Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende olaparib som adjuverende behandling af BRCA1/2-muteret, HER2-negativ brystkræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. olaparib
2. Forhandlingsnotat fra Amgros vedr. olaparib
3. Ansøgers endelige ansøgning vedr. olaparib

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

22.01.2024

Vedr.: Udkast til Medicinrådets anbefaling vedr. olaparib som adjuverende behandling af BRCA 1/2-muteret, HER2-negativ brystkræft

AstraZeneca takker for muligheden for at komme med bemærkninger til ovenstående udkast til anbefaling.

Overordnet ønsker AstraZeneca at gøre opmærksom på det faktum, at hvor den generelle prognose for tidlig brystkræft er god, er indikationen for denne ansøgning i en population med højere risiko for tilbagefald eller død, hvilket også anerkendes i rapporten fra Medicinrådet. Der er dermed indenfor denne indikation et større udækket behandlingsbehov end hvad er tilfældet for den overordnede population.

Endvidere henledes opmærksomheden på, at olaparib er den eneste aktive behandling som er blevet undersøgt og har vist positive overlevelsesresultater i denne *tidlig, høj-risiko, gBRCA1/2-muteret HER2-negativ brystkræft*-population og repræsenterer samtidig en targeteret behandlingsmulighed specifikt mod disse arvelige mutationer.

Specifikt ønsker AstraZeneca at kommentere på følgende punkter i rapporten:
1. Usikkerheder i sammenligningen af OlympiA-studiet med dansk klinisk praksis
2. Omkostninger til BRCA test
3. Andre observationer

1)
AstraZeneca anerkender, at der er usikkerheder forbundet med sammenligninger i denne ansøgning, ligesom det er tilfældet i større eller mindre grad i størstedelen af de ansøgninger Medicinrådet modtager.

Den primære usikkerhed forbundet med effekten af olaparib sammenlignet med nuværende dansk klinisk praksis skyldes, at de anbefalede behandlinger for tidlig triple-negativ brystkræft, pembrolizumab og capecitabine, ikke er undersøgt i denne population. I den anledning ønsker AZ at gøre opmærksom, at der var tilsvarende usikkerheder forbundet med Medicinrådets anbefaling af adjuverende pembrolizumab, da Keynote-522-studiet[1] hverken gjorde det muligt at vurdere effekten af neoadjuverende og adjuverende pembrolizumab separat eller at sammenligne pembrolizumab og capecitabine, hvilket er fremhævet i både olaparib- og pembrolizumab-vurderingsrapporterne.[2] Danske guidelines anbefaler i øvrigt kun adjuverende capecitabine *når der ikke er mulighed for targeteret behandling*.[3] Derudover har capecitabine ikke nogen EMA-godkendelse til denne indikation.

Vurderingsrapporten(olaparib) angiver, at *de fleste* danske patienter med triple-negativ brystkræft i dag vil modtage platinholdig kemoterapi i kombination med pembrolizumab, og at denne behandling ikke var standardbehandling under OlympiA-studiet. Desuden fremgår det af rapporten, at de cirka 50% OlympiA patienter, som modtog adjuverende kemoterapi, udgør en *væsentligt højere andel* end nuværende dansk klinisk praksis. AstraZeneca er ikke bekendt med data der beskriver andelen af patienter, der modtager neoadjuverende kemoterapi med hhv. pembrolizumab og platinholdig kemoterapi, og der er ikke i vurderingsrapporten angivet en reference for disse sammenligninger med dansk praksis.

2)
Vedrørende omkostninger til BRCA-test mener AstraZeneca, at også i høj-risiko HR+/HER2-gruppen bør de fleste af patienterne allerede testes og identificeres efter danske retningslinjer[4]. Fx. viste et norsk studie, at ved anvendelse af testkriterier tilsvarende danske kriterier blev 85-90% af gBRCAm-patienter identificeret[5]. Hvis der er et udokumenteret skel mellem, hvad der anbefales i retningslinjer og den aktuelle testrate for højrisiko HR+/HER2- patienter, mener AstraZeneca ikke, at det er rimeligt, at en anbefaling af olaparib skal bære disse omkostninger, selv om indførelsen af olaparib muligvis ville føre til større overholdelse af testretningslinjerne. Test for gBRCA-mutationer for danske brystkræftpatienter har været udført i ca. 25 år, uafhængig af tilgængeligheden af PARP-hæmmere, blandt andet for at muliggøre risikoreducerende kirurgi samt identifikation af raske mutationsbærere, som vil være i øget risiko for udvikling af kræft.

Hvis olaparib bærer den potentielle stigning i testomkostninger estimeret af Medicinrådet, tilføjer det ca. DKK 60.000 til forskel i omkostninger pr. vundet QALY (ICER), hvilket svarer til mere end halvdelen af forskellen mellem virksomhedens hovedanalyse og den tilsvarende lavet af Medicinrådet for HR+/HER2- gruppen. Uden øgede

BRCA-testomkostninger ville ICER derfor være omkring DKK 360.000 pr. vundet QALY i stedet for DKK 420.000 i Medicinrådets hovedanalyse (analyse udført med AIP).

3)
På side 41 fremgår det, at PARP-hæmmerne olaparib og niraparib kun er EMA-godkendt til patienter med platinsensitiv kræft i æggestokkene, æggelederne eller primær kræft i bughinden. AstraZeneca mener, at denne kommentar er forkert og vildledende og vil derfor opfordre til at kommentaren slettes i den endelige rapport. Olaparib er også godkendt til adenocarcinom af pankreas efter behandling med platinholdig kemoterapi, til behandling af prostatacancer som mono- eller kombinationsbehandling uagtet tidligere behandling med platinholdig kemoterapi og både metastatisk og tidlig brystkræft uagtet tidligere behandling med platinholdig kemoterapi. I PAOLA-1 studiet i æggestokkræft inkluderedes patienter som efter primær operation ikke havde makroskopisk sygdom[6], og dermed var det ikke muligt at evaluere platinsensitivitet. Denne population udgjorde mere end halvdelen af patienterne, og påstanden på side 41 er derfor ikke korrekt da olaparib er blevet undersøgt på tværs af tumortyper og både med og uden tidligere behandling med platinholdig kemoterapi, og med eller uden kendt respons på denne. Endelig er tidligere behandling med platinholdig kemoterapi ikke ensbetydende med platinresistens, og vi opfordrer derfor til at denne del udelades af den endelige rapport, da det bliver spekulativt og ikke relevant for sammenligning med klinisk praksis.

På side 45 refereres til veliparib og Brightness studiet.Veliparib adskiller sig væsentligt fra øvrige PARP-hæmmere, på grund af sin lavere "PARP-trapping" egenskaber, hvilket også fremhæves i Brightness-publikationen som central for PARP-hæmmeres effekt[7]. Veliparib har i øvrigt ikke nogen regulatorisk godkendelse og som fremhævet undersøgte Brightness studiet en population uafhængig af gBRCA-mutationer, så AstraZeneca opfordrer til at udelade denne del, da vi ikke mener den bidrager til vurderingen af olaparib.

Vi ser frem til at modtage den endelige afgørelse.

Med venlig hilsen

Mette Lange, Market Access Manager
Rasmus Eliasen, Therapeutic Area Lead

AstraZeneca AS

Referencer:
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25.01.2024
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.02.2024
Leverandør	AstraZeneca
Lægemiddel	Lynparza (olaparib)
Ansøgt indikation	Lynparza (olaparib) som adjuverende behandling af BRCA1/2-muteret, HER2- negativ brystkræft
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Lynparza (olaparib):

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	SAIP (DKK) pr. 01.04.2024	Rabatprocent ift. AIP
Lynparza	100 mg	56 stk.	15.682,06	[redacted]	[redacted]	[redacted]
Lynparza	150 mg	56 stk.	15.688,70	[redacted]	[redacted]	[redacted]

Aftaleforhold

Amgros har en igangværende aftale med leverandøren, som gælder frem til den 31.03.2024. Den nye aftale vil starte den 01.04.2024, [redacted].

Konkurrencesituationen

Der er ingen andre lægemidler godkendt til denne indikation.

Tabel 2: Lægemiddeludgifter pr. patient for et års behandling

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Lynparza	150 mg	56 stk.	300 mg 2 gange dagligt	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Assessment of Lynparza (olaparib) as 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 early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy

- Submitted by AstraZeneca October 14th ,2022.
- New version (fewer pages) submitted by AstraZeneca October 24th ,2022
- 1st validation received from DMC August 25th ,2023
- Additional comments received from DMC September 28th ,2023
- Updated application submitted by AstraZeneca October 10th ,2023
- 2nd validation received from DMC October 17, 2023
- Updated application submitted by AstraZeneca October 24th ,2023

Table of contents

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

1. Basic information

Contact information

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Overview of the pharmaceutical	
Proprietary name	Lynparza
Generic name	Olaparib
MA holder in Denmark	AstraZeneca AB
ATC code	L01XK01
Pharmacotherapeutic group	poly [ADP-ribose] polymerase inhibitors (PARPi)
Active substance(s)	Olaparib
Pharmaceutical form(s)	Tablets 150 mg and 100 mg
Mechanism of action	Olaparib is an oral potent inhibitor of PARP1, PARP2, and PARP3. These PARP enzymes are required for the efficient repair of DNA single-strand breaks. During the repair process, after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. Olaparib, when bound to the active site of DNA-associated PARP, prevents dissociation from DNA, blocking repair of the single-strand break
Dosage regimen	2 tablets of 150 mg twice daily. 100 mg can be used for dose reductions. Treatment in OlympiA was 12 months or to progression/AEs/death
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Lynparza is indicated as 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 early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy

Overview of the pharmaceutical	
Other approved therapeutic indications	***Ovarian cancer:*** Lynparza (tablets) is indicated as monotherapy for the: • maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2- mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. • maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Lynparza in combination with bevacizumab is indicated for the: • maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability. ***Breast cancer:*** • Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. (tablet formulation) ***Adenocarcinoma of the pancreas:*** • Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. (tablet formulation) ***Metastatic castration resistant prostate cancer*** • Lynparza is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. • Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.
Will dispensing be restricted to hospitals?	Yes. Labelled BEGR

Overview of the pharmaceutical	
Combination therapy and/or co-medication	No
Packaging – types, sizes/number of units, and concentrations	100mg and 150 mg pack. 56 tablets per pack
Orphan drug designation	No

2. Abbreviations

AACR	American Association for Cancer Research
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASR	Age-standardised rate
AST	Aspartate transaminase
AUC	Area under the curve
BCR	Best complete response
BER	Base excision repair
BICR	Blinded independent central review
BID	Twice daily
BRCA	Breast cancer susceptibility gene
CNS	Central nervous system
CPS	Carbamoyl phosphate synthase
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	*Ductal carcinoma* in situ
DCO	Data cut-off
DDFS	Distant disease-free survival
DDR	DNA damage response
DFS	Disease-free survival
EFS	Event-free survival
EMA	European Medicines Agency

FAS	Full analysis set
g*BRCA*m	Germline breast cancer susceptibly mutation
GHQ	General health questionnaire
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HRD	Homologous recombination deficiency
HRR	Homologous recombinational repair
HRT	Hormone replacement *therapy*
HRQoL	Health related quality of life
IDFS	Invasive disease-free survival
ITC	Indirect treatment comparison
ITT	Intent-to-treat
MDS	Myelodysplastic syndromes
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
OS	Overall survival
ORR	Objective response rate
PARPi	Poly (ADP-ribose) polymerase inhibitors
PCR	Polymerase chain reaction
PFS	Progression-free survival
PRO	Patient reported outcome
QoL	Quality of life
RCT	Randomised controlled trial
RFS	Recurrence-free survival
RWE	Real world evidence
SAE	Serious adverse event
SAS	Safety analysis set
s*BRCA*m	Somatic breast cancer susceptibly mutation
SLR	Systematic literature review
SOC	Standard of care
SSB	Single-strand break
STEEP	Standardized Definitions for Efficacy End Points
t*BRCA*m	Targeted breast cancer susceptibly mutation
TNBC	Triple negative breast cancer
ULN	Upper limit of normal

3. Tables and Figures

Tables:

Figures:

4. Summary

Lynparza is a first-in-class PARPi [1] in breast cancer, and the presence of *BRCA*m is a selective marker for enhanced response to Lynparza. OlympiA is the first phase III, double-blinded, placebo-controlled, randomised clinical trial testing a PARPi as an adjuvant therapy. The study investigated the efficacy and safety of Lynparza (300 mg twice daily for one year) for the adjuvant treatment of adult patients with non-metastatic, early, invasive adenocarcinoma of the breast that is HER2-negative (either TNBC or HR-positive/HER2-negative) [2].

Enrolled patients have undergone definitive local treatment in addition to at least six cycles of adjuvant or neoadjuvant chemotherapy containing anthracyclines, taxanes or a combination of both, and have a documented germline mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected to be deleterious. In order to allocate these, 1835 patients were randomised from June 2014 to May 2019.

In late July 2022, Lynparza gained marketing authorisation from the European Medicines Agency (EMA) to be used in line with the OlympiA trial. Accordingly, Lynparza is indicated to be used as 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 early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy. The EPAR has been published and is used as reference in the application [3].

This application is mainly covering outcomes from DCO2(12 July 2021), and with a median follow-up of 2.5 and 3.5 years, respectively, that provides data on invasive disease-free survival (IDFS), distant disease-free survival (DDFS), overall survival (OS), health-related quality of life (HRQoL) and safety outcomes. In some sections also data from DCO1(27th March 2020) is included.

Efficacy of olaparib in OlympiA

The OlympiA trial was conducted in collaboration with the US National Cancer Institute NRG Oncology and demonstrated that olaparib, administered to patients with g*BRCA*m, high-risk, HER2-negative, early breast cancer for up to one-year, improves OS as well as invasive IDFS and distant DDFS versus placebo. OlympiA reported early on the recommendation of the Independent Data Monitoring Committee (IDMC) [4]. The study met its primary endpoint of investigator-assessed IDFS. At DCO2 the median duration of follow-up was 3.5 years for the olaparib arm and 3.6 years in the placebo arm. A statistically and clinically meaningful IDFS benefit was observed in patients treated with olaparib compared with those treated with placebo (37.2% reduction in risk of invasive disease; hazard ratio 0.628; 95% CI 0.504, 0.779; p=0.0000233). Sustained separation in IDFS Kaplan-Meier survival curves was observed and the benefit observed with olaparib was maintained beyond one year of treatment; 4-year IDFS in the olaparib arm was 82.7% compared to 75.4% in the placebo arm, translating to an absolute improvement of 7.3% (95% CI 3.6, 11.3).

The secondary endpoint of DDFS also showed a statistically and clinically meaningful benefit of olaparib vs placebo in the ITT population . At DCO2 the hazard ratio for DDFS favoured olaparib (HR: 0.61; 95% CI: 0.48, 0.77; p=0.0000421), and showed a statistically significant 39.3% reduction in risk of distant recurrence for patients treated with olaparib versus placebo. Also, at DCO2, the treatment with olaparib significantly improved OS versus placebo with HR 0.68; (98.5.% CI 0.47, 0.97; P = 0.009) showing a 32% reduction in risk of death. The boundary for a 2-sided significance test of the OS HR was p< 0.015.

Overall, the OlympiA study demonstrates that olaparib, administered for up to one year, is associated with a significantly longer survival free of invasive or distant disease and significantly better OS, compared with placebo in patients with g*BRCA*m, high-risk, HER2-negative, early breast cancer, following surgical treatment and neoadjuvant or adjuvant chemotherapy.

Health-related quality of life, safety and tolerability of olaparib in OlympiA

The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score and EORTC QLQ-C30 global health status/QoL scores were selected as the PROs in OlympiA. These questionnaires were completed at baseline (before randomisation) and every six months for a period of two years. At the DCO2 no clinically meaningful differences in HRQoL or fatigue scores were observed between patients receiving olaparib and placebo over the course of the study; this indicates olaparib's potential to improve the patients' prognosis, while maintaining HRQoL.

From the DCO2 of OlympiA, it can be concluded that olaparib has an acceptable safety and tolerability profile. A greater number of all-grade AEs and Grade ≥3 AEs were observed in the olaparib arm versus the placebo arm (all-grade AEs: olaparib 91.8%; placebo 83.8%, Grade ≥3 AEs: olaparib 24.5%; placebo 11.3%). SAEs were reported in a similar proportion of patients in both treatment arms, 8.7% in the olaparib arm vs. 8.6% in the placebo arm. Anaemia was the only Grade 3 AE occurring in more than 5% of patients. 10.8% (olaparib) and 4.6%(placebo) of patients discontinued treatment due to AE's Accordingly, most AEs were non-serious, mild or moderate in severity, and did not result in treatment discontinuation [2, 4, 6]. The most common AEs were nausea and fatigue in the olaparib and placebo arms, respectively. AEs observed with olaparib treatment were consistent with the known safety profile of olaparib. At DCO2, the incidence of MDS/AML and leukaemia in olaparib-treated patients was low and in line with the previously reported frequency. Notably, since study onset, MDS/AML has been reclassified as an adverse drug reaction for olaparib and has also been categorised as an important identified risk in the risk management plan. [2, 4, 6].

From the interim analysis of OlympiA and supported by DCO2, it can be concluded that olaparib has an acceptable safety and tolerability profile, and thatAEs observed across the treatment course with olaparib do not negatively impact patient QoL.

Summary of OlympiA clinical outcome

The OlympiA trial has shown that one-year of adjuvant olaparib significantly reduce the risk of recurrence and prevent progression to metastatic disease among patients with g*BRCA*m, high-risk, HER2-negative, early breast cancer, whilst maintaining patient HRQoL. Moreover, olaparib also significantly improved OS with an acceptable AE profile and no evidence of excess or new cases of MDS or AML.

Olaparib therefore has the potential to drive a step change in the treatment of patients with g*BRCA*m, high-risk, HER2-negative, early breast cancer, addressing the considerable unmet clinical need for individualised, targeted treatments in this patient population. Both the clinical and HE sections of this application will show/use the DCO2 data if they are available for the specific endpoint

Economic value of Lynparza

The cost-effectiveness (CE) results for the ITT population were calculated by weighing the results of the separate analyses of the prespecified and stratified subgroups HER2-/HR+ and TNBC. The results for these two subgroups are then combined to provide estimates of the cost-effectiveness in the ITT-HER2-negative population (ITT-population).

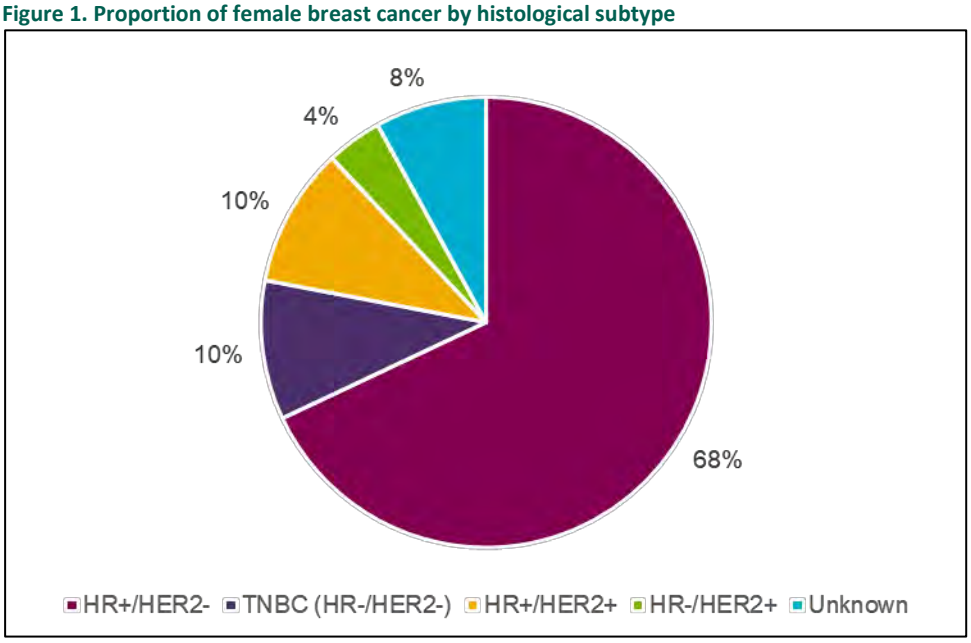
The resulting incremental cost-effectiveness ratio was 270 866 kr. per QALY gained for olaparib compared to watch and wait in the ITT-population. The incremental cost per patient was estimated to be DKK 325 479 over a lifetime horizon and the incremental QALYs estimated to be 1.20. Results were mainly driven by patients receiving olaparib spending longer time in the disease-free state and less time in more severe health states, as the risk of recurrence is reduced. The sensitivity and scenario analyses indicated that the results were robust for variations of uncertain variables. Based on the results from the health-economic analysis olaparib can most likely be considered cost-effective vs. watch and wait as an adjuvant treatment in patients with gBRCAm, high risk HER2-negative, early breast cancer.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

The majority of breast cancers are diagnosed as HR-positive/HER2-negative, with data from the SEER program indicating that ~68% and 10% of all female breast cancer patients are diagnosed with HR-positive/HER2-negative and TNBC (triple negative breast cancer) disease, respectively (Figure 1) [5, 6].

Figure 1. Proportion of female breast cancer by histological subtype



Source: *NCI SEER Program, 2020 [6].*

The prevalence of BRCAm breast cancer has been investigated in a published analysis conducted by AstraZeneca, which assessed the mutation status of tumours from patients across the US, Canada and Europe. This analysis indicated that 6.6–14.6% of breast tumours have detectable loss-of-function BRCA mutations; approximately 3–5% were of germline origin and at least 2% of somatic origin (Table 1) [7-9].
European primary breast cancer patient populations, which report that 1.7–7.3% of patients have gBRCAm disease; considering sBRCAm, a single European study on patients diagnosed with primary breast cancer reports a prevalence of 3% [10].

Table 1. Prevalence of germline and somatic BRCAma in breast cancer

Data source	Number of samples		Percentage with germline, or somatic *BRCA* mutations (n/N)								
			All samples			TNBC			Non-TNBC		
	Overall	TNBC	g*BRCA*m	s*BRCA*m	t*BRCA*m	g*BRCA*m	s*BRCA*m	t*BRCA*m	g*BRCA*m	s*BRCA*m	t*BRCA*m
Polak et al 2017[89]	992 (100%)	145 (14.6%)	4.3% (43/992)	2.2% (22/992)	6.6% (65/992)	13.8% (20/145)	6% (8/145)	19.3% (28/145)	2.7% (23/847)	1.7% (14/847)	4.4% (37/847)
Lai et al (submitted)[b]	1,082 (100%)	112 (10.4%)	4.6% (50/1,082)	2.2% (24/1,082)	8.7% (94/1,082)	10.7% (12/112)	4.7% (5/112)	18.8% (21/112)	3.9% (38/970)	2.0% (19/970)	7.5% (73/970)
Lai et al (submitted)[c]	5,381 (100%)	Unknown	>3.7% (197/5,381)	>2.3% (127/5,381)	9.5% (513/5,381)	TNBC status unknown			TNBC status unknown		
Sokol et al 2020	21,164 (100%)	911 (TNBC known for a subset of patients)	>3.2% (684/21,164)	>2.2% (470/21,164)	8.8% (1,852/21,164)	Mutation frequencies not broken down by TNBC status		9.4% (86/911)	Mutation frequencies not broken down by TNBC status		8.3% (112/1352)

Footnotes: *[a]Only loss of function mutations are counted. [b]Based on TCGA data. [c]Based on classification of samples analysed at Foundation Medicine (US) with computational algorithm to predict germline/somatic status according to Sun et al 2018 [11]. Not all BRCA mutations were evaluable for germline/somatic origin*

The analysis conducted by AstraZeneca also demonstrates that the incidence of BRCA mutations is higher in TNBC patients compared with non-TNBC patients. Approximately 19% of TNBC tumours have detectable loss-of-function BRCA mutations (approximately 11–14% and 5–6% of germline and somatic origin respectively); contrastingly, approximately 4–8% of non-TNBC tumours have detectable loss-of-function BRCA mutations (approximately 3–4% and 2% of germline and somatic origin respectively) [7, 8].

Typically, mutation carrier patients are younger and have a family history of breast and/or ovarian cancer. Breast cancer diagnosis in women with gBRCAm disease occurs at a considerably younger age than in non-gBRCAm patients (including sBRCAm patients) [12]. A European study found the mean age at diagnosis to be 40.2–46.4 years in patients with gBRCAm disease [13], which contrasts to a median age at diagnosis of 65 years for sBRCAm patients matched to non BRCA-mutated patients [12].

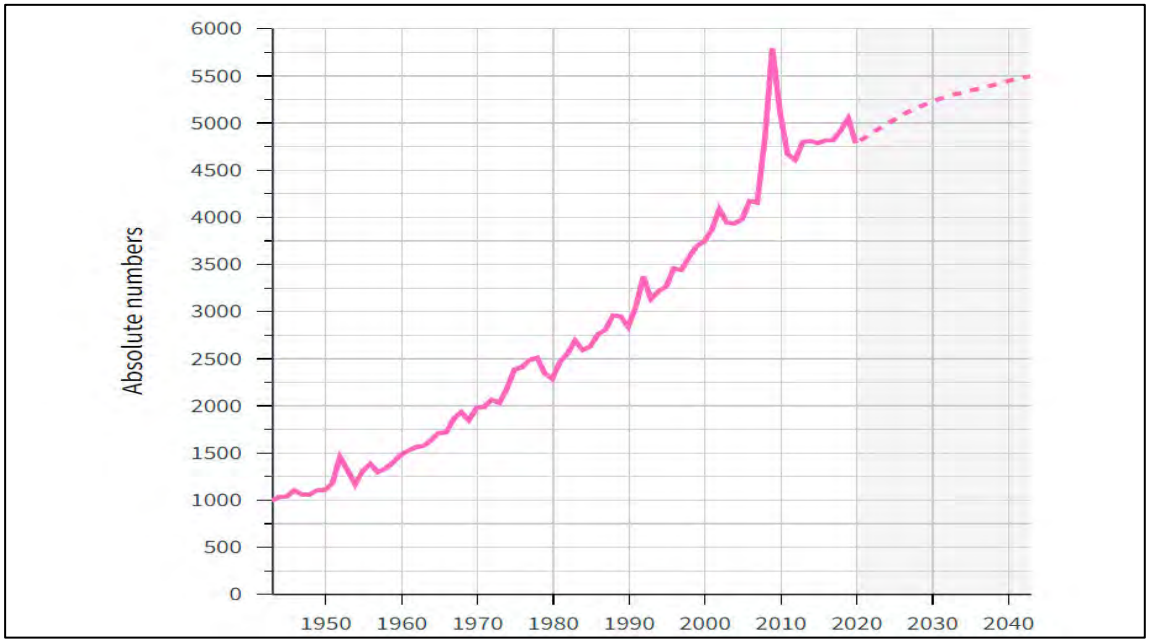
The prognosis of the patient population eligible for olaparib, i.e. high risk, gBRCAm, HER2-negative early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy is difficult to describe as the OlympiA study is the only study evaluating this patient population. Therefore, the control group of OlympiA is the best representation of the prognosis of the patient population eligible for olaparib.

A Danish registry study of 237 patients with gBRCAm mutations showed that patients with gBRCA1m and gBRCA2m had 10-year DFS-rates of 74 % and 88 %, respectively, and 10-year OS-rates of 78 % and 88 %, respectively [14]. The study showed that 49 % had lymph-node negative disease, 52 % had tumors smaller than 20 mm and one third were grade 1-2 [14], altogether representing a lower risk population than OlympiA [2]. Another Danish study looking at an unselected population of 508 patients without known gBRCAm status, 59 % had lymph node negative disease, 60 % had tumors smaller than 20 mm and 70 % had grade 1-2 [15]. While the latter study did not include any survival data of the population, the characteristics suggest that patients with gBRCAm in general has more high risk characteristics than an overall breast cancer population, and furthermore that the patients eligible for olaparib represent a higher risk-population with a higher unmet medical need.

Expected patient number(OlympiA)

Breast cancer(women only) incidence in 2021 was 4829 according to NORDCAN [16]. Based on trend estimates the actual number is assumed to increase to 5067 new cases in 2023. See Figure 2.

Figure 2. Incidence of breast cancer(women) and future trend



***Source**: Nordcan*

A Danish study by Rudolf et al. 2021 reports that there will be 48% patients (2432) in stage I, 37% (1875) in stage II, 9% (456) in stage III and 5% in stage IV [17]. In alignment with patient characteristics for the OlympiA study [4], we regard stage I-III as a relevant population for this application, meaning in total 4763 patients. See Figure 3 below. According to Danish reports, ~10% (476) will have TNBC and ~75% (3572) is estimated to be HR-positive/HER2-negative, and of these, ~15% (61) and ~5% (116) will have an inherited (germline) BRCAm, respectively [12, 18, 19]. Testing rate peak shown in below Figure 3 is based on an ambition to reach at least 85% in TNBC and 65% in HR-positive/HER2-negative. Since clinical experts' estimates that on average ~80% of TNBC receives neo-adjuvant and ~15% adjuvant treatment, this will in numbers mean 49 and 9 patients, respectively. Clinical experts' further estimates that on average ~50% of these neo-adjuvant and ~90% of these adjuvant treated will be of high-risk, meaning 24 and 8 patients, respectively. When calculating number of high-risk patients for HR-positive/HER2-negative, it is based on clinical experts' input where on average ~10% will receive neo-adjuvant and ~43% adjuvant treatment, meaning 12 and 49, respectively, and of these, ~88% neo-adjuvant and ~90% adjuvant will be of high-risk, giving a patient number of 10 and 44, respectively.
The following definitions of high-risk disease has been considered/defined, which is in alignment with Danish guidelines for use of neoadjuvant or adjuvant chemotherapy:

TNBC patients:

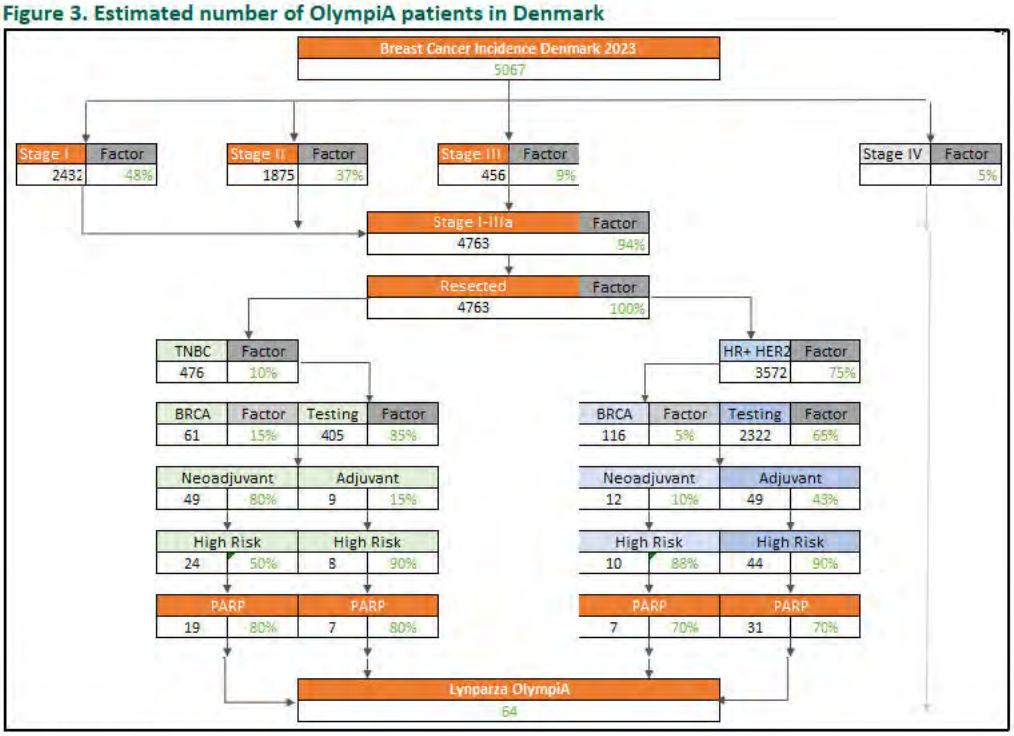
- tumor size >2 cm and/or positive lymph nodes at the time of diagnosis, following adjuvant chemotherapy
- non-pCR post neoadjuvant treatment

HR-positive/HER2-negative patients:

- tumour size >5 cm or ≥4 positive lymph nodes, or 1-3 positive lymph nodes in combination with a grade 3 malignancy at time of diagnosis, following adjuvant chemotherapy
- residual cancer burden 2 or 3 post neoadjuvant treatment

All may not be eligible for a PARPi, hence it is estimated that 80% of TNBC will be suitable for olaparib regardless of whether one has received neo- or adjuvant treatment beforehand, meaning 19 and 7 patients, respectively. Same matters for HR-positive/HER2-negative, where it is estimated that 70% could be potential candidates to receive olaparib, meaning 7 neo-adjuvant and 31 adjuvant treated patients. In total these estimation of percentages, with according calculations, will give a number of 64 high-risk gBRCAm HER2-negative patients, as eligible for olaparib treatment. See Figure 3 below reflecting above calculations.

Figure 3. Estimated number of OlympiA patients in Denmark



**based on trending incidence 2023*

Table 2. Incidence and prevalence in the past 5 years

Year	2015	2016	2017	2018	2019	2020	2021
Incidence in Denmark per 100 000	145,4	147,2	145,7	146,9	148,9	139,7	142,7
Prevalence in Denmark	64 546	66 517	68 325	70 164	72 188	73926	75 601
Prevalence of HER2-negative bc cancer*	54 864	55 539	58 076	59 639	61 360	62837	64261

Note: *Prevalence HER2-negative breast cancer assumed to be equal to incidence (~85%). Source: DBCG, Nye kræfttilfælde Sundhedsstyrelsen.file:///C:/Users/ktgp476/Downloads/Kraefttilfaelde%202021%20(3).pdf

Prevalence of HER2-negative per year is mentioned in Table 2 as this was the population of investigation in the OlympiA study and consisted of both TNBC and HR-positive BRCAm patients as relevant candidates for olaparib [2] .

Table 3. Estimated number of patients eligible for treatment

Year	2023	2024	2025	2026
Breast cancer incidence	5 067	5 087	5 108	5 128
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	64	64	65	65

Source: NORDCAN ; DBCG, https://www.dbcg.dk/images/PDF/Rapporter/DBCG_%C3%A5rsrapport_2020_Publiceret_FINAL.pdf. 2020.

The numbers in
Table 3 are based on breast cancer incidence estimates of 0.4% increment per year and that 1.26% per year will be relevant as candidates for Lynparza treatment based on assumptions given in Figure 3. However, the incidence has been going up and down in recent year.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

While the DMC has published treatment guidelines for ER (Estrogene Receptor) positive and HER2 negative in locally advanced and metastatic breast cancer, there are currently no treatment directed for patients with BRCA1/2-mutations who have HR-positive/HER2-negative, early breast cancer and have previously been treated with neoadjuvant or adjuvant treatment. So, at the time being, adjuvant capecitabine is recommended to patients with TNBC (ER-negative tumour (<1%)) or an ER (1-9%) positive tumor with non-luminal subtype (eg HER2-enriched or basal-like at PAM50) [20]. Patients with ER (≥ 10%) positive tumour and/or 1-9% ER positive tumour with luminal A/B subtype (eg at PAM50) is beside of chemo recommended to be treated with endocrine therapy [20].

There are several factors that account for whether a patient would be more suitable to receive neoadjuvant or adjuvant systemic treatment [21, 22]. Neoadjuvant chemotherapy for operable breast cancer is often reserved for women who desire breast conservation surgery but are not initially candidates; this may be because of a large tumour or because of small breasts. Other reasons include rendering inoperable tumours operable, and time-saving initiatives to allow time for genetic testing or the planning of breast reconstruction in patients undergoing elective mastectomy [23]. Patients with TNBC are often recommended to undergo neoadjuvant chemotherapy, as their subsequent response is a prognostic indicator. Compared with other breast cancer biomarker-defined subpopulations, patients with TNBC have been observed to achieve significantly higher response rates to neoadjuvant anthracycline/cyclophosphamide-based chemotherapy; however, TNBC patients with refractory disease after neoadjuvant chemotherapy have significantly worse survival compared with non-TNBC patients, particularly in the first three years [24].

Capecitabine is used **off-label** after anthracycline and taxane failure in patients with TNBC [25], however consistent evidence of a treatment effect in this setting is lacking. In the CIBOMA Phase III trial, capecitabine did not significantly prolong DFS vs observation (hazard ratio 0.82; 95% CI 0.63, 1.06; p=0.136), and there was no statistically significant difference in OS between study arms (adjusted HR according to stratification factors 0.88; 95% CI 0.64, 1.23; p=0.456) [26]. In an exploratory analysis of CIBOMA, patients who received neoadjuvant chemotherapy and did not obtain a pathological complete response experienced no meaningful DFS benefit of taking capecitabine, compared to the observation patient group (hazard ratio 1.12; 95% CI 0.64, 1.97; p=0.68) [27]. Contrastingly, the Phase III CREATE-X trial assessing standard post-surgical treatment with or without capecitabine was terminated early after meeting its primary endpoint at the interim analysis [28]. In CREATE-X, DFS was longer in the capecitabine group than the control group (74.1% vs 67.6% of patients were alive and free from recurrence or second cancer at five years; p=0.01); patients who received capecitabine also experienced a greater five-year OS rate than the control group (89.2% vs 83.6%; p=0.01) [28]. However, from current studies we do not know the effect of capecitabine in a specific subgroup as BRCAm patients. Nor do we know the effect of other relevant (neo)adjuvant study treatments shown in Table 4, since gBRCAm as an biomarker was not in scope of evaluating the outcome of these.

5.2.2 Choice of comparator (placebo)

The comparator for this application is placebo. No treatment besides of olaparib is currently EMA-approved or recommended by DMC for adjuvant treatment of early high-risk HER2-negative breast cancer with BRCA1/2-mutations and who previously has been treated with neoadjuvant or adjuvant chemotherapy.

5.3 The intervention (olaparib tablets)

Olaparib tablets are administered orally at a recommended dose of 300 mg (2 x 150 mg tablets) twice daily (BID). The administration of olaparib should start no later than eight weeks after completion of last treatment and should be continued for up to 12 months, or until progression of the underlying disease or unacceptable toxicity, or whichever occurs first [3]. Patients should also receive adjuvant endocrine therapy per local policy and/or international guidelines [21, 29]. Prior to initiation of olaparib treatment for the indication proposed here, patients must have confirmation of a deleterious or suspected deleterious germline BRCA1/2 mutation (gBRCA1/2m) using a validated test. As performed in current clinical routine, patients will additionally need to be confirmed as HER2-negative, prior to initiation of olaparib treatment in the OlympiA indication.

Prior to initiation of olaparib treatment in the OlympiA indication, patients must have confirmation of a deleterious or suspected deleterious germline *BRCA*1/2 mutation using a validated test. *BRCA* mutation status can be determined by genetic testing, with several commercial tests available. Myriad Genetics, Inc has extensive experience in *BRCA*m detection and has been chosen as a partner in developing a companion diagnostic for g*BRCA*m testing in the OlympiA trial [30]. The Myriad BRCA analysis testing platform was used in the OlympiA trial and can determine g*BRCA*m status via a simple blood test or oral rinse sample [22]. Patients will also need to be confirmed as HER2-negative, prior to initiation of olaparib treatment in the OlympiA indication. For all details around olaparib see also “Overview of Pharmaceuticals” in the first section of this application.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

OlympiA is a phase III, double-blind, placebo-controlled, multicentre, international, randomised controlled trial (RCT; NCT02032823) examining the clinical benefit of olaparib therapy in patients with *gBRCAm*, HER2-negative, early breast cancer who have received surgical treatment and prior neoadjuvant or adjuvant chemotherapy. Olaparib or placebo treatment was continued for a maximum of 12 months. In this setting interventions of interest could be immune-oncology drugs (atezolizumab and pembrolizumab), cyclin-dependent kinase (CDK) 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib), olaparib, capecitabine, and endocrine therapy. Some of the treatments are currently undergoing investigation in the (neo)adjuvant setting for early breast cancer, but none ofthese are BRCAm and therefore target a broader patient populations(table 4). Due to this and as OlympiA is a H2H study a SLR has not been performed/included.

The EPAR has been consulted:https://www.ema.europa.eu/en/documents/variation-report/lynparza-h-c-3726-ii-0051-g-epar-assessment-report-variation_en.pdf

Table 4. Overview of treatments currently under investigation in the (neo)adjuvant setting for early breast cancer (non-exhaustive)

Trial	Trial details	Key results
Abemaciclib		
MonarchE (Phase III)[4, 22, 31, 32]	**Population**: high-risk, node-positive, HR-positive/HER2-negative early-stage breast cancer (N=5,637) **Randomisation point**: after surgery (patients had not received any systemic therapy for advanced disease) **Study treatment**: endocrine therapy with or without abemaciclib	395 IDFS events observed at the interim analysis (median follow-up: 19 months). Abemaciclib plus endocrine therapy demonstrated superior IDFS vs endocrine therapy alone, with a 28.7% reduction in the risk of developing invasive disease (hazard ratio 0.713; 95% CI 0.583, 0.871; p=0.0009); immature data indicate little difference in OS between treatment arms in the ITT population (39 deaths, 1.4% in the abemaciclib arm and 37 deaths, 1.3% in the control arm).
Pembrolizumab		
KEYNOTE-522 (Phase III)[33, 34]	**Population**: early-stage high-risk, TNBC breast cancer (N=1,174) **Randomisation point**: initiation of neo-adjuvant chemotherapy **Study treatment**: neoadjuvant chemotherapy (paclitaxel plus carboplatin) with neoadjuvant pembrolizumab or placebo	At the first interim analysis (of the first 602 patients who underwent randomisation), the percentage of patients with pCR was significantly higher in the pembrolizumab plus chemotherapy arm than the placebo plus chemotherapy arm (64.8% vs 51.2%, respectively; estimated treatment difference: 13.6%; 95% CI 5.4, 21.8; p<0.001). In the ITT population, patients in the pembrolizumab plus chemotherapy arm experienced a 37% reduction in EFS events compared with the placebo plus chemotherapy arm (hazard ratio, 0.63; 95% CI 0.43, 0.93); the three-year EFS rate was 84.5% with pembrolizumab plus chemotherapy compared with 76.8% with placebo plus chemotherapy. In the subgroup of patients who did not achieve pCR, at a median follow-up of 39.1 months, those who received pembrolizumab had a EFS rate of 67.4% vs. 56.8% . These rates were substantially lower than patients who achieved pCR (pembrolizumab: 94.4%; placebo: 92.5%).
Capecitabine		
CREATE-X (Phase III)[28]	**Population**: neoadjuvant-treated, post-operative, HER2-negative residual invasive breast cancer (N=910) **Randomisation point**: after neo-adjuvant chemotherapy **Study treatment**: standard post-surgical treatment with or without capecitabine	CREATE-X was terminated early as it met the primary endpoint at the interim analysis. Patients who received capecitabine had a longer period of DFS than the control group (74.1% vs 67.6% of patients were alive and free from recurrence or second cancer at 5 years; p=0.01).Patients who received capecitabine also experienced a greater 5-year OS rate than the control group (89.2% vs 83.6%; p=0.01).
CIBOMA (Phase III)[27]	**Population**: operable, node-positive-or node negative with tumour ≥1 cm TNBC, with prior anthracycline- and/or taxane-containing chemotherapy (N=867) **Randomisation point**: after neo-adjuvant or adjuvant chemotherapy **Study treatment**: capecitabine treatment or observation	After a median follow-up time of 7.3 years, a total of 225 DFS events were observed, 105 (23.4%) in the capecitabine arm and 120 (28%) in the observation arm; it was concluded that DFS was not significantly prolonged with capecitabine vs observation (HR, 0.82; 95% CI 0.63 to 1.06; p=0.136). In patients receiving capecitabine who had previously received neoadjuvant chemotherapy and did not obtain a pCR, there was no significant difference in DFS compared with the observation patient cohort, where patients received no additional treatment (hazard

Trial	Trial details	Key results
		ratio, 1.12; 95% CI 0.64, 1.97; p=0.68). In addition, there was no statistically significant difference in OS between study arms (adjusted hazard ratio according to stratification factors, 0.88; 95% CI 0.64 to 1.23; p=0.4562).

It is also worth noting that several other PARPi (including fluzoparib, talazoparib, veliparib and niraparib) are being investigated for the treatment of HER2-negative, *gBRCA*m breast cancer; however, these treatments is being explored for more advanced disease and are not currently being investigated in the adjuvant setting.

6.2 List of relevant studies

Table 5. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
1)Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. Tutt et al.N Engl J Med 2021; 384:2394-2405 [2] https://www.nejm.org/doi/full/10.1056/nejmoa2105215 **2)**Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. Annals of Onc. Volume 33, Issue 12, p 1250-1268. 2022. Geyer CE et al. [35] https://www.annalsofoncology.org/article/S0923-7534(22)04165-5/fulltext	OlympiA	NCT02032823	June 2014 through May 2019	Olaparib vs placebo in adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy

7. Efficacy and safety

7.1 Efficacy and safety of olaparib compared to placebo

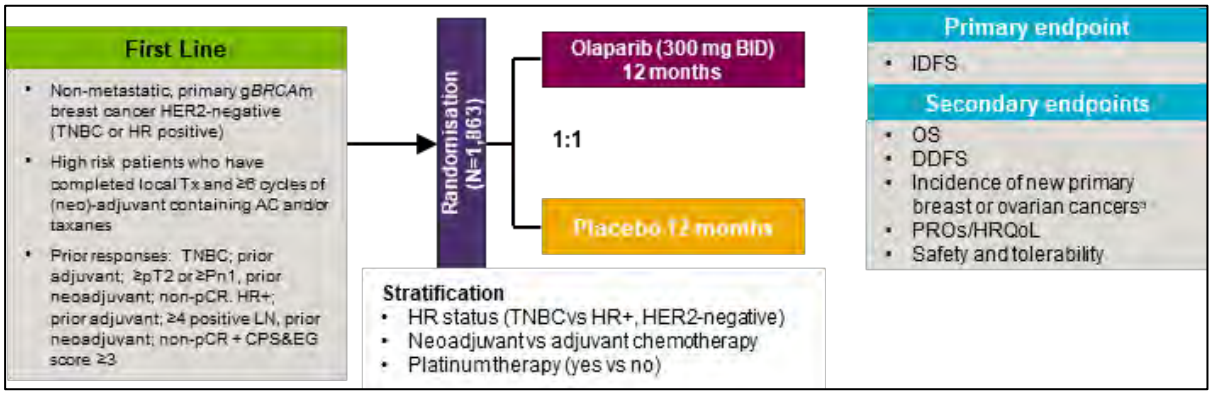
7.1.1 Relevant studies

OlympiA

OlympiA is a phase III, double-blind, parallel group, placebo controlled, multicentre randomized controlled trial, which aimed to assess the efficacy and safety of olaparib (300 mg twice daily for one year) versus placebo as an adjuvant treatment in the selected patient population (Figure 4Table 5). A total of 1836 patients were randomized 1:1 to either study arm based on inclusion/exclusion criteria as described. Patients were stratified based on HR status (ER and/or PR-positive/HER2-negative vs. TNBC), chemotherapy type (neoadjuvant vs. adjuvant), and the prior use of platinum therapy for current breast cancer (yes vs. no). Following the first dose of olaparib or placebo, patients were treated until recurrence of disease, diagnosis of a second primary malignancy, treatment discontinuation or treatment completion. Treatment duration was for up to a maximum of 12 months. The primary measure for olaparib efficacy was IDFS (Figure 4). Secondary endpoints include:

- OS
- DDFS
- Incidence of new primary breast or ovarian cancers.

Figure 4. OlympiA study design



***Footnotes**: [a]Incidence of any new cancers, including new primary breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer.. **Source**: [4, 30] [4, 30].*

The included patients were adult patients with histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that had a high-risk phenotype (definition see Table 6). Further requirements included documented germline BRCA1 or BRCA2 mutation and adequate treatment history including surgery and adjuvant or neoadjuvant chemotherapy. Patient disposition is summarized in Appendix B. The median total intended treatment duration for olaparib and placebo was 364 days and 365 days respectively (range olaparib 1-492, placebo 2-414) and the median actual treatment duration 350 days (range 1-420 days) and 359 days (range 2-404 days), respectively. Exhaustive patient characteristics are presented in Appendix B**.** Patient groups receiving olaparib and placebo were well balanced across key baseline characteristics and well matched in terms of age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and prior treatment.

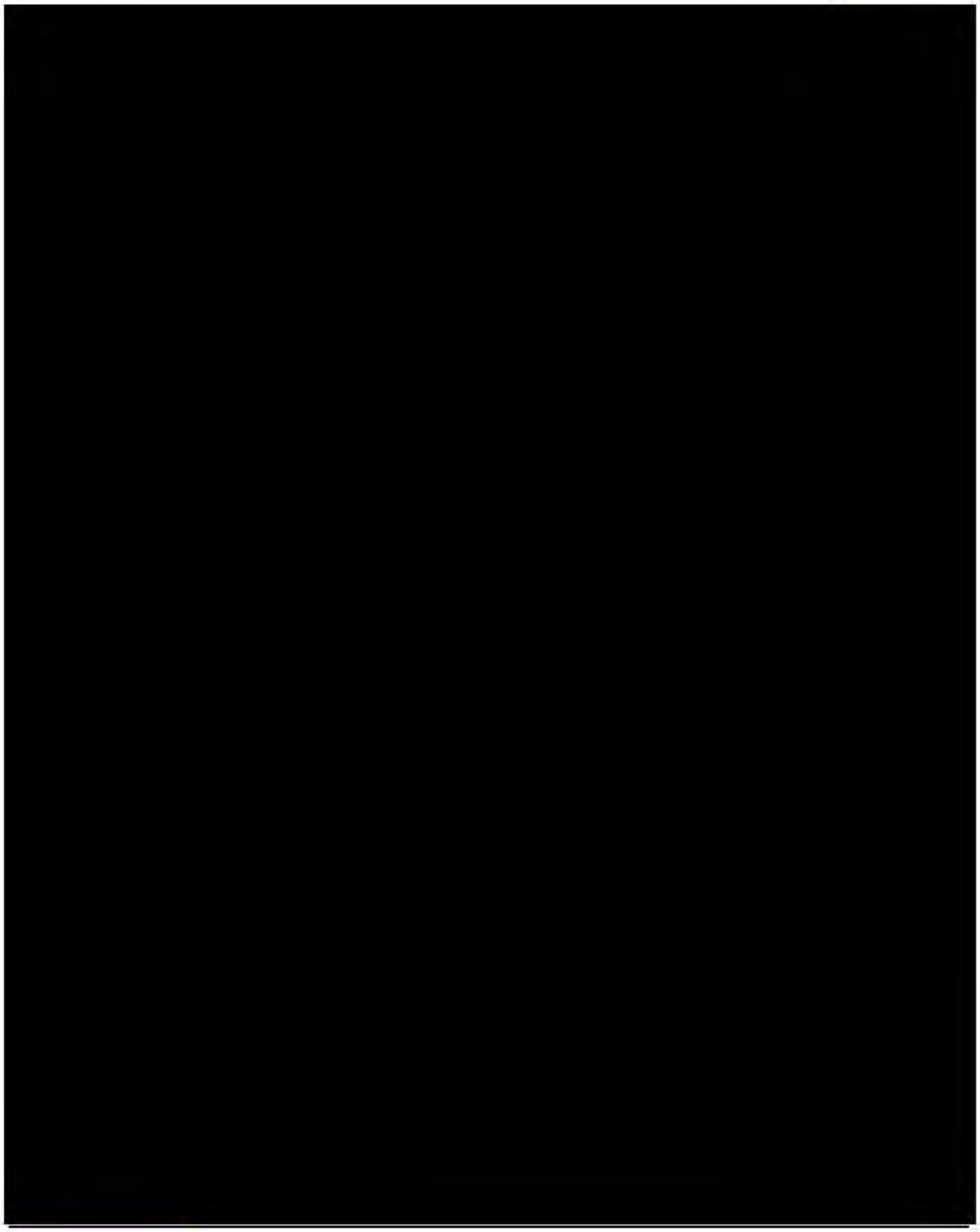
Table 6. High risk breast cancer in OlympiA (differentially defined by the timing of previous chemotherapy and HR status)

Population	Definition of high risk disease
Patients who underwent initial surgery and received adjuvant chemotherapy	• TNBC patients must have been axillary node-positive (and any tumour size) or axillary node negative with invasive primary tumour pathological size >2 cm • HR-positive /HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes
Patients who underwent neoadjuvant chemotherapy followed by surgery	• TNBC patients must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pathological complete response [non-pCR]) • HR-positive /HER2-negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non-pCR) and a CPS&EG score ≥3

Source: *OlympiA Clinical Study Protocol [4, 30]*

Baseline characteristics ITT is included in Appendix and below we have listed them below for the TNBC and HR+ populations as this was requested by DMC (table 7 and 8).

