

Bilag til Medicinrådets vurdering af olaparib til adjuverende behandling af voksne patienter med germline BRCA1/2-mutation og HER2-negativ brystkræft

*Patienter med høj-risiko, tidlig brystkræft, der
tidligere har modtaget neoadjuverende eller
adjuverende kemoterapi*

Vers. 2.0



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

28.05.2026

Re.: “Vurderingsrapport”. Olaparib in early HER2- high-risk BRCAm breast cancer (OlympiA).

AstraZeneca would like to thank the DMC for the opportunity to comment on the above report. Below are the major points/findings that we would like the DMC to take into consideration during the final evaluations of the OLYMPIA application.

Costs

TNBC population.

The DMC excludes the costs of neoadjuvant pembrolizumab on the basis that the analysis focuses on the comparison of adjuvant treatments, and that patients in the olaparib arm are also expected to receive neoadjuvant pembrolizumab in Danish clinical practice. However, there are several potential uses of olaparib in the neoadjuvant and adjuvant TNBC setting:

- as adjuvant monotherapy after chemotherapy in pembrolizumab-ineligible patients
- as a replacement for adjuvant pembrolizumab in patients with gBRCAm TNBC
- in patients considered unsuitable for further pembrolizumab
- in combination with pembrolizumab after neoadjuvant pembrolizumab plus chemotherapy (a possibility according to DBCG guidance, although not explored in clinical trial settings).

We therefore consider that the DMC’s assessment report does not fully reflect the range of clinically relevant uses of olaparib in Danish patients with TNBC. There is also a methodological inconsistency between the efficacy assumption applied and the costs included in the analysis. The assumed relative effect of pembrolizumab versus olaparib is based on the hazard ratio from KEYNOTE-522. That estimate reflects the effect of pembrolizumab administered in both the neoadjuvant and adjuvant phases. In the current cost comparison, however, only the cost of adjuvant pembrolizumab is included. The analysis therefore applies an efficacy estimate generated from a combined neoadjuvant-adjuvant regimen while including only part of the corresponding treatment cost. On this basis, the DMC’s base case for the TNBC population should be regarded as conservative.

ER+/HER2- population.

In a scenario analysis, the DMC compares a treatment sequence of olaparib followed by ribociclib with abemaciclib, stating that the purpose is to illustrate the costs of such a sequence relative to adjuvant abemaciclib under an assumption of equivalent efficacy. However, in this scenario, the intervention arm includes the additional treatment cost of ribociclib without reflecting any potential additional clinical benefit associated with the treatment sequence with olaparib followed by ribociclib. The scenario therefore applies a highly conservative assumption whereby extra cost is included for olaparib without any corresponding benefit.

Serious Adverse Events:

The DMC mentions concerns regarding the increased risk of developing new cancers during treatment with olaparib, particularly MDS/AML. This is listed in the olaparib summary of product characteristics as an adverse reaction under

section 4.4 '*Special warnings and precautions for use*'. In the OlympiA study, few cases of MDS/AML were reported, and there was no difference between the two treatment arms, as also mentioned in table 18 of the 'Vurderingsrapport'.

We look forward to receive the final evaluation of the OlympiA application.

Kind regards



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Forhandlingsnotat

28.05.2026
 LSC/DBS

Dato for vurdering i Medicinrådet	24.06.2026
Leverandør	AstraZeneca
Lægemiddel	Lynparza (olaparib)
Ansøgt indikation	Monoterapi eller i kombination med endokrin behandling til adjuverende behandling af voksne patienter med germline BRCA1/2-mutationer, som har HER2-negativ, tidlig højrisiko-brystkræft, og tidligere behandlet med neoadjuverende eller adjuverende kemoterapi
Nyt lægemiddel/ indikationsudvidelse	Indikationsudvidelse (revurdering)

Prisinformation

Amgros har følgende pris på Lynparza:

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Rabat ift. AIP
Lynparza	100 mg (56 stk.)	14.699,67	██████	██████
Lynparza	150 mg (56 stk.)	14.705,89	██████	██████

Aftaleforhold

Amgros har en eksisterende aftale på Lynparza. Aftalen gælder til den 31.03.2027 med mulighed for at forlænge i 2x6 måneder. Der er inkluderet mulighed for prisregulering i aftalen.

Konkurrencesituationen

Lynparza vurderes på to patientpopulationer:

- Patienter med dobbelt-negativ brystkræft hvor Lynparza sammenlignes med Keytruda (pembrolizumab) (80 %) og capecitabin (20 %).
- Patienter med ER+/HER2-negativ brystkræft hvor Lynparza sammenlignes med Verzenios (abemaciclib).

Tabel 2 viser lægemiddeludgifter i relation til andre lægemidler:

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Lynparza	150 mg (56 stk.)	600 mg dagligt, oral		
Keytruda	790 mg (1 stk.)	790 mg hver 6. uge, s.c.*		
Verzenios	150 mg (56 stk.)	300 mg dagligt, oral		

*Max behandlingslængde for adjuverende behandling med Keytruda er 7 måneder (5 serier hver 6. uge), jf. Medicinrådets vurderingsrapport.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering
England	Anbefalet	Link til vurdering

Opsummering

Amgros har en eksisterende aftale på Lynparza, der gælder til den 31.03.2027



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.

Re-application October 9th 2025

Updated February 25th 2026

Updated March 24th 2026

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]



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Abbreviations

AIC	Akaike information criteria	HRQoL	Health related quality of life
ALP	Alkaline phosphatase	HSUV	Health state utility value
ALT	Alanine transaminase	ICER	Incremental cost-effectiveness ratio
AML	Acute myeloid leukaemia	IDFS	Invasive disease-free survival
ANC	Absolute neutrophil count	ITC	Indirect treatment comparison
ASR	Age-standardised rate	ITT	Intent-to-treat
AST	Aspartate transaminase	IV	Intravenous
AUC	Area under the curve	LY	Life year
BCR	Best complete response	mBC	Metastatic breast cancer
BER	Base excision repair	MMRM	Mixed model for repeated measures
BIC	Bayesian information criteria	MRI	Magnetic resonance imaging
BICR	Blinded independent central review	OS	Overall survival
BID	Twice daily	ORR	Objective response rate
BRCA	Breast cancer susceptibility gene	PARPi	Poly (ADP-ribose) polymerase inhibitors
CNS	Central nervous system	PFS	Progression-free survival
CSR	Clinical study report	PH	Proportional hazards
CT	Computed tomography	PRO	Patient reported outcome
CTCAE	Common Terminology Criteria for Adverse Events	QALY	Quality adjusted life year



DCIS	Ductal carcinoma in situ	QoL	Quality of life
DCO	Data cut-off	RCT	Randomised controlled trial
DDFS	Distant disease-free survival	RFS	Recurrence-free survival
DDR	DNA damage response	RWE	Real world evidence
DFS	Disease-free survival	SAE	Serious adverse event
DSU	Decision support unit	SAS	Safety analysis set
EFS	Event-free survival	sBRCAm	Somatic breast cancer susceptibly mutation
EMA	European Medicines Agency	SC	Subcutaneous
EQ-5D-3L	EuroQoL 5-dimensions 3-level	SLR	Systematic literature review
EQ-5D-5L	EuroQoL 5-dimensions 5-level	SMR	Standardised mortality rate
FAS	Full analysis set	SOC	Standard of care
gBRCAm	Germline breast cancer susceptibly mutation	TNBC	Triple negative breast cancer
G-T	Grambsch-Therneau	TP	Transition probabilities
HER2	Human epidermal growth factor receptor 2	TP(X)	Transition number in the excel model
HR	Hormone receptor / Hazard ratio (depends on context)	TSD	Technical support document
HRD	Homologous recombination deficiency	TTD	Time to treatment discontinuation
HRR	Homologous recombinational repair	WTP	Willingness to pay

1. Regulatory information on the medicine

Overview of the medicine

Proprietary name Lynparza

Generic name Olaparib



Overview of the medicine

Therapeutic indication as defined by 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
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sweden
ATC code	L01XK01
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	August 3 rd 2022
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	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: 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



Overview of the medicine

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:

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

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.

In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Other indications that have been evaluated by the DMC (yes/no)

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.

Recommended

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. **KRIS recommendation**

In combination with bevacizumab 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 positive status defined by either a BRCA1/2 mutation and/or genomic instability.

Recommended

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.

Partly recommended

In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. **Partly**



Overview of the medicine

	recommended.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? No this is a reapplication based on an EMA approval from 2022, and reimbursement evaluations are completed in the rest of the Nordics
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	100 mg and 150 mg pack. 56 tablets per pack

2. Summary table

Summary

Indication relevant for the assessment	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
Dosage regimen and administration	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
Choice of comparator	In the OlympiA study placebo is the comparator. Pembrolizumab (TNBC only) and abemaciclib (HR+ only) are the comparators for the ITCs. On request from the DMC capecitabine (TNBC) has been included in the cost-minimisation analysis with a 20 % share (80 % pembrolizumab). Capecitabine is not regulatory approved in the indication and has not been assessed by DMC. Due to this we have not included a detailed description of the product and the CREATE-X study in section 6. Pembrolizumab DMC approval 2023: The DMC recommends pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by pembrolizumab monotherapy as adjuvant treatment after surgery for patients who do not achieve complete tumour shrinkage after surgery (non-pCR). The treatment is for patients with locally advanced or early triple-negative breast cancer (TNBC) who are at high-risk of recurrence.



Summary	
	Abemaciclib DMC approval Sep 2025: The DMC recommends abemaciclib in combination with endocrine therapy as adjuvant treatment of early ER+/HER2-negative breast cancer after surgery. The recommendation applies to patients at high risk of recurrence: • Patients with macrometastases in 2 sentinel nodes (without axillary clearance) • Patients with lymph node-positive disease and tumour ≥ 5 cm or grade 3 • Patients with ≥ 4 positive lymph nodes (pN2-3)
Prognosis with current treatment (comparator)	The prognosis for breast cancer is generally good, with approximately 80% being diagnosed early in their disease with stage I-II, with an expected 3-year survival between 95% and almost 100% [24]. However, TNBC patients, regardless of stage at diagnosis, have a worse prognosis, with a higher risk of recurrence and death compared to other breast cancer patients [25] [2]. 5-year survival for patients with early-stage TNBC who have received neoadjuvant/adjuvant treatment is 82.5%, (DBCG database for the period 2016-2019 (n=1419). For HR+ HER2 negative high risk early breast cancer patients who have received neoadjuvant/adjuvant treatment and diagnosed in 2014–2019 (DBCG database (n= 1587), five-year OS and iDFS were 89.8% and 81.2%, respectively, and hence worse outcomes than lower risk patients. Cumulative DRFS event rates were 14.8%, hence higher than lower risk patients [1].
Type of evidence for the clinical evaluation	H2H vs placebo. ITCs vs pembrolizumab and capecitabine in TNBC and vs. abemaciclib in HR+
Most important efficacy endpoints (Difference/gain compared to comparator)	<u>OlympiA (DCO3):</u> • iDFS (ITT) 6.1 years: Olaparib: 79.6% Placebo: 70.3% HR =0.65 (0.53, 0.78) • iDFS (TNBC) 6.1 years: HR = 0.65 (0.53, 0.81) • iDFS (ER and/or PgR pos) 6.1 years: HR=0.681(0.437, 1.051) • OS (ITT) 6.1 years: olaparib: 87.5% vs. placebo 83.2% HR=0.72 (0.56, 0.93) • OS (TNBC) 6.1 years: HR = 0.71 (0.54, 0.94) • OS (HR+) 6.1 years: HR = 0.814 (0.469 - 1.404) <u>ITC olaparib TNBC (OlympiA) vs. pembrolizumab (Keynote-522)</u> <u>iDFS/EFS:</u> Olaparib (TNBC) vs. pembrolizumab (ITT): • HR = 1.00 (0.73; 1.39)



Summary

Olaparib (TNBC) vs. pembrolizumab (TNBC non-PCR):

- HR = 0.91 (0.63; 1.30)

Olaparib (TNBC) neo-adj vs. pembrolizumab (TNBC non-PCR):

- HR = 0.91 (0.61; 1.35)

OS:

Olaparib (TNBC) vs. pembrolizumab (ITT):

- HR = 1.08 (0.73; 1.61)

Olaparib (TNBC) vs. pembrolizumab (TNBC non-PCR) :

- HR = 0.94 (0.61; 1.43)

Olaparib (TNBC) neo-adj vs. pembrolizumab (TNBC non-PCR):

- HR = 1.22 (0.78; 1.89)

ITC olaparib TNBC (OlympiA) vs. Capecitabine (CREATE-X)

IDFS

- HR = 1.12 (0.71, 1.77)

OS:

HR = 1.37 (0.74, 2.54)

ITC olaparib **TNBC (OlympiA) vs. Capecitabine (CIBOMA, all patients, TNBC)**

IDFS

- HR = 0.80 (0.57, 1.11)

OS:

- HR = 0.78 (0.50, 1.20)

ITC olaparib **HR+ (OlympiA) vs. abemaciclib (MonarchE, ITT):**

IDFS:

- HR = 1.00 (0.63, 1.58)

OS:

- HR = 0.90 (0.51, 1.61)

See Appendix C for further details regarding the comparison of olaparib and pembrolizumab, capecitabine and abemaciclib.

Most important serious adverse events for the intervention and comparator

OlympiA ITT (DCO2 12 July 2021): 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



Summary

SAE, although only reported in 15 patients (1.6%) in the olaparib arm and 1 patient (0.1%) in the placebo arm.

Pembrolizumab KEYNOTE 522 ITT (DCO March 22, 2024):

Serious treatment-related adverse events occurred in 34.1% of the patients in the pembrolizumab–chemotherapy arm and in 20.1% in the placebo–chemotherapy patient-group. Treatment-related adverse events led to death in 4 patients (0.5%) and in 1 patient (0.3%), respectively. **Immune-mediated** adverse events of any grade occurred in 35.0% of the patients in the pembrolizumab–chemotherapy arm vs. 13.1% in the placebo–chemotherapy arm. For Grade 3 or higher events the rate was 13.0% vs 1.5%.

MonarchE:

The most common hematologic AEs graded 3 or higher in the abemaciclib arm were neutropenia (27.5%), anemia (9.5%), and leukopenia (10.7%). Diarrhea was the most frequent non-hematologic AE reported in the abemaciclib arm (83.5% (any grade)); and 9.8% grade ≥ 3 . Diarrhea leading to discontinuation was 1.2%. Interstitial lung disease/pneumonitis: Overall, there were 23 (7.0%) interstitial lung disease events in the abemaciclib arm 5 (1.5%) cases were grade ≥ 3 .

Impact on health-related quality of life

In OlympiA, HRQoL was assessed using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires. No clinical meaningful differences between treatment arms were observed and altogether, the PROs data showed that olaparib does not negatively impact long-term HRQoL in patients with *gBRCAm*, high-risk, HER2-negative, eBC. FACIT-Fatigue: change from baseline at 12 months, olaparib vs. placebo: -1.5 (95% CI: -2.8, -0.2). Health economic model: Equal HSUV was applied for both treatment arms.

Type of economic analysis that is submitted

TNBC: Cost-effectiveness analysis (vs. watch and wait)
TNBC: Cost-minimisation analysis (vs. weighted pembrolizumab [80%] and capecitabine [20%])
HER2-/HR+: Cost-minimisation analysis (vs. abemaciclib)
Semi-Markov model

Data sources used to model the clinical effects

OlympiA, Danish life tables, OlympiAD, IMpassion 130, and KEYNOTE-522, MonarchE, CREATE-X and CIBOMA

Data sources used to model the health-related quality of life

OlympiA, mapping algorithm by Crott & Briggs, Lidgren et al 2007

Life years gained

1.40 years

QALYs gained

1.23 QALY



Summary

Incremental costs	306 147 DKK vs. watch and wait
	-26 715 DKK vs. pembrolizumab/capecitabine
	-2 050 DKK vs. abemaciclib
ICER (DKK/QALY)	248 905 DKK/QALY
Uncertainty associated with the ICER estimate	Based on sensitivity analyses, robust assumptions. Greatest variation in the ICER was experienced with changes in discount rate for benefits, the time horizon, and when applying the Gompertz distribution to the comparator arm TP6. Structural uncertainty due to use of external data, and no direct use of OS data from OlympiA in the model (OS data are only used for validation purposes)
Number of eligible patients in Denmark	Incidence early HER-, gBRCA: 28 patients with TNBC and 43 patients with HR+ breast cancer or total 71.
	Prevalence: Not relevant
Budget impact (in year 5)	TNBC:
	206 610 DKK
	HER2-/HR+: -8 955 337 DKK

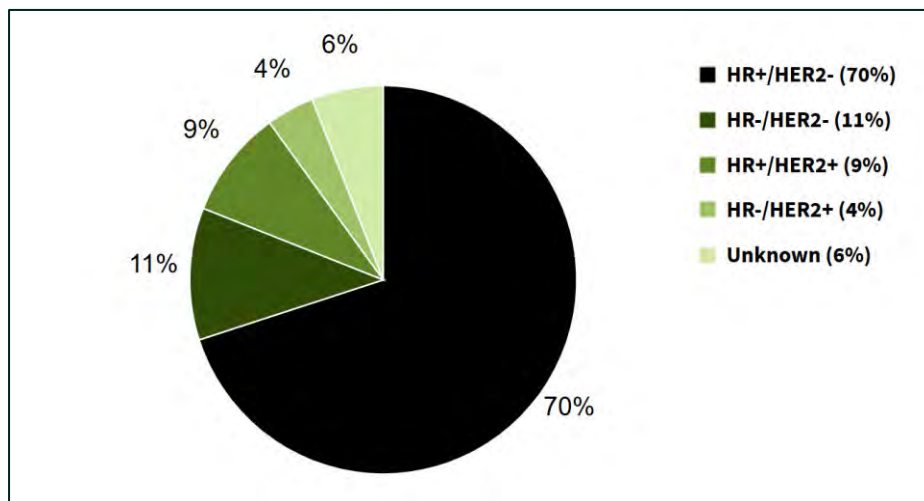
3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

The majority of breast cancers are diagnosed as HR-positive/HER2-negative (HR+/HER2-), with data from the SEER program indicating that 70% and 11% of all female breast cancer patients are diagnosed with HR+/HER2- and triple negative breast cancer (HR-/HER2- or TNBC) disease, respectively (Figure 1)[2].



Figure 1. Proportion of female breast cancer by histological subtype



Source: NCI SEER Program, 2018 -2022 [2]

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)[3-5]. Similarly, studies examining the prevalence of *gBRCAm* in unselected European primary breast cancer patient populations, have reported that 1.7–7.3% of patients have *gBRCAm* disease and 3% have *sBRCAm* disease.[6]

Table 1. Prevalence of germline and somatic *BRCAm* in breast cancer

Data source	Number of samples		All samples			Percentage with germline, or somatic <i>BRCA</i> mutations (n/N)					
	Overall	TNBC	<i>gBRCAm</i>	<i>sBRCAm</i>	<i>tBRCAm</i>	TNBC			Non-TNBC		
						<i>gBRCAm</i>	<i>sBRCAm</i>	<i>tBRCAm</i>	<i>gBRCAm</i>	<i>sBRCAm</i>	<i>tBRCAm</i>
Polak et al 2017 ^a	992 (100%)	145 (14.0%)	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			Mutation frequencies not broken down by TNBC status		
								9.4% (86/911)			8.3% (112/1352)

Footnotes: ^aOnly loss of function mutations are counted. ^bBased on TCGA data. ^cBased on classification of samples analysed at Foundation Medicine (US) with computational algorithm to predict germline/somatic status according to Sun et al 2018[7]. 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, including HR+ HER2- 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) [3, 4]. 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) [6]. A European study found the mean age at diagnosis to be



40.2–46.4 years in patients with *gBRCAm* disease [8], which contrasts to a median age at diagnosis of 65 years for *sBRCAm* patients matched to non BRCA-mutated patients [6]. 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. The study showed that 49% had lymph-node negative disease, 52% had tumors smaller than 20 mm and one third were grade 1-2 [9], altogether representing a lower risk population than OlympiA. 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.

3.2 Patient population

Breast cancer (women only) incidence in 2024 was 5398 (Table 2) according to latest report from Sundhedsstyrelsen.

Table 2. Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	4862	5062	5159	5415	5398
Prevalence in Denmark	73926	75601	77269	79098	80963

Source: Cancerregisteret pr. 2. maj 2025, Sundhedsdatastyrelsen

A Danish study by Rudolf et al. 2021 showed that 48% of patients were in stage I, 37% in stage II, 9% in stage III and 5% in stage IV [10]. In alignment with patient characteristics of the OlympiA study [11], we regard stage I-III as the relevant population for this application, meaning in total 5074 patients based on the 2024 Breast cancer incidence (Figure 2 and Table 3).

According to Danish reports, ~10% (n=508) will have TNBC (in line with the 11% in Figure 1) and ~75% (n=3806) is estimated to be HR+/HER2-; of these, ~15% (n=61) and ~5% (n=116) will have an inherited (germline) *BRCAm*, respectively [6, 12, 13]. Testing rate peak shown in Figure 2 is based on an ambition to reach at least 85% in TNBC and 65% in HR+/HER2- disease which leads to 432 and 2475 patients tested for *gBRCAm*.



Since clinical experts estimate that on average ~80% of TNBC patients receive neo-adjuvant and ~15% adjuvant treatment, this will in numbers mean 52 and 10 patients, respectively. Clinical experts further estimate that on average ~50% of these neo-adjuvant, and ~90% of these adjuvant treated patients will be of high-risk, meaning 26 and 9 TNBC patients, respectively, would be eligible for Olaparib (Figure 2).

Similarly for HR+/HER2–, based on clinical experts' input, on average ~10% of patients will receive neo-adjuvant and ~45% adjuvant treatment, meaning 13 and 56, respectively, and of these, ~90% neo-adjuvant and ~90% adjuvant will be of high-risk, resulting in 12 and 50 HR+/HER2– patients being eligible for Olaparib, respectively (Figure 2).

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

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

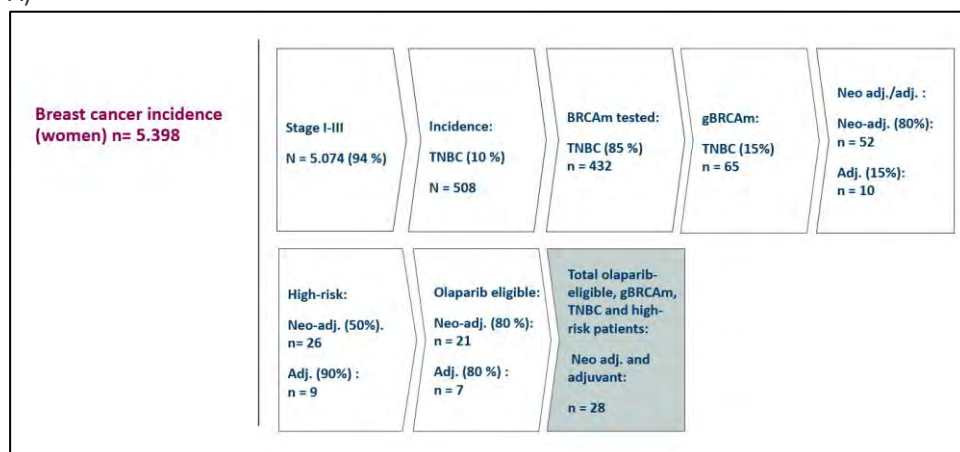
HR+/HER2– patients

- 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 patients may not be eligible for a PARPi, hence it is estimated that 80% of TNBC and 70% HR+/HER2– patients will be suitable for olaparib regardless of whether a patient has received neo- or adjuvant treatment beforehand, meaning 21 and 7 TNBC patients, and 8 neo-adjuvant and 35 adjuvant treated HR+/HER2– patients respectively. In total, 71 high-risk gBRCAm HER2- negative patients are eligible for olaparib treatment (Figure 2).

Figure 2. Estimated incidence of olaparib eligible, high-risk TNBC(A) and HR+/HER2- (B) gBRCAm patients in Denmark

A)





B)

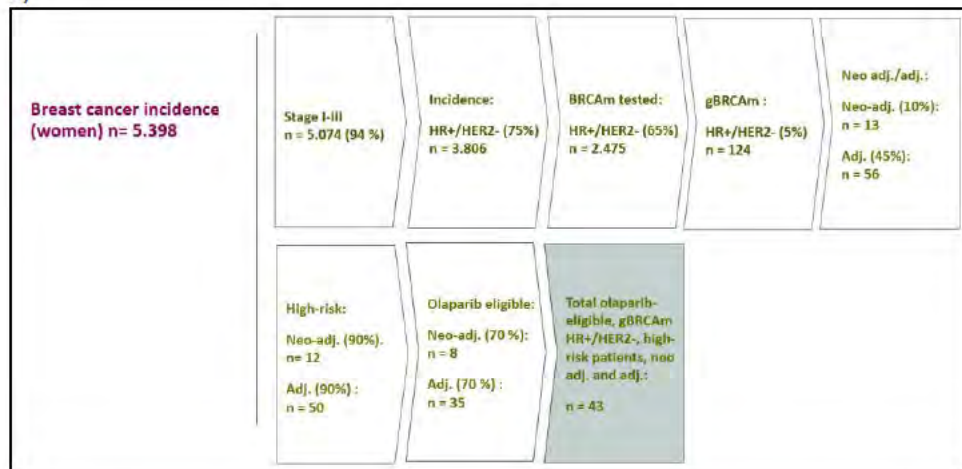


Table 3. Estimated number of HER2- early breast cancer, gBRCAm patients eligible for olaparib treatment

Year	2026	2027	2028	2029	2030
Number of patients in Denmark who are eligible for treatment in the coming years	71	71	70	70	70

3.3 Current treatment options

In early breast cancer treatment is given with the aim for cure, constituted by a combination of local therapy (surgery and radiation therapy) and systemic oncological therapy. Decisions on the appropriate treatment for HER2-negative, early breast cancer are commonly guided by HR status.

TNBC

Neoadjuvant Chemotherapy

Patients with TNBC are often offered neoadjuvant chemotherapy to shrink the breast tumour with the aim to assess treatment response and optimize surgical outcome. Pathological complete response (pCR, yT0/Tis N0), i.e. no residual cancer in the breast or lymph nodes after neoadjuvant therapy, is a predictor of therapy response and good prognosis, and correlates with improved survival. In the case where neoadjuvant therapy does not achieve a pCR, further adjuvant treatment escalation can be explored to reduce the risk of relapse and progression to disseminated disease, which is associated with a poor prognosis (median survival less than 2 years). Neoadjuvant therapy may be offered to TNBC patients: - with tumours > 20 mm and/or N+ disease - with tumour size > 10 mm ≤ 20 mm instead of surgery and adjuvant chemotherapy if preoperative treatment is deemed beneficial for the patient. Treatment consists of a combination of epirubicin and cyclophosphamide (EC) every 2 weeks or every 3 weeks (4 series in total) followed by



carboplatin every 3 weeks in combination with paclitaxel weekly on days 1, 8, and 15 (4 series in total).

Adjuvant therapy

The post-operative/post-neo- adjuvant treatment is organized according to whether the treatment achieves pCR and dependent on the neoadjuvant treatment given. In patients where treatment achieves pCR, patients are treated with radiotherapy if indicated. Adjuvant options for patients where pCR is not achieved (non-pCR) are Capecitabine, Pembrolizumab or a combination of both according to Danish Clinical Guidelines. For patients with gBRCAm, Olaparib is recommended as per guidelines.

Adjuvant Capecitabine

For TNBC patients with non-pCR, adjuvant treatment will consist of capecitabine (6-8 series of 1,000 mg/m², twice daily for 14 days followed by a one-week break) in addition to any radiotherapy. 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. Whereas in the CREATE-X study Capecitabine reduced the risk of recurrence and death in TNBC with non-pCR, in the CIBOMA Phase III trial, capecitabine did not significantly prolong DFS vs observation (HR=0.82; 95% CI 0.63, 1.06; p=0.136), and there was no statistically significant difference in OS between study arm and SOC (adjusted HR according to stratification factors 0.88; 95% CI 0.64, 1.23; p=0.456) [14]. In an exploratory analysis of CIBOMA, patients who received neoadjuvant chemotherapy and did not obtain a pCR, experienced no meaningful DFS benefit of taking capecitabine, compared to the observation patient group (HR=1.12; 95% CI 0.64, 1.97; p=0.68) [15]. 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 [16]. 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) [16].

OlympiA and CREATE-X studies differ from each other on a number of important parameters that do not allow a formal indirect statistical comparison. The CREATE-X study randomised post-operative Asian HER-negative patients with non-pCR. In addition, there is a difference in the neoadjuvant treatment in both studies. Additionally, neither study does evaluate the effect of capecitabine in the gBRCAm subgroup and real-world data indicate that Capecitabine-treated TNBC patients with *BRCAm* tend to have a shorter IDFS, DDFS and OS than those with *BRCAwt* [17]. The DMC has earlier, at the time of the last application, agreed that capecitabine is not relevant as a comparator for this evaluation.

