risk-estimates-by-age-for-brca-mutations.

[21] Narod SA. BRCA mutations in the management of breast cancer: the state of the art. Nature reviews Clinical oncology. 2010;7(12):702-7.

[22] Robson ME, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients (pts) with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm). Journal of clinical oncology. 2017;35(15).

[23] Anders CK, Winer EP, Ford JM, Dent R, Silver DP, Sledge GW, et al. Poly(ADP-ribose) polymerase inhibition: "Targeted" therapy for triple-negative breast cancer. Clinical Research. 2010;16(19):4702-10.

[24] Robert M, Frenel JS, Gourmelon C, Patsouris A, Augereau P, Campone M. Olaparib for the treatment of breast cancer. Expert Opin Investig Drugs. 2017;26(6):751-9.

[25] Esserman LJ, Joe BN. Clinical features, diagnosis, and staging of newly diagnosed breast cancer. In: Burstein H, Vora SR, editors. UpToDate. Waltham, MA. (cited 29.08.2017): UpToDate; 2017

[26] Hayes DF. Tumor node metastasis (TNM) staging classification for breast cancer. In: Chagpar AB, editor. UpToDate. Waltham, MA. (cited 14.08.2017): UpToDate; 2014.

[27] National Cancer Institute -Surveillance, Epideemiology, and End Results. Cancer Stat Facts: Female Breast Cancer. 2017 [Cited 2017-08-29];Available from: https://seer.cancer.gov/statfacts/html/breast.html.

[28] Brufsky AM. Delaying chemotherapy in the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Clinical Medicine Insights: Oncology. 2015(9):137-47.

[29] Institute for Health Metrics and Evaluation. Global Burden of Disease, Injuries, and Risk Factors Study 2010. [Cited 2017-08-29];Available from: http://www.healthdata.org/austria.

[30] Nihr H. Olaparib (Lynparza) for metastatic breast cancer with germline BRCA mutation – second line. Birmingham: NIHR Horizon Scanning Research&Intelligence Centre; 2016.

[31] Friedlander M, Gebski V, Gibbs E, Bloomfield R, Hillpert F, Wenzel L, et al. Health-related quality of life (HRQOL) and patient-centered outcomes with maintenance olaparib compared with placebo following chemotherapy in patients with germline (g) BRCA-mutated platinum-sensitive relapsed serous ovarian cancer (PSR SOC): SOLO2 phase III trial. . J Clin Oncol 2017;35(Suppl; abstr 5507).

[32] Bayraktar S, Glück S. Management of women with BRCA1/2 mutation-associated breast cancer. Management. 2012;1(2):157-64.

[33] Vidula N, Rugo HS. Cyclin-dependent kinase 4/6 inhibitors for the treatment of breast cancer: A review of preclinical and clinical data. Clin Breast Cancer. 2016;16(1):8-17.

[34] American Cancer Society. Signs and symptoms of breast cancer. 2016 [cited 2017-08-14]; Available from: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-signs-symptoms.

[35] Laura J Esserman M, MBABonnie N Joe, MD, PhD. Clinical features, diagnosis, and staging of newly diagnosed breast cancer. In: Harold Burstein M, PhD, editor. UpToDate. Waltham, MA. (cited 14.08.2017): UpToDate; 2016.

[36] National Cancer Institute. Breast Cancer. [cited 2017-08-14]; Available from: https://www.cancer.gov/types/breast.

[37] National Comprehensive Care Network (NCCN). Stage IV Breast Cancer. 2015 [Cited 2017-08-29];Available from: https://www.nccn.org/patients/pdf/guidelines/quick_guide/nccn_quick_guide-breast_stage_iv.pdf.

[38] Wörmann B, Aebi S, Decker T, Fehm T, Greil R, Harbeck N, et al. Leitlinien - Mammakarzinom der Frau. onkopedia leitlinien; 2016 [cited 2017-08-14]; Available from: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-der-frau/@@view/html/index.html#IDoEAPAC.