[redacted]



[redacted]

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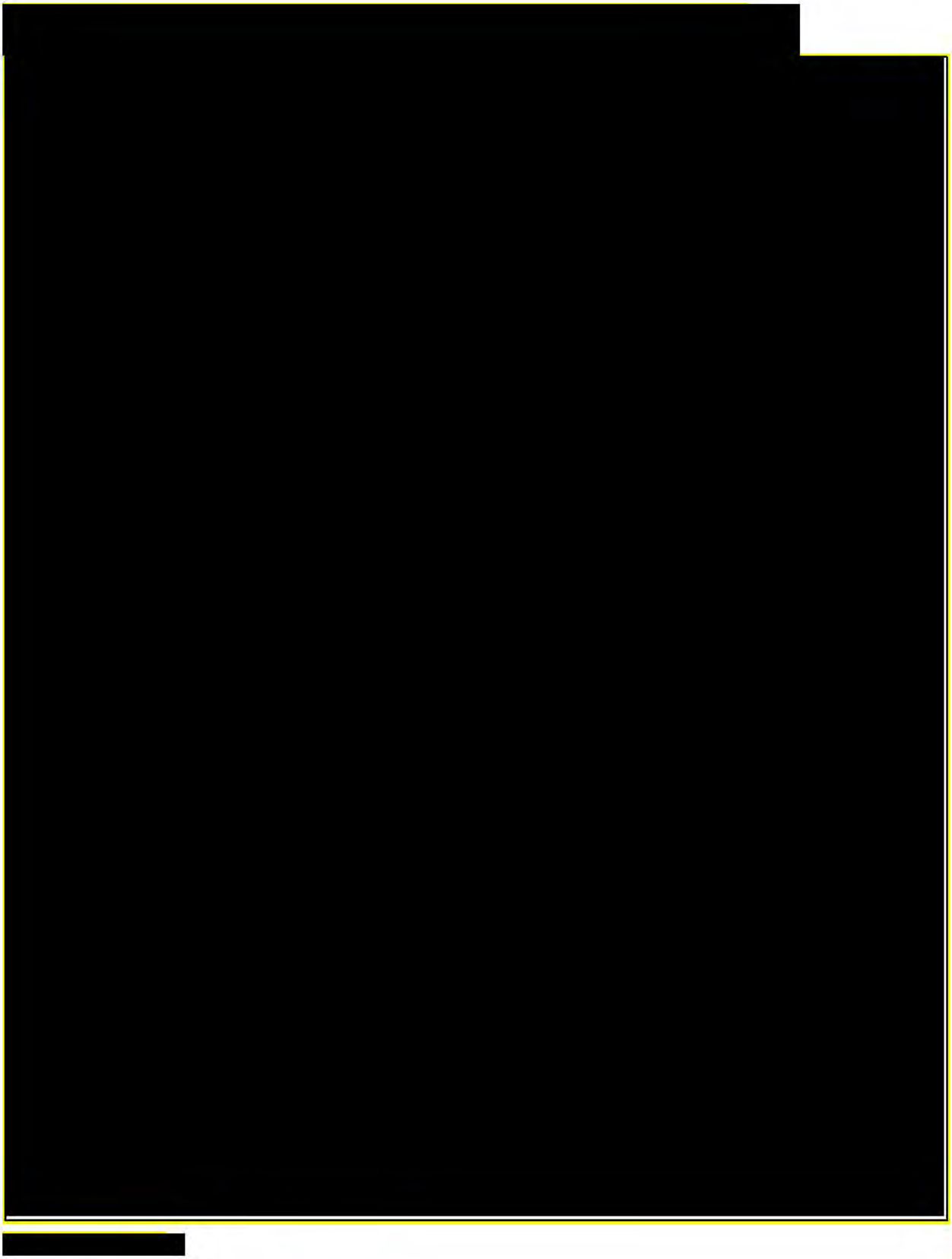


7.1.2 Efficacy and safety – results per study

The OlympiA trial demonstrated that olaparib, administered to patients with gBRCAm, high-risk , HER2-negative, early breast cancer for up to one year, improves OS (significant in DC02), IDFS and DDFS when

compared to placebo. Two analysis have been conducted (DCO1 and DCO2) and efficacy results from the two analysis are summarised in Table 9. Number of patient available for the different endpoint is shown in Table 10.

Table 9. Comparison of OlympiA efficacy results at IA IDFS (DCO1) and current OS IA2 (DCO2)

	Prior IA IDFS analysis Median follow-up 2.5 years	Current IA2 OS analysis Median follow-up 3.5 years
IDFS hazard ratios (CI)	*0.58 (99.5% CI: 0.41, 0.82)*	0.63 (95% CI: 0.50, 0.78)
P value needed for significance	*0.005*	N/A
P value observed at analysis	*< 0.0001*	N/A
Difference in IDFS rate (CI)	*3 Yr. 8.8% (95% CI: 4.5, 13.0)*	3 Yr. 8.8% (95% CI: 5.0, 12.6) 4 Yr. 7.3% (95% CI: 3.0, 11.5)
DDFS hazard ratios (CI)	*0.57 (99.5% CI: 0.39, 0.83)*	0.61 (95% CI: 0.48, 0.77)
P value needed for significance	*0.005*	N/A
P value observed at analysis	*< 0.0001*	N/A
Difference in DDFS rate (CI)	*3 Yr. 7.1% (95% CI: 3.0, 11.1)*	3 Yr. 7.0% (95% CI: 3.5, 10.6) 4 Yr. 7.4% (95% CI: 3.6, 11.3)
OS hazard ratios (CI)	***0.68 (99% CI: 0.44, 1.05)***	0.68 (98.5% CI: 0.47, 0.97)
P value needed for significance	***0.010***	0.015
P value observed at analysis	***0.024***	0.009
Difference in OS rate (CI)	***3 Yr. 3.7%** (95% CI: 0.3, 7.1)*	3 Yr. 3.8% (95% CI: 0.9, 6.6) 4 Yr. 3.4% (95% CI: -0.1, 6.8)

Source: *[35-37]*

Table 10. Analysis set

Analysis Set	Description	Number	Outcomes Analysed
Full analysis set (FAS)[a]	ITT, all randomised patients	1,836 patients in total (921 olaparib, 915 placebo)	Efficacy
	Mature cohort ITT, the first 900 randomised patients only	900 patients in total (449 olaparib, 451 placebo)	Efficacy
Safety analysis set (SAS)	All patients who received at least one treatment dose and had at least one safety follow-up assessment	1,815 patients in total (911 olaparib, 904 placebo)	Safety and tolerability
PRO Analysis Set	Patients who started treatment and who provided evaluable baseline FACIT-Fatigue or EORTC QLQ-C30 data (evaluable meaning at least one sub-scale baseline score was determined)	1,751 patients in total (876 olaparib, 875 placebo)	HRQoL

Footnotes: *[a]Analysis based on treatment arm randomised to, rather than treatment received.*

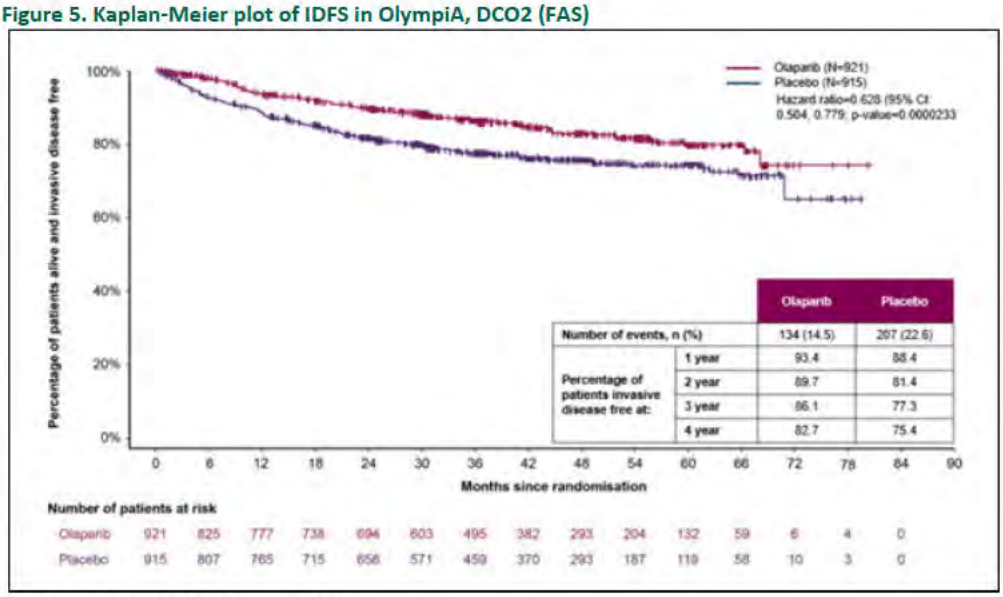
IDFS (DCO2)

At the second interim analysis (DCO2), consistent with DCO1, a statistically and clinically meaningful investigator-assessed IDFS benefit was observed in patients treated with olaparib compared with those treated with placebo). At the time of the analysis (data maturity 18.6%) a 37.2% reduction in risk of invasive disease recurrence or death was observed for patients in the olaparib arm compared with the placebo arm (HR: 0.63; 95% CI: 0.50, 0.78; p=0.0000233)(

Figure 5). Sustained separation in the KM-curves was observed and, based on KM estimates, the statistically significant IDFS HR translated into a clinically meaningful increase in the percentage of patients who remained invasive disease free in the olaparib arm at 1 year (93.4%), 2 years (89.7%), 3 years (86.1%), and 4 years (82.7%)

compared with 88.4%, 81.4%, 77.3%, and 75.4% respectively, in the placebo arm. Median duration of follow-up was 3.5 years in the olaparib arm and 3.6 years in the placebo arm [35].

Figure 5. Kaplan-Meier plot of IDFS in OlympiA, DCO2 (FAS)



Footnotes: *DCO2: 12 July 2021.and [35]*

For all categories of IDFS (invasive loco-regional, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive malignancy, or death from any cause), the incidence was either lower in the olaparib arm compared to the placebo arm or similar in both arms. Distant disease recurrence occurred more frequently than local disease recurrence, distant CNS disease recurrence occurred in 2.6% of patients in the olaparib arm and 4.2% in the placebo arm, whereas non-CNS distant recurrence occurred in 6.9% vs. 10.7% in the olaparib and placebo arms respectively. Local disease occurrence occurred in 1.0% and 1.3% of patients in the olaparib and placebo arms respectively.

In the subgroup analysis conducted to assess consistency of treatment across a range of clinical, prognostic, and demographic characteristics, it was demonstrated that the IDFS benefit remaining consistent across stratification and prespecified subgroups, including prior chemotherapy (neoadjuvant versus adjuvant), prior platinum therapy use, HR status, and BRCA status (BRCA1m vs. BRCA2m). These data underline how severe recurrence can be in patients with gBRCAm, high risk , HER2-negative early breast cancer and the importance of an effective treatment in preventing recurrence.

Table 11. Summary of OlympiA efficacy endpoints, DCO2 (FAS)

		Olaparib (N=921)	Placebo (N=915)
IDFS			
Number of events, n (%)		134 (14.5)	207 (22.6)
Estimate of hazard ratio[a]		0.628	
95% CI for hazard ratio[b, c]		(0.504, 0.779)	
Log-rank test: p-value[d]		0.0000233	
	1 year	93.4 (91.5, 94.9)	88.4 (86.1, 90.3)
	2 years	89.7 (87.4, 91.6)	81.4 (78.7, 83.8)

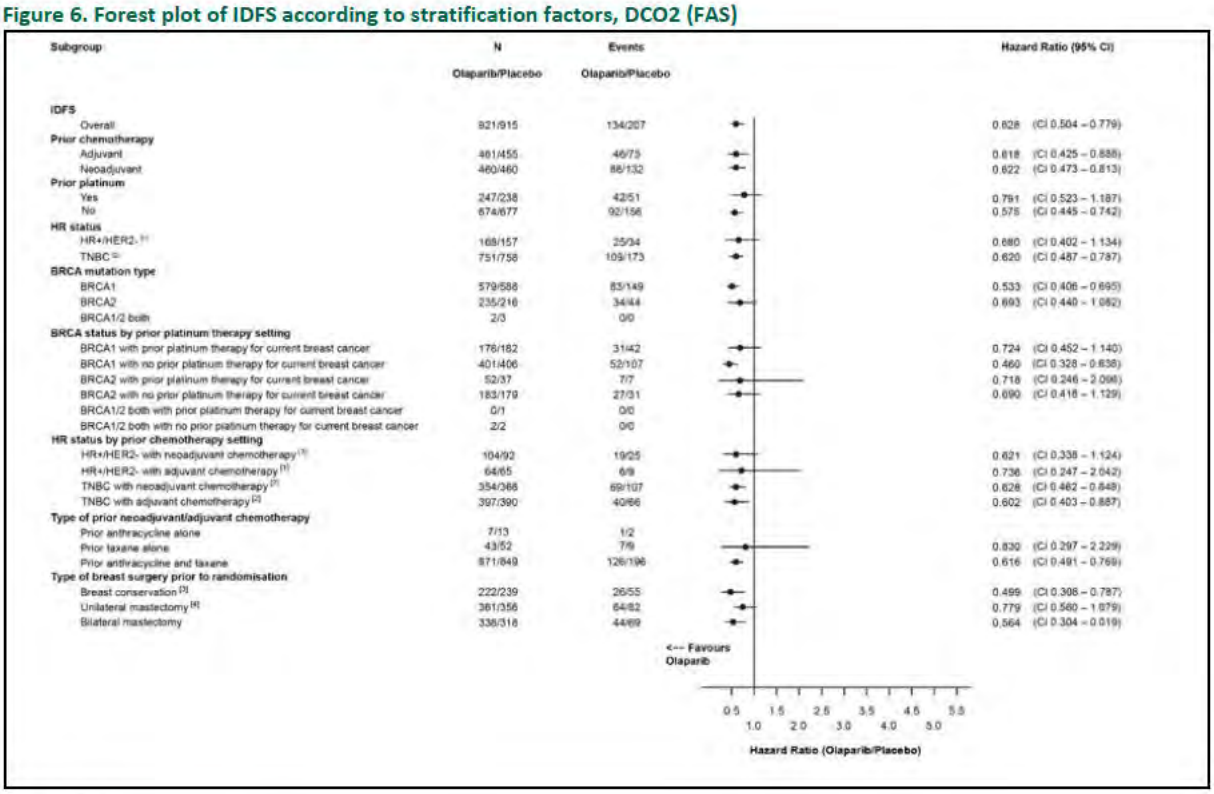
		Olaparib (N=921)	Placebo (N=915)
Percentage (95% CI) of patients free of invasive disease at:	3 years	86.1 (83.5, 88.3)	77.3 (74.3, 80.0)
	4 years	82.7 (79.6, 85.4)	75.4 (72.2, 78.3)
Median clinical follow-up time, years (minimum–maximum)		3.5	3.6
Type of IDFS event, n (%)			
Distant CNS recurrence		24 (2.6)	38 (4.2)
Distant excluding CNS recurrence		64 (6.9)	98 (10.7)
Regional (ipsilateral) recurrence		9 (1.0)	18 (2.0)
Local (ipsilateral) recurrence		9 (1.0)	12 (1.3)
Contralateral invasive breast cancer		15 (1.6)	18 (2.0)
New primary cancers		11 (1.2)	23 (2.5)
Deaths without a prior IDFS event		2 (0.2)	0 (0)
OS			
Number of events, n (%)		75 (8.1)	109 (11.9)
Estimate of hazard ratio[a]		0.678	
95% CI for hazard ratio[b, c]		(0.503, 0.907)	
98.5% CI for hazard ratio[b, e]		(0.468, 0.973)	
Log-rank test: p-value[d, f]		0.0091	
Percentage (95% CI) of patients alive at:	1 year	98.0 (96.9, 98.8)	96.9 (95.5, 97.9)
	2 years	95.0 (93.3, 96.2)	92.8 (90.9, 94.3)
	3 years	92.8 (90.8, 94.4)	89.1 (86.7, 91.0)
	4 years	89.8 (87.2, 91.9)	86.4 (83.6, 88.7)
Median clinical follow-up time, years (minimum–maximum)		3.5	3.6
DDFS			
Number of events, n (%)		107 (11.6)	172 (18.8)
Estimate of hazard ratio[a]		0.607	
95% CI for hazard ratio[b, c]		(0.476, 0.771)	
Log-rank test: p-value[d]		0.0000421	
Percentage (95% CI) of patients free of distant disease at:	1 year	94.4 (92.6, 95.7)	90.3 (88.2, 92.1)
	2 years	90.6 (88.4, 92.4)	84.0 (81.4, 86.3)
	3 years	88.0 (85.5, 90.1)	81.0 (78.1, 83.5)
	4 years	86.5 (83.8, 88.8)	79.1 (76.0, 81.8)
Median clinical follow-up time, years (minimum–maximum)		3.5	3.5

Footnotes: *DCO2: 12 July 2021. [a]Estimate of the treatment hazard ratio based on the stratified Cox's Proportional Hazards Model; <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors are the same as those used in the stratified log-rank test. [b]The CI for the hazard ratio was estimated using the profile likelihood approach. [c]Exploratory, not inferential. [d]p-value from a stratified log-rank test. Stratification is by chemotherapy type (2 levels: adjuvant vs neoadjuvant), HR status (2 levels: ER and/or PR-positive/HER2-negative vs TNBC) and prior platinum therapy (2 levels: yes vs no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. [e]Inferential, according to alpha spending rules for the interim analysis of OS.* **Source:** *AstraZeneca Data on File (OlympiA Efficacy Analysis DCO2) and [35]*

Subgroup analysis of IDFS (DCO2)

Subgroup analyses were undertaken to assess consistency of treatment effect across a range of important clinical, prognostic and demographic characteristics, including prior chemotherapy status, prior platinum therapy use, HR status, and BRCA mutation type (Figure 15). The subgroup analyses demonstrate that the IDFS benefit observed in the ITT population was consistent across stratification and pre-specified subgroups.

Figure 6. Forest plot of IDFS according to stratification factors, DCO2 (FAS)



Source: *[35]*

IDFS in TNBC and HR+/HER2-

To support the subgroup analysis above we have (as requested by DMC) included the Kaplan-Meier plot of IDFS in OlympiA for the TNBC and HR+ population below [redacted]

[redacted]

[redacted]

[redacted]

7.1.3 OS (DCO2)

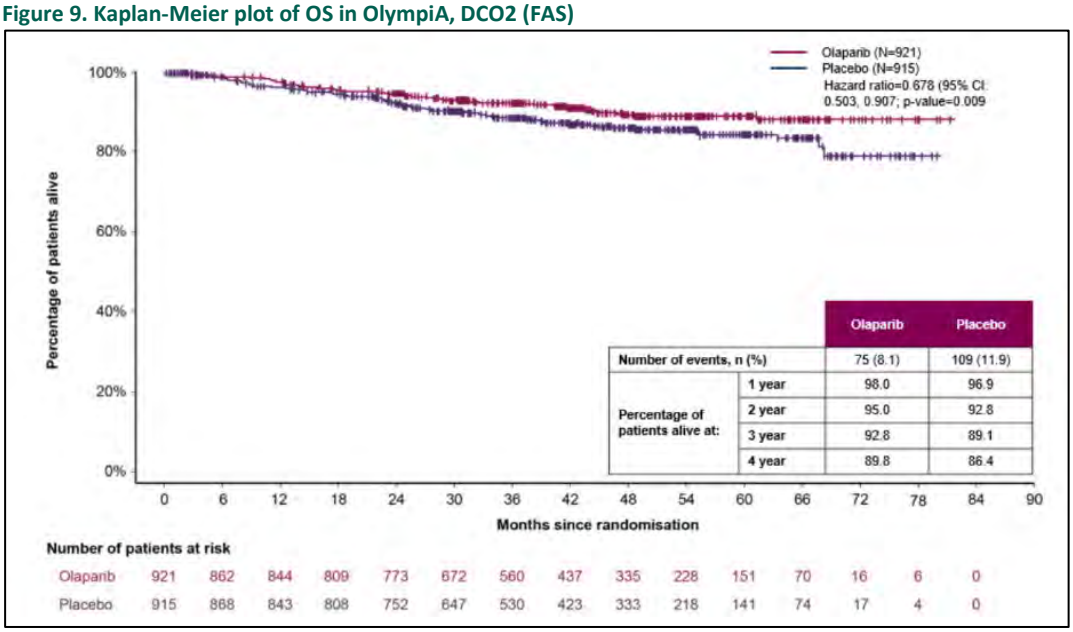
At DCO2, the OS data were 10.0% mature (184 events/1,836 patients). These data suggest that, in patients with g*BRCA*m, high-risk, HER2-negative, early breast cancer, olaparib treatment provides a statistically significant improvement in OS, compared with placebo (Figure 9):

- The HR for OS favoured olaparib (HR= 0.678; 98.5% CI 0.468, 0.973; 95% CI 0.503, 0.907 p=0.0091), indicating a 32.2% reduction in risk of death for patients treated with olaparib vs placebo.
- Based on KM-estimates, the percentage of patients who remained alive was higher in the olaparib arm at 1 year (98.0%), 2 years (95.0%), 3 years (92.8%) and 4 years (89.8%), compared with 96.9%, 92.8%, 89.1% and 86.4%, respectively, in the placebo arm.
- Median follow-up for OS was 3.5 years in the olaparib arm and 3.6 years in the placebo arm.

The efficacy demonstrated in the IDFS outcome measure was supported by secondary endpoints. Accordingly, at DCO2 with an OS data maturity of 10%, olaparib treatment showed to provide a statistically significant improvement in OS compared to placebo in patients with gBRCAm, high risk, HER2-negative, early breast cancer [38]. The HR for OS remained at a similar level as compared with previous interim analysis and significantly favoured olaparib (HR: 0.68; 98.5% CI: 0.47, 0.97; p=0.009) which showed to bring a 32.2% reduction in risk of death for patients treated with olaparib versus placebo[35].

Based on Kaplan-Meier estimates, the percentage of patients who remained alive was higher in the olaparib arm at 1 year (98.0%), 2 years (95.0%), 3 years (92.8%) and 4 years (89.8%), compared with 96.9%, 92.8%, 89.1% and 86.4%, respectively, in the placebo arm, stating a difference of 3.8% (95% CI: 0.9, 6.6) at 3 years and 3.4% (95% CI: -0.1, 6.8) at 4 years in OS rate. Median follow-up for OS was 3.5 years in the olaparib arm and 3.6 years in the placebo arm [35].

Figure 9. Kaplan-Meier plot of OS in OlympiA, DCO2 (FAS)



Footnotes: *DCO2: 12 July 2021.* ***Source****: [35]*

OS in TNBC and HR+/HER2-

KM-plot for the two subpopulations TNBC and HR+ are shown below:

[redacted]

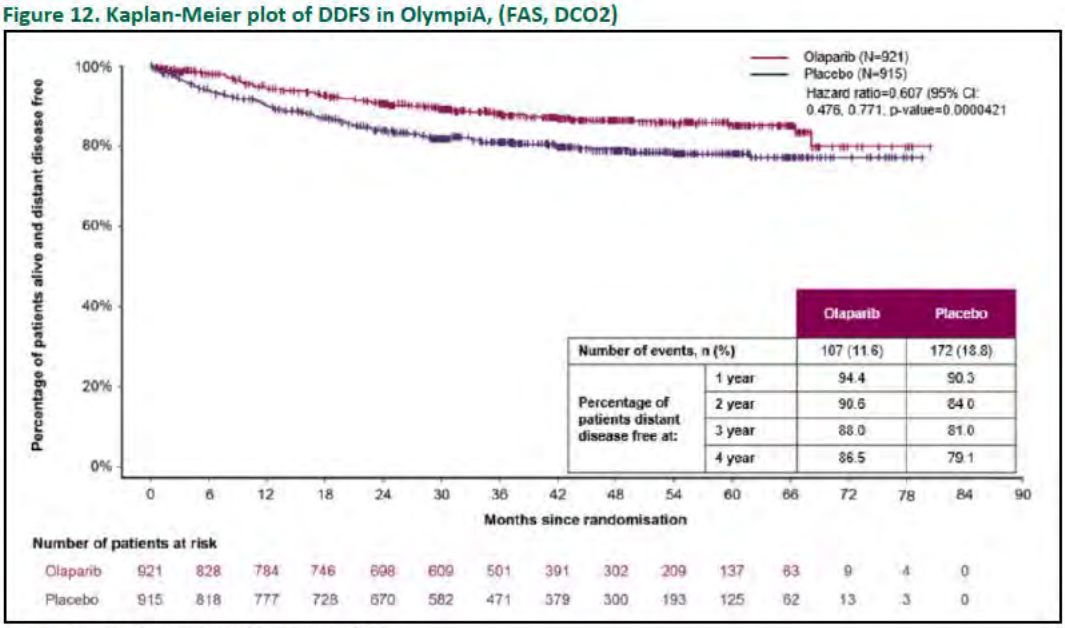
7.1.4 DDFS (DCO2)

Statistically and clinically meaningful benefit of olaparib vs. placebo was demonstrated in the DDFS endpoint at DCO2 with DDFS data at 15.2% maturity. The results of the DDFS analyses were consistent with analyses at DCO1, and the FAS analyses of IDFS [38].

The HR for DDFS favoured olaparib (HR: 0.61; 95% CI: 0.48, 0.77; p=0.0000421), showing a statistically significant 39.3% reduction in risk of distant recurrence for patients treated with olaparib versus placebo (Figure 12). Medians were not reached for DDFS at the first analysis. Based on Kaplan-Meier estimates, there was an increase in the percentage of patients who remained free of distant disease in the olaparib arm at 1 year (94.4%), 2 years (90.6%), 3 years (88.0%) and 4 years (86.5%), compared with 90.3%, 84.0%, 81.0% and 79.1%, respectively, in the placebo arm, stating a difference of 7.0% (95% CI: 3.5, 10.6) at 3 years, and 7.4% (95% Ci: 3.6, 11.3) at 4 years, in DDFS rate. The median duration of follow-up was 3.5 years in both the olaparib arm and the placebo arm [35].

In addition to the analyses of the ITT population, additional subgroup analyses were undertaken based on prior chemotherapy status, prior platinum therapy use, HR status and BRCA mutation type. The subgroup analyses demonstrate a consistent treatment benefit of olaparib over placebo, with results consistent with the analysis of DDFS in the ITT population.

Figure 12. Kaplan-Meier plot of DDFS in OlympiA, (FAS, DCO2)



Footnotes: *DCO2: 12 July 2021.* ***Source:*** *[35]*

7.1.5 Incidence of new primary breast or ovarian cancer (DCO2)

At DCO2, the incidences of contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer, without considering competing risks (Table 12), were generally low (<3%), but slightly numerically lower in the olaparib arm (2.2%, 0.1%, 0.1% and 0%, respectively) compared with the placebo arm (2.4%, 0.7%, 0.4% and 0%, respectively).

Table 12. A summary of all new cancers that occurred post randomisation in OlympiA, DCO2, FAS

Number (%) of patients with	Olaparib (N=921)	Placebo (N=915)
Contralateral invasive breast cancer	20 (2.2)	22 (2.4)
Contralateral non-invasive breast cancer	2 (0.2)	4 (0.4)
New primary ovarian cancer[a]	2 (0.2)	10 (1.1)
Ovarian cancer	1 (0.1)	6 (0.7)
Fallopian tube cancer	1 (0.1)	4 (0.4)
Peritoneal cancer	0 (0)	0 (0)
New primary invasive non-breast non-ovarian malignancies	10 (1.1)	14 (1.5)

Footnotes: *DCO2: 12 July 2021. Summary of new cancers without considering competing risks. This [a]Includes new primary ovarian, fallopian, and peritoneal cancers, without considering competing risks. One patient was captured in the database with ovarian cancer recurrence* ***Source:*** *AstraZeneca Data on File (OlympiA Efficacy Analysis DCO2 [35].*

At DCO2, the incidences of new primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer, without considering

competing risks, were generally low (<3%), but slightly numerically lower in the olaparib arm (2.4%, 0.1%, 0.1%, and 0%, respectively) compared with the placebo arm (2.8%, 0.7%, 0.4%, and 0%, respectively) [35].

7.1.6 Safety (DCO2)

A summary of AEs reported in the OlympiA trial(DCO2) can be found in table 13 . Most patients experienced one or more AE during the study course, with the incidence of AEs observed to be higher in the olaparib arm than the placebo arm; around a quarter of the patients in the olaparib arm had Grade ≥3 AEs (24.5%) compared with 11.3% in the placebo arm. Most AEs observed were non-serious, mild or moderate in severity and did not result in treatment discontinuation. The incidence of AEs leading to death and SAEs were similar between the treatment arms [35].

Despite the observed incidence of AEs, no detrimental impact of treatment on HRQoL was observed in OlympiA. This suggests that the AEs experienced during treatment did not have a negative effect on patient HRQoL. Furthermore, the overall safety and tolerability data of olaparib in OlympiA are generally consistent with the known safety profile of olaparib treatment across the various indications in which it has been studied. [35, 39].

Table 13. Summary of AEs in OlympiA, DCO2 (SAS)

AEs	Olaparib (N=911)	Placebo (N=904)
All Grade AEs, n (%)	836 (91.8)	758 (83.8)
Grade ⩾3 AEs, n (%)	223 (24.5)	102 (11.3)
SAEs, n (%)	79 (8.7)	78 (8.6)
Deaths, n (%)	1 (0.1)	2 (0.2)
Dose interruptions due to AEs, n (%)	286 (31.4)	99 (11.0)
Dose reductions due to AEs, n (%)	213 (23.4)	33 (3.7)
Discontinuations due to AEs, n (%)	98 (10.8)	42 (4.6)

Footnotes: *DCO2: 12 July 2021. Includes AEs with an onset date or that worsens on or after the first dose date and up to and including 30 days following date of last dose of olaparib/placebo. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. CTCAE Version 4.03. MedDRA Version 24.0.* ***Source:*** *AstraZeneca Data on File (OlympiA Safety Analysis DCO2) [35, 40].*

Grade ≥3 AEs(DCO2)

AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 were reported in 24.5% of olaparib-treated patients and 11.3% of placebo-treated patients. In the olaparib arm, the most common Grade ≥3 AEs (reported in >2% of patients) were in the SOCs of blood and lymphatic system disorders (9.4%), investigations (7.7%) and infections and infestations (2.3%). In the placebo arm no SOCs were reported at a frequency of >2% of patients; Grade ≥3 AEs were most common (reported in >1% of patients) in the SOCs of infections and infestations (2.0%), investigations (1.8%) and neoplasms (benign, malignant and unspecified; 1.3%). Anaemia was the only Grade ≥3 AE reported in ≥5% of patients (8.7% of olaparib-treated patients vs 0.3% of placebo-treated patients) [35].

SAEs(DCO2)

SAEs were reported in a similar proportion of patients in both treatment arms, 8.7% in the olaparib arm vs 8.6% in the placebo arm. The most common system organ class (SOC) for reported SAEs in the olaparib arm was blood and lymphatic system disorders and in the placebo arm was neoplasms benign, malignant and unspecified (including cysts and polyps). Anaemia was the most common SAE, although only reported in 15 patients (1.6%) in the olaparib arm and 1 patient (0.1%) in the placebo arm [35].

AEs of special interest(DCO2)

AEs of special interest for olaparib, which are AEs considered to be potential risks associated with olaparib treatment, are summarised in table 14. Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and new primary malignancies were considered AEs of special interest in OlympiA as they may be related to agents that affect DNA repair, including chemotherapy. Pneumonitis has been observed in previous trials of olaparib. At DCO2, the incidence of MDS/AML and leukaemia in olaparib-treated patients was low and in line with the previously reported frequency. Notably, since study onset, MDS/AML has been reclassified as an adverse drug reaction for olaparib and has also been categorised as an important identified risk in the risk management plan. New primary malignancies were reported in 25 patients (2.7%) in the olaparib arm and 45 patients (5.0%) in the placebo arm [35].

A small proportion of pneumonitis and radiation pneumonitis events (9 patients, 1.0%) occurred in the olaparib arm, a similar rate to that reported in the placebo arm (12 patients, 1.3%).

Table 14. AEs of special interest for olaparib , DCO2, SAS

AEs	n (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
MDS/AML and leukaemia	2 (0.2)	3 (0.3)
New primary malignancies[a]	25 (2.7)	45 (5.0)
Pneumonitis and radiation pneumonitis, n (%)	9 (1.0)	12 (1.3)

Footnotes: *DCO2: 12 July 2021. [a]Includes AML and leukaemia, numbers are subject to change upon release of updated CSR due to differences in categorisation.* ***Source:*** *[35]*

Discontinuations

See below Table 15 for overview of dose reduction and discontinuations.

Table 15. Dose interruptions, reductions, and discontinuations due to AEs, interim analysis (SAS)

	N (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
Dose interruption due to AEs[a]	236 (31.4)	103 (11.4)
Dose reduction due to AEs[b]	205 (22.5)	32 (3.5)
Discontinuation due to AEs[c]	90 (9.9)	38 (4.2)

Footnotes: *DCO1: 27 March 2020. [a]Dose interruption is an AE leading to temporary discontinuation of olaparib or placebo. [b]Dose reduction is an AE leading to dose reduction of olaparib or placebo. Patients may have had more than one AE leading to dose reduction. [c]Olaparib or placebo permanently stopped. CTCAE Version 4.03. MedDRA Version 22.1 [35].*

7.1.7 HRQoL and Patient Reported Outcomes (DCO2)

HRQoL instruments in OlympiA:

- **FACIT-Fatigue:** The FACIT-Fatigue is a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function. The score ranges from 0 to 52 with higher scores indicating less fatigue; a score **difference of 3 points** is defined as a clinically meaningful change.

- **EORTC QLQ-C30:** The EORTC QLQ-C30 is a questionnaire that assesses the quality of life of cancer patients; as well as assessing global health status and HRQoL, it assesses important functioning domains (e.g. physical, emotional and role) and common cancer symptoms (e.g. fatigue, pain, nausea/vomiting and appetite loss). All EORTC QLQ-C30 domains range in score from 0 to 100; higher scores on HRQoL and functioning scales indicate better HRQoL/functioning, whereas higher scores on symptom scales indicates a worse symptom severity. A score **difference of 10 points** is defined as a clinically meaningful change.

At DCO2, baseline compliance rates for the FACIT-Fatigue were high (99.4% for olaparib; 99.7% for placebo) and decreased to >80% at 6 and 12 months, >70% at 18 months and >65% at 24 months in both the olaparib and placebo arms.

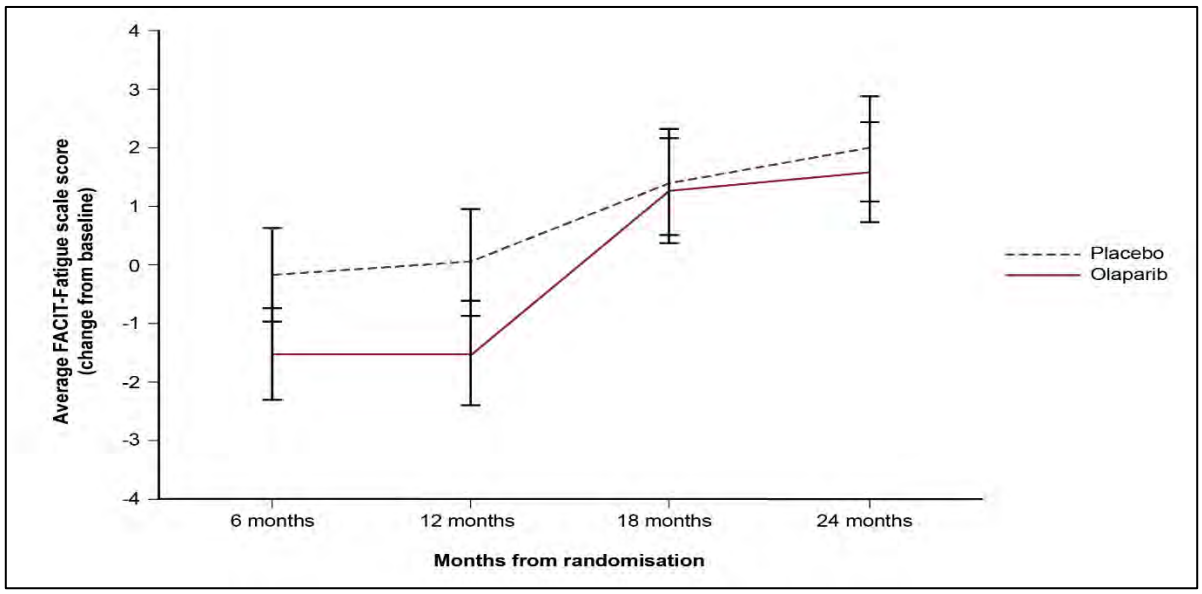
Mean baseline FACIT-Fatigue scores were comparable between treatment arms for patients who had received prior neoadjuvant treatment and prior adjuvant treatment (Table 15). For both the prior neoadjuvant and adjuvant treatment subgroups, patients treated with olaparib experienced small, non-clinically meaningful decreases from baseline in mean FACIT-Fatigue scores after 6 and 12 months of treatment and scores for the placebo arm generally remained stable; small differences in adjusted least squared (LS) mean change scores between the olaparib and placebo arms were observed at 6 and 12 months for both the prior neoadjuvant (-1.3 at 6 months; p=0.022 [nominal], -1.6 at 12 months; p=0.017 [nominal]) and adjuvant (-1.3 at 6 months; p=0.017 [nominal], -1.3 at 12 months; p=0.025 [nominal]) treatment groups.
At Months 18 and 24, mean FACIT-Fatigue scores for patients in the olaparib arm returned to baseline for both the prior neoadjuvant and adjuvant treatment groups (Figure 13 and Figure 14). Adjusted LS mean change from baseline scores were comparable for the olaparib and placebo arms, with small increases observed in both the prior neoadjuvant and adjuvant treatment groups, and with no clinically meaningful differences observed between treatment arms.

Table 15. Change from baseline for FACIT-Fatigue score at 6 and 12 months in OlympiA (MMRM), DCO2 (PRO analysis set)

Parameter	Baseline score, mean (SD)	6 months		12 months	
		LS Mean	95% CI	LS Mean	95% CI
Patients who had previously completed neoadjuvant chemotherapy					
Olaparib (n=373)	39.4 (10.42)	-1.5	-2.3, -0.7	-1.4	-2.3, -0.5
Placebo (n=356)	39.7 (9.51)	-0.2	-1.0, 0.6	0.1	-0.8, 1.0
Difference	–	-1.3	-2.4, -0.2	-1.6	-2.8, -0.3
p-value	–	0.022		0.017	
Patients who had previously completed adjuvant chemotherapy					
Olaparib (n=375)	40.9 (9.03)	-0.7	-1.4, 0.1	-0.8	-1.6, 0.0
Placebo (n=403)	40.7 (8.83)	0.6	-0.1, 1.3	0.5	-0.3, 1.3
Difference	–	-1.3	-2.3, -0.2	-1.3	-2.4, -0.2
p-value	–	0.017		0.025	

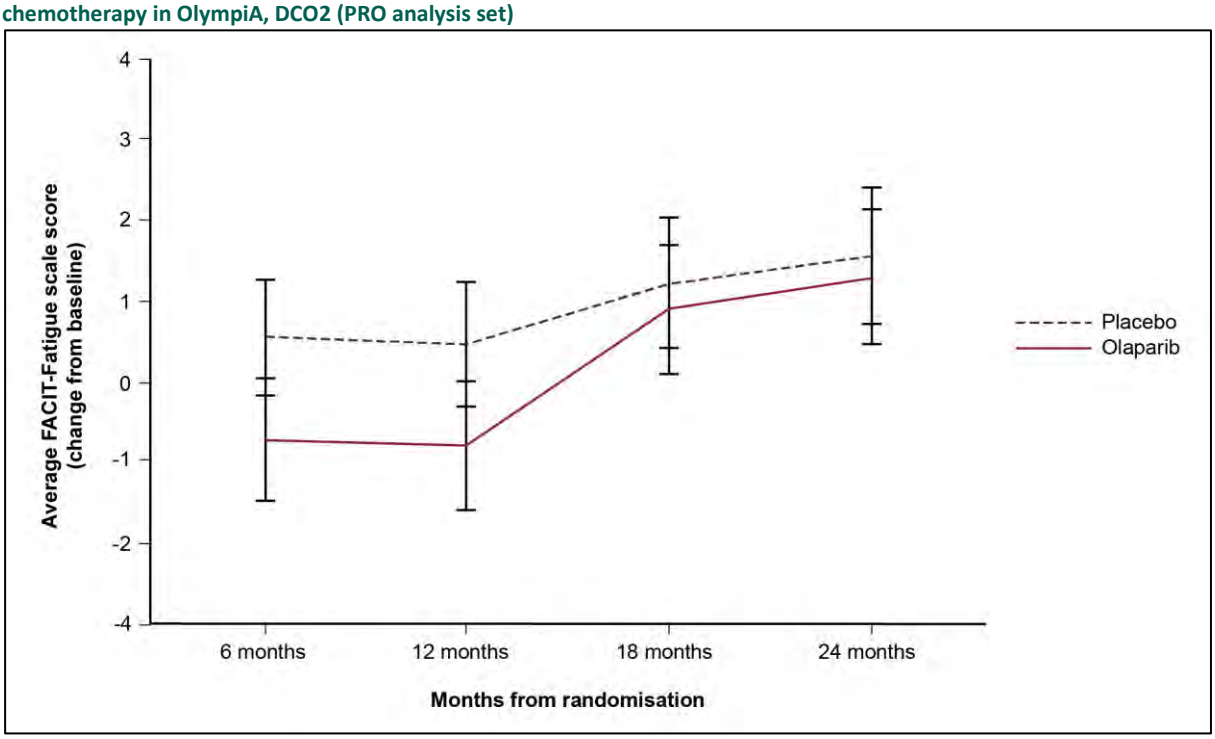
Footnotes: *DCO2: 12 July 2021. Only patients with an evaluable baseline form were included. Adjusted LS mean changes, p-values (2-sided) and 95% CI were obtained from MMRM analysis of the change from baseline. The model included treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction. FACIT-Fatigue score ranges from 0 to 52 with higher scores indicating less fatigue. Difference was the value for olaparib minus placebo.* ***Source:*** *AstraZeneca Data on File (OlympiA PRO Analysis DCO2) [35, 41].*

Figure 13. Mean change from baseline of FACIT-Fatigue scores in patients who had received prior neoadjuvant chemotherapy in OlympiA, DCO2 (PRO analysis set)



Footnotes: *DCO2: 12 July 2021. FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue. Adjusted least-square mean changes and 95% CI are obtained from MMRM analysis of the change from baseline. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.*
Source: *AstraZeneca Data on File (OlympiA PRO Analysis DCO2 [41])*

Figure 14. Mean change from baseline of FACIT-Fatigue scores in patients who had received prior adjuvant chemotherapy in OlympiA, DCO2 (PRO analysis set)



Footnotes: *DCO2: 12 July 2021. FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue. Adjusted least-square mean changes and 95% CI are obtained from MMRM analysis of the change from baseline. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.* ***Source:*** *AstraZeneca Data on File (OlympiA PRO Analysis DCO2 [41]).*

Altogether, the patient reported outcomes data shows that olaparib does not negatively impact long-term HRQoL in patients with gBRCAm, high risk, HER2-negative, early breast cancer [42].

Summary of clinical and safety section

The OlympiA trial shows that one-year of adjuvant olaparib significantly reduce the risk of recurrence and prevent progression to metastatic disease among patients with g*BRCA*m, high-risk, HER2-negative, early breast cancer, whilst maintaining patient HRQoL. Moreover, beside of improving this latter mentioned IDFS and DDFS with similar effect in size, olaparib also significantly improved OS with an acceptable adverse event profile and no evidence of excess MDS or AML.

8. Other trials of Olaparib in HER2-negative early breast cancer

A full summary of clinical trials of olaparib conducted in HER2-negative, early breast cancer patient populations can be found in Table 16.

Table 16. Summary of clinical trials in HER2-negative, early breast cancer

<table>
<tr><th>Trial summary</th><th>Intervention(s) assessed</th><th>Efficacy results</th><th>Safety results</th><th>Reference</th></tr>
<tr>
<td><u>OlympiA</u>
NCT02032823
Phase III, randomised, parallel group, double-blind study, in gBRCAm, HER2-negative, early breast cancer
N=1,836

OS update:
Geyer CE Jr,; OlympiA. Ann Oncol. 2022 Dec;33(12):1250-1268. [35]</td>
<td>Arm 1: Olaparib 300 mg BID (up to a maximum of 12 months)
Arm 2: Placebo BID (up to a maximum of 12 months)</td>
<td>Summary of IDFS, OS and DDFS events, FAS
<table>
<tr><th></th><th>Olaparib (n=921)</th><th>Placebo (n=915)</th></tr>
<tr><td>IDFS events, n %</td><td>106 (11.5)</td><td>178 (19.5)</td></tr>
<tr><td>DDFS events, n %</td><td>89 (9.7)</td><td>152 (16.6)</td></tr>
<tr><td>OS events, n %</td><td>59 (6.4)</td><td>86 (9.4)</td></tr>
</table>
</td>
<td>Summary of AEs in OlympiA, SAS
<table>
<tr><th></th><th>Olaparib (n=911)</th><th>Placebo (n=904)</th></tr>
<tr><td>Any AE, n %</td><td>835 (91.7)</td><td>753 (83.3)</td></tr>
<tr><td>Any Grade ≥3 AE, n %</td><td>221 (24.3)</td><td>102 (11.3)</td></tr>
<tr><td>Any AE leading to discontinuation, n %</td><td>90 (9.9)</td><td>38 (4.2)</td></tr>
</table>
</td>
<td>AstraZeneca Data on File (OlympiA CSP) [30]; AstraZeneca Data on File (OlympiA CSR) [36].</td>
</tr>
<tr>
<td>GeparOLA
NCT02789332
Phase II, randomised, parallel group, open label study in HER2-negative, early breast cancer with homologous recombination deficiency
N=107</td>
<td>Arm 1:
Paclitaxel with carboplatin 80 mg/m² iv weekly in combination with carboplatin AUC 2 iv weekly for 12 weeks followed by 4 cycles of epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² either every 3 or every 2 weeks followed by surgery)
Arm 2: Paclitaxel with olaparib (paclitaxel 80 mg/m² iv weekly in combination with olaparib tablets 100 mg twice daily for 12 weeks followed by 4 cycles of epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² either</td>
<td>pCR results stratified by HR status and patient age
<table>
<tr><th></th><th>Olaparib+ Paclitaxel pCR rate (90%CI)</th><th>Carboplatin +Paclitaxel pCR rate (90%CI)</th></tr>
<tr><td>HR-positive patients (n = 29)</td><td>52.6% (32.0%, 72.6%)</td><td>20.0% (3.7%, 50.7%)</td></tr>
<tr><td>HR-negative patients (n = 77)</td><td>56.0% (43.4%, 68.0%)</td><td>59.3% (41.7%, 75.2%)</td></tr>
<tr><td>Patients aged < 40 (n = 32)</td><td>76.2% (56.3%, 90.1%)</td><td>45.5% (20.0%, 72.9%)</td></tr>
<tr><td>Patients aged ≥ 40 (n = 74)</td><td>45.8% (33.4%, 58.6%)</td><td>50.0% (32.7%, 67.3%)</td></tr>
</table>
</td>
<td>Summary of AEs in GeparOLA
<table>
<tr><th></th><th>Olaparib+ Paclitaxel (n=69)</th><th>Carboplatin +Paclitaxel (n=37)</th></tr>
<tr><td>Any AE, n %</td><td>68 (98.6)</td><td>37 (100)</td></tr>
<tr><td>Any Grade ≥3 AE, n %</td><td>36 (52.2)</td><td>33 (89.2)</td></tr>
</table>
</td>
<td>Fasching et al., 2019 [43]
ClinicalTrials.gov 2020 [44]</td>
</tr>
</table>

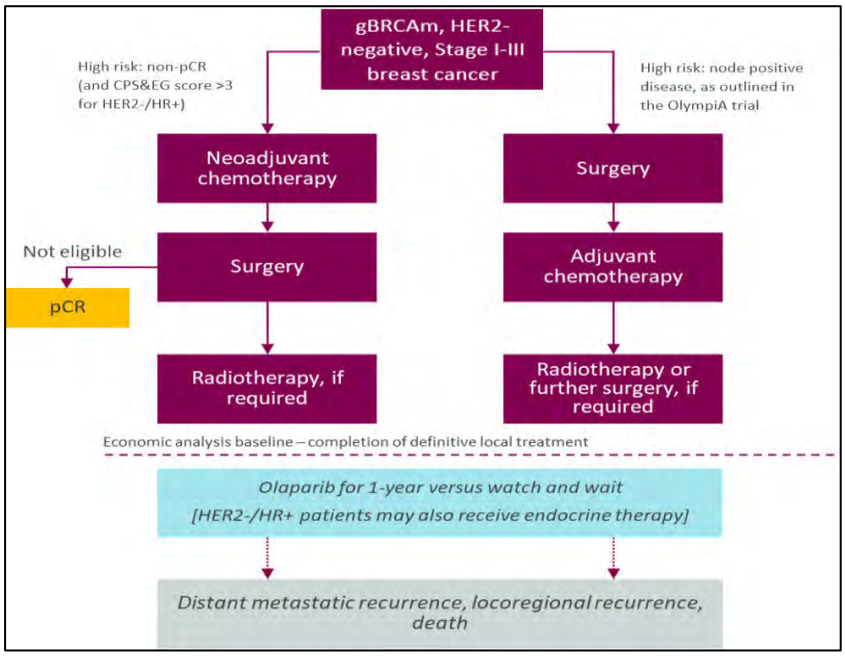
	every 3 or every 2 weeks followed by surgery)			
PARTNER NCT03150576 Phase II/III, randomised, parallel group, open label study, in TNBC and/or g*BRCA*m breast cancer (neoadjuvant setting) N=527	**Arm 1:** Paclitaxel 80mg/m2 day 1, 8 & 15, every 3 weeks, carboplatin AUC 5 day 1, every 3 weeks **Arm 2:** Paclitaxel 80mg/m2 on days 1, 8 & 15 every 3 weeks, carboplatin AUC 5 Day 1, every 3 weeks, olaparib oral 150mg BID, day -2 to day 10 every 3 weeks **Arm 3:** Paclitaxel 80mg/m2 on days 1, 8 & 15 every 3 weeks, carboplatin AUC 5 day 1, every 3 weeks, olaparib oral 150mg twice daily, day 3 to day 14 every 3 weeks	No info	No info	Abraham et al., 2018 [45] ClinicalTrials.gov 2017 [46]
PHOENIX DDR/Anti-PD-L1 (NCT03740893) Phase IIa, randomised, parallel group, open label study in non-metastatic TNBC, neoadjuvant resistant breast cancer N=81	**Arm 1:** Standard care reference cohort **Arm 2:** Olaparib 300 mg oral BID (up to 12 months) **Arm 3:** AZD6738 160 mg oral BID (up to 12 months) **Arm 4:** Durvalumab 1500 mg IV (once every month for up to 12 months)	No info	No info	ClinicalTrials.gov 2020 [47]

9. Health economic analysis

9.1 Model

A cost-effectiveness (CE) model has been developed to estimate the costs and health outcomes of adjuvant olaparib vs. standard of care in patients with gBRCAm, high risk HER2-negative early breast cancer (eBC) in Denmark. In the base case analysis, the CE model assesses the cost-effectiveness of adjuvant olaparib versus 'watch and wait' (proxied by the placebo arm in the OlympiA trial) in patients that have completed definitive local treatment including neoadjuvant or adjuvant chemotherapy. The treatment pathway captured in the model is represented in Figure 15. A discussion on the most relevant comparator for the health-economic analysis is provided in section 5.2.2.

Figure 15. Treatment pathway in the CE model



For the base case analysis, the incremental cost-effectiveness ratio for the HER2-negative ITT-population was estimated from the weighted average of the incremental costs and effectiveness of treatment in the HER2-/HR+ and TNBC subgroups, following the methods of Murphy et al [48].

The long-term patterns of recurrence have been observed to differ between the HER2-/HR+ and TNBC subgroups, and therefore the cost-effectiveness is assessed separately in the two subgroups. For patients with TNBC the risk of recurrence is highest during the first 5 years after diagnosis, with a significant decrease and plateauing of the recurrence rate thereafter [49-52]. In contrast, patients with HER2-/HR+ disease remain at a constant risk of recurrence for at least 20 years after diagnosis [52, 53]. An illustration of the contrasting risk patterns is provided in Figure 16 adapted from Sopik et al [52]. These graphs show the annual rate of disease recurrence following diagnosis of invasive breast cancer in 2312 patients treated at Women's College hospital, Toronto, Canada. In this study, all distant recurrences for TNBC (Figure 16A) occurred in the first six years following diagnosis, whilst distant recurrences for HR+ disease (Figure 16B) occurred at an approximately constant rate throughout the 20-year follow-up. The difference in recurrence patterns were also validated by two Danish breast cancer experts, who confirmed that recurrence is rare for TNBC patients after 5 years, while HER2-/HR+ patients have a lifetime risk of recurrence [54].

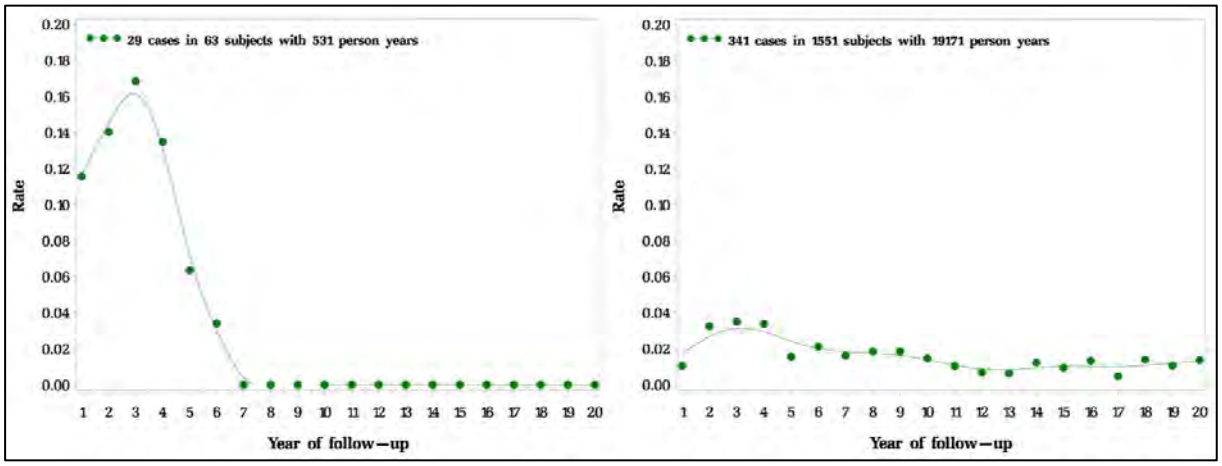
In the OlympiA study, there was no statistical evidence of differential treatment effect by HR subgroup, with the benefit of olaparib being observed irrespective of HR status [2]. Therefore, we consider the gBRCAm HER2-negative high risk population (i.e. OlympiA ITT population) as one unique group. Whether the risk of recurrence patterns observed by HR status are similar between the overall HER2-negative population and the high risk HER2-negative gBRCAm subgroup is unknown. It is possible that gBRCAm HER2-/HR+ patients are more similar to TNBC patients, but no long-term data for HER2-negative gBRCAm patients could be identified in the literature.