(Neo-)Adjuvant Pembrolizumab

Due to recent evidence provided by KEYNOTE-522 study, Pembrolizumab therapy is an additional option in the early neo-/adjuvant TNBC setting in Denmark. The DMC recommends weight-based administration of pembrolizumab and no further adjuvant pembrolizumab if pCR is achieved (see below), different to the trial. The recommendation is based on data from the phase 3, double-blind, randomized, placebo-



controlled trial, investigating whether the addition of pembrolizumab to neoadjuvant chemotherapy would significantly increase the percentage of pCR in previously untreated stage II or stage III TNBC [18]. Patients were stratified before randomization on the basis of nodal status (positive or negative), tumour size (T1 [diameter, >1.0 cm to 2.0 cm] to T2 [diameter, >2.0 cm to 5.0 cm] or T3 [diameter, >5.0 cm] to T4), and frequency of carboplatin administration (once weekly or once every 3 weeks). Patients were randomly assigned, in a 2:1 ratio, to the experimental arm, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab, or the comparator arm, neoadjuvant placebo plus chemotherapy followed by adjuvant placebo.

In the neoadjuvant phase, patients received four cycles of an intravenous infusion of pembrolizumab (200 mg) or placebo once every 3 weeks plus paclitaxel (80 mg per square meter of body-surface area once weekly) plus carboplatin (at a dose based on an area under the concentration–time curve of 5 mg per milliliter per minute once every 3 weeks or 1.5 mg per milliliter per minute once weekly in the first 12 weeks) (first neoadjuvant treatment), followed by four cycles of pembrolizumab or placebo plus doxorubicin (60 mg per square meter) or epirubicin (90 mg per square meter) plus cyclophosphamide (600 mg per square meter once every 3 weeks in the subsequent 12 weeks) (second neoadjuvant treatment). Patients who either completed or discontinued the first neoadjuvant treatment could start the second neoadjuvant treatment or undergo surgery, and those who completed or discontinued the second neoadjuvant treatment could undergo surgery.

Patients underwent definitive surgery (breast conservation or mastectomy with sentinel lymph-node evaluation or axillary dissection) at 3 to 6 weeks after the last treatment cycle of the neoadjuvant phase. In the adjuvant phase, patients received radiation therapy as indicated and either pembrolizumab or placebo, administered once every 3 weeks for up to nine cycles. Adjuvant therapy with capecitabine was not allowed.

On April 27th 2023 The DMC made a **partial** approval of KEYNOTE 522:

- DMC recommended pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by pembrolizumab monotherapy as adjuvant treatment after surgery for patients who do not achieve complete tumour shrinkage after surgery (**non-pCR**). The treatment is for patients with locally advanced or early triple-negative breast cancer who are at high-risk of recurrence.
- DMC did not recommend pembrolizumab as adjuvant treatment (after surgery) for patients with locally advanced or early triple-negative breast cancer at high-risk of recurrence who achieve complete tumour regression (**pCR**) after neoadjuvant treatment with pembrolizumab in combination with chemotherapy.

HR+

At either part of the treatment journey HR+ HER2- patients should be treated with endocrine therapy. Antiresorptive therapy is indicated for patients ongoing on ovarian suppression. For most HR-positive, HER2-negative, screening-detected breast cancer, surgery is the initial treatment modality, whereas for selected patients, neoadjuvant systemic therapy may be preferred. The post-operative/post-neo- adjuvant treatment is



organized according to whether neoadjuvant treatment has been given and dependent on risk classification.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy can be indicated instead of adjuvant chemotherapy, for patients with larger tumours or clinical nodal involvement and thus high risk of recurrence or death (T0-3, N2, M0). Other indicators are cases where knowledge of prognostic index or genomic factors is absent or where preoperative treatment is considered beneficial for assessing treatment responses and optimizing surgical outcomes. Neoadjuvant chemotherapy consists of eight cycles of anthracyclines and taxanes, which can be given dose dense.

Adjuvant endocrine therapy (in combination with CDK4/6 inhibitors)

Type and length (5-10 yrs) of adjuvant endocrine therapy (primarily aromatase inhibitors or tamoxifen, selectively exemestane), primarily depends on menopausal status, age, prognosis or comorbidity and is selectively combined with GnRH agonists (goserelin) to reach ovarian suppression. PSI score assessments can indicate the need for adjuvant chemotherapy in addition to endocrine therapy [19].

The addition of targeted therapy is recommended for selected patients with genetic mutations in BRCA1/2 or a high risk of recurrence. For high-risk patients with gBRCAm, Olaparib is recommended in the guidelines. Based on the monarchE study [20-22], two years of CDK4/6 inhibitor abemaciclib is recommended in addition to endocrine treatment for high-risk patients after completion of primary treatment with surgery, (neo)adjuvant chemotherapy and radiotherapy by guidelines and DMC [23, 24]. Patients must meet the following high-risk criteria:

- macrometastases in 2 sentinel nodes (axillary lymph node dissection)
- lymph node-positive disease and a tumour ≥ 5 cm or grade 3
- ≥ 4 positive lymph nodes (pN2-3)

In postmenopausal women with 1-3 positive lymph nodes, consideration should be taken when it comes to patient's expected remaining lifetime, and therefore abemaciclib is only recommended for patients with a PSI score = 4. [23, 24]

Adjuvant Chemotherapy

Generally, HR+ HER2- patients with a need for chemotherapy treatment and with T1-2, N0-1, M0 are indicated 6 cycles of adjuvant chemotherapy with taxanes or anthracyclines sequentially given or 6 cycles of docetaxel and cyclophosphamide.

Premenopausal patients with lymph node spread but unknown pN stage are recommended 8 cycles of chemotherapy (ddEC followed by paclitaxel – or vice versa). Postmenopausal patients with 1-2 positive SNs, but unknown pN stage, are treated according to PSI, (unknown pN stage classified as min PSI 2). For patients with PSI 2, PAM50 can be used as a guide for the selection of chemotherapy). For patients with PSI 2 and non-luminal A subtype, 6 series of chemotherapy (DC or EC/pac) are recommended. Patients with PSI 3-4 are recommended 8 series of chemotherapy (ddEC followed by paclitaxel – or vice versa).



3.4 The intervention

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 [25]. Patients with HR-positive/HER2-negative disease should also receive adjuvant endocrine therapy per local policy and/or international guidelines [26, 27].

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. *BRCA* mutation status can be determined by genetic testing, with several commercial tests available. The Myriad *BRCA* analysis testing platform was used in the OlympiA trial to determine *gBRCAm* status via a simple blood test or oral rinse sample [28]. 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. For all details around olaparib (Table 4) see also “Overview of Pharmaceuticals” in the first section of this application.

Table 4. Overview of intervention

Overview of intervention	
Indication relevant for the assessment	EMA indication: Lynparza is indicated as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline <i>BRCA1/2</i> -mutations who have HER2-negative high-risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy
ATMP	No
Method of administration	Tablets
Dosing	2 tablets of 150 mg BID. 100 mg for dose reductions.
Dosing in the health economic model (including relative dose intensity)	2 tablets of 150 mg twice daily, 100% RDI
Should the medicine be administered with other medicines?	Adjuvant endocrine therapy in patients with hormone-receptor-positive disease was given according to local guidelines.
Treatment duration / criteria for end of treatment	Treatment in OlympiA was 12 months or until progression/AEs/death
Necessary monitoring, both during administration and during the treatment period	Blood tests to monitor for haematological toxicity, e.g. anaemia was recommended



Overview of intervention

Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	A valid germline BRCA test is needed
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Package size(s)	56 tablets
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3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

In OlympiA, HER2-negative ((HR (ER and/or PR)-positive or TNBC) patients with presence of a germline mutation in the BRCA1 and/or BRCA2 genes (*gBRCAm*) and with early breast cancer (invasive that is non-metastatic (stages I–III)) were 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 ($\geq$ pN1, any tumour size) or axillary node negative (pN0) with invasive primary tumour pathological size >2 cm ($\geq$ pT2)
 - HR+/HER2– 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+/HER2– 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+)

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+/HER2– disease who were at similarly high-risk of recurrence following neoadjuvant chemotherapy and surgery as compared to those with TNBC [3, 29]. 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 [30, 31], and gene expression profiles or molecular recurrence scores [26]. Furthermore, whilst the use of the CPS&EG score potentially defines a narrower population of HR+/HER2– 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 Olaparib 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 [32, 33]. The results of the OlympiA trial are 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 in OlympiA compared to real life, [29].

BRCA testing:

Testing for BRCA is a well-established pathology procedure in Denmark. According to Danish guidelines, referral for testing occurs when the invasive tumor component is ER-negative and HER2 normal and/or has “basal-like” gene expression. In conclusion, all TNBC breast cancer patients have for many years been refereed to BRCA testing. The guidelines mention the importance because pathogenic variants of the BRCA gene are not only associated with breast cancer but also increased risk of ovarian cancer and serous adenocarcinoma and can inform surgical procedures. [34]

DMCG/DBCG guidelines

Despite not yet being recommended by the DMC, olaparib is mentioned in the Danish guidelines from DMCG/DBCG as follows for **TNBC** patients:



<i>ER-negativ, HER2-normal (samt basal-like og Her2-E/HER2 normal)</i>	
38. Post-præoperativ capecitabin (A) eller pembrolizumab (B) eller en kombination (D) anbefales til patienter med non-ytpCR (yT0/Tis N0(i)-) uanset RCB-klasse - efter præoperativ kemoterapi givet grundet ER-negativ, HER2-normal brystkræft afhængig af evt. komorbiditet	
OBS adjuverende pembrolizumab til patienter med pCR er ikke anbefalet som standardbehandling af Medicinrådet.	
Klinisk Retningslinje Kræft	DBCG
39. Dog anbefales patienter med BRCA-mutation og non-pCR – uanset klasse - olaparib (A) eller pembrolizumab (B) som monoterapi eller i kombination (C)	
OBS adjuverende pembrolizumab er kun anbefalet som monoterapi af Medicinrådet	

The guidelines also mention the combination of olaparib and pembrolizumab, however, this regimen is not EMA or DMC approved and should be considered off-label.

Olaparib, given together with anti-hormone therapy, is also recommended for patients with gBRCAm **HR+ HER2-** disease and high risk of recurrence, who have received:

- adjuvant chemotherapy and radiotherapy, ≥ 4 N+ at the time of diagnosis, or
- NACT and subsequently have non-pCR.[23]

23. Tillæg af målrettet behandling anbefales til udvalgte patienter med ER-positiv, HER2 lav brystkræft eller en medfødt patogen variant i BRCA1 eller BRCA2 og høj risiko for tilbagefald (A)

3.5 Choice of comparator(s)

TNBC

The active comparator for this application is pembrolizumab (Table 5) while placebo is the comparator in the OlympiA trial. No treatment besides of olaparib is currently EMA-approved or recommended by DMC for adjuvant treatment of early high-risk TNBC breast cancer **with BRCA1/2- mutations** and who previously has been treated with neoadjuvant or adjuvant chemotherapy. The treatment effect of capecitabine and pembrolizumab in gBRCAm patients is not well documented. Capecitabine is not indicated in the OlympiA setting and not assessed by DMC but was use as comparator in the DMC validation of pembrolizumab. The DMC recommends pembrolizumab in combination with chemotherapy as neoadjuvant treatment followed by pembrolizumab monotherapy as adjuvant treatment after surgery for patients who do not achieve complete tumour shrinkage after surgery (non-pCR). The treatment is for patients with locally advanced or early TNBC who are at high-risk of recurrence.

The below table has only been filled out for pembrolizumab and not for placebo (comparator arm in OlympiA).



Table 5. Overview of comparator

Overview of comparator	
Generic name	Pembrolizumab + (paclitaxel and carboplatin)
ATC code	L01FF02
Mechanism of action	KEYTRUDA® is a humanised monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with the ligands PD-L1 and PDL2.
Method of administration	I.v
Dosing	The SMPC recommended dose of KEYTRUDA® as part of combination therapy is 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. In Denmark the DMC has recommended (off-label) weight-based dosing
Dosing in the health economic model (including relative dose intensity)	200 mg every 3 weeks, RDI 100%
Should the medicine be administered with other medicines?	The KEYNOTE-522 is pembrolizumab + paclitaxel and carboplatin. After surgery adjuvant pembrolizumab
Treatment duration/ criteria for end of treatment	Pembrolizumab or placebo, administered once every 3 weeks for up to nine cycles. Adjuvant therapy with capecitabine was not allowed. Trial treatment was discontinued for disease progression that precluded definitive surgery, disease recurrence, or unacceptable toxic effects.
Need for diagnostics or other tests (i.e. companion diagnostics)	PD-L1 expression was assessed in formalin-fixed tumor samples at a central laboratory with the use of the PD-L1 IHC 22C3 pharmDx assay (Agilent) . Patients were eligible for the trial regardless of PD-L1 expression status.
Package size(s)	Strength: 100 mg KEYTRUDA® 25 mg/ml concentrate for solution for infusion. One vial of 4 ml concentrate contains 100 mg pembrolizumab.

Additional treatment in the neoadjuvant phase

In the neoadjuvant phase, patients received four cycles of an intravenous infusion of pembrolizumab (200 mg) or placebo once every 3 weeks plus paclitaxel (80 mg per square meter of body-surface area once weekly) plus carboplatin (at a dose based on an area under the concentration–time curve of 5 mg per milliliter per minute once every 3 weeks or 1.5 mg per milliliter per minute once weekly in the first 12 weeks) (first neoadjuvant treatment), followed by four cycles of pembrolizumab or placebo plus doxorubicin (60 mg per square meter) or epirubicin (90 mg per square meter) plus



cyclophosphamide (600 mg per square meter once every 3 weeks in the subsequent 12 weeks) (second neoadjuvant treatment). Patients who either completed or discontinued the first neoadjuvant treatment could start the second neoadjuvant treatment or undergo surgery, and those who completed or discontinued the second neoadjuvant treatment could undergo surgery. Patients underwent definitive surgery (breast conservation or mastectomy with sentinel lymph-node evaluation or axillary dissection) 3 to 6 weeks after the last cycle of the neoadjuvant phase. In the **adjuvant phase**, patients received radiation therapy as indicated and pembrolizumab or placebo once every 3 weeks for up to nine cycles. Study treatment was discontinued in patients with disease progression or recurrence or unacceptable toxic effects.

HR+

The comparator is CDK4/6 inhibitor abemaciclib (MonarchE study), as it is the recommended/1st ranked CDK4/6 inhibitor in the “Behandlingsvejledning” valid from May 1st 2026.

Table 6. Overview of comparator

Overview of comparator	
Generic name	Abemaciclib
ATC code	L01FF02
Mechanism of action	Selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), and most active against Cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein (Rb) phosphorylation, blocking cell cycle progression from the G1 to the S-phase of cell division, leading to suppression of tumour growth. In oestrogen receptor-positive breast cancer cell lines, sustained target inhibition with abemaciclib prevented rebound of Rb phosphorylation resulting in cell senescence and apoptosis.
Method of administration	Oral
Dosing	150 mg twice daily.
Dosing in the health economic model (including relative dose intensity)	150 mg twice daily, 100% RDI
Should the medicine be administered with other medicines?	In combination with adjuvant endocrine therapy (ET)
Treatment duration/ criteria for end of treatment	Abemaciclib should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs.



Overview of comparator

Need for diagnostics or other tests (i.e. companion diagnostics) NA

Package size(s) Verzenios 50 mg 28 tabl.
Verzenios 100 mg 28 and 56 tabl.
Verzenios 150 mg 28 and 56 tabl.

3.6 Cost-effectiveness of the comparator(s)

Pembrolizumab was partly recommended by DMC April 27th 2023 and the cost-effectiveness has been assessed.

Abemaciclib was recommended by DMC September 3rd 2025 and is part of a treatment guideline in early HR+ breast cancer and ranked 1st choice from May 1st 2026.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 7. Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
IDFS [OlympiA]	DCO2: 12 July 2021	Time from randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, new cancer or death from any cause	Investigator-assessed using the STEEP system definition; must be cytologically/histologically confirmed.
Overall survival (OS) [OlympiA]	DCO2:12 July 2021 DCO3: 05 June 2024	Time from randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, new cancer or death from any cause	Investigator-assessed.
DDFS [OlympiA]	DCO2:12 July 2021	Time from randomisation until documented evidence of first distant recurrence of breast cancer	Investigator-assessed, including the following events: distant recurrence, death attributable to any cause, second primary non-breast invasive cancer.



Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Incidence of new primary breast/ovarian cancers [OlympiA]	DCO2: 12 July 2021	Number and percentage of patients with documented evidence of contralateral invasive breast cancer, contralateral non-invasive breast cancer and new primary ovarian, fallopian tube and peritoneal cancers	Date of new cancer incidence.
HRQoL [OlympiA]	DCO2: 12 July 2021	Effect of olaparib HRQoL and PROs compared with placebo. Change from baseline for EORTC QLQ-C30 Global health status QOL 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.	FACIT-Fatigue symptoms and EORTC QLQ-C30. Measured: 6, 12, 18 and 24 months after randomisation EORTC QLQ-C30 scores range from 0 to 100 with higher score indicating better quality of life. FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue.
Pathological complete response (pCR) rate [Keynote-522]	DCO March 23, 2023. 5 years median follow-up	pCR rate (ypT0/Tis ypN0) is defined as the percentage of participants without residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy.	Using the definition of ypT0/Tis ypN0. Up to approximately 27-30 weeks
EFS [Keynote-522]	DCO March 23, 2023	Time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence, second primary malignancy (breast or other cancers) or death due to any cause.	Up to around 8 years



Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
OS [Keynote-522]	DCO March 22, 2024. 7 th prespecified interim analysis	OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of the analysis will be censored at the date of the last follow-up.	Time from randomization to death. Up to 8 years
Percentage of participants who experience an adverse event (AE) [Keynote-522]	DCO April 24, 2019. 2 nd interim analysis and March 23, 2023	An AE is defined as any untoward medical occurrence in a participant administered study treatment which does not necessarily have to have a causal relationship with this treatment.	Monitored throughout the trial and for 30 days after discontinuation of treatment (90 days for serious adverse events) and graded according to the Common Terminology Criteria for Adverse Events, version 4.0, of the National Cancer Institute. Up to 61 weeks
IDFS, defined by STEEP criteria. Primary endpoint. [MonarchE]	54 months	Measured from the date of randomization to the date of first occurrence of any of the following: • Ipsilateral invasive breast • tumor recurrence • Regional invasive breast • cancer recurrence • Distant recurrence • Death attributable to any cause • Contralateral invasive breast cancer and second primary non-breast invasive cancer	All randomly assigned patients were followed for local/regional and distant recurrence and OS. At each visit, patients were assessed by medically qualified individual for AEs and any signs or symptoms of recurrence. At clinic visits, central chemistry and hematology laboratories were drawn, performance status was assessed, and physical examinations were conducted. Test to confirm recurrence after discretion of treating medically qualified individuals.
DRFS [MonarchE]	54 months	Measured from the date of randomization to the first occurrence of distant recurrence or death due to any cause. Patients for whom no distant recurrence event observed were censored at the day of their last disease recurrence	



Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		assessment or date of randomization	
OS [MonarchE]	54 months	Time from the date of randomization to the date of death from any cause	

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

In neoadjuvant/adjuvant studies it can be difficult to assess the overall survival (OS) effect of the intervention as these studies will require a significantly longer follow-up time, as patients have a longer life expectancy compared to studies assessing treatment for metastatic disease. It can be difficult to assess the effect of the intervention as OS is also affected by subsequent lines of treatment lines and cross-over. The primary endpoint of the trial is invasive disease-free survival (iDFS) defined as time from randomisation to date of first loco-regional or distant recurrence or new cancer or death from any cause. Based on the above, iDFS defined as time from randomisation to date of first loco-regional or distant recurrence or new cancer or death from any cause is the most relevant and clinically relevant endpoint and without being influenced by any subsequent lines of therapy.

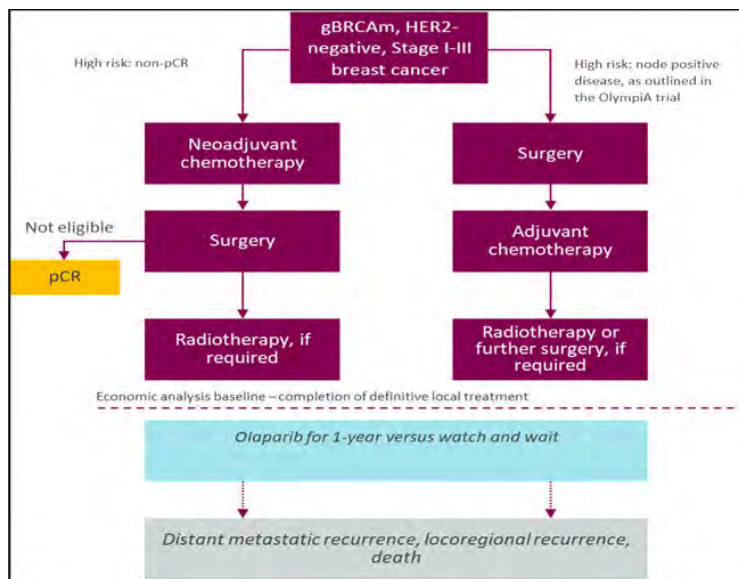
4. Health economic analysis

A cost-effectiveness model has been developed to estimate the costs and health outcomes of adjuvant olaparib versus standard of care in patients with *gBRCAm*, high-risk HER2-negative early breast cancer (eBC) in Denmark.

In the base case analysis in the TNBC population, the cost-effectiveness 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 a completed definitive local treatment including neoadjuvant or adjuvant chemotherapy. The cost-effectiveness model is also used for the cost-minimisation analysis of olaparib versus a weighted comparator of pembrolizumab (neoadjuvant and adjuvant treatment) and capecitabine (adjuvant) in the TNBC population. In the HER2-/HR+ population, olaparib is compared with abemaciclib in a cost-minimisation analysis using the same model structure as for the TNBC population. The treatment pathway captured in the cost-effectiveness model is shown in Figure 3.



Figure 3. Treatment pathway in the cost-effectiveness model



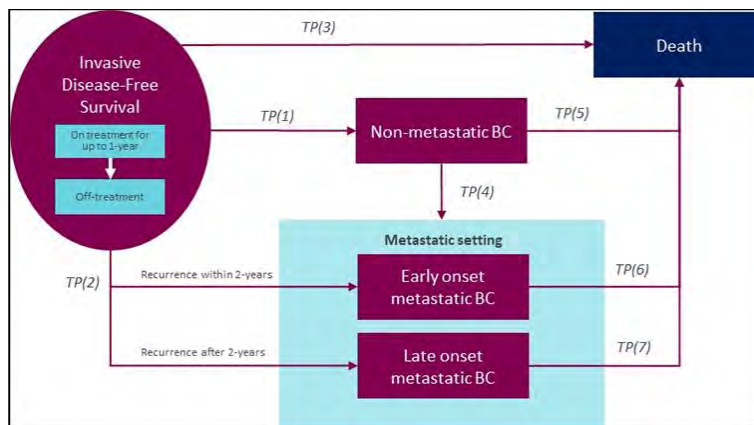
In the TNBC population, the risk of recurrence is higher during the first 5 years after diagnosis, with a significant decrease and plateauing of the recurrence rate thereafter [35-38]. Sopik et al presents the annual rate of disease recurrence following diagnosis of invasive breast cancer in 2 312 patients treated at Women’s College hospital, Toronto, Canada. In this study, all distant recurrences for TNBC occurred in the first six years following diagnosis. For HR+ disease, the distant recurrences occurred at an approximately constant rate throughout the 20-year follow-up. The difference in recurrence pattern was 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 [39].

4.1 Model structure

A five-state semi-Markov model was developed in Microsoft Excel®. The five health states in the model are ‘IDFS’, ‘non-mBC’, ‘early onset mBC’, ‘late onset mBC’ and ‘Death’. A schematic of the model state structure is presented in Figure 4.



Figure 4. Schematic of model diagram



Footnote: 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-mBC:** 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 mBC:** 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 mBC. As mBC is considered incurable, all patients that enter this state are assumed to receive palliative surgery, radiotherapy and/or drug therapy.
- **Late onset mBC:** 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 mBC, 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.

A classification of non-metastatic and metastatic recurrence closely follows the endpoint definitions of IDFS (primary) and DDFS (secondary) in OlympiA [29]. These endpoints were based on the standardized definitions for disease- and distant-free survival as



outlined in the STEEP criteria [3, 40]. 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 4 above. The modelled treatment pathway is further described in Appendix M and further details on the estimation of transition probabilities are provided in Section 8 and Appendix D.

4.2 Model features

The main features of the economic model are described in Table 8.

Table 8. Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with germline BRCA1/2-mutations who have high-risk HER2-negative early breast cancer (eBC) previously treated with neoadjuvant or adjuvant chemotherapy	In line with Section 3.2
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (57 years)	To capture all relevant differences in health outcomes and costs between the treatments included, in line with DMC guidelines Based on the time from the baseline average age of 43 years to 100 years old
Cycle length	1 month (30.4 days)	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
Half-cycle correction	Yes	The life table approach is used to estimate half-cycle corrected state occupancy over time. Implemented for all outcomes and costs, except for one-off costs (e.g., subsequent treatment and terminal costs) or outcome adjustments (e.g., adverse



Model features	Description	Justification
		events), and the cost of olaparib
Discount rate	3.5%	3.5% for all years, in line with DMC guidelines
Intervention	Olaparib	Intervention in scope for the application
Comparator(s)	TNBC: Watch and wait (cost-effectiveness analysis) Pembrolizumab (80%) and capecitabine (20%) (cost-minimisation analysis) HER2-/HR+: Abemaciclib (cost-minimisation analysis)	According to national treatment guidelines
Outcomes	IDFS OS for validation TTD for treatment duration	Due to immature OS data in OlympiA, IDFS from the trial was used in combination with external data

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment approach in the application is partly based on the head-to-head study, and partly on a pragmatic indirect treatment comparison to pembrolizumab.

This is supported by a literature search described in Appendix H. In Table 9, the literature used in the clinical assessment is listed.



Table 9. Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	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 [29] 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. [41] https://www.annalsof-oncology.org/article/S0923-7534(22)04165-5/fulltext	OlympiA	NCT02032823	June 2014 through May 2019 DCO1: 17 March 2020. DCO2: 12 July 2021 DCO3: 5 June 2024	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
Schmid P et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med 2020 Feb. [18]	KEYNOTE-522	NCT03036488	Start: March 7th 2017 End: Sep 30th 2025 DCO's:	Comparator to olaparib as standard neoadjuvant and adjuvant therapy for early TNBC in Denmark.



Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Schmid P et al. Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022 Feb [18] Schmid, P. et al. Pembrolizumab or placebo plus chemotherapy followed by pembrolizumab or placebo for early-stage TNBC: Updated EFS results from the phase III KEYNOTE-522 study Annals of Oncology, Volume 34, S1257 Schmid P. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. N Engl J Med. 2024 Nov 28;391(21):1981-1991.[42]			November 15, 2018: First interim for pCR rates (ESMO 2019) May 27, 2020: Update for EFS and safety (SABCS 2020) March 22, 2022: Extended follow-up, EFS and OS (ASCO 2022) March 22, 2024: Final results for overall survival and updated EFS (Schmid et al. 2024)	
Johnston, Stephen R D et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE):	MonarchE	NCT03155997	Start: 12/07/2017 Completion: 16/03/2020 Data cut-off 03/07/2023	OlympiA early HR+ BRCam subpopulation vs abemaciclib combined with endocrine therapy



Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. The Lancet Oncology, Volume 24, Issue 1, 77 - 90				
Priya Rastogi et al., Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative, High-Risk Early Breast Cancer: Results From a Preplanned MonarchE Overall Survival Interim Analysis, Including 5- Year Efficacy Outcomes. JCO. 2024 Jan			5 years OS	

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

The OlympiA clinical trial and published literature were used to derive the health-related quality of life estimates applied in the health economic model. The EORTC QLQ-C30 data collected in the OlympiA clinical trial was used to derive the HSUV for the IDFS health state (the HSUV for non-mBC was assumed the same as for IDFS). As data were only routinely collected every 6 months up to recurrence or for a maximum of 2 years in OlympiA, the HSUVs for metastatic breast cancer and disutilities related to AEs were sourced from external data sources (see Section 10.2). A systematic literature review (SLR) was completed to identify the relevant HSUVs and is further described in Appendix I. Table 10 summaries the sources for the HSUV and disutilities applied in the health economic analysis.



Table 10. Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Data on file, OlympiA clinical study report [3]	Health state utility (IDFS, Non-mBC)	Section 10.2.3
Lidgren M, Wilking N, Jönsson B, Rhenberg C. Health related quality of life in different states of breast cancer. Qual Life Res. 2007;16(6):1073-81. [43]	Health state utility (early onset mBC, late onset mBC)	Section 10.3.4
NICE, Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer, TA563 2019.[44] From: https://www.nice.org.uk/guidance/ta563	Disutility (anaemia)	Section 10.3.4
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84. [45]	Disutility (neutropenia, leukopenia)	Section 10.3.4

5.3 Literature used for inputs for the health economic model

All clinical input used to inform the health economic model except utility decrements for adverse events has been sourced from the OlympiA trial. No systematic literature search was performed as the comparators are placebo (covered by the OlympiA trial) and pembrolizumab. For the comparison to pembrolizumab, the approach is based on the ITC, which suggest similar efficacy and hence a cost-minimisation approach is used based on clinical efficacy data from OlympiA combined with dosing information from KEYNOTE-522.