[39] Anders CK, Carey LA. Epidemiology, risk factors and clinical approach to ER/PR negative, HER2-negative (Triple-negative) breast cancer. In: Hayes DF, Vora SR, editors. UpToDate. Waltham, MA. (cited 29.08.2017): UpToDate; 2017.

[40] Kandula M, Kalyan Kumar C, Ammi Raju YS. Molecular mechanism and targeted therapy options of triple-negative (ER, PgR, HER-2/neu) breast cancer: Review. World Journal of Oncology. 2013;4(3):137-41.

[41] National Cancer Institute - Genetics of Breast and Gynecologic Cancers (PDQ®). 2017 [Cited 2017-09-01];Available from: https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq.

[42] Kaufman B, Shapira-Frommer R, Audeh MW, Friedlander M, Balmana J, Mitchell G, et al. Olaparib Monotherapy in Patients with Advanced Cancer and Germline BRCA1/2 Mutation. J Clin Oncol. 2014;32.

[43] Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol. 2011;12:852-61.

[44] Apothekerverlag. Warenverzeichnis Apothekerverlag Online. [2017-09-06]; Available from: http://warenverzeichnis.apoverlag.at/.

[45] Robson ME, Im SA, Senkus E, Xu B, Domchek S, Masuda N, et al. Supplementary Appendix to: Robson M, et al. Olaparib for Metastatic Germline BRCA-mutated Breast Cancer (OlympiAD). N Engl J Med. 2017;377:523-33.

[46] Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet (London, England). 2010;376(9737):235-44.

[47] EUnetHTA -European Network for Health Technology Assessment. Internal validity of randomized controlled trials. 2013 [Cited 2017-09-02];Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[48] Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of Oncology: official journal of the European Society for Medical Oncology. 2015;26(8):1547-73.

[49] Wild C, Grössmann N, Bonanno PV, Bucsics A, Furst J, Garuoliene K. Utilisation of the ESMO-MCBS in practice of HTA. Annals of Oncology: official journal of the European Society for Medical Oncology. 2016;27(11):2134-6.

[50] Kast K, Rhiem K. Familial breast cancer - targeted therapy in secondary and tertiary prevention. Breast care (Basel, Switzerland). 2015;10(1):27-31.

12 Appendix

Table 4: Characteristics of the OlmpiAD trial [12, 45]

Title: Assessment of the efficacy and safety of olaparib monotherapy versus physicians choice chemotherapy in the treatment of MBC patients with germline BRCA1/2 mutations (OlympiAD) [22]			
Study identifier	NCT02000622, D0819C00003, EudraCT2013-005137-20, OlympiAD		
Design	Randomized, controlled, open-label, multicentre, international (19 countries), phase III study		
	Duration of main phase:		April 7, 2014-November 27, 2015: randomized 302 patients December 9, 2016: final primary outcome data collected, 77.5% of patients had BICR-assessed disease progression
	Duration of run-in phase:		not applicable
	Duration of extension phase:		not applicable
	Median duration of follow-up:		Olaparib group: 14.5 months (2.1-29.5); Chemotherapy group: 14.1 months (0-28.2)
Hypothesis	Interventional/Treatment To evaluate the safety and efficacy of olaparib monotherapy versus physician's choice chemotherapy (capecitabine, vinorelbine or eribulin) by BICR-assessed PFS using RECIST 1.1		
Funding	AstraZeneca		
Treatments groups	Olaparib (n = 205 full analysis; n = 205 safety analysis)		300 mg tablets twice daily until disease progression or unacceptable toxicity
	Chemotherapy (physician's choice): (n = 97 full analysis; 91 safety analysis) Capecitabine (n = 41) Eribulin (n = 34) Vinorelbine (n = 16)		Until disease progression or unacceptable toxicity 2500 mg/m² oral daily for 14 days, every 21 days 1.4 mg/m² intravenously on days 1 and 8, every 21 days 30 mg/m² intravenously on days 1 and 8, every 21 days
	Notes		After disease progression, treatment was at the discretion of the investigator Crossover to olaparib was not permitted
Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	Time from randomization to BICR-assessed disease progression (RECIST 1.1) or death by any cause; when approximately 75% of patients have experienced progression. Assessed at baseline, every 6 weeks for 6 months then every 12 weeks until progression for up to 7 years.
	Overall survival (secondary endpoint)	OS	Assessed at time of PFS analysis and when approximately 60% of patients have died by any cause (average 15 months after randomization); every 8 weeks following objective disease progression for up to 7 years.
	Second progression (secondary endpoint)	PFS2	Time from randomization to second progression, defined as objective radiological or symptomatic progression, or death. Assessed at time of PFS analysis and at final OS analysis; every 8 weeks for up to 7 years following first objective disease progression.
	Objective response rate (secondary endpoint)	ORR	ORR by BICR using RECIST 1.1 assessed at time of PFS analysis. Assessed at baseline, every 6 weeks for the first 6 months, then every 12 weeks until objective disease progression up to 7 years.
	Health-related QoL (secondary endpoint)	HRQoL	Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire completed at baseline and every 6 weeks until disease progression up to 7 years.
	Safety and tolerability (secondary endpoint)	AE	Assessment of AEs graded by CTCAE (v4.0)
Database lock	Last updated: May 25, 2017		
Results and Analysis			