Therefore, it was considered relevant to take into account the evidence on long-term recurrence patterns available in the literature for the TNBC and HER2-/HR+ subgroups separately.

When modelled, the difference in baseline risk of recurrence after diagnosis between TNBC and HER2-/HR+ disease is expected to impact on the long-term costs and health outcomes of adjuvant treatment. This warrants their consideration as separate subgroups when modelling the risk of recurrence after diagnosis in the CE model, while the rest of the clinical parameters can be modelled as one population.

Figure 16. Annual rate of distant recurrence over time (in years) following diagnosis of invasive breast cancer among patients with TNBC (A) and HER2-/HR+ (B) disease

A B

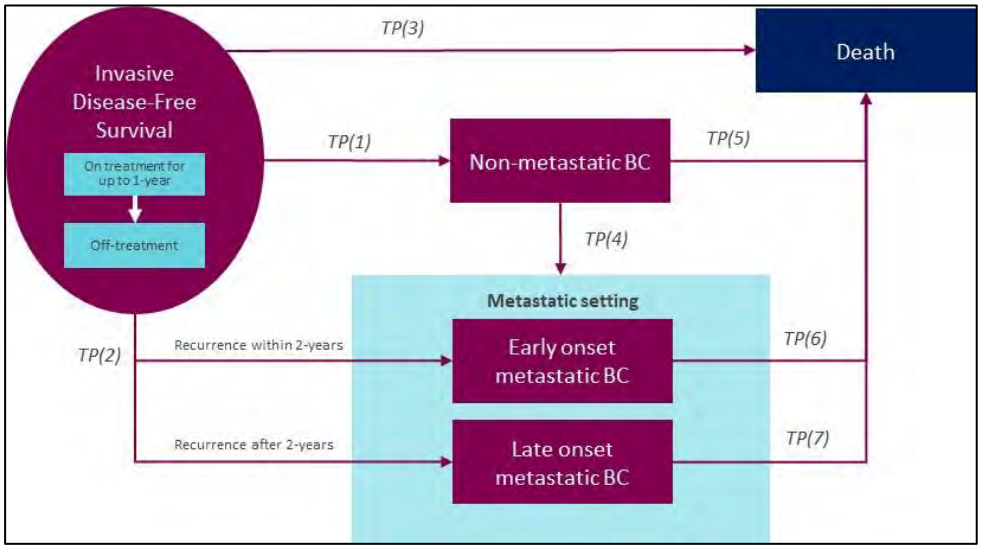


***Source**: [52]*

9.2 Model structure

A five-state semi-Markov state transition model was developed in Microsoft Excel®. The five health states in the model are 'IDFS', 'Non-metastatic breast cancer, 'early onset mBC', 'late onset mBC' and 'Death'. A schematic of the model state structure is presented in Figure 17.

Figure 17. Schematic of model diagram



Abbreviation: TP: transition probability. The TP(X) refers to the transition number in the Excel model.

The model is 'Semi-Markov' as the transition probabilities between states can vary based on the time-spent in each health state. In the Excel model, this is modelled using *tunnel* states that track the time spent in each state over time.

The health states are defined as follows:

- **IDFS – invasive disease-free survival:** A state where patients are free of disease recurrence (metastatic or non-metastatic disease) having previously completed local treatment and adjuvant or neoadjuvant chemotherapy
- **Non-metastatic breast cancer:** A state where patients have experienced local or regional ipsilateral recurrence or have contralateral invasive breast cancer. Patients are assumed to undergo further surgery, radiotherapy and/or drug therapy to treat the recurrence of disease.
- **Early onset metastatic breast cancer:** A state where patients have experienced distant recurrence during the first 2-years after completing local treatment (i.e., recurrence during the first 2-years of the time horizon). Following the definition of distant disease-free survival in OlympiA, distant recurrence includes new primary non-breast invasive malignancies as well as CNS and non-CNS distant metastatic breast cancers. As metastatic breast cancer is considered incurable, all patients that enter this state are assumed to receive palliative surgery, radiotherapy and/or drug therapy.
- **Late onset metastatic breast cancer:** A state where patients have experienced a distant recurrence event beyond the first 2-years after completing local treatment (i.e., recurrence after the first 2-years of the time horizon). As with early onset metastatic breast cancer, patients that enter the late onset state are assumed to receive palliative surgery, radiotherapy and/or drug therapy.
- **Death:** Absorbing state for deaths from any cause

The classifications of non-metastatic and metastatic recurrence closely follow the endpoint definitions of IDFS (primary) and DDFS (secondary) in OlympiA [2]. These endpoints were based on the standardised definitions for disease- and distant-disease -free survival as outlined in the STEEP criteria [7, 55]. The events leading to the non-metastatic and metastatic states are considered to incur similar treatment and management costs, and result in similar levels of health-related quality of life and survival burden.

In total, there are seven possible transitions between health states in the model, as shown in Figure 17 above and outlined in Table 71 in Appendix G. The modelled treatment pathway is described below. Further detail on the estimation of transition probabilities is provided in section 9.4 and Appendix G.

9.2.1 Disease-free survival

All patients enter the model in the IDFS health state having completed local treatment and neoadjuvant or adjuvant chemotherapy. In the intervention arm, patients immediately initiate 1-year treatment with adjuvant olaparib. After discontinuation or completion of treatment, patients that remain free of disease recurrence undergo watch and wait, comprising routine follow-up and screening for recurrence. In the comparator arm, patients undergo watch and wait from model entry to disease recurrence or death. In both arms, patients with HER2-/HR+ disease may also receive adjuvant endocrine therapy alongside olaparib or watch and wait, until disease recurrence, death or for a fixed maximum duration (6.8 years in the base case[1]).

From the IDFS state, patients may experience one of three events:

- TP1: develop a locoregional recurrence or contralateral breast cancer and enter the non-metastatic breast cancer state
- TP2: develop a distant metastatic recurrence or second primary non-breast invasive malignancy and enter the disease states for metastatic breast cancer
- TP3: experience death from any cause prior to a non-metastatic or metastatic disease recurrence

These events cover the breadth of outcomes considered in the primary endpoint of IDFS in OlympiA. Both recurrence events and death are modelled as an irreversible process such that patients are unable to return to IDFS. The treatment pathways after developing metastatic or non-metastatic breast cancer are described below.

9.2.2 Metastatic recurrence pathway

Patients that develop a distant metastatic recurrence in the first 2-years of the time horizon are assumed to enter the 'early onset metastatic breast cancer' state. After 2-years, patients that develop a distant metastatic recurrence enter the 'late onset metastatic recurrence state'. Patients can enter the metastatic state from the disease-free state or the non-metastatic state. From the metastatic states, patients may transition to the death state (TP6 and TP7).

The risk of death after metastatic cancer was assumed to differ based on the timing of recurrence, defined as 'early' (TP6) and 'late' (TP7) onset. This is to reflect that patients with early recurrence tend to have more aggressive disease that is less responsive to subsequent palliative treatment than patients who experience late recurrence and are likely to have more indolent disease. This approach is supported by evidence from the clinical literature for HER2-negative patients (Table 17).

The model includes an option to set the time point for 'early' versus 'late' onset metastatic breast cancer to 1, 2 (base case), or 3 years. In the base case, the timing of early and late recurrence was based on the 2-year definition. This time point was selected based on literature data showing consistently poor post-recurrence survival in patients that recur within 2-years (Table 17). The alternative time points of 1 and 3 years were considered in sensitivity analysis.

For both 'early' and 'late' onset metastatic breast cancer, the treatment pathway is captured by a single health state, as opposed to multiple states reflecting lines of treatment or progression states within metastatic disease. This simplified approach to the modelling of metastatic breast cancer was necessary to use OlympiA data to inform the risk of death for 'early onset' metastatic breast cancer. This is because information on progression status after distant recurrence was not available from OlympiA or routinely reported in the literature, thus preventing the use of a more complex, multi-state model for metastatic disease.

[1] The duration of endocrine therapy is user definable in the model.

Further, the inclusion of additional health states of progression-free and progressed disease for metastatic cancer would not materially impact on results as the poor prognosis of patients with BRCAm metastatic breast cancer (median post-recurrence survival of 9.8-14.3 months in OlympiA (data on file), see [redacted] in section 3 of Appendix G) limits the periods spent in pre- and post-progression states. Where possible, the economic and health state utility values assigned to the metastatic disease states were adjusted to reflect the costs and outcomes of treatment for both the pre- and post-progression stages of metastatic disease (e.g., including the modelling of drug costs for first and subsequent lines).

9.2.3 Non-metastatic recurrence pathway

Patients that enter the non-metastatic breast cancer health state remain in this state until the onset of distant metastatic breast cancer (TP4) or death (TP5). As described above, patients that develop a distant metastatic recurrence in the first 2-years of the time horizon enter the 'early onset' metastatic breast cancer state and those that have recurrence after 2-years enter the 'late onset' state. All patients that enter the non-metastatic recurrence state are assumed to be at risk of distant recurrence or death immediately upon entering the state.

In OlympiA, the post-recurrent survival of patients with non-metastatic disease suggests that BRCA HER2-negative patients are at a relatively high - and immediate - risk of developing metastatic breast cancer or death after a locoregional event (see [redacted] section 2 of Appendix G). This is further supported by data on the proportion of patients undergoing surgery after locoregional recurrence (50 of 81 had surgery, 61.7% (data on file), which suggests that not all patients are eligible to receive curative treatment followed by adjuvant chemotherapy. Because of this, the OlympiA model excludes the state of remission and allows for the development of distant metastatic disease upon entering the non-metastatic disease state. The potential for long-term remission amongst patients with non-metastatic disease that received potentially curative surgery was captured by the survival rates from OlympiA.

Table 17. Summary of literature evidence on the impact of time to recurrence on survival after diagnosis of metastatic

Study	Population	Definition – early vs. late	Post-recurrence survival for early vs. late
McKenzie et al [56] Prospective outcomes in sporadic vs. hereditary breast cancer (POSH) cohort study	Young women (aged < 40 years) with initially localised disease from 127 hospitals in the United Kingdom	Recurrence time: <24 months 24-60 months 60 months plus	2-year post-recurrence survival <24 months: 25% 24-60 months: 43% 60+ months: 49%
Lobbezoo et al [57]	Consecutive patients diagnosed with metastatic breast cancer from 8 hospitals in the Netherlands	Metastatic free interval <2 years >2 years	Median survival from recurrence <2 years: 9.1 months >2 years: 27.9 months
Dawood et al [58]	A cohort of female patients diagnosed from 1992 to 2007 with either de novo stage IV or relapsed breast cancer at the Department of Breast Medical Oncology of The University of Texas M. D. Anderson Cancer Center	Disease-free interval <6 months 6-24 months 2-5 years 5 years plus	Median survival from recurrence <6 months: 17.4 months 6-24 months: 17.3 months 2-5 years: 30.4 months 5 years plus: 47.4 months

9.3 Perspective of analysis, discounting, time horizon and cycle length

The base-case analysis includes both direct treatment and healthcare utilization costs as well as patient time and transportation costs associated with the treatment in accordance with a limited societal perspective.

In the base case, the costs and health outcomes (life years and quality-adjusted life years) of treatment were modelled over a lifetime horizon of 57 years (based on the time from the baseline average age of 43 years to 100 years old) and discounted at an annualised rate of 3.5% up to 35 years and 2.5% thereafter, as per the guidelines from the Danish Ministry of Finance.

The use of a lifetime horizon ensures that all relevant differences in the costs and health outcomes of adjuvant olaparib and watch and wait are captured. For scenario analyses, the model provides the option to alter the discount rates and time horizon used in the analysis.

The model adopts a one-month cycle length, which is equivalent to 30.4 days (365.25 days divided by 12 calendar months). This cycle length is consistent with the recommended frequency of monitoring for haematological toxicities over the 1-year olaparib treatment and the expected shortest period between follow-up visits.

The life table approach is used to estimate half-cycle corrected state occupancy over time. The half-cycle correction is used in calculating most outcomes and costs in the model. The exceptions include any factors modelled as one-off costs (e.g., subsequent treatment and terminal disease costs) or outcome adjustments (e.g., adverse events), and the costs of adjuvant olaparib. The costs of 1-year olaparib treatment are modelled on the proportion of patients on drug at the start of each month to capture the costs of unused tablets in patients that discontinue treatment before the end of each monthly cycle.

9.4 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

9.4.1 Presentation of input data used in the model and how they were obtained

The primary data source for the CE model is the OlympiA trial [2, 7]. The statistical analysis of OlympiA was conducted on patient-level data from the second interim OS analysis of the OlympiA trial (DCO2, 12th July 2021).

In addition to the OlympiA trial data, the model uses data from external studies in BRCA mutated HER2-negative metastatic breast cancer to inform the modelling of survival from the 'late onset' metastatic breast cancer state. These include data from the OlympiAD (olaparib versus single chemotherapy) trial [59, 60], the IMpassion130 trial of atezolizumab in metastatic TNBC [61], and a real-world study of CDK 4/6 inhibitor treatment [62]. These external data sets are used as data to assess survival after 'late onset' metastatic breast cancer in OlympiA are not yet mature enough (median follow-up for IDFS was approximately 3.5 years at DCO2).

To support the clinical plausibility of model extrapolations, the model further utilizes all-cause mortality life table data from Statistics Denmark to constrain the risk of death from any state to be greater than or equal to the background risk of death by age [63]. The Danish lifetables are also used to inform the transition from IDFS to death, which could not be modelled using OlympiA data due to low event numbers (n=2 for olaparib and n=0 placebo). The background mortality risk is matched on the age and gender characteristics of the OlympiA trial population. The mortality risk is further adjusted for the excess mortality associated with germline BRCA mutations [64]. Further detail is provided in Appendix G.

With the Semi-Markov state transition approach, the overall survival status of the cohort is modelled based on the transitions between states [65]. Whilst mortality data from OlympiA is used to inform the state transition

risks from the 'non-metastatic' and 'early mBC' states to death (e.g., time from distant metastatic breast cancer to death), the secondary endpoint of OS is not used as a clinical input to the model. The OS endpoint is instead used to validate the model predictions, and to ensure that the model accurately estimates the time from randomisation to death in OlympiA. Further detail on the choice of modelling approach is provided in section 8.2.

Table 71 in Appendix G details the data sources used for each transition in the model. Further details regarding the data sources and the methodology used for each model transition are also presented in Appendix G.

9.4.2 Modelling of subgroup outcomes

The model evaluates the cost-effectiveness of adjuvant olaparib vs. watch and wait in the ITT-HER2-negative population, and the prespecified and stratified subgroups of HER2-/HR+ and TNBC. **For the base case analysis, we focus on the study subgroups, which are combined to provide estimates of cost-effectiveness in the ITT-HER2-negative population (see section 9.1).** The use of subgroup results to inform the base case ensures greater flexibility in capturing the difference in the long-term risk of recurrence for HER2-/HR+ and TNBC patients, as described previously in section 9.1.

For the base case, the IDFS for the TNBC population was modelled using subgroup data from OlympiA, whilst the IDFS of patients with HER2-/HR+ was modelled using data from the ITT population. The option to model the efficacy of olaparib and watch and wait for the TNBC population on IDFS using survival models fitted to the ITT population of OlympiA as proxy for the subgroup results was considered in sensitivity analysis.

As the TNBC subgroup of OlympiA represents approximately 82% of the ITT population, the event numbers and data were of sufficient maturity to support subgroup modelling for this population. The use of ITT data in place of subgroup data for HER2-/HR+ to model IDFS is justified on the following grounds:

- At the interim OS analysis (DCO2), it was not possible to reliably estimate the survival of patients with HER2-/HR+ in OlympiA using conventional subgroup analysis (i.e., fitting models to a subset of the study) due to the limited number of IDFS events observed in this subgroup (n=25 for olaparib vs. n=34 for placebo) [2, 7]. The relatively small number of events observed for this population greatly limits the scope of statistical analysis for IDFS, and post-recurrence survival, for input to the model.
- In OlympiA, there was no statistical evidence of differential treatment effect by hormone receptor subgroup, with the benefit of olaparib being observed irrespective of hormone receptor status [2]. Similar trends were observed in the phase 3 trials of PARP inhibitor treatment in the later line setting of BRCA mutated metastatic breast cancer, where the comparative efficacy of PARP treatment (including olaparib) versus chemotherapy was observed across TNBC and HER2-/HR+ subgroups [66]. These data support the use of the primary ITT analysis to model the relative efficacy of olaparib in the HER2-/HR+ population
- The *baseline* (i.e., in the placebo arm) survival rates for IDFS in the HER2-/HR+ and TNBC subgroups of OlympiA were similar across the duration of study follow-up (see Table 18). These data support the use of the primary ITT analysis to model the baseline efficacy of placebo in the HER2-/HR+ populations
- A limitation of using ITT data as proxy for HER2-/HR+ population is that in general TNBC typically has worse prognosis than HER2-/HR+ and ITT will reflect TNBC more than HER2-/HR+. However, this is a high-risk population and hence TNBC and HER2-/HR+ will be more similar than for a general population with these histological types.

The non-metastatic recurrence pathway (TP4 and TP5) and the transition probabilities for 'early onset' metastatic breast cancer to death (TP6) were modelled using ITT data from OlympiA.

[redacted]

[redacted]

9.4.3 Relationship between the clinical documentation, data used in the model and Danish clinical practice

9.4.3.1 Patient population

The patient populations in the CE model are based on the ITT, and the HR+ and TNBC subgroups of the OlympiA study (Table 19) [2]. These populations provide the primary clinical data for the CE model, and are used to model outcomes for the ITT, and the HER2-/HR+ and TNBC populations (see Appendix C for more details about baseline characteristics).

In general, the OlympiA study population is considered representative of patients that will be eligible for adjuvant olaparib in the Danish clinical practice. The cost-effectiveness of olaparib in the HER2-negative intention to treat (ITT)-population is modelled based on a weighted average of incremental costs and effectiveness in the subgroups of HER2-/HR+ and TNBC, to take differences in long-term recurrence risks between TNBC and HER2-/HR+ patients into account.

Table 19. Baseline characteristics of patients in the CE model

Patient Characteristics	Olaparib (N=921)	Placebo/'watch and wait' (N=915)
Age (years)		
Mean (SD)	43.0 (9.82)	43.6 (10.12)
Median (range)	42.0 (22–77)	43.0 (24–78)
Sex, n (%)		
Female	919 (99.8)	911 (99.6)
Male	2 (0.2)	4 (0.4)
HR status, n (%)		
TNBC	753 (81.8)	758 (82.8)
ER and/or PR-positive, HER2-negative	168 (18.2)	157 (17.2)
Prior chemotherapy, n (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)

Source: [2]

9.4.3.2 Intervention

The intervention in the model is 1-year adjuvant treatment with olaparib tablets at a dose of 300mg twice daily. Treatment is administered until recurrence of disease, tolerability issues, or adverse events or until completion of the 1-year treatment period. After discontinuation or completion of treatment, patients are assumed to undergo watch and wait until recurrence.

Table 20. Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	The recommended dose of Lynparza is 300 mg (two 150 mg tablets) taken twice daily, equivalent to a total daily dose of 600 mg.	600 mg according to the recommended daily dose	Expected to follow indicated dose
Length of treatment (time on treatment) (mean/median)	12 months	12 months	12 months
Criteria for discontinuation	Patients can continue treatment until radiological disease progression, unacceptable toxicity or for up to 52 weeks	Time to treatment discontinuation in trial	SmPC expected to be followed in Denmark , hence treatment until radiological disease progression, unacceptable toxicity or for up to 52 weeks
The pharmaceutical's position in Danish clinical practice	New neo/adjuvant treatment option for BRCAm-positive HER2-negative patients		

9.4.3.3 Comparators

The comparator to olaparib in the health economic evaluation is watch and wait, as olaparib is currently the first and only medicine specifically targeting gBRCAm in early breast cancer.

Other treatment options in the adjuvant setting are adjuvant abemaciclib (high risk HER2-/HR+), (neo)adjuvant pembrolizumab (TNBC) and adjuvant capecitabine (see section 5.2), which however have no documented evidence in a gBRCAm early breast cancer patient population. Therefore, neither of these treatments were considered to be relevant comparators for this analysis.

9.4.3.4 Relative efficacy outcomes

The main efficacy outcomes from the OlympiA trial and how they are used in the model are summarized in Table 21. The clinical relevance of these enpdoints is summarized in Table 22. The efficacy estimations and parametrization are covered in more detail in section 9.5 and Appendix G.

Table 21. Summary of text regarding relative efficacy outcomes

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study (IDFS)	IDFS curves from the OlympiA study	IDFS curves from OlympiA used for the modelling
Secondary endpoint (endpoint's name)	OS	OS from OlympiA used only for validation purposes

Table 22. Summary of text regarding relevance of clinical efficacy outcomes

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study (endpoint's name)	IDFS curves from the OlympiA study	Relevant endpoint for patients in Denmark	Definition of IDFS relevant for Danish clinical practice
Secondary endpoint (endpoint's name)	OS from OlympiA	Relevant endpoint for patients in Denmark	Used for validation purposes

9.4.3.5 Adverse reaction outcomes

Adverse reaction outcomes are covered in section 7.1.7.

9.5 Extrapolation of relative efficacy

9.5.1 Time to event data – summarized

As mentioned above (see also Figure 17), the model uses clinical data from both the OlympiA trial and external data to estimate the risk of recurrencies and mortality over time (Table 23).

Table 23. Summary of clinical events and transitions in the model.

Clinical event	Transition	Difference between arms?	Data source
Disease recurrence	**TP1, TP2**	Favours Olaparib	OlympiA – iDFS
Mortality for disease free patients	**TP3**	Same risk	Background mortality (lifetables)
From non-distant to metastatic recurrence or death	**TP4, TP5**	Same risk	OlympiA – time from non-distant recurrence to metastatic recurrence or death
Mortality in early onset metastatic disease	**TP6**	Favours placebo	OlympiA – time from distant metastases to death
Mortality in late onset metastatic disease	**TP7**	Same risk	OlympiAD, BROCADE3 – time from distant metastases to death

The transition probabilities are explained in further detail in Table 71 in Appendix G.

9.5.1.1 Adverse reaction outcomes

Adverse reaction outcomes are covered in section 7.1.7.

9.5.2 General approach to survival analysis and state transition modelling

The state transition probabilities were estimated following NICE Decision Support Unit (DSU) guidance Technical Support Document (TSD) 19 [65], and Putter et al [67]. This involved fitting a series of parametric survival models (exponential, lognormal, Weibull, loglogistic, Generalised Gamma, Gompertz and Gamma) to patient-level data for all transitions in the model. These survival models are used to predict outcomes during the follow-up of the OlympiA trial, and up to a lifetime horizon.

Following NICE DSU guidance TSD14 [68] and Danish DMC guidelines, the parametric survival analysis included:

- An assessment of the proportional hazards assumption to determine the suitability of using independent models fitted to each arm or joint models that are fitted to a data set containing both arms with a covariate for treatment group
- Generation of statistical goodness of fit measures such as Akaike (AIC) and Bayesian information criteria (BIC)
- Visual inspection of model fit to the trial data
- An assessment of the clinical plausibility of extrapolation

The choice of preferred model focused mainly on model fit to the data and the clinical plausibility of extrapolations. Following DSU guidance, the same model was preferred in both arms.

The modelling approach and the choice of preferred model for each transition probability in the health economic model are presented in detail in Appendix G (Section 1: TP1, TP2, TP3, Section 2: TP4, TP5, and Section 3: TP6, TP7).

9.6 Documentation of health-related quality of life (HRQoL)

9.6.1 Overview of health state utility values (HSUV)

In the base case analysis, the OlympiA HRQoL data are utilised to inform the IDFS and non-metastatic breast cancer health state utility (HSU) values, using the Crott and Briggs mapping algorithm [69]. The HSU value for the 'early' and 'late' onset metastatic breast cancer is extracted by the study of Lidgren et al [70]. In the base case, the age adjustment follows the utilities included in the DMC guidelines. In a scenario analysis, the HSU values were age-adjusted using the general population HSU norm equation from Ara and Brazier et al [71].

Further details around the OlympiA HRQoL data, the mapping algorithms, utilities used in published literature, the utilities age adjustment and the HRQoL impact of treatment-related AEs in the adjuvant setting are presented in Appendix H and I.

9.6.2 Health state utility values used in the health economic model

A summary of the HSU used in the base case and the sensitivity analysis are presented in Table 24.
Alongside the base case settings, alternative data sources for HSUs are explored. These include scenario analyses that test the impact of using alternative utilities and mapping algorithms for the HSU of IDFS in OlympiA.

Table 24. Utilities values used in economic model

Scenarios for sensitivity analysis				
Health state	Base case	Scenario 1) using the Longworth et al mapping algorithm	Scenario 2) using Lloyd et al for the mBC states	Scenario 3) using Lidgren et al data for all health states
IDFS	0.869 (0.865, 0.873)*	0.802 (0.797, 0.807)	0.869 (0.865, 0.873)	0.779 (0.700; 0.849)
Non-metastatic BC	0.869 (0.865, 0.873)**	0.802 (0.797, 0.807)	0.869 (0.865, 0.873)	0.779 (0.745; 0.811)
'Early' and 'late' mBC	0.685 (0.62, 0.735)***	0.685 (0.62, 0.735)	0.521 (0.052)	0.685 (0.620; 0.735)
Source(s)	OlympiA Crott and Briggs mapping [69] Lidgren et al [70]	OlympiA Longworth mapping [72] Lidgren et al [70]	OlympiA Crott and Briggs mapping [69] Lloyd et al [73]	Lidgren et al [70]
Base case rationale	*The OlympiA data represents the only source of HSU for patients with gBRCAm, HER2-negative, high risk early breast cancer. **The HSU for the non-metastatic breast cancer state was assumed equal to the HSU for IDFS. ***As HRQoL data were not routinely collected after recurrence in OlympiA, external literature data from Lidgren et al were used for the post recurrence states of 'early' and 'late' metastatic breast cancer [70].			

9.6.3 Adverse Event Impact

The model includes the health-related quality-of-life impact of treatment-related adverse events (AEs) in the adjuvant setting. The impact of AEs experienced by patients receiving subsequent treatment are not considered in the analysis. This is justified on the basis that post-recurrence AEs would impact both arms of the model, and therefore have a minimal influence on incremental results.

The criteria applied for inclusion of AEs in the model was:

- Severity Grade ≥3: AEs were included if they were classified as CTCAE Grade 3 or above. The costs of Grade 1 and 2 events are assumed to be negligible and omitted from the analysis.
- Incidence of >3%: AE were included if they have occurred in more than 3% of patients in either treatment arm

The frequency, duration and disutility of the included AEs are reported in Table 25.

Table 25. Adverse event frequency, disutility, and duration

Adverse event (grade 3 or above)	Disutility and source of data	Olaparib		Watch and Wait		Source of duration
		Incidence of grade 3 or above [7]	Duration in days	Incidence of grade 3 or above [7]	Duration in days	
Anaemia	-0.119 (TA563) [74]	8.7%	72.44	0.3%	35.92	OlympiA [7], median duration
Leukopenia	-0.35 [75]	3.0%	28.92	0.3%	31.05	Same as neutropenia assumption
Neutropenia	-0.35 [75]	4.9%	28.92	0.8%	31.05	OlympiA [7], median duration
Total QALY impact of AEs		**-0.0042**		**-0.0004**		-

The total QALY impact of AEs is estimated for each arm of the model, based on the incidence, duration, and disutility of each event. The total QALY is then applied to the first cycle in the model. This one-off QALY adjustment therefore accounts for the impact of AEs during the 1-year of adjuvant treatment.

9.7 Resource use and costs

The modelled costs and healthcare resource use associated with the lifetime treatment and management of patients with gBRCAm, high risk, HER2-negative, early breast cancer comprised the following:

- Adjuvant therapy costs, including acquisition and monitoring of treatment
- Treatment costs for recurrence of disease, including drug, surgery, and radiotherapy-related costs
- Disease management and monitoring costs
- End of life costs

For the base case, unit cost data were obtained from several sources including DRG costs from Sundhedsstyrelsen [76] and Medicinrådet [77], and previous Medicinrådet assessments. The pharmaceutical prices were extracted from the medicinpriser.dk price database in June 2022. The resource use data were obtained from two clinical expert interviews [54].

9.7.1 Intervention and comparator costs and resources

The following sections provide a summary of the intervention and comparator treatment costs in the model, as well as the costs of treatments for non-metastatic and metastatic breast cancer.

For TNBC, the intervention in the model is 1-year adjuvant treatment with olaparib tablets at a dose of 300mg twice daily. Treatment is administered until recurrence of disease, tolerability issues, or adverse events or until completion of the 1-year treatment period. After discontinuation or completion of treatment, patients are assumed to undergo watch and wait until recurrence.

The comparator is watch and wait (proxied by placebo in OlympiA), which comprises monitoring and surveillance for disease recurrence. No drug costs are assigned to watch and wait. The resource utilisation for watch and wait were captured in the costs of disease management and monitoring assigned to the IDFS health state. These costs are applied to both arms of the model. Further detail on these costs is provided in section 9.7.3.

For HER2-/HR+, the intervention in the model is 1-year adjuvant treatment with olaparib tablets (300mg twice daily) alongside a background regimen of adjuvant endocrine therapy, as indicated. The comparator is watch and wait plus background endocrine therapy. Treatment with endocrine therapy is assumed to continue until disease recurrence, or for a maximum of 6.8 years in the base case. The model includes the option to vary the maximum duration of endocrine therapy use.

9.7.2 Adjuvant therapies

9.7.2.1 Olaparib

Olaparib is available in 150 mg and 100 mg film-coated tablet formulations and comes in pack size of 56 tablets. The 100 mg tablet is available for dose reduction. The 28-day treatment cost (AIP) with olaparib is 31 377.40 kr. (medicinpriser.dk October 2023). The cost per model cycle (monthly [30.4375 days]) is 34 108.91 kr. No administration costs are assumed on the basis that therapy is given orally and can be initiated at a regular medical visit.

The duration of treatment with adjuvant olaparib is modelled on the percentage of patients that remained on study drug in the olaparib arm of the OlympiA trial. This is estimated from the Kaplan-Meier probabilities for the time from randomisation to discontinuation of study drug from any cause.

The KM data for ITT and the TNBC and HR+/HER2- subgroups are shown in [redacted]

The time to discontinuation data in OlympiA appropriately reflects the expected duration of adjuvant olaparib treatment and includes the impact of disease recurrence and adverse events on the duration of treatment.

In OlympiA, most patients completed up to 1 year of treatment (median time from first to last dose of 364.0 days [7]). In DCO1, of 911 patients treated, 5 had treatment durations, measured as the time from first to last dose, of at least 400 days [7]. These longer than expected durations of treatment can be attributed to interruptions in the treatment course, with 4 of 5 patients having an actual duration (duration minus time with dose interruptions) that ranged from 369 to 374 days[2]. Therefore, in the model, the total duration of treatment is limited to 12 months, in line with the actual duration (excluding time with dose interruptions) in OlympiA and the recommend duration of adjuvant olaparib in early breast cancer. In the Excel model, the total costs of adjuvant olaparib are calculated as the monthly cost multiplied by the proportion on drug at the start of each month of the 12 cycles of treatment, e.g., from month 0 to month 11. The use of the start of cycle occupancy to model drug costs ensures that the model captures the costs of unused tablets for patients that discontinue treatment before completing each month's supply of treatment.

9.7.2.2 Endocrine therapy (HER2-/HR+ only)

In the OlympiA trial, patients with HER2-/HR+ disease were allowed to continue concurrent treatment with endocrine therapy as per local guidelines. Of those with HER2-/HR+ tumours, 86.9% of olaparib patients (146 of 168) and 92.4% of placebo patients (145 of 157) received endocrine therapy, including tamoxifen, anastrozole, and letrozole [7].

In the model, patients with HER2-/HR+ are assumed to receive adjuvant endocrine therapy until disease recurrence, death or for a user-definable maximum duration of treatment. The costs of adjuvant endocrine therapy are modelled based on the numbers occupying the IDFS state over time. The share of patients receiving adjuvant endocrine therapy (90%) was based on clinical expert input. The clinical experts mentioned that at least 90% of patients will receive endocrine therapy and mostly be compliant [54]. The maximum duration of therapy was also based on clinical expert input and was set to 6.08 years (i.e. 21.5% of the patients receive treatment for approximately 10 years and 78.5% of the patients approximately 5 years) in the base case [54]. Alternative scenarios regarding the duration of endocrine therapy were considered in the sensitivity analysis.

The monthly cost of endocrine treatment is modelled as a weighted average of the costs of tamoxifen, anastrozole and letrozole. The share of treatment is modelled based on clinical expert input [54]. The healthcare resource utilisation for the monitoring and administration of endocrine therapies are assumed to be captured by the routine disease management costs assigned to the IDFS state. The costs of administration or monitoring for endocrine therapy are therefore set to zero in the base case. A summary of the monthly adjuvant costs is provided in Table 26.

Table 26. Monthly costs (kr.) of adjuvant endocrine therapy

Therapy	Case mix of treatments (%)	Daily dose of endocrine therapy	Pack size	Cost* (AIP) per pack (kr)	Monthly** acquisition cost (kr)	Administration costs per month (kr)
Letrozole	57.5%	2.5mg	100 x 2.5mg tablets	145.00	44.13	0
Anastrozole	2.5%	1mg	98 x 1mg tablets	36.96	11.48	0
Tamoxifen	40%	20mg	100 x 20mg tablets	159.00	48.40	0

*Source: * Medicinpriser.dk, October 2023 prices; ** Monthly costs based on 30.44 days*

[2] *At DCO2, there was no change in the median or maximum treatment duration for olaparib, suggesting no change in trends in treatment durations between DCOs. At the time of analysis, further summaries of the safety results are pending.*

Based on 90% of patients receiving adjuvant endocrine therapy, the weighted-average cost per model cycle (monthly [30.4375 days]) of endocrine therapy is 40.52 kr. (weighted average cost based on the case-mix of treatment multiplied by 90%).

9.7.3 Treatment of non-metastatic and metastatic breast cancer

Patients that enter the non-metastatic or metastatic disease states are assumed to receive additional treatment comprising surgical intervention, radiotherapy, and drug-based intervention. The share of treatment depends on the health state (non-metastatic or metastatic), prior adjuvant treatment (olaparib or watch or wait), and the hormone status (HR+ or TNBC) of patients. The share for each subsequent treatment based on input from two Danish experts, while prices were obtained from public sources (Medicinpriser.dk for pharmaceuticals and DRG 2023 for IV administration, radiotherapy and surgery).

In the Excel model, the costs of drug, surgical, and radiotherapy treatment of non-mBC and mBC are modelled as a series of weighted average total treatment costs (drug, surgery, radiotherapy) that are applied as one-off costs to each patient entering the health state. This simplified approach to the modelling of subsequent treatment costs has been applied and accepted in numerous past appraisals in oncology.

For non-mBC, subsequent treatment options include chemotherapies such as capecitabine, docetaxel plus cyclophosphamide, and paclitaxel + cyclophosphamide + epirubicin, and for HER2-/HR+ patients letrozole (aromatase inhibitor). For mBC, subsequent treatment options also include chemotherapies such as capecitabine (if not used before), eribulin, docetaxel or, for TNBC only, atezolizumab+ nab-paclitaxel. For HER2-/HR+ patients, aromatase inhibitors can be used either as monotherapy (letrozole, fulvestrant) or in combination (abemaciclib + letrozole or fulvestrant, everolimus + exemestane).

More details on the costs for treatment of non-metastatic and metastatic breast cancer are described in Appendix J.

9.7.4 Health state costs and resource use

The costs of disease monitoring and management are modelled via a series of health state costs. These costs reflect the utilisation of resources during the routine care of breast cancer patients, including consultations with oncologists, and nurses as well as the routine tests required to monitor and manage ongoing disease.

In the Excel model, the health state costs are modelled using a time-in-state method, where an estimated monthly cost of care is applied to the proportion of patients occupying each state over time. These costs are independent of treatment arm, such that the same healthcare costs apply to olaparib and watch and wait patients who occupy the same state. As outlined previously, the lifetable approach is used to apply a half-cycle correction to these costs.

The monthly health state costs for IDFS are presented over the periods of years 0-1, years 1-5 and years 5 and beyond. This is to reflect the changing patterns of care over the course of follow-up for patients with IDFS. For the non-mBC, the patterns of care are expected to remain approximately constant over the first 5 years, while for the mBC health states, the patterns of care are expected to remain approximately constant over time.
Table 27 summarises the health state costs and resource use in the base case. The resource use data was based on Danish clinical expert input [54].

Overall, for the base case, the monthly costs of supportive care in the IDFS state are 490.55 kr. in year 0-1, and 5.83 kr. from year 1 and beyond. The monthly cost of supportive care increases upon disease recurrence to 792.92 kr. for non-mBC and 2 013.43 kr. for mBC. This reflects the additional care required to monitor and manage the care of patients with recurrent disease.

Table 27. Unit costs (kr) and resource use by state in the model based on clinical expert input [54].*

Resource items	Unit cost (kr)	Frequency (per 1-month cycle)					Source of unit cost
		IDFS (0-12 months)	IDFS (12-60 months)	IDFS (Year 5+)	Non-mBC (0-60 months)	mBC	
Oncologist visit	1 375.00	0.21 (2.5 per year)	0.02 (0.25 per year)		0.25 (3 per year)	0.25 (3 per year)	DRG: 23MA04 Kontrolundersøgelse. DRG-takster 2023 [76]
Cancer nurse visit	453.00	0.17 (2 per year)					Visit + preparation and documentation + overhead costs. Sygeplejersker, Timeløn [DKK]. Værdisætning af enhedsomkostninger [77]
Cancer nurse phone call	569.00		0.04 (0.5 per year)				DRG: 65TE01 Telefon- og videokonsultation. DRG-takster 2022 [76]
Computed tomography (CT) scan – thoracic	2 023.00	0.04 (0.5 per year)					DRG: 30PR07 CT-scanning, ukompliceret. DRG-takster 2023 [76]
Computed tomography (CT) scan – thoracic and abdomen	2 023.00				0.25 (3 per year)	0.25 (3 per year)	DRG: 30PR07 CT-scanning, ukompliceret. DRG-takster 2023 [76]
Mammogram	699.00		0.0042 (0.05 per year)	0.0031 (0.0375 per year)			DRG: 30PR14 Mammografi, ukompliceret. DRG-takster 2023 [76]
Patient time cost per hour**	203.00	0.15 (1.8 per year)	0.01 (0.1 per year)	0.0016 (0.02 per year)	0.21 (2.5 per year)	0.21 (2.5 per year)	Værdisætning af enhedsomkostninger [77]
Patient transport cost***	140.00	0.83 (10 per year)	0.05 (0.6 per years)	0.0063 (0.08 per year)	1.00 (12 per year)	1.00 (12 per year)	Værdisætning af enhedsomkostninger [77]
Full blood count	400.7				0.25 (3 per year)	0.25 (3 per year)	As proposed for Kadcyla (HER2+ eBC) submission - Medicinrådet 2020 p.16 [78]
Total cost (kr)		692.10	31.60	2.20	949.70	949.70	

* Based on estimates on average frequency of visits from two clinical experts

** Time costs are based on the assumption that CT scans take 30 min, office visits 20 min and mammograms 30 min.

*** Based on travel to oncology outpatient visits, oncology nurse visits, CT scans and mammography. Blood tests are assumed to be taken at the same time as medical visits and does not require extra travelling.

9.7.4.1 End of life costs and resource use

The costs of end of life or terminal care are modelled as a one-off cost applied to patients that enter the death state. These costs reflect the additional care required in the months prior to death. These costs have been included in numerous previous cancer appraisals and economic models. The end of life cost in the base case is 81 288.00 kr. This value is based on DRG 08MP14, "Svulst, ondartet, u. implantat, pat. mindst 18 år". The rationale for including this cost is that cancer patients incur additional costs shortly before death, as they are typically hospitalized for complications or receive care from home care teams.

As death events from the IDFS state are likely to include non-cancer events, the model includes the option of applying the end-of-life care costs only to events originating from the non-mBC or mBC states, or to all deaths irrespective of prior health status (i.e., including deaths from the IDFS state).

In the base case, deaths from IDFS were assumed to be non-cancer related meaning that cancer-related end-of-life care costs would not apply to these events. This potentially underestimates the costs of end-of-life care as BRCA patients remain at an increased risk of cancer and other illnesses, and therefore some cancer-related deaths may occur. In sensitivity analysis, the end-of-life care costs were assumed to apply to all deaths.

9.7.4.2 Adverse Event unit costs and resource use

The costs of treatment-related AEs in the adjuvant setting are included in the base case analysis. The costs of AEs for subsequent treatment lines are not considered on the basis that they are likely to be similar across arms and would thus have a minimal impact on results.

The criteria applied for inclusion of AEs in the model was:

- Severity Grade ≥3: AEs were included if they were classified as CTCAE Grade 3 or above. The costs of Grade 1 and 2 events are assumed to be negligible and omitted from the analysis.
- Incidence of ≥3%: AE must have occurred in at least 3% of patients in either treatment arm

The frequency and costs of treating these AEs are reported in Table 28.

Table 28. Adverse event costs (kr.)

Adverse event (grade 3 or above)	Unit cost (kr.)	Incidence of grade 3 or above [7] at DCO2[3]		Source for unit costs
		Olaparib	Watch and wait	
Anaemia	5 738.00	8.70%	0.30%	1 Oncologist visit and 1 blood transfusion (DRG 2022: 23MA04 Kontrolundersøgelse; DRG2022: 16PR02 Transfusion of blood, other) [76]
Leukopenia	1 515.00	3.00%	0.30%	1 oncologist visit (DRG: 23MA04 Kontrolundersøgelse. DRG-takster 2022) [76]
Neutropenia	1 515.00	4.90%	0.80%	1 oncologist visit (DRG: 23MA04 Kontrolundersøgelse. DRG-takster 2022) [76]
Total cost (kr.)		**618.99**	**33.88**	

The total costs of managing AEs are implemented as a one-off cost in the first cycle of the model. This approach may result in an overestimation of AEs costs in the analysis; however, given the limited treatment duration and manageable tolerability profile of adjuvant olaparib, this simplification is thought to have a minor impact on the overall cost-effectiveness results.

[3] Safety results were consistent across DCO1 and DCO2

9.7.4.3 Miscellaneous unit costs and resource use

In the base case, the cost of BRCA testing is excluded on the basis that testing is likely to be standard practice at the time of launch. However, the impact of BRCA testing related costs to identify patients eligible for adjuvant olaparib in early breast cancer are considered in the sensitivity analysis.

The total cost of BRCA testing is estimated from the unit cost of genetic BRCA testing (4 113 kr) [79] multiplied by the additional number of patients needed to test beyond those already tested based on the current guidelines, to identify one BRCA patient.

The exact proportion of patients currently tested in clinical practice is not fully known, due to missing registry documentation and differences in local practice. Additionally, under the current guidelines, any patient can be eligible for BRCA testing based on clinicians judgement, in case of emerging treatment relevance (e.g. local therapy or PARP inhibitor use).

For the HER2-/HR+ subgroup, the number of patients needed to test is calculated as one divided by the prevalence of gBRCA mutation in patients with HER2-/HR+ disease. Based on literature [80] and expert advice, it was assumed that the prevalence of gBRCA mutation in patients with HER2-/HR+ disease is around 5%. Therefore, the number of patients needed to test to identify one gBRCA patient is estimated to be 20. This number is then multiplied by the proportion of patients not currently tested for gBRCA mutations, to be able to calculate the potential additional testing required due to the introduction of olaparib.

9.8 Results

Table 29 contains a summary of the key model inputs for the base case.

Table 29. Summary of model input parameters for base case

Variable	TNBC Value	HER2-/HR+ Value	Measurement of uncertainty in probabilistic analysis	Reference sections
Analysis settings				
Time horizon	57 years		N/A	9.3
Discount rate – effectiveness	3.5% up to 35 years and 2.5% thereafter		N/A	9.3
Discount rate – costs	3.5% up to 35 years and 2.5% thereafter		N/A	9.3
Structural assumptions				
Time point for determining early vs. late recurrence	24 months		Normal distribution	9.2.2
Long-term risk of recurrence	60 months	999 months (no reduction in risk)	Normal distribution for TNBC	Appendix G
Efficacy parameters				
IDFS survival probabilities (TP1-TP2)	Gompertz (source of efficacy: subgroup)	Lognormal (source of efficacy: ITT)	Multivariate normal distribution on survival parameters	Appendix G
Standardised mortality ratio for excess mortality of BRCA mutations	1.46 (standard error=0.592)		Lognormal distribution	Appendix G
Background all-cause mortality (TP3)	Statistics Denmark 2022		Fixed, not sampled	Appendix G

Probability of recurrence that is non-distant/distant	Non-distant: 23.8% Distant: 76.2%		Beta distribution	Appendix G
Non-metastatic to metastatic (TP4) or death (TP5)	TP4: Lognormal TP5: Exponential		Multivariate normal distribution on survival parameters	Appendix G
'Early onset' metastatic breast cancer to death (TP6)	Exponential (both arms)		Multivariate normal distribution on survival parameters	Appendix G
'late onset' metastatic breast cancer to death (TP7)	Chemotherapy: Lognormal Pembrolizumab + paclitaxel or carboplatin: Hazard ratio applied to the survival rate for chemotherapy (assuming equal efficacy for pembrolizumab and atezolizumab) Case mix shown in Table 81	Chemotherapy: Lognormal CDK4/6 inhibitor: Log-logistic Case mix shown in Table 81	Multivariate normal distribution on survival parameters Hazard ratio sampled using lognormal Case mix based on Dirichlet distribution	Appendix G
Cost inputs				
Time on adjuvant olaparib	Kaplan-Meier curve in TNBC subgroup	Kaplan-Meier curve in HER2-/HR+ subgroup	Beta distribution on the monthly probability of discontinuation of treatment	9.7.1
Monthly cycle cost of olaparib (kr)	34 108.91	34 108.91	Fixed, not sampled	9.7.1
Monthly cycle cost of adjuvant endocrine therapy (kr)	-	66.11	Fixed, not sampled	9.7.2
Non-mBC (Drug acquisition) (kr)	1 900.11	1 895.01	Dirichlet on market shares, Gamma for durations	9.7.3, Appendix J
Non-mBC (Drug administration) (kr)	7 843.20	5 555.60		9.7.3, Appendix J
Non-mBC (Surgery/radiotherapy) (kr)	25 222.58	25 222.58	Beta on probability of procedure, lognormal on resource use	9.7.3, Appendix J
Early onset mBC (Drug acquisition) [olaparib] (kr)	190 420.10	255 518.54	Dirichlet on market shares, Gamma for durations	9.7.3, Appendix J
Early onset mBC (Drug administration) [olaparib] (kr)	28 340.91	0.00		9.7.3, Appendix J
Early onset mBC (Procedure) [olaparib] (kr)	27 632.20	27 632.20	Beta on probability of procedure, lognormal on resource use	9.7.3, Appendix J
Early onset mBC (Drug acquisition) [Watch and wait] (kr)	190 420.10	255 518.54	Dirichlet on market shares, Gamma for durations	9.7.3, Appendix J
Early onset mBC (Drug administration) [Watch and wait] (kr)	28 340.91	0.00		9.7.3, Appendix J

Early onset mBC (Procedure) [Watch and wait] (kr)	28 926.64	28 926.64	Beta on probability of procedure, lognormal on resource use	9.7.3, Appendix J
Late onset mBC (Drug acquisition) [olaparib] (kr)	87 475.08	282 919.72	Dirichlet on market shares, Gamma for durations	9.7.3, Appendix J
Late onset mBC (Drug administration) [olaparib] (kr)	12 944.96	4 435.17		9.7.3, Appendix J
Late onset mBC (Procedure) [olaparib] (kr)	28 926.64	28 476.15	Beta on probability of procedure	9.7.3, Appendix J
Late onset mBC (Drug acquisition) [Watch and wait] (kr)	87 475.08	282 919.72	Dirichlet on market shares, Gamma for durations	9.7.3, Appendix J
Late onset mBC (Drug administration) [Watch and wait] (kr)	12 944.96	4 435.17		9.7.3, Appendix J
Late onset mBC (Procedure) [Watch and wait] (kr)	28 476.15	28 476.15	Beta on probability of procedure, lognormal on resource use	9.7.3, Appendix J
Health state IDFS 0-12 months (kr)	692.10		Fixed, not sampled	9.7.4
Health state IDFS 12-60 months (kr)	31.60		Fixed, not sampled	9.7.4
Health state IDFS 60 months plus (kr)	2.20		Fixed, not sampled	9.7.4
Health state non-mBC 0-60 months (kr)	949.70		Fixed, not sampled	9.7.4
Health state mBC	949.70		Fixed, not sampled	9.7.4
End of life costs (one-off) (kr)	81 288.00		Fixed, not sampled	9.7.4
Health state utility inputs				
IDFS	0.869		Beta distribution	9.6.2
Non-mBC	0.869		Beta distribution	9.6.2
mBC (early and late)	0.685		Beta distribution	9.6.2

Table 30 provides a summary of the major assumptions in the base case model.

Table 30. Major assumptions in the base case model

Assumption	Rationale/Support
Structural assumptions	
Conditional probability that failure of IDFS is a non-distant recurrence is constant over time	The proportion of events leading to distant or non-distant recurrence is assumed to remain constant over time. This is consistent with the approaches used in past economic models in HER2-positive disease [126-128] (see Appendix G)
Treatment pathway for metastatic breast cancer is captured by a single health state	Information on progression status after distant recurrence was not available from OlympiA preventing the use of a more complex, multi-state model for metastatic disease. The inclusion of further states for progression within mBC would not be expected to materially impact on results. (see section 9.2.2)
The risk of death after metastatic cancer was dependent on the timing of recurrence, defined as 'early' and 'late'	The separation of mBC into states for 'early' and 'late' recurrence is supported by studies showing that patients who relapse early tend to have significantly worse post-recurrence outcomes than patients who relapse later (Table 17). This is consistent with the approaches used in past economic models in HER2-positive disease [126-128] (see section 9.2.2)

Patients with non-metastatic recurrence may develop distant metastatic disease at any time after locoregional event. Treatment pathway for non-metastatic breast cancer is captured by a single health state, and excludes a state of "remission"	Consistent with data from OlympiA, patients with locoregional recurrence were assumed to be at risk of metastatic disease upon entering the non-metastatic breast cancer state. This differs to the approaches adopted in past models that assumed zero risk of recurrence whilst receiving adjuvant therapy in the first 12 months after non-metastatic recurrence. Not all patients underwent curative intent surgery with adjuvant chemotherapy after locoregional recurrence in OlympiA (62% had surgery after locoregional recurrence). Patients that did not undergo surgery would not be considered in remission, as defined in past models. (see section 9.2.3)
Short-term recurrence in patients with TNBC and HER2-/HR+	In line with the observed hazard rate, the model assumes that the hazard of recurrence for olaparib is less than or equal to the hazard for placebo. Beyond the point at which the hazards converge, the effect of olaparib is assumed the same as placebo such that no continued benefit of treatment is assumed. (see Appendix G)
Long-term recurrence in patients with TNBC and HER2-/HR+	In line with the literature and clinical expert opinion (see section 7.1), the model assumes that the risk of recurrence for patients with TNBC declines to zero by year 5 and that patients with HER2-/HR+ disease are at a lifetime risk of recurrence. (see Appendix G)
1-month cycle length	The model cycle length is consistent with the recommended monthly frequency of monitoring for haematological toxicities over the 1-year olaparib treatment, and is consistent with the cycle lengths used in past models for HER2-postive early breast cancer [126-129] (see 9.3)
Half-cycle correction	The life table approach is used to estimate half-cycle corrected state occupancies over time (see section 93)
A lifetime (57 years) time horizon was used	The use of a lifetime horizon is consistent with approaches accepted in past reimbursement submissions and ensures that all relevant differences in the costs and health outcomes of adjuvant olaparib and watch and wait are captured (see section 9.3)
Treatment lines	Adjuvant therapy with olaparib or watch and wait as well as subsequent therapies for non-metastatic (1st line) and metastatic recurrences (1st and 2nd line)
Clinical parameter estimates	
Risk of death prior to recurrence is modelled based on life table background mortality, adjusted to reflect excess mortality from BRCA mutations	The Statistics Denmark lifetables are also used to inform the transition from IDFS to death, which could not be modelled using OlympiA data due to low event numbers (n=2 for olaparib and n=0 placebo). Patients with BRCA mutations are at an increased risk of other cancers and deaths from other causes. The model includes an excess mortality adjustment for BRCA status using the standardized mortality ratio from Mai et al [99]. In a simplifying assumption, the mortality ratio is assumed to be constant over time. (see section 1 in Appendix G)
Risks of distant recurrence or death after non-mBC are independent of treatment arm	There were too few events within the individual arms of OlympiA to reliably estimate TP4 and TP5 for the olaparib and watch and wait arms of the model. The transition probabilities were therefore estimated from a pooled dataset containing data from both arms. The resulting probabilities were applied to both arms of the model. This approach was also validated by Danish clinical experts [37]. This leads to a conservative estimate of the post-recurrence survival of patients with locoregional recurrence in the olaparib arm. (see Appendix G)
Risk of death after 'early' onset mBC differs by treatment arm	The model reflects the observed post-recurrence survival of patients in OlympiA, which suggests that patients that had distant recurrence after olaparib had a numerically shorter post-recurrence survival than for placebo patients. These trends may be attributed to several factors, including differences in the treatments administered after recurrence and imbalances in the characteristics and prognosis of patients with distant recurrence following olaparib and placebo treatment. The approach to model separately the two treatment arms for this outcome was also validated by Danish clinical experts [37]. (see Appendix G)
Risk of death after 'late' onset mBC are the same across arms	In the 'late' onset mBC setting, patients are likely to receive similar treatment options across arms and have a similar response to therapy. This approach was also validated by Danish clinical experts [37]. (see Appendix G)

9.8.1 Base case results - TNBC

For the base case, the cost-effectiveness of adjuvant olaparib versus watch and wait was separately estimated for the subgroups of TNBC and HER2-/HR+. These results were then combined to estimate the ICER of adjuvant olaparib versus watch and wait in the full label population of gBRCA mutated, HER2-negative, early breast cancer. Throughout this section, the ICER is defined as the incremental cost per QALY gained. The base case results for adjuvant olaparib versus watch and wait in BRCAm TNBC population are shown in Table 31.