Table 11. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. Tutt et al. N Engl J Med 2021; 384:2394-2405 [29]	TPP, IDFS, TDT, Adverse events	Clinical trial of interest for comparison	Sections 8, 9, and 10



6. Efficacy

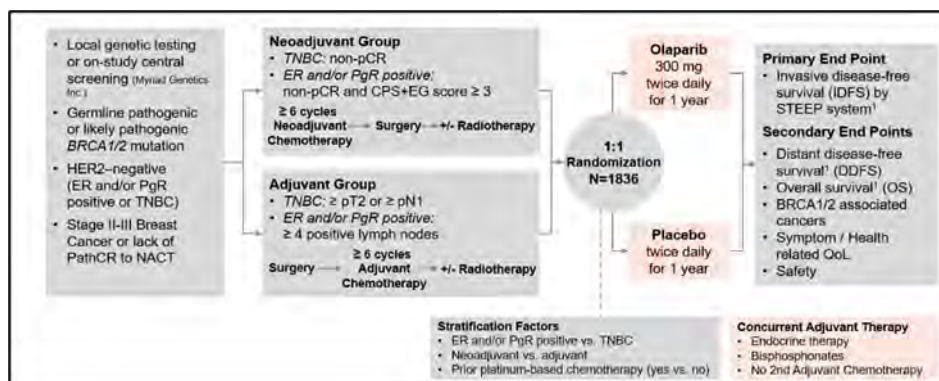
6.1 Efficacy of olaparib vs. placebo for adjuvant treatment of patients with *gBRCA1/2*-mutations who have high-risk early TNBC previously treated with neoadjuvant or adjuvant chemotherapy

6.1.1 Relevant studies

OlympiA is a phase III, double-blind, parallel group, placebo controlled, multicentre randomized controlled trial. The OlympiA trial is coordinated by the Breast International Group (BIG) in partnership with NRG Oncology, the US National Cancer Institute (NCI), the Frontier Science & Technology Research Foundation (FSTRF), AstraZeneca and MSD. BIG is an international not-for-profit organisation for academic breast cancer research groups from around the world, based in Brussels, Belgium. OlympiA 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 5, Table 12). A total of 1836 patients were randomized 1:1 to either study arm based on inclusion/exclusion criteria as described in Figure 5. 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 5). Secondary endpoints included:

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

Figure 5. OlympiA study



Source: [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 12). 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 12. 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 [3, 11]

Baseline characteristics

Baseline characteristics for OlympiA and subgroups are included in Appendix A.



Table 13. Overview of study design for studies included in the comparison

NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
OlympiA	Phase III, double-blind, parallel group, placebo-controlled, multicentre RCT	Study Start Date: April 22, 2014 Primary Completion Date: March 27, 2020 Estimated Study Completion Date: May 28, 2029	Patients with gBRCAm, HER2-negative, early breast cancer who have received surgical treatment and prior neoadjuvant or adjuvant chemotherapy. stratified by HR status, receipt of prior neoadjuvant or adjuvant chemotherapy and prior platinum therapy. ECOG 0-1.	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	Placebo	Primary endpoint: IDFS. Secondary endpoints include DDFS, OS and safety. The median duration of follow-up was 3.5 years for ITT and 3.6 years in the TNBC group in the second data cut-off. Median follow-up for OS was 6.1 years in DCO3.
KEYNOTE-522	Double-blinded randomized placebo-controlled phase 3 study. Enrolled patients were randomly assigned 2:1. No cross-over was allowed between the phases. Patients were stratified before randomization according to nodal status (positive or negative), tumour size (T1 to T2 or T3 to T4), and schedule of carboplatin administration (once weekly or every 3 weeks).	Actual Study Start Date: March 7, 2017 Estimated Primary Completion Date: September 30, 2025 Estimated Study Completion Date: September 30, 2025	Has newly diagnosed, locally advanced, centrally confirmed TNBC. Has previously untreated locally advanced non-metastatic (M0) TNBC: • T1c, N1-N2 • T2, N0-N2 • T3, N0-N2 • T4a-d, N0-N2	Neoadjuvant: pembrolizumab + chemo (N=784) vs placebo + chemo (N=390) Adjuvant: pembrolizumab plus radiotherapy (N=784) vs placebo plus radiotherapy (N=390)	Neoadjuvant: placebo + chemo Adjuvant: placebo + radiotherapy	Primary endpoint: pathological complete response, EFS. Secondary endpoints include OS and safety. At the data-cutoff March 22, 2024, the median follow-up was 75.1 months (range, 65.9 to 84.0).



6.1.2 Comparability of studies

It is important to note that the randomisation points in KEYNOTE-522 and OlympiA differ significantly:

- KEYNOTE-522 randomised patients with previously untreated stage II or III TNBC to receive neoadjuvant therapy with pembrolizumab plus chemotherapy, or placebo plus chemotherapy; following surgery, patients received adjuvant pembrolizumab or placebo.
- Thus, all patients in KEYNOTE-522 received neoadjuvant therapy, whereas only 39.4% of patients in OlympiA had TNBC and received neoadjuvant therapy (i.e. the subgroup most comparable to KEYNOTE-522).

Table 14. Summary of feasibility, olaparib vs pembrolizumab (TNBC patients)

	Olaparib (OlympiA) vs pembrolizumab (KEYNOTE-522) in TNBC
Study design	✗ Different treatment settings (neoadjuvant/adjuvant vs adjuvant)
Population	✓ International (Asian and non-Asian)
	✓ TNBC
	✓ KEYNOTE-522 included 'mixed' risk patients, although EFS and OS data are available for 'high-risk' subgroup of patients who did not report a pCR and considered comparable with patients who received neoadjuvant chemotherapy in OlympiA ✗ gBRCAm status unknown in KEYNOTE-522
Treatment regimens	✗ KEYNOTE-522 (intervention arm) included pembrolizumab in the neoadjuvant phase
Outcomes	✗ IDFS, EFS and OS not comparable due to different randomisation point
	✗ OS data not available for non-pCR cohort of KEYNOTE-522
ITC feasibility	Not recommended due to significant differences in setting/randomisation point, populations and outcomes

Source: AstraZeneca Data on File (Feasibility Assessment).[46]

The feasibility assessment demonstrates that KEYNOTE-522 does not provide comparator data considered sufficiently appropriate to permit an ITC of olaparib vs pembrolizumab in a population that is fully aligned with OlympiA, due to the following reasons:

- BRCA status of patients in KEYNOTE-522 is unknown
- In KEYNOTE-522, baseline data are not available for the high-risk subgroup for which EFS and OS data were reported, and patients were not stratified according to risk. As such, it may not be feasible to use the total population baseline data as a proxy for



the high-risk subgroup, and there may be imbalances in baseline characteristics across the two treatment arms, which may introduce bias in the estimated treatment effect

- IDFS, EFS and OS data are not comparable across OlympiA and KEYNOTE-522 due to differences in the point of randomisation.

Furthermore, anchored MAIC analyses are not considered to be a feasible approach to indirect comparison of olaparib with pembrolizumab using IPD from OlympiA and comparator data from KEYNOTE-522; this is for the following reasons:

- No baseline data are reported for the high-risk subpopulation of KEYNOTE-522.
- MAICs would require data from the TNBC subgroup of OlympiA that received neoadjuvant chemotherapy, which comprised a relatively small sample of the total study population (39.4%) and would lead to high levels of uncertainty in ITC estimates.
- By matching the OlympiA population to KEYNOTE-522, any subsequent estimates generated would be relevant to the comparator trial and would not be aligned with the total OlympiA population.
- gBRCAm status is a key prognostic factor that cannot be adjusted for, as all patients in OlympiA are gBRCAm.

6.1.2.1 Comparability of patients across studies

Table 15. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	OlympiA (TNBC)		KEYNOTE 522	
	Olaparib (751)	Placebo (758)	Pembro + Ctx (784 comp.)	Placebo + Ctx (390)
Age (median)	42	43	49 (22-80)	48 (24-79)
Menopausal status% Pre/Post			55.9/44.0	56.7/43.3
Prior platinum therapy Yes/No%	29/71	28.5/71.5	NA	NA
BRCA mutated%	99.5	99.1	NA	NA
Race, n (%)				
White			504 (64.3)	242 (62.1)
Asian			149 (19.0)	89 (22.8)
Black or African American			38 (4.8)	15 (3.8)
Native Hawaiian or other Pacific Islander			1 (0.1)	0
American Indian or Alaska Native			14 (1.8)	7 (1.8)



	OlympiA (TNBC)		KEYNOTE 522	
	Olaparib (751)	Placebo (758)	Pembro + Ctx (784) comp.]	Placebo + Ctx (390)
Other/Multiple			13 (1.7)	6 (1.5)
Missing			65 (8.3)	31 (7.9)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The patient population in the CE model is based on the TNBC subgroup of the OlympiA study. In general, the OlympiA study population is considered representative of patients that will be eligible for adjuvant olaparib in Danish clinical practice.

Key characteristics of the relevant patient population, applied in the health economic model and considered representative of the Danish clinical practice are presented in Table 16.

Table 16. Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (assumed the same as the TNBC population in OlympiA)	Value used in health economic model (TNBC population in OlympiA)
Age (mean)	43.3	43.3
Female (%)	99.9	99.9
Patient weight (mean)	68.7	68.7
Patient height (mean)	167	167
Body surface area	1.77	1.77

6.1.4 Efficacy – results per study OlympiA

At a median follow-up of 6.1 years (DCO3) in eligible patients, who had completed local treatment and standard neoadjuvant or adjuvant chemotherapy, results showed that olaparib demonstrated sustained and clinically meaningful improvements in the primary and secondary endpoints of IDFS and DDFS. Olaparib reduced the risk of invasive breast cancer recurrence, second cancers or death by 35% (HR=0.65; 95% CI 0.53-0.78) and reduced the risk of distant disease recurrence or death by 35% (HR=0.65; 95% CI; 0.53-0.81) versus placebo (Table 17). The benefit with Olaparib was consistent across all key subgroups, including patients with high-risk, hormone-receptor-positive disease. OS results showed that olaparib reduced the risk of death by 28% (HR=0.72; 95% CI 0.56-0.93) versus placebo. In addition, 87.5% of patients treated with olaparib remained alive versus 83.2% of those on placebo.



Table 17. Summary of OlympiA efficacy endpoints, DCO3 (FAS)

	Olaparib (N=921)	Placebo (N=915)
IDFS		
Number of events, n (%)	178 (19.3)	258 (28.2)
Estimate of hazard ratio	0.65 (0.648)	
95% CI for hazard ratio	(0.53, 0.78)	
Log-rank test: p-value		
Median clinical follow-up time, years (minimum–maximum)	5.9 m	6.1 m
Type of IDFS event, n (%)		
Distant recurrence	106 (11.5)	149 (16.3)
Distant CNS recurrence	26 (2.8)	40 (4.4)
Distant excluding CNS recurrence	80 (8.7)	109 (11.9)
Regional (ipsilateral) recurrence	11 (1.2)	22 (2.4)
Local (ipsilateral) recurrence	11 (1.2)	12 (1.3)
Contralateral invasive breast cancer	26 (2.8)	36 (4.0)
Second primary non-breast malignancies	20 (2.2)	37 (4.0)
Deaths without a prior IDFS event	4 (0.4)	2 (0.2)
OS		
Number of events, n (%)	107 (11.6)	143 (15.6)
Estimate of hazard ratio	0.72	
95% CI for hazard ratio	(0.56, 0.93)	
Median clinical follow-up time, years (minimum–maximum)	6.2 m	6.1 m
DDFS		
Number of events, n (%)	142 (11.6)	207 (18.8)
Estimate of hazard ratio	0.65 (0.653)	
95% CI for hazard ratio	(0.53, 0.81)	
Log-rank test: p-value		
Median clinical follow-up time, years (minimum–maximum)	5.9 m	6.1 m

Footnotes: DCO3: Source: San Antonio 2024 [47]



Table 18. Analysis set

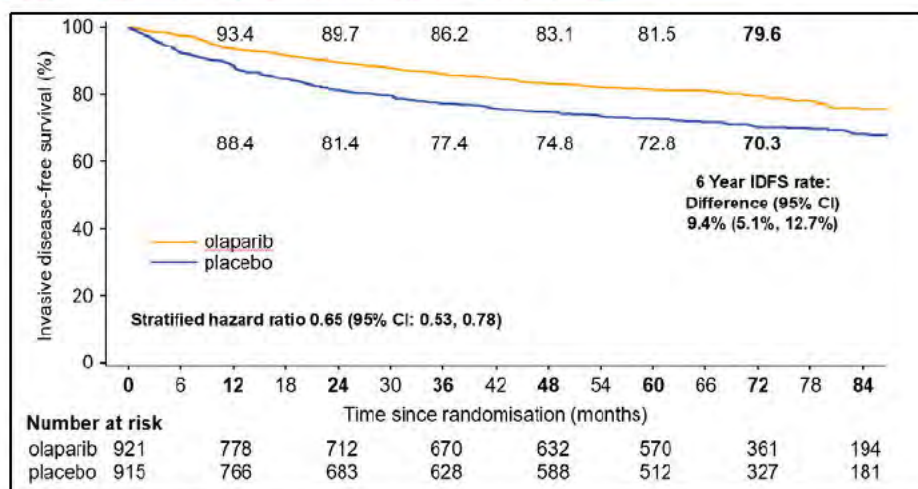
Analysis Set	Description	Number	Outcomes Analysed
Full analysis set (FAS)^a	ITT, all randomised patients	1,836 patients in total (921 olaparib, 915 placebo)	Efficacy
	Mature cohort ITT, the first 900 randomised patients only	900 patients in total (449 olaparib, 451 placebo)	Efficacy
Safety analysis set (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: ^aAnalysis based on treatment arm randomised to, rather than treatment received.

6.1.4.1 IDFS (DCO3)

At the third interim analysis (DCO3), consistent with DCO2, a statistically and clinically meaningful investigator-assessed IDFS benefit was observed in patients treated with olaparib compared with those treated with placebo (Figure 6).

Figure 6. Kaplan-Meier plot of IDFS in OlympiA, DCO3 (FAS)



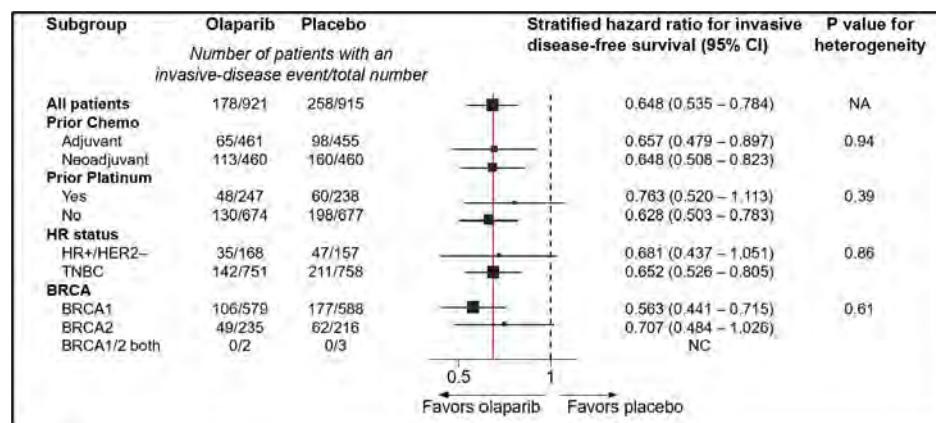
Source: DCO3: San Antonio 2024 [47]



Subgroup analysis of IDFS (DCO3)

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 (Figure 7). 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.

Figure 7. Subgroup analysis of IDFS (DCO3)



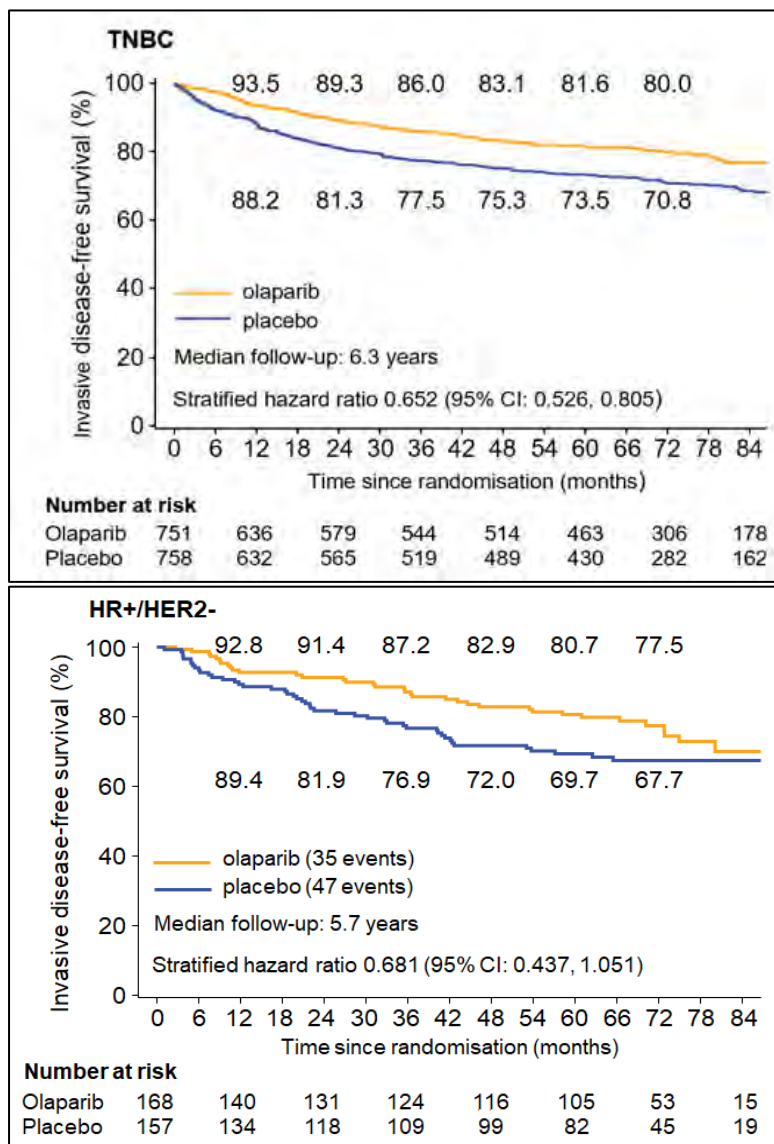
Source: DCO3: San Antonio 2024 [47]

IDFS in TNBC (DCO3)

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 IDFS, DDFS and OS in the ITT population. Subgroup analysis of the TNBC population has identical outcome as ITT, and the outcome in the HR+/HER2- subgroup is similar. See below for KM plot (Figure 8).



Figure 8. IDFS in the TNBC (top) and HR+/HER2- (bottom) subgroups



Source: DCO3: San Antonio 2024 [47]

6.1.4.2 OS (DCO3)

At DCO3, the OS data were 10.0% mature (184 events/1,836 patients). These data suggest that, in patients with *gBRCAm*, high-risk, HER2-negative, early breast cancer, olaparib treatment provides a statistically significant improvement in OS, compared with placebo (Figure 9):

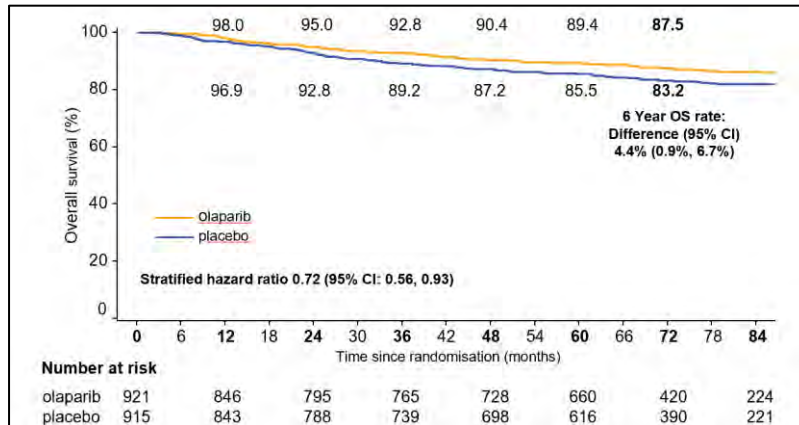
- The HR for OS favoured olaparib (HR= 0.72; 95 CI 0.56, 0.93), indicating a 28% reduction in risk of death for patients treated with olaparib vs placebo.
- Median follow-up for OS was 6.1 years

The efficacy demonstrated in the IDFS outcome measure was supported by secondary



endpoints.

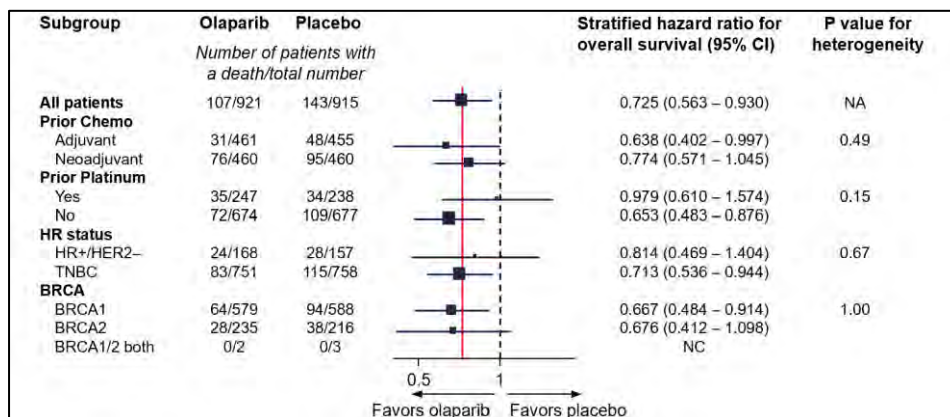
Figure 9. Kaplan-Meier plot of OS in OlympiA, DCO3 (FAS)



Source: DCO3 San Antonio 2024 [47]

OS in Subgroups

Figure 10. Subgroup analysis of OS



Source: DCO3 San Antonio 2024 [47]

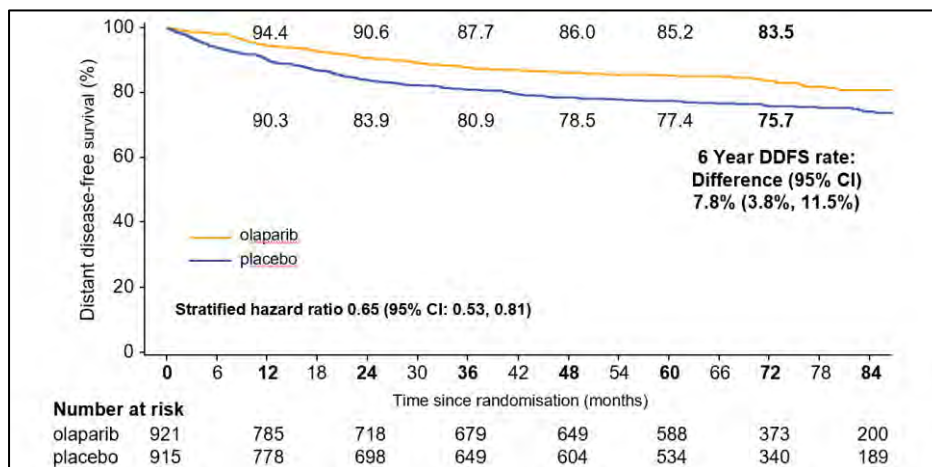
The gBRCAm TNBC subgroup showed a 29% reduction in risk of death for patients treated with olaparib vs. placebo and is in line with ITT results (Figure 10, Figure 11). The HR+/HER2- subgroup showed a 19% reduction in risk of death for patients treated with olaparib vs. placebo, but the difference compared with the TNBC subgroup is not significant (P value: 0.67).



Statistically and clinically meaningful benefit of olaparib vs. placebo was demonstrated in the DDFS endpoint at DCO3. The results of the DDFS analyses were consistent with analyses at DCO2, and the FAS analyses of IDFS [38]. The HR for DDFS favoured olaparib (HR: 0.65; 95% CI: 0.53, 0.81), showing a statistically significant 35% reduction in risk of distant recurrence for patients treated with olaparib versus placebo (Figure 12).



Figure 12. KM of DDFS (ITT)

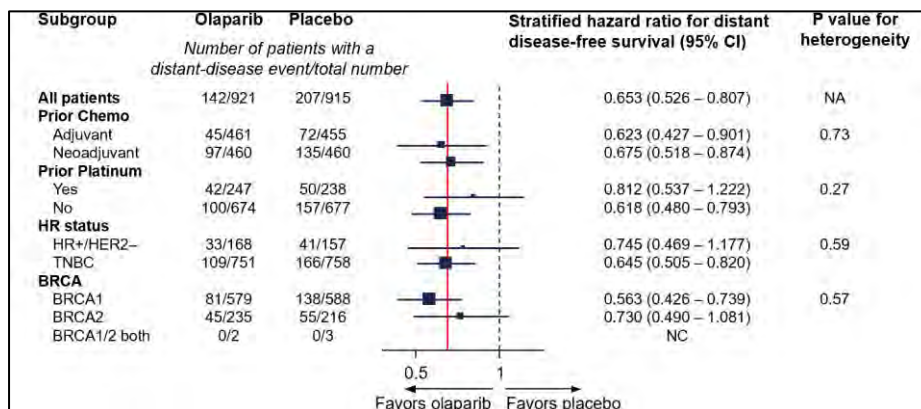


Footnotes: DCO3: Source: San Antonio 2024 [47]

DDFS in Subgroups

Below are the results from the individual subgroups.

Figure 13. Subgroup analysis of DDFS



Footnotes: DCO3: Source: San Antonio 2024 [47]

6.1.5 Incidence of new primary breast or ovarian cancer (DCO3)

At DCO3, 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 compared with the placebo arm (Table 20).

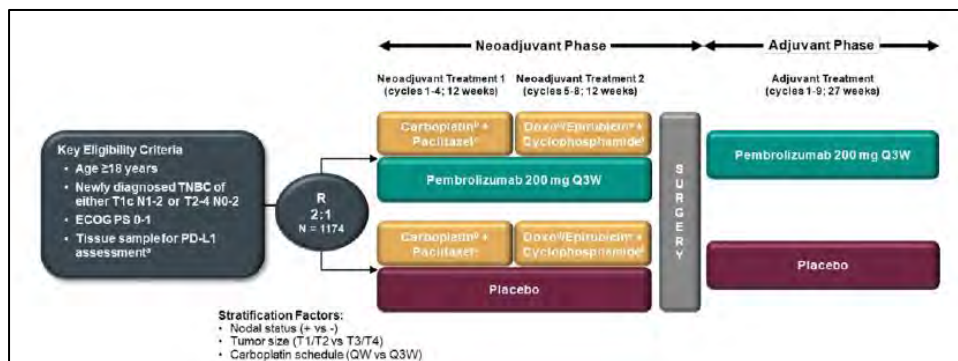


6.2 Efficacy of pembrolizumab in early TNBC. KeyNote-522

6.2.1 Relevant studies KeyNote-522

KEYNOTE-522 is a phase 3, double-blind, randomized, placebo-controlled trial. Patients were stratified before randomization based on nodal status (positive or negative), tumour size (T1 [diameter, >1.0 cm to 2.0 cm] to T2 [diameter, >2.0 cm to 5.0 cm] or T3 [diameter, >5.0 cm] to T4 [locally advanced disease]), and frequency of carboplatin administration (once weekly or once every 3 weeks). Patients were randomly assigned, in a 2:1 ratio, to neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab (pembrolizumab–chemotherapy group) or neoadjuvant placebo plus chemotherapy followed by adjuvant placebo (placebo–chemotherapy group).

Figure 14. Keynote-522 study design



Footnotes: Neoadjuvant phase starts from first neoadjuvant treatment and ends after definitive surgery incl. post treatment. Adjuvant phase starts from first adjuvant treatment and is incl. radiation therapy and post treatment. **Source:** Adapted from Peters et al. 2020

6.2.1.1 Event-Free Survival (EFS)

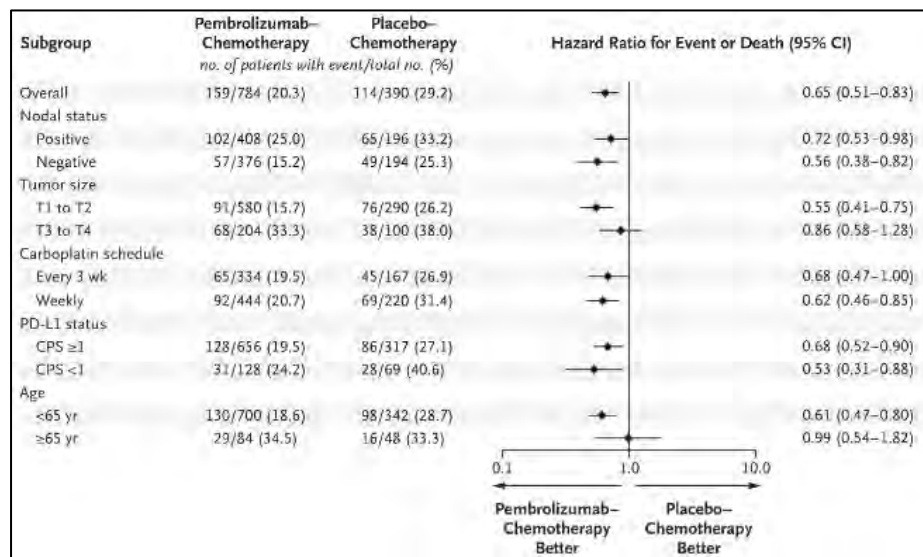
The data-cut-off date was March 22, 2024 and the median follow-up was 75.1 months (range, 65.9 to 84.0). A total of 159 patients (20.3%) in the pembrolizumab–chemotherapy arm vs. 114 patients (29.2%) in the placebo–chemotherapy group had an event or died (HR = 0.65; 95% CI, 0.51 to 0.83). The estimated 5-year EFS was 81.2% (78.3 to 83.8) in the pembrolizumab–chemotherapy group and 72.2% (67.4 to 76.4) in the placebo–chemotherapy arm. The most common first event in both arms was distant recurrence, with 77 events (9.8%) for the pembrolizumab–chemotherapy patients vs. 56 events (14.4%) in the placebo–chemotherapy patient group.