Title: Assessment of the efficacy and safety of olaparib monotherapy versus physicians choice chemotherapy in the treatment of MBC patients with germline BRCA1/2 mutations (OlympiAD) [22]

Study identifier	NCT02000622, D0819C00003, EudraCT2013-005137-20, OlympiAD			
Analysis description	**Primary Analysis** A total of 230 PFS events were needed to provide 90% power to show a statistically significant difference in PFS between groups. Efficacy data were analysed on an intent-to-treat basis, and safety was assessed in all patients who received at least one dose of assigned treatment. Primary analysis of PFS was based on BICR and performed using a stratified log-rank test. Kaplan-Meier was used to generate time-to-event curves from which medians were calculated. For the primary endpoint, a log-rank test (stratified by hormone receptor status and previous chemotherapy use) was used to compare the Kaplan-Meier curved in two treatment groups. Hazard ratios and confidence intervals were estimated from the log-rank statistics. Exploratory sensitivity analyses were conducted to exclude patients who did not receive the assigned treatment. OS was compared between groups using a stratified log-rank test. The mean change from baseline in QLQ-C30 score across all time points was analysed using a mixed model for repeated measures. Kaplan-Meier curves were used to compare time to a clinically meaningful decrease in QLQ-C30 score between the two groups.			
Analysis population	Inclusion	✲ Adults (aged ≥18 years) with HER2-negative MBC that was hormone-receptor positive or triple negative ✲ Deleterious or suspected deleterious germline BRCA mutation; confirmed by centralized BRACAnalysis (Myriad Genetics in all but 5 patients) ✲ Histologically or cytologically confirmed breast cancer with evidence of metastatic disease ✲ Prior therapy with an anthracycline and a taxane in either an adjuvant or metastatic setting ✲ Prior platinum allowed as long as no breast cancer progression occurred on treatment or if given in adjuvant/neoadjuvant setting at least 12 months from last dose to study entry elapsed ✲ ER/PR breast cancer positive patients must have received and progressed on at least one endocrine therapy (adjuvant or metastatic) or have disease is believed to be inappropriate for endocrine therapy ✲ ECOG performance status 0-1 ✲ Adequate bone marrow, kidney and liver function		
	Exclusion	✲ Prior PARPi treatment ✲ Patients with HER2-positive disease ✲ More than 2 prior lines of chemotherapy for MBC ✲ Untreated and/or uncontrolled brain metastases ✲ Prior malignancy unless curatively treated and disease-free for > 5 years prior to entry. Prior adequately treated non-melanoma skin cancer, in situ cancer of the cervix, DCIS or stage I grade 1 endometrial cancer were allowed. ✲ Known HIV infection ✲ Pregnant or breast-feeding women		
	Characteristics		Olaparib (n = 205)	Chemotherapy (n = 97)
	Median age, years (range)		44 (22–76)	45 (24–68)
	Male sex, n (%)		5 (2.4)	2 (2.1)
	Race or ethnic group, n (%) Caucasian Asian Other		 134 (65.4) 66 (32.2) 5 (2.4)	 63 (64.9) 28 (28.9) 6 (6.2)
	ECOG performance status, n (%) 0 1		 148 (72.2) 57 (27.8)	 62 (63.9) 35 (36.1)
	BRCA mutation type, n (%) BRCA1 BRCA2 BRCA1 and BRCA2		 117 (57.1) 84 (41.0) 4 (2.0)	 51 (52.6) 46 (47.4) 0 (0)
	Hormone-receptor status, n (%) Hormone-receptor positive Triple negative		 103 (50.2) 102 (49.8)	 49 (50.5) 48 (49.5)
	New MBC, n (%)		26 (12.7)	12 (12.4)
	Previous chemotherapy for MBC, n (%)		146 (71.2)	69 (71.1)
	Previous platinum-based therapy for BC, n (%)		60 (29.3)	26 (26.8)