In the base case, adjuvant olaparib was associated with an incremental gain in life years (1.42) and QALYs (1.23) versus watch and wait. One year treatment with adjuvant olaparib was associated with incremental costs of 323 694 kr versus watch and wait. The resulting ICER was 262 545 kr per QALY gained.

Table 31. Deterministic base case results in the TNBC population – discounted

Technologies	Total costs (kr)	Total LYG	Total QALYs	Inc. Cost (kr)	Inc. LYG	Inc. QALYs	ICER (kr)
Watch and wait	90 417	16.79	14.19				
Olaparib	414 111	18.21	15.42	323 694	1.42	1.23	262 545

The full breakdown of the cost and QALY components of the analysis are presented in Table 32 and Table 33, respectively.

The cost of adjuvant olaparib was the largest contributor to the total incremental costs of treatment, accounting for 91.3% of the difference in total costs across arms. Drug acquisition costs for 'early onset' mBC accounted for 3.3% of the absolute incremental difference between arms. As individual items, all other cost components accounted for less than 1.5% of the absolute incremental difference between arms.

The largest contributor to incremental QALYs and LYs was the health effects of IDFS, which accounted for 87.2% of the total absolute incremental QALYs. The incremental QALYs for 'early onset mBC' accounted for 7.2% of the difference between arms, followed by non-mBC and 'late onset mBC'. The health impact of AEs had a minimal impact on the incremental results of the analysis (<1% of incremental QALYs).

The model predicts that adjuvant olaparib is associated with an additional (undiscounted) 3.02 years of IDFS versus watch and wait over a 57-year lifetime [30.87 years for olaparib versus 27.85 years for watch and wait]. The predicted undiscounted life years was 31.40 years for olaparib and 28.71 years for watch and wait.

Table 32. Breakdown of costs (kr) by health state and resource item (TNBC) – discounted

Health state/cost category	Olaparib (kr)	Watch and wait (kr)	Increment (kr)	% Absolute increment
IDFS				
Treatment acquisition costs	346 584	0	346 584	91.3%
Treatment administration costs	0	0	0	0.0%
Monitoring costs	4 071	0	4 071	1.1%
Background therapy costs	0	0	0	0.0%
Disease management costs: Y1	8 048	7 755	293	0.1%
Disease management costs: Y2-5	1 201	1 087	113	0.0%
Disease management costs: Y5+	357	321	36	0.0%
Time and travel costs	2 227	2 114	113	0.0%
Testing costs	0	0	0	0.0%
AE costs	574	31	542	0.1%

Non-mBC				
Drug acquisition costs	79	116	-37	0.0%
Surgery & radiotherapy costs	1 051	1 539	-488	0.1%
Treatment admin & monitoring costs	327	479	-152	0.0%
Disease management costs	2 202	3 226	-1 025	0.3%
Time and travel costs	423	619	-197	0.1%
Early onset mBC				
Drug acquisition costs	15 637	28 254	-12 616	3.3%
Surgery & radiotherapy costs	2 269	4 292	-2 023	0.5%
Treatment admin & monitoring costs	2 327	4 205	-1 878	0.6%
Disease management costs	1 163	3 164	-2 001	0.5%
Time and travel costs	223	607	-384	0.1%
Late onset mBC				
Drug acquisition costs	7 018	7 819	-801	0.2%
Surgery & radiotherapy costs	2 285	2 545	-261	0.1%
Treatment admin & monitoring costs	1 039	1 157	-118	0.0%
Disease management costs	1 640	1 828	-188	0.0%
Time and travel costs	315	351	-36	0.0%
Death				
Terminal care costs	13 052	18 909	-5 857	1.3%
Total	**414 111**	**90 417**	**323 694**	**100.0%**

Table 33. Breakdown of QALYs by health state (TNBC) – discounted

Health state	QALYs – Olaparib	QALYs – Watch and wait arm	Increment	% Absolute increment
IDFS	15.088	13.642	1.446	87.2%
Non-mBC	0.166	0.244	-0.078	4.7%
Early onset mBC	0.070	0.190	-0.120	7.2%
Late onset mBC	0.098	0.109	-0.011	0.7%
AEs	-0.004	0.000	-0.004	0.2%
TOTAL	**15.418**	**14.185**	**1.233**	**100.0%**

Table 34. Breakdown of LYs by health state (TNBC) – discounted

Health state	LYs – Olaparib	LYs – Watch and wait arm	Increment	% Absolute increment
IDFS	17.773	16.068	1.705	85.8%
Non-mBC	0.193	0.283	-0.090	4.5%
Early onset mBC	0.102	0.278	-0.176	8.8%
Late onset mBC	0.144	0.160	-0.016	0.8%
TOTAL	**18.212**	**16.789**	**1.423**	**100.0%**

9.8.2 Base case results - HER2-/HR+

The base case results for adjuvant olaparib versus watch and wait in gBRCA, HER2-/HR+ are shown in Table 35. In the base case, adjuvant olaparib was associated with an incremental gain in life years (1.22) and QALYs (1.06) versus watch and wait. One year treatment with adjuvant olaparib was associated with incremental costs of 333 782 kr. versus watch and wait. The resulting ICER was 316 031 kr per QALY gained.

Table 35. Deterministic base case results in the HER2-/HR+ population – discounted

Technologies	Total costs (kr)	Total LYG	Total QALYs	Inc. Cost (kr)	Inc. LYG	Inc. QALYs	ICER (kr)
Watch and wait	195 069	14.40	12.11				
Olaparib	528 852	15.62	13.16	333 782	1.22	1.06	316 031

The full breakdown of the cost and QALY components of the analysis are presented in Table 36 and Table 37. The cost of adjuvant olaparib was the largest contributor to the total incremental costs of therapy, accounting for 91.9% of the total incremental costs. The drug acquisition costs of 'early' mBC contributed to 3.8% of the incremental costs, whilst all other individual parameters contributed around 1% or less.

The largest contributor to incremental QALYs and LYs was the health effects of IDFS, which accounted for 87.2% of the incremental QALYs. The incremental QALYs for 'early onset mBC' accounted for 7.7% of the total difference between arms, followed by non-mBC and 'late onset mBC'. The health impact of AEs had a minimal impact on the incremental results (<1% of incremental QALYs).

The model predicts that adjuvant olaparib is associated with an additional (undiscounted) 2.46 years of IDFS versus watch and wait over a 57-year lifetime [23.31 years for olaparib versus 20.86 years for watch and wait]. The predicted undiscounted life years was 25.27 years for olaparib versus 23.05 years for watch and wait.

Table 36. Breakdown of costs by health state and resource item (HER2-/HR+) – discounted

Health state/cost category	Olaparib (kr)	Watch and wait (kr)	Increment (kr)	% Absolute increment
IDFS				
Treatment acquisition costs	354 286	0	354 286	91.9%
Treatment administration costs	0	0	0	0.0%
Monitoring costs	4 162	0	4 162	1.1%
Background therapy costs	2 361	2 175	186	0.0%
Disease management costs: Y1	8 068	7 754	314	0.1%
Disease management costs: Y2-5	1 199	1 095	104	0.0%
Disease management costs: Y5+	268	238	30	0.0%
Time and travel costs	2 182	2 070	111	0.0%
Testing costs	0	0	0	0.0%
AE costs	574	31	542	0.1%
Non-mBC				
Drug acquisition costs	171	200	-30	0.0%
Surgery & radiotherapy costs	2 275	2 668	-393	0.1%
Treatment admin & monitoring costs	501	588	-87	0.0%
Disease management costs	4 727	5 559	-832	0.2%
Time and travel costs	907	1 067	-160	0.0%
Early onset mBC				
Drug acquisition costs	20 574	35 340	-14 766	3.8%
Surgery & radiotherapy costs	2 225	4 001	-1 776	0.5%
Treatment admin & monitoring costs	0	0	0	0.0%
Disease management costs	1 140	2 950	-1 811	0.5%
Time and travel costs	219	566	-348	0.1%
Late onset mBC				
Drug acquisition costs	76 560	77 425	-865	0.2%
Surgery & radiotherapy costs	7 706	7 793	-87	0.0%
Treatment admin & monitoring costs	1 200	1 214	-14	0.0%
Disease management costs	8 341	8 434	-93	0.0%
Time and travel costs	1 601	1 619	-18	0.0%
Death				
Terminal care costs	27 605	32 282	-4 677	1.2%
Total	**528 852**	**195 069**	**333 782**	**100%**

Table 37. Breakdown of QALYs by health state (HER2-/HR+) – discounted

Health state	QALYs – Olaparib	QALYs – Watch and wait arm	Increment	% Absolute increment
IDFS	12.253	11.014	1.238	87.2%
Non-mBC	0.354	0.417	-0.063	4.5%
Early onset mBC	0.068	0.177	-0.109	7.7%
Late onset mBC	0.492	0.498	-0.006	0.4%
AEs	-0.004	0.000	-0.004	0.3%
TOTAL	**13.163**	**12.107**	**1.056**	**100.0%**

Table 38. Breakdown of LYs by health state (HER2-/HR+) – discounted

Health state	LYs – Olaparib	LYs – Watch and wait arm	Increment	% Absolute increment
IDFS	14.370	12.915	1.455	85.8%
Non-mBC	0.415	0.488	-0.073	4.3%
Early onset mBC	0.100	0.259	-0.159	9.4%
Late onset mBC	0.732	0.740	-0.008	0.5%
TOTAL	**15.617**	**14.401**	**1.215**	**100.00%**

9.8.3 Base case results - HER2-negative (ITT population)

For the base case, the ICER for the gBRCA mutated, HER2-negative population was estimated as the weighted average of incremental costs and QALYs for adjuvant olaparib in the HER2-/HR+ and TNBC subgroups. This follows the methodology used to determine the cost-effectiveness of histology-independent cancer drugs in the recent NICE DSU report by Murphy et al [48].

Table 39 shows the weighted-average incremental costs, QALYs and LYs, as well as the ICER generated based on the prevalence of HER2-/HR+ (17.7%) and TNBC (82.3%) in OlympiA.

Table 39. Deterministic base case results in the HER2-negative ITT population – discounted

	Prevalence in OlympiA study	Incremental costs (kr)	Incremental LYG	Incremental QALYs	ICER (kr per QALY gained)
HER2-/HR+	17.70%	333 782	1.22	1.06	316 031
TNBC	82.30%	323 694	1.42	1.23	262 545
HER2-negative (ITT)	**100.00%**	325 479	1.39	1.20	270 866

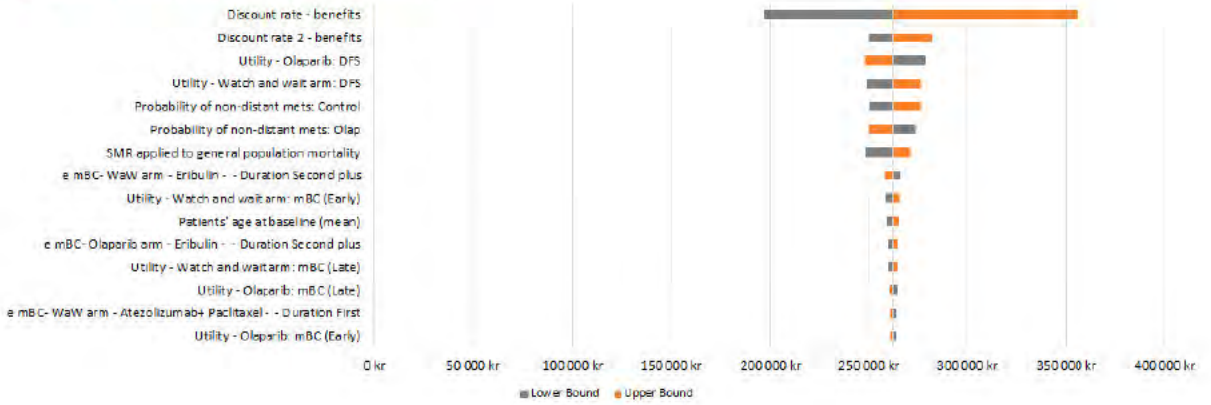
9.9 Sensitivity analyses - TNBC

9.9.1 Deterministic sensitivity analysis

The DSA was performed on 311 model input parameters. This included model settings such as the discount rate, clinical inputs such as the standardised mortality ratio and the probability of an IDFS event that is a non-distant recurrence, cost inputs such as duration of subsequent treatment, and the health state utility inputs. Other key model parameters such as the shape and scale parameters of the survival models are considered as part of the scenario analysis and PSA.

The results of the DSA, in terms of the top 15 most influential parameters on the spread of the cost-effectiveness results are shown in Figure 21 and Table 40.

Figure 21. Tornado diagram for DSA in TNBC



The results of the DSA show that variation in the discount rate for health benefits, the utility assigned to IDFS, the probability of non-distant metastasis and the excess mortality risk associated with a BRCA mutation had the greatest influence on base case results. The change in discount rate up to 35 years had the largest absolute impact on results, with the ICER ranging from 197 191 kr at a 1.5% discount rate, to 355 095 kr at a 6.0% discount rate. The discount rate for benefits beyond 35 years had the second largest impact, with the ICER ranging from 250 984 kr at a 1.5% discount rate, to 282 249 kr at a 6.0% discount rate.

Table 40. Results of DSA for TNBC (discounted)

Position	Parameter	Base case value	Lower Value	Upper value	Lower ICER (kr)	Upper ICER (kr)
1	Discount rate - benefits	3.5%	1.5%	6.0%	197 191	355 095
2	Discount rate – benefits, beyond 35 years	2.5%	1.5%	6.0%	250 984	282 249
3	Utility - Olaparib arm: DFS	0.869	0.865	0.873	278 323	248 630
4	Utility - Watch and wait arm: DFS	0.869	0.865	0.873	249 745	276 539
5	Probability of non-distant metastasis: Watch and wait	0.238	0.178	0.303	251 010	276 395
6	Probability of non-distant	0.238	0.162	0.323	273 921	250 821

Position	Parameter	Base case value	Lower Value	Upper value	Lower ICER (kr)	Upper ICER (kr)
	metastasis: Olaparib					
7	SMR applied to general population mortality	1.460	1.040	1.760	249 065	271 078
8	Early mBC- Watch and wait arm - Eribulin - Duration First	7.100	5.777	8.558	266 134	258 593
9	Utility - Watch and wait arm: mBC (Early)	0.685	0.626	0.741	259 115	265 897
10	Patients' age at baseline (mean)	43.300	42.795	43.805	259 816	265 341
11	e mBC- Olaparib arm - Eribulin - - Duration Second plus	7.100	5.777	8.558	260 559	264 733
12	Utility - Watch and wait arm: mBC (Late)	0.685	0.626	0.741	260 561	264 463
13	Utility - Olaparib arm: mBC (Late)	0.685	0.626	0.741	264 352	260 847
14	e mBC- WaW arm - Atezolizumab+ Paclitaxel - Duration First	7.000	5.695	8.437	263 799	261 165
15	Utility - Olaparib: mBC (Early)	0.685	0.626	0.741	263 830	261 334

9.9.2 Scenario analysis

Table 41 provides a summary of the results of the scenario analysis for TNBC. The proportion change in ICER versus the base case is colour coded based on the direction of effect; orange indicates increasing ICER, and green indicates decreasing ICER. The scenarios that resulted in a greater than 5% change in ICER versus the base case are highlighted in grey.

The results of the scenario analysis indicate that the model is sensitive to the following assumptions:

- Time horizon – ICER increases from 262 545 kr in the base case to 317 226 kr at a time horizon of 30 years
- Health state utility for IDFS – ICER increases up to 296 636 kr using alternative input for IDFS
- Choice of survival model for TP6 in the placebo arm – ICER increases to 282 879 kr with the loglogistic distribution

The model results were insensitive (<5% change in ICER) to the following scenarios and parameters:

- Choice of time point for determining early vs. late recurrence
- Patients' age at baseline
- Time point at which patients are no longer at risk of recurrence (up to 15 years)
- Using treatment arm-specific probabilities of IDFS being a non-distant recurrence event
- Choice of survival distribution for TP4 and TP5 (non-mBC to mBC or death)

- Choice of survival distribution for TP6 in Olaparib arm (early mBC to death)
- Choice of survival distribution for TP7 (late mBC to death)
- Health state utility assigned to the mBC state
- Use of ITT efficacy data (instead of subgroup data) to model the IDFS for TNBC

Overall, the results of the scenario analyses suggest that the base case is robust to variations in input parameters.

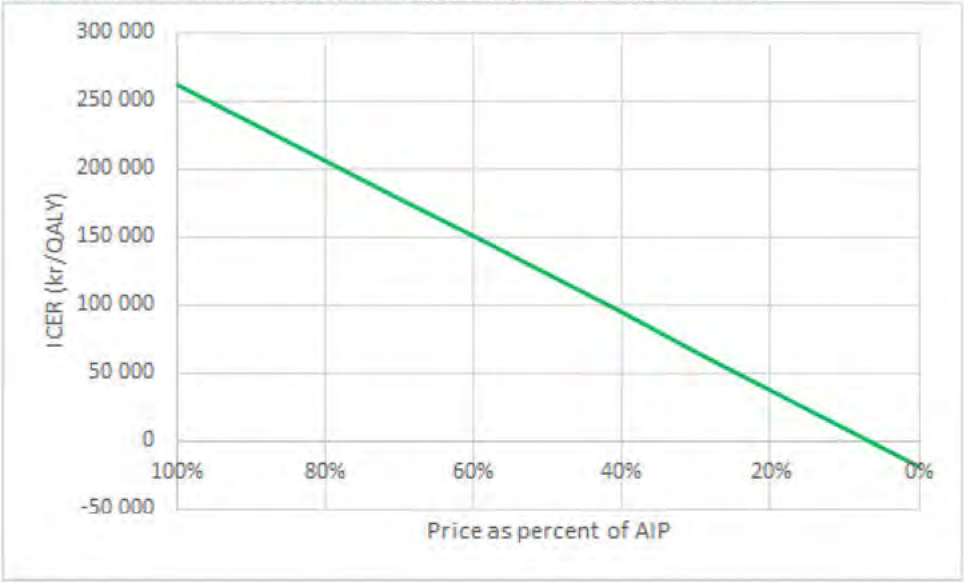
Table 41. Results of scenario analyses for TNBC (discounted)

Scenario Label	Incremental costs (kr)	Incremental QALYs	ICER (kr per QALY)	% change vs base case
Base case	323 694	1.23	262 545	-
Time horizon – 30 years	323 720	1.02	317 226	20.83%
Time horizon – 40 years	323 700	1.17	276 073	5.15%
Time horizon – 50 years	323 694	1.23	263 250	0.27%
Time point for determining early vs. late recurrence (12 months)	326 213	1.25	261 055	-0.57%
Time point for determining early vs. late recurrence (36 months)	322 869	1.22	264 671	0.81%
Patients' age at baseline: 45 years old	323 703	1.19	272 558	3.81%
Time point at which patients are no longer at risk of recurrence – 7 years	324 018	1.21	267 032	1.71%
Time point at which patients are no longer at risk of recurrence – 10 years	324 162	1.21	268 988	2.45%
Time point at which patients are no longer at risk of recurrence – 15 years	324 199	1.20	269 468	2.64%
OS hazard ratio for pembrolizumab in 1st line mBC: 0.73§	323 702	1.23	262 438	-0.04%
TP6 – Assume the same risk of death across arms	324 249	1.27	255 699	-2.61%
Apply end-of-life costs to all deaths	326 189	1.23	264 570	0.77%
TP1/TP2 distribution – Loglogistic	323 932	1.27	254 103	-3.22%
TP1/TP2 distribution – Lognormal	324 188	1.26	258 076	-1.70%
TP1/TP2 distribution – Generalised Gamma	324 667	1.21	267 342	1.83%
TP4 distribution – Exponential	323 679	1.24	261 436	-0.42%
TP4 distribution – Weibull	323 749	1.25	259 178	-1.28%
TP4 distribution – Loglogistic	323 717	1.24	261 700	-0.32%
TP5 distribution – Lognormal	323 554	1.23	263 651	0.42%
TP5 distribution – Loglogistic	323 585	1.23	263 400	0.33%
TP5 distribution – Gompertz	323 423	1.22	264 634	0.80%
TP5 distribution – Generalised Gamma	323 473	1.22	264 297	0.67%
TP6 distribution (Olap) – Weibull	323 709	1.23	262 347	-0.08%
TP6 distribution (Olap) – Loglogistic	324 145	1.26	257 129	-2.06%
TP6 distribution (Olap) – Gompertz	323 945	1.25	259 549	-1.14%
TP6 distribution (Placebo) – Weibull	323 540	1.22	264 488	0.74%
TP6 distribution (Placebo) – Loglogistic	322 142	1.14	282 879	7.74%
TP6 distribution (Placebo) – Gompertz	322 698	1.17	275 023	4.75%
TP6 distribution (Placebo) – Generalised Gamma	323 195	1.20	268 923	2.43%
TP7 distribution for chemotherapy – Weibull	323 711	1.23	262 333	-0.08%
TP7 distribution for chemotherapy – Loglogistic	323 681	1.23	262 689	0.05%
TP7 distribution for chemotherapy – Generalised Gamma	323 694	1.23	262 536	0.00%
Utility source – OlympiA Longworth mapping	323 694	1.13	287 109	9.36%
Utility source (using Lloyd et al for the mBC states)	323 694	1.26	256 017	-2.49%
Utility source (Lidgren et al. 2007 for all health states)	323 694	1.09	296 636	12.98%
Probability of non-mBC – by treatment arm	323 618	1.24	260 162	-0.89%
Source of efficacy data for TNBC: ITT with Gompertz distribution for both arms	323 825	1.23	263 734	0.45%

Scenario Label	Incremental costs (kr)	Incremental QALYs	ICER (kr per QALY)	% change vs base case
Source of efficacy data for TNBC: ITT with lognormal distribution for both arms	324 993	1.21	267 894	2.04%
* OlympiA data pooled across arms: 90% (291 of 325) ** Maximum duration: 5-years based on the recommended duration of treatment in the marketing authorisation of letrozole				

The price sensitivity is illustrated in Figure 22, which ranges from the base case ICER of 262 545 kr/QALY when price is at 100% of AIP (list price) to olaparib being dominant (higher effects and lower cost) at zero price.

Figure 22. ICER as function of the price as percent of the AIP list price – TNBC



9.9.3 Probabilistic sensitivity analysis

The PSA is a method that can be used to estimate the full parametric uncertainty (or joint distribution) surrounding the results of the cost-effectiveness analysis. It is conducted through the repeated re-sampling of all major input parameters using probability distributions (e.g., normal) to generate a series of sampled estimates of the cost-effectiveness results under uncertainty. For efficacy parameters and the utilities, the standard errors were estimated based on study data. For AE disutilities, resource use or duration of subsequent therapy, the SE was estimated based on the assumption that the SE was 10% of the parameter value. The 10% is a modelling assumption, but should be capturing the overall uncertainty well. The treatment duration and resource use (e.g., frequency of follow-up visits) are to a large extent based on fixed schedules (such as 6 cycles of chemotherapy). Usually, patient monitoring is dependent on the patient status (progression free or progressed), and it is expected to be quite standard over time.

The correlation for efficacy parameters was taken into account by covariance matrices based on the clinical data, while other parameters were modelled as independent.

The results of the PSA are presented alongside the deterministic results in . Based on 1000 simulations, the PSA results produced a mean ICER of 253 550 kr per QALY gained. The mean incremental costs and QALYs were 322 245 kr. and 1.27, respectively. The PSA results were consistent with the deterministic results (Table 42).

Table 42. Probabilistic and deterministic base case results in the TNBC population – discounted

Technologies	Total costs (kr)	Total LYG	Total QALYs	Inc. Cost (kr)	Inc. LYG	Inc. QALYs	ICER (kr)
Probabilistic results based on 1000 simulations							
Watch and wait	95 047	16.94	14.30				
Olaparib	417 292	18.41	15.57	322 245	1.47	1.27	253 550
Deterministic results							
Watch and wait	90 417	16.79	14.19				
Olaparib	414 111	18.21	15.42	323 694	1.42	1.23	262 545

The PSA results were stable for the number of simulations used. When the number of simulations varied between 500 and 5000, the ICER varied between DKK x and y per QALY. In relative terms, this is just a variation of 2.5% of the ICER and some variation is expected as this is a probabilistic simulation. Hence, 1000 iterations should be sufficient for the PSA.

Figure 23 and Figure 24 display the cost-effectiveness plane and CEAC for olaparib versus watch and wait in TNBC.

The probabilities that adjuvant olaparib is cost-effective versus watch and wait in TNBC are:

- 99% at 600 000 kr. threshold
- 100% at 800 000 kr. threshold
- 100% at 1 000 000 kr. threshold

All simulations were in the north-east quadrant of the cost-effectiveness plane, where olaparib is both more costly and more effective than watch and wait.

Figure 23. Cost-effectiveness plane for TNBC probabilistic analysis

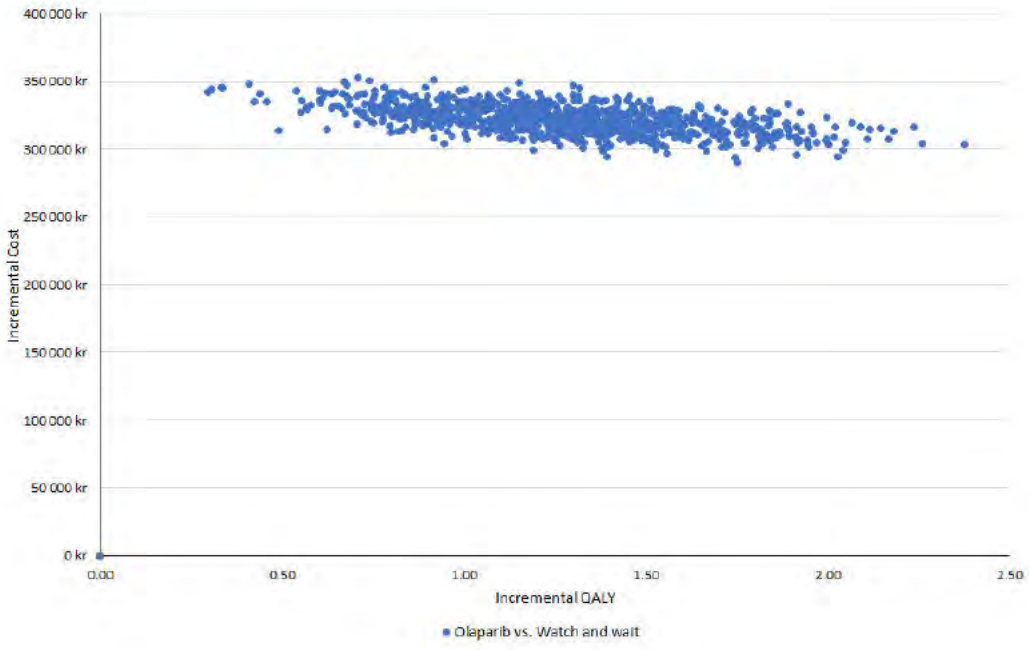
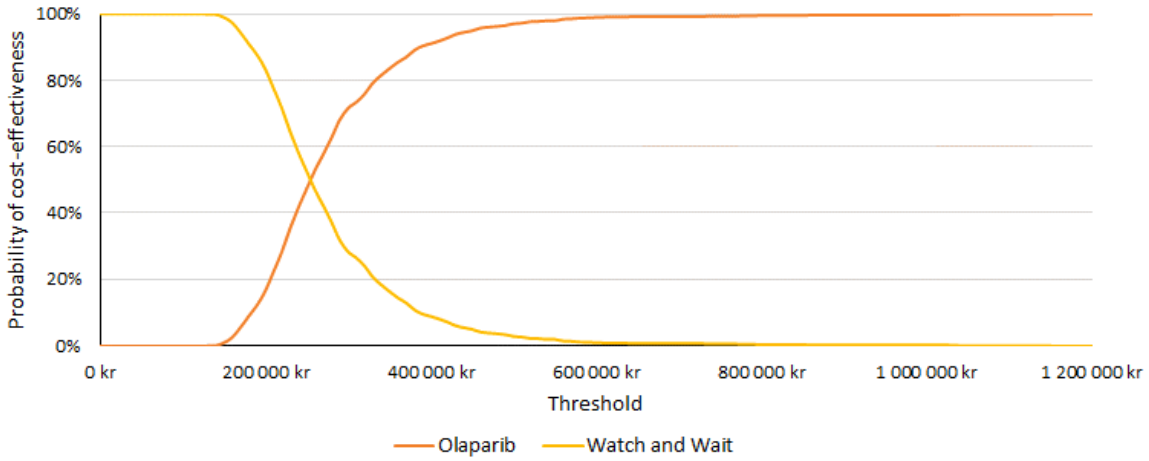


Figure 24. Cost-effectiveness acceptability curve for TNBC probabilistic analysis

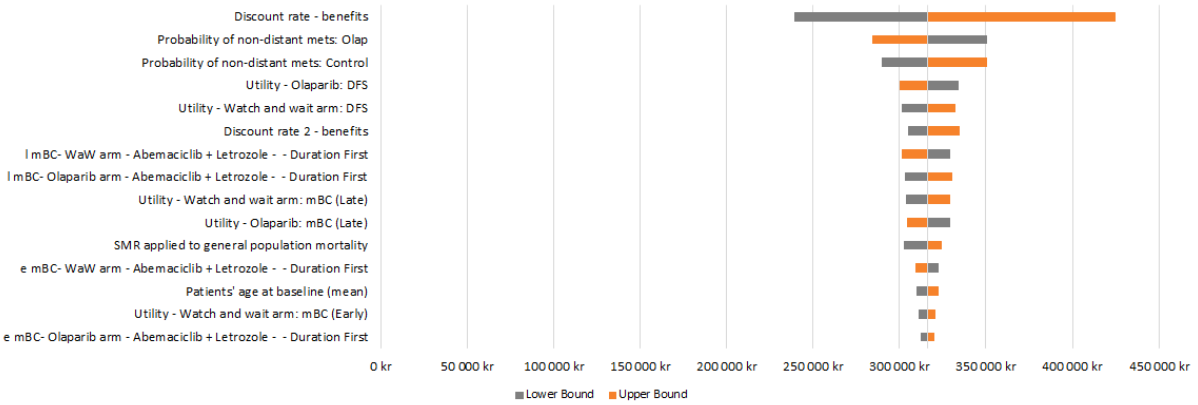


9.10 Sensitivity analyses – HER2-/HR

9.9.4 Deterministic sensitivity analysis

The results of the DSA, in terms of the top 15 most influential parameters on the spread of the cost-effectiveness results for HER2-/HR+ are shown in Figure 25 and Table 43.

Figure 25. Tornado diagram for DSA in HER2-/HR+



The results of the DSA show that variation in the discount rate for health benefits, the probability of an IDFS event being a non-distant recurrence and the utility assigned to IDFS had the greatest influence on base case results. The change in discount rate up to 35 years had the largest absolute impact on results, with the ICER ranging from 239 435 kr. at a 1.5% discount rate, to 424 848 kr at a 6.0% discount rate.

Table 43. Results of DSA for HER2-/HR+ (discounted)

Position	Parameter	Base case value	Lower Value	Upper value	Lower ICER (kr)	Upper ICER (kr)
1	Discount rate - benefits	3.5%	1.5%	6.0%	239 435	424 848
2	Probability of non-distant metastasis: Olaparib	0.238	0.162	0.323	350 427	284 556
3	Probability of non-distant metastasis: Watch and wait	0.238	0.178	0.303	289 985	350 389
4	Utility - Olaparib: DFS	0.869	0.865	0.873	333 979	300 109
5	Discount rate 2 – benefits (beyond 35 years)	2.5%	1.5%	6.0%	301 468	331 859
6	Utility - Watch and wait arm: DFS	0.869	0.865	0.873	305 111	334 197
7	l mBC- WaW arm - Abemaciclib + Letrozole - Duration First	16.000	13.018	19.285	328 912	301 842
8	l mBC- Olaparib arm - Abemaciclib + Letrozole - Duration First	16.000	13.018	19.285	303 295	330 062
9	Utility - Watch and wait arm: mBC (Late)	0.685	0.626	0.741	303 727	328 712
10	Utility - Olaparib: mBC (Late)	0.685	0.626	0.741	329 204	304 431
11	SMR applied to general population mortality	1.460	1.040	1.760	302 932	324 371
12	e mBC- WaW arm - Abemaciclib + Letrozole - Duration First	16.000	13.018	19.285	322 179	309 259
13	Patients' age at baseline (mean)	43.200	42.131	44.269	310 284	322 065
14	Utility - Watch and wait arm: mBC (Early)	0.685	0.626	0.741	311 541	320 429
15	e mBC- Olaparib arm - Abemaciclib + Letrozole - Duration First	16.000	13.018	19.285	312 452	319 974

9.9.5 Scenario analysis

Table 44 contains a summary of the results of the scenario analysis for HER2-/HR+.
The results of the scenario analysis indicate that the model is sensitive to the following assumptions:

- Time horizon – ICER increased to 366 057 kr at a time horizon of 30 years
- Choice of survival model for IDFS (TP1/TP2) – ICER ranges from 158 523 kr (exponential) to 372 223 kr (Weibull)
- Health state utility for IDFS and other health states – use of alternative values increases the ICER up to 357 181 kr
- Use of loglogistic or Gompertz for TP6 distribution in placebo arm – ICER increases up to 343 200 kr
- Inclusion of BRCA testing costs – ICER increased up to 386 128 kr

The model results were insensitive (<5% change in ICER) to the following scenarios:

- Choice of time point for determining early vs. late recurrence
- Patients' age at baseline
- Duration of endocrine therapy
- Using treatment arm-specific probabilities of IDFS being a non-distant recurrence event
- Choice of survival distribution for TP4 and TP5 (non-mBC to mBC or death)
- Choice of survival distribution for TP6 in olaparib arm (early mBC to death)
- Choice of survival distribution for TP7 (late mBC to death)
- Health state utility assigned to the mBC state

Overall, the results of the scenario analysis suggest that the base case is robust to variations in most input parameters.

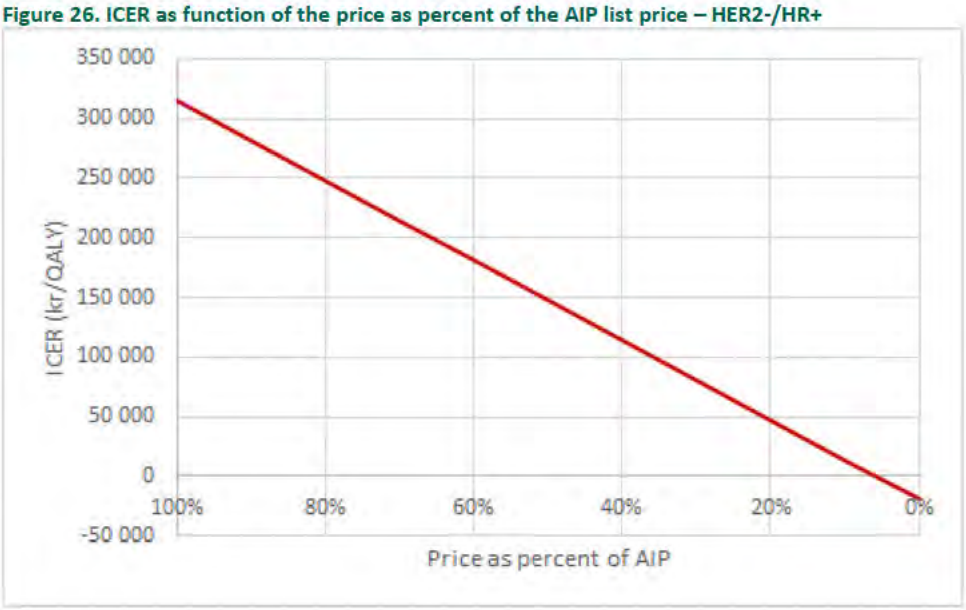
Table 44. Results of scenario analyses

Scenario Label	Incremental cost (kr)	Incremental QALY	ICER (kr per QALY)	% change vs base case
Base case	351 074	1.08	324 303	-
Time horizon – 30 years	332 906	0.91	366 057	15.83%
Time horizon – 40 years	333 537	1.02	328 028	3.80%
Time horizon – 50 years	333 767	1.05	316 640	0.19%
Time point for determining early vs. late recurrence (12 months)	333 559	1.06	313 318	-0.86%
Time point for determining early vs. late recurrence (36 months)	333 799	1.05	318 860	0.89%
Patients' age at baseline: 45 years old	333 624	1.02	326 394	3.28%
Include BRCA1/2 testing costs: 65% tested	362 573	1.06	343 291	8.63%
Include BRCA1/2 testing costs: 85% tested	407 816	1.06	386 128	22.18%
Endocrine therapy: 90%* of patients for maximum duration 5 years**	333 747	1.06	315 997	-0.01%
Endocrine therapy: 90%* of patients for maximum duration 10 years (assumption)	333 899	1.06	316 142	0.03%
TP6 – Assume the same risk of death across arms	334 326	1.09	306 538	-3.00%
Apply end-of-life costs to all deaths	335 491	1.06	317 649	0.51%
TP1/TP2 distribution – Loglogistic	336 803	0.97	347 308	9.90%
TP1/TP2 distribution – Gompertz	328 819	1.19	276 801	-12.41%
TP1/TP2 distribution – Generalised Gamma	336 607	0.96	350 789	11.00%
TP4 distribution – Exponential	333 711	1.06	314 718	-0.42%
TP4 distribution – Weibull	333 563	1.07	312 101	-1.24%
TP4 distribution – Loglogistic	333 727	1.06	315 052	-0.31%
TP5 distribution – Lognormal	333 570	1.05	317 434	0.44%
TP5 distribution – Loglogistic	333 618	1.05	317 108	0.34%
TP5 distribution – Gompertz	333 355	1.05	318 723	0.85%
TP5 distribution – Generalised Gamma	333 434	1.05	318 293	0.72%
TP6 distribution (Olap) – Weibull	333 798	1.06	315 755	-0.09%
TP6 distribution (Olap) – Loglogistic	334 225	1.08	308 510	-2.38%
TP6 distribution (Olap) – Gompertz	334 029	1.07	311 862	-1.32%
TP6 distribution (Placebo) – Weibull	333 639	1.05	318 607	0.82%
TP6 distribution (Placebo) – Loglogistic	332 334	0.97	343 200	8.60%
TP6 distribution (Placebo) – Gompertz	332 853	1.00	332 668	5.26%
TP6 distribution (Placebo) – Generalised Gamma	333 318	1.03	324 503	2.68%
TP7 distribution for chemotherapy – Weibull	333 783	1.06	316 021	0.00%
TP7 distribution for chemotherapy – Loglogistic	333 782	1.06	316 034	0.00%
TP7 distribution for chemotherapy – Generalised Gamma	333 782	1.06	316 031	0.00%

Scenario Label	Incremental cost (kr)	Incremental QALY	ICER (kr per QALY)	% change vs base case
TP7 Late: CDK4/6 inhibitor – Weibull	333 788	1.06	315 886	-0.05%
TP7 Late: CDK4/6 inhibitor – Lognormal	333 780	1.06	316 088	0.02%
TP7 Late: CDK4/6 inhibitor – Gamma	333 785	1.06	315 946	-0.03%
Utility source – OlympiA Longworth mapping	333 782	0.97	345 678	9.38%
Utility source (using Lloyd et al for the mBC states)	333 782	1.08	308 015	-2.54%
Utility source (Lidgren et al. 2007 for all health states)	333 782	0.93	357 181	13.02%
Probability of non-mBC – by treatment arm	333 702	1.08	309 872	-1.95%
* OlympiA data pooled across arms: 90% (291 of 325) ** Maximum duration: 5-years based on the recommended duration of treatment in the marketing authorisation of letrozole				

The price sensitivity is illustrated in Figure 26, which ranges from the base case ICER of 316 031 kr/QALY when price is at 100% of AIP (list price) to olaparib being dominant (higher effects and lower cost) at zero price.

Figure 26. ICER as function of the price as percent of the AIP list price – HER2-/HR+



9.9.6 Probabilistic sensitivity analysis

The results of the PSA are presented alongside the deterministic results in Table 45. Based on 1000 simulations, the PSA results produced a mean ICER of 297 222 kr. per QALY gained. The mean incremental costs and QALYs were 331 639 kr. and 1.12, respectively. The PSA results were consistent with the deterministic results.

Table 45. Probabilistic and deterministic base case results in the HER2/HR+ population – discounted

Technologies	Total costs (kr)	Total LYG	Total QALYs	Inc. Cost (kr)	Inc. LYG	Inc. QALYs	ICER (kr)
Probabilistic results based on 1000 simulations							
Watch & wait	196 804	14.51	12.19				
Olaparib	528 443	15.80	13.30	331 639	1.29	1.12	297 222
Deterministic results							
Watch & wait	195 069	14.40	12.11				
Olaparib	528 852	15.62	13.16	333 782	1.22	1.06	316 031

Figure 27 and Figure 28 display the cost-effectiveness plane and CEAC for olaparib versus watch and wait.
The probabilities that adjuvant olaparib is cost-effective versus watch and wait in HER2-/HR+ are:

- 87% at 600 000 kr threshold
- 93% at 800 000 kr threshold
- 96% at 1 000 000 kr threshold

The vast majority of simulations were in the north-east quadrant of the cost-effectiveness plane, where olaparib is more costly and more effective than watch and wait.

Figure 27. Cost-effectiveness plane for HER2-/HR+ probabilistic analysis

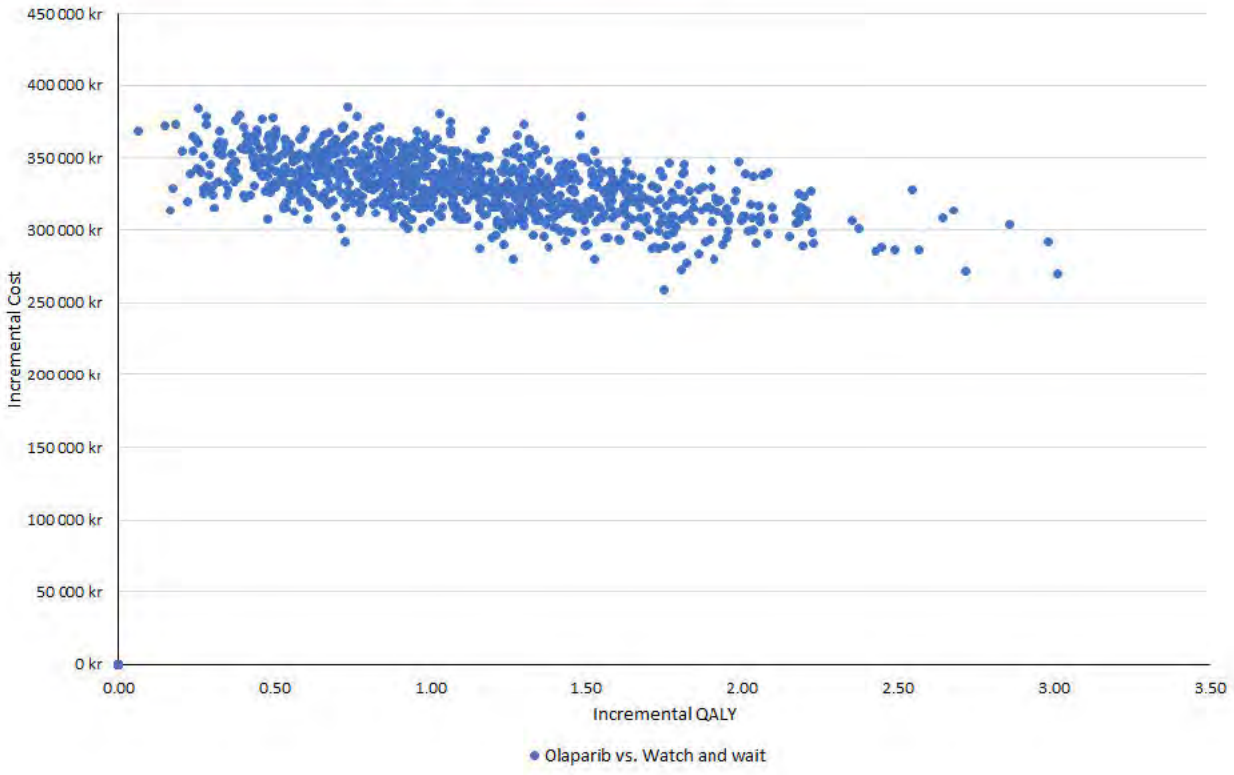
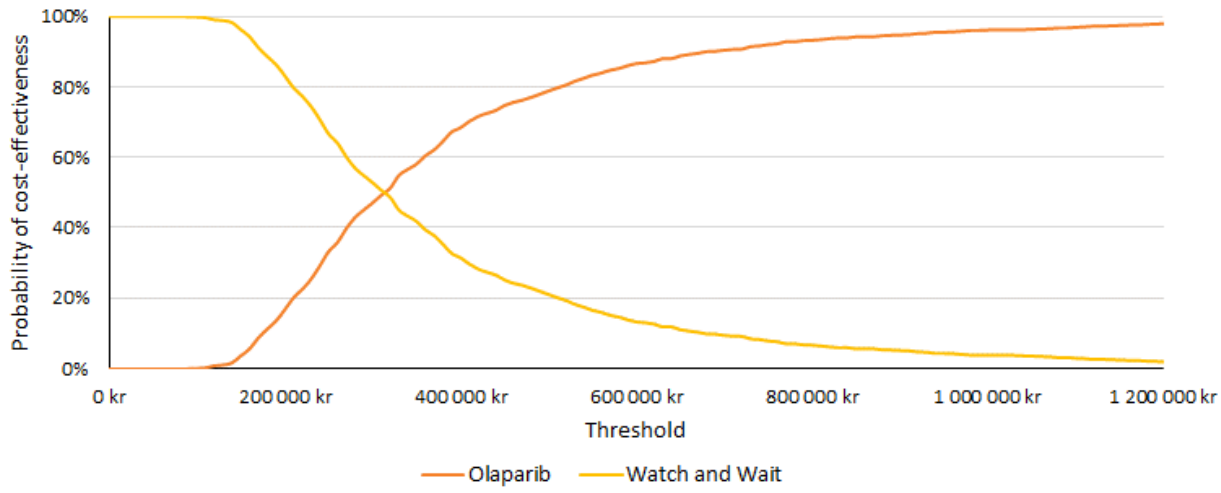


Figure 28. Cost-effectiveness acceptability curve for HER2-/HR+ probabilistic analysis



9.10 Sensitivity analyses – HER2-negative (ITT population)

9.10.1 Scenario analysis

Considering the outcomes of the scenario analyses for the two subgroups, some key scenarios were investigated for the overall HER2-negative population. Table 46 contains a summary of the results of these scenario analyses.
The results of the scenario analyses indicate that the model is sensitive to the following assumptions:

- Time horizon – ICER increased to 325 080 kr at a time horizon of 30 years
- Utility source (Lidgren et al. 2007 for all health states) – ICER increased to 306 052 kr
- Use of loglogistic or lognormal for TP6 distribution in placebo arm – ICER increases up to 292 205 kr

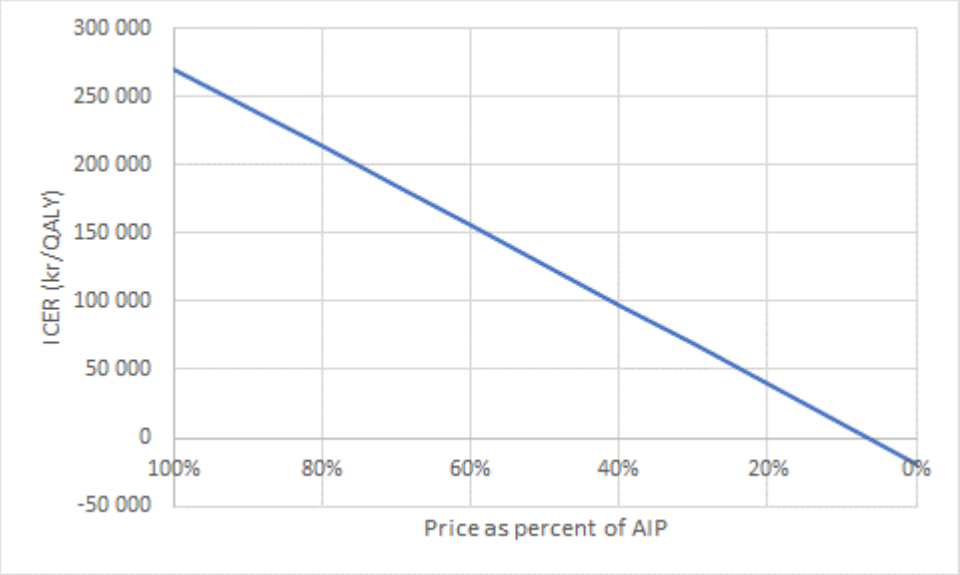
Overall, the results of the scenario analysis suggest that the base case is robust to variations in most input parameters.

Table 46. Results of scenario analyses for HER2-negative (discounted)

Scenario Label	Incremental cost (kr)	Incremental QALY	ICER (kr per QALY)	% change vs base case
Base case	325 479	1.20	270 886	-
Time horizon – 30 years	325 346	1.00	325 080	20.01%
Include BRCA1/2 testing costs	338 583	1.20	281 772	4.03%
Patients' age at baseline: 45	325 459	1.16	280 967	3.73%
TP1/TP2 distribution – Loglogistic for both subgroups and both arms	326 210	1.22	267 207	-1.35%
TP1/TP2 distribution – Gompertz for both subgroups and both arms	325 008	1.24	261 240	-3.55%
TP1/TP2 distribution – Generalised Gamma for both subgroups and both arms	326 781	1.17	279 463	3.17%
TP4 distribution - Weibull	325 486	1.22	267 403	-1.28%
TP4 distribution - Loglogistic	325 489	1.21	269 998	-0.32%
TP4 distribution - Gompertz	325 473	1.22	266 955	-1.44%
TP5 distribution - Loglogistic	325 360	1.20	271 753	0.33%
TP5 distribution - Gompertz	325 181	1.19	273 042	0.80%
TP5 distribution - Generalized Gamma	325 236	1.19	272 692	0.67%
TP6 distribution (Placebo) - Loglogistic	323 946	1.11	292 205	7.88%
TP6 distribution (Placebo) - Gompertz	324 495	1.14	283 957	4.83%
TP6 distribution (Placebo) - Generalised Gamma	324 987	1.17	277 553	2.47%
TP6 distribution (Placebo) - Lognormal	323 989	1.11	291 776	7.72%
Utility source (Lidgren et al. 2007 for all health states)	325 479	1.06	306 052	12.99%

The price sensitivity is illustrated in Figure 29, which ranges from the base case ICER of 270 866 kr/QALY when price is at 100% of AIP (list price) to olaparib being dominant (higher effects and lower cost) at zero price.

Figure 29. ICER as function of the price as percent of the AIP list price – HER2- (ITT)



10. Budget impact analysis

10.1 Population

The model uses the total female population as a starting point and the specific target population is estimated based on the disease characteristics of patients in the indication. The patient population is described in section 5.1. Given the epidemiology, it is estimated that around [redacted] patients per year would be eligible for treatment with olaparib in the adjuvant breast cancer setting in Denmark (Figure 3 in section 5.1).

10.2 Market shares

Market shares have been estimated separately for each subpopulation (TNBC [Table 47, Table 48] and HER2-/HR+[Table 49, Table 50]) as the uptake and peak market share might be slightly higher in the BRCAm-positive TNBC group. Other treatments might also get recommended in the neoadjuvant/adjuvant setting, such as pembrolizumab for TNBC and abemaciclib for HER2-/HR+. These treatment might then also receive some market shares, but these have not been included in the market share estimates as they are not yet recommended in these settings. In addition, as mentioned previously, both pembrolizumab and abemaciclib have broader indications without specific data on BRCAm-positive patients. Pembrolizumab treatment is initiated in the neoadjuvant setting together with chemotherapy and has an earlier randomization point.

10.2.1 Market shares in TNBC

Table 47. Scenario *without* Olaparib

	2024	2025	2026	2027	2028
Olaparib	0%	0%	0%	0%	0%
No treatment	100%	100%	100%	100%	100%

Table 48. Scenario *with* Olaparib

	2024	2025	2026	2027	2028
Olaparib	60%	70%	80%	85%	90%
No treatment	40%	30%	20%	15%	10%

10.2.2 Market shares in HER2-/HR+

Table 49. Scenario *without* Olaparib

	2024	2025	2026	2027	2028
Olaparib	0%	0%	0%	0%	0%
No treatment	100%	100%	100%	100%	100%

Table 50. Scenario *with* Olaparib

	2024	2025	2026	2027	2028
Olaparib	40%	50%	60%	70%	75%
No treatment	60%	50%	40%	30%	25%

10.3 Number of patients

The estimated number of patients in Table 51 and Table 52 build on the patient number estimates from section 5.1 and the market shares in Table 47 - Table 50 above.