Subgroup analysis of EFS

The effect was consistent across defined subgroup (Figure 15).



Figure 15. Subgroup plot EFS



6.2.1.2 Secondary Endpoints OS

At the DCO March 22, 2024, median follow-up (range) was 75.1 months (65.9–84.0), 115 patients (14.7%) in the pembrolizumab group and 85 pts (21.8%) in the placebo arm had died; the HR was 0.66 (95% CI, 0.50–0.87; $P=0.0015$). The 60 months OS rate (95% CI) was 86.6% (84.0–88.8) vs. 81.7% (77.5–85.2), respectively. The benefit of pembrolizumab on OS was generally consistent across prespecified subgroups, including those defined by PD-L1 expression and nodal status [42].

6.3 Olaparib compared to abemaciclib for early HER2- HR+ breast cancer

6.3.1 Relevant studies

For details about OlympiA study (ITT) see section 6.1.1



Table 22. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Study design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
OlympiA	Phase III, double-blind, parallel group, placebo-controlled, multicentre RCT	Study Start Date: April 22, 2014 Primary Completion Date: March 27, 2020 Estimated Study Completion Date: May 28, 2029	Patients with gBRCAm, HER2-negative, early breast cancer who have received surgical treatment and prior neoadjuvant or adjuvant chemotherapy. stratified by HR status, receipt of prior neoadjuvant or adjuvant chemotherapy and prior platinum therapy. ECOG 0-1.	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	Placebo	Primary endpoint: IDFS. Secondary endpoints include DDFS, OS and safety. The median duration of follow-up was 3.5 years for ITT and 3.6 years in the TNBC group in the second data cut-off. Median follow-up for OS was 6.1 years in DCO3.
MonarchE, NCT03155997	Multicentre, open-label, randomised, Phase III trial	Open-label study with abemaciclib plus standard	Patients with HR+/HER2-, node-	Abemaciclib plus standard adjuvant endocrine	Standard adjuvant endocrine therapy of	Primary outcome measures:



Study name, NCT number (reference)	Study design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
		adjuvant endocrine therapy for up to 2 years. After the end of the study treatment period, in both treatment arms patients continued to receive adjuvant endocrine therapy for a cumulative duration of at least 5 years and up to 10 years.	positive, high-risk eBC.	therapy, 150mg, twice daily, with at least 6-hour separating dose, for up to 2 years or until discontinuation criteria are met.	physician's choice, taken as prescribed	Invasive Disease-Free Survival (IDFS) (baseline to recurrence or death from any cause (up to 32 months)) Secondary outcome measures • IDFS for Participants with Ki-67 Index $\geq 20\%$ (Baseline to recurrence or death from any Cause (approximately 10 years)) • Distant Relapse-Free Survival (DRFS) (baseline to distant recurrence or death from any cause (up to 32 months)) • OS (Baseline to Death from Any Cause (approximately 10 Years)) • Pharmacokinetics: Minimum Steady State Concentration ($C_{min,ss}$) of abemaciclib (day 1 (2 hours post-dose), days 30, 60, 90 post-dose) • Change from baseline on the Functional Assessment of Cancer Therapy Breast - (FACT-B) (Baseline, Follow Up (approximately 3 Years)) • Change From Baseline on the Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES) (Baseline, follow up (approximately 3 years)) • Change from baseline on the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) (Baseline, Follow Up (approximately 3 years)) • Change from baseline on the EuroQol Five-Dimension Five-Level Questionnaire (EQ-5D-5L) (Baseline, Follow Up (Approximately 3 Years))



6.3.2 Comparability of studies

Table 23. Summary of feasibility, olaparib vs abemaciclib (HR-positive/HER2-negative patients)

	Olaparib (OlympiA) vs abemaciclib (monarchE) in HR-positive/HER2-negative breast cancer
Study design	✓ Same treatment setting (adjuvant) and similar comparators
Population	✓ International (Asian and non-Asian)
	✓ HR-positive/HER2-negative
	✓ High-risk definitions not equivalent but similar
	✗ gBRCAm status unknown in monarchE ✗ Ki-67 score unknown in OlympiA
Treatment regimens	✓ Endocrine therapy in majority (OlympiA) or all (monarchE) patients
Outcomes	✓ IDFS in both studies
	✓ OS in both studies
ITC feasibility	Feasible but subject to limitations due to unknown gBRCAm status in monarchE and Ki-67 score in OlympiA

Whilst the feasibility assessment demonstrates that monarchE is sufficiently similar to OlympiA, in terms of population, randomisation point and outcomes, monarchE is not considered to provide robust data to permit an ITC of olaparib vs abemaciclib for the following reasons:

- BRCA status of patients in monarchE is unknown; this is particularly relevant, as results from a real-world study suggest that treatment outcomes with CDK4/6 inhibitors may be worse in patients with gBRCAm metastatic breast cancer compared with patients with wildtype and unknown gBRCA status, suggesting potential differences in tumour biology
- The proportion of patients with a high Ki-67 score is unknown in OlympiA
- The piecewise hazard ratio estimates within each year in monarchE decrease over time, suggesting an improvement in the relative treatment effect of abemaciclib over time; this indicates that the proportional hazards assumption is not appropriate and therefore that the total hazard ratio estimate may not be considered robust.



Furthermore, anchored MAIC analyses are not considered to be a feasible approach to indirect comparison of olaparib with abemaciclib using IPD from OlympiA and comparator data from monarchE for the following reasons:

- By matching the OlympiA Population to monarchE, any subsequent estimated generated would be relevant to the comparator trial, and would not be aligned with the OlympiA population
- gBRCAm status is a potential effect modifier for CDK4/6 inhibitors that cannot be adjusted for, as all patients in OlympiA are gBRCA-mutated and the gBRCAm status of patients in monarchE is unknown

6.3.2.1 Comparability of patients across studies

Table 24. Baseline characteristics of patients in included studies for the comparative analysis of efficacy and safety. HR+.

	OlympiA (HR+)		MonarchE (ITT/HR+) [22]	
	Olaparib (168)	Placebo (157)	Abemaciclib +ET (2808)	ET (2829)
Age (median)	42.0	42.0	51 (44-60)	51 (44-50)
Sex (%) Female/Male	99.4/0.6	97.5/2.5	99.3/0.7	99.5/0.5
Menopausal status % Pre/Post			43.5/56.5	43.5/56.5
Prior platinum therapy Yes/No%	16.7/83.3	14.6/85.4	NA	NA
BRCA mutated %	99.4	99.4	NA	NA
Race, n (%)				
White			69.3	69.9
Asian			24.0	23.6
Black/African American			2.0	1.9
Native Hawaiian/Pacific Islander			0.1	0.1
American Indian/Alaska Native			2.3	2.1
Other/Multiple			0.8	0.9
Missing			NA	NA

6.3.3 Comparability of study population(s) with Danish patients eligible for treatment

The patient population in the cost-minimisation analysis of olaparib versus abemaciclib in HR+ patients, is based on the HR+ subgroup of the OlympiA study. In general, the



OlympiA study population is considered representative of patients that will be eligible for adjuvant olaparib in Danish clinical practice.

Key characteristics of the relevant patient population, applied in the health economic model and considered representative of the Danish clinical practice are presented in Table 25.

Table 25. Characteristics of the relevant Danish population and input parameters in the health economic model. HR+

	Value in Danish population (assumed the same as the HR+ population in OlympiA)	Value used in health economic model (HR+ population in OlympiA)
Age (mean)	43.2	43.2
Female (%)	99.9	99.9
Patient weight (mean)	68.7	68.7
Patient height (mean)	167	167
Body surface area	1.77	1.77

6.3.4 Analysis method

6.3.5 Effect – results OlympiA HR+

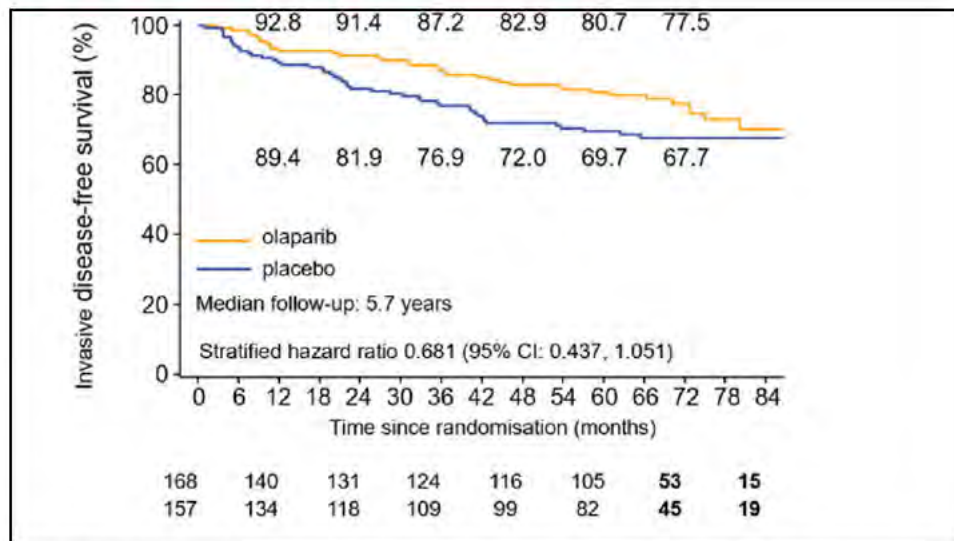
6.3.5.1 IDFS (DCO3)

Data for the HER2-negative HR+ subgroup from the DCO3.

At DCO3 (05 June 2024), with longer follow-up and increased maturity of events, the subgroup analyses were generally consistent with the analysis in the overall FAS population, with insufficient statistical evidence to indicate a differential treatment effect in the pre-defined subgroups.



Figure 16. IDFS in HER2-negative HR+ subgroup (DCO3)



Source: San Antonio 2024

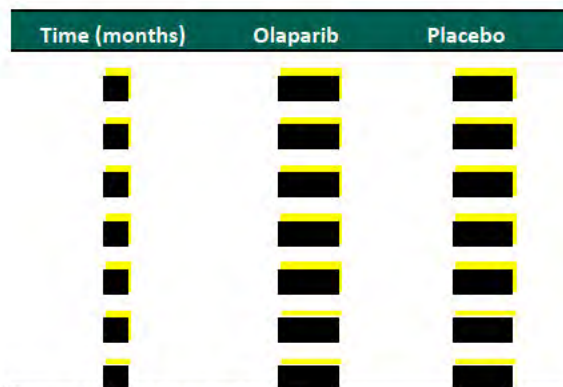
6.3.5.2 OS HR+ (DCO3)

At the time of DCO3 (05 June 2024), the OS data were 13.6% mature. In the HR+ subgroup 24 out of 168 in the olaparib arm and 28 out of 157 patients had died (Figure 17).



Source: AstraZeneca CSR DCO3 [48]

Time (months)	Olaparib	Placebo
0		
6		
12		
18		
24		
30		
36		
42		
48		
54		
60		
66		
72		
78		
84		



Source: OlympiA DCO3 data-on-file

6.3.6 Effect – results MonarchE

The MonarchE study investigated the efficacy and safety of abemaciclib in combination with ET. Results reported in the following section relates to Cohort 1, as this cohort matches the EMA indication and Danish clinical practice. Given that Cohort 1 started enrolment 1 year earlier than Cohort 2 and included 91% of the ITT population, the evolution of follow-up time observed in the ITT population at each analysis time point is entirely driven by patients enrolled in Cohort 1. The relevant efficacy outcomes presented are based on the latest data cut (July 2023), with a median follow-up time of 54 months. In cohort 1, IDFS, DRFS, and OS were consistent with the ITT population.

6.3.6.1 IDFS

A total of 935 patients experienced IDFS events, including 382 (14.9%) in the abemaciclib + ET arm and 533 (21.5%) in the ET alone arm. With the additional follow-up, abemaciclib plus ET reduced the risk of developing invasive disease by 33.0% (stratified HRa=0.670, (0.588, 0.764), $p < 0.001$) vs. ET alone. 5-year IDFS rate was 83.2% vs 75.3%.

6.3.6.2 DRFS

A total number of 802 DRFS events were observed, including 325 in the abemaciclib + ET arm and 477 in the ET alone arm. The DRFS (stratified HRa=0.665 (0.577, 0.765), reflecting a 33 % reduction in the risk of developing distant relapse, and a 7.1% difference. 5-year DRFS rates were 85.6% vs. 78.5%.

6.3.6.3 OS

A total number of 420 deaths (8.2%) were observed, including 197 (7.7%) in the abemaciclib + ET arm and 223 (8.7%) in the ET alone arm. The HRa estimate for OS was 0.894 (0.737, 1.084) $p=0.254$. OS data was immature at this point in time.



7. Comparative analyses of efficacy

In the absence of head-to-head evidence comparing olaparib with pembrolizumab/capecitabine and abemaciclib, indirect treatment comparisons (ITC) were performed to estimate the relative treatment effect of the treatments (see Appendix C).

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The primary data source for the cost-effectiveness model is the OlympiA clinical trial [3, 29]. The statistical analysis of OlympiA was conducted on patient-level data from the third interim OS analysis of the OlympiA trial (DCO3, 05 June 2024).

In addition to the OlympiA trial data, the model uses data from external studies in BRCaM HER2-negative mBC to inform the modelling of survival from the 'late onset mBC' state. These include data from the OlympiAD (olaparib versus single chemotherapy) trial [49, 50] and the IMpassion 130 trial of atezolizumab in metastatic TNBC [51]. These external data sets are used as data to assess survival after 'late onset' mBC in OlympiA are not yet mature enough (median follow-up for IDFS was approximately 6 years at DCO3).

To support the clinical plausibility of model extrapolations, the model further utilises 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 [52]. 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 for placebo). The background mortality risk is further adjusted for the excess mortality associated with germline BRCA mutations [53]. Further detail is provided in Appendix D.1. With the Semi-Markov state transition approach, the overall survival status of the cohort is modelled based on the transitions between states [54]. 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 mBC 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. Table 27 presents the clinical data from the OlympiA trial and the external data used in the model to estimate the risk of recurrences and mortality over time.



Table 27. Summary of clinical events and transitions in the model

Clinical event	Transition	Difference between arms (olaparib vs placebo)	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, IMpassion 130 – time from distant metastases to death

In addition, in the cost-minimization analysis of olaparib versus pembrolizumab, the Kaplan-Meier curve of time to treatment discontinuation from KEYNOTE-522 was used to estimate the cost of pembrolizumab in the neoadjuvant therapy phase [55].

8.1.1 Extrapolation of efficacy data

The state transition probabilities were estimated following NICE Decision Support Unit (DSU) guidance Technical Support Document (TSD) 19 [54], and Putter et al.[56] this involved fitting series of parametric survival models (exponential, lognormal, Weibull, log-logistic, Generalized 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 [57] 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 D. Furthermore, Appendix D also presents the observed time-to-event data for olaparib and placebo based on DCO3 of OlympiA and all investigated extrapolation functions over the full-time horizon.

8.1.1.1 Extrapolation of IDFS (TP1 and TP2)

Table 28. Summary of assumptions associated with extrapolation of IDFS (TP1 and TP2), TNBC

Method/approach	Description/assumption
Data input	OlympiA (TNBC subpopulation)
Model	Exponential, Weibull, Lognormal, Log-logistic, Generalised Gamma, Gompertz and Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Olaparib: Lognormal Watch and wait: Lognormal
Function with best BIC fit	Olaparib: Lognormal Watch and wait: Lognormal
Function with best visual fit	Olaparib: all models had a reasonable fit to observed data. Watch and wait: all models (except exponential) had a reasonable fit to observed data
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib: Gompertz Watch and wait: Gompertz
Validation of selected extrapolated curves (external evidence)	Olaparib: Not available Watch and wait: 5 years: 77.02%; 10 years: 71.% [57]
Function with the best fit according to external evidence	Olaparib: N/A Watch and wait: Lognormal, log-logistic and Generalised Gamma (at 10 years)
Selected parametric function in base case analysis	Olaparib: Gompertz Watch and wait: Gompertz
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A



Method/approach	Description/assumption
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of IDFS (TP1 and TP2)

Table 29. Summary of assumptions associated with extrapolation of IDFS (TP1 and TP2), HR+

Method/approach	Description/assumption
Data input	OlympiA (HER2-/HR+ subpopulation)
Model	Exponential, Weibull, Lognormal, Log-logistic, Generalised Gamma, Gompertz and Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Olaparib: Lognormal Watch and wait: Lognormal
Function with best BIC fit	Olaparib: Lognormal Watch and wait: Lognormal
Function with best visual fit	Olaparib: all models had a reasonable fit to observed data. Watch and wait: all models (except exponential) had a reasonable fit to observed data
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib: Gompertz Watch and wait: Gompertz
Validation of selected extrapolated curves (external evidence)	Olaparib: Not available Watch and wait: 5 years: 78%; 10 years: 64%
Function with the best fit according to external evidence	Olaparib: N/A Watch and wait: Lognormal, log-logistic and Generalised Gamma (at 10 years)
Selected parametric function in base case analysis	Olaparib: Lognormal Watch and wait: Lognormal (not directly applied in the analysis)
Adjustment of background mortality with data from Statistics Denmark	N/A



Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.3 Extrapolation of non-metastatic disease to metastatic breast cancer (TP4)

Table 30. Summary of assumptions associated with extrapolation of non-mBC to mBC (TP4)

Method/approach	Description/assumption
Data input	OlympiA (pooled across treatment arms, ITT population)
Model	Exponential, Weibull, Lognormal, Log-logistic, Generalised Gamma, Gompertz and Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Exponential
Function with best BIC fit	Exponential
Function with best visual fit	All models had a similar fit to the observed data
Function with best fit according to evaluation of smoothed hazard assumptions	Gamma
Validation of selected extrapolated curves (external evidence)	Not available
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Log-logistic
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A



Method/approach	Description/assumption
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.4 Extrapolation of non-metastatic disease to death (TP5)

Table 31. Extrapolation of non-metastatic disease to death (TP5)

Method/approach	Description/assumption
Data input	OlympiA (pooled data across treatment arms, ITT population)
Model	Exponential, Weibull, Lognormal, Log-logistic, Generalised Gamma, Gompertz and Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Generalised Gamma
Function with best BIC fit	Exponential
Function with best visual fit	All models had a similar fit to the observed data
Function with best fit according to evaluation of smoothed hazard assumptions	Lognormal
Validation of selected extrapolated curves (external evidence)	Not available
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Exponential
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A



8.1.1.5 Extrapolation of early onset mBC to death (TP6)

Table 32. Extrapolation of early onset mBC to death (TP6)

Method/approach	Description/assumption
Data input	OlympiA (ITT population)
Model	Exponential, Weibull, Lognormal, Log-logistic, Generalised Gamma, Gompertz and Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Olaparib: Gompertz Watch and wait: Log-logistic
Function with best BIC fit	Olaparib: Gompertz Watch and wait: Log-logistic
Function with best visual fit	Olaparib: Gompertz Watch and wait: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib: Gompertz Watch and wait: Gompertz
Validation of selected extrapolated curves (external evidence)	Post-distant recurrence survival in patient with 'early onset mBC' of ~0% at 10 years [58]
Function with the best fit according to external evidence	Olaparib: Exponential Watch and wait: Exponential
Selected parametric function in base case analysis	Olaparib: Exponential Watch and wait: Exponential
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A



8.1.1.6 Extrapolation of late onset mBC to death (TP7)

Table 33. Extrapolation of late onset mBC to death (TP7)

Method/approach	Description/assumption
Data input	OlympiAD (external data to OlympiA) AZ RWE study (Collins et al 2021)
Model	Exponential, Weibull, Lognormal, Log-logistic, Generalised Gamma, Gompertz and Gamma
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	OlympiAD: Olaparib: Lognormal Chemotherapy: Lognormal Flatiron: CDK4/6 inhibitor: Log-logistic
Function with best BIC fit	OlympiAD: Olaparib: Lognormal Chemotherapy: Lognormal Flatiron: CDK4/6 inhibitor: Log-logistic
Function with best visual fit	OlympiAD: Olaparib: Lognormal Chemotherapy: Lognormal Flatiron: CDK4/6 inhibitor: Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib: Not available Watch and wait: Not available
Validation of selected extrapolated curves (external evidence)	12% at 5 years based on the SEER database [59]
Function with the best fit according to external evidence	Olaparib: N/A Watch and wait: N/A



Method/approach	Description/assumption
Selected parametric function in base case analysis	OlympiAD: Olaparib: Lognormal Chemotherapy: Lognormal Flatiron: CDK4/6 inhibitor: Log-logistic
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.2 Calculation of transition probabilities

Table 34 presents the data sources used for each transition in the model while further details regarding the data sources and the methodology used for each model transition are presented in Appendix D.

Table 34. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
IDFS	Non-mBC (TP1) mBC (TP2)	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 population (see Appendix D.1 for further details) The Lognormal distribution was used for both treatment arms for the HER2-/HR+ population (see Appendix D.1 for further details) 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	OlympiA, DCO3

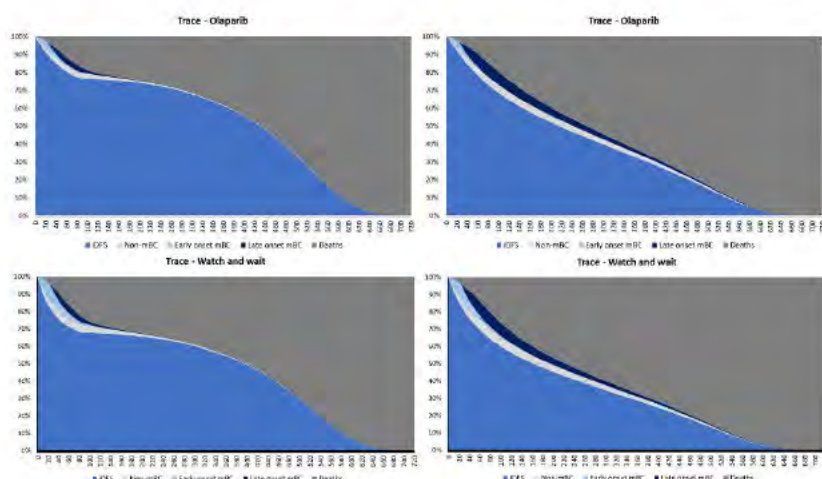


	Death (TP3)	The risk of death without recurrence is modelled using all-cause mortality data from Statistics Denmark life tables The background mortality risk is matched on the age-, gender and BRCA status of the model population	Danish general population mortality adjusted for excess mortality risk in BRCA patients using data from Mai et al [53]
Non-mBC	mBC (TP4)	Time from non-metastatic disease recurrence to metastatic disease recurrence. Patients that died prior to metastatic diagnosis were censored at their event time The log-logistic distribution was used for long-term extrapolation	OlympiA, DCO3
	Death (TP5)	Time from non-metastatic disease recurrence to death. Patients that had metastatic recurrence were censored at their event time. The exponential distribution was used for long-term extrapolation	OlympiA, DCO3
Early onset mBC	Death (TP6)	Time from early metastatic disease recurrence to death. The exponential distribution was used for both arms for long-term extrapolation	OlympiA, DCO3
Late onset mBC	Death (TP7)	Time from first-line treatment to death in patients with mBC [external data]	Final OS analysis of OlympiAD [50] A real-world study if CDK4/6 inhibitor treatment in gBRCAm mBC using the Flatiron health data base [60]. BRCAm subgroup of IMpassion 130 clinical trial [51]



Figure 18 presents the health state occupancy over time for olaparib (top) and watch and wait (bottom) derived from the cost-effectiveness model.

Figure 18. Health state occupancy in the cost-effectiveness model for olaparib (top) and watch and wait (bottom) in the TNBC population (left) and HR+ population (right)



The clinical relevance of efficacy endpoints in the OlympiA trial is summarised in Table 35. The efficacy estimations and parameterisation are covered in more detail in Section 8 and Appendix D.

Table 35. 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 study (IDFS)	IDFS curves from the OlympiA study	Relevant endpoint for patients in Denmark	Definition of IDFS relevant for Danish clinical practice
Secondary endpoint (OS)	OS from OlympiA	Relevant endpoint for patients in Denmark	Used for validation purposes

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.



8.3 Modelling effects of subsequent treatments

See section 4.

8.4 Other assumptions regarding efficacy in the model

As described in Section 7 and Appendix C, the ITC estimates indicate no difference in IDFS/EFS and OS between olaparib and pembrolizumab. Therefore, a cost-minimisation analysis is conducted for this analysis and the efficacy data for olaparib in the model are also applied to the pembrolizumab arm.

8.5 Overview of modelled average treatment length and time in model health state

Table 36 presents the modelled average and median IDFS for olaparib and watch and wait in the cost-effectiveness analysis for TNBC patients. In OlympiA, the median IDFS was not reached at DCO3. In the cost-minimisation analyses of TNBC and HER2-/HR+ patients, IDFS of the comparator arms are assumed to be equal to olaparib. Table 37 presents the average treatment length for each treatment included in the model, and the average time spent in each health state by treatment arm in both the TNBC and HER2-/HR+ populations.

Table 36. Estimates in the model - IDFS

	Modelled average IDFS (reference in Excel)	Modelled median IDFS (reference in Excel)	Observed median from relevant study
Olaparib	361.55 months (Markov!M8)	432.00 months (12*Efficacy!F43)	Not reached
Watch and wait	321.41months (Markov!M9)	395.00 months (12*Efficacy!F47)	Not reached

Table 37. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length (months)	IDFS (months)	Non-mBC (months)	Early onset mBC (months)	Late onset mBC (months)
TNBC					
Olaparib	9.28	361.55	6.09	1.64	3.07
Watch and wait	0.00	321.41	8.57	4.55	3.65



Pembrolizumab	3.22	361.55	6.09	1.64	3.07
Capecitabine	4.92				
HER2-/HR+					
Olaparib	9.50	253.85	15.50	1.49	17.69
Abemaciclib	18.70	253.85	15.50	1.49	17.69

9. Safety

See Appendix N.

10. Documentation of health-related quality of life (HRQoL)

The OlympiA trial did not include EQ-5D. Hence, the health-related quality of life was estimated through a mapping algorithm identified from the literature. The study included EORTC QLQ-C30 and FACIT-Fatigue as patient reported outcome measures.

Table 38. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	OlympiA trial	Health utilities through mapping algorithm
FACIT-Fatigue	OlympiA trial	Only used for descriptive purposes

The HRQoL instruments are described in section 10.1 and in section 10.2. The health state utility for the metastatic state was obtained from the literature and this is further described in Appendix I and Section 10.3.

10.1 Presentation of the health-related quality of life instruments

10.1.1 Study design and measuring instrument

HRQoL was evaluated using the validated EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 questionnaire was developed to assess HRQoL and is the most commonly used



cancer-specific tool in oncology. It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation and has been used in breast cancer trials.

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F Scale) is a 13-item questionnaire that assesses patient self-reported fatigue and its impact upon daily activities and function [61]. Response options for each item range from 0 (Not at all) to 4 (Very much), where higher scores indicate greater patient-reported fatigue. The FACIT-F scale was originally developed to evaluate fatigue associated with anaemia in cancer patients and has been used as an endpoint in clinical trials in various cancer populations including breast cancer and non-small cell lung cancer. Content validity of the FACIT-F has been demonstrated in a large sample of mixed cancer patients (n>300). Reliability (internal consistency, test-retest reliability, criterion validity, and responsiveness/sensitivity to change) of the FACT-F has also been documented [61].

10.1.2 Data collection

The overall compliance rate in the Olaparib arm was 87.9% and 87.8% in the placebo group for FACIT-Fatigue. Compliance rate was defined as number of patients with an evaluable baseline form (at least one subscale score can be determined) and at least one evaluable follow-up form divided by the number of patients expected to have completed at least a baseline form (Table 39). Compliance rates for EORTC QLQ-C30 were similar, ranging from 100% and 99.9% for olaparib and placebo at baseline to 66.8% and 69.3% at 24 months.