Title: Assessment of the efficacy and safety of olaparib monotherapy versus physicians choice chemotherapy in the treatment of MBC patients with germline BRCA1/2 mutations (OlympiAD) [22]			
Study identifier	NCT02000622, D0819C00003, EudraCT2013-005137-20, OlympiAD		
	≥2 Metastatic sites, n (%)	159 (77.6)	72 (74.2)
	Location of metastasis, n (%) Bone only Other	 16 (7.8) 189 (92.2)	 6 (6.2) 91 (93.8)
	Measurable disease, n (%)	167 (81.5)	66 (68.0)
	QoL, n Baseline QLQ-C30	191 3.9±1.2	73 -3.6±2.2

Abbreviations: AE = adverse event, BRCA1 = BReast CAncer gene 1, BRCA2 = BReast CAncer gene 2, CTCAE = Common Terminology Criteria for Adverse Events, BC = breast cancer, BICR = blinded independent central review, ECOG = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, ER = estrogen-receptor, HER2 = human epidermal growth factor receptor type 2, MBC = metastatic breast cancer, ORR = objective response rate, OS = overall survival, PARPi = poly(adenosine diphosphate-ribose) polymerase inhibitor, PFS = progression-free survival, PFS2 = second progression, PR = progesterone-receptor, QoL = quality of life, RECIST = Response Evaluation Criteria in Solid Tumours

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [47]

Criteria for judging risk of bias		**Risk of bias**
Adequate generation of randomisation sequence: 2:1 olaparib vs IV chemotherapy by investigator or designate via a centralized interactive voice/web response system (IVRS) which randomly assigned patients stratified by prior chemotherapy use in metastatic setting (yes/no), HR-status (HR+ /TNBC) and prior platinum therapy (yes/no).		unclear
Adequate allocation concealment: IVRS generated random allocation sequence; investigator declared prior to randomization their choice of chemotherapy (capecitabine, vinorelbine or eribulin)		unclear
Blinding:	**Patient:** open-label, patients unmasked to treatment assignment	no
	Treating physician: open-label, investigators unmasked to treatment assignment	no
	Outcome assessment: open-label, tumour response assessed by investigator and BICR; exploratory post-hoc sensitivity analyses were conducted to ensure study conclusions were robust to deviations between the IVRS and stratification factors and corresponding subgroups derived from electronic case reports	unclear
Selective outcome reporting unlikely: outcomes reported as specified in protocol; withdrawals and drop-outs reported		no
No other aspects which increase the risk of bias: industry funded the study, assisted with study design, data collection, analysis, interpretation, writing, and revisions		yes
Risk of bias – study level		high

Abbreviations: BICR = blinded independent central review