Table 51. Number of patients in TNBC

	Number of patients with olaparib		Number of patients without olaparib	
Year	**Olaparib**	**Watch and wait**	**Olaparib**	**Watch and wait**
2024	[redacted]	[redacted]	0.0	[redacted]
2025			0.0	
2026			0.0	
2027			0.0	
2028			0.0	
Total over 5 years			**0.0**	

Table 52. Number of patients in HER2-/HR+

	Number of patients with olaparib		Number of patients without olaparib	
Year	Olaparib	Watch and wait	Olaparib	Watch and wait
2024	[redacted]	[redacted]	0.0	[redacted]
2025			0.0	
2026			0.0	
2027			0.0	
2028			0.0	
Total over 5 years			0.0	

The number of patients in the ITT population (HER2-) is obtained by adding TNBC and HER2-/HR+ together (Table 53 = Table 51 + Table 52).

Table 53. Number of patients based on the ITT population

	Number of patients with olaparib		Number of patients without olaparib	
Year	Olaparib	Watch and wait	Olaparib	Watch and wait
2024	[redacted]	[redacted]	0.0	[redacted]
2025			0.0	
2026			0.0	
2027			0.0	
2028			0.0	
Total over 5 years			0.0	

10.4 Expenditure per patient

The expenditure per patient builds on the cost and resource used described in section 9.7.The cost per patient is shown from a lifetime perspective in **Table 54** and

Table 55. The cost difference between olaparib and watch and wait is the largest in the first year as olaparib is a one-year treatment, while there are cost **savings of a few thousand kr. in later years as more patient get recurrences in the watch and wait group (**Table 56 **and** Table 57**).** The cost per patient for the whole population would depend on the proportions of patients with TNBC and HER2-/HR+ in Danish clinical practice, but would be somewhere between the costs for the subgroups, i.e. with a total cost difference per patient between [redacted]. and 351 000 kr. for olaparib vs. watch and wait over a lifetime perspective.

Table 54. Expenditure per patient for TNBC – lifetime perspective (DKK)

Health state/cost category iDFS	Olaparib (kr)	Watch and wait (kr)	Increment (kr)
Treatment acquisition costs	346 584	0	346 584
Treatment administration costs	0	0	0
Monitoring costs	4 071	0	4 071
Background therapy costs	0	0	0
Disease management costs: Y1	8 048	7 755	293
Disease management costs: Y2-5	1 201	1 087	113
Disease management costs: Y5+	357	321	36
Time and travel costs	2 227	2 114	113
Testing costs	0	0	0
AE costs	574	31	542
Non-mBC			
Drug acquisition costs	79	116	-37
Surgery & radiotherapy costs	1 051	1 539	-488
Treatment administration costs	327	479	-152
Disease management costs: Y1-5	2 202	3 226	-1 025
Time and travel costs	423	619	-197
Early onset mBC			
Drug acquisition costs	15 637	28 254	-12 616
Surgery & radiotherapy costs	2 269	4 292	-2 023
Treatment administration costs	2 327	4 205	-1 878
Disease management costs	1 163	3 164	-2 001
Time and travel costs	223	607	-384
Late onset mBC			
Drug acquisition costs	7 018	7 819	-801
Surgery & radiotherapy costs	2 285	2 545	-261
Treatment administration costs	1 039	1 157	-118
Disease management costs	1 640	1 828	-188
Time and travel costs	315	351	-36
Death			
Terminal care costs	13 052	18 909	-5 857
TOTAL	**414 111**	**90 417**	**323 694**

Table 55. Expenditure per patient for HER2-/HR+ – lifetime perspective

Health state/cost category iDFS	Olaparib (kr)	Watch and wait (kr)	Increment (kr)
Treatment acquisition costs	354 286	0	354 286
Treatment administration costs	0	0	0
Monitoring costs	4 162	0	4 162
Background therapy costs	2 361	2 175	186
Disease management costs: Y1	8 068	7 754	314
Disease management costs: Y2-5	1 199	1 095	104
Disease management costs: Y5+	268	238	30
Time and travel costs	2 182	2 070	111
Testing costs	0	0	0
AE costs	574	31	542
Non-mBC			
Drug acquisition costs	171	200	-30
Surgery & radiotherapy costs	2 275	2 668	-393
Treatment administration costs	501	588	-87
Disease management costs: Y1-5	4 727	5 559	-832
Time and travel costs	907	1 067	-160
Early onset mBC			
Drug acquisition costs	20 574	35 340	-14 766
Surgery & radiotherapy costs	2 225	4 001	-1 776
Treatment administration costs	0	0	0
Disease management costs	1 140	2 950	-1 811
Time and travel costs	219	566	-348
Late onset mBC			
Drug acquisition costs	76 560	77 425	-865
Surgery & radiotherapy costs	7 706	7 793	-87
Treatment administration costs	1 200	1 214	-14
Disease management costs	8 341	8 434	-93
Time and travel costs	1 601	1 619	-18
Death			
Terminal care costs	27 605	32 282	-4 677
TOTAL	528 852	195 069	333 782

Table 56. Cost per patient over the first 5 years – TNBC (DKK)

Olaparib

Year	Drug acquisition cost	Drug administration cost	Treatment monitoring cost	Disease management costs	Surgery & radiotherapy costs	AE management cost	Background therapy cost*	End of life costs	BRCA testing cost	Total
2024	355 255	1 396	4 071	8 371	1 605	574	0	1 113	0	372 384
2025	7 013	1 124	0	833	1 282	0	0	2 305	0	12 557
2026	2 628	450	0	841	1 055	0	0	2 030	0	7 005
2027	1 968	334	0	817	781	0	0	2 003	0	5 903
2028	1 289	216	0	709	503	0	0	1 829	0	4 546
Total yr 1-5	**368 153**	**3 520**	**4 071**	**11 571**	**5 225**	**574**	**0**	**9 280**	**0**	**402 394**

**Only applied to HR+*

Watch and Wait

Year	Drug acquisition cost	Drug administration cost	Treatment monitoring cost	Disease management costs	Surgery & radiotherapy costs	AE management cost	Background therapy cost*	End of life costs	BRCA testing cost	Total
2024	17 774	2 861	0	8 474	3 410	31	0	1 690	0	34 240
2025	10 563	1 690	0	1 348	1 992	0	0	3 343	0	18 936
2026	3 057	519	0	1 286	1 212	0	0	3 103	0	9 177
2027	1 975	331	0	1 113	769	0	0	3 006	0	7 195
2028	1 302	216	0	886	499	0	0	2 513	0	5 416
Total yr 1-5	**34 671**	**5 616**	**0**	**13 107**	**7 882**	**31**	**0**	**13 656**	**0**	**74 963**

****Only applied to HR+***

Difference

Year	Drug acquisition cost	Drug administration cost	Treatment monitoring cost	Disease management costs	Surgery & radiotherapy costs	AE management cost	Background therapy cost*	End of life costs	BRCA testing cost	Total
2024	337 481	-1 465	4 071	-103	-1 805	542	0	-578	0	338 144
2025	-3 550	-566	0	-515	-711	0	0	-1 037	0	-6 380
2026	-428	-69	0	-445	-157	0	0	-1 073	0	-2 172
2027	-7	3	0	-296	11	0	0	-1 003	0	-1 292
2028	-14	1	0	-177	4	0	0	-684	0	-870
Total yr 1-5	**333 482**	**-2 096**	**4 071**	**-1 536**	**-2 657**	**542**	**0**	**-4 375**	**0**	**327 431**

Table 57. Cost per patient over the first 5 years – HER2-/HR+ (DKK)

Olaparib

Year	Drug acquisition cost	Drug administration cost	Treatment monitoring cost	Disease management costs	Surgery & radiotherapy costs	AE management cost	Background therapy cost*	End of life costs	BRCA testing cost	Total
2024	365 481	74	4 162	8 341	1 546	574	474	1 029	0	381 681
2025	9 424	59	0	805	1 285	0	432	2 278	0	14 284
2026	8 620	181	0	831	1 075	0	398	1 822	0	12 927
2027	7 317	152	0	903	906	0	369	1 324	0	10 970
2028	6 310	130	0	940	777	0	343	1 531	0	10 031
Total yr 1-5	**397 152**	**597**	**4 162**	**11 820**	**5 589**	**574**	**2 016**	**7 984**	**0**	**429 892**

**Only applied to HR+*

Watch and Wait

Year	Drug acquisition cost	Drug administration cost	Treatment monitoring cost	Disease management costs	Surgery & radiotherapy costs	AE management cost	Background therapy cost*	End of life costs	BRCA testing cost	Total
2024	22 693	150	0	8 399	3 246	31	456	1 691	0	36 667
2025	12 725	77	0	1 235	1 788	0	402	3 081	0	19 307
2026	10 458	217	0	1 230	1 294	0	364	2 641	0	16 204
2027	8 339	171	0	1 227	1 023	0	334	2 155	0	13 249
2028	6 881	140	0	1 175	840	0	309	2 272	0	11 617
Total yr 1-5	**61 096**	**756**	**0**	**13 265**	**8 190**	**31**	**1 865**	**11 839**	**0**	**97 044**

**Only applied to HR+*

Difference

Year	Drug acquisition cost	Drug administration cost	Treatment monitoring cost	Disease management costs	Surgery & radiotherapy costs	AE management cost	Background therapy cost*	End of life costs	BRCA testing cost	Total
2024	342 788	-76	4 162	-58	-1 700	542	17	-662	0	345 014
2025	-3 300	-18	0	-430	-503	0	31	-803	0	-5 024
2026	-1 839	-36	0	-399	-219	0	34	-818	0	-3 277
2027	-1 022	-19	0	-324	-117	0	35	-831	0	-2 279
2028	-571	-10	0	-235	-63	0	34	-741	0	-1 586
Total yr 1-5	**336 056**	**-160**	**4 162**	**-1 446**	**-2 602**	**542**	**151**	**-3 855**	**0**	**332 849**

10.5 Budget impact

The budget impact is obtained by combining the cost per patient with the patient numbers. The budget impact for the TNBC subgroup is shown in Table 58, and the estimates for HER2-/HR+ and for all BRCAm+ HER2-in Table 59 and Table 60 .

10.5.1 Base case budget impact

Table 58. Budget impact TNBC

Olaparib is recommended	2024	2025	2026	2027	2028	Total
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	51 520	84 044	92 020	98 001	101 597	427 182
Treatment monitoring cost	63 513	74 099	84 684	89 977	95 270	407 543
Disease management costs	218 718	246 413	273 135	297 339	317 678	1 353 284
Surgery & radiotherapy costs	60 497	97 943	122 480	140 158	151 398	572 475
AE management cost	9 271	10 682	12 092	12 797	13 502	58 344
Background therapy cost*	0	0	0	0	0	0
End of life costs	34 934	106 635	170 833	233 606	288 324	834 332
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib is NOT recommended						
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	74 374	119 844	134 302	143 847	150 282	622 649
Treatment monitoring cost	0	0	0	0	0	0
Disease management costs	220 331	256 615	292 425	324 508	350 929	1 444 807
Surgery & radiotherapy costs	88 649	142 264	176 029	198 206	213 084	818 232
AE management cost	810	810	810	810	810	4 050
Background therapy cost*	0	0	0	0	0	0
End of life costs	43 946	133 898	220 322	306 981	381 969	1 087 116
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 59. Budget impact HER2-/HR+

Olaparib is recommended	2024	2025	2026	2027	2028	Total
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	4 559	7 022	14 914	21 299	26 796	74 591
Treatment monitoring cost	63 260	79 075	94 890	110 705	118 612	466 542
Disease management costs	318 281	359 867	401 529	444 216	486 555	2 010 449
Surgery & radiotherapy costs	97 500	153 456	194 128	225 922	254 841	925 847
AE management cost	9 428	11 489	13 551	15 612	16 642	66 722
Background therapy cost*	17 602	33 943	49 499	64 483	78 989	244 516
End of life costs	54 199	160 218	248 711	316 493	391 393	1 171 015
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib is NOT recommended						
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	5 712	8 751	17 593	24 809	30 927	87 793
Treatment monitoring cost	0	0	0	0	0	0
Disease management costs	319 158	367 722	417 795	469 475	520 706	2 094 856
Surgery & radiotherapy costs	123 337	193 671	246 342	289 442	326 050	1 178 842
AE management cost	1 184	1 184	1 184	1 184	1 184	5 920
Background therapy cost*	17 340	33 135	47 953	62 029	75 502	235 958
End of life costs	64 262	185 427	292 917	383 702	482 774	1 409 083
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 60. Budget impact HER2- (ITT population)

Olaparib is recommended	2024	2025	2026	2027	2028	Total
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	56 079	91 066	106 935	119 300	128 393	501 773
Treatment monitoring cost	126 773	153 174	179 574	200 682	213 882	874 085
Disease management costs	537 000	606 280	674 664	741 555	804 234	3 363 733
Surgery & radiotherapy costs	157 997	251 399	316 608	366 080	406 239	1 498 322
AE management cost	18 700	22 171	25 643	28 409	30 144	125 067
Background therapy cost*	17 602	33 943	49 499	64 483	78 989	244 516
End of life costs	89 134	266 853	419 544	550 099	679 717	2 005 347
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib is NOT recommended						
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	80 086	128 595	151 895	168 656	181 209	710 442
Treatment monitoring cost	0	0	0	0	0	0
Disease management costs	539 489	624 337	710 220	793 982	871 634	3 539 663

Surgery & radiotherapy costs	211 986	335 935	422 371	487 649	539 133	1 997 074
AE management cost	1 994	1 994	1 994	1 994	1 994	9 970
Background therapy cost*	17 340	33 135	47 953	62 029	75 502	235 958
End of life costs	108 208	319 326	513 239	690 683	864 743	2 496 199
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.5.2 Scenario analyses for the budget impact

Scenario analyses for the budget impact can be found in Appendix K. These show the sensitivity of the results for varying the market shares.

11. Discussion on the submitted documentation

The OlympiA study demonstrates that olaparib administered for 1 year, is associated with a significantly longer survival, free of invasive or distant disease than with placebo in patients with gBRCAm, high risk , HER2-negative, early breast cancer, following surgical treatment and neoadjuvant or adjuvant chemotherapy [26, 132]. Overall, the clinical outcomes and QoL assessments all indicate that olaparib treatment provides a clinically meaningful benefit in this population. The OlympiA study, is the first study to report the effect of a PARP-inhibitor as adjuvant therapy on survival endpoints in patients with early breast cancer. The study results indicate the value of supplementing the current standard of care for patients with gBRCAm, high risk, HER2-negative, early breast cancer requiring adjuvant or neoadjuvant chemotherapy.

As there is currently no highly efficacious and well tolerated therapy approved for this gBRCAm patient population, olaparib has the potential to drive a step change in the treatment of patients with gBRCAm, high risk, HER2-negative, early breast cancer, addressing the unmet need for an efficacious treatment in the adjuvant setting where long term remission and cure are most attainable.

Based on data from the OlympiA trial, the incremental cost-effectiveness of adjuvant olaparib versus a watch and wait strategy was assessed in patients with gBRCAm, high risk HER2-negative early breast cancer. The watch and wait strategy was considered the most relevant comparator, as olaparib is currently the only medicine specifically targeting gBRCAm in early breast cancer.

The OlympiA trial showed efficacy in the pre-specified subgroups. In the health-economic analysis, the pre-specified HER2-/HR+ and TNBC subgroups are modelled separately because the recurrence patterns differ between the HER2-/HR+ and the TNBC subpopulations. Furthermore, no long-term data on recurrence patterns are available to inform and validate the model for the full ITT-population. Therefore, in the base case analysis, the cost-effectiveness is modelled separately for the prespecified and stratified subgroups and the results are then weighed together to reflect the full ITT population.

A key strength of the health economic model is the functionality to separately assess the cost-effectiveness of adjuvant olaparib in TNBC and HER2-/HR+ disease. This gives the flexibility to separately assess each population, taking into account the long-term recurrence risk differences observed in published literature by receptor group. Then the subgroups estimates can be combined to estimate the ICER for the full population of BRCAm, HER2-negative disease.

The main limitation of the evaluation is that OS data from the study are still immature. Due to data immaturity, data from external studies in BRCAm HER2-negative mBC were used to inform the modelling of survival from the 'late onset' metastatic breast cancer state. Through the validation exercise it was observed that the model accurately predicts the

Kaplan Meier curves for both IDFS and OS across both HER2-/HR+ and TNBC. When extrapolated, the landmark OS for the watch and wait arm closely match those of long-term external data for both TNBC [104] and HER2-/HR+ [88]. Therefore, it can be argued that survival extrapolations are based on the best available evidence.

The base case results of the economic analysis indicate that treatment with olaparib is associated with substantial health benefit with an ICER of 270 866 kr per QALY gained when compared with watch and wait (ICER for TNBC: 262 545 kr; ICER for HR+/ HER2: 316 031 kr). The life years gained with olaparib over a patient's lifetime are 1.39 (discounted) for the ITT population. This translates to a QALY gain of 1.20 (discounted).

The robustness of the results were explored through a series of sensitivity analyses. The deterministic sensitivity analysis and the scenario analyses showed that the results were most sensitive to discount rates for health outcomes, the length of the time horizon, the health state utility for IDFS, the inclusion of gBRCAm testing in the analysis and the extrapolation method selected for modelling the transition probabilities for 'early onset' metastatic breast cancer to death. Importantly, all ICERs generated through these analyses were below 450 000 kr. The probabilistic results were closely aligned with the deterministic base case, and olaparib has 100% and 94% probability of being cost-effective at a WTP threshold of 800 000 kr per QALY gained for TNBC and HR+/ HER2- patients, respectively.

12. List of experts

[redacted]

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Appendix A Literature search for efficacy and safety of intervention and comparator(s)

SLR was not performed as OlympiA is a H2H study vs. standard treatment

Table 61. Summary of studies reporting the efficacy of capecitabine, olaparib, and pembrolizumab among patients with mixed- or high-risk TNBC

Study	Interventions	Outcome	HR (95% CI)
High risk (N=6)			
Olaparib (N=1)			
Tutt (2021), OlympiA (NCT02032823), 23 countries [2]	Olaparib (N=751) vs placebo (N=758)	iDFS	0.56 (0.43, 0.73)
Capecitabine (N=5)			
Lluch (2020), GEICAM/2003-11_CIBOMA/2004-01, eight countries (Spain, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, and Venezuela) [26]	Capecitabine (NR) vs observation (NR) [high-risk subgroup]	DFS	1.12 (0.64, 1.97)
Masuda (2017), CREATE-X, multinational (Japan and South Korea) [28]	Endocrine therapy/radiotherapy plus capecitabine (N=139) vs endocrine therapy/radiotherapy (N=147) [TNBC subgroup]	OS	0.52 (0.30, 0.90)
		DFS	0.58 (0.39, 0.87)
Mayer (2021), ECOG-ACRIN EA1131 (NCT02445391), US [81]	Capecitabine (N=213) vs platinum therapy (N=199)	OS	1.32 (0.87, 2.00)
		iDFS	1.16 (0.82, 1.63)
		RFS	1.09 (0.77, 1.54)
O'Shaughnessy (2015), NCT00089479 [82]	Doxorubicin plus cyclophosphamide followed by docetaxel and capecitabine (N=396) vs doxorubicin plus cyclophosphamide followed by docetaxel (N=384) [TNBC subgroup]	OS	0.62 (0.41, 0.94)
		DFS	0.81 (0.57, 1.15)
Schneider (2021), BRE12-158 (NCT02101385), US [83]	Capecitabine (N=74) vs observation (N=38)	OS	0.59 (0.29, 1.23)
		DFS	0.48 (0.26, 0.89)
		DDFS	0.51 (0.26, 0.98)
	Pembrolizumab (N=18) vs capecitabine (N=74)	OS	0.96 (0.33, 2.79)
		DFS	0.92 (0.37, 2.29)
		DDFS	0.91 (0.34, 2.47)
	Olaparib (N=12) vs capecitabine (N=74)	OS	2.90 (0.97, 8.66)
		DFS	3.29 (1.23, 8.83)
		DDFS	2.68 (1.01, 7.12)
Mixed-risk (N=8)			
Capecitabine (N=7)			
Joensuu (2012), FinXX (NCT00114816), multinational (Finland and Sweden) [84]	Docetaxel plus capecitabine followed by cyclophosphamide plus epirubicin plus capecitabine (N=93) vs docetaxel followed by cyclophosphamide plus epirubicin plus fluorouracil (N=109) [TNBC subgroup]	RFS	0.48 (0.26, 0.88)
Joensuu (2017), FinXX (NCT00114816),	Docetaxel plus capecitabine followed by cyclophosphamide plus epirubicin plus capecitabine (N=93) vs docetaxel followed by	OS	0.55 (0.31, 0.96)

multinational (Finland and Sweden) [85]	cyclophosphamide plus epirubicin plus fluorouracil (N=109) [TNBC subgroup]	RFS	0.53 (0.31, 0.92)
Joensuu (2022), FinXX (NCT00114816), multinational (Finland and Sweden) [86, 87]	Docetaxel plus capecitabine followed by cyclophosphamide plus epirubicin plus capecitabine (N=93) vs docetaxel followed by cyclophosphamide plus epirubicin plus fluorouracil (N=109) [TNBC subgroup]	OS	0.59 (0.36, 0.97)
Li (2020), CBCSG010 (NCT01642771), China [88]	Capecitabine and docetaxel followed by capecitabine, epirubicin, and cyclophosphamide (N=308) vs docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide (N=302)	OS	0.67 (0.37, 1.22)
		DFS	0.66 (0.44, 0.99)
		DDFS	0.63 (0.39, 1.00)
		RFS	0.59 (0.38, 0.93)
Lluch (2020), GEICAM/2003-11_CIBOMA/2004-01, eight countries (Spain, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, and Venezuela) [26]	Capecitabine (N=448) vs observation (N=428)	OS	0.92 (0.66, 1.28)‡
		DFS	0.77 (0.59, 1.00)‡
Martin (2015), GEICAM/2003-10 (NCT00129389), Spain [89]	Epirubicin plus docetaxel followed by capecitabine (N=95) vs epirubicin plus cyclophosphamide followed by docetaxel (N=71) or [TNBC subgroup]	iDFS	1.19 (0.70, 2.04)
Wang (2021), SYSUCC-001 (NCT01112826), China [90]	Capecitabine (N=222) vs observation (N=221)	OS	0.75 (0.47, 1.19)
		DFS	0.64 (0.42, 0.95)
		DDFS	0.60 (0.38, 0.92)
		RFS	0.72 (0.46, 1.13)
Pembrolizumab (N=1)			
Schmid (2021), KEYNOTE-522 (NCT03036488), 21 countries [91]	Neoadjuvant: pembrolizumab plus chemotherapy (N=784) vs placebo plus chemotherapy (N=390) Adjuvant: pembrolizumab plus radiotherapy (N=784) vs placebo plus radiotherapy (N=390)	OS	0.72 (0.51, 1.02)

Table 62. Summary of key studies reporting the efficacy of olaparib, capecitabine, and CDK4/6 inhibitors among patients with high-risk, hormone receptor-positive breast cancer

Study	Intervention	Outcome	HR (95% CI)
Olaparib (N=1)			
Tutt (2021), OlympiA (NCT02032823), 23 countries [2]	Olaparib (N=168) vs placebo (N=157)	iDFS	0.70 (0.38, 1.27)
Capecitabine (N=1)			
Masuda (2017), CREATE-X, multinational (Japan and South Korea) [28]	Endocrine therapy/radiotherapy plus capecitabine (N=304) vs endocrine therapy/radiotherapy (N=297) or [hormone-receptor-positive subgroup]	OS	0.73 (0.38, 1.40)
		DFS	0.81 (0.55, 1.17)
CDK4/6 inhibitors (N=4)			
Harbeck (2021), monarchE (NCT03155997), 38 countries [92]	Endocrine therapy plus abemaciclib (N=2,808) vs endocrine therapy alone (N=2,829)	iDFS (8 July 2020 data cut)	0.71 (0.58, 0.87)
		iDFS (1 April 2021 data cut)	0.70 (0.59, 0.82)
		DDFS (8 July 2020 data cut)	0.69 (0.55, 0.86)
		DDFS (1 April 2021 data cut)	0.69 (0.57, 0.83)
Harbeck (2022), monarchE (NCT03155997), 38 countries [93]	Endocrine therapy plus abemaciclib (N=2,808) vs endocrine therapy alone (N=2,829)	(OS 8 July 2020 data cut)	1.091 (0.818, 1.455)
		OS (1 April 2021 data cut)	0.767 (0.511, 1.152)
Johnston (2020), monarchE† (NCT03155997) [32]	Endocrine therapy plus abemaciclib (N=2,808) vs endocrine therapy alone (N=2,829)	iDFS	0.75 (0.60, 0.93)
		DDFS	0.72 (0.56, 0.92)
Loibl (2021), Penelope-B (NCT01864746) [94]	Endocrine therapy plus palbociclib (N=631) vs endocrine therapy plus placebo (N=619)	OS	0.87 (0.61, 1.23)
		iDFS	0.93 (0.74, 1.17)
		RFS	0.83 (0.49, 1.39)

Appendix B Main characteristics of included studies

Table 63. Overview of study included

Trial name: OlympiA	NCT number: NCT02032823
Objective	OlympiA is a Phase III, double-blind, placebo-controlled, multicentre, randomised controlled trial (RCT; NCT02032823) examining the clinical benefit of adjuvant olaparib therapy in patients with *gBRCAm*, HER2-negative, early breast cancer who have received surgical treatment and prior neoadjuvant or adjuvant chemotherapy
Publications – title, author, journal, year	Tutt, A. N. J. Et al. (2021) [2]. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med, 384(25), 2394-2405. doi:10.1056/NEJMoa2105215
Study type and design	OlympiA is a Phase III, double-blind, parallel group, placebo-controlled, multicentre RCT
Sample size (n)	OlympiA randomised 1,863 patients to the two treatment arms (1:1 olaparib:placebo) and stratified by HR status, receipt of prior neoadjuvant or adjuvant chemotherapy and prior platinum therapy. 921 olaparib, 915 placebo

Trial name: OlympiA	NCT number: NCT02032823
Main inclusion and exclusion criteria	**Inclusion criteria:** • Histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that is one of the following phenotypes: 1. Triple negative breast cancer defined as: ER and PgR negative AND HER2 negative (not eligible for anti-HER2 therapy) 2. ER and/or PgR positive, HER2 negative • Documented germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). • Completed adequate breast and axilla surgery. • Completed at least 6 cycles neoadjuvant or adjuvant chemotherapy containing anthracyclines, taxanes or the combination of both. Prior platinum as potentially curative treatment for prior cancer (e.g. ovarian) or as adjuvant or neoadjuvant treatment for breast cancer is allowed. • ECOG 0-1. **Exclusion criteria:** • Any previous treatment with a PARP inhibitor, including olaparib and/or known hypersensitivity to any of the excipients of study treatment. • Patients with second primary malignancy. EXCEPTIONS are: 1. adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, Ductal Carcinoma in situ (DCIS) of the breast, stage 1 grade 1 endometrial carcinoma 2. other solid tumours and lymphomas (without bone marrow involvement) diagnosed ≥ 5 years prior to randomisation and treated with no evidence of disease recurrence and for whom no more than one line of chemotherapy was applied. • Concomitant use of known strong CYP3A inhibitors or moderate CYP3A inhibitors. The required washout period prior to starting study treatment is 2 weeks. Concomitant use of known strong (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil). The required washout period prior to starting study treatment is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. • Evidence of metastatic breast cancer
Intervention	Olaparib 300 mg bid. Following the first dose of treatment, patients were treated until recurrence of disease, diagnosis of a second primary malignancy, treatment discontinuation or treatment completion. Treatment duration was for up to a maximum of 12 months
Comparator(s)	Placebo bid
Follow-up time	The median duration of follow-up was 2.3 years for the olaparib arm and 2.5 years in the placebo arm
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Primary endpoints:

- Invasive Disease Free Survival (IDFS) [Time Frame: From date of randomisation to data cut off: 27 March 2020 (approximately 5 years 11 months)]

An IDFS event is defined as the first occurrence of loco-regional or distant recurrence or new cancer or death from any cause.

Secondary endpoints:

1. Distant Disease Free Survival (DDFS) [Time Frame: From date of randomisation to data cut off: 27 March 2020 (approximately 5 years 11 months)]
    - A DDFS event is defined as documented evidence of first distant recurrence of breast cancer or death from any cause

2. Overall Survival (OS) [Time Frame: From date of randomisation to data cut off: 27 March 2020 (approximately 5 years 11 months)]
    - An OS event is defined as death by any cause.

3. Number of Participants With Contralateral Breast Cancers, New Primary Ovarian Cancer, New Primary Fallopian Tube Cancer and New Primary Peritoneal Cancer [Time Frame: From date of randomisation to data cut off: 27 March 2020 (approximately 5 years 11 months)]
    - Number of patients with contralateral invasive breast cancer, contralateral non-invasive breast cancer, new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer. Analysis of contralateral breast cancers exclude patients with a bilateral mastectomy prior to randomisation. Analysis of new primary ovarian cancers excludes male patients and patients with a bilateral oophorectomy prior to randomisation. Analysis of new primary fallopian tube cancer excludes male patients and patients with a bilateral salpingectomy prior to randomisation. Analysis of new primary peritoneal cancers excludes male patients.

4. Change From Baseline for FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue) Score for Participants Who Completed Neoadjuvant Chemotherapy [Time Frame: 6 and 12 months after randomisation]
    - Change from baseline for FACIT-Fatigue Score at 6 and 12 months for patients who completed neoadjuvant chemotherapy. Adjusted least-square mean changes and 95% Confidence Interval (CI) are obtained from mixed model for repeated measures (MMRM) analysis of the change from baseline. Only patients with evaluable baseline forms are included. FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue.

5. Change From Baseline for FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue) Score for Participants Who Completed Adjuvant Chemotherapy [Time Frame: 6 and 12 months after randomisation]
    - Change from baseline for FACIT-Fatigue Score at 6 and 12 months for patients who completed adjuvant chemotherapy. Adjusted least-square mean changes and 95% CI are obtained from mixed model for repeated measures (MMRM) analysis of the change

Trial name: OlympiA	NCT number: NCT02032823

from baseline. Only patients with evaluable baseline forms are included. FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue.

6. Change From Baseline for EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questions 30) Scores for Participants Who Completed Neoadjuvant Chemotherapy [Time Frame: 6 and 12 months after randomisation]

   - Change from baseline for EORTC QLQ-C30 Global health status QOL (Quality of Life) Score at 6 and 12 months for patients who completed neoadjuvant chemotherapy. Adjusted least-square mean changes and 95% CI are obtained from mixed model for repeated measures (MMRM) analysis of the change from baseline. Only patients with evaluable baseline forms are included. EORTC QLQ-C30 scores range from 0 to 100 with higher score indicating better quality of life.

7. Change From Baseline for EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questions 30) Scores for Participants Who Completed Adjuvant Chemotherapy [Time Frame: 6 and 12 months after randomisation]

   - Change from baseline for EORTC QLQ-C30 Global health status QOL (Quality of Life) Score at 6 and 12 months for patients who completed adjuvant chemotherapy. Adjusted least-square mean changes and 95% CI are obtained from mixed model for repeated measures (MMRM) analysis of the change from baseline. Only patients with evaluable baseline forms are included. EORTC QLQ-C30 scores range from 0 to 100 with higher score indicating better quality of life.

Method of analysis	Efficacy analyses were based on the intention-to-treat population, which included all the patients who had undergone randomization. Survival functions were estimated by means of the Kaplan–Meier method. The stratified Cox proportional-hazards model was used to estimate the hazard ratio and confidence intervals, and the comparison of survival between trial groups was tested by stratified log-rank testing. Because of the early period when the hazard ratio was very low, the Cox assumption was not confirmed. According to our statistical analysis plan, restricted mean survival time was calculated, and the results supported those obtained from the Cox model analysis. Safety was assessed in the population of patients who received at least one dose of olaparib or placebo. The trial was designed with a sample size of 1800 patients such that the primary analysis would be triggered by 330 events of invasive disease or death in the intention-to-treat population. These conditions would provide the trial with 90% power to detect a hazard ratio of 0.7 under the assumption of a two-sided 5% significance level.
Subgroup analyses	In addition to the analyses of the ITT population, additional subgroup analyses were undertaken based on prior chemotherapy status, prior platinum therapy use, HR status and BRCA mutation type. The subgroup analyses demonstrate a consistent treatment benefit of olaparib over placebo, with results consistent with the analysis of DDFS in the ITT population.
Other relevant information	No

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 64. Summary of patient demographics in OlympiA, interim analysis (FAS)

Patient Characteristics	Olaparib (N=921)	Placebo (N=915)
Age (years)[a]		
Mean (SD)	43.0 (9.82)	43.6 (10.12)
Median (range)	42.0 (22–77)	43.0 (24–78)
Sex, n (%)		
Female	919 (99.8)	911 (99.6)
Male	2 (0.2)	4 (0.4)
Race, n (%)		
White	626 (68.0)	599 (65.5)
Asian	259 (28.1)	272 (29.7)
Black or African American	19 (2.1)	29 (3.2)
Native Hawaiian or other Pacific Islander	1 (0.1)	0
American Indian or Alaska Native	3 (0.3)	1 (0.1)
Other	3 (0.3)	6 (0.7)
Missing	10 (1.1)	8 (0.9)

Footnotes: *DCO1: 27 March 2020. [a]Age was calculated as the patients age at randomisation..*
Source: *AstraZeneca Data on File (OlympiA CSR);[36] Tutt et al. 2021;[2] OlympiA EPAR Table 8 [3]*

Table 65. Summary of patient baseline disease characteristics in OlympiA, interim analysis (FAS)

Patient Characteristics	Olaparib (N=921)	Placebo (N=915)
ECOG Performance Status, n (%)		
0	824 (89.5)	804 (87.9)
1	97 (10.5)	111 (12.1)
≥2	0	0
Missing	0	0
Clinical AJCC stage, n (%)		
IA	103 (11.2)	85 (9.3)
IB	0	0
IIA	329 (35.7)	334 (36.5)
IIB	190 (20.6)	195 (21.3)
IIIA	128 (13.9)	111 (12.1)
IIIB	28 (3.0)	30 (3.3)
IIIC	42 (4.6)	56 (6.1)
IV	0	0
Missing	101 (11.0)	104 (11.4)
HR status, n (%)		
TNBC	753 (81.8)	758 (82.8)
ER and/or PR-positive, HER2-negative	168 (18.2)	157 (17.2)
***BRCA* status, n (%)**		
BRCA1 mutated	656 (71.2)	669 (73.1)
BRCA2 mutated	260 (28.2)	238 (26.0)
BRCA1 and *BRCA2* mutated	2 (0.2)	5 (0.5)
Prior chemotherapy		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Prior therapy in the neoadjuvant/adjuvant setting		

Patient Characteristics	Olaparib (N=921)	Placebo (N=915)
Anthracycline and taxane regimen	871 (94.6)	849 (92.8)
Anthracycline regimen (without taxane)	7 (0.8)	13 (1.4)
Taxane regimen (without anthracycline)	43 (4.7)	52 (5.7)
Missing	0	1 (0.1)
Prior breast cancer surgery, n (%)		
Non-conservative surgery	698 (75.8)	673 (73.6)
Conservative surgery	223 (24.2)	240 (26.2)
Unknown	0	0 (0.2)

Footnotes: *DCO1: 27 March 2020.*
Source: *AstraZeneca Data on File (OlympiA CSR) [36]; Tutt et al. 2021 [2]*

Table 66. Patient disposition in OlympiA, DC02 (FAS)

Patient Disposition	Olaparib (N=921)	Placebo (N=915)
Randomised, n (%)	921 (100)	915 (100)
Treated, n (%)	911 (98.9)	904 (98.8)
Ongoing study treatment, n (%)	0 (0)	0 (0)
Patients who completed treatment per CSP, n (%)	674 (73.2	715 (78.1)
Discontinued study treatment,[a] n (%)	237 (25.7)	189 (20.7)
AE	98 (10.6)	43 (4.7)
Lost to follow-up	2 (0.2)	1 (0.1)
Patient decision to stop study drug	59 (6.4)	30 (3.3)
Patient decision to provide survival status only	11 (1.2)	4 (0.4)
Patient decision to withdraw	13 (1.4)	6 (0.7)
Death	1 (0.1)	0
Disease recurrence	40 (4.3)	80 (8.7)
Severe non-compliance to CSP	0	5 (0.5)
Other	13 (1.4)	20 (2.2)
Median duration of treatment, days (range)[b]		
Median duration of treatment (actual treatment exposure)	350 (1–420)	359 (2–404)
Median duration of follow-up, years		
Median duration of follow-up	3.5 (0–6.7)	3.6 (0–6.6)

Footnotes: *DCO2: 12 July 2021. Patient disposition in the FAS. [a]Percentages were calculated from number of patients who received treatment. [b]Data obtained using the SAS rather than FAS.* ***Source:*** *[2, 95]*

Comparability of patients across studies

Not relevant

Comparability of the study populations with Danish patients eligible for treatment

OlympiA is a collaborative study, coordinated worldwide and conducted by Breast International Group (BIG) in partnership with Frontier Science, NRG Oncology (National Cancer Institute [NCI] supported National Clinical Trials Network Group) and AstraZeneca and is therefore governed externally to AstraZeneca.

In OlympiA, HER2-negative ((HR [ER and/or PR]-positive or TNBC) patients with presence of a mutation in the BRCA1 and/or BRCA2 genes (this may be gBRCAm or sBRCAm) and with early breast cancer (invasive that is non-metastatic (stages I–III)) was enrolled and defined as high risk based on the following to ensure that a similar population in terms of risk of recurrence was enrolled across biomarker subgroups and specific criteria:

- Patients who underwent initial surgery and received adjuvant chemotherapy:
    - TNBC patients must have been axillary node-positive (≥pN1, any tumour size) or axillary node negative (pN0) with invasive primary tumour pathological size >2 cm (≥pT2)
    - HR-positive/HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes (pN2a)
- Patients who underwent neoadjuvant chemotherapy followed by surgery:
    - TNBC patients must have residual invasive breast cancer in the breast and/or resected lymph nodes (non-pathological complete response [non-pCR]) (T1+, N1+)
    - HR-positive/HER2-negative patients must have residual invasive cancer in the breast and/or the resected lymph nodes (non-pCR) and a CPS&EG score ≥3 (T1+, N1+)

So, as outlined above, recurrence risk was defined based on biomarker status and the presence of residual disease or positive pathologically-confirmed lymph nodes, following local treatment and adjuvant or neoadjuvant chemotherapy. Of particular note, OlympiA used the CPS&EG score (a score that incorporates ER status and tumour grade with pre-treatment clinical stage [CS] and post-treatment pathologic stage [PS]) to provide a standardized, trial-appropriate approach to identifying patients with HR-positive/HER2-negative disease who were at similarly high risk of recurrence following neoadjuvant chemotherapy and surgery as those with TNBC [2, 30].

In clinical practice, a variety of methods may be used to identify patients at high risk of recurrence, likely based on local practice and clinical experience. The definitions of high risk used in OlympiA are anticipated to be broadly consistent with these; for example, potential considerations in clinical practice are known to include the presence of residual disease after surgery [96, 97], and gene expression profiles or molecular recurrence scores [21]. Furthermore, whilst the use of the CPS&EG score potentially defines a narrower population of HR-positive/HER2-negative patients than would occur in clinical practice, the intent of the CPS&EG score in determining risk status is aligned with that of the approaches used in clinical practice.
Accordingly, danish clinical experts also expressed that in real life clinical practice, more patients would have been regarded as high risk based on local practice than the ones included in the OlympiA trial according to CPS&EG score. Nevertheless, danish clinical experts confirmed that patients included in the OlympiA trial owns at least the same criteria that would have been regarded as high risk according to local clinical practice in Denmark, but less strict would also have been sufficient, meaning that some relevant high risk candidates for Lynparza was left out of the OlympiA study. To decide on pathological diagnosis of breast cancer and severeness, the danish local practice is amongst others

influenced by the World Health Organization (WHO) classification and AJCC TNM staging system; the AJCC TNM staging system describes tumour size (T), the spread of cancer to nearby lymph nodes (N) and the presence of metastases [98, 99].

However, the results of the OlympiA trial is by danish clinical experts believed to be transferable to a high risk population in Denmark in respect of the BRCAm status. The latter regardless of HR status although HR-positive consisted of a smaller study group compared to real life, due to later enrolment allowance, as a protocol amendment had to be in place to allow endocrine therapy to be combined with Lynparza in order to mimic real life clinical practice as much as possible. Hence, TNBC ended up consisting the largest study group due to longer recruitment period, versus the HR-positive group, before the OlympiA trial was recommend to end enrolment as the primary endpoint was successfully achieved [2].

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 67. Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Median overall survival (OS)	Time from the date of randomisation until death due to any cause. Investigator-assessed [2, 30].	According to guidance provided by the EMA and FDA, OS should be used as the standard clinical benefit endpoint in oncology clinical trials [100, 101]	OS is a key outcome for clinicians and patients.
Median Invasive Disease Free Survival (IDFS)	Time from randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, new cancer or death from any cause [2, 30] Investigator-assessed using the STEEP system definition; must be cytologically/histologically confirmed [2, 102]	IDFS is a well-established and widely accepted endpoint in early breast cancer, recognised by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) [100, 101].	IDFS provides a suitable interim measure before OS data are available, as OS is often long in this patient population [55]. IDFS captures a robust overview of clinically relevant effects of a treatment [103] and has been correlated with OS [104]
Median Distant Disease Free Survival (DDFS)	Time from randomisation until documented evidence of first distant recurrence of breast cancer.	DDFS includes distance recurrence or death. Distant recurrence is generally considered a greater threat to patient survival (vs. local recurrence) as distant	DDFS has as IDFS been highly associated with OS in breast cancer [104].

Outcome measure	Definition	Validity	Clinical relevance
	Investigator-assessed, including the following events: distant recurrence, death attributable to any cause, second primary non-breast invasive cancer [2, 30].	recurrence is the main predictor of death in these patients. However, DDFS does not capture as many clinically relevant effects of a therapy as IDFS.	

Results per study

Table 68. Summary of clinical results in OlympiA

Results of OlympiA N Engl J Med 2021; 384:2394-2405										NCT02032823	
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IDFS (events, number (%)	Olaparib	921	106 (11.5)* 134 (14.5)**	8.0 %* 8.1 %**	4.65%, 11.24%* 4.53%, 11.61%**		HR= 0.58* HR= 0.63**	99.5 % CI: (0.41,0.82)* 95 % CI: (0.50, 0.78)**	0.000007* 0.0000233**	Outcome based on Kaplan-Meier estimates and HR on the stratified Cox's Proportional Hazards Model. CI for absolute values calculated by AstraZeneca	DCO1* DCO2**
	Placebo	915	178 (19.5)* 207 (22.6)**								
OS (events, number (%)	Olaparib	921	59 (6.4)* 75 (8.1)**	3.0 %* 3.8 %**	0.53%, 5.46%* 1.03%, 6.51%**		HR= 0.68* HR= 0.68**	99% CI: (0.44, 1.05)*	0.0236* 0.009**	Outcome based on Kaplan-Meier estimates and HR on the stratified Cox's Proportional Hazards Model. At DCO1* the OS data were 7.9% mature (145 events/1.836	DCO1* DCO2**
	Placebo	915	86 (9.4)* 109 (11.9)**								

							98.5 %CI: (0.47, 0.97)**		patients). At DCO2**, the OS data was 10.0% mature (184 events/1.836 patients. Median follow-up for OS was 2.4 years in the olaparib arm and 2.5 years in the placebo arm. CI for absolute values calculated by AstraZeneca	
OS (alive) at 3 years	Olaparib	921	92.0 % (89.6, 93.9)* 92.8 % (90.8, 94.4)**	0.037* 0.037**		HR: 0.68* HR= 0.68**	99% CI: (0.44,1.05)* 98.5 CI: (0.47, 0.97)**	0.0236* 0.009**	Based on Kaplan-Meier estimates	DCO1* DCO2**
	Placebo	915	88.3 % (85.4, 90.7)* 89.1% (86.7, 91.0)**							
DDFS (events, number (%)	Olaparib	921	89 (9.7)* 107 (11.6)**	6.9 %* 7.2 %**	3.87%, 10.02%* 3.91%, 10.45%**	HR= 0.57* HR=0.607**	99.5 % CI: (0.39, 0.83)* 95 % CI: (0.48, 0.77)**	0.0000257* 0.0000421**	Outcome based on Kaplan-Meier estimates and HR on the stratified Cox's Proportional Hazards Model. CI for absolute values calculated by AstraZeneca	DCO1* DCO2**
	Placebo	915	152 (16.6)* 172 (18.8)**							

Note: Efficacy results are from DCO1* (27 March 2020) and DCO2** (12 July 2021) [3, 36].

Results of OlympiA N Engl J Med 2021; 384:2394-2405										NCT02032823	
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IDFS (events, number (%))	Olaparib	921	106 (11.5)* 134 (14.5)**	8.0 %* 8.1 %**			HR= 0.58* HR=0.63**	99.5 % CI: (0.41, 0.82)* 95 % CI: (0.50, 0.78)**	0.000007* 0.000023**	Outcome based on Kaplan-Meier estimates and HR on the stratified Cox's Proportional Hazards Model.	DCO1* DCO2**
	Placebo	915	178 (19.5)* 207 (22.6)**								
OS (events, number (%))	Olaparib	921	59 (6.4)* 75 (8.1)**	3.0 %* 3.8 %**			HR= 0.68* HR= 0.68**	99% CI: (0.44, 1.05)* 98.5 % CI: (0.47, 0.97)**	0.0236* 0.009**	Outcome based on Kaplan-Meier estimates and HR on the stratified Cox's Proportional Hazards Model. At DCO1* the OS data were 7.9% mature (145 events/1.836 patients). At DCO2**, the OS data was 10.0% mature (184 events/1.836 patients.	DCO1* DCO2**
	Placebo	915	86 (9.4)* 109 (11.9)**								

Results of OlympiA N Engl J Med 2021; 384:2394-2405								NCT02032823	
								Median follow-up for OS was 2.4 years in the olaparib arm and 2.5 years in the placebo arm.	
OS (alive) at 3 years	Olaparib	921	92.0 % (89.6, 93.9)* 92.8 % (90.8, 94.4)**	0.037* 0.037**		HR: 0.68* HR= 0.68**	99% CI: (0.44, 1.05)* 98.5 % CI: (0.47, 0.97)**	0.0236* 0.009**	Based on Kaplan-Meier estimates	DCO1* DCO2**
	Placebo	915	88.3 % (85.4, 90.7)* 89.1% (86.7, 91.0)**							
DDFS (events, number (%))	Olaparib	921	89 (9.7)* 107 (11.6)**	6.9 %* 7.2 %**		HR= 0.57* HR=0.61**	99.5 % CI: (0.39, 0.83)* 95 % CI: (0.48, 0.77)**	0.000026* 0.000042**	Outcome based on Kaplan-Meier estimates and HR on the stratified Cox's Proportional Hazards Model.	DCO1* DCO2**
	Placebo	915	152 (16.6)* 172 (18.8)**							

Note: Efficacy results are from DCO1* (27 March 2020) and DCO2** (12 July 2021) [2, 3, 36]

Appendix E Safety data for intervention and comparator(s)

Table 69. SAEs and CTCAE Grade≥3 AEs reported in OlympiA (≥3 in either arm) DC02, SAS

SAEs	N (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
Patients with any SAEs	79 (8.7)	78 (8.6)
Blood and lymphatic system disorders	**18 (2.0)**	**1 (0.1)**
Anaemia	15 (1.6)	1 (0.1)
Febrile neutropenia	3 (0.3)	0 (0)
Gastrointestinal disorders	4 (0.5)	6 (0.7)
Abdominal pain	0 (0)	3 (0.3)
Infections and infestations	16 (1.8)	15 (1.7)
Device related infection	3 (0.3)	2 (0.2)
Mastitis	3 (0.3)	6 (0.7)
General disorders and administration site conditions	5 (0.5)	4 (0.4)
Pyrexia	1 (0.1)	3 (0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.5)	19 (2.1)
Breast cancer	1 (0.1)	3 (0.3)
Malignant melanoma	1 (0.1)	4 (0.4)
Ovarian cancer	0 (0)	4 (0.4)
Injury, poisoning and procedural complications	4 (0.4)	8 (0.9)

Wound dehiscence	1 (0.1)	4 (0.4)
Grade ≥3 AEs	**N (%)a**	
	Olaparib (N=911)	**Placebo (N=904)**
Patients with any CTCAE Grade ⩾3 AE	223 (24.5)	102 (11.3)
Blood and lymphatic system disorders	86 (9.4)	3 (0.3)
Anaemia	79 (8.7)	3 (0.3)
Febrile neutropenia	6 (0.7)	0
Investigations	70 (7.7)	16 (1.8)
Neutrophil count decreased	45 (4.9)	7 (0.8)
White blood cell count decreased	27 (3.0)	3 (0.3)
Lymphocyte count decreased	12 (1.3)	0
ALT increased	3 (0.3)	1 (0.1)
Infections and infestations	21 (2.3)	18 (2.0)
Mastitis	3 (0.3)	4 (0.4)
Device related infection	3 (0.3)	2 (0.2)
Gastroenteritis	3 (0.3)	0
General disorders and administration site conditions	19 (2.1)	10 (1.1)
Fatigue	16 (1.8)	6 (0.7)

Gastrointestinal disorders	18 (2.0)	9 (1.0)
Nausea	7 (0.8)	
Vomiting	6 (0.7)	0
Diarrhoea	3 (0.3)	3 (0.3)
Abdominal pain	2 (0.2)	3 (0.3)
Nervous system disorders	12 (1.3)	7 (0.8)
Syncope	3 (0.3)	2 (0.2)
Vascular disorders	8 (0.9)	10 (1.1)
Hypertension	5 (0.5)	9 (1.0)
Embolism	3 (0.3)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.5)	12 (1.3)
Ovarian cancer	0	3 (0.3)
Psychiatric disorders	5 (0.5)	6 (0.7)
Depression	0	3 (0.3)

Footnotes: *DCO2: 12 July 2021. Includes SAEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo. Sorted by decreasing frequency in the olaparib arm for SOC and PT. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. MedDRA Version 22.1. [a]Number (%) of patients with AEs of CTCAE Grade ⩾3, sorted by decreasing frequency for SOC and by decreasing frequency in the olaparib arm order for PT. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date or that worsened on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo. CTCAE Version 4.03. MedDRA Version 22.1.* ***Source*** *[40]*

Appendix F Comparative analysis of efficacy and safety

Table 70. Summary of OlympiA efficacy endpoints, DC02 (FAS)

		Olaparib (N=921)	Placebo (N=915)
IDFS			
Number of events, n (%)		134 (14.5)	207 (22.6)
Estimate of hazard ratio[a]		0.628	
95% CI for hazard ratio[b, c]		(0.504, 0.779)	
Log-rank test: p-value[d]		0.0000233	
Percentage (95% CI) of patients free of invasive disease at:	1 year	93.4% (91.5%, 94.9%)	88.4% (86.1%, 90.3%)
	2 year	89.7% (87.4%, 91.6%)	81.4% (78.7%, 83.8%)
	3 year	86.1% (83.5%, 88.3%)	77.3% (74.3%, 80.0%)
	4 years	82.7% (79.6%, 85.4%)	75.4% (72.2%, 78.3%)
Median clinical follow-up time (years) (minimum-maximum)		3.5	3.6
Type of IDFS event[f]			
Distant CNS recurrence		24 (2.6)	38 (4.2)
Distant excluding CNS recurrence		64 (6.9)	98 (10.7

Regional (ipsilateral) recurrence		9 (1.0)	18 (2.0)
Local (ipsilateral) recurrence		9 (1.0)	12 (1.3)
Contralateral invasive breast cancer		15 (1.6)	18 (2.0)
New primary cancers		11 (1.2)	23 (2.5)
Deaths without a prior IDFS event		2 (0.2)	0 (0)
OS			
Number of events, n (%)		75 (8.1)	109 (11.9)
Estimate of hazard ratio[a]		0.678	
95% CI for hazard ratio[b, c]		(0.503 , 0.907)	
98.5% CI for hazard ratio[b, e]		(0.468 , 0.973)	
Log-rank test: p-value[d]		0.009	
Percentage (95% CI) of patients alive at:	1 year	98.0% (96.9%, 98.8%)	96.9 (95.5, 97.9)
	2 years	95.0% (93.3%, 96.2%)	92.8% (90.9%, 94.3%)
	3 years	92.8% (90.8%, 94.4%)	89.1% (86.7%, 91.0%)
	4 years	89.8% (87.2%, 91.9%)	86.4% (83.6%, 88.7%)
Median clinical follow-up time (years) (minimum-maximum)		3.5	3.6

DDFS			
Number of events, n (%)		107 (11.6)	172 (18.8)
Estimate of hazard ratio[a]		0.607	
95% CI for hazard ratio[b, c]		(0.476, 0.771)	
Log-rank test: p-valued		0.0000421	
Percentage (95% CI) of patients free of distant disease at:	1 year	94.4% (92.6%, 95.7%)	90.3% (88.2%, 92.1%)
	2 years	90.6% (88.4%, 92.4%)	84.0% (81.4%, 86.3%)
	3 years	88.0% (85.5%, 90.1%)	81.0% (78.1%, 83.5%)
	4 years	86.5% (83.8%, 88.8%)	79.1% (76.0%, 81.8%)
Median clinical follow-up time (years) (minimum-maximum)		3.5	3.5

Footnotes: *DCO2: 12 July 2021. [a]Estimate of the treatment hazard ratio based on the stratified Cox's Proportional Hazards Model; <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors are the same as those used in the stratified log-rank test. [b]The CI for the hazard ratio was estimated using the profile likelihood approach. [c]Exploratory, not inferential. [d]p-value from a stratified log-rank test. Stratification is by chemotherapy type (2 levels: adjuvant vs. neoadjuvant), hormone receptor status (2 levels: ER and/or PR-positive/HER2-negative vs. TNBC) and prior platinum therapy (2 levels: yes vs. no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. [e]Inferential, according to alpha spending rules for the interim analysis of overall survival.[f] If two recurrence events were reported within 2 months of each other this was referred to as a simultaneous event and was considered as a single event. In this situation the worst case was taken as the event 'type', but the date of recurrence was the earliest date of the two events.*

Source: *[37]*

Appendix G Extrapolation

Assessment of model fit

The overall fit of the 'semi-Markov' model to the trial data was assessed by comparing landmark IDFS (i.e., proportion occupying the IDFS state) and OS (i.e., proportion alive) at years 1, 2, 3 and 4 in the model, with the landmark results of the trial.