Table 39. Pattern of missing data and completion for FACIT-Fatigue

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	Olaparib (876)	5 (0.6)	876	871 (99.4)
	Placebo (875)	3 (0.3)	875	872 (99.7)
6 months	Olaparib (876)	126 (14.3)	829	703 (84.8)
	Placebo (875)	68 (7.8)	805	737 (91.6)
12 months	Olaparib (876)	128 (14.6)	784	656 (83.7)
	Placebo (875)	84 (9.6)	762	675 (85.6)



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
18 months	Olaparib (876)	199 (22.7)	763	564 (73.9)
	Placebo (875)	172 (19.7)	724	549 (75.8)
24 months	Olaparib (876)	214 (24.4)	737	523 (71.0)
	Placebo (875)	194 (22.2)	690	485 (70.3)

10.1.3 HRQoL results

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.

- 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.

Together, the PRO data indicate that olaparib does not negatively impact long-term HRQoL in patients with gBRCAm, high-risk, HER2-negative, early breast cancer. Mean (SD) baseline EORTC QLQ-C30 global health status/QoL functioning scores were comparable between the treatment arms for patients who had received prior neoadjuvant treatment (69.4 [19.20] in the olaparib arm and 68.9 [19.42] in the placebo arm) and prior adjuvant treatment (71.3 [19.14] in the olaparib arm and 71.6 [19.22] in the placebo arm. At 24 months, the EORTC QLQ-C30 Global health status QoL were also comparable between the treatment arms for patients who had received prior neoadjuvant treatment (71.8 [22.77] in the olaparib arm and 77.3 [21.39] in the placebo arm) and prior adjuvant treatment (76.1 [21.09] in the olaparib arm and 77.8 [20.64] in the placebo arm.

FACIT-SCORE

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 40). 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 19. 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 40. HRQoL FACIT-Fatigue score summary statistics

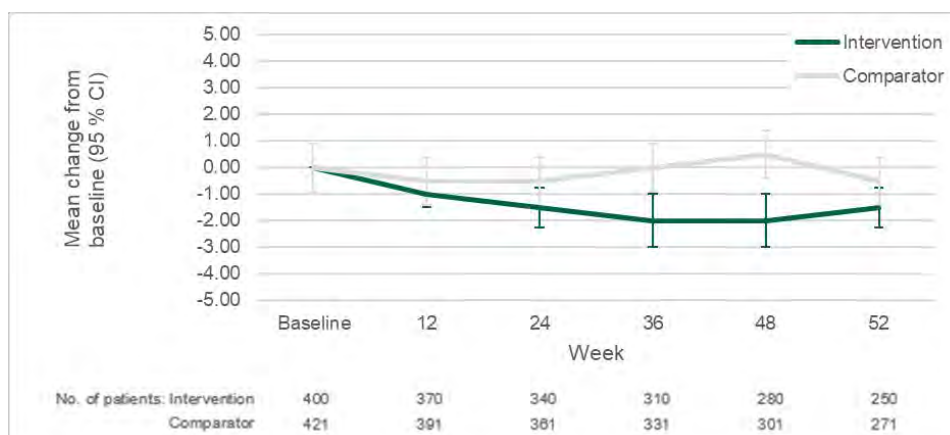
Parameter	Baseline score, mean (SD)	6 months		12 months	
		LS Mean	95% CI	LS Mean	95% CI
Patients who had previously completed neoadjuvant chemotherapy					
Olaparib (n=373)	39.4 (10.42)	-1.5	-2.3, -0.7	-1.4	-2.3, -0.5
Placebo (n=356)	39.7 (9.51)	-0.2	-1.0, 0.6	0.1	-0.8, 1.0
Difference	—	-1.3	-2.4, -0.2	-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) [62]

Figure 19. Mean change from baseline through the different data collection time points for both the intervention and comparator



10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

In OlympiA, HRQoL was assessed using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires, as described in Section 10.1. No EQ-5D-3L or EQ-5D-5L data were collected in the study.

In the absence of EQ-5D-3L or EQ-5D-5L data, HSU values were estimated by mapping from the EORTC QLQ-C30 data collected at DCO1 of OlympiA using the published algorithm by Crott and Briggs (see Appendix K). These data were considered 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.

As data were only routinely collected every 6 months up to recurrence or for a maximum of 2 years in OlympiA, the HSUs for AEs, metastatic and non-mBC were sourced from external data sources (Table 43). In the base case analysis, the HSUs for 'early' and 'late' onset mBC were based on data from Lidgren et al. [43]. The Lidgren study was selected because the reported values were relevant to the health state structure of the model. HSU values from Lloyd et al [63] 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 that reported the same mean HSU value between patients with primary (i.e., IDFS) and non-mBC.

The HSU values are age-adjusted using the general population HSU norm equation from Ara and Brazier et al [64].



10.2.1.1 Mapping

As mentioned above, in the absence of EQ-5D-3L or 5L data, HSU values were estimated by mapping from the EORTC QLQ-C30 data collected in OlympiA using published algorithms [65]. Please refer to Appendix K for further information on the analysis.

10.2.2 Disutility calculation

The model includes the HRQoL impact of treatment-related 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 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. The disutilities and durations of AEs has been sourced from publications and a previous HTA submission, see Table 43.

10.2.3 HSUV results

The HSUV derived from OlympiA and applied in the health economic model are presented in Table 41. Literature derived HSUVs and disutilities are presented in Table 43.

Table 41. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
IDFS	0.869 [0.865- 0.873]	EORTC- QLQ-C30 to EQ-5D-3L through Crott and Briggs mapping algorithm [65]	UK	The OlympiA data represents the only source of HSU for patients with gBRCAm, HER2-negative, high-risk early breast cancer
Non-mBC	0.869 [0.865- 0.873]	EORTC- QLQ-C30 to EQ-5D-3L through Crott and Briggs mapping algorithm [65]	UK	The HSU for the non-mBC state was assumed equal to the HSU for IDFS.



10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

The HSUVs and disutilities sourced from the literature and applied in the health economic model are presented in Table 43.

Table 42. Overview of health state utility values [and disutilities] – N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs – N/A				
HSUV A – N/A				
HSUV B – N/A				
[Disutilities] – N/A				

Table 43. Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments	Duration of AE (days)***
HSUV					
'Early' and 'late' mBC	0.685 [0.62– 0.735]	EQ-5D-3L*	UK [66]	As HRQoL data were not routinely collected after recurrence in OlympiA, external literature data	N/A



	Results [95% CI]	Instrument	Tariff (value set) used	Comments	Duration of AE (days)***
				from Lidgren et al were used for the post recurrence states of 'early' and 'late' mBC	
AE disutility					
Anaemia	-0.119	EQ-5D-3L*	UK	Derived from NICE TA563 [44]	Olaparib: 72.44 Watch and wait: 35.92
Leukopenia	-0.09	EQ-5D-3L*	UK**	Assumed the same as neutropenia	Olaparib: 28.92 Watch and wait: 31.05
Neutropenia	-0.09	EQ-5D-3L*	UK**	Nafees et al [45]	Olaparib: 28.92 Watch and wait: 31.05

* The study utilised the EQ-5D instrument. However, the document does not specify whether the 3-level (3L) or 5-level (5L) version of the EQ-5D was used. Given the publication date of the study (≤ 2010), it is assumed that the EQ-5D-3L version was used. ** The document does not specify the exact tariffs used. It is likely that the UK tariffs was used.*** Median duration of anaemia and neutropenia are derived from OlympiA while duration of leukopenia is assumed the same as neutropenia. The duration of AEs related to treatment with pembrolizumab are assumed to be the same as for treatment with olaparib.

11. Resource use and associated costs

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

- Neoadjuvant therapy cost of pembrolizumab (only included in the cost-minimisation analysis versus pembrolizumab)
- Adjuvant therapy costs, including acquisition, administration and monitoring of treatment
- Treatment costs for recurrence of disease, including drug, surgery, and radiotherapy-related costs
- Disease management costs
- Costs related to management of AEs



- Patient costs
- End of life costs.

For the base case, unit costs were obtained from several sources including DRG costs from Sundhedsstyrelsen [67] and Medicinrådet,[68] and previous Medicinrådet assessments. The pharmaceutical prices were extracted from the medicinpriser.dk price database in October 2026 [69]. The resource use data were obtained from two clinical expert interviews [39].

11.1 Medicines - intervention and comparator

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 mBC. The intervention in the model is 1-year adjuvant treatment with olaparib tablets at a dose of 300 mg twice daily. The comparators in the TNBC population are watch and wait (proxied by placebo in OlympiA) and a weighting of pembrolizumab (80%) and capecitabine (20%), and in the HER2-/HR+ population the comparator is abemaciclib. Watch and wait comprises monitoring and surveillance for disease recurrence. No drug costs are assigned to watch and wait. The resource utilization for watch and wait was captured in the costs of disease management and monitoring assigned to the IDFS health state. These costs are applied to all treatment arms of the model. Further detail on these costs is provided in Section 11.4. Table 44 presents the medicines (intervention and comparators) used in the model.

Table 44. Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Olaparib	300 mg or 200 mg	100%	Twice daily for 12 months	No
Watch and wait	N/A	N/A	N/A	N/A
Pembrolizumab (adjuvant treatment)	2mg/kg	100%	Every three weeks for 9 cycles	No
Capecitabine	1 000 mg ²	100%	8 cycles of 21-day treatment cycles (24 weeks)	No
Abemaciclib	150 mg twice daily	100%	24 months	No

Olaparib

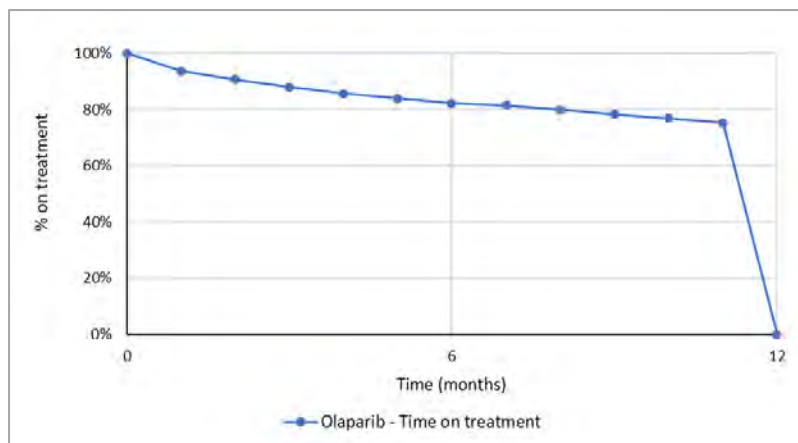
The intervention in the model is 1-year adjuvant treatment with olaparib tablets at a dose of 300 mg twice daily. Treatment is administered until recurrence of disease, tolerability issues, AEs or until completion of the 1-year treatment period. After discontinuation or completion of treatment, patients are assumed to undergo watch and wait until recurrence. Olaparib is available in 150 mg and 100 mg film-coated tablet formulations and comes in pack sizes of 56 tablets. The 100 mg tablet is available for



dose reduction. The distribution between the 150 mg and 100 mg packs is assumed to be reflected in the available sales data. These data implies that 60% of patients use the 150 mg pack with a targeted dose of 600 mg daily and 40% use the 100 mg pack with a targeted dose of 400 mg daily. This distribution is applied in the base case and results in a 28-day treatment cost (AIP) with olaparib of 29 406.80 DKK (medicinpriser.dk February 2026). The cost per model cycle (30.4375 days) is 31 966.77 DKK.

The duration of treatment with adjuvant olaparib is modelled on the percentage of patients that remain on study drug in the olaparib arm of the OlympiA trial (Figure 20). This is estimated from the Kaplan-Meier probabilities for the time from randomisation to discontinuation of study drug from any cause.

Figure 20. Kaplan-Meier probabilities of time to discontinuation of adjuvant olaparib in TNBC patients.



The time to discontinuation data in OlympiA appropriately reflects the expected duration of adjuvant olaparib treatment and includes the impact of disease recurrence and AEs 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)[3]. In DC01, of 911 patients treated, 5 had treatment durations, measured as the time from first to last dose, of at least 400 days. 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 minutes time with dose interruptions) that ranged from 369 to 374 days. 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 recommended duration of adjuvant olaparib in early breast cancer. In the Excel model, the total cost of adjuvant olaparib is 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. In addition, a monthly cost of a full blood count (408.20 DKK) is included as treatment monitoring during the time when patients receive olaparib [70].



Pembrolizumab (cost-minimisation analysis, TNBC population)

To capture the treatment cost of pembrolizumab in the cost-minimisation analysis versus olaparib, the cost of the neoadjuvant treatment phase was derived separately and added to the cost of the adjuvant treatment phase. In the neoadjuvant setting patients should be treated with pembrolizumab 200 mg, intravenously, every 3 weeks for 8 treatment cycles or alternatively 400 mg every 6 weeks for 4 treatment cycles in combination with chemotherapy. The cost of chemotherapy was excluded from the cost-minimisation analysis since it was assumed that patients treated with adjuvant olaparib would also have received neoadjuvant chemotherapy. The duration of neoadjuvant treatment is modelled using the time to treatment discontinuation curve from KEYNOTE-522 (reflecting 0.43 years of neoadjuvant treatment) [55]. In the adjuvant phase, patients should be treated with pembrolizumab 200 mg, intravenously, every 3 weeks for 9 treatment cycles or alternatively 400 mg every 6 weeks over 5 treatment cycles. In KEYNOTE-522 the average time on adjuvant treatment was 0.32 years (3.84 months) [55]. KEYNOTE-522 did not present the duration of treatment curve for adjuvant pembrolizumab and therefore, the time to discontinuation curve of olaparib from OlympiA was used to estimate the time on treatment for patients receiving adjuvant pembrolizumab but a maximum treatment length of 3.84 months to reflect the 9 treatment cycles was included. The adjuvant treatment costs were calculated in the same way as described for olaparib above. After discontinuation or completion of treatment with adjuvant pembrolizumab, patients are assumed to undergo watch and wait until recurrence. In addition, it is assumed that patients require a full blood count at each administration of pembrolizumab (408.20 DKK every 3 weeks) as treatment monitoring during the time the patients receive adjuvant pembrolizumab.

Pembrolizumab is available in 100 mg vials (4 ml vials in the strength 25mg/ml) to a 21-day treatment cost (AIP) of 42 241.06 DKK which results in a cost of 61 224.39 DKK per model cycle (30.4375 days) (medicinpriser.dk February 2026), with the fixed 200 mg dose used in KN522. In Danish clinical practice, weight-based dosing of pembrolizumab (2 mg/kg) is recommended and have therefore been included as the base-case in the cost-minimisation analysis. Applying weight-based dosing and the mean weight derived from the OlympiA clinical trial (68.7 kg), the 21-day treatment cost (AIP) is 41 354 DKK with wastage and 28 410.20 DKK without wastage, resulting in a cost per model cycle (30.4375 days) of 59 938.68 DKK with wastage and 41 177.88 DKK without wastage. The fixed dose of pembrolizumab is applied in a scenario analysis (Appendix Q). In the cost-minimisation analysis for the TNBC population, pembrolizumab was included in the weighted comparator arm with capecitabine and represented 80% of the comparator.

Capecitabine (cost-minimization analysis, TNBC population)

The cost of capecitabine was included in the comparator arm of the cost-minimisation analysis for the TNBC population (weighted as 20% of the comparator arm in the adjuvant phase). The time to discontinuation curve for olaparib based on the OlympiA clinical trial was used as an estimation of the TTD curve and applying the treatment duration of 24 weeks (assuming 8 cycles of 21-day treatment cycles) based on the CREATE-X clinical trial [16]. The targeted dose, based on Danish clinical practice, is 1 000 mg per square meter of body surface area. Given the weight of the relevant patient



population, the targeted dose of capecitabine included in the cost-minimization analysis is 1 770 mg twice daily. The dose is distributed between tablets of 150 mg and 500 mg.

Capecitabine is available as 150 mg, 300 mg and 500 mg packages with 60 or 120 tablets to a cost of 616 DKK (for 60 tablets), 567 DKK (for 60 tablet), and 539 DKK (for 120 tablets), respectively. The cost per model cycle (30.4375 days) without wastage is 645.30 DKK assuming the cost per mg of the 500 mg pack, and a cost per model cycle (30.4375 days) with wastage of 1 380,17 DKK (assuming 2 tablets of 150 mg and 3 tablets of 500 mg twice daily).

Abemaciclib (cost-minimization analysis, HR+ population)

In the cost-minimisation analysis for the HR+ population, the cost of abemaciclib was included for the comparator arm. The targeted dose of abemaciclib is 150 mg twice daily and patients are receiving treatment for two years. The cost of treatment was calculated based on the TTD curve derived from the MonarchE clinical trial as presented in the DMC report of the abemaciclib evaluation [24].

Abemaciclib is available in 50 mg, 100 mg and 150 mg packages with 56 tablets to a cost (AIP) of 17 325.48 DKK per pack. Given the targeted dose of 600 mg per day and since the 150 mg pack results in the lowest cost per mg, the 150 mg pack was included in the analysis and the cost per model cycle (30.4375 days) was 18 833,73 DKK with and without wastage.

Treatment of non-metastatic and mBC

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) and prior adjuvant treatment (olaparib or watch and wait [in the cost-minimisation analysis the share of treatments for the pembrolizumab arm is assumed the same as for olaparib]). 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)[3, 62]. 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 [3]. For these patients, the aim of surgery is the complete resection of the tumour [71]. 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 [72]. This was also validated by Danish clinical experts [39]. 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 cost 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) [3, 62]. 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 cost of radiotherapy was assumed to be the same across health states in



the model. Table 45 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 [39]. 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.

Table 45. List of treatment options per state included in the base case

State	Treatment options
Non-mBC	Capecitabine
Patients may receive only one line of treatment	Docetaxel plus Cyclophosphamide IV
	Paclitaxel + Cyclophosphamide + Epirubicin IV
	Letrozole
mBC	Capecitabine
Patients may receive one or more lines of treatment	Eribulin
	Paclitaxel
	Letrozole
	Anastrozole
	Fulvestrant
	Paclitaxel
	Docetaxel
	Atezolizumab + nab-paclitaxel
	Abemaciclib + Letrozole

In the Excel model, the cost 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 of pre- versus post-progression in mBC, 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 BRCAm patients in OlympiA, a simplified approach to the modelling of subsequent costs was preferred. Table 46 summarises the unit costs of drug acquisition and Table 47 presents the unit costs of radiotherapy and surgery for non-mBC and mBC.



The description of the weighted averages of drug, surgery and radiotherapy costs for patients in the 'non-mBC', 'early onset mBC' and 'late onset mBC' health states are provided in Appendix O.

Table 46. Unit costs (DKK) of drug therapies considered in the base case

Treatment	Dose per vial/tablet (mg)	Pack size	Cost per pack* (AIP) (DKK)	Price per mg (DKK)
Cytotoxic chemotherapy				
Capecitabine	150	60	616.00	0.07
	300	60	567.00	0.03
	500	120	539.00	0.01
Cyclophosphamide	200	1	67.00	0.34
	500	1	192.00	0.38
	1000	1	335.00	0.34
Eribulin	0.88	1	2 050.00	2 329.55
Paclitaxel	100	1	110.50	1.11
	150	1	1 500.00	10.00
	300	1	201.50	0.67
Docetaxel	20	1	35.00	1.75
	80	1	150.00	1.88
	160	1	309.00	1.93
Abraxane (nab-paclitaxel)	100	1	1 791.25	17.91
Epirubicin IV	200	1	442.76	2.21
Immunotherapy				
Pembrolizumab	100	1	20 677.00	206.77
Atezolizumab	840	1	19 424.58	23.12
	1200	1	27 749.39	23.12
Endocrine therapy				
Letrozole	2,5	100	33.77	0.14
Anastrozole	1	100	124.00	1.24
Fulvestrant	250	2	462.00	0.92
PARP inhibitor				
Olaparib	100	56	14 699.67	2.62
	150	56	14 705.89	1.75

Source: * Medicinpriser.dk, February 2026 prices [69]



Table 47. Unit costs (DKK) of radiotherapy and surgery for non-mBC and mBC

Treatment	Unit cost (DKK)	Data source of unit cost
Radiotherapy	7 905.00	An average of 3-4 fractions for costs based on KEE input (DRG 2026: 27MP06 Strålebehandling, konventionel, 3-4 fraktioner) [67]
Surgery for non-mBC	42 882.00	Radical mastectomy [combination of : (DC501) brystkræft i den centrale del af mamma and (KHAC25) Radikal mastektomi)]; 09MP03 - Stor mammakirurgisk operation - Sundhedsdatastyrelsen. DRG-takster 2026 [67]
Surgery for mBC	105 930.50	Average between intracranial surgery and decompression surgery of the spinal cord (DRG 2026: 26MP17 and 08MP06) [67]

11.2 Medicines– co-administration

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.[3]

In the model, patients with HER2-/HR+ disease 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 [39]. 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 in both treatment arms [39].

The monthly cost of endocrine treatment is modelled as a weighted average of the costs of tamoxifen, anastrozole, letrozole and exemestane. The share of treatment is modelled based on clinical expert input [39]. The healthcare resource utilisation for the monitoring and administration of endocrine therapies is 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.

The distribution of ET therapy was for olaparib derived from the OlympiA clinical trial, and for abemaciclib arm it was derived from the DMC evaluation of abemaciclib. The distribution of ET therapy per treatment arm is presented in Table 48.



Table 48. Distribution and monthly cost of adjuvant endocrine therapy in HER2-/HR+ patients

ET therapy	% use in olaparib arm	% use in abemaciclib arm	Pack size	Cost per month (DKK)	Reference
Letrozole	57.5%	60.0%	100 x 2.5 mg tablets	10.3	OlympiA clinical trial, DMC evaluation of abemaciclib, Medicinpriser.dk [3, 24, 69]
Anastrozole	2.5%	5.0%	100 x 1 mg tablets	37.7	
Tamoxifen	40.0%	30.0%	100 x 20 mg tablets	48.4	
Exemestane	0.0%	5.0%	100 x 25 mg tablets	1 030.4	

11.3 Administration costs

No administration cost of olaparib was assumed, due to the per oral administration. No active treatment is administered for the watch and wait treatment arm, hence no administration cost was included. In the cost-minimisation analysis for the TNBC population, the cost related to the IV administration of pembrolizumab was included while no treatment cost of capecitabine was included due to the per oral administration. In the HR+ population, no administration costs were included as both olaparib and abemaciclib have oral administration. An overview of the administration costs is presented in Table 49.

Table 49. Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oral	Daily	0	N/A	Assumed to be 0
IV	Depending on treatment	1 625	09MA98 MDC09 1- dagsgruppe, pat. mindst 7 år Sundhedsdatastyrelsen.	DRG takster 2026 [67]
SC	N/A	0.00	N/A	Assumed to be 0

11.4 Disease management costs

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, watch and wait, and pembrolizumab patients who occupy the same state. As outlined previously, the lifetable approach is used to apply 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 127 in 0 summarises the health state costs and resource use in the base case. The resource use data was based on Danish clinical expert input [39]. Costs related to patient time and transport are presented in Section 11.7.

11.5 Costs associated with management of adverse events

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 $\geq 3\%$: AE must have occurred in at least 3% of patients in either treatment arm.

The cost of each AE included in the model are presented in Table 50.

As presented in Appendix N, in the comparison with pembrolizumab/capecitabine, the user can either apply the same AEs and frequencies to the pembrolizumab/capecitabine arm as experienced by patients on olaparib in OlympiA or apply the AEs and frequencies as experienced by patients in the pembrolizumab arm in KEYNOTE 522 and patients in the capecitabine arm in CREATE-X (Schmid et al 2024 and Masuda et al. 2017). A similar approach was included in the HER2-/HR+ and the cost-minimisation analysis versus abemaciclib. The user could either apply the same AEs and frequencies to the abemaciclib arm as experienced by olaparib patients in the OlympiA clinical trial or apply the AEs and frequencies as experienced by abemaciclib patients in the MonarchE clinical trial [22]. For the additional AEs included for pembrolizumab, capecitabine and abemaciclib when applying the KEYNOTE 522, CREATE-X and MonarchE estimates, respectively, the cost per event is assumed to be represented by a visit to an oncologist (1 605.00 DKK, DRG: 23MA04, DRG-takster 2026 [67]). Scenarios where AEs in the pembrolizumab/capecitabine arm are derived from KEYNOTE 522 and CREATE-X, and where AEs in the abemaciclib arm are derived from MonarchE have been included in sensitivity analysis (Appendix Q).



Table 50. Cost associated with management of adverse events derived from OlympiA

	DRG code	Unit cost/DRG tariff
Anaemia	23MA04 kontrolundersøgelse; 16PR02 transfusion of blood, other. [67]	5 774.00
Leukopenia	23MA04 kontrolundersøgelse. [67]	1 605.00
Neutropenia	23MA04 kontrolundersøgelse. [67]	1 605.00

11.6 Subsequent treatment costs

Please see section “Treatment of non-mBC and mBC” in chapter 11.1 and Appendix O.

Table 51. Medicines of subsequent treatments – N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A				
N/A				

11.7 Patient costs

A limited societal perspective was considered for the health economic assessment including patient costs and transportation. Routine care (clinic visits) was included in line with the DMC’s catalogue of unit costs. See Table 52 for the patient time assumed per resource or activity included in the model. It is assumed that CT scans take 30 minutes, office visits 20 minutes and mammograms 30 minutes. Travel costs are included for visits to oncology outpatient visits, CT scans and mammograms. Blood tests are assumed to be taken at the same time as medical visits and does not require extra travelling.

In addition, given the IV administration of pembrolizumab (Section 11.3), the cost of patient travel time (one roundtrip) and 30 min of patient time was added for each administration of pembrolizumab (both in the neoadjuvant and adjuvant phase).

Table 52. Patient time (minutes) per activity included in the model

Activity	Patient time (minutes per resource)
CT scan	30.00
Office visit	20.00
Mammogram	30.00
Patient travel time	Roundtrip



Table 53. Patient costs used in the model

Activity	Cost (DKK)
Patient time (per hour)	188.00
Transportation (per transport)	140.00

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Terminal care cost

In the cost-minimisation analyses comparing olaparib with pembrolizumab and capecitabine, and comparing olaparib with abemaciclib, the terminal care costs have been excluded from the analysis as these would result in the same cost in the intervention and comparator arms. However, in the cost-effectiveness analysis comparing olaparib with watch and wait (TNBC population), terminal care costs have been included in a scenario analysis (Appendix Q).

In a scenario for the cost-effectiveness analysis, 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 scenario analysis is 86 794.00 DKK. 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 hospitalised 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). Deaths from IDFS were assumed to be non-cancer related meaning that cancer-related end-of-life 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 death may occur. In a second scenario analysis (Appendix Q), the end-of-life care costs were assumed to apply to all deaths.

Testing cost

In the base case analysis for the TNBC population, 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 to adjuvant olaparib in early breast cancer are considered in a scenario analysis. For the HR+ patients, the cost of BRCA testing has been included in the base case analysis.



The total cost of BRCA testing is estimated from the unit cost of genetic BRCA testing (4 113 DKK) 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 clinician's judgement, in case of emerging treatment relevance (e.g., local therapy or PARP inhibitor use).

For the HR+ patients, the number of patients needed to test is calculated as one divided by the prevalence of gBRCA mutation in patients with HR+ disease. Based on literature and expert advice, it was assumed that the prevalence of gBRCA mutation in patients with HR+/HER2- 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.

12. Results

12.1 Base case overview – TNBC population

An overview of the base case cost-effectiveness analysis and cost-minimisation analysis performed for the comparison of olaparib with watch and wait and pembrolizumab/capecitabine, respectively for the TNBC population, are presented in Table 54.

Table 54. Base case overview – TNBC population

Feature	Description
Comparator	Watch and wait (cost-effectiveness analysis) Pembrolizumab (80%), capecitabine (20%) (cost-minimisation analysis)
Type of model	Semi-Markov model
Time horizon	57 years (life time)
Treatment line	1 st line, and subsequent treatment as treatment of recurrence (1 st line and 2 nd line plus)
Measurement and valuation of health effects	Health-related quality of life measured with EORTC QLQ-C30 in OlympiA, mapped to EQ-5D using the algorithm published by Crott & Briggs. Age-adjustment using equation from Ara and Brazier et al.
Costs included	Medicine costs Administration cost Monitoring costs Disease management cost Costs of adverse events



Feature	Description
	Subsequent treatment costs and treatment of recurrence Patient costs End of life costs (included as a scenario)
Dosage of medicine	Olaparib: Fixed dose, 60% 300 mg twice daily and 40% 200 mg twice daily for 12 months Watch and wait: N/A Pembrolizumab (adjuvant): weight-based dose, 2mg/kg every 3 weeks for 9 cycles Capecitabine: 1 000 mg ² twice daily for the first 14 days of a 21-day treatment cycle, over 8 cycles
Average time on treatment	Olaparib: 9,28 months Watch and Wait: N/A Pembrolizumab: 3,22 months Capecitabine: 4,92 months
Parametric function for IDFS	Olaparib: Gompertz Watch and wait: Gompertz
Parametric function for OS	Olaparib: N/A Watch and wait: N/A
Inclusion of waste	Not in base case
Average time in model health state	
IDFS	Olaparib: 361.55 months; watch and wait: 321.41 months
Non-mBC	Olaparib: 6.09 months; watch and wait: 8.57 months
Early onset mBC	Olaparib: 1.64 months; watch and wait: 4.55 months
Late onset mBC	Olaparib: 3.07 months; watch and wait: 3.65 months
Death	Olaparib: 311.65 months; watch and wait: 345.82 months

12.1.1 Base case results -TNBC population

The base case results, by model health state, of the cost-effectiveness analysis of olaparib versus watch and wait are presented in Table 55. Over the lifetime time horizon, the total, discounted, cost of olaparib was 386 924 DKK compared with 80 777 DKK for watch and wait. The key driver of results was the acquisition cost of olaparib, considering that no acquisition, administration or monitoring cost was assigned to the watch and wait arm.