The modelled landmark rates of IDFS and OS were compared to external data from studies reporting long-term IDFS, DDFS or OS by receptor status (see section 4 of this Appendix).

A targeted review identified the study by Copson et al [105] that reported relevant 10-year DDFS results for BRCAm TNBC. Limited data were available on the IDFS or DDFS of BRCAm patients with high risk, HER2-/HR+ disease. In the absence of these data, the plausibility of model extrapolation was based on the comparison with distant recurrence rates from the meta-analysis by Pan et al [53]. This study reported recurrence rates for patients treated with adjuvant endocrine therapy over a 20-year period and included results that were stratified by the number of positive nodes. This enabled the selection of recurrence data that approximately matches the high risk inclusion criteria of OlympiA; patients with 4 or more positive nodes [53]. The external data from Copson [105] and Pan [53] were used to determine the best fitting models for the watch and wait arm and they are presented in detail in this appendix (Appendix G), section 4.

Table 71. Description of transitions and data sources within economic model

ID	Transitions	Data Source	Different risks by treatment arm	Notes/ definition of statistical endpoint and parametric survival models used for long-term extrapolation	Number at risk	Number of events
TP1, TP2	IDFS to 'non-metastatic breast cancer' or 'metastatic breast cancer'	OlympiA, DCO2 [2, 7, 106]	Survival in favour of olaparib as observed in OlympiA	Time from randomisation to distant recurrence, non-distant recurrence, or death (primary endpoint of IDFS). The Gompertz distribution was used for both arms for the TNBC subgroup, on the basis that it was the best fitting model in terms of AIC score for both arms. Also it yields the closest predictions of observed hazard rates, the closest prediction of 5-year IDFS and reasonable prediction of 10-year IDFS for watch and wait compared to external data. The lognormal distribution was used for both arms for the HER2-/HR+ subgroup, on the basis that it was the best fitting model for olaparib and the second-best fitting for the watch and wait arm in terms of AIC score. Also, it yields the closest predictions of 10-, 15- and 20-year IDFS for watch and wait compared to external data. The transition probabilities for TP1 and TP2 are estimated by apportioning the risk of IDFS to distant or non-distant recurrence events, under the assumption that the probability of a non-distant recurrence is constant over time For further details see section 1 in Appendix G.	ITT olaparib, n=921 Placebo, n=915	ITT olaparib, n=134 Placebo, n=207
TP3	IDFS to 'Death'	Danish general population mortality [63] adjusted for excess mortality risk in BRCA patients using data from Mai et al [64]	Same risk	The risk of death without recurrence is modelled using all-cause mortality data from the Statistics Denmark life tables The background mortality risk is matched on the age-, gender and BRCA status of the model population as outlined in section 1 in Appendix G.	-	-
TP4	'non-metastatic breast cancer' to 'metastatic breast cancer'	OlympiA, DCO2 [2, 7, 106]	Same risk	Time from non-metastatic disease recurrence to metastatic disease recurrence. Patients that died prior to metastatic diagnosis were censored at their event time. The risk of metastatic recurrence was pooled across arms given limited event numbers and because the risks observed were similar by arm. The lognormal distribution was used for long-term extrapolation, on the basis that it was the best fitting model in terms of AIC score. For further details see section 2 in Appendix G.	Pooled across arms, n=81	Pooled across arms, n=15

TP5	'non-metastatic breast cancer' to Death	OlympiA, DCO2 [2, 7, 106]	Same risk	Time from non-metastatic disease recurrence to death. Patients that had metastatic recurrence were censored at their event time. The risk of metastatic recurrence was pooled across arms given limited event numbers and because the risks observed were similar by arm. The exponential distribution was used for long-term extrapolation. This selection was guided by the goodness of fit statistics and the fact that it was considered to better reflect the risk of death trends overtime for non-metastatic breast cancer patients compared to other distributions. For further details see section 2 in Appendix G.	Pooled across arms, n=81	Pooled across arms, n=3
TP6	'early onset metastatic breast cancer' to Death	OlympiA, DCO2 [2, 7, 106]	Survival in favour of patients randomised to placebo as observed in OlympiA	Time from early metastatic disease recurrence to death. The exponential distribution was used for both arms for long-term extrapolation. This selection was guided by the goodness of fit statistics. Also it was judged to provide the most plausible predictions at 5- and 10-years for watch and wait when compared to literature estimates. The same distribution was selected for both arms for consistency. For further details see section 3 in Appendix G.	Olaparib, n=105 Placebo, n=169	Olaparib, n=70 Placebo, n=103

TP7	'late onset metastatic breast cancer' to Death	Final OS analysis of OlympiAD [60] A real-world study of CDK4/6 inhibitor treatment in gBRCAm mBC using the Flatiron health data base [62] BRCAm subgroup of IMpassion 130 clinical trial [61]	Same risk	Time from first-line treatment to death in patients with metastatic breast cancer [external data] OlympiAD: The lognormal distribution was used for the chemotherapy arm, on the basis that it was the best fitting model in terms of AIC and BIC scores Collins et al.: The loglogistic distribution was used for the CDK4/6 inhibitor plus endocrine therapy arm, on the basis that it was the best fitting model in terms of AIC and BIC scores IMpassion 130: The OS hazard ratio for atezolizumab plus nab-paclitaxel versus nab-paclitaxel as first-line treatment in patients with metastatic TNBC from the BRCAm subgroup of the IMpassion 130 clinical trial is used as a proxy for the pembrolizumab plus paclitaxel effect due to absence of BRCAm specific efficacy data for pembrolizumab. For further details see section 3 in Appendix G.	OlympiAD: olaparib, n=59 Chemotherapy, n=28 Collins et al.: CDK4/6 inhibitor plus endocrine therapy n=36 IMpassion 130: PD-L1 and BRCA1/2 mutation positive n=44	OlympiAD: olaparib, n=30 Chemotherapy, n=21 Collins et al.: CDK4/6 inhibitor plus endocrine therapy n=13 IMpassion 130: PD-L1 and BRCA1/2 mutation positive n=20

***Table note**: The total numbers at risk of death after "early onset" metastatic breast cancer in OlympiA is 274 (n=105 + n=169 = 274). This comprises 258 patients that had distant metastatic breast cancer from IDFS (n=99 + n=159 =258), 15 patients that had distant metastatic breast cancer after non-distant metastatic disease, and 1 placebo patient that was censored for IDFS at day 0.5 due to a pre-randomisation event but had a distant metastatic event during follow-up. The post-recurrence survival of this patient is included in the analysis for TP6 but is not included as an event in the analysis of TP1-2.*

1. Modelling of IDFS (TP1, TP2 and TP3)

The modelling of IDFS was conducted in four stages:

1. the fitting of parametric survival models to the primary endpoint of IDFS of OlympiA
2. adjustment for the short- and long-term rate of recurrence in TNBC and HER2-/HR+ (TP1 and TP2)
3. the apportioning of the hazard rate for IDFS to the cause-specific hazards of distant (TP1) and non-distant recurrences (TP2) using a constant conditional probability of a developing a non-distant recurrence
4. and the modelling of deaths without recurrence (TP3) using the BRCA-inflated age- and gender-matched background mortality.

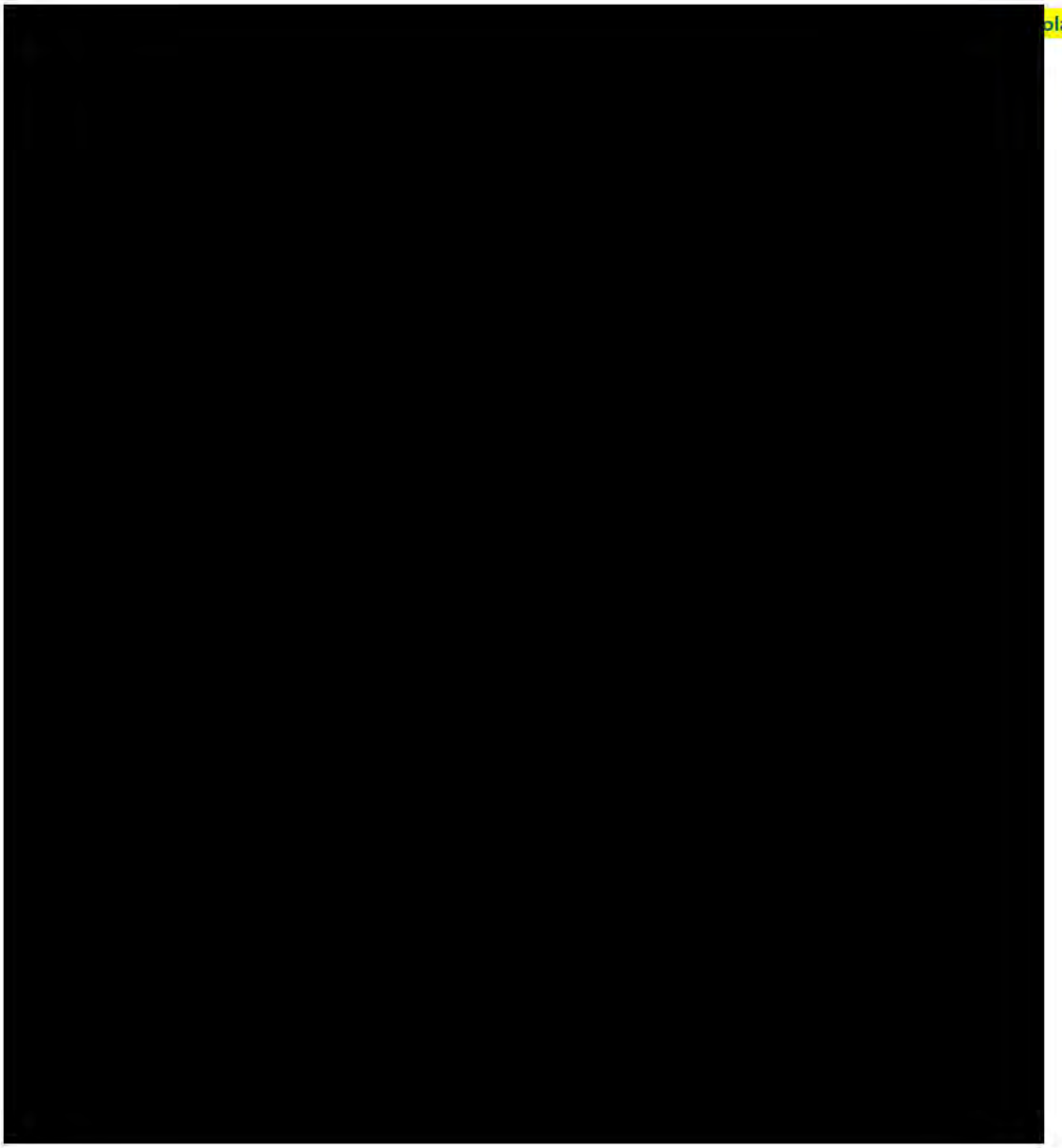
The derivation of the clinical parameters for TP1, TP2 and TP3 is outlined in the following sections. The general approach to survival analysis and state transition modelling is covered in section 9.5.2.

Step one: parametric survival analysis for IDFS (TP1 and TP2)

At the interim analysis of IDFS, an assessment of proportional hazards (PH) was conducted as part of the planned statistical analysis of the OlympiA trial. The PH assumption was assessed by visual inspection of the log-cumulative hazards plot and using the Grambsch–Therneau (G-T) test. Under PH, the log-cumulative hazards plot will show approximately parallel lines by arm, and the G-T test would not be statistically significant (p>0.05).

The assessment of PH for IDFS was conducted on the data from DCO2. In the TNBC and ITT (proxy for HR+) populations of OlympiA, the unadjusted G-T test results were p=0.0065 and p=0.0018 respectively. The Schoenfeld and log-cumulative hazard plots [redacted] for TNBC and [redacted] for ITT as proxy for HR+) showed evidence of non-PH in the form of a non-horizontal log-hazard ratio and non-parallel lines between arms, respectively. These results indicate that the PH assumption does not hold for this endpoint.

olaparib



A series of independent parametric survival models was fitted to patient-level data from each arm of OlympiA. The statistical goodness of fit was reported in terms of the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores, where a lower score indicates improved fit (Table 72).
For TNBC, the best fitting models according to AIC score were the:

- Gompertz (1st in both arms)
- lognormal (2nd in both arms)
- loglogistic (3rd for olaparib) and,
- Generalised Gamma (3rd for placebo)

Similar trends were observed for BIC score with the exception that the exponential model was best fitting on BIC for the olaparib arm, followed by the Gompertz. For placebo, the exponential was the worst fitting on both AIC and BIC score, and the worst fitting model for AIC in the olaparib arm. Both the Weibull (5th) and Gamma (6th) functions performed poorly on AIC and BIC in both arms.
For the ITT population (proxy for HER2-/HR+), the best fitting models according to AIC were the:

- lognormal (1st for olaparib and 2nd for placebo)
- Gompertz (2nd for olaparib and 1st for placebo)
- loglogistic (3rd for olaparib) and,
- Generalised Gamma (3rd for placebo)

As with the TNBC population, the BIC scores for olaparib favoured the exponential model followed by the lognormal. For placebo, Gompertz remained best fitting on BIC, followed by lognormal. The exponential was the worst ranked function for AIC and BIC for the placebo arm and ranked 5th (of 7) for AIC in the olaparib arm. Both the Weibull (5-6th) and Gamma (6-7th) functions performed poorly on AIC and BIC in both arms.

Overall, the Gompertz and lognormal were consistently the best fitting functions according to AIC and BIC score across arms and populations.

Table 72. AIC and BIC values for the parametric survival models fitted to the time from randomisation to distant

Model	Rank on lowest AIC/BIC by arm	Olaparib [O]		Placebo [P]	
		AIC	BIC	AIC	BIC
Time from randomisation to disease recurrence or death (TNBC)					
Exponential	[O]: 7 / 1 - [P]: 7/7	1428.04	1432.66	2098.13	2102.76
Weibull	[O]: 5 / 5 - [P]: 5/5	1426.93	1436.18	2060.75	2070.01
Loglogistic	[O]: 3 / 4 - [P]: 4/3	1425.84	1435.08	2056.86	2066.12
Lognormal	[O]: 2 / 3 - [P]: 2/2	1424.02	1433.26	2050.79	2060.05
Gompertz	[O]: 1 / 2 - [P]: 1/1	1423.86	1433.11	2047.87	2057.13
Generalised Gamma	[O]: 4 / 7 - [P]: 3/4	1425.95	1439.82	2052.41	2066.30
Gamma	[O]: 6 / 6 - [P]: 6/6	1427.26	1436.5	2063.23	2072.50
Time from randomisation to disease recurrence or death (ITT data used as proxy for HR+)					
Exponential	[O]: 5 / 1 - [P]: 7/7	1750.43	1755.26	2508.00	2512.82
Weibull	[O]: 6 / 5 - [P]: 5/5	1750.93	1760.58	2472.80	2482.43
Loglogistic	[O]: 3 / 4 - [P]: 4/4	1749.86	1759.51	2468.38	2478.02
Lognormal	[O]: 1 / 2 - [P]: 2/2	1748.18	1757.83	2461.37	2471.01
Gompertz	[O]: 2 / 3 - [P]: 1/1	1748.88	1758.53	2458.98	2468.62
Generalised Gamma	[O]: 4 / 7 - [P]: 3/3	1749.98	1764.45	2463.04	2477.50
Gamma	[O]: 7 / 6 - [P]: 6/6	1751.14	1760.80	2475.40	2485.04

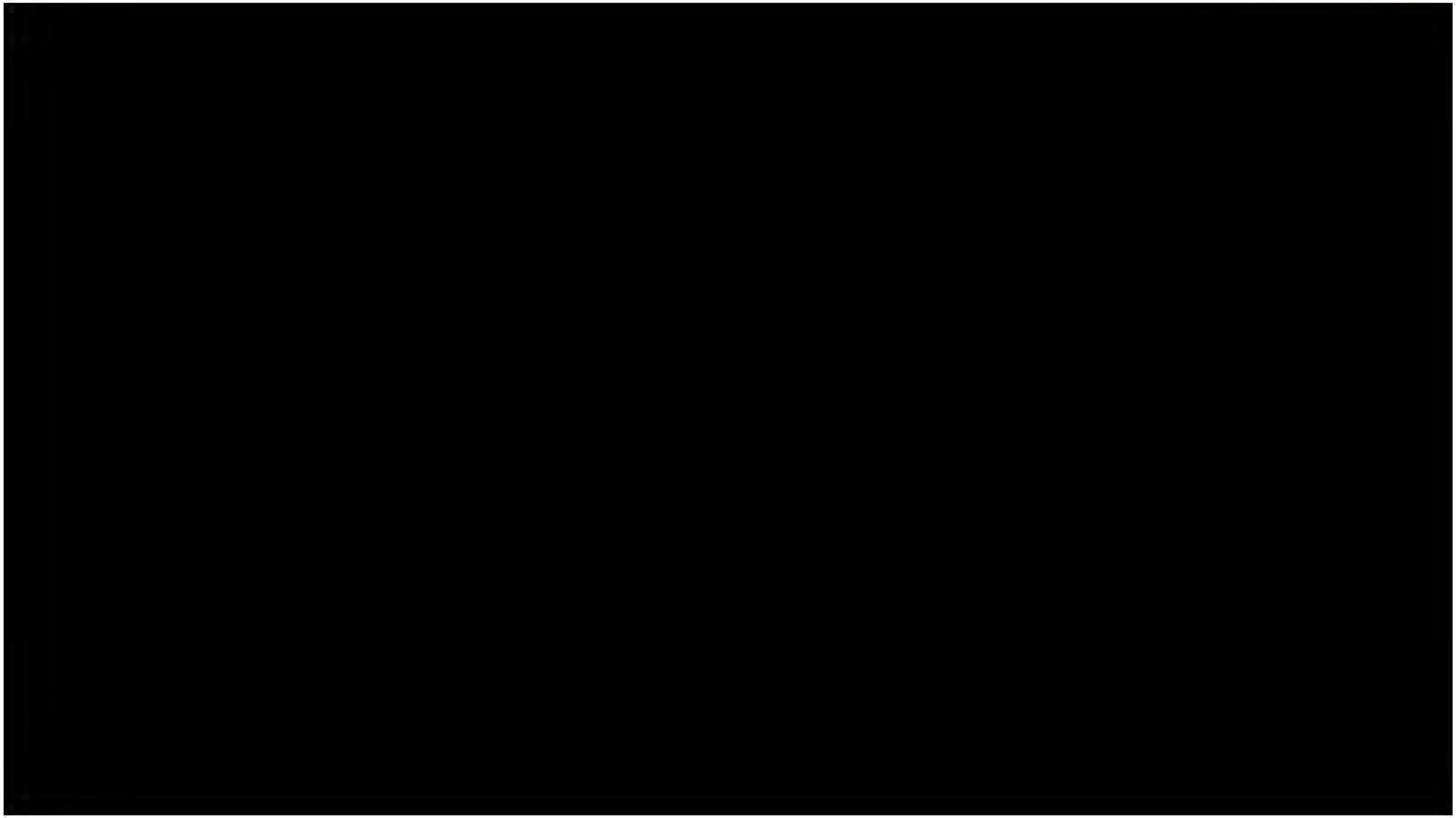
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

The fit of the models to the Kaplan-Meier plot for IDFS is shown in [redacted] (olaparib) and [redacted] (placebo) for TNBC and [redacted] (olaparib) and Figure 36 (placebo) for ITT (proxy for HER2-/HR+). A comparison of the modelled and observed smoothed hazard rate by arm and population is also shown in Figure 37.

For the olaparib arm, all models provided a reasonable prediction of the Kaplan-Meier probabilities for IDFS up to the end of study follow-up (~78 months). For the placebo arm, most models yielded a reasonable fit to the Kaplan-Meier for IDFS. The exponential model gave a notably poor fit to the data and was found to overestimate survival in the first 2-years and underestimate placebo survival at later time points.

In the comparison of modelled and observed hazard rates (Figure 37), the Gompertz model yielded the closest prediction of the observed hazards during the first 4 years of follow-up for the placebo arm in both the TNBC and ITT (proxy for HER2-/HR+) populations. After 4-years, the observed hazard rate is highly uncertain due to study attrition (median follow-up at DCO2 of ~ 3.5 years). The observed hazard showed an uncharacteristic increase in the hazard rate for placebo patients. None of the fitted models accurately predicted the hazards observed in this period. All the models predicted either an approximately constant or decreasing hazard over time.

For the olaparib arm, the Gompertz, and lognormal models provided the closest prediction of the hazard rates in both the TNBC and ITT (proxy for HER2-/HR+) populations. This is in line with the rankings of best fitting models based on AIC and BIC. The long-term trend in the hazard rate for olaparib was similar to placebo, with rates that are predicted to be approximately constant or decreasing over time.



A summary of the goodness of fit of the models to the data from both arms of the study is shown in Table 73. In summary, the Gompertz and lognormal models consistently provide the best fit to the IDFS data in OlympiA and are therefore considered the primary candidate models for the base case. The loglogistic and Generalised Gamma models are suitable alternative options with a plausible fit to the data. For the olaparib arm, the exponential provided a reasonable fit to the data but was shown to poorly estimate IDFS for the placebo arm. The Weibull and Gamma distributions were consistently amongst the worst fitting models based on statistics and visual fit to IDFS, across the arms and populations of OlympiA.

Table 73. Overview of characteristics for models fitted to IDFS in the TNBC and ITT populations of OlympiA

Characteristic	TNBC		ITT (proxy for HER2-/HR+)	
	Olaparib	Placebo	Olaparib	Placebo
Proportional hazards	× - Does not hold		× - Does not hold	
Trend in hazard rates over time	✓ - Hazards converge at approximately 3-years		✓ - Hazards converge at approximately 3-years	
Goodness of fit based on AIC, BIC, and visual fit to data (✓ = best fitting, ~ = plausible fit, × = poor fit)				
Exponential	~	×	~	×
Weibull	×	×	×	×
Loglogistic	~	~	~	~
Lognormal	✓ (2nd)	✓ (2nd)	✓ (1st)	✓ (2nd)
Gompertz	✓ (1st)	✓ (1st)	✓ (2nd)	✓ (1st)
Generalised Gamma	~	~	~	~
Gamma	×	×	×	×

Step two: adjustments for the short- and long-term risk of recurrence in TNBC and HER2-/HR+ (TP1 and TP2)

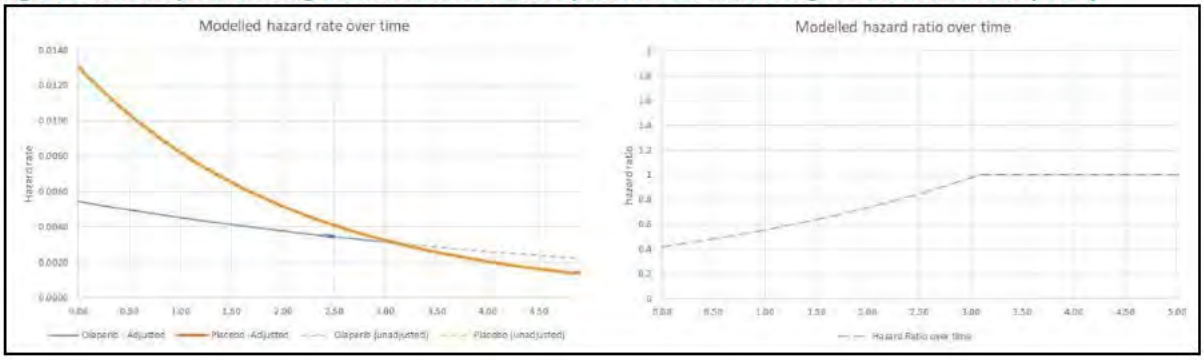
To ensure clinically plausible extrapolations, the modelled short- and long-term risk of recurrence in TNBC and HER2-/HR+ subgroups was adjusted as described below.

As the follow-up of OlympiA (median of approximately 3.5 years) extends beyond the end of treatment for olaparib (1-year), it is expected that any waning of treatment effect would be captured in the existing survival data. To identify that, the observed hazard rates for IDFS in the olaparib and placebo arms were plotted over time. The plots showing the smoothed hazard rates for IDFS indicate that the hazard rate for olaparib is expected to converge to the same long-term rate as placebo by year 3-4 [redacted] Beyond year 4, the hazard rate is uncertain, although the trends suggest a similar or lower rate of recurrence or death for olaparib when compared to placebo. To reflect this in the model, the modelled hazard rates for olaparib were adjusted such that they are always lower than or equal to placebo. At the point at which the hazard rates crossed, the hazard rates are assumed the same across arms and no further benefit of treatment is assumed.

[redacted]

An illustration of the adjusted and unadjusted hazard rates based on the Gompertz model for TNBC (both arms) is shown in Figure 39. This is presented alongside the modelled hazard ratio for olaparib versus placebo.

Figure 39. Model plots showing the hazard rates for IDFS per arm over time, alongside the hazard ratio (TNBC)



For the Gompertz model, the hazard rates are predicted to converge at year 3, in line with the observed hazard rates in Figure 37. The corresponding hazard ratio for olaparib versus placebo is predicted to be below 1.0 during the first 3-years, before converging to a fixed value of 1.0 (i.e., no difference) from year 3 onwards. This is broadly in line with the trends in the observed hazard rates from years 3 onwards in OlympiA and is therefore indicative of the long-term survival of the trial population.

Beyond study follow-up, the long-term risk of recurrence in patients with TNBC and HER2-/HR+ is expected to differ significantly, with TNBC patients experiencing a plateauing of the recurrence rate after 5-7 years post-diagnosis and HER2-/HR+ patients remaining at a constant risk of recurrence to at least 20 years after diagnosis (See section 9.1). This was also confirmed by Danish clinical experts, who also suggested that recurrence after 4-5 years is very rare for the TNBC patients [54].

To capture the patterns of long-term recurrence for TNBC, the risk of recurrence (i.e. transition hazard rates for non-metastatic (TP1) and metastatic (TP2) recurrence) in patients with TNBC was assumed equal to zero from year 5 of the time horizon in the base case analysis. This is consistent with data from long-term studies in early breast cancer **[49-52]**. This assumption was tested in the sensitivity analysis to the base case using alternative time points of 7, 10 and 15 years. Beyond year 5, the TNBC patients in the IDFS state remain at risk of death from

other causes (inflated for excess mortality risks associated with a BRCA mutation). For patients with HER2-/HR+ disease, the risk of recurrence was assumed to remain throughout the lifetime horizon of the model.

Step three: conditional probability of a non-distant recurrence (TP1 and TP2)

The conditional probability of developing a non-distant recurrence having experienced an IDFS event was estimated from the summary of first IDFS event in OlympiA (Table 74) [2, 7].

At DCO2, 134 patients (14.5% of the total cohort) in the olaparib arm and 207 patients (22.6% of the total cohort) in the placebo arm experienced an IDFS event. Of the 134 patients with an IDFS event in the olaparib arm, 33 had experienced a non-distant recurrence comprising 9 regional recurrences, 9 local recurrences and 15 contralateral invasive breast cancer events. The conditional probability of an IDFS event being a non-distant recurrence for olaparib was estimated at 24.6%. For the placebo arm, 48 of 207 patients with an IDFS event had experienced a non-distant recurrence, comprising 18 regional recurrences, 12 local recurrences and 18 contralateral invasive breast cancer events. The associated probability of an IDFS event being a non-distant recurrence for placebo was 23.2%.

Table 74. Summary of type of first IDFS event and estimation of probability of a non-distant or distant recurrence in OlympiA (DCO2)

Transition in the model	Type of event in OlympiA	Olaparib, N=921 n (% of total patients)	Placebo, N=915 n (% of total patients)	Total, N=1836 N
TP1, TP2 and TP3	Any IDFS event	134 (14.5%)	207 (22.6%)	341
Non-metastatic recurrence (TP1)	Regional (ipsilateral) recurrence	9 (1.0%)	18 (2.0%)	27
	Local (ipsilateral) recurrence	9 (1.0%)	12 (1.3%)	21
	Contralateral invasive breast cancer	15 (1.6%)	18 (2.0%)	33
Probability of any IDFS event being a non-distant recurrence		24.6% (33/134)	23.2% (48/207)	23.8% (81/341)
Metastatic recurrence (TP2)	Distant CNS recurrence	24 (2.6%)	38 (4.2%)	62
	Distant non-CNS recurrence	64 (6.9%)	98 (10.7%)	162
	New primary cancers	11 (1.2%)	23 (2.5%)	34
(TP3)	Deaths without IDFS	2 (0.2%)	0 (0%)	2
Probability of any IDFS event being a distant recurrence, new cancer, or death		75.4% (101/134)	76.8% (159/207)	76.2% (260/341)

For the base case, the conditional probability of non-distant recurrence was assumed the same across arms given the lack of evidence that olaparib treatment has any impact on the type of event experienced. This is supported by the consistent event probabilities observed across arms; 24.6% for olaparib and 23.2% for placebo. The conditional probability was set to 23.8% based on the total numbers of IDFS (N=341) and non-distant recurrence (n=81) events across arms. The corresponding conditional probability of a distant recurrence was 76.2%. Hence, most patients with recurrence would enter the metastatic disease states over the model lifetime.
The option to model the conditional probability of a distant or non-distant recurrence using data from each arm of the study was explored in sensitivity analysis. This leads to small differences in the types of recurrences experienced by patients in each arm of the comparison.

Step four: modelling of transitions from IDFS to death (TP3)

The cause-specific hazard rate for the transition of IDFS to death was modelled using all-cause mortality data from the Statistics Denmark life tables . The mortality data was matched on the baseline age (43 years) and the gender (100% female in a simplifying assumption) profile of the OlympiA population. The *annualised* mortality rates for females aged 43 to 100 years old were used to model the risk of death for each year of the model time horizon. The annual rates were converted to monthly rates and assumed to be constant over each year.

The age- and gender-matched life table mortality rates were further adjusted to reflect the excess mortality associated with a germline BRCA mutation versus the general population. This adjustment was performed using the standardised mortality ratio (SMR=1.46, 95% confidence interval 0.5-2.82) from Mai et al [64], which captures excess mortality for persons with a germline BRCA mutation and aged <50 years old. The SMR was used to capture the lifetime excess mortality risks from other illnesses that may lead to shortened life expectancy in persons with germline BRCA mutations.

Figure 40 shows the all-cause mortality curve for the general population and with adjustment for BRCA status. Figure 41 shows the cause-specific hazard rate for TP3.

Figure 40. The all-cause mortality curve for the general population (female, aged 43 years at baseline) and persons with

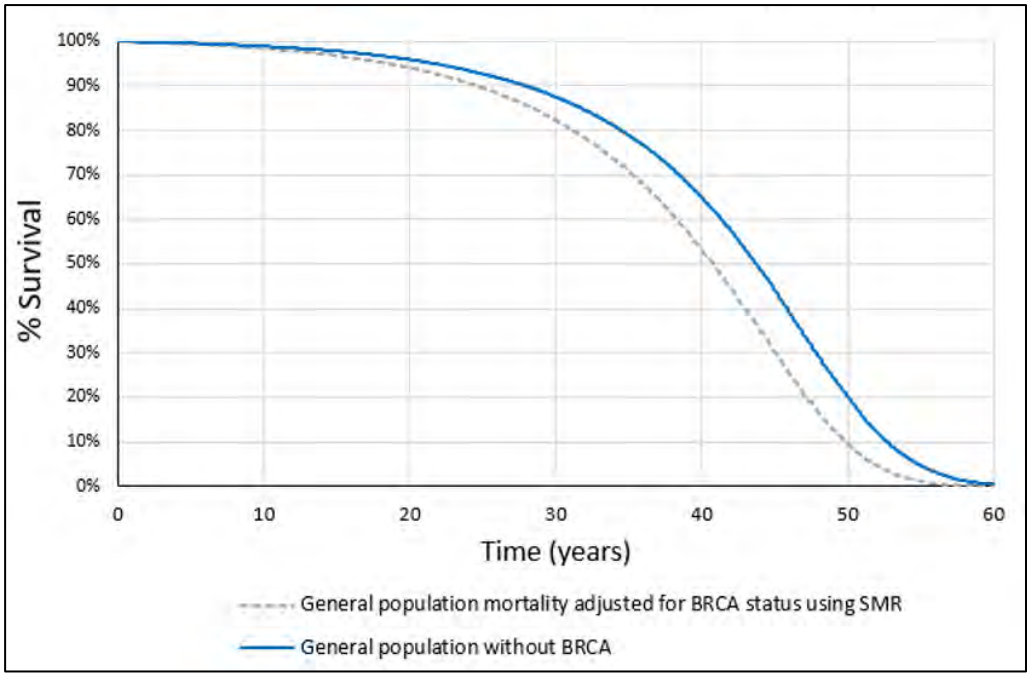
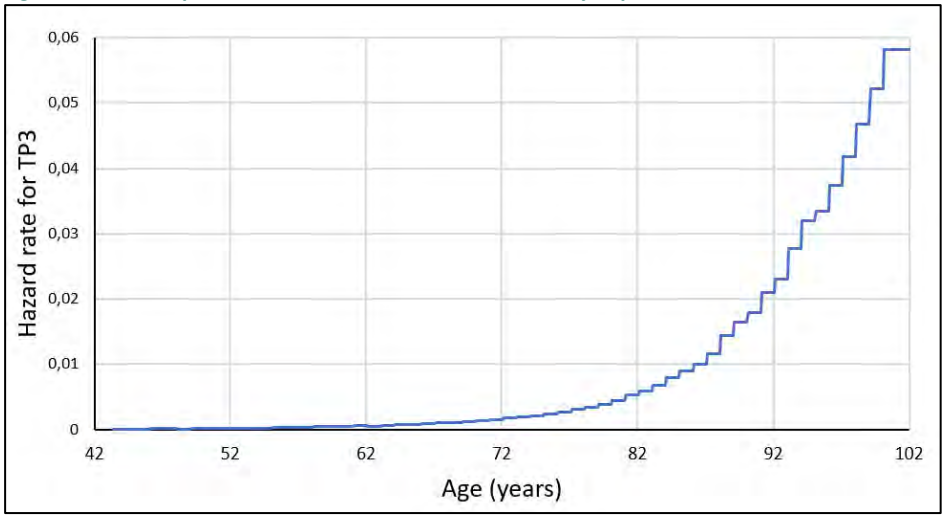


Figure 41. Cause-specific hazard rate for all-cause mortality in persons with BRCA mutations



The impact of varying the SMR on results was assessed in the sensitivity analysis for the base case.

Overall model fit and plausibility of extrapolation of IDFS

The landmark survival probabilities for IDFS in patients with TNBC and HER2-/HR+ as predicted by the cost-effectiveness model are shown in Table 75 and Table 76, respectively. These estimates were obtained using the survival models for IDFS (step one) with adjustment for the short- and long-term rate of recurrence (step two), and the modelling of death without recurrence (step four).

For TNBC, the Gompertz survival model was selected for the base case analysis on the basis that:

- According to AIC score, the Gompertz was the best fitting model in both arms of OlympiA, see Table 72
- The Gompertz model yielded the closest prediction of the observed hazard rate for IDFS in TNBC (Figure 37)
- When compared to external data [105], the Gompertz model gave the closest prediction of 5-year IDFS for watch and wait and a reasonable prediction of 10-year IDFS (72.1% versus 71.15% in Copson et al). The lognormal and the Generalised Gamma models gave closer predictions at 10 years compared to external data, however the Gompertz model was preferred because it gave the best predictions of the observed hazard rates, the closest prediction of 5-year IDFS compared to external data and it was the best fitting model according to the AIC score.

Based on goodness of fit and the plausibility of extrapolation, the Gompertz model was judged to provide the most reliable estimate of long-term IDFS for watch and wait. The same model was used for the olaparib arm in line with standard guidance [68].

For HER2-/HR+, the lognormal model[4] was selected for the base case analysis on the basis that:

- According to AIC score, the lognormal was the best fitting model for olaparib and the second-best fitting for the watch and wait arm of OlympiA, see Table 72
- When compared to the external data [53], the lognormal model had the closest fit to IDFS at 10, 15 and 20 years for watch and wait (with adjuvant endocrine therapy). The Gompertz model had the closest prediction to the 5-year IDFS in the external study. At the landmarks of 10, 15, and 20 years, the Gompertz model significantly overestimates the IDFS of patients with HER2-/HR+ treated with adjuvant endocrine therapy.

Based on goodness of fit and the plausibility of extrapolation, the lognormal model was judged to provide the most reliable estimate of long-term IDFS for watch and wait. The same model was used for the olaparib arm in line with standard guidance [68].

[4] Modelled using ITT data as a proxy for HER2-/HR+, see section 9.4.2

Table 75. Comparison of model fit to observed data for IDFS in TNBC (includes short- and long-term risk adjustment)

Arm/analysis	IDFS model [AIC/BIC rank]	Years since start of model										
		1	2	3	4	5	10	15	20	40	50	57
TNBC – no recurrence risk after 5 years; No treatment effect beyond the point where hazards are the same across arms												
Olaparib	**Observed**	93.5%	89.3%	86.0%	83.1%							
	Exponential	95.3%	90.8%	86.6%	82.5%	78.6%	77.8%	76.6%	74.4%	42.1%	7.6%	0.3%
	Weibull	94.4%	90.1%	86.2%	82.6%	79.3%	78.5%	77.3%	75.1%	42.5%	7.6%	0.3%
	Loglogistic	94.3%	89.9%	86.0%	82.5%	79.4%	78.6%	77.4%	75.2%	42.5%	7.6%	0.3%
	Lognormal [2nd]	94.0%	89.4%	85.7%	82.6%	80.0%	79.2%	77.9%	75.7%	42.8%	7.7%	0.3%
	Gompertz [1st]	94.0%	89.3%	85.5%	82.8%	81.0%	80.2%	79.0%	76.7%	43.4%	7.8%	0.3%
	Generalised Gamma	94.1%	89.5%	85.8%	82.6%	79.9%	79.1%	77.8%	75.6%	42.8%	7.7%	0.3%
	Gamma	94.5%	90.1%	86.2%	82.6%	79.3%	78.5%	77.3%	75.1%	42.5%	7.6%	0.3%
Watch and wait	**Observed**	88.2%	81.2%	77.1%	75.2%							
	Exponential	92.5%	85.6%	79.1%	73.2%	67.7%	67.0%	65.9%	64.1%	36.2%	6.5%	0.2%
	Weibull	88.9%	83.0%	78.3%	74.3%	70.8%	70.1%	69.0%	67.1%	37.9%	6.8%	0.2%
	Loglogistic	88.7%	82.6%	77.9%	74.1%	70.9%	70.1%	69.0%	67.1%	37.9%	6.8%	0.2%
	Lognormal [2nd]	88.1%	82.1%	77.8%	74.4%	71.6%	70.9%	69.7%	67.8%	38.3%	6.9%	0.2%
	Gompertz [1st]	87.9%	81.0%	76.9%	74.4%	72.9%	72.1%	71.0%	69.0%	39.0%	7.0%	0.2%
	Generalised Gamma	87.9%	81.9%	77.8%	74.5%	71.8%	71.1%	70.0%	68.0%	38.5%	6.9%	0.2%
	Gamma	89.0%	83.0%	78.2%	74.1%	70.4%	69.7%	68.6%	66.6%	37.7%	6.8%	0.2%
External data	POSH study, TNBC subset, Copson et al [105]	-	85.89%	-	-	77.02%	71.15%	-	-	-	-	-

Table 76. Comparison of model fit to observed data for IDFS in HR+ (modelled using ITT as proxy for subgroup data)

Arm/analysis	IDFS model [AIC/BIC rank]	Years since start of model										
		1	2	3	4	5	10	15	20	40	50	57
HR+ Lifetime risk of recurrence; No treatment effect beyond the point where hazards are the same across arms												
Olaparib	**Observed (HER2-/HR+)**	92.8%	91.4%	86.1%	80.1%							
	Exponential	95.2%	90.6%	86.3%	82.1%	78.2%	60.9%	47.1%	36.0%	7.8%	0.9%	0.0%
	Weibull	94.7%	90.2%	86.1%	82.3%	78.8%	63.7%	52.4%	43.3%	14.2%	2.0%	0.1%
	Loglogistic	94.6%	90.0%	85.9%	82.2%	78.9%	65.6%	56.4%	49.1%	20.5%	3.4%	0.1%
	Lognormal [1st]	94.2%	89.5%	85.6%	82.4%	79.5%	68.8%	61.2%	54.7%	24.7%	4.2%	0.1%
	Gompertz [2nd]	94.4%	89.7%	85.7%	82.7%	80.7%	76.9%	75.4%	73.2%	41.7%	7.6%	0.3%
	Generalised Gamma	94.4%	89.6%	85.7%	82.3%	79.3%	68.6%	61.5%	55.4%	25.7%	4.4%	0.2%
	Gamma	94.7%	90.3%	86.2%	82.3%	78.7%	63.2%	50.8%	40.5%	11.0%	1.4%	0.0%
Watch and wait	**Observed (HER2-/HR+)**	89.4%	82.4%	78.0%	76.6%							
	Exponential	92.5%	85.6%	79.1%	73.2%	67.7%	45.6%	30.6%	20.3%	2.5%	0.2%	0.0%
	Weibull	89.3%	83.2%	78.4%	74.2%	70.6%	56.6%	46.6%	38.5%	12.7%	1.8%	0.1%
	Loglogistic	89.0%	82.8%	78.0%	74.0%	70.6%	58.5%	50.3%	43.8%	18.3%	3.0%	0.1%
	Lognormal [2nd]	88.5%	82.3%	77.9%	74.4%	71.4%	61.1%	54.3%	48.5%	21.9%	3.7%	0.1%
	Gompertz [1st]	88.4%	81.4%	77.1%	74.4%	72.6%	69.2%	67.8%	65.8%	37.5%	6.9%	0.2%
	Generalised Gamma	88.3%	82.2%	77.9%	74.5%	71.6%	61.9%	55.5%	50.1%	23.2%	4.0%	0.1%
	Gamma	89.4%	83.3%	78.3%	74.0%	70.1%	55.0%	43.8%	34.9%	9.5%	1.2%	0.0%
External data	Meta-analysis of long-term survival with adjuvant endocrine therapy; subgroup with 4 or more nodes [53]	-				78%*	64%*	55%*	48%*			-
*estimated based on 1-risk of disease recurrence (22%, 36%, 45%, 52%)												

2. Modelling of the non-metastatic recurrence pathway (TP4 and TP5)

The transition probabilities for non-metastatic to metastatic breast cancer (TP4) and non-metastatic breast cancer to death (without metastatic diagnosis) (TP5) were modelled using data from the OlympiA trial [2, 7].

For TP4, the cause-specific hazard was estimated by fitting parametric survival models to data on the time from non-metastatic recurrence (i.e., locoregional or contralateral breast cancer) to distant metastatic recurrence (i.e., distant recurrence, new non-breast cancer) with deaths without recurrence treated as a censoring event. Similarly, for TP5, the cause-specific hazard was estimated using parametric survival models fitted to data on the time from non-metastatic recurrence to death, with distant metastatic recurrence treated as a censoring event. Only patients that had a non-distant recurrence event during the follow-up of OlympiA were included in the analysis.

At the interim OS analysis of OlympiA (DCO2), 81 patients had experienced a non-metastatic recurrence: 33 patients from the olaparib arm and 48 patients from the placebo arm. Of the 81 patients with non-metastatic recurrence, 15 had experienced a distant metastatic recurrence and 3 had died without recurrence during follow-up. Within individual arms, there were too few events to separately estimate TP4 and TP5 for the olaparib and placebo arms of the model. The post-recurrence survival (i.e., time from non-metastatic recurrence to death) of patients with non-metastatic recurrence did not suggest a survival benefit for the placebo arm [redacted] Therefore, to maximise the sample for analysis, TP4 and TP5 were estimated from a pooled dataset containing data from both arms. The resulting transition probabilities were applied to both arms of the model. This leads to a conservative estimate of the post-recurrence survival of patients with locoregional recurrence in the olaparib arm of the model given the marginal improvement in post-recurrence survival for the olaparib arm in [redacted] This approach (i.e. to assume that the risk of further recurrence or death in patients with non-metastatic recurrence is the same for both arms) was validated by Danish clinical experts who considered it to be a reasonable assumption [54].

Parametric survival analysis for non-metastatic breast cancer (TP4 and TP5)

A series of parametric survival models were fitted to the cause-specific time to event data for TP4 and TP5. For both analyses, the number of patients at risk was 81 and the number of events were 15 (distant metastatic disease) for TP4 and 3 (deaths) for TP5.

The AIC and BIC statistics for each model are shown in Table 77. For TP4 (->mBC), the AIC and BIC scores favoured the lognormal (1st for AIC) and exponential (1st for BIC), respectively. For TP5 (->death), the Generalised Gamma was the best fitting model according to AIC and the exponential was best fitting according to BIC.

Table 77 AIC and BIC values for the parametric survival models fitted to data on the time from non-distant metastatic currence to distant metastatic and the time from non-distant metastatic recurrence to death

Model	Rank on lowest AIC/BIC by arm	Pooled data (N=81) (Olaparib, N=33, Placebo, N=48)	
		AIC	BIC
Time from non-metastatic recurrence to distant metastatic recurrence (death censored) [TP4]			
Exponential	2 / 1	159.99	162.38
Weibull	5 / 5	160.70	165.48
Loglogistic	3 / 3	160.33	165.12
Lognormal	1 / 2	159.61	164.40
Gompertz	7 / 6	161.57	166.36
Generalised Gamma	6 / 7	161.54	168.72
Gamma	4 / 4	160.49	165.28
Time from non-metastatic recurrence to death (distant metastatic recurrence) [TP5]			
Exponential	2 / 1	43.25	45.65
Weibull	6 / 5	45.10	49.89
Loglogistic	5 / 4	45.04	49.83
Lognormal	4 / 3	44.58	49.37
Gompertz	3 / 2	44.25	49.04
Generalised Gamma	1 / 7	43.23	50.41
Gamma	7 / 6	45.12	49.91

The fit of the models to the Kaplan-Meier probabilities for non-metastatic to metastatic recurrence (TP4) and for non-metastatic to death (TP5) are shown in Figure 43 and Figure 44, respectively. These graphs provide an indication of model fit and should be viewed with caution given that Kaplan-Meier plots of competing risks such as TP4 and TP5 are biased by informative censoring.

For TP4, most survival models accurately predicted the Kaplan-Meier probabilities for non-metastatic to metastatic disease. The models produced similar predictions of survival from disease recurrence, which was broadly consistent with literature estimates of 5-year disease-free survival after locoregional recurrence of 38% [107]. The Kaplan-Meier plots that accompany these data suggest that the rate of recurrence decreases over time, consistent with the patterns typically associated with lognormal and loglogistic models. Guided by the goodness of fit statistics, the lognormal model was thus selected as the preferred model for TP4. The impact of using other models for TP4 on the base case results was considered in sensitivity analysis.

For TP5, all models yielded a reasonable fit to the Kaplan-Meier probabilities for non-metastatic recurrence to death. At the end of the follow-up, models such as the Gompertz or Generalised Gamma tended to predict a plateauing of the risk of death without recurrence, whilst all other models predicted a continuous and ongoing risk of death. The trend towards a reduction in the risk of death prior to recurrence is highly uncertain given the very low number of events in the analysis (n=3). Further, the estimation of multi-parameter models, such as the Gompertz or Generalised Gamma, on limited data potentially increases the chance of inappropriate

extrapolation. Therefore, for TP5, the exponential model was selected for the base case. The impact of using other models for TP5 on the base case results were considered in sensitivity analysis.

3. Modelling of the metastatic recurrence pathway (TP6 and TP7)

Early onset metastatic breast cancer (TP6)

The transition probabilities for 'early onset' metastatic breast cancer to death (TP6) were modelled using data on the time from distant metastatic recurrence to death in the OlympiA trial. These data represent the survival outcomes of patients who had distant recurrence during the approximate 3.5-year median follow-up of OlympiA (DCO2).

At the second interim OS analysis of OlympiA (DCO2), 105 patients from the olaparib arm and 169 patients from the placebo arm had experienced a distant metastatic recurrence. This included patients whose first IDFS event was a distant recurrence (n=100[5] for olaparib and n=159 for placebo), and patients that experienced a distant recurrence after first experiencing a locoregional or contralateral invasive breast cancer event (n=5 for olaparib and n=10 for placebo).

In total, there were 70 deaths after metastatic recurrence in the olaparib arm, and 103 deaths after metastatic recurrence in the placebo arm. The median time to death was 9.8 [95% confidence interval 7.4 to 12.3] months in the olaparib arm versus 14.3 [95% confidence interval 11.7 to 19.6] months in the placebo arm. The Kaplan-Meier plot for post-distant metastatic recurrence survival by arm is shown in Figure 45.

The median survival after distant recurrence in the olaparib arm (median 9.8 months) was numerically shorter than for placebo (median 14.3 months). This difference in post-recurrence survival can be attributed to several factors including differences in the treatments administered after recurrence and imbalances in the characteristics and prognosis of patients with distant recurrence following olaparib and placebo treatment.
The greater use of PARP inhibitor treatment after metastatic recurrence in the placebo arm (25.4% vs. 13.3%) is expected to have improved the post-recurrence survival of placebo versus olaparib patients. Several phase 3

[5] 1 patient had experienced a distant recurrence during follow-up but had been censored for their event in the IDFS summary

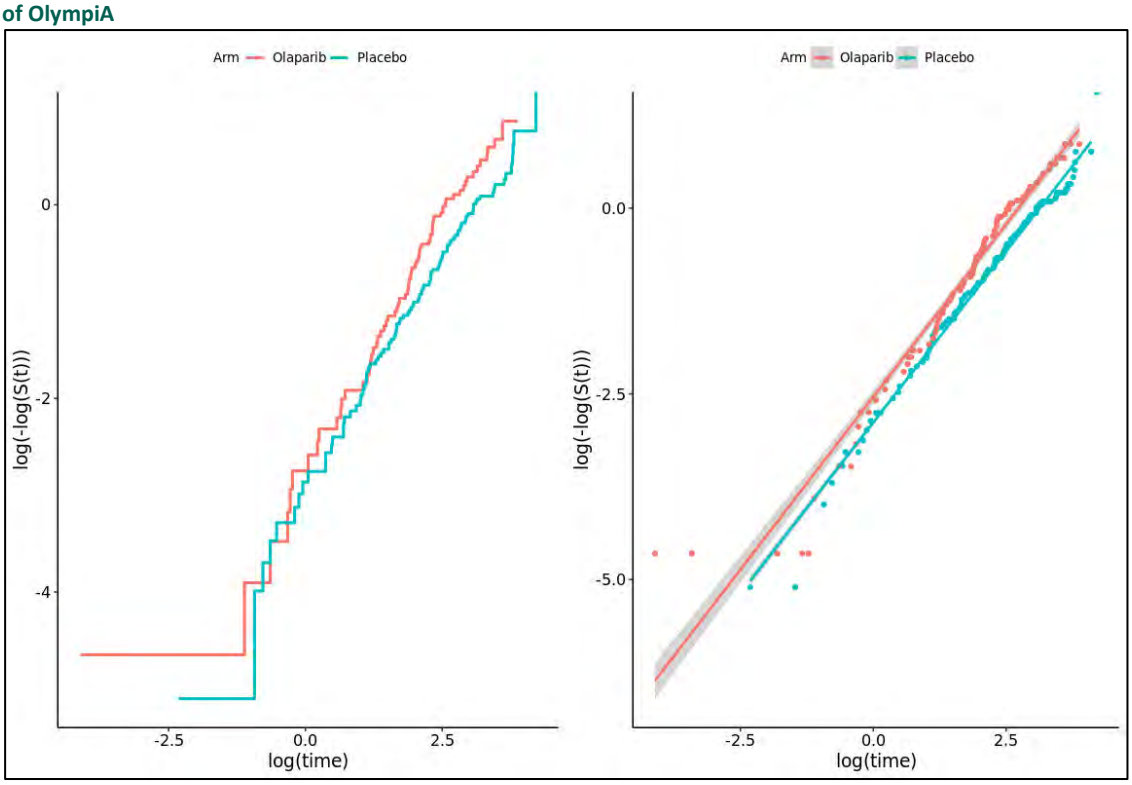
randomised trials have demonstrated a median OS benefit for PARP inhibitors versus chemotherapy in BRCA-mutated mBC [60, 66].

For the base case, the transition probabilities for 'early onset' metastatic breast cancer to death (TP6) were modelled separately by treatment arm using data from the OlympiA trial. This approach was validated by Danish clinical experts [54]. The impact of applying the same transition probabilities across arms for TP6 is tested in sensitivity analysis. For this analysis, the transition probabilities for the olaparib arm are modelled using the survival rates estimated from the placebo arm of OlympiA.

Parametric survival analysis for metastatic breast cancer (TP6)

A series of parametric survival models were fitted to the time to event data for TP6. Due to evidence of non-proportional hazards from the overlapping of Kaplan-Meier probabilities across study arms at the beginning of the survival curve for TP6 (Figure 45), the survival models were fitted independently to each arm of the study. This is supported by the log-cumulative hazards plot for TP6, which showed lack of proportionality in the survival curves (Figure 46).

Figure 46. Log-cumulative hazards versus log-time plot of post-metastatic recurrence for the placebo and olaparib arms of OlympiA



The AIC and BIC statistics for the fitted models are shown in Table 78. For the olaparib arm, the exponential was the best fitting on both BIC and AIC. For the placebo arm, the Gompertz was best fitting on AIC, and the exponential was best fitting on BIC.