Over the time horizon, the total, discounted, cumulative LYs was 17.52 and 16.12 in the olaparib and watch and wait arm, respectively. The total, discounted, QALYs was 14.86 for olaparib and 13.63 for watch and wait. The resulting ICER of the cost-effectiveness analysis of olaparib versus watch and wait over a 57-year time horizon for patients with early, high-risk TNBC was 248 905 DKK. Indicating that olaparib could be a cost-effective treatment alternative for this patient population.



Table 55. Base case results of cost-effectiveness analysis (olaparib vs. watch and wait), discounted estimates

Health state/category	Olaparib	Watch and wait	Difference
IDFS health state			
Treatment acquisition	324 818	0	324 818
Treatment administration	0	0	0
Monitoring costs	4 148	0	4 148
Background therapy costs	0	0	0
Disease management costs: Y1	9 069	8 802	267
Disease management costs: Y2-5	1 390	1 255	135
Disease management costs: Y5+	334	296	39
Patient costs (time and travel)	2 184	2 082	102
AE costs	629	35	594
Non-mBC & mBC health states			
Treatment acquisition	22 116	34 126	-12 010
Surgery and radiotherapy costs	7 207	10 469	-3 262
Treatment admin and monitoring	3 980	6 105	-2 125
Disease management costs	9 585	15 273	-5 688
Patient costs (time and travel)	1 465	2 334	-869
Death health state			
Terminal care costs	0	0	0
Total costs	386 924	80 777	306 147
LYs gained (IDFS)	16.84	15.03	1.81
LYs gained (Non-mBC)	0.35	0.50	-0.15
LYs gained (Early onset mBC)	0.13	0.34	-0.21
LYs gained (Late onset mBC)	0.20	0.24	-0.04
Total LYs	17.52	16.12	1.40
QALYs (IDFS)	14.34	12.80	1.54
QALYs (Non-mBC)	0.30	0.43	-0.13
QALYs (Early onset mBC)	0.09	0.23	-0.15
QALYs (Late onset mBC)	0.14	0.16	-0.03
QALYs (adverse reactions)	0.00	0.00	0.00
Total QALYs	14.86	13.63	1.23
Incremental costs per LY gained			218 075
Incremental cost per QALY gained (ICER)			248 905



Table 56 presents the results from the cost-minimisation analysis of olaparib and pembrolizumab/capecitabine in the TNBC population. The total, discounted cost over the 57-year time horizon, applying the AIP drug cost in both treatment arms, was 386 924 DKK for olaparib and 413 639 DKK for pembrolizumab/capecitabine, which results in an incremental cost of -26 715 DKK. The difference in total cost was mainly driven by the acquisition cost of pembrolizumab/capecitabine. The administration cost also differed between the treatment arms considering that pembrolizumab is administered intravenously with an associated cost, compared with the oral administration of olaparib with no associated cost.

Table 56. Base case results of cost-minimisation analysis (olaparib vs. pembrolizumab), discounted estimates, TNBC

Health state/category	Olaparib	Pembrolizumab/capecitabine	Difference
IDFS			
Treatment acquisition	324 818	330 592	-5 774
Treatment administration	0	16 693	-16 693
Monitoring costs	4 148	2 404	1 744
Background therapy costs	0	0	0
Disease management costs: Y1	9 069	9 069	0
Disease management costs: Y2-5	1 390	1 390	0
Disease management costs: Y5+	334	334	0
Patient costs (time and travel)	2 184	8 175	-5 991
AE costs	629	629	0
Non-mBC & mBC health states			
Treatment acquisition	22 116	22 116	0
Surgery and radiotherapy costs	7 207	7 207	0
Treatment admin and monitoring	3 980	3 980	0
Disease management costs	9 585	9 585	0
Patient costs (time and travel)	1 465	1 465	0
Death			
Terminal care costs	0	0	0
Total costs	386 924	413 639	-26 715
Total LYs	17.52	17.52	0
Total QALYs	14.86	14.86	0



Health state/category	Olaparib	Pembrolizumab/capecitabine	Difference
Incremental costs per LY gained			N/A
Incremental cost per QALY gained (ICER)			N/A

12.2 Base case overview – HR+ population

An overview of the base case cost-minimisation analysis performed for the comparison of olaparib with abemaciclib for the HR+ population, is presented in Table 57.

Table 57. Base case overview – HR+ population

Feature	Description
Comparator	Abemaciclib (cost-minimisation analysis)
Type of model	Semi-Markov model
Time horizon	57 years (life time)
Treatment line	1 st line, and subsequent treatment as treatment of recurrence (1 st line and 2 nd line plus)
Measurement and valuation of health effects	N/A
Costs included	Medicine costs Administration cost Monitoring costs Disease management cost Costs of adverse events Subsequent treatment costs and treatment of recurrence Testing cost Patient costs End of life costs (included as a scenario)
Dosage of medicine	Olaparib: Fixed dose, 60% 300 mg twice daily and 40% 200 mg twice daily for 12 months Abemaciclib: 150 mg twice daily for 2 years
Average time on treatment	Olaparib: 9.50 months Abemaciclib: 18.70 months
Parametric function for IDFS	Olaparib: Lognormal Abemaciclib: assumed the same as olaparib
Parametric function for OS	Olaparib: N/A Abemaciclib: N/A
Inclusion of waste	Not in base case
Average time in model health state IDFS	Olaparib: 253.85 months



Feature	Description
Non-mBC	Olaparib: 15.50 months
Early onset mBC	Olaparib: 1.49 months
Late onset mBC	Olaparib: 17.69 months
Death	Olaparib: 395.46 months

Table 58 presents the results from the cost-minimisation analysis of olaparib and abemaciclib in the HR+ population. The total, discounted cost over the 57-year time horizon, applying the AIP drug cost in both treatment arms, was 529 239 DKK for olaparib and 531 289 DKK for abemaciclib, which results in an incremental cost of -2 050 DKK. The difference in total cost was mainly driven by the treatment acquisition cost and BRCA testing cost.

Table 58. Base case results of cost-minimisation analysis (olaparib vs. abemaciclib), discounted estimates, HR+

Health state/category	Olaparib	Abemaciclib	Difference
IDFS			
Treatment acquisition	332 036	362 306	-30 270
Treatment administration	0	0	0
Monitoring costs	4 240	2 290	1 950
Background therapy costs	1 380	3 900	-2 520
Disease management costs: Y1	9 168	9 168	0
Disease management costs: Y2-5	1 389	1 389	0
Disease management costs: Y5+	237	237	0
Testing costs	28 791	0	28 791
Patient costs (time and travel)	2 151	2 151	0
AE costs	629	629	0
Non-mBC & mBC health states			
Treatment acquisition	103 618	103 618	0
Surgery and radiotherapy costs	15 401	15 401	0
Treatment admin and monitoring	2 115	2 115	0
Disease management costs	24 363	24 363	0
Patient costs (time and travel)	3 723	3 723	0
Death			



Health state/category	Olaparib	Abemaciclib	Difference
Terminal care costs	0	0	0
Total costs	529 239	531 289	-2 050
Total LYs	14.89	14.89	0
Total QALYs	12.55	12.55	0
Incremental costs per LY gained			N/A
Incremental cost per QALY gained (ICER)			N/A

12.3 Sensitivity analyses

Sensitivity analyses in form of a deterministic sensitivity analysis, probabilistic sensitivity analyses and scenarios analyses have been run and are presented in Appendix Q.

13. Budget impact analysis

The model uses the total female population in Denmark as a starting point and the specific targeted population is estimated based on the disease characteristics of patients in the indication. The patient population is described in Section 3.2. Given the epidemiology, it is estimated that around 28 patients per year would be eligible for treatment with olaparib in the adjuvant TNBC setting, and 43 patients in the HER2-/HR+ setting in Denmark.

For TNBC, in a scenario where olaparib is not recommended, pembrolizumab/capecitabine is assumed to be used by a majority of patients with the watch and wait alternative being considered for 10% of the population. In a scenario where olaparib is recommended, the market share for olaparib is expected to increase over time, ranging from 20% in year 1 to 90% in year 5 assuming that olaparib will absorb the watch and wait market shares and an increasing proportion of the pembrolizumab/capecitabine market shares. For HER2-/HR+, in a scenario where olaparib is not recommended, it is assumed that all patients would receive abemaciclib. In the scenario where olaparib is recommended, the market shares for olaparib is expected to increase relatively fast. The same assumption as for the pembrolizumab/capecitabine arm is assumed with markets shares for olaparib are ranging from 20% in year 1 to 90% in year 5. Table 59 presents the number of new patients expected to be treated over the next 5-year period, including assumptions about market shares for the TNBC and HER2-/HR+ population. The expenditure per patient builds on the cost and resources described in Section 11.

The budget impact is obtained by combining the cost per patient with the patient numbers. The budget impact for the TNBC and HER2-/HR+ populations is presented in Table 60. For the TNBC population, the analysis shows that recommending olaparib results in total costs ranging from 10 235 387 DKK in year 1 to 10 576 846 DKK in year 5, while in a scenario where olaparib is not recommended the total cost is 9 397 673 DKK in year 1 and 10 370 235 DKK in year 5. This translates to a budget impact of 837 714 DKK in



year 1 206 610 DKK in year 5. In the HER2-/HR+ population, the analysis shows that recommending olaparib results in total costs ranging from 10 583 142 DKK in year 1 to 18 747 261 DKK in year 5, while in a scenario where olaparib is not recommended the total cost is 9 410 384 DKK in year 1 and 27 702 598 DKK in year 5. This translates to a budget impact of 1 172 758 DKK in year 1 followed by savings of 4 137 682 in year 3 and savings of 8 955 337 DKK in year 5.

Number of patients (including assumptions of market share)

Table 59. Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) in the TNBC and HR+ populations

	Year 1	Year 2	Year 3	Year 4	Year 5
TNBC					
Recommendation					
Olaparib	6	17	24	25	25
Watch and wait	0	0	0	0	0
Pembrolizumab	22	11	4	3	3
Non-recommendation					
Olaparib	0	0	0	0	0
Watch and wait	3	3	3	3	3
Pembrolizumab	25	25	25	25	25
HR+					
Recommendation					
Olaparib	9	26	37	39	39
Abemaciclib	34	17	6	4	4
Non-recommendation					
Olaparib	0	0	0	0	0
Abemaciclib	43	43	43	43	43

Budget impact

Table 60. Expected budget impact of recommending the medicine for the indication in the TNBC and HR+ populations

	Year 1	Year 2	Year 3	Year 4	Year 5
TNBC					
The medicine under consideration is recommended	DKK 10 235 387	DKK 10 384 339	DKK 10 378 798	DKK 10 465 671	DKK 10 576 846
The medicine under consideration is NOT recommended	DKK 9 397 673	DKK 9 809 560	DKK 10 019 066	DKK 10 205 708	DKK 10 370 235
Budget impact of the recommendation	DKK 837 714	DKK 574 780	DKK 359 732	DKK 259 964	DKK 206 610



	Year 1	Year 2	Year 3	Year 4	Year 5
HR+					
The medicine under consideration is recommended	DKK 10 583 142	DKK 25 488 806	DKK 21 808 272	DKK 18 991 675	DKK 18 747 261
The medicine under consideration is NOT recommended	DKK 9 410 384	DKK 24 982 678	DKK 25 945 954	DKK 26 852 303	DKK 27 702 598
Budget impact of the recommendation	DKK 1 172 758	DKK 506 128	DKK -4 137 682	DKK -7 860 628	DKK -8 955 337

14. List of experts



15. References

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Appendix A. Main characteristics of studies included

Main characteristics of studies included are shown in Table 61.

Table 61. Main characteristics of studies 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 <i>gBRCAm</i> , 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.		
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]

- 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
 - 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
 - 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 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.
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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

Baseline characteristics OlympiA:

Table 62. Baseline demographic and disease characteristics (TNBC subset) (FAS)DCO: 27 Mar 2020)

Patient characteristics	Olaparib (N=751)	Placebo (N=758)
Age (years)		
Mean (SD)	42.9	43.6
Median (range)	42.0	43.0
Sex, n (%)		
Female	750	758
Male	1	0
BRCA mutation status		
BRCA1	10	10
BRCA2	10	10
BRCA1/2	10	10



Patient characteristics	Olaparib (N=751)	Placebo (N=758)
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Prior platinum therapy		
Yes	218 (29.0)	214 (28.5)
No	533 (71.0)	542 (71.5)
Baseline BRCA status		
BRCA1 mutated	600 (79.9)	616 (81.3)
BRCA2 mutated	147 (19.6)	135 (17.8)
BRCA1 and BRCA2 mutated	2 (0.3)	5 (0.7)
No gBRCA mutations	2 (0.3)	2 (0.3)
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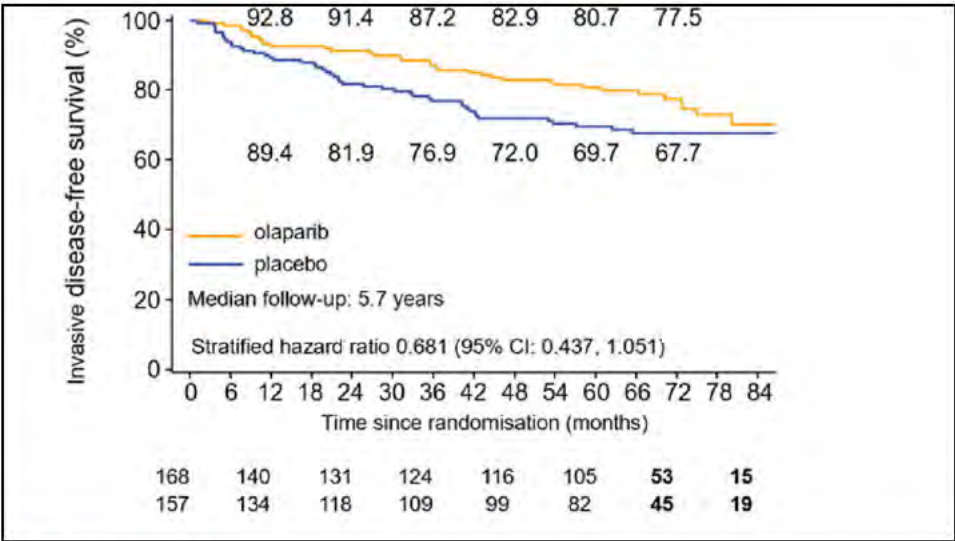


Patient characteristics	Olaparib (N=751)	Placebo (N=758)

15.1.1 Data from HER2-negative HR+ subgroup

Although AstraZeneca has only applied for an assessment of the TNBC subgroup from OlympiA, the DMC has request that we include available data for the HER2-negative HR+ subgroup from the DCO3.

Figure 21. IDFS in HER2-negative HR+ subgroup (DCO3)



Source: San Antonio 2024



Source: AstraZeneca CSR DCO3 [48]

Table 63. Baseline characteristics in HER2-negative HR+

Patient characteristics	Olaparib (N=168)	Placebo (N=157)
Age (years)		



Patient characteristics	Olaparib (N=168)	Placebo (N=157)
Mean (SD)	43.0	43.5
Median (range)	42.0	42.0
Sex, n (%)		
Female	167 (99.4)	153 (97.5)
Male	1 (0.6)	4 (2.5)
Age, years		
18-64	158 (93.4)	148 (94.2)
65-74	8 (4.8)	10 (6.4)
≥75	2 (1.2)	1 (0.6)
ECOG performance		
0	167 (99.4)	153 (97.5)
1	1 (0.6)	4 (2.5)
ECOG performance at baseline		
0	167 (99.4)	153 (97.5)
1	1 (0.6)	4 (2.5)
ECOG performance at week 12		
0	167 (99.4)	153 (97.5)
1	1 (0.6)	4 (2.5)
ECOG performance at week 24		
0	167 (99.4)	153 (97.5)
1	1 (0.6)	4 (2.5)
ECOG performance at week 36		
0	167 (99.4)	153 (97.5)
1	1 (0.6)	4 (2.5)
Prior platinum therapy		
Yes	28 (16.7)	23 (14.6)
No	140 (83.3)	134 (85.4)
Baseline BRCA status		
BRCA1 mutated	54 (32.1)	53 (33.8)
BRCA2 mutated	113 (67.3)	103 (65.6)
BRCA1 and BRCA2 mutated	0 (0.0)	0 (0.0)
No gBRCA mutations	0 (0.0)	1 (0.6)
Missing	1 (0.6)	0 (0.0)
BRCA1/2 mutation status		
BRCA1 mutated	54 (32.1)	53 (33.8)
BRCA2 mutated	113 (67.3)	103 (65.6)
BRCA1 and BRCA2 mutated	0 (0.0)	0 (0.0)
No gBRCA mutations	0 (0.0)	1 (0.6)
Missing	1 (0.6)	0 (0.0)



Patient characteristics	Olaparib (N=168)	Placebo (N=157)
██████████	██████████	██████████
██████████	██████████	██████████
Prior therapy in the neoadjuvant/adjuvant setting		
Anthracycline and taxane	168 (100)	154 (90.1)
Anthracycline regime	0 (0.0)	1 (0.6)
Taxane regimen	0 (0.0)	2 (1.3)
Missing	0 (0.0)	0 (0.0)
██		
██	██████████	██████████
██	██████████	██████████
██████████	██████████	██████████

Trial name: Keynote-522	NCT number: NCT03036488
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Objective	The purpose of this study is to evaluate the efficacy and safety of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs. placebo as adjuvant therapy in participants who have early triple negative breast cancer (TNBC)
Publications – title, author, journal, year	Schmid P, Cortes J, Dent R, Puztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Untch M, Fasching PA, Cardoso F, Andersen J, Patt D, Danso M, Ferreira M, Mouret-Reynier MA, Im SA, Ahn JH, Gion M, Baron-Hay S, Boileau JF, Ding Y, Tryfonidis K, Aktan G, Karantza V, O'Shaughnessy J; KN522 Investigators. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. <i>N Engl J Med.</i> 2022 Feb 10;386(6):556-567. doi: 10.1056/NEJMoa2112651. PMID: 35139274. Schmid P, Cortes J, Puztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KN522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. <i>N Engl J Med.</i> 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663. Schmid P, Cortes J, Dent R, McArthur H, Puztai L, Kümmel S, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Im SA, Untch M, Fasching PA, Mouret-Reynier MA, Foukakis T, Ferreira M, Cardoso F, Zhou X, Karantza V, Tryfonidis K, Aktan G, O'Shaughnessy J; KEYNOTE-522 Investigators. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer. <i>N Engl J Med.</i> 2024;391(21):1981-1991. doi:



Trial name: Keynote-522

NCT number:
NCT03036488

10.1056/NEJMoa2409932. PMID: 39282906

Study type and design

Double-blinded randomized placebo-controlled phase 3 study. Enrolled patients were randomly assigned 2:1. No cross-over was allowed between the phases. Quadruple masking of participant, care provider, investigator, and outcomes assessor. Patients were stratified before randomization according to nodal status (positive or negative), tumor size (T1 to T2 or T3 to T4), and schedule of carboplatin administration (once weekly or every 3 weeks).

Status: Active, not recruiting

Actual Study Start Date: March 7, 2017

Estimated Primary Completion Date: September 30, 2025. Estimated Study Completion Date: September 30, 2025

Sample size (n)

N=1174

Main inclusion criteria

- Has newly diagnosed, locally advanced, centrally confirmed TNBC, as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines.
- Has previously untreated locally advanced non-metastatic (M0) TNBC defined as the following combined primary tumor (T) and regional lymph node (N) staging per current American Joint Committee of Cancer (AJCC) staging criteria for breast cancer as assessed by the investigator based on radiological and/or clinical assessment:
 - T1c, N1-N2
 - T2, N0-N2
 - T3, N0-N2
 - T4a-d, N0-N2
- Provides a core needle biopsy consisting of at least 2 separate tumor cores from the primary tumor at screening to the central laboratory.
- Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 performed within 10 days of treatment initiation.
- Demonstrates adequate organ function
- Males and female participants of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 12 months after the last dose of study treatment for participants who have received cyclophosphamide, and 6 months after the last dose of study treatment for participants who did not.

Main exclusion criteria

- Has a history of invasive malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
- Has received prior chemotherapy, targeted therapy, and radiation therapy within the past 12 months.
- Has received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), antiprogrammed death - ligand 1 (anti-PD-



Trial name: Keynote-522

**NCT number:
NCT03036488**

L1), or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., cytotoxic T-lymphocyte-associated antigen-4 [CTLA-4], OX-40, CD137 [tumor necrosis factor receptor superfamily member 9 (TNFRSF9)]) or has previously participated in a pembrolizumab (MK-3475) clinical study.

- Is currently participating in or has participated in an interventional clinical study with an investigational compound or device within 4 weeks of the first dose of treatment in this current study.
- Has received a live vaccine within 30 days of the first dose of study treatment.
- Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (i.e., dosing exceeding 10 mg daily of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
- Has a known history of HIV.
- Has known active Hepatitis B or Hepatitis C.
- Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Has an active infection requiring systemic therapy.
- Has significant cardiovascular disease, such as: history of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months OR
- congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF
- NYHA Class III or IV.
- Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of
- the study, starting with the screening visit through 12 months after the last dose of study
- treatment for participants who have received cyclophosphamide, and for 6 months after the last
- dose of study treatment for participants who have not.
- Has a known hypersensitivity to the components of the study treatment or its analogs.
- Has a known history of active tuberculosis.

Intervention

Pembrolizumab + Chemotherapy (n = 784)

Pembrolizumab:

200 mg administered IV on Day 1 of each 3-week cycle (Q3W) for a total of 17 cycles



Trial name: Keynote-522

NCT number:
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Carboplatin:

AUC5 on day 1 of Cycles 1-4 of the neoadjuvant phase of the study OR
AUC 1.5 on Days 1, 8, 15 of Cycles 1-4 of the neoadjuvant phase of the
study; IV infusion.

Paclitaxel:

80 mg/m² on days 1, 8 and 15 of Cycles 1-4 in the neoadjuvant phase of
the study; IV infusion.

Doxorubicin:

60 mg/m² on Day 1 of Cycles 5-8 of the neoadjuvant phase of the
study; IV injection.

Epirubicin:

90 mg/m² On Day 1 of Cycles 5-8 of the neoadjuvant phase of the study;
IV injection.

Cyclophosphamide:

600 mg/m² On Day 1 of Cycles 5-8 of the neoadjuvant phase of the
study; IV infusion.

Comparator(s)

Placebo + Chemotherapy (n = 390)

Placebo:

Normal saline administered IV on Day 1 of each 3-week cycle (Q3W) for
a total of 17 cycles

Carboplatin:

AUC5 on day 1 of Cycles 1-4 of the neoadjuvant phase of the study OR
AUC 1.5 on Days 1, 8, 15 of Cycles 1-4 of the neoadjuvant phase of the
study; IV infusion.

Paclitaxel:

80 mg/m² on days 1, 8 and 15 of Cycles 1-4 in the neoadjuvant phase of
the study; IV infusion.

Doxorubicin:

60 mg/m² on Day 1 of Cycles 5-8 of the neoadjuvant phase of the
study; IV injection.

Epirubicin:

90 mg/m² On Day 1 of Cycles 5-8 of the neoadjuvant phase of the study;
IV injection.

Cyclophosphamide

600 mg/m² On Day 1 of Cycles 5-8 of the neoadjuvant phase of the
study; IV infusion.

Follow-up time

DCO March 23 2021 median follow-up 39.1 months (30.0; 41.0)

DCO March 22, 2024 median follow-up 75.1 months (65.9; 84.0)



Trial name: Keynote-522		NCT number: NCT03036488
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	Primary endpoints: - Pathological complete response (pCR) rate using the definition of ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; noninvasive breast residuals allowed) at the time of definitive. - Event-free Survival (EFS) as assessed by Investigator Secondary endpoints: - Percentage of participants who experience an adverse event (AE) - Percentage of participants who discontinue study treatment due to an AE - Health-related quality of life (HRQoL) as reported in EORTC-QLQ-C30 and EORTC-QLQBR23 Other endpoints: - pCR rate using an alternative definition, ypT0 ypN0 (i.e., no invasive or noninvasive residual in breast or nodes) at the time of definitive surgery - pCR rate using the definition of ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; noninvasive breast residuals allowed) at the time of definitive surgery. - EFS in participants with tumors expressing PD-L1 - pCR rate using an alternative definition, ypT0/Tis (i.e., absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement) at the time of definitive surgery - OS	
Method of analysis	Efficacy was assessed in the intention-to-treat population, which included all randomized patients. The stratified method of Miettinen and Nurminen with weights proportional to the stratum size, was used to compared between-group difference in the percentages of patients with pCR (defined as ypT0/Tis for the co-primary endpoint). The Kaplan-Meier (KM) method was used to estimate rates of event-free survival, and a stratified log-rank test for treatment comparisons. Hazard ratios and associated 95% confidence intervals(CI) were analyzed with the use of a stratified Cox proportional-hazards model and Efron's method of handling ties to assess the magnitude of treatment difference. Safety was assessed in the as-treated population, which included all patients who had undergone randomization and received at least one trial drug, underwent surgery, or both.	
Subgroup analyses	- Nodal status: Positive vs. Negative - Tumor size: T1/T2 vs. T3/T4 - Choice of Carboplatin (Cb): Q3W vs. Weekly	



Trial name: Keynote-522	NCT number: NCT03036488
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- Tumor PD-L1 status applies to all subjects with locally advanced TNBC (positive vs. negative)
- Menopausal status (for females only; pre- vs. post-menopausal)
- Age (<65 years vs. ≥65 years)
- Geographic region (Europe/Israel/North America/Australia vs Asia vs. Rest of World)
- Ethnic origin (Hispanic vs. Non-Hispanic)
- ECOG performance status (0 vs. 1)
- HER2 status (1+ by IHC vs. 0 by IHC)

Other relevant information NA

Study name MonarchE	NCT number: NCT03155997
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Objective To demonstrate that abemaciclib in combination with ET as adjuvant therapy is superior compared to ET alone in improving IDFS as defined by STEEP as 1L treatment for patient with HR+/HER2-, node-positive, high-risk early breast cancer.

Publications – title, author(s), journal, year

- Abemaciclib Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). Johnston, S.R.D., et al., Journal of Clinical Oncology, 2020. 38(34): p. 3987-3998.
- Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results from a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. Rastogi P, et al., Journal of Clinical Oncology, 2024. 42(9):987-993.

Study type and design Multicenter, open-label, randomized, Phase III trial to compare the efficacy and safety of abemaciclib in combination with ET versus ET alone in 1L treatment of patients with HR+/HER2-, node-positive, high-risk EBC.

Number of trial participants (N) 5,637 patients randomized in the trial

Primary inclusion criteria

- Male or female ≥18 years
- Confirmed HR+, HER2- status with high risk EBC
- Undergone definitive surgery of primary breast tumour and randomised within 16 months of surgery
- If on ET at study entry, may have up to 12 weeks of ET following the last nonendocrine therapy



Study name MonarchE

NCT number:
NCT03155997

Fulfil one of the following criteria:

- Fulfil one of the following criteria:

Pathological tumour involvement in ≥ 4 ipsilateral axillary lymph nodes, or
Pathological tumour involvement in 1-3 ipsilateral axillary lymph node(s) and at least 1 of the following:

- Grade 3 disease
- Tumour size ≥ 5 cm
- Ki-67 index of $\geq 20\%$

Primary exclusion criteria

- Metastatic disease, node-negative breast cancer, inflammatory breast cancer
- *Previous history of breast cancer except for ipsilateral ductal carcinoma in-situ treated by locoregional therapy alone ≥ 5 years ago*
- Pregnant or lactating
- Previous exposure to CDK 4 & 6 inhibitors
- Prior ET for breast cancer prevention or raloxifene
- Any previous history of venous thromboembolic event
- Active systemic infections or viral load

Intervention

Abemaciclib, 150 mg BID in combination with ET, 2,808 patients were randomized to receive abemaciclib in combination with ET

Comparator(s)

ET alone, 2,829 patients was randomized to receive ET alone in the trial

Follow-up time

Median follow-up of 76.2 months

Is the study used in the health economic model?

Yes

Primary, secondary, and exploratory outcomes

The primary endpoint was invasive disease-free survival (IDFS) as assessed by the investigator, according to STEEP system.