Table 78. AIC and BIC values for the parametric survival models fitted to data on the time from metastatic recurrence to death

Model	Rank on lowest AIC/BIC by arm	Olaparib, N=105, Placebo, N=169	
		AIC	BIC
Time from metastatic recurrence to death – olaparib arm [TP6]			
Exponential	1 / 1	521.45	524.10
Weibull	4 / 4	523.23	528.54
Loglogistic	3 / 3	522.39	527.70
Lognormal	7 / 7	530.99	536.29
Gompertz	2 / 2	522.06	527.37
Generalised Gamma	6 / 6	524.53	532.49
Gamma	5 / 5	523.38	528.69
Time from metastatic recurrence to death – placebo arm [TP6]			
Exponential	2 / 1	857.49	860.62
Weibull	4 / 4	857.69	863.95
Loglogistic	3 / 3	857.62	863.88
Lognormal	7 / 6	859.17	865.43
Gompertz	1 / 2	857.19	863.45
Generalised Gamma	5 / 7	858.05	867.44
Gamma	6 / 5	858.21	864.47

The fit of the models to the Kaplan-Meier probabilities for TP6 are shown in [redacted] for the olaparib arm and [redacted] for the placebo arm.

For the placebo arm, all the models yielded a similar and reasonable prediction of survival up to around 2-years. After this time point, there was divergence in the fit of the models to the Kaplan-Meier data. The Gompertz model tended to overestimate the survivorship towards the end of the study, whilst the exponential tended to underestimate survivorship. Under extrapolation, the probabilities of survival at 5- and 10-years after 'early onset metastatic breast cancer' were 12.4% and 4.8% for Gompertz and 7.7% and <1% for exponential, respectively. The survival estimates for the exponential model were judged to provide the most plausible prediction when compared to literature estimates of post-distant recurrence survival in patients with 'early onset metastatic breast cancer' (5.4% at 5-years and ~0% at 10 years [56]).

For the olaparib arm, all the models yielded similar and reasonable prediction of survival up to around 2-years. After 2-years, most models tended to underestimate the tail of the curve. Under extrapolation, the probabilities of survival at 5- and 10-years after 'early onset metastatic breast cancer' were approximately 5.1% and 1.6% for the Gompertz and 1.8% and <1% for the exponential, respectively. For consistency with the placebo arm, the exponential model was used in the base case for the modelling of TP6 for the olaparib group.

Late onset metastatic breast cancer (TP7)

The transition probabilities for 'late onset' metastatic breast cancer to death (TP7) were modelled using external data to the OlympiA trial (see section 9.4).
To reflect the breadth of potential treatment options and associated outcomes after 'late onset metastatic breast cancer', the transition probabilities for TP7 were modelled as a 'weighted-average' of survival probabilities (S(t)) for first-line treatments of BRCA mBC.
Following clinical guidelines [108] and clinical expert input [54], the first-line treatment options available to patients with BRCA mBC in Denmark are:

1. Single chemotherapy
2. CDK4/6 inhibitor plus endocrine therapy (HER2-/HR+ only)
3. Atezolizumab plus nab-paclitaxel (TNBC and PD-L1≥10)

The transition probabilities for each treatment regimen were modelled using data from three studies that reported the OS of patients with BRCA mutations in a first line mBC setting:

- Single chemotherapy: **OlympiAD study** [59, 60] (clinical trial)
- CDK 4/6 inhibitor plus endocrine therapy: **Collins et al** [62] (Flatiron real world study)
- Atezolizumab plus paclitaxel: BRCAm biomarker subgroup of **IMpassion 130** study [61] (clinical trial)

The OlympiAD study was a randomised, open-label, phase 3 trial of olaparib versus Treatment of Physician Choice [TPC] (capecitabine, vinorelbine, eribulin) in patients with gBRCAm HER2-negative mBC who had received ≤ 2 lines of chemotherapy for mBC. In the study, a subgroup of patients had not previously received chemotherapy for mBC and were therefore undergoing first-line treatment for mBC [59, 60]. Individual subject-level data from the first-line subgroup were used to model the survival of first-line treatment with single chemotherapy.

The study by Collins et al was a retrospective study of the patterns and effectiveness of CDK4/6 inhibitor treatment in patients with HER2-/HR+, gBRCAm mBC, using data from the Flatiron Health database (2013-2018) [62]. Of the 85 gBRCAm patients included in this study, 36 had received a CDK4/6 inhibitor treatment as a first-line intervention. Individual subject-level data from the first-line subgroup were used to model the survival of first-line treatment with CDK4/6 inhibitor plus endocrine therapy.

Atezolizumab plus nab-paclitaxel is preferred in Denmark for the PD-L1≥10 TNBC patients who require first line treatment for metastatic disease. The OS hazard ratio for atezolizumab plus nab-paclitaxel versus nab-paclitaxel from the BRCA mutated subgroup of the IMpassion 130 clinical trial was used.

The IMpassion 130 study was a phase 3 randomised, double-blind, study of atezolizumab plus nab-paclitaxel versus nab-paclitaxel as first-line treatment in 902 patients with metastatic TNBC. As part of a sub study of IMpassion 130, the efficacy of treatment was evaluated based on immune biomarkers and BRCA1/2 alterations [61]. Of 612 patients tested, 89 (14.5%) had BRCA1/2 mutations [61]. Of these, approximately 50% (45 of 89) were PD-L1 positive and eligible for atezolizumab treatment based on its European marketing authorisation [61]. In patients that were both PD-L1 and BRCA1/2 mutation positive, the hazard ratio of OS for atezolizumab was 0.55 (95%CI 0.21 to 1.41).

The OlympiAD and Collins et al studies were identified from a previous systematic literature review of randomised clinical trials in gBRCA mutated mBC [109], and from previous AstraZeneca real world studies. Both studies were selected based on their relevance to the population (gBRCA, HER2-negative, mBC and treated at a first line) and the availability of subject-level survival data for analysis. The IMpassion 130 study was identified from clinical guidelines [22].

An overview of the clinical characteristics of the OlympiAD and Collins et al study populations is provided in Table 79. In both data sets, the mean time from diagnosis to randomisation (OlympiAD) or start of CDK4/6

inhibitor treatment (Flatiron) was greater than 2-years indicating that patients in the studies were likely to have developed metastatic disease in a 'late onset' setting (ranged from 4.5 to 5.0 years). The baseline ECOG performance status of patients in the studies (60-80% with normal activity) suggests worse overall health status versus the baseline of OlympiA (>85% with normal activity). This is consistent with clinical expectations of worsening health status following metastatic diagnosis. Baseline data were not available for the BRCA1/2 mutation positive subgroup of IMpassion 130. Overall, these studies were considered the best available evidence to inform the survival estimates for 'late onset' BRCA mBC.

Table 79. Summary of clinical characteristics for OlympiAD and Flatiron health database study

Characteristic	OlympiAD 1st line subgroup, unless otherwise stated [60]		Flatiron health database (all patients, 1st line specific not available) [62] N=85
Treatment group	Olaparib, n=59	TPC, n=28	CDK4/6 inhibitor, n=36
Number of events	30 (51%)	21 (75%)	13 (36%)
Hormone receptor positive, %	39.0%	42.9%	100%
Triple-negative, %	61.0%	57.1%	0%
Time from diagnosis, mean	4.8 years (ITT population)	4.7 years (ITT population)	4.5 years (1 641 days / 365.25 days per year)
ECOG performance status 0 (normal activity), %	79.7%	60.7%	60.4% (29 of 48 with known ECOG status)

Due to paucity of data, further adjustment or matching to the OlympiA population was not performed. In all three studies, there was insufficient baseline data on the surgical outcomes of patients at primary diagnosis to match to the high risk status of OlympiA. Additionally, the first-line subgroup data of OlympiAD was pooled across TNBC and HR+ groups. The overall first-line subgroup data were thus assumed to apply to both populations. This ensured adequate sample size and event numbers to provide robust estimates of survival for TP7.

Estimating the weighted-average survival probabilities

The cumulative survival probabilities for PARP inhibitor, chemotherapy, and CDK4/6 inhibitor treatment of 'late onset' mBC were modelled using parametric survival models fitted to individual subject data from the OlympiAD and Collins et al studies [60, 62]. As individual subject-level data were not available for IMpassion 130, the efficacy of atezolizumab (as proxy for pembrolizumab) was modelled by combining the survival estimates for chemotherapy treatment from OlympiAD with the OS hazard ratio of atezolizumab plus nab-paclitaxel versus nab-paclitaxel alone from IMpassion 130 [61].

The individual treatment survival probabilities were then combined as a weighted average of survival probabilities based on an assumed case mix of treatment for 'late onset mBC' using the following equation:

$$S(t) = \sum \pi_i \times \hat{S}(t)_i$$

Where π_i is the case weight used for treatment i[6], and $\hat{S}(t)_i$ is the associated survival probability.

The following sections detail the fitting of parametric survival models to the subject-level data from OlympiAD and Collins et al, the derivation of case weights for estimating the weighted-average survival probabilities, and a summary of the weighted-average survival probabilities for TP7 in the base case.

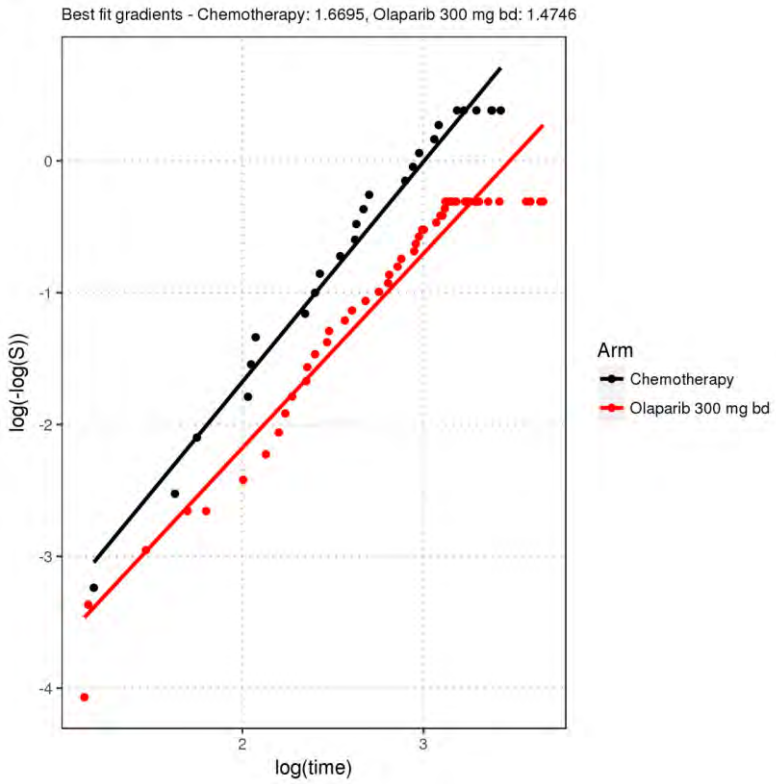
[N]In the Excel model, the survival probabilities for 'late onset mBC' are estimated based on the case mix data entered in the "Efficacy" sheet. The costs of treatment for 'late onset mBC' are based on the case mix data entered in the relevant cost sheets. The same case mix is used to estimate the effectiveness and costs of treatment for 'late onset mBC'.

Parametric survival analysis for 'Late onset' metastatic breast cancer (TP7)

A series of parametric survival models were fitted to the time to event data from OlympiAD and Collins et al [59, 60, 62].

For OlympiAD, the event time was defined as the time from randomisation to death from any cause. The PH assumption for the first-line subgroup of OlympiAD was assessed by visual inspection of the log-cumulative hazards plot (Figure 49). This was used to inform the choice of survival model. The lack of proportionality in the curves for olaparib and TPC supports the fitting of independent curves to each arm of the study population.

Figure 49. Log-cumulative hazards versus log-time plot for first-line subgroup of OlympiAD



For Collins et al [62], the event time was defined as time from the start date of first line CDK4/6 inhibitor treatment to death from any cause. The PH assumption was not considered for the Flatiron study given that only one study population was analysed, i.e., first-line gBRCAm patients treated with CDK4/6 inhibitors.

The AIC and BIC statistics for the models fitted independently to each treatment arm of OlympiAD and Collins et al are shown in Table 80. For both the olaparib and TPC arms of OlympiAD, the lognormal was the best fitting model according to both AIC and BIC, with the loglogistic model having the second-best fit on both scores. For the CDK4/6 inhibitor group of Collins et al. [62], the loglogistic was the best fitting according to AIC and BIC, and the lognormal model was second best.

Table 80. AIC and BIC values for the parametric survival models fitted to data on the time from metastatic recurrence to death in OlympiAD and Collins et al

Model	Rank on lowest AIC/BIC by arm	Olaparib, N=59, Placebo, N=28, N=36 CDK4/6 inhibitor treatment	
		AIC	BIC
Time from metastatic recurrence to death – olaparib arm of first line OlympiAD group [TP7]			
Exponential	6 / 6	281.91	283.98
Weibull	5 / 4	279.05	283.21
Loglogistic	2 / 2	276.49	280.65
Lognormal	1 / 1	275.64	279.80
Gompertz	7 / 7	282.67	286.82
Generalised Gamma	3 / 5	277.26	283.49
Gamma	4 / 3	277.88	282.04
Time from metastatic recurrence to death – TPC arm of first line OlympiAD group [TP7]			
Exponential	6 / 6	171.69	173.02
Weibull	3 / 3	166.64	169.3
Loglogistic	2 / 2	165.32	167.98
Lognormal	1 / 1	164.95	167.61
Gompertz	5 / 5	169.53	172.2
Generalised Gamma	4 / 4	166.95	170.94
Gamma	3 / 3	166.64	169.30
Time from metastatic recurrence to death – First line CDK4/6 inhibitor treatment in Flatiron study [TP7]			
Exponential	7 / 7	133.26	134.84
Weibull	4 / 4	125.04	128.2
Loglogistic	1 / 1	123.74	126.91
Lognormal	2 / 2	124.15	127.32
Gompertz	6 / 6	128.19	131.36
Generalised Gamma	5 / 5	126.09	130.84
Gamma	3 / 3	124.24	127.40

The fit of the models to the Kaplan-Meier probabilities for TP7 are shown in Figure 50 for OlympiAD and Figure 51 for Collins et al. [62].

Figure 50. Fit of parametric survival models to the Kaplan-Meier data for metastatic to death by arm in the first-line

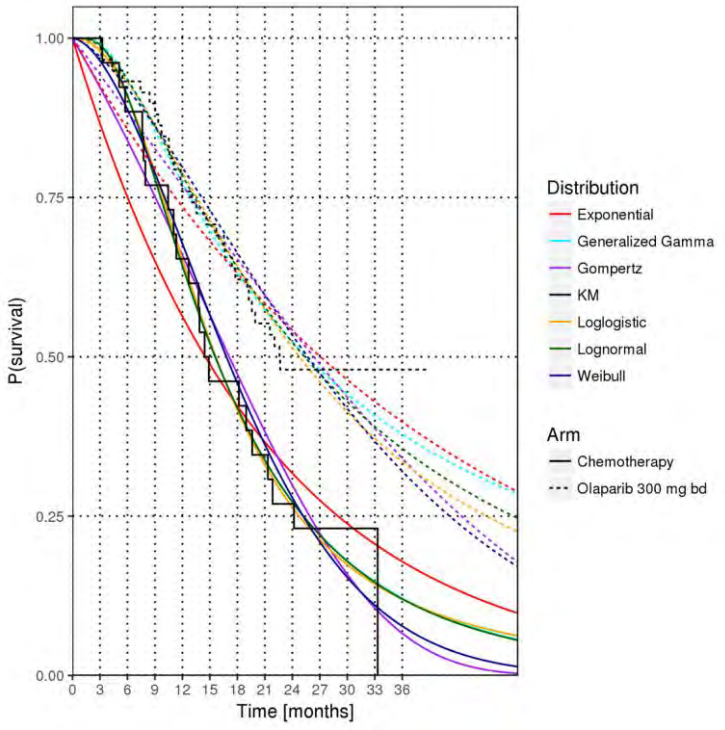
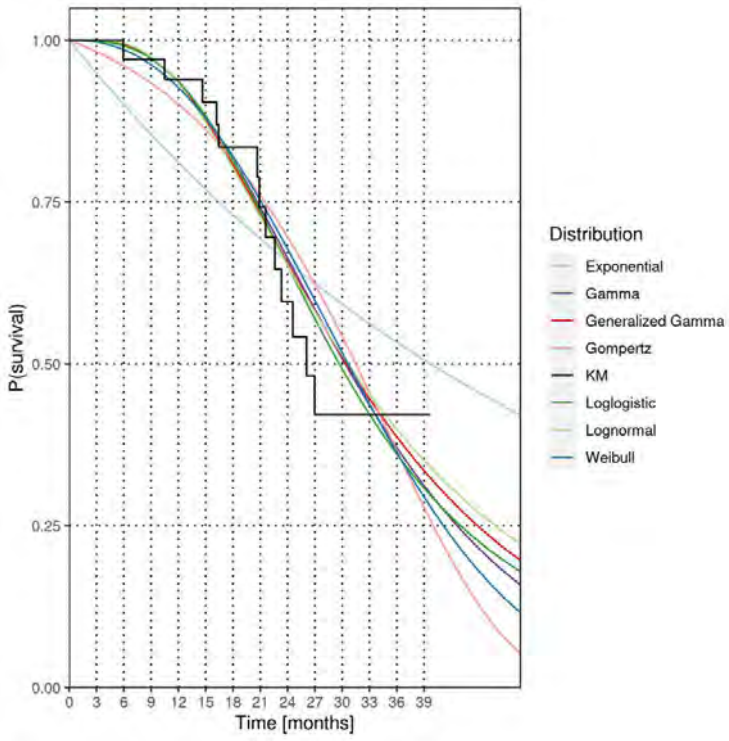


Figure 51. Fit of parametric survival models to the Kaplan-Meier data for metastatic to death for the first-line subgroup



For the TPC arm of OlympiAD, most models provided a robust fit to the Kaplan-Meier data. The Exponential model had a poor overall fit to the trial data, underestimating survival in the initial period and overestimating survival towards the end of follow-up. The best fitting models according to AIC and BIC (lognormal and loglogistic) provided similar levels of fit to the trial data and had consistent predictions under extrapolation. Therefore, for

the base case, the lognormal (best on AIC and BIC) was used to model the outcomes of single chemotherapy treatment on TP7.

For the first line CDK4/6 inhibitor population of Collins et al, most models provided a reasonable fit to the Kaplan-Meier data up to approximately 21 months of follow-up. The Exponential model had a poor overall fit to the trial data, underestimating survival in the initial period and overestimating survival at the tail. From month 21, all the models tended to poorly fit the tail of the Kaplan-Meier curve. The tail of the *observed* Kaplan-Meier curve for Collins et al is highly uncertain due to the limited numbers at risk after this time point; 16 at month 21, declining to 12 and 7 by months 24 and 30, respectively. For the base case, the loglogistic (best on AIC and BIC) was used to model the outcomes of CDK4/6 inhibitor treatment on TP7.

Case weights for modelling outcomes in late onset metastatic breast cancer

A summary of the weights used to derive the 'weighted-average' survival probabilities for TP7 is provided in Table 81. The case mix was informed by Danish clinical experts [54].

For TNBC, the population was assumed to receive a case mix of single chemotherapy (carboplatin or eribulin) and atezolizumab plus nab-paclitaxel based on local clinical expert input [54].

For HER2-/HR+, a case mix of single-agent chemotherapy (e.g. carboplatin, eribulin, vinorelbine or capecitabine) and CDK4/6 inhibitor plus endocrine therapy (abemaciclib plus letrozole) use was assumed based on local clinical expert input [54].

In the model, it is assumed that all patients with 'Late onset' metastatic breast cancer are likely to receive similar treatment options by HR status. Therefore, the same mixes of treatments based on HR status were applied across arms for the base case. It is also assumed that all patients will have similar responses to the subsequent therapies considering that they have been recurrence-free for a long period of time. This approach was validated by Danish clinical experts who considered it to be a reasonable assumption [54].

Table 81. Case mix of treatment in the 'late onset' mBC state based on clinical expert input [54]

	Olaparib	Placebo	Efficacy data source
TNBC			
Single chemotherapy	85%	85%	TPC arm of the 1st line subgroup of OlympiAD
Atezolizumab plus nab-paclitaxel	15%	15%	TPC arm of the 1st line subgroup of OlympiAD, adjusted for the hazard ratio benefit of atezolizumab from IMpassion130
HER2-/HR+			
Single chemotherapy	10%	10%	TPC arm of the 1st line subgroup of OlympiAD
CDK4/6 inhibitor plus endocrine therapy (abemaciclib plus letrozole)	90%	90%	Real world effectiveness study of CDK4/6 inhibitors in gBRCAm mBC

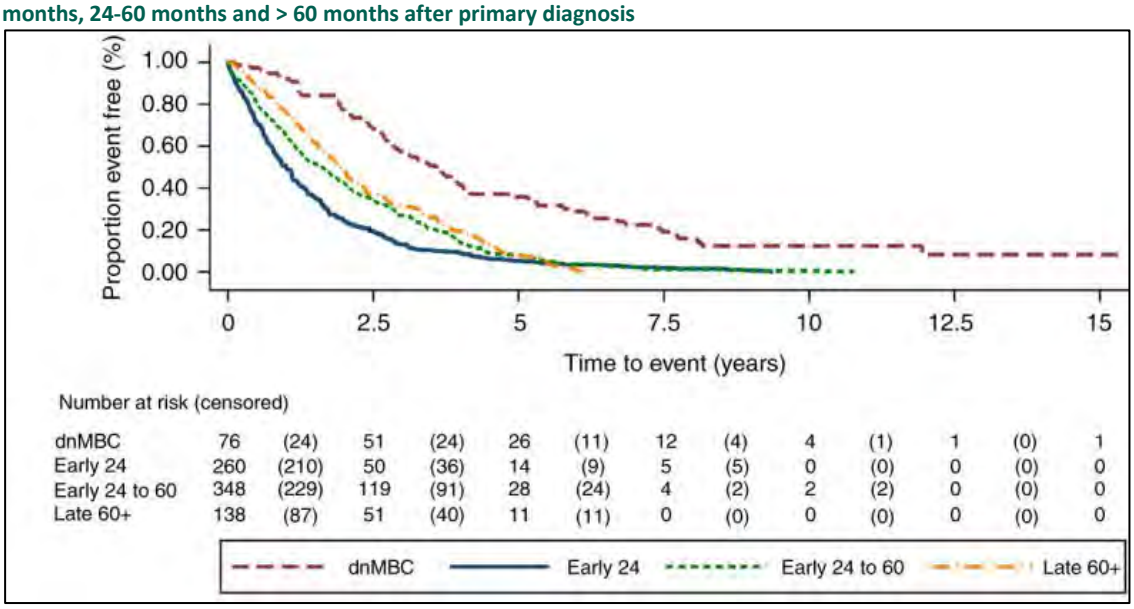
Weighted-average survival for TP7

The weighted-average survival probabilities for TP7 were modelled using the survival parameters from the OlympiAD and the Collins et al. real world effectiveness study, the hazard ratio of OS from IMpassion130 [0.55 (95%CI 0.21 to 1.41)], and the case mix probabilities from Table 81.

Figure 53 shows the weighted-average survival probabilities for TP7 in TNBC and HER2-/HR+. The modelled probabilities are compared to the Kaplan-Meier data of OlympiAD and Collins et al and to the survival probabilities for TP6 ('early onset mBC'). As the same case weights are applied to both arms, the corresponding survival probabilities for TP7 are the same across arms.

For TNBC, TP7 is modelled using a case mix of survival probabilities for single chemotherapy (OlympiAD) and atezolizumab plus paclitaxel (used as proxy for pembrolizumab plus paclitaxel or carboplatin). The median survival for TP7 is approximately 18 months, with approximately 7.5% of patients predicted to be alive at 5-years after diagnosis of 'late onset' metastatic TNBC. The 5-year relative survival estimates for distant TNBC from the SEER database is 12% [110]. However, a slightly higher estimate from the SEER database is expected since it reflects a general TNBC population and not a BRCA mutated high risk subgroup with potentially more aggressive disease. When compared to the survival probabilities for 'early onset' mBC (TP6), the model predicts improved median survival for those with 'late' versus 'early' disease (Figure 53). This is consistent with the post-recurrence survival reported in the UK POSH study by McKenzie et al [56] (Figure 52). The post-recurrence survival difference between 'late' and 'early' onset seems to last longer in the McKenzie et al study. However, this study includes general breast cancer patients and not high risk TNBC patients with BRCA mutation who have more aggressive disease. This might explain why the difference is smaller in our population.

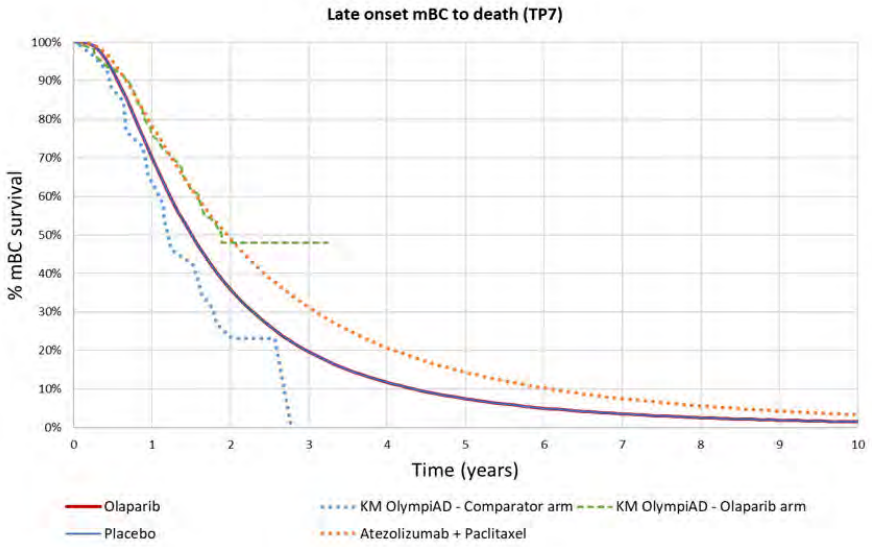
Figure 52. Post-distant recurrence survival for subjects with de novo and recurrent disease that occurred within 24 months, 24-60 months and > 60 months after primary diagnosis

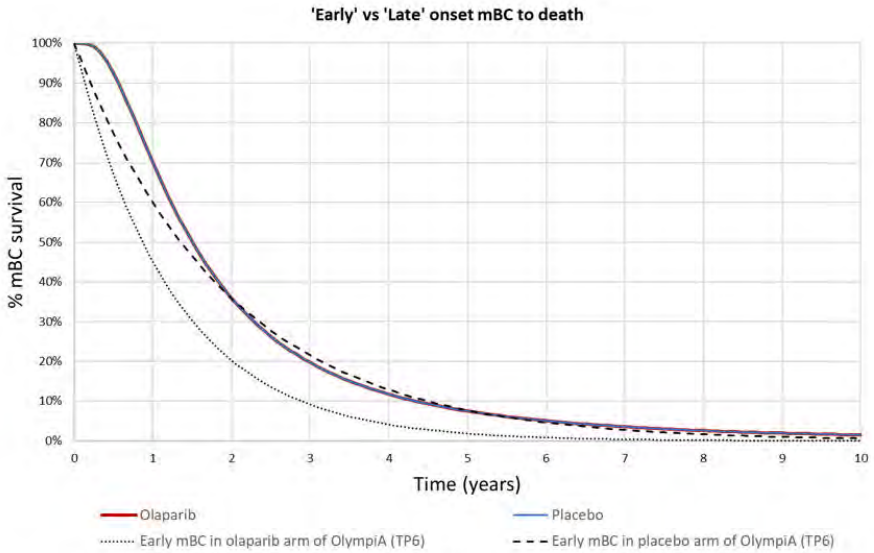


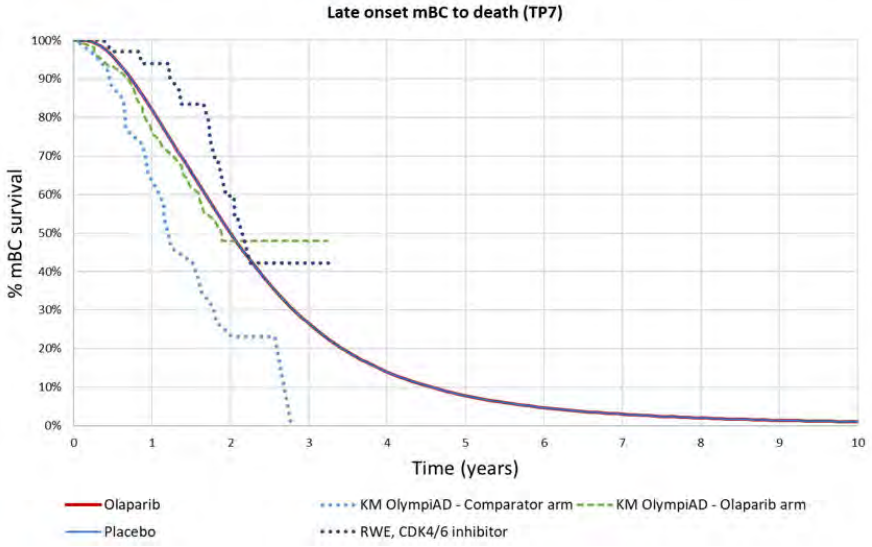
Abbreviation: dnMBC – de novo mBC

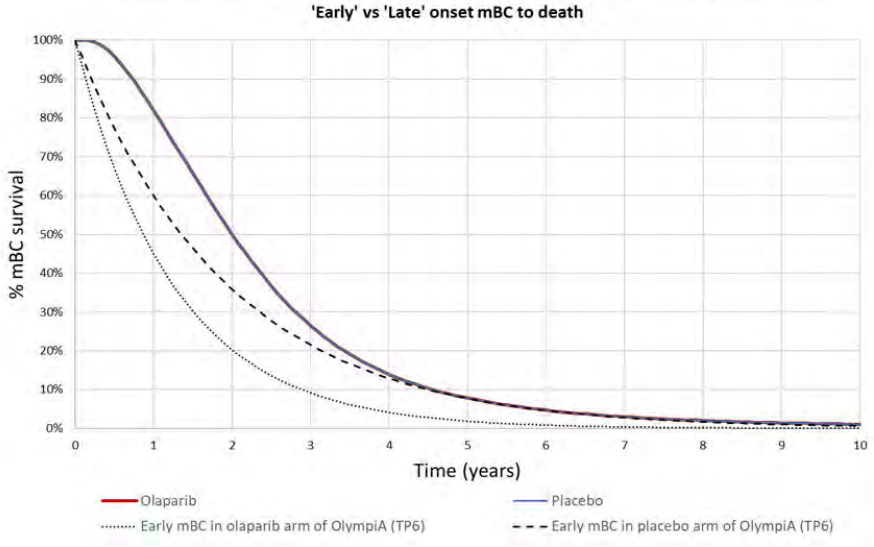
For HER2-/HR+, TP7 is modelled using a case mix of survival probabilities for the TPC arm of OlympiAD and CDK4/6 inhibitor treatment from Collins et al [62]. The resulting weighted-average survival probabilities for TP7 fall between the Kaplan-Meier estimates for each study. The median survival for TP7 is 2-years with 7.8% of patients alive at 5-years after diagnosis of 'late onset' HR+ mBC. The model predicts improved outcomes for patients with 'late' [TP7] versus 'early' [TP6] onset HR+ disease (Figure 53).

Figure 53. Weighted-average survival probabilities for 'late onset mBC' [TP7] in TNBC (upper) and HR+ (bottom) versus Kaplan-Meier data of OlympiAD and Collins et al (left) and the survival probabilities for 'early onset mBC' [TP6] (right)


Late onset mBC to death (TP7)
% mBC survival
Time (years)
Olaparib
Placebo
KM OlympiAD - Comparator arm
Atezolizumab + Paclitaxel
KM OlympiAD - Olaparib arm


'Early' vs 'Late' onset mBC to death
% mBC survival
Time (years)
Olaparib
Placebo
Early mBC in olaparib arm of OlympiA (TP6)
Early mBC in placebo arm of OlympiA (TP6)


Late onset mBC to death (TP7)
% mBC survival
Time (years)
Olaparib
Placebo
KM OlympiAD - Comparator arm
RWE, CDK4/6 inhibitor
KM OlympiAD - Olaparib arm


'Early' vs 'Late' onset mBC to death
% mBC survival
Time (years)
Olaparib
Placebo
Early mBC in olaparib arm of OlympiA (TP6)
Early mBC in placebo arm of OlympiA (TP6)

4. Validation of model clinical extrapolations

Figure 54 shows the long-term model projections of IDFS and OS for the HER2-/HR+ and TNBC populations. The Kaplan-Meier graphs for DCO2 are overlaid on the projections.

The long-term projections illustrate the difference in the modelled risk profile across TNBC and HER2-/HR+ patients. For TNBC, the risk of recurrence was assumed to plateau at year 5 based on expert advice and clinical evidence. This leads to a flattening of the OS curve. Over the long-term, the risk of death is driven primarily by all-cause mortality which increases with age. For HER2-/HR+, the risk of recurrence was assumed to remain throughout the model time horizon, leading to a gradual decline in survivorship on both the IDFS and OS curves. These trends are consistent with the literature evidence discussed previously in section 9.1.

Overall, the model accurately predicts the Kaplan Meier curves for both IDFS and OS across both HER2-/HR+ and TNBC (**Figure 54**). This is further supported by the comparison of landmark OS probabilities in Table 82.

For TNBC, the model projections of OS at years 1 to 4 are within a margin of 1.5% points of all the observed landmark probabilities. When extrapolated, the landmark OS for the watch and wait arm closely match those of external data [105] with model versus observed estimates of [redacted] at 5- and 10 years, respectively. For HER2-/HR+, the model projections are within a margin of 2.6% points of the observed landmarks in OlympiA. When extrapolated, the modelled OS for watch and wait are consistent with external data at landmarks of 10 [redacted] data), 15 (59.4% model versus 60% data) and 20 years [redacted] data) [53][g].

[g] The modelled landmark OS for the HER2-/HR+ group were compared to the risk of breast cancer death data from Pan et al. Data on any-cause mortality were not reported by Pan et al. The small percentage difference in OS between data sources may be due to the inclusion of non-breast cancer related deaths in the economic model.

Table 82. Comparison of landmark estimates of overall survival in OlympiA and external literature data sources with model predictions in TNBC and HER2-/HR+

Landmark (years)	Olaparib arm			Watch and wait arm		
	Kaplan-Meier estimate of OS	Model prediction of OS	Absolute difference in OS	Kaplan-Meier estimate of OS	Model prediction of OS	Absolute difference in OS
TNBC (*landmark from Copson et al [105])						
1	[redacted]					1.41%
2						1.33%
3						0.70%
4						1.01%
5						-
10						-
HER2-/HR+ (u						s risk of death from breast cancer)
1						1.54%
2						2.19%
3						1.02%
4						0.34%
5						-
10						-
15						-
20						-

5. Summary of extrapolations over the time horizon

This section summarizes the extrapolations for all parametric distributions over the whole time horizon. Extrapolations for IDFS (TP1, TP2 and TP3) are in [redacted]

Figure 59. Both adjusted [redacted] and unadjusted (

[redacted] extrapolations are shown for TNBC and HR+ respectively. Extrapolation modelling of the non-metastatic recurrence pathway (TP4 and TP5) are in [redacted]. Finally, extrapolation modelling of the metastatic recurrence pathway (TP6 and TP7) are presented in Figure 62 and

Figure 63.

Extrapolation modelling of IDFS (TP1, TP2 and TP3)

[redacted])

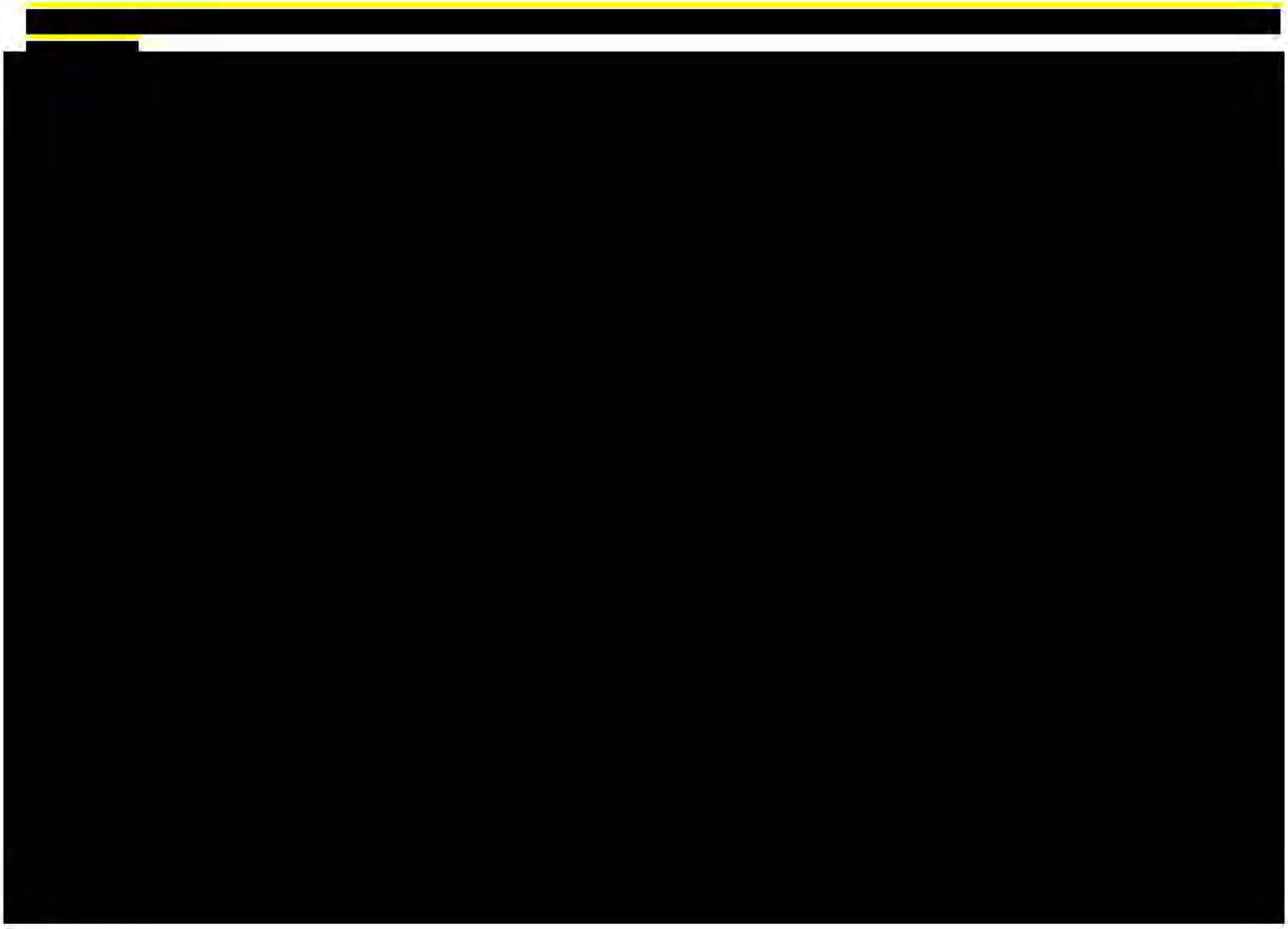
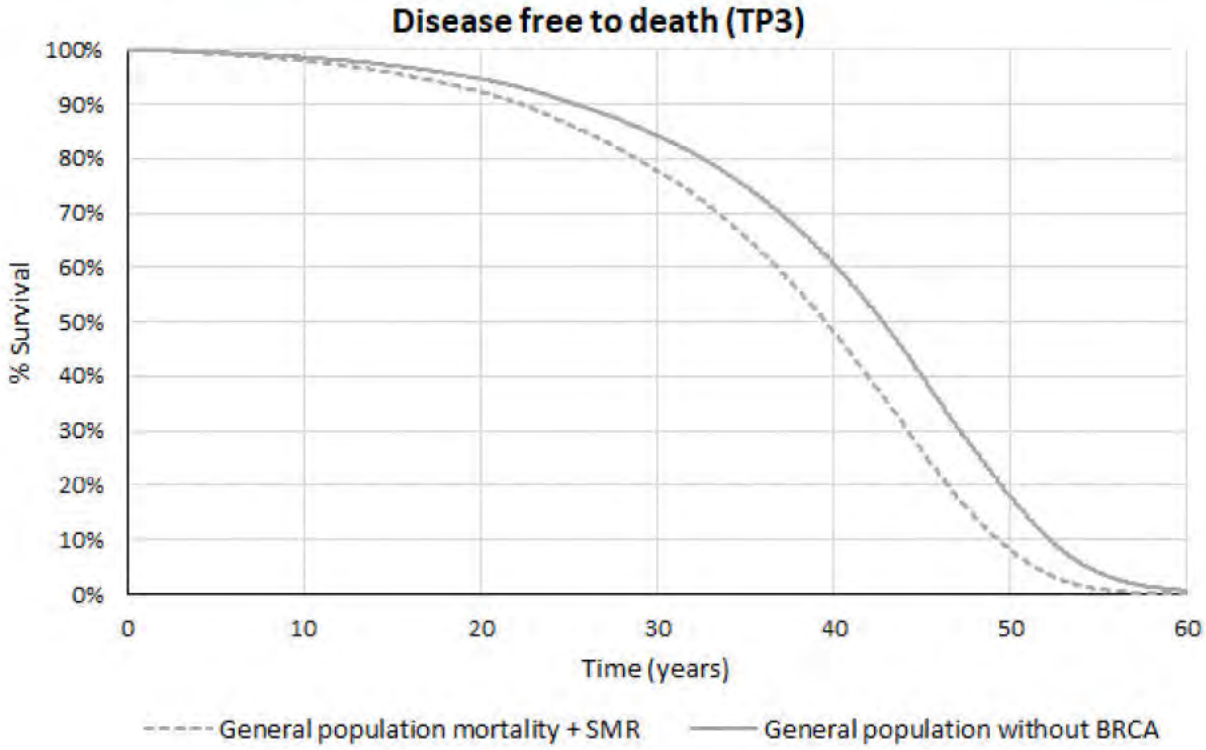


Figure 59. The all-cause mortality curve for the general population (female, aged 43 years at baseline) and long-term extrapolations for IDFS to death (general population mortality + standardized mortality ratio)



Extrapolation modelling of the non-metastatic recurrence pathway (TP4 and TP5)

[redacted]

[redacted]

Extrapolation modelling of the metastatic recurrence pathway (TP6 and TP7)

Figure 62. Kaplan-Meier data and long-term extrapolations for early onset metastatic BC to Death (TP6)

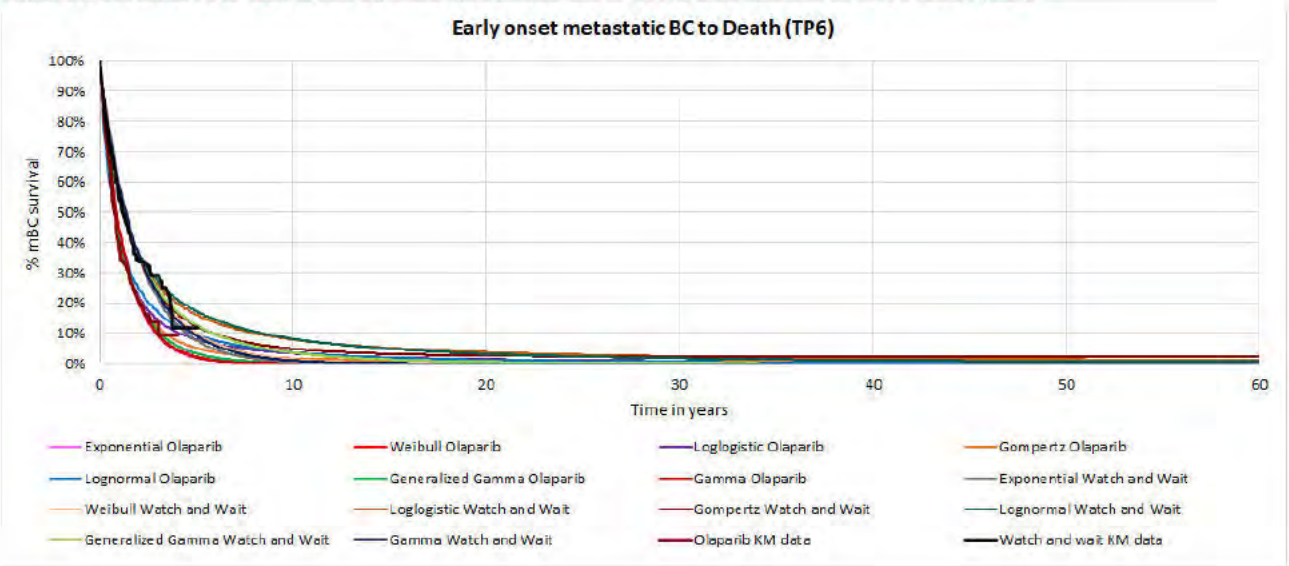
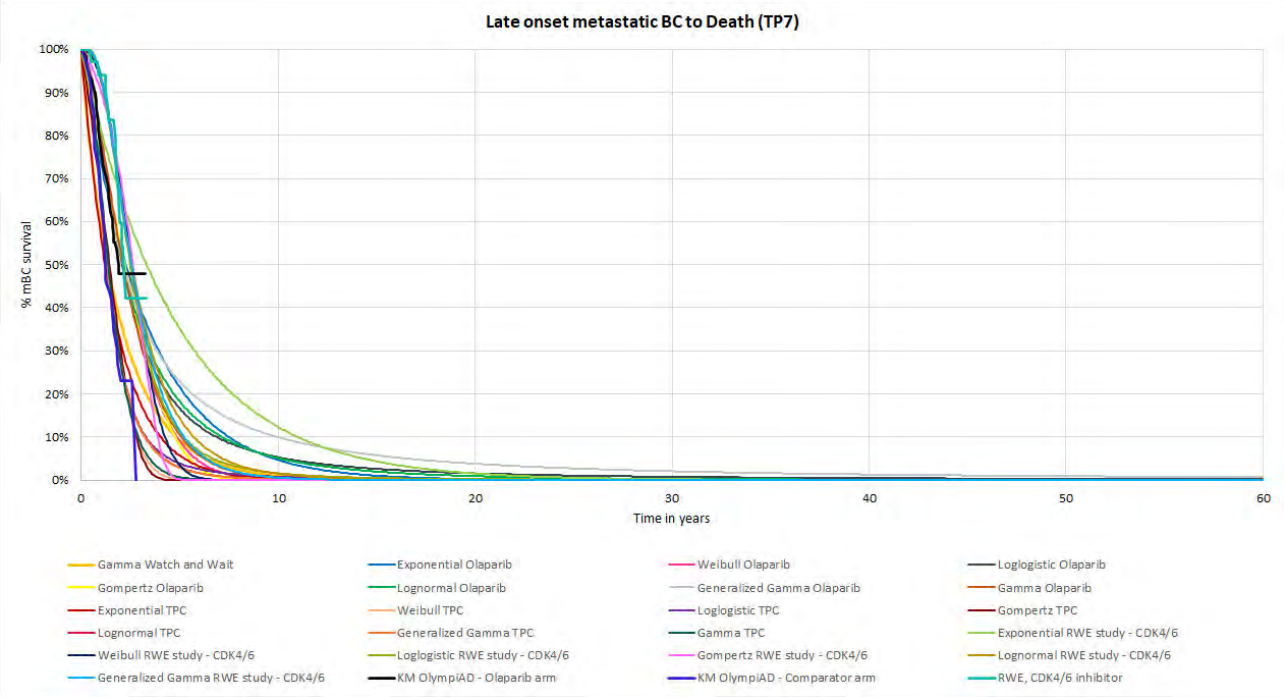


Figure 63. Kaplan-Meier data and long-term extrapolations for late onset metastatic BC to Death (TP7)



Appendix H – Literature search for HRQoL data

Published estimates of the HSU of patients with early breast cancer (eBC) were identified via a systematic literature review. The purpose of the literature search was to identify HSUVs associated with patients with early breast cancer.

Search strategy

The following sources were searched to identify potentially relevant publications:

- Electronic databases;
- Reference lists of eligible studies;
- Conference proceedings;
- Global HTA bodies;
- Additional relevant websites.

The following electronic databases were interrogated via the OVID platform using the search strategies detailed below:

- Embase, 1974 to present;
- MEDLINE® 1946 to present, incorporating:
    - MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations;
    - MEDLINE® Daily;
- EBM Reviews, incorporating:
    - The HTA database;
    - The National Health Service Economic Evaluation Database (NHS EED);
    - Cochrane Central register of Controlled Trials (CENTRAL) (clinical/HSUV SLRs only);
    - Database of Abstracts of Reviews of Effects (DARE) (clinical/HSUV SLRs only);
    - The Cochrane Database of Systematic Reviews (clinical/HSUV SLRs only);
- EconLit, 1886 to present (economic evaluation and cost/resource SLRs only).

The original database searches for Embase, MEDLINE, and EBM reviews (HTA and NHS EED) were conducted on the 24th of December 2020 and were updated on the 12th of January 2022.

Eligibility criteria applied throughout the review are summarised in Table 83.

Table 83. Eligibility criteria

CRITERIA	INCLUSION CRITERIA	EXLUSION CRITERIA
POPULATION	Inclusion criteria for the OlympiA study are: Adult female and male patients (≥18 years) with germline BRCA mutations (BRCA1 and/or BRCA 2) and non-metastatic primary invasive HER2-negative adenocarcinoma of the breast, who have: • Completed adequate breast and axilla surgery • Completed ≥6 cycles of neo-adjuvant or adjuvant chemotherapy (anthracyclines or taxanes (or combination of both), or prior platinum) However, criteria for the current SLRs will be adult female and male patients (≥18 years) with non-metastatic primary invasive adenocarcinoma of the breast who are receiving treatment in the post-surgical adjuvant setting.	• Patients with advanced breast cancer.
INTERVENTION	-	-
OUTCOMES	Utilities for e.g. directly elicited (TTO, SG) or generic preference-based utilities (e.g. EQ-5D, SF-6D) for relevant health states	-
STUDY DESIGN	No restriction, to include • Resource use studies • Clinical studies • Longitudinal studies • Utility elicitation studies • Database studies • Epidemiological studies	-
TERRITORY OF INTEREST	-	-
DATE OF PUBLICATION	-	-
LANGUAGE OF PUBLICATION	English abstracts of foreign publications will be considered. Studies published in a non-English language will be flagged, and their inclusion decided in conjunction with AstraZeneca.	-

Once the searches were completed in the appropriate electronic databases, duplicate citations were removed, and potentially relevant citations were exported to an Excel® database. Individual citations were then screened against the pre-defined eligibility criteria based on title and abstract.

The full text of citations included at the abstract screening stage were obtained to ascertain whether the publications do indeed meet the eligibility criteria. Citations excluded at this stage were assigned a detailed explanation of the reason for exclusion at the full publication review.

The inclusion/exclusion of citations, both, at the title/abstract phase and the full publication phase, were conducted by two independent analysts. Any disputes were referred to the project manager and resolved by consensus.

Results

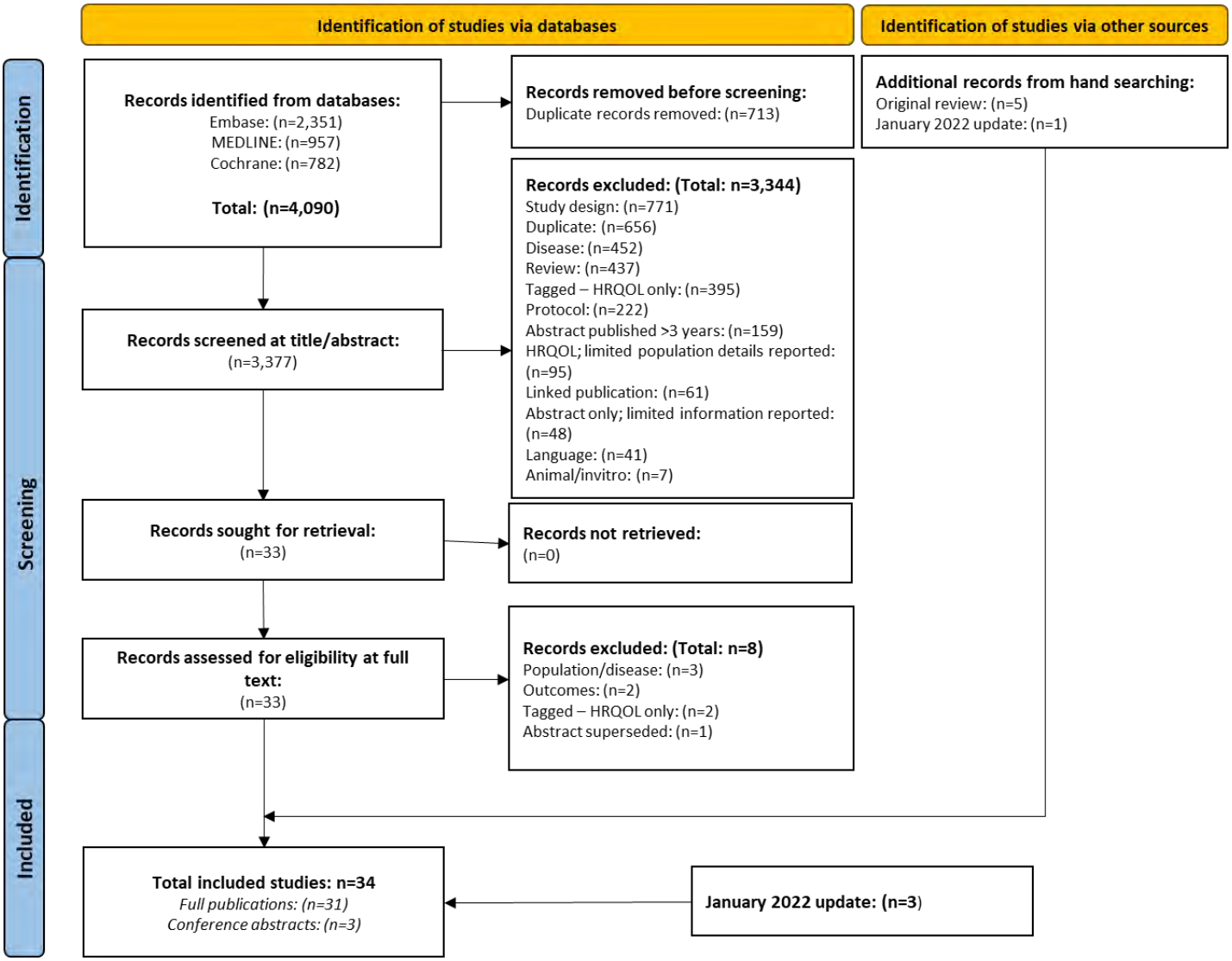
In the original review (December 2020), the electronic databases identified a total of 4,090 citations. Following removal of 713 duplicates, 3,377 citations were screened on the basis of title and abstract. Of these, 395 were tagged as they reported HRQOL data for the population of interest. A total of 33 were considered to be potentially relevant and were ordered for full text review. At this stage, a further eight citations were excluded, of which two were tagged as they reported HRQOL data. Hand searching yielded five additional relevant publications. Therefore, a total of 30 publications reporting HSUVs associated with patients with eBC were identified for final inclusion in the review (full publication, N=27; conference abstracts, N=3) [70, 102, 111-138].