Secondary endpoints were:

- IDFS in Ki67 high population
- Disease relapse-free survival
- Overall survival



Study name MonarchE		NCT number: NCT03155997		
		• Treatment-emergent adverse events, serious adverse events, hospitalizations, Laboratory measures, Vital signs, and physical examinations • Pharmacokinetics • Health-related quality of life (HRQoL) Other endpoints: • IDFS in C1-Ki67L population • IDFS in C2 population" • DRFS in Ki-67H population • DRFS in Ki-67L population • DRFS in C2 population		
Analysis method				Efficacy, including invasive disease-free survival, distant relapse-free survival, and overall survival, was assessed in the ITT population, and in cohort 1, cohort 2, and in prespecified subpopulations of cohort 1 Ki-67 high (≥20%) or cohort 1 Ki-67 low (<20%) populations. For each efficacy endpoint, the Kaplan-Meier method was used to estimate the efficacy outcomes in each treatment group, including the absolute difference in rates estimated by means of normal approximation at each year up to a timepoint when fewer than 200 patients were at risk. HRs were estimated by means of stratified Cox proportional hazard models. The proportional hazards assumption was tested by means of a time-varying Cox model and a regression of the weighted Schoenfeld residuals over time.
Subgroup analyses				• Age • Region • Menopausal status • Prior chemotherapy • Race • Baseline Eastern Cooperative Oncology Group performance status • Primary tumor size, cm • No. of positive lymph nodes • Histologic grade • Progesterone receptor Tumor stage
Other relevant information				NA



Appendix B. Efficacy results per study

Results per study

Table 64. Results per study

Results of OlympiA NCT number: NCT02032823										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	
DDFS DCO2	Olaparib	921	107 (11.6)	7.2%	(3,91, 10.45)		HR= 0.607	(0.48, 0.77)	0.0000421	
	Placebo	915	172 (18.8)							
DDFS DCO3	Olaparib	921	142 (15.4)	7.2%			HR= 0.65	(0.53, 0.81)		
	Placebo	915	207 (22.6)							
DDFS, TNBC DCO3	Olaparib	751	109				HR=0.645	(0.505, 0.820)		
	Placebo	758	166							
DDFS, HR+/HER2 -DCO3	Olaparib	168	33 (19.6%)	6.5%			HR=0.745	(0.469, 1.177)		
	Placebo	157	41 (26.1)							



Results of OlympiA NCT number: NCT02032823										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	References
iDFS	Olaparib	921	134 (14.5)	8.1%			HR= 0.63	(0.50, 0.78)	0.000023	
DCO 2	Placebo	915	207 (22.6)							
iDFS	Olaparib	921	178 (19.3)	8.9%			HR= 0.648	(0.535, 0.784)	NA	Median follow-up 6.1 years with maximum follow-up of 9.6 years
DCO 3	Placebo	915	258 (28.2)							Judy E. Garber San Antonio 2024
iDFS, TNBC	Olaparib	751	142 (18.9)	8.9%			HR=0.652	(0.526, 0.805)	NA	Judy E. Garber San Antonio 2024
DCO 3	Placebo	758	211 (27.8)							
iDFS, HR+/HER2 -	Olaparib	168	35 (20.8)	9.1%			HR=0.681	(0.437, 1.051)	NA	Judy E. Garber San Antonio 2024
DCO 3	Placebo	157	47 (29.9)							
OS DCO2	Olaparib	921	75 (8.1)	3.8%			HR=0.68	(0.47, 0.97)	0.009	



Results of OlympiA NCT number: 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		
	Placebo	915	109 (11.9)							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).	
OS DCO 3	Olaparib	921	107 (11.6)	4.0%			HR=0.725	(0.563, 0.930)			Judy E. Garber San Antonio 2024
	Placebo	915	143 (15.6)								
OS TNBC, DCO 3	Olaparib	751	83 (11.1)	4.1%			HR=0.713	(0.536, 0.944)			Judy E. Garber San Antonio 2024
	Placebo	758	115 (15.2)								



Results of OlympiA NCT number: 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		
OS HR+/HER2 -, DCO 3	Olaparib	168	24 (14.3)	3.5%			HR=0.814	(0.469, 1.404)			Judy E. Garber San Antonio 2024
	Placebo	157	28 (17.8)								



Appendix C. Comparative analysis of efficacy

Results from the comparative analysis of olaparib and pembrolizumab, capecitabine and abemaciclib in the TNBC and HR+ populations are presented in Table 65. The results were not directly applied in the economic analysis but contributed to the decision to perform a cost-minimisation analysis in the comparison with pembrolizumab/capecitabine and abemaciclib. The comparative analysis is further described below.

Table 65. Comparative analysis of studies comparing olaparib to pembrolizumab, capecitabine and abemaciclib for patients with early BC (TNBC and HR+)

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
iDFS TNBC vs EFS non-PCR	OlympiA vs. Keynote-522	NA	NA	NA	HR = 0.91	0.63-1.30	NA	Bucher method	No
iDFS TNBC neo-adj vs EFS non-PCR	OlympiA vs. Keynote-522	NA	NA	NA	HR = 0.91	0.61-1.35	NA	Bucher method	No
OS TNBC vs OS non PCR	OlympiA vs. Keynote-522	NA	NA	NA	HR = 0.94	0.61-1.43	NA	Bucher method	No
OS TNBC neo-adj vs. OS non-PCR	OlympiA vs. Keynote-522	NA	NA	NA	HR = 1.06	0.66-1.68	NA	Bucher method	No
iDFS TNBC vs. DFS TNBC	OlympiA vs CREATE-X	NA	NA	NA	HR=1.12	0.71-1.77	NA	Bucher method	No



Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
OS TNCB vs- OS TNBC	OlympiA vs. CREATE-X	NA	NA	NA	HR=1.37	0.74-2.54	NA	Bucher method	No
iDFS TNBC vs DFS all patients (TNBC)	OlympiA vs. CIBOMA	NA	NA	NA	HR=0.80	0.57-1.11	NA	Bucher method	No
OS TNBC vs OS all patients (TNBC)	OlympiA vs. CIBOMA	NA	NA	NA	HR=0.78	0.50-1.20	NA	Bucher method	No
IDFS HR+ vs. IDFS ITT	OlympiA vs. MonarchE	NA	NA	NA	HR = 1.00	0.63-1.58	NA	Bucher method	No
OS HR+ vs. OS ITT	OlympiA vs. MonarchE	NA	NA	NA	HR = 0.90	0.51-1.61	NA	Bucher method	No



C.1 Differences in definitions of outcomes between studies

The indirect comparison of olaparib and pembrolizumab was performed for the outcomes IDFS/EFS and OS based on the OlympiA and KEYNOTE-522 clinical trials. In KEYNOTE-522, patients were randomised in the neoadjuvant setting compared with post-surgery in OlympiA. The indirect comparison of olaparib and abemaciclib was performed for the outcomes IDFS and OS based on OlympiA and MonarchE clinical trials.

C.2 Method of synthesis

The indirect comparison was performed using the Bucher method, an approach that preserves randomisation and the transitivity of treatment effects, with placebo as the common comparator.

HR estimates for pembrolizumab versus placebo were obtained from KEYNOTE-522 for the ITT population and the non-PCR population [42, 73]. The HR estimates for capecitabine were derived from the TNBC population of the CREATE-X clinical trial and from all patients (TNBC) in the CIBOMA clinical trial [14, 16]. The HR estimates for abemaciclib + ET versus ET alone were obtained from the MonarchE ITT population [74]. For OlympiA, the TNBC and HR+ populations and estimates based on DCO3 were used for the analysis [48].

C.3 Results from the comparative analysis

As presented in Table 66, the indirect comparison of olaparib and pembrolizumab in the TNBC population and when utilising the estimates from the non-PCR population from KEYNOTE-522, the results indicate a numerical benefit for olaparib versus pembrolizumab. Although, the estimate is close to 1 and not statistically significant. When utilising the estimates from the ITT population in KEYNOTE-522, the ITC estimate indicates no difference in IDFS/EFS and a numerical benefit for pembrolizumab in OS. Although, again, the estimates are close to 1 and not statistically significant. The results of the comparative analysis of olaparib and pembrolizumab, indicate no difference between the treatments in the relevant population. Therefore, a cost-minimisation analysis was performed in the comparison of olaparib and pembrolizumab (as described in Section 4).

In the comparison of olaparib and capecitabine both the CREATE-X and CIBOMA clinical trials have been utilized [14, 16]. As indicated in Table 66, using either trial, the HRs derived through the Bucher method are not statistically significant. Although, in the comparison using the CREATE-X clinical trial, the estimates indicate a numerical benefit for capecitabine while using the CIBOMA clinical trial, there is a numerical benefit for olaparib. Due to the estimates not being statistically significant, the results indicate no difference between the treatment arms and therefore, a cost-minimisation analysis is performed for the comparison of olaparib and capecitabine. However, as described in Section 3.3 and presented in Table 66, there is conflicting evidence on the efficacy of



adjuvant capecitabine for TNBC patients. Whereas in the CREATE-X study capecitabine reduced the risk of recurrence and death in TNBC, in the CIBOMA clinical trial, capecitabine did not significantly prolong DFS and there was no statistically significant difference in OS between the study arms. In addition, real-world data indicate that capecitabine-treated TNBC patients with BRCAm tend to have a shorter IDFS, DDFS and OS than those with BRCAwt [17]. In addition, there are differences between the three clinical trials (OlympiA, CREATE-X and CIBOMA) [3, 14, 16]. OlympiA investigated the efficacy in BRCAm high-risk patients, whereas CREATE-X predominantly investigated Asian high-risk patients, and CIBOMA investigates the efficacy in a mixed and high-risk, non-Asian TNBC population. There were also differences in the neoadjuvant regimens as CREATE-X did not include platinum-based agents while OlympiA did. Furthermore, the CREATE-X study used higher dosing compared with the tolerated use in a non-Asian population while the CIBOMA study used dosing aligned with dosing used in non-Asian populations. Therefore, it could be considered conservative assuming no difference in efficacy between olaparib and capecitabine in the patient population relevant for this reimbursed application.

Similar to the comparison with pembrolizumab, the indirect comparison of olaparib and abemaciclib results in estimates close to 1, indicating no difference between the treatment arms. The estimates are not statistically significant. Therefore, a cost-minimisation analysis was performed in the comparison of olaparib and abemaciclib (as described in Section 4). The efficacy of abemaciclib specifically for BRCAm patients is uncertain. There are study results in the metastatic breast cancer setting suggesting that CDK4/6 inhibitors have reduced efficacy in patients with gBRCAm compared to the broader HR+/HER2- breast cancer population. While pivotal clinical trials establishing CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) did not include pre-specified subgroup analyses for gBRCAm patients, retrospective studies and real-world data have consistently indicated poorer outcomes in this subset [60, 75, 76]. In Bruno et al., median OS was 31.4 months for BRCAm patients (n=15) compared with 49.3 months for BRCAwt patients (n=45) (P=0.006). In Collins et al., median OS was 26 months for BRCAm patients (n=85) compared with 37 months for BRCAwt patients (n=774). However, the evidence in the adjuvant HR+/HER2- breast cancer setting is more limited, which means that we cannot adjust for potentially worse outcomes of abemaciclib for BRCAm patients.



Table 66. Results from the comparative analysis of olaparib vs. pembrolizumab and capecitabine for the TNBC population and olaparib vs. abemaciclib for the HR+ population

Population	Endpoint	HR (95% CI)		
		Direct estimate: olaparib vs SoC	Direct estimate: pembrolizumab or abemaciclib vs SoC	ITC: Olaparib vs pembrolizumab, capecitabine or abemaciclib
OlympiA TNBC, KEYNOTE-522 ITT	IDFS/EFS	0.652 (0.526, 0.805)	0.65 (0.51, 0.83)	1.00 (0.73, 1.39)
OlympiA TNBC, KEYNOTE-522 non-PCR	IDFS/EFS	0.652 (0.526, 0.805)	0.72 (0.54, 0.96)	0.91 (0.63, 1.30)
OlympiA TNBC, KEYNOTE-522 ITT	OS	0.713 (0.536, 0.944)	0.66 (0.50, 0.87)	1.08 (0.73, 1.61)
OlympiA TNBC, KEYNOTE-522 non-PCR	OS	0.713 (0.536, 0.944)	0.76 (0.56, 1.05)	0.94 (0.61, 1.43)
OlympiA TNBC, CREATE-X TNBC	IDFS/DFS	0.652 (0.526, 0.805)	0.58 (0.39, 0.87)	1.12 (0.71, 1.77)
OlympiA TNBC, CREATE-X TNBC	OS	0.713 (0.536, 0.944)	0.52 (0.30, 0.90)	1.37 (0.74, 2.54)
OlympiA TNBC, CIBOMA all patients (TNBC)	IDFS/DFS	0.652 (0.526, 0.805)	0.82 (0.63, 1.06)	0.80 (0.57, 1.11)
OlympiA TNBC, CIBOMA all patients (TNBC)	OS	0.713 (0.536, 0.944)	0.92 (0.66, 1.28)	0.78 (0.50, 1.20)
OlympiA HR+, MonarchE ITT	IDFS	0.681 (0.437, 1.051)	0.680 (0.599, 0.772)	1.00 (0.63, 1.58)
OlympiA HR+, MonarchE ITT	OS	0.814 (0.469, 1.404)	0.903 (0.749, 1.088)	0.90 (0.51, 1.61)

C.4 Efficacy – results per [outcome measure]

Not applicable.



Appendix D. Extrapolation

D.1 Extrapolation of IDFS (TP1, TP2 and TP3)

TNBC and HER2-/HR+ patients

D.1.1 Data input

The modelling of IDFS was conducted in four stages:

1. The fitting of parametric survival models to the primary endpoint of IDFS of OlympiA (described in Section D.1.2 to D.1.7).
2. Adjustment for the short- and long-term rate of recurrence in TNBC and HER2-/HR+ disease (TP1 and TP2) (described in Section D.1.7).
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 developing a non-distant recurrence (described in Section D.1.7).
4. The modelling of deaths without recurrence (TP3) using the BRCA-inflated age- and gender-matched background mortality (described in section D.1.7).

D.1.2 Model

Standard parametric models were used to extrapolate IDFS from OlympiA data, the following distributions were used:

- Exponential
- Weibull
- Lognormal
- Log-logistic
- Generalised Gamma
- Gompertz
- Gamma

D.1.3 Proportional hazards

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 DCO3. In the TNBC population of OlympiA, the unadjusted G-T test results was $p=0.0116$ and in the HER2-/HR+ population it was $p=0.0618$. The Schoenfeld and log-cumulative hazards plot showed evidence of non-PH in the form of a non-horizontal log-hazard ratio and non-parallel lines between arms, respectively, in both populations. These results indicate that the PH assumption does not hold for this endpoint. The Schoenfeld and log-cumulative hazards plot for IDFS are presented in Figure 23 and Figure 24 for TNBC and

Figure 25 and Figure 26 for HER2-/HR+.

Figure 23. Schoenfeld residual of IDFS for the placebo and olaparib arms of OlympiA (TNBC)

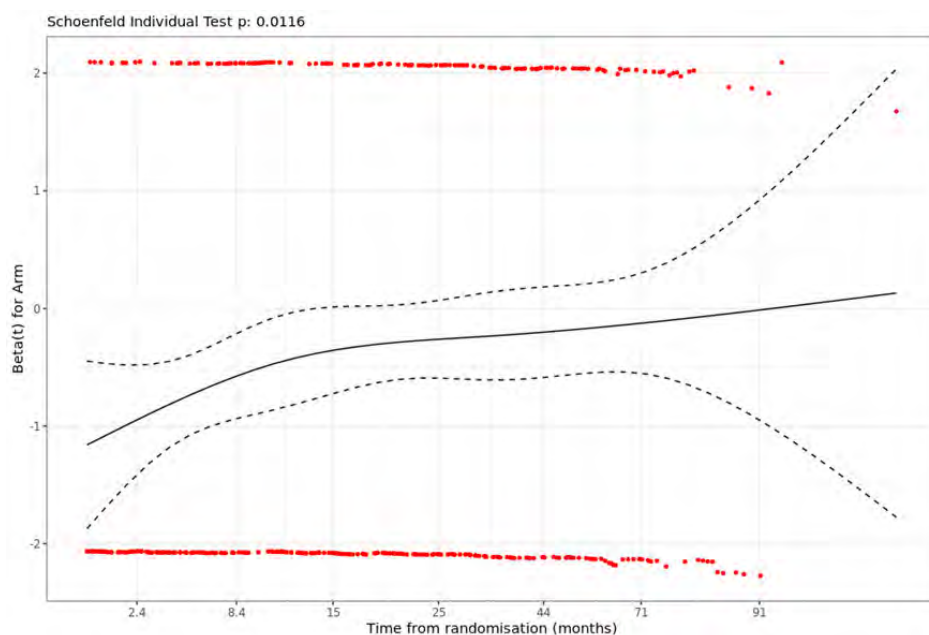


Figure 24. Log-cumulative hazards versus log-time plot of IDFS for the placebo and olaparib arms of OlympiA (TNBC)

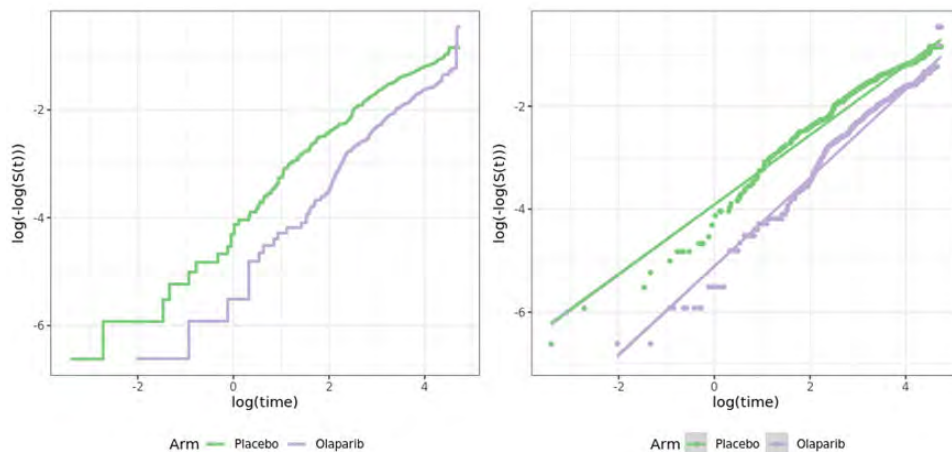




Figure 25. Schoenfeld residual of IDFS for the placebo and olaparib arms of OlympiA (HR+)

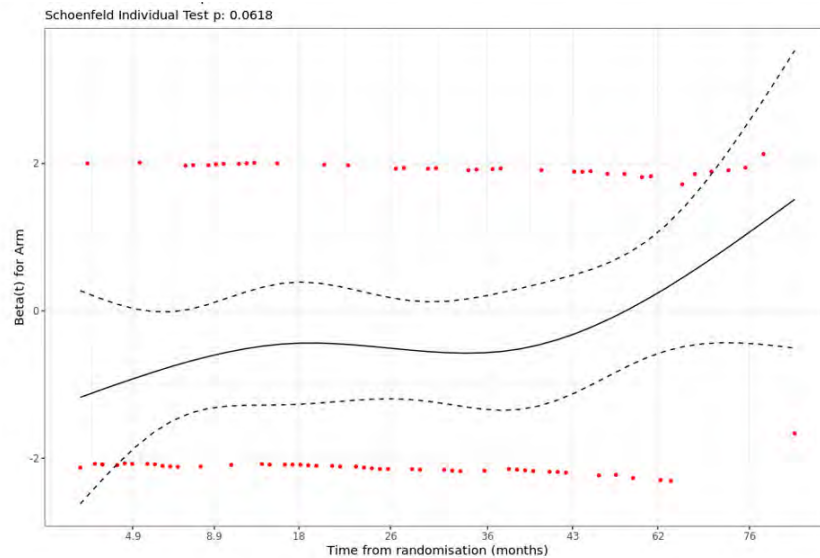
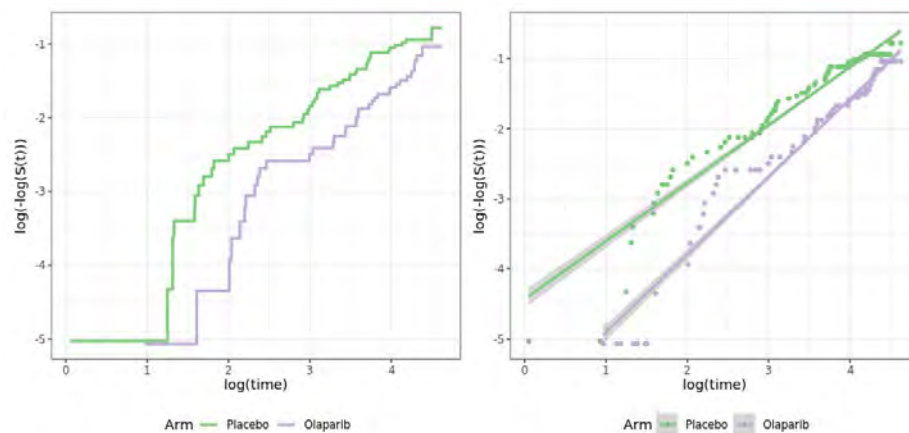


Figure 26. Log-cumulative hazards versus log-time plot of IDFS for the placebo and olaparib arms of OlympiA (HR+)



D.1.4 Evaluation of statistical fit (AIC and BIC)

- 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 Akaike information criteria (AIC) and Bayesian information criteria (BIC) scores, where a lower score indicates improved fit. For the TNBC population, the best fitting models according to AIC score were the: Lognormal (1st in both arms)
- Gompertz (2nd for olaparib, and 4th for placebo) and,
- Generalised Gamma (2nd for placebo and 3rd for olaparib)



- Log-logistic (3rd for placebo and 4th for olaparib)

Similar trends were observed for BIC score with the exception that the third best fitting for olaparib was log-logistic. For both placebo and olaparib, the exponential was the worst fitting on both AIC and BIC score.

Overall, the lognormal, Gompertz, log-logistic and Generalised Gamma were consistently the best fitting functions according to AIC and BIC score across arms (Table 67).

For the HER2-/HR+ population, the best fitting models according to AIC score were the:

- Exponential (1st for olaparib and 7th for placebo)
- Lognormal (2nd for olaparib, and 1st for placebo) and,
- Log-logistic (3rd for olaparib and 4th for placebo)
- Generalized gamma (7th for olaparib and 2nd for placebo)

For olaparib, the same trends were observed for BIC score, while for placebo lognormal was the best fitting model based on the BIC score followed by Gompertz and exponential.

Overall, the lognormal and log-logistic models were consistently the best fitting functions according to AIC and BIC score across arms (Table 67).

Table 67. AIC and BIC values for the parametric survival models fitted to IDFS (TNBC, HR+)

Model	Rank on lowest AIC/BIC by arm	Olaparib (O)		Placebo (P)	
		AIC	BIC	AIC	BIC
TNBC					
Exponential	O: 7/7 P: 7/7	1914.3	1918.9	2657.3	2661.9
Weibull	O: 5/4 P: 5/5	1905.8	1915.0	2594.7	2604.0
Lognormal	O: 1/1 P: 1/1	1900.6	1909.8	2582.7	2592.0
Log-logistic	O: 4/3 P: 3/3	1904.1	1913.4	2590.0	2599.3
Gompertz	O: 2/2 P: 4/4	1902.4	1911.7	2592.4	2601.7
Generalized Gamma	O: 3/6 P: 2/2	1902.6	1916.4	2584.3	2598.2
Gamma	O: 6/5 P: 6/6	1906.6	1915.8	2598.1	2607.4



HER2-/HR+

Exponential	O: 1/1 P: 7/3	462.0	465.2	581.3	584.4
Weibull	O: 5/5 P: 5/6	463.9	470.2	580.3	586.5
Lognormal	O: 2/2 P: 1/1	462.9	469.2	575.9	582.0
Log-logistic	O: 3/3 P: 4/4	463.8	470.1	578.8	584.9
Gompertz	O: 6/6 P: 3/2	464.0	470.3	576.4	582.6
Generalized Gamma	O: 7/7 P: 2/5	464.9	474.2	575.9	585.1
Gamma	O: 4/4 P: 6/7	463.9	470.2	580.9	587.0

D.1.5 Evaluation of visual fit

The fit of the models to the Kaplan-Meier plot for IDFS in the TNBC population is shown in Figure 27 (olaparib) and Figure 28 (placebo), and for the HER2-/HR+ population in Figure 29 (olaparib) and Figure 30 (placebo). For the olaparib arm, in both TNBC and HER2-/HR+ patients, all models provided a reasonable prediction of the Kaplan-Meier probabilities for IDFS up to the end of study follow-up. 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 for both the TNBC and HER2-/HR+ populations and was found to overestimate survival in the first years and underestimate placebo survival at later time points.

Figure 31 presents the observed data for olaparib and placebo from OlympiA (DCO3) and all extrapolations for each arm over the full-time horizon.