In the January 2022 update, the electronic databases identified a total of 649 citations. Following removal of 213 duplicates as well as 174 de-duplicates from the previous search results, 262 citations were screened on the basis of title and abstract. Of these, 62 were tagged as they reported HRQOL data for the population of interest. A total of 13 were considered to be potentially relevant and were ordered for full text review. At this stage, a further 10 citations were excluded, of which three were tagged as they reported HRQOL data. Hand searching yielded one additional relevant publication. Therefore, a total of four publications reporting HSUVs associated with patients with EBC were identified for final inclusion in the update review (full publication, N=4; conference abstracts, N=0) [139-142].

Overall, a total of 34 publications reporting HSUVs for patients with eBC were identified for final inclusion across the original review and the January 2022 update (full publications, N=31; conference abstracts, N=3) [70, 102, 111-142]. In addition, 462 studies reporting use of generic and/or disease specific HRQOL instruments were tagged.

The flow of studies through review is summarised in the PRISMA flow diagram in Figure 64.

Figure 64. PRISMA flow diagram for the HSUV review



In total, the literature review in early breast cancer identified 5 unique studies that reported HSU values derived via the EQ-5D-3L or EQ-5D-5L and the UK value set. A summary of the HSU values extracted from these studies is provided in Table 84. No relevant Danish study was identified.

The studies by Conner-Spady et al [114, 115] reported HSU values collected from a prospective longitudinal study of HRQoL in 52 breast cancer patients receiving high dose chemotherapy and undergoing stem cell transplantation at the Tom Baker Cancer centre in Calgary from 1995 to 1998. HSUs were summarised according to treatment status during follow-up. These studies had a relatively small sample size and to our knowledge have not been used to inform cost-effectiveness evaluations in past technology appraisals.

The study by Lidgren et al [70] reported HSU from 361 consecutive breast cancer patients attending an outpatient clinic at Karolinska University hospital between April and May 2005. The study was cross-chapteral and reported HSUs according to diagnosis status, including patients in the first year after primary breast cancer, and in the years after locoregional or metastatic recurrence. The study was conducted in Denmark, and the reported HSUs were evaluated using the UK social tariff for the EQ-5D-3L. Therefore, it was considered relevant for the current analysis.

The multinational study by Criscitiello et al investigated the HRQoL of patients with HER2-/HR+ early breast cancer in the United States, Japan, France, Germany, Italy, Spain, and the UK [139]. Health status was evaluated using the EQ-5D-5L, and mapped to HSUs using country-specific value sets, including the crosswalk UK societal tariff by van Hout et al [143]. The study reports a high-level of HRQoL for early breast cancer patients that are disease-free, with scores that are comparable to general population normative values. The HSU's reported for the UK cohort could be considered applicable to the current analysis.

Finally, the real-world UK study by Verrill et al aimed to assess how living in each stage of HER2+ breast cancer treatment (patients with early breast cancer currently receiving adjuvant treatment; patients with early breast cancer who have completed adjuvant parenteral therapy; and patients with mBC) impacts directly on patients' HRQoL and productivity [142]. Health status was measured using the EQ-5D-5L, and mapped to HSUs using the crosswalk UK societal tariff by van Hout et al [143]. Similar to Criscitiello et al [139], the HSUs reported in Verrill et al could be considered applicable to the current analysis.

Overall, none of the identified studies reported HSU values that could be considered fully representative of patients eligible for adjuvant olaparib given the lack of data for patients with gBRCAm, HER2-negative, high risk early breast cancer. In terms of health status, only Lidgren et al [70] reported values that may be relevant to the state structure of the model. However, in the context of the IDFS state, the mapped HSU values from OlympiA are considered more appropriate than Lidgren et al given that they more closely represent the health status of patients eligible for adjuvant olaparib (gBRCAm, HER2-negative, high risk).

Table 84. Summary of literature estimates of HSUs in early breast cancer

Study, country	Population, sample size	Method used to derive utilities	Health states	HSU value (95% CI) [SD]
Conner-Spady 2001 [115]	Population: patients with EBC, stages II/III, at high risk of relapse Sample size: N=52	Instrument: EQ-5D-3L Tariff: UK tariff – Dolan et al (1997)	Patients with stage II/III EBC, mean value at baseline (N=40)	0.77 [0.16]
			Patients with stage II/III EBC, mean value on day 1 of the third cycle of fluorouracil + adriamycin + cyclophosphamide (N=NR)	0.76 [0.11]
			Patients with stage II/III EBC, mean value 3 weeks after administration of high dose chemotherapy (N=40)	0.57 [0.28]
			Patients with stage II/III EBC, mean value 8 weeks post-high dose chemotherapy (N=NR)	0.78 [0.17]
Conner-Spady, 2005 [114]	Population: patients with EBC, stages II/III, at high risk of relapse Sample size: N=52	Instrument: EQ-5D-3L Tariff: UK tariff – Dolan et al (1997)	Patients with stage II/III EBC, mean value pre-induction (N=48)	0.78 [0.18]
			Patients with stage II/III EBC, mean value on day 1 of the third cycle of fluorouracil + adriamycin + cyclophosphamide (N=48)	0.75 [0.18]
			Patients with stage II/III EBC, mean value 3 weeks after administration of high dose chemotherapy (N=48)	0.61 [0.29]
			Patients with stage II/III EBC, mean value at 6 months (N=45)	0.79 [0.19]
			Patients with stage II/III EBC, mean value at 12 months (N=40)	0.84 [0.19]
			Patients with stage II/III EBC, mean value at 18 months (N=36)	0.84 [0.13]
			Patients with stage II/III EBC, mean value at 24 months (N=37)	0.89 [0.13]
Lidgren, 2007 [70] Denmark	Population: patients with a prior diagnosis of breast cancer Sample size: N=345	Instrument: EQ-5D-3L and TTO (not included in table) Tariff: EQ-5D-3L: UK tariff - Dolan (1997) [144] TTO: NA	Patients in the first year after primary breast cancer, mean EQ-5D-3L score (N=72; 21%)	0.696 (0.634; 0.747)
			Patients in the first year after recurrence, mean EQ-5D-3L scores (N=21; 6%)	0.779 (0.700; 0.849)
			Patients in the second and following years after primary breast cancer/recurrence, mean EQ-5D-3L score (N=177; 53%)	0.779 (0.745; 0.811)
			Patients in the metastatic disease state, mean EQ-5D-3L score (N=65; 19%)	0.685 (0.620; 0.735)
Criscitiello, 2021 Multi-national (The US, Japan, France, Germany, Italy, Spain, and the UK) [139]	Population: patients with HER2-/ HR+ EBC, stages I-III, either receiving adjuvant treatment or under post-adjuvant surveillance	Instrument: EQ-5D-5L Tariff for UK: van Hout, 2012 [143]	Patients with stage I-III EBC, UK (N=63)	0.872
Verrill, 2020 UK [142]	Population: patients with	Instrument: EQ-5D-5L	Currently undergoing treatment for EBC, TTO tariff (N=86)	0.809 (0.170)

	HER2+ early or metastatic breast cancer. Sample size: N=299	Tariff: Devlin et al (2016) [145] and van Hout et al (2012) [143]	Patients with EBC who completed treatment and were in remission, TTO tariff (N=108)	0.818 (0.181)
			Patients receiving treatment for metastatic breast cancer, TTO tariff (N=97)	0.695 (0.262)
			Currently undergoing treatment for EBC, crosswalk tariff (N=86)	0.728 (0.197)
			Patients with EBC who completed treatment and were in remission, crosswalk tariff (N=108)	0.732 (0.216)
			Patients receiving treatment for metastatic breast cancer, crosswalk tariff (N=97)	0.603 (0.271)

Some further utility sources were identified based on a search of utilities used in previous HTA submissions. The following HTA websites were searched to identify relevant previous regulatory submissions in this indication (no time restriction):

- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/
- Sottish Medicines Consortium (SMC): https://www.scottishmedicines.org.uk/
- Canadian Agency for Drugs and Technologies in Health (CADTH): https://cadth.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC): http://www.pbs.gov.au/pbs/home

A total of 7 NICE and CADTH HTA submissions were identified by the SLR of economic evaluations conducted alongside the original review. As mentioned above, this further review identified some additional references, but the only one we have included in the model is the one by Lloyd et al. (2006) [73], which has been used in several NICE evaluations in breast cancer (TA632, TA612, TA569, TA424).

Appendix I Mapping of HRQoL data

Health related quality of life data from OlympiA

In OlympiA, HRQoL was assessed using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires. The FACIT-Fatigue is a well-established instrument for measuring the impact of fatigue on daily activities and function, whilst the QLQ-C30 is a standard measure of cancer-specific HRQoL. These questionnaires were selected to measure the impact of treatment-related fatigue on quality of life, as well as the general physical and emotional status of patients as they continue to recover from the chemotherapy, surgery and/or radiation therapy received prior to randomisation. No EQ-5D-3L or EQ-5D-5L data were collected in the study.

The FACIT-Fatigue and EORTC QLQ-C30 were completed at baseline (prior to randomisation) and every 6 months for a period of 2-years. For both instruments, compliance rates were high at baseline (>99% in both arms) and remained above 65% at all visits (see section 7.1.8). Overall, there was no clinically meaningful change in HRQoL across the study follow-up and no meaningful difference in HRQoL between arms, as it is described in chapter 9.6. These findings suggest no detrimental impact of treatment with olaparib on HRQoL.

In the absence of EQ-5D-3L or 5L data, HSU values were estimated by mapping from the EORTC QLQ-C30 data collected at DCO1 of OlympiA[8] using published algorithms. These data were considered the most robust and applicable source of HSU data for the IDFS state of the model given they are based on HRQoL data collected in patients with gBRCAm early breast cancer. Therefore, they were used in the base case analysis. No mapping algorithm relevant for breast cancer was found converting QLQ-C30 to EQ-5D-5L.

The HSUs generated in this analysis were valued based from a United Kingdom societal perspective using the EQ-5D-3L value set by Kind et al [146]. EORTC QLQ-C30 mapping algorithms were identified from the Health Economics Research Centre mapping database by Dakin et al [147]. Fifteen published algorithms mapping EORTC QLQ-C30 to EQ-5D were identified. Of the 15 algorithms, four were conducted in patients with multiple myeloma, three in lung cancer, two in breast cancer, two in gastrointestinal cancer (gastric and oesophageal), and one each in colorectal and prostate cancer. Two algorithms reported mapping in cohorts comprising a mix of cancers. As cancer is a highly heterogeneous disease with symptoms and quality of life that can vary significantly across tumour types, the mapping analysis for OlympiA focused on studies that reported in breast cancer or included a subset of breast cancer patients. Studies meeting these criteria were Crott and Briggs, Kim et al and Longworth et al [69, 72, 125].

As data were only routinely collected every 6 months up to recurrence or for a maximum of 2 years in OlympiA, the HSUs for adverse events, metastatic and non-metastatic breast cancer were sourced from external data sources, including previous appraisals and the literature (see sections 9.6 and Appendix H). In the base case analysis, the HSUs for 'early and 'late' onset metastatic breast cancer were based on data from Lidgren et al [70]. The Lidgren et al study was selected because the reported values were relevant to the health state structure of the model. The HSU values from Lloyd et al [73] were used in sensitivity analysis.

The HSU for non-mBC was assumed the same as IDFS in the base case. This is supported by data from Lidgren et al [70] that reported the same mean HSU value between patients with primary (i.e., IDFS) and non-metastatic breast cancer.

EORTC QLQ-C30 in OlympiA versus population norms

The EORTC QLQ-C30 subscale scores for function and symptoms in OlympiA (all observations pooled) were compared to the published general population normative data from Nolte et al [148]. To ensure comparability with OlympiA, the general population normative data were based on scores from females aged 40-49 years old.

Figure 65 and Figure 66 display the mean EORTC QLQ-C30 general health, functioning and symptom scores for OlympiA and the population norm data. For general health and functioning scales, a higher score represents an improved level of health or functioning. For the symptom scales, a higher score represents a higher level of symptomology or problems.

In general, the OlympiA population had similar or higher functioning scores and similar or lower major symptom scores versus the population norms. For the general health and emotional functioning scales, the OlympiA population scored higher than the population norm. For all other subscales (physical, role, cognitive and social), there was no clinically meaningful (<3 points, in line with definition used in the OlympiA Clinical Study Report [7]) difference in mean scores between OlympiA and the population norms, **Error! Reference source not found.**.

[8] Relatively few additional EORTC QLQ-C30 records were available with the additional follow-up at DCO2, and therefore, data from DCO1 were used.

On the symptom scales, the OlympiA population reported a lower score than the population norm on all domains except for financial difficulties. The domain of financial difficulties was higher for OlympiA patients indicating worse problems with financial burdens. This domain tends to have limited correlation with the domains of the EQ-5D and was not included in the final mapping analysis by Crott and Briggs [69]. This suggests that any differences in financial difficulties are unlikely to result in health state utility differences between the general population and OlympiA. These results suggest that the OlympiA population has a generally comparable symptom burden to the age- and gender-matched general population.

Figure 65. Comparison of EORTC QLQ-C30 functioning scores in OlympiA (from mapping report) versus general

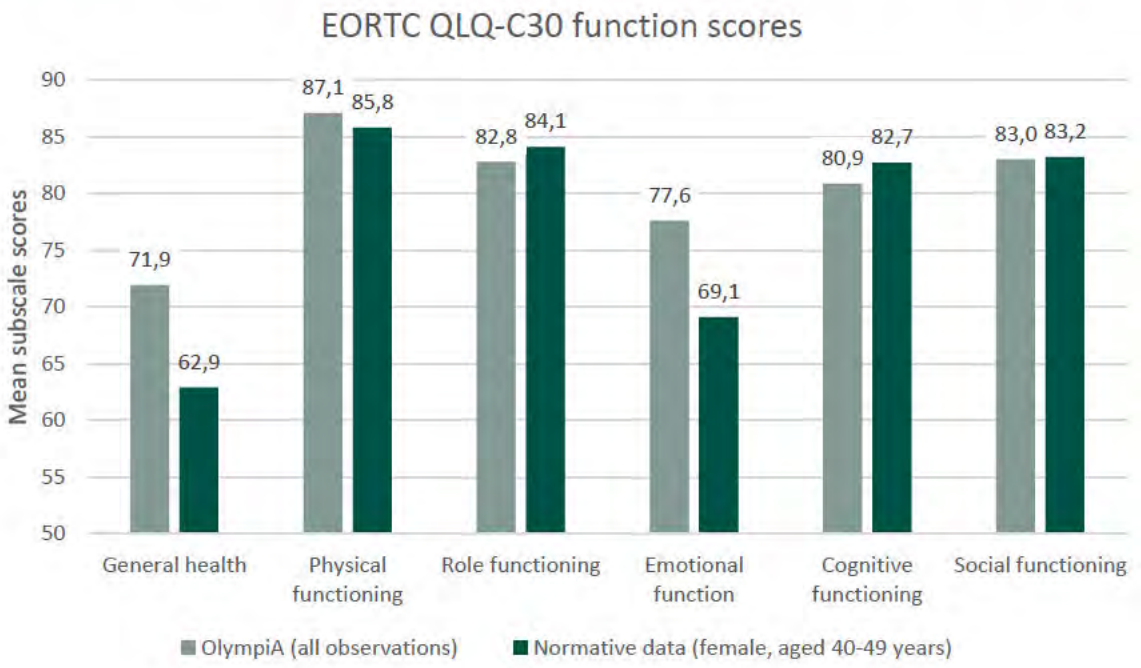
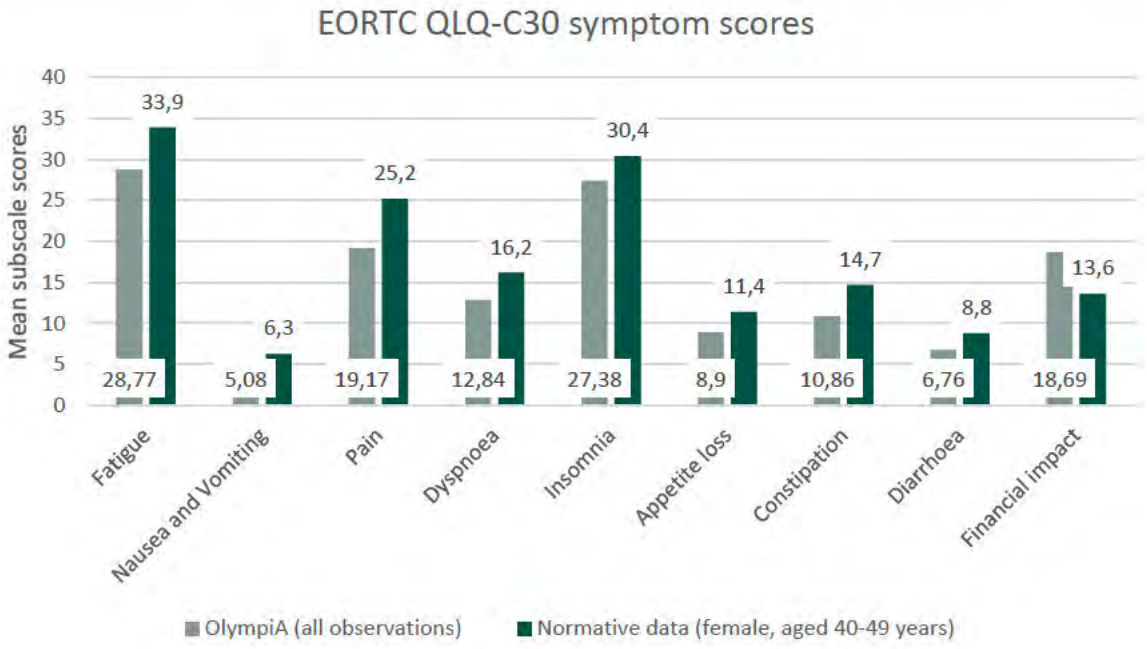


Figure 66. Comparison of EORTC QLQ-C30 symptom scores in OlympiA (from mapping report) versus general population



Mapping analysis

Published mapping algorithms were identified from the online HERC mapping database (accessed October 2021; https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies). Only algorithms with HSUs derived from the UK value set were considered in the analysis. Two relevant published algorithms were identified; Crott and Briggs reported direct mapping of the QLQ-C30 to UK EQ-5D-3L HSUs and Longworth et al reported indirect mapping of the QLQ-C30 to the domains of the EQ-5D-3L.

The algorithm by Crott and Briggs [69] was used in the base case analysis as the mapping was performed in a similar patient population (locally advanced breast cancer versus mix of cancers in Longworth et al) to OlympiA and has been used in previous appraisals for HER2-negative breast cancer [149]. HSUs based on the mapping by Longworth et al [72] were included in a sensitivity analysis to the base case.

Mapped HSUs were summarised using descriptive statistics and mixed effects repeated measures regression analysis. The regression analysis was used to determine the impact of randomised group and recurrence status on HSU. This method accounts for the repeated measurement of HSU by subject and provides valid results under the assumption that missing data are missing at random. For input to the cost-effectiveness model, the HSU for IDFS was derived from the regression analysis using the least squares mean method. This provides an estimate of the mean HSU for IDFS that appropriately accounts for the correlation between repeated measures of HRQoL data in OlympiA, and further adjusts for baseline HSU and the recurrence status of patients at the time data were collected [150]. A summary of the mean HSUs based on Crott and Briggs is presented by arm and follow-up period in Table 85.

Table 85. Summary statistics for mapped HSU using Crott and Briggs algorithm (capped at 1) by arm and study period

	Treatment	N	Mean	SD	Median	Min	Max
Baseline	Olaparib 300 mg bd	875	0.863	0.134	0.900	0.132	1
	Placebo	879	0.867	0.127	0.898	0.139	1
Study follow-up and recurrence-free	Olaparib 300 mg bd	2224	0.867	0.122	0.900	0.007	1
	Placebo	2222	0.872	0.118	0.901	0.032	1
Study follow-up and post-recurrence	Olaparib 300 mg bd	13	0.763	0.216	0.833	0.227	0.989
	Placebo	47	0.840	0.147	0.889	0.384	1

In the primary analysis of mapped HSU values based on EORTC QLQ-C30 in OlympiA [2], there was no meaningful difference in mean HSU across visits (0.86 to 0.87 for baseline versus follow-up visits) or between arms of the study (0.867 to 0.872 for olaparib and placebo, respectively). Relatively few HSU values were collected after recurrence in OlympiA as the study did not require HRQoL data collection during the post-recurrence survival follow-up [2, 7]. Any data collected during this period are outside the planned scheduled visits of the study and may therefore be subject to selection bias. The results of the regression analysis are summarised in Table 86.

Table 86. Results of linear regression analysis on mapped HSUs (capped at 1.0) from OlympiA using Crott and Briggs algorithm

Fixed effects	Estimate	95% Confidence interval and p-value
Intercept	0.871	0.865, 0.877 (<0.001)
Olaparib vs. Placebo	-0.004	-0.013, 0.005 (0.352)
Baseline HSU – mean(baseline)	0.461	0.426, 0.495 (<0.001)
Recurrence (vs. recurrence-free)	-0.027	-0.054, 0.001 (0.056)
Observations: 4424, Number of subjects: 1532		

The results of the regression analysis suggest no statistically significant (at 5% level) or meaningful difference (<0.08 [151]) in HSU between the arms of OlympiA (olaparib vs. placebo = -0.004, p=0.352). These results support the use of the same IDFS HSU across the olaparib and placebo arms of the model. The least squares mean estimate of the HSU for IDFS (i.e., recurrence-free), averaged across arms, was 0.869 (95%CL 0.865-0.873). This value was used to model the HSU of IDFS in the cost-effectiveness model.

In the regression analysis, there was no statistically significant (at 5% level) or meaningful (<0.03) difference in HSU comparing post versus pre-recurrence scores (-0.027, p=0.056). The absence of an effect of recurrence on HSU is likely due to the limited data collected after recurrence, as described previously. The data collected after recurrence are therefore not considered in the economic model. Alternative data are obtained from the published literature as described in section 9.6.

Additional regression analyses were performed to assess the impact of hormone receptor status on HSU. There was no significant or meaningful impact of HR+ versus TNBC status on HSU (-0.001, p=0.895). Further, there was no impact of receptor status on the HSU of post versus pre-recurrence (interaction term -0.016, p=0.690). The HSU from the ITT population of OlympiA was therefore used to model the HSU of IDFS in both the TNBC and HR+ populations.

It is acknowledged that the HSU value for the disease free (DF) state (0.869) from the OlympiA mapping analysis using the Crott & Briggs (2010) algorithm is slightly higher than the disease-free HSU values observed and/or included in previous appraisals in HER+ disease. However, there has been increasing evidence from empirical

literature that patient reported HRQoL amongst patients with early breast cancer who are and remain disease-free over time is generally high, with reported scores comparable to general population scores [139, 142, 152, 153].

Appendix J Costs for treatment of non-metastatic and metastatic breast cancer

Introduction

Patients that enter the non-metastatic or metastatic disease states are assumed to receive additional treatment comprising surgical intervention, radiotherapy, and drug-based intervention. The share of treatment depends on the health state (non-metastatic or metastatic), prior adjuvant treatment (olaparib or watch or wait), and the hormone status (HR+ or TNBC) of patients.

At the time of DCO2 of OlympiA, post-recurrence surgery had been reported in 53 of 143 olaparib patients and 79 of 218 placebo patients with any recurrence event (ITT population) [7, 106]. These included surgeries that were performed after recurrence for non-mBC and during the treatment of mBC. As noted in the OlympiA clinical study protocol, locoregional recurrence (non-mBC) was to be treated with curative intent, where possible [7]. For these patients, the aim of surgery is the complete resection of the tumour [154][9]. In patients with mBC, surgery is given with palliative intent, and may be combined with stereotactic radiotherapy to manage the complications of brain or bone metastasis [155]. This was also validated by Danish clinical experts [54]. The type of surgery administered is therefore likely to differ by health state in the model. To reflect this, the model includes separate input parameters for the costs of surgery in non-mBC and mBC.

In OlympiA, radiotherapy was used to treat both non-mBC and mBC and was reported in 39 of 143 olaparib patients and 70 of 218 placebo patients with any recurrence event (ITT population) [7, 106]. Information on the dose of radiotherapy used in OlympiA was not available. The type of radiotherapy administered is likely to vary based on local practice and the tissue being targeted for treatment. As a simplifying assumption, the costs of radiotherapy were assumed to be the same across health states in the model.

Table 87 provides the list of treatment options considered for gBRCAm patients with non-mBC or mBC in the base case analysis. The therapy options included were those recommended by the consulted clinical experts [54]. In the non-mBC state, patients are assumed to receive only one line of therapy. For mBC, patients may receive one or more lines of treatment.

[9] Information on the type of post-event surgery were not available from OlympiA

Table 87. List of treatment options per state included in the base case

State	Treatment options
Non-metastatic breast cancer Patients may receive only one line of treatment	Capecitabine Docetaxel plus Cyclophosphamide IV Paclitaxel + Cyclophosphamide + Epirubicin IV Letrozole (HER2-/HR+ only)
Metastatic breast cancer Patients may receive one or more lines of treatment	Capecitabine (if not used before) Eribulin Docetaxel IV Atezolizumab+ nab-paclitaxel (TNBC only) Letrozole (HR+ only) Fulvestrant (HR+ only) Abemaciclib + letrozole (HR+ only) Abemaciclib + fulvestrant (HR+ only) (if letrozole used before) Everolimus + exemestane (HR+ only)

In the Excel model, the costs of drug, surgical, and radiotherapy treatment of non-mBC and mBC are modelled as a series of weighted average total treatment costs (drug, surgery, radiotherapy) that are applied as one-off costs to each patient entering the health state. This simplified approach to the modelling of subsequent treatment costs has been applied and accepted in numerous past appraisals in oncology.

The modelling of subsequent treatment costs as a one-off cost can lead to the overestimation of treatment costs as it ignores the effects of discounting on costs that accrue throughout the time spent within the post-recurrence state. Discounting would have a minimal impact on the costs of surgery and radiotherapy treatment, as these costs are likely to accrue within a short period after recurrence. For drug therapy, the costs of treatment are likely to accrue more gradually than captured in the model. The absence of health states for the individual lines or pre- versus post-progression in mBC (see section 9.2.2 for further rationale), prevents the accurate modelling of drug costs using a time-in-state method (e.g., monthly costs applied to each month in the state). Further, this method is ill-suited to the modelling of therapies with a fixed number of cycles (e.g., carboplatin), as it would require the complex modelling and tracking of individual treatment durations. As the costs of subsequent treatment are generally limited due to the widespread use of generic chemotherapies, and are of limited duration due to the poor post-recurrence survival of gBRCAm patients in OlympiA, a simplified approach to the modelling of subsequent costs was preferred.

Further detail on the data sources used to estimate the treatment costs of non-mBC and mBC in the base case is provided below.

Unit costs for drug acquisition and administration

Table 88 and Table 89 summarise the unit costs of drug acquisition and administration, respectively considered in the base case. Table 90 summarises the unit costs of radiotherapy and surgery for non-mBC and mBC.

Table 88. Unit costs (kr) of drug therapies considered in the base case

Treatment	Dose per vial/tablet (mg)	Pack Size	Cost* (AIP) (kr)	Price per mg (kr)
Endocrine therapy				
Letrozole	2.5	100	145.00	0.58
Anastrozole	1	98	36.96	0.38
Fulvestrant	250	2	463.00	0.93
Tamoxifen	20	100	159.00	0.08
Exemestane	25	100	3650.00	1.46
Platinum chemotherapy				
Carboplatin	150	1	95.00	0.63
	450	1	226.00	0.50
Cytotoxic chemotherapy				
Capecitabine	150	60	669.00	0.07
	500	120	578.00	0.01
Eribulin	0.88	1	2 282.55	2 593.81
Vinorelbine (IV)	50	10	1 240.00	2.48
Paclitaxel	100	1	110.50	1.11
	150	1	1 500.00	10.00
	300	1	201.50	0.67
Epirubicin (IV)	200	1	442.76	2.21
Everolimus	10	30	19 500.00	65.00
Immunotherapy				
Pembrolizumab	100	1	22 058.88	220.59
Atezolizumab	**840**	**1**	**20 722.76**	**24.67**
	1200	**1**	**29 603.93**	**24.67**
PARP inhibitor				
Talazoparib	0.25	30	**11 701.85**	**1 560.25**
	1	30	**35 102.88**	**1 170.10**
CDK 4/6 Inhibitors				
Abemaciclib	150	56	18 483.35	2.20
Palbociclib	125	21	22 853.83	8.71
Ribociclib	200	63	22 797.30	**1.81**

*Source: * Medicinpriser.dk, October 2023 prices*

Table 89. Unit costs (kr) of administration of drug therapies

Administration type	Unit cost (kr)	Source
Oral	0.0	Assumed to be 0 costs
IV	1 634.0	DRG: 09MA98 MDC09 1-dagsgruppe, pat. mindst 7 år Sundhedsdatastyrelsen. DRG-takster 2023 [76]
SC	0.0	Assumed to be 0 costs

Table 90. Unit costs (kr) of radiotherapy and surgery for non-mBC and mBC

Treatment	Unit costs (kr)	Data source of Unit cost
Radiotherapy	5 701	An average of 3-4 fractions for costs based on KEE input (DRG 2023: 27MP06 Strålebehandling, konventionel, 3-4 fraktioner) [76]
Surgery for non-mBC	39 401.00	**Radical mastectomy [combination of: (DC501) brystkræft i den centrale del af mamma and (KHAC25) Radikal mastektomi)]: 09MP03 - Stor mammakirurgisk operation - Sundhedsdatastyrelsen.** DRG-takster 2023 [76]
Surgery for mBC	100 752.50	Average between intracranial surgery and decompression surgery of the spinal cord (DRG 2023: 26MP17 and 08MP06) [76]

Non-metastatic breast cancer

A summary of the surgery and radiotherapy costs for non-mBC is provided in Table 91 and Table 92. In line with the clinical inputs for non-mBC (see Appendix G, section 2), the proportions of patients receiving radiotherapy and surgery in non-mBC were obtained from the post-event summary data of the OlympiA study that was pooled across arms and populations [7]. Of the 81 patients with non-mBC at DCO2, 13 had received radiotherapy (16.0%) and 50 had undergone surgery (61.7%) (data on file). The one-off total per patient cost of radiotherapy and surgical procedures for non-mBC was 25 222.58 kr.

Table 91. Probabilities and costs (kr) of radiotherapy and surgery for non-mBC (TNBC and HER2-/HR+)

Treatment	Proportion	N	Unit costs (kr)
Radiotherapy	16.0%	81	5 701.0
Surgery	61.7%	81	39 401.0

The one-off total cost of treatment for non-mBC is the same across arms of the model. Only one line of treatment is assumed on the basis that further treatment would be received only after progression to mBC. The drug costs of mBC are captured separately.

The summaries of the systemic drug therapy costs for non-mBC in TNBC and HER2-/HR+ patients are provided in Table 92 and Table 93, respectively. The doses and treatment durations are validated and the shares of treatments are informed by clinical expert input [54].

The one-off total costs of drug treatment for non-mBC in TNBC and HER2-/HR+ were 9 743..31 kr (1 900.11 kr 'acquisition' plus 7 843.20 kr 'administration') and 7 450.61 kr (1 895.01 kr 'acquisition' plus 5 555.60 kr 'administration'), respectively as presented in Table 92.

Table 92. Summary of total one-off costs (kr) for non-mBC by receptor status

Receptor status	Health state	Total per patient cost (kr)
TNBC	Drug acquisition	1 900.11
	Drug administration	7 843.20
	Surgery/radiotherapy	25 222.58
HER2-/HR+	Drug acquisition	1 895.01
	Drug administration	5 555.60
	Surgery/radiotherapy	25 222.58

Table 93. Costs (kr) and market shares of treatment for non-mBC (TNBC)

Treatment	Regimen	Number of cycles (21 days) of treatment	Source for treatment duration	Market share	Treatment costs per cycle (kr)	Administration costs per cycle (kr)
Capecitabine	2000mg per m^2 ‡ per day on days 1 to 14 followed by 7 days rest Administration type: Oral	7.1	Mean number of cycles of chemotherapy in the OlympiAD trial **[60]**, data on file	10%	477.43	0.00
Docetaxel plus cyclophosphamide	Docetaxel: 75mg per m^2 and Cyclophosphamide: 600mg per m^2 once every 21 days [www.lmk.dk] Administration type: IV	E+C: 6	Clinical expert input **[54]**	80%	D+C: 325.44	D+C: 1 634.00
‡ The body surface area is estimated to be 1.77 m^2, using the Cornell University Body Surface Area calculator **[156]**. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).						

Table 94. Costs (kr) and market shares of treatment for non-mBC (HR+)

Treatment	Regimen	Number of cycles of treatment	Source for treatment duration	Market share of treatment	Treatment costs per cycle (kr)	Administration costs per cycle (kr)
Capecitabine	2000mg per m^2 ‡ per day on days 1 to 14 followed by 7 days rest Administration type: Oral	7.1 (21-days cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [60], data on file	5%	477.43	0.00
Docetaxel plus cyclophosphamide	Docetaxel: 75mg per m^2 and Cyclophosphamide: 600mg per m^2 once every 21 days [www.lmk.dk] Administration type: IV	E+C: 6	Clinical expert input [54]	50%	D+C: 325.24	D+C: 1 634.00
Paclitaxel plus Cyclophosphamide plus Epirubicin	Cyclophosphamide: 600mg per m^2 ‡ once every 21 days Epirubicin: 90mg per m^2 ‡ and followed by Paclitaxel: 80mg per m^2 ‡ weekly Administration type: IV	C + E: 4 P: 4 (21-days cycles)	Clinical expert input [54]	50%	P + C + E: 988.44	P + C + E: 1 634.00
Letrozole	2.5mg daily tablet Administration type: Oral	13.9 (monthly cycles)	Median exposure to anastrozole in the phase 3 FALCON study [157]	90%	44.13	0.00

‡ The body surface area is estimated to be 1.77 m^2, using the Cornell University Body Surface Area calculator [156]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).

'Early onset' metastatic breast cancer

A summary of the surgery and radiotherapy costs for 'early' mBC is provided in Table 91and Table 95. The costs of surgery and radiotherapy were the same across receptor populations on the basis that receptor status is not expected to impact on the decision to undergo either procedure. In line with the clinical inputs for 'early' mBC (see Appendix G, section 3), the proportions of patients receiving radiotherapy and surgery in 'early onset' mBC were obtained from the post-event summary data from each arm of the OlympiA study (DCO2) separately [7] (Table 96).

The one-off total costs of radiotherapy and surgical procedures per patient for 'early' mBC are 26 221.70 kr for the olaparib arm and 27 633.15 kr for the watch and wait arm.

Table 95. Probabilities and costs (kr) of radiotherapy and surgery for 'early' mBC (pooled across TNBC and HER2-/HR+)

Arm	Treatment	Probability of procedure	N*	Unit costs (kr)
Olaparib	Radiotherapy	30.5%	105	5 701.00

	Surgery	25.7%	105	100 752.50
Watch and wait	Radiotherapy	37.3%	169	5 701.00
	Surgery	26.6%	169	100 752.50
*based on the number of patients with distant recurrence in OlympiA				

The one-off total cost of treatment for 'early' mBC is assumed to differ based on receptor status, and for TNBC patients it is also assumed to differ based on prior therapy (olaparib or watch and wait).

Patients that enter the 'early' mBC state may receive multiple lines of palliative treatment until death. Based on post-progression summaries from the OlympiAD trial in gBRCAm mBC, 75% of patients are assumed to receive more than one line of treatment [60]. The mean number of subsequent treatment lines is equal to 1.70 based on data from OlympiAD [60]. The total treatment cost for mBC is therefore estimated as:

$$Total\ cost = Cost_{1st\ line} + 0.75 \times Cost_{2nd\ line+} \times 1.7$$

The summaries of the systemic drug therapy costs for 'early' mBC in TNBC and HER2-/HR+ patients are provided in Table 97 and Table 98, respectively. The doses and treatment durations are validated and the shares of first and second-line treatments by subgroup are informed by clinical expert input [54]. Market shares do not always sum to 100% as a proportion of patients do not receive systemic drug therapy in each line, especially not in later stages.

The one-off total costs of drug treatment (all lines) per patient for 'early' mBC in TNBC are 190 420.10 kr in the olaparib arm and the watch and wait arm. The one-off total cost of drug treatment (all lines) per patient for 'early' mBC in HER2-/HR+ is 255 518.54 kr in both olaparib and watch and wait arms. A summary of the total per patient costs for 'early' mBC by arm and receptor status is provided in Table 96.

Table 96. Summary of total per patient costs (kr) for 'early' mBC by arm and receptor status

Receptor status	Arm	Health state	Total one-off cost (kr)
TNBC	Olaparib	Drug acquisition (all treatment lines)	190 420.10
		Drug administration (all treatment lines)	28 340.91
		Procedure (surgery or radiotherapy)	27 632.20
	Watch and wait	Drug acquisition (all treatment lines)	190 420.10
		Drug administration (all treatment lines)	28 340.91
		Procedure (surgery or radiotherapy)	28 926.62
HER2-/HR+	Olaparib	Drug acquisition (all treatment lines)	255 518.54
		Drug administration (all treatment lines)	0.00
		Procedure (surgery or radiotherapy)	27 632.20
	Watch and wait	Drug acquisition (all treatment lines)	255 518.54
		Drug administration (all treatment lines)	0.00
		Procedure (surgery or radiotherapy)	28 926.62

Table 97. Costs (kr) and market shares of treatment for 'early onset' mBC (TNBC)

Treatment	Regimen	Number of cycles of treatment	Source for treatment duration	Olaparib Arm		Placebo arm		Treatment costs per cycle (kr)	Administration costs per cycle (kr)
				Market share of treatment at 1st line	Market share of treatment at 2nd line or later	Market share of treatment at 1st line	Market share of treatment at 2nd line or later		
Capecitabine (or single chemotherapy in general)*	2000mg per m^2 ‡ per day on days 1 to 14 followed by 7 days rest Administration type: Oral	7.1 (21-day cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [60], data on file	85%	0%	85%	0%	477.43	0.00
Atezolizumab+ nab-Paclitaxel	840mg dose at days 1 and 15, followed by 100mg/m^2 nab-paclitaxel over 30 minutes on days 1, 8 and 15 of each 28-day cycle Administration type: IV	7 (21-day cycles)	Median number of cycles in IMpassion130 trial [91]	15%	-	15%	-	50 882.56	3 268.00

* Single chemotherapy could include carboplatin, capecitabine, eribulin, vinorelbine, paclitaxel or docetaxel used as monotherapy. We are here including one (capecitabine) for simplicity, as the costs do not differ very much between standard chemotherapies.
‡ The body surface area is estimated to be 1.77 m^2, using the Cornell University Body Surface Area calculator [156]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).

Table 98. Costs (kr) and market shares of treatment for 'early onset' mBC (HR+)

Treatment	Regimen	Number of cycles of treatment	Source for treatment duration	Olaparib Arm		Placebo arm		Treatment costs per cycle (kr)	Administration costs per cycle (kr)
				Market share of treatment at 1st line	Market share of treatment at 2nd line or later	Market share of treatment at 1st line	Market share of treatment at 2nd line or later		
Capecitabine	2000mg per m^2 ‡ per day on days 1 to 14 followed by 7 days rest Administration type: Oral	7.1 (21-day cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [60], data on file	12.5%	27.5%	12.5%	27.5%	477.43	0.00
Letrozole	L: 2.5mg daily Administration type: Oral	13.9 (28-day cycles)	Median exposure to anastrozole in the phase 3 FALCON study [157]	85%	20%	85%	20%	44.13	0.00
Anastrozole	1mg daily Administration type: Oral	13.9 (28-day cycles)	Median exposure to anastrozole in the phase 3 FALCON study [157]	0.0%	30.0%	0.0%	30.0%	11.48	0.00
Fulvestrant		1 (loading dose) + 15.0 (subsequent months)	Median exposure to fulvestrant in the phase 3 FALCON study [157]	0.0%	17.5%	0.0%	17.5%	1 006.61 (loading), 503.31 (subsequent)	0.00

‡ The body surface area is estimated to be 1.77 m^2, using the Cornell University Body Surface Area calculator [156]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).

'Late onset' metastatic breast cancer

A summary of the surgery and radiotherapy costs for 'late' mBC is provided in Table 90 and Table 99. The costs of surgery and radiotherapy were the same across receptor populations on the basis that receptor status is not expected to impact on the decision to undergo either procedure.

In line with the clinical inputs for 'late' mBC, the proportions of patients receiving radiotherapy and surgery in 'late onset' mBC are assumed to be the same across arms. Therefore they were obtained from the pooled post-event summaries of the OlympiA study [7] (Table 99).

The one-off total costs of radiotherapy and surgical procedures per patient for 'late' mBC is 28 476.15 kr for both arms of the model (Table 99).

Table 99. Probabilities and costs (kr) of radiotherapy and surgery for 'late' mBC (TNBC and HER2-/HR+)

Arm	Treatment	Probability of procedure	N*	Unit costs (kr)
Olaparib	Radiotherapy	34.7%	105	5 701.00
	Surgery	26.3%	105	100 752.50
Watch and wait	Radiotherapy	34.7%	169	5 701.00
	Surgery	26.3%	169	100 752.50
*based on the number of patients with distant recurrence in OlympiA				

As for 'early' onset mBC, patients in the 'late' onset state could receive multiple lines of palliative treatment. The calculation of treatment costs followed those described previously, assuming the same proportion (75%) of patients receive more than one line of treatment and incur the same mean number of subsequent treatment lines (1.7) [60].

The summaries of the systemic drug therapy costs for 'late' mBC in TNBC and HER2-/HR+ patients are provided in Table 101 and Table 102, respectively. The doses and treatment durations are validated and the shares of first and second-line treatments by subgroup are informed by clinical expert input [54].

The share of first-line treatment is based on the case mixes used to model the weighted-average survival after 'late onset' mBC as described in Table 81 (section 3 in Appendix G). For single chemotherapy (60% of use in TNBC and 40% for HER2-/HR+, Table 81), patients are assumed to receive a mix of carboplatin and eribulin for TNBC, and a mix of carboplatin, capecitabine, eribulin and vinorelbine for HER2-/HR+, based on clinical expert input [54]. The share of chemotherapies is assumed to be equally split amongst these treatments.

The one-off total costs of drug treatment (all lines) per patient for 'late' mBC in TNBC and HER2-/HR+ are 87 475.08 kr and 282 919.72 kr respectively (Table 100).

Table 100. Summary of total one-off costs (kr) for 'late' mBC by arm and receptor status

Receptor status	Arm	Health state	Total per patient cost (kr)
TNBC	Olaparib	Drug acquisition (all treatment lines)	87 475.08
		Drug administration (all treatment lines)	12 944.96
		Procedure (surgery or radiotherapy)	28 476.15
	Watch and wait	Drug acquisition (all treatment lines)	Same as olaparib arm
		Drug administration (all treatment lines)	
		Procedure (surgery or radiotherapy)	
HER2-/HR+	Olaparib	Drug acquisition (all treatment lines)	282 919.72
		Drug administration (all treatment lines)	4 435.17
		Procedure (surgery or radiotherapy)	28 476.15
	Watch and wait	Drug acquisition (all treatment lines)	Same as olaparib arm
		Drug administration (all treatment lines)	
		Procedure (surgery or radiotherapy)	

Table 101. Costs (kr) and market shares of treatment for 'late onset' mBC (TNBC)

Treatment	Regimen	Number of cycles of treatment	Source for treatment duration	Olaparib Arm and Placebo arm		Treatment costs per cycle (kr)	Administration costs per cycle (kr)
				Market share of treatment at 1st line	Market share of treatment at 2nd line or later		
Capecitabine	2000mg per m^2 ‡ per day on days 1 to 14 followed by 7 days rest Administration type: Oral	7.1 (21-day cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [60], data on file	85%	2.5%	477.43	0.00
Eribulin	1.23 mg per m^2 ‡ on days 1 and 8 of a 21-day cycle Administration type: IV	7.1 (21-day cycles)	As for capecitabine (Mean number of cycles of chemotherapy in the OlympiAD trial [60], data on file)	0%	20%	16 369.51	3 268.00
Paclitaxel	Paclitaxel: 175mg per m^2 ‡ on day 1 of each 21-day cycle Administration type: IV	6 (21-day cycles)	Maximum of 6 cycles	0%	42.5%	208.05	1 634.00
Atezolizumab+ nab-Paclitaxel	840mg dose at days 1 and 15, followed by 100mg/m^2 nab-paclitaxel over 30 minutes on days 1, 8 and 15 of each 28-day cycle Administration type: IV	7 (21-day cycles)	Median number of cycles in IMpassion130 trial [91]	15%	0%	51 592.70	1 634.00
‡ The body surface area is estimated to be 1.77 m^2, using the Cornell University Body Surface Area calculator [156]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).							

Table 102. Costs (kr) and market shares of treatment for 'late onset' mBC (HR+)

Treatment	Regimen	Number of cycles of treatment	Source for treatment duration	Olaparib Arm		Placebo arm		Treatment costs per cycle (kr)	Administration costs per cycle (kr)
				Market share of treatment at 1st line	Market share of treatment at 2nd line or later	Market share of treatment at 1st line	Market share of treatment at 2nd line or later		
Capecitabine	2000mg per m^2 ‡ per day on days 1 to 14 followed by 7 days rest Administration type: Oral	7.1 (21-day cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [60], data on file	5%	26%	5%	26%	477.43	0.00
Eribulin	1.23 mg per m^2 ‡ on days 1 and 8 of a 21-day cycle Administration type: IV	7.1 (21-day cycles)	As for capecitabine	5%	6%	5%	6%	16 369.51	3 268.00
Paclitaxel	Paclitaxel: 175mg per m^2 ‡ on day 1 of each 21-day cycle Administration type: IV	6 (21-day cycles)	Maximum of 6 cycles	0%	6%	0%	6%	208.05	1 634.00
Docetaxel	Docetaxel: 75mg per m^2 on day 1 of each 21-day cycle Administration type: IV	6 (21-day cycles)	Maximum of 6 cycles	0%	6%	0%	6%	49.78	1 634.00
Abemaciclib plus letrozole	A: 150mg twice daily L: 2.5mg daily Administration type: Oral	16 (28-day cycles)	Median number of abemaciclib treatment cycles in the phase 3 MONARCH3 study [158]	90%	0%	90%	0%	18 523.95	0.00

Anastrozole	1mg daily Administration type: Oral	13.9 (28-day cycles)	Median exposure to anastrozole in the phase 3 FALCON study [157]	0.0%	30.0%	0.0%	30.0%	11.48	0.00
‡ The body surface area is estimated to be 1.77 m^2, using the Cornell University Body Surface Area calculator [156]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).									

Appendix K Scenario analyses for the budget impact

The sensitivity analyses and scenarios would have a similar impact on budgets as on the cost per patient. The sensitivity for various model parameters is evident from the sensitivity analyses for the cost and QALY analysis. However, market shares are also important for the total budget impact. Hence, the sensitivity analysis for the budget impact focuses on market shares. Since the market shares for olaparib in adjuvant breast cancer in the new scenarios may differ from the base case estimates, scenario analyses were created with higher and lower market shares for olaparib. **Table 103** - **Table 106** show budget impact results where market shares for olaparib have been either increased or decreased by 10 percentage points compared with the base case market shares in section 10.2.

Table 103. Budget impact TNBC with 10% lower market shares for olaparib

Olaparib is recommended	2024	2025	2026	2027	2028	Total
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	55 329	89 375	97 544	103 515	107 110	452 874
Treatment monitoring cost	52 928	63 513	74 099	79 392	84 684	354 616
Disease management costs	218 987	248 068	276 030	301 087	321 953	1 366 124
Surgery & radiotherapy costs	65 189	104 547	129 522	147 167	158 396	604 821
AE management cost	7 861	9 271	10 682	11 387	12 092	51 293
Background therapy cost*	0	0	0	0	0	0
End of life costs	36 436	110 929	178 115	243 781	300 539	869 800
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib is NOT recommended						
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	74 374	119 844	134 302	143 847	150 282	622 649
Treatment monitoring cost	0	0	0	0	0	0
Disease management costs	220 331	256 615	292 425	324 508	350 929	1 444 807
Surgery & radiotherapy costs	88 649	142 264	176 029	198 206	213 084	818 232
AE management cost	810	810	810	810	810	4 050
Background therapy cost*	0	0	0	0	0	0
End of life costs	43 946	133 898	220 322	306 981	381 969	1 087 116
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 104. Budget impact HER2-/HR+ with 10% lower market shares for olaparib

Olaparib is recommended	2024	2025	2026	2027	2028	Total
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	4 847	7 383	15 422	21 887	27 429	76 968
Treatment monitoring cost	47 445	63 260	79 075	94 890	102 797	387 467

Disease management costs	318 501	361 776	405 063	449 115	492 480	2 026 935
Surgery & radiotherapy costs	103 959	161 895	203 457	235 746	264 938	969 995
AE management cost	7 367	9 428	11 489	13 551	14 581	56 417
Background therapy cost*	17 536	33 758	49 175	64 013	78 370	242 853
End of life costs	56 715	165 891	257 715	328 997	407 129	1 216 447
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib is NOT recommended						
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	5 712	8 751	17 593	24 809	30 927	87 793
Treatment monitoring cost	0	0	0	0	0	0
Disease management costs	319 158	367 722	417 795	469 475	520 706	2 094 856
Surgery & radiotherapy costs	123 337	193 671	246 342	289 442	326 050	1 178 842
AE management cost	1 184	1 184	1 184	1 184	1 184	5 920
Background therapy cost*	17 340	33 135	47 953	62 029	75 502	235 958
End of life costs	64 262	185 427	292 917	383 702	482 774	1 409 083
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

With 10% lower market shares for olaparib, the budget impact for all patients (HER2- ITT) is estimated at DKK [redacted] over 5 years compared with DKK [redacted] in the base case.

Table 105. Budget impact TNBC with 10% higher market shares for olaparib

Olaparib is recommended	**2024**	**2025**	**2026**	**2027**	**2028**	**Total**
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	47 711	78 712	86 497	92 486	96 085	401 491
Treatment monitoring cost	74 099	84 684	95 270	100 563	105 855	460 471
Disease management costs	218 449	244 757	270 241	293 592	313 404	1 340 444
Surgery & radiotherapy costs	55 805	91 338	115 438	133 148	144 401	540 129
AE management cost	10 682	12 092	13 502	14 207	14 912	65 395
Background therapy cost*	0	0	0	0	0	0
End of life costs	33 432	102 342	163 550	223 432	276 109	798 865
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib is NOT recommended						
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	74 374	119 844	134 302	143 847	150 282	622 649
Treatment monitoring cost	0	0	0	0	0	0
Disease management costs	220 331	256 615	292 425	324 508	350 929	1 444 807
Surgery & radiotherapy costs	88 649	142 264	176 029	198 206	213 084	818 232
AE management cost	810	810	810	810	810	4 050
Background therapy cost*	0	0	0	0	0	0
End of life costs	43 946	133 898	220 322	306 981	381 969	1 087 116

Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 106. Budget impact HER2-/HR+ with 10% higher market shares for olaparib

Olaparib is recommended	**2024**	**2025**	**2026**	**2027**	**2028**	**Total**
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	4 271	6 662	14 407	20 710	26 163	72 214
Treatment monitoring cost	79 075	94 890	110 705	126 520	134 427	545 617
Disease management costs	318 062	357 958	397 994	439 317	480 631	1 993 962
Surgery & radiotherapy costs	91 041	145 017	184 799	216 099	244 744	881 700
AE management cost	11 489	13 551	15 612	17 673	18 703	77 028
Background therapy cost*	17 667	34 129	49 823	64 953	79 608	246 180
End of life costs	51 684	154 545	239 707	303 989	375 658	1 125 582
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib is NOT recommended						
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration cost	5 712	8 751	17 593	24 809	30 927	87 793
Treatment monitoring cost	0	0	0	0	0	0
Disease management costs	319 158	367 722	417 795	469 475	520 706	2 094 856
Surgery & radiotherapy costs	123 337	193 671	246 342	289 442	326 050	1 178 842
AE management cost	1 184	1 184	1 184	1 184	1 184	5 920
Background therapy cost*	17 340	33 135	47 953	62 029	75 502	235 958
End of life costs	64 262	185 427	292 917	383 702	482 774	1 409 083
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

With 10% higher market shares for olaparib, the budget impact for all patients (HER2- ITT) is estimated at DKK [redacted] over 5 years compared with DKK [redacted] in the base case.