Figure 27. Fit of parametric survival models to the Kaplan-Meier data for IDFS for olaparib in OlympiA (TNBC)

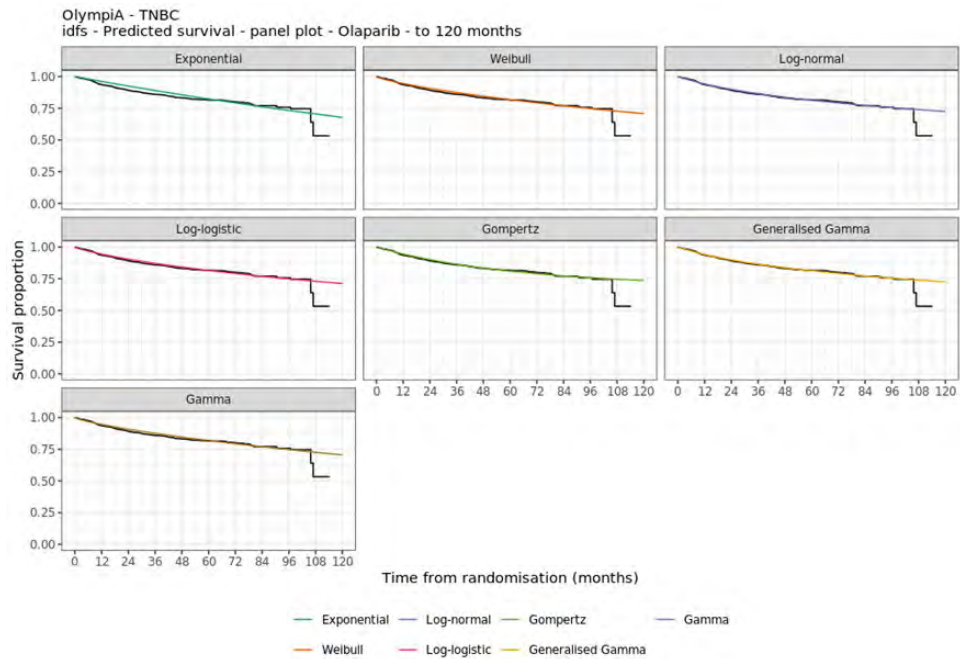


Figure 28. Fit of parametric survival models to the Kaplan-Meier data for IDFS for placebo in OlympiA (TNBC)

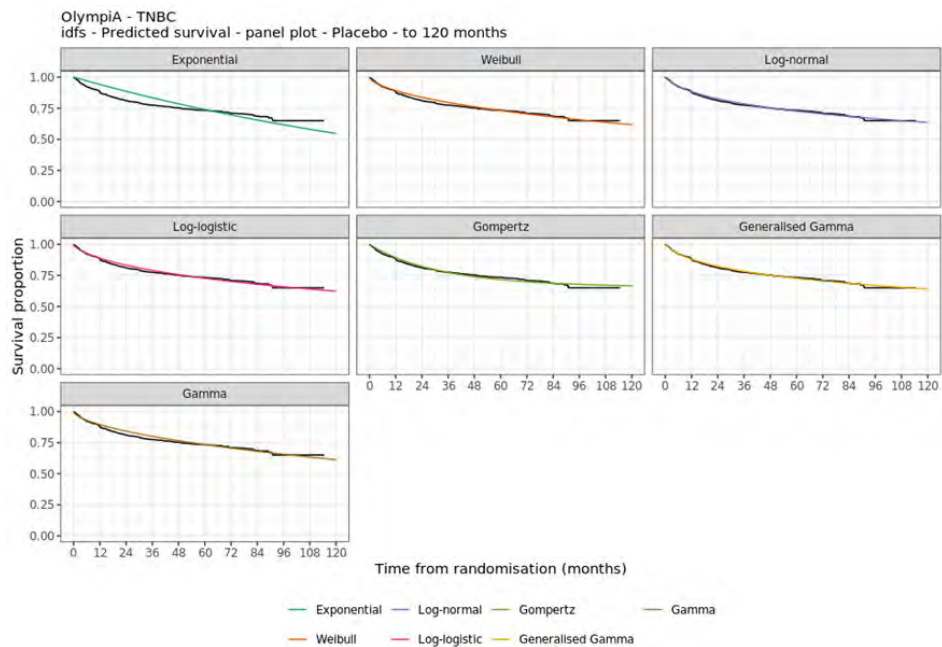




Figure 29. Fit of parametric survival models to the Kaplan-Meier data for IDFS for olaparib in OlympiA (HR+)

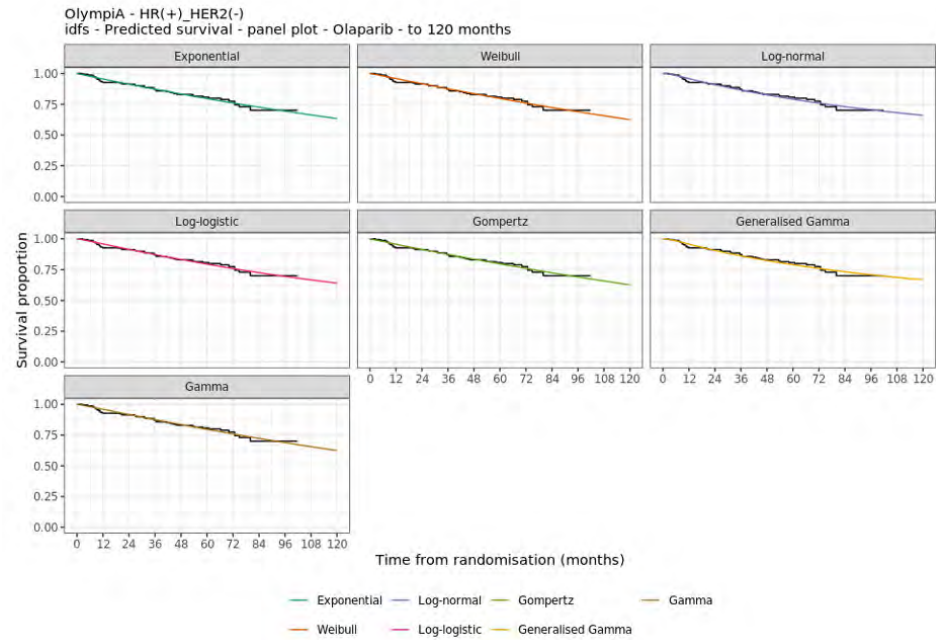


Figure 30. Fit of parametric survival models to the Kaplan-Meier data for IDFS for placebo in OlympiA (HR+)

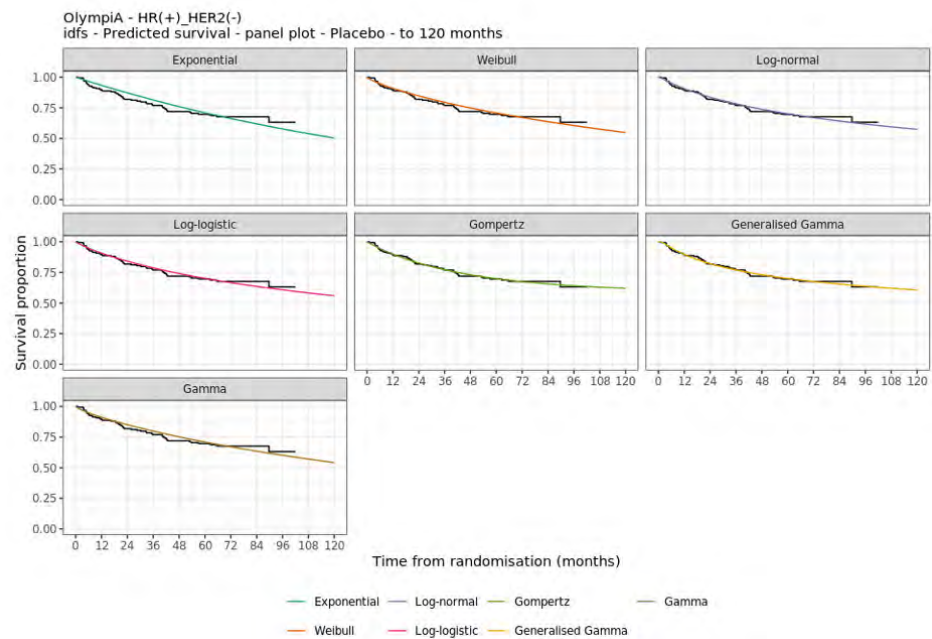
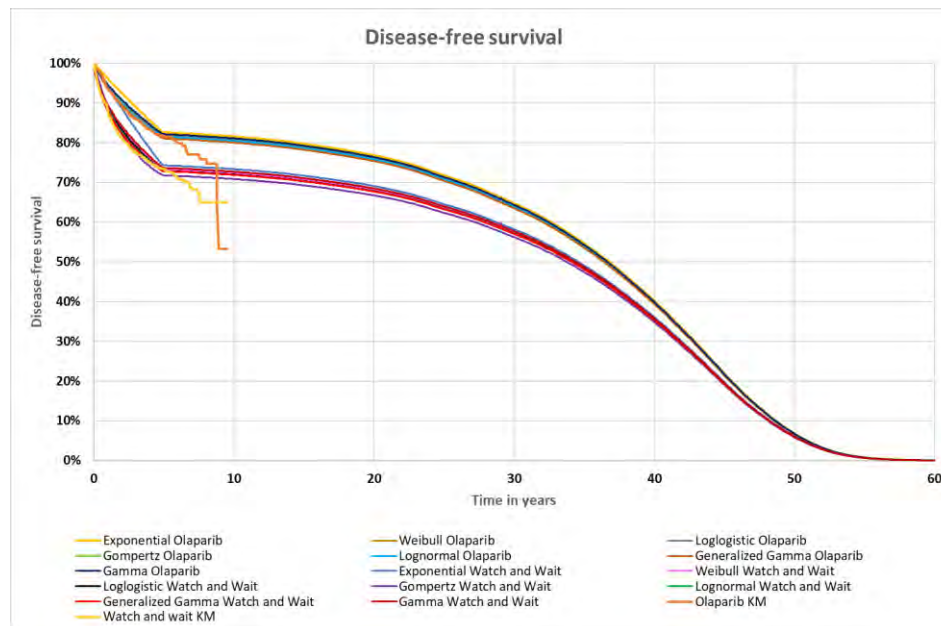




Figure 31. Observed time-to-event data and extrapolations for olaparib and watch and wait over the time horizon (adjusted for long-term survival)



D.1.6 Evaluation of hazard functions

For the olaparib arm, the Gompertz and lognormal models provided the closest prediction of the hazard rates in the TNBC population. This is in line with the rankings of the best fitting models based on AIC and BIC. All models predicted either an approximately constant or decreasing hazard over time.

In the comparison of modelled and observed hazard rates, the Gompertz model yielded the closest prediction of the observed hazards during the first 4 years of follow-up for the placebo arm in the TNBC population. After 4 years, the observed hazard rate is highly uncertain due to study attrition. 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. The long-term trend in hazard rate for placebo was, similar to olaparib, with rates that are predicted to be approximately constant or decreasing over time.

Among HER2-/HR+ patients, the lognormal model provided the closest prediction of the hazard rates for both the olaparib and placebo arms (

Figure 34). This is also in line with the rankings of the best fitting models based on AIC and BIC.



Figure 32. Predicted hazard versus the observed smoothed hazards (dotted line) for olaparib in TNBC population (OlympiA)

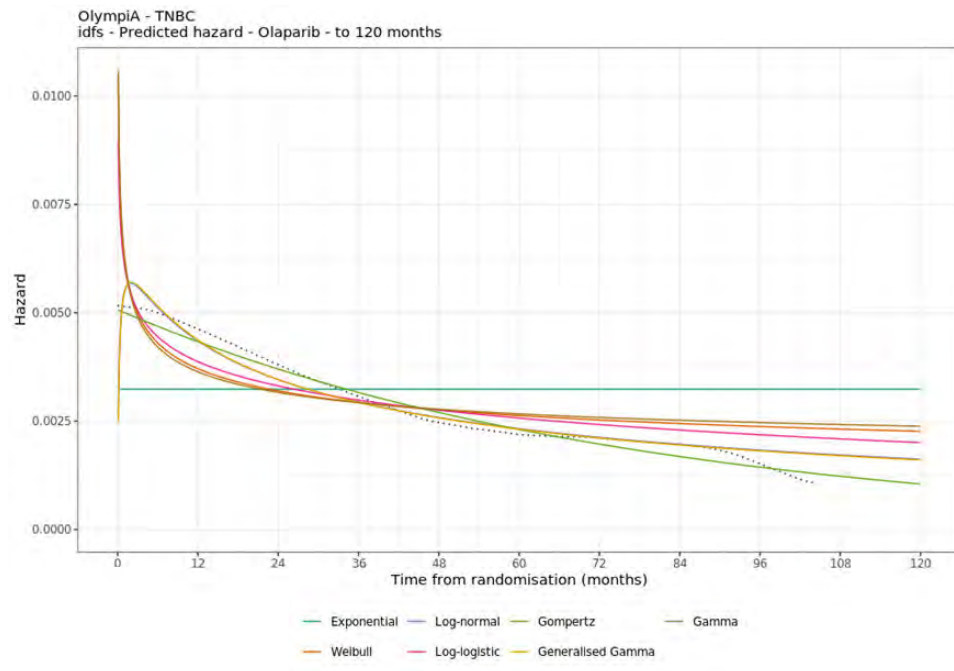


Figure 33. Predicted hazard versus the observed smoothed hazards (dotted line) for placebo in TNBC population (OlympiA)

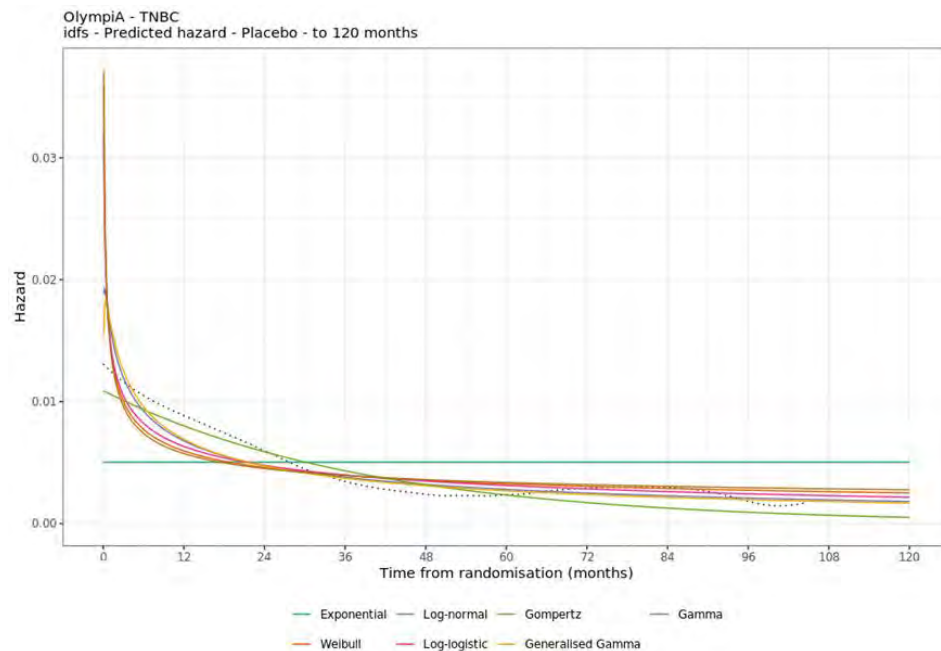
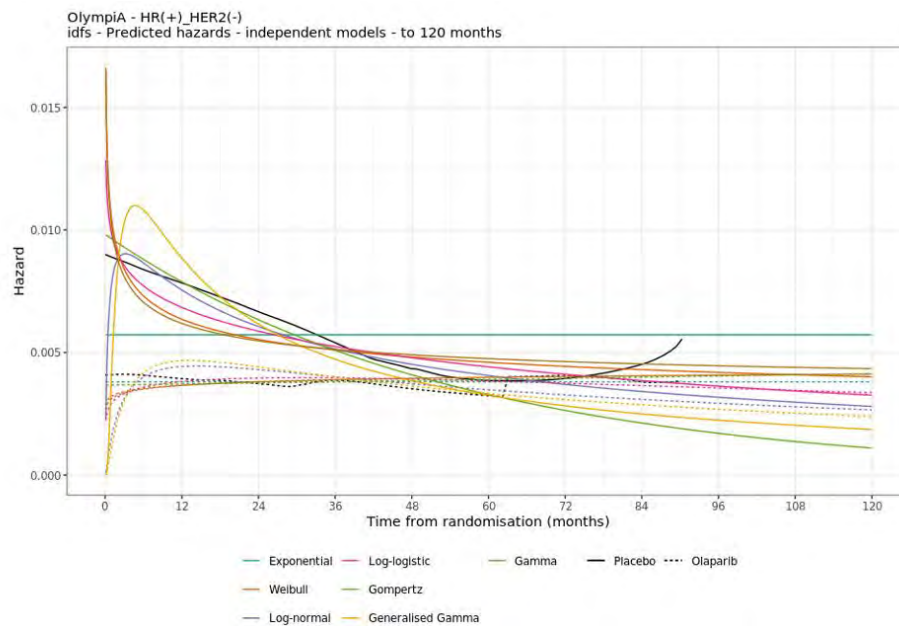




Figure 34. Predicted hazard versus the observed smoothed hazards for olaparib and placebo in HR+ population (OlympiA)



D.1.7 Validation and discussion of extrapolated curves

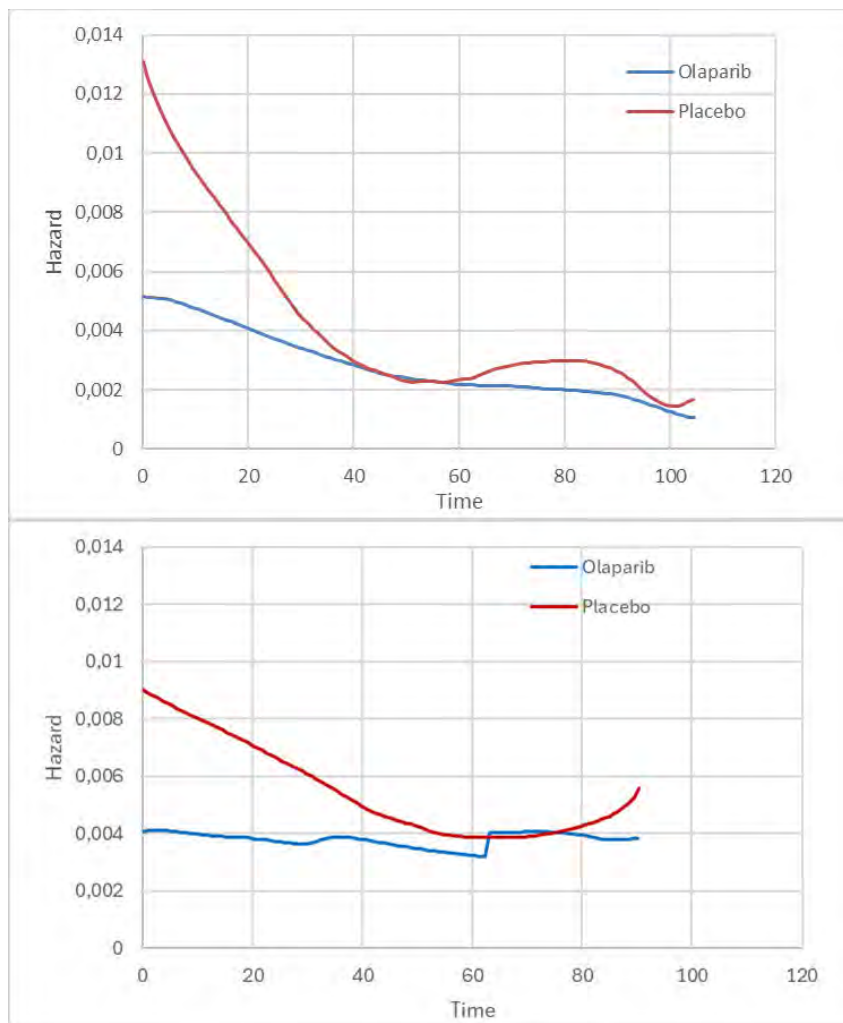
Adjustments for the short- and long-term risk of recurrence in TNBC (TP1 and TP2)

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

As the follow-up of OlympiA 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 in the olaparib and placebo arms were plotted over time for TNBC and HER2-/HR+. 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 around 43 months in the TNBC population. For the HER2-/HR+ patients, the curves are more uncertain but seem to start converging around the same time. Beyond 43 months, the hazard rate is uncertain, although the trends suggest a similar rate of recurrence or death for olaparib when compared with 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 rate crossed, the hazard rates are assumed the same across arms and no further benefit of treatment is assumed.



Figure 35. Smoothed hazard plots for IDFS by treatment arm for TNBC (top), HR+ (bottom)



Beyond the follow-up, patients with TNBC experience a plateauing of the recurrence rate after 5-7 years post-diagnosis. This was also confirmed by Danish clinical experts, who also suggested that recurrence after 4-5 years is very rare for TNBC patients [39]. To capture the patterns of long-term recurrence for TNBC and due to the visual fit to the IDFS data from latest data cut in the clinical trial, 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 7 of the time horizon in the base case analysis. This is consistent with data from long-term studies in early breast cancer indicating that the risk from year 5 is low but not 0 [35-38]. This assumption was tested in the sensitivity analysis to the base case using alternative time points of 5, 10 and 15 years. Beyond year 7, 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).

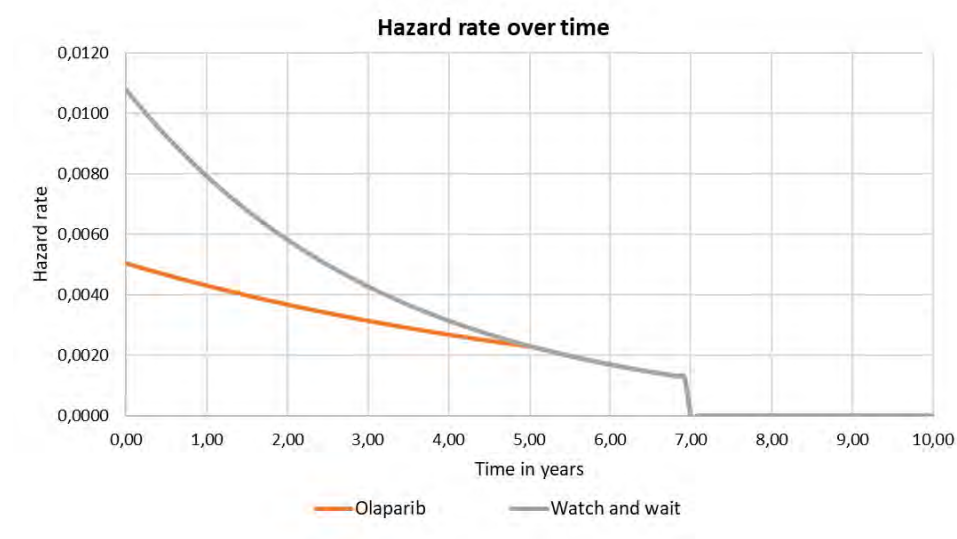
For the Gompertz model for TNBC patients, the hazard rates are predicted to converge at 5 years which is reasonable compared with the observed hazard in Figure 35. Given the evidence about the plateauing of the recurrence rate among TNBC patients, as described above, the hazard rate for non-metastatic and metastatic recurrence is set to zero at



year 7. An illustration of the adjusted hazard based on the Gompertz model for both treatment arms is presented in Figure 36.

For patients with HER2-/HR+ disease, the risk of recurrence was assumed to remain throughout the lifetime horizon of the model.

Figure 36. Model plots showing the hazard rates for IDFS per arm over time (TNBC)



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 68)[29, 48].

At DCO3, 178 patients (19.3% of the total cohort) in the olaparib arm and 258 patients (28.2% of the total cohort) in the placebo arm experienced an IDFS event. Of the 178 patients with an IDFS event in the olaparib arm, 48 had experienced a non-distant recurrence comprising 11 regional recurrences, 11 local recurrences and 26 contralateral invasive breast cancer events. The conditional probability of an IDFS event being a non-distant recurrence for olaparib was estimated at 27.0%. For the placebo arm, 70 of 258 patients with IDFS events had experienced a non-distant recurrence, comprising 22 regional recurrences, 12 local recurrences and 36 contralateral invasive breast cancer events. The associated probability of an IDFS event being a non-distant recurrence for placebo was 27.1%.



Table 68. Summary of type of first IDFS event and estimation of probability of a non-distant recurrence in OlympiA (DCO3)

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, TP3	Any IDFS event	178 (19.3%)	258 (28.2%)	436
	Regional (ipsilateral) recurrence	11 (1.2%)	22 (2.4%)	33
	Local (ipsilateral) recurrence	11 (1.2%)	12 (1.3%)	23
	Contralateral invasive breast cancer	26 (2.8%)	36 (3.9%)	62
Probability of any IDFS event being a non-distant recurrence		27.0% (48/178)	27.1% (70/258)	27.1% (118/436)
Metastatic recurrence (TP2)	Distant CNS	26 (2.8%)	40 (4.4%)	66
	Distant non-CNS recurrence	80 (8.7%)	109 (11.9%)	189
	New primary cancers	20 (2.2%)	37 (4.0%)	57
(TP3)	Deaths without IDFS	4 (0.4%)	2 (0.2%)	6
Probability of any IDFS event being a distant recurrence, new cancer, or death		73.0% (130/178)	72.9% (188/258)	72.9% (318/436)

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; 27.0% for olaparib and 27.1% for placebo. The conditional probability was set to 27.1% based on the total numbers of IDFS (N=436) and non-distant recurrence (n=118) events across arms. The corresponding conditional probability of a distant recurrence was 72.9%. 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 (see Appendix Q). This leads to small differences in the types of recurrences experienced by patients in each arm of the comparison.

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, [53] 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 37 shows the all-cause mortality curve for the general population and with adjustment for BRCA status and Figure 38 shows the cause-specific hazard rate for TP3.

Figure 37. The all-cause mortality curve from the general population (female, aged 43 years at baseline) and the general population mortality curve adjusted for BRCA status

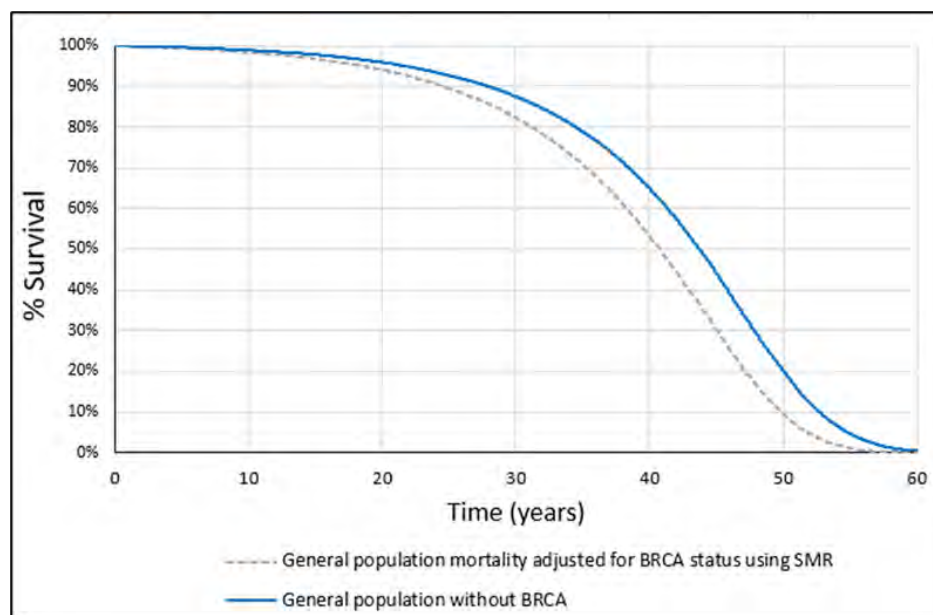
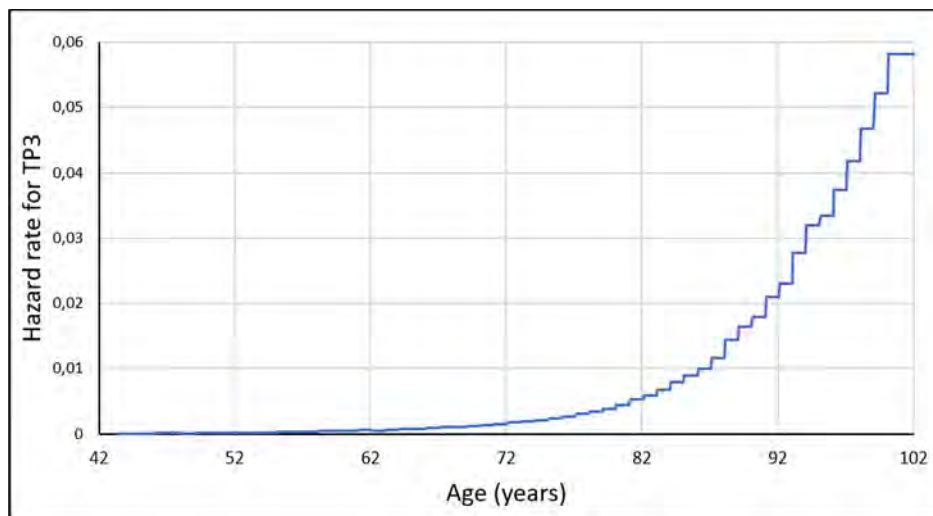




Figure 38. Cause-specific hazard rate for all-cause mortality in persons with BRCA mutation



Overall model fit and plausibility of extrapolations

In summary, the Gompertz and lognormal models consistently provide the best fit to the IDFS data in the TNBC population in OlympiA and are therefore considered the primary candidate models for the base case. The log-logistic and Generalized 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. However, it was the worst fitting model according to AIC and BIC in both arms. The Weibull and Gamma distributions were consistently amongst the worst fitting models based on statistics and visual fit of the observed hazard for TNBC patients in OlympiA. For the HER2-/HR+ population, the lognormal model was the best fitting model in the placebo arm and the second-best fitting in the olaparib arm. The exponential model was the best fitting in the olaparib arm but the 7th best fitting in the placebo arm, while the second-best fitting model for placebo was Generalized Gamma but this was the 7th best fitting in the olaparib arm. Given the preference of utilizing the same model in both treatment arms and since the lognormal model provided a good fit to the data in both treatments it was considered an appropriate base case model in the HER2-/HR+ population.

The landmark survival probabilities for IDFS in patients with TNBC and HER2/HR+ disease as predicted by the cost-effectiveness model are presented for olaparib and placebo in Table 69. These estimates were obtained using the survival models for IDFS with adjustment for short- and long-term rate of recurrence and the modelling of death without recurrence as described in the sections above. As presented in the table, the long-term IDFS predicted in the TNBC population, was similar between the models in both treatment arms. Furthermore, in comparison with the external evidence at 5 and 10 years, all models in the watch and wait arm yielded reasonable estimates. When comparing the four models with the best fit according to AIC (lognormal, Gompertz, log-logistic and Generalised Gamma), there was only marginal differences in the long-term predictions. Therefore, the decision was guided by the predictions of the observed hazard rates, where the Gompertz model yielded the closest prediction in both



treatment arms. For HER2-/HR+ population the models yielded some differences in the long-term estimates in each treatment arm. For placebo, the Gompertz model resulted in the estimates closest to the external data although the estimates in year 15 and year 20 were somewhat overestimated. Given that a cost-minimisation analysis is conducted for HER2-/HR+ patients and the efficacy of abemaciclib is assumed equal to olaparib, the curve selection is of less importance for this patient population. Therefore, the base case was set to the lognormal model given the goodness of fit statistics and visual fit of the model as described above.



Table 69. Comparison of model fit to observed data for IDFS in TNBC and HR+ patients with olaparib and watch and wait (includes short- and long-term risk adjustment)

Arm/analysis	IDFS model	1	2	3	4	5	10	15	20	40	50	57
TNBC												
Olaparib	Observed	93.5	89.3	86.0	83.1	81.6						
	Exponential	96.1	92.3	88.7	85.2	81.8	74.8	73.4	70.9	38.3	7.3	0.3
	Weibull	94.4	90.5	87.1	84.1	81.2	75.6	74.1	71.7	38.7	7.3	0.3
	Log-logistic	94.3	90.3	86.8	83.8	81.0	75.5	74.1	71.6	38.6	7.3	0.3
	Lognormal	94.1	89.7	86.2	83.3	80.7	75.8	74.4	71.9	38.8	7.4	0.3
	Gompertz	94.4	89.9	86.1	83.1	80.4	76.2	74.8	72.3	39.0	7.4	0.3
	Generalised Gamma	93.7	89.3	85.8	82.9	80.3	75.4	74.0	71.5	38.6	7.3	0.3
	Gamma	94.5	90.6	87.3	84.2	81.3	75.6	74.1	71.7	38.7	7.3	0.3
Watch and wait	Observed	88.2	81.3	77.5	75.3	73.5						
	Exponential	94.0	88.4	83.1	78.1	73.4	64.3	63.1	61.0	32.9	6.3	0.3
	Weibull	89.1	83.6	79.4	75.8	72.6	66.7	65.5	63.3	34.1	6.5	0.3
	Log-logistic	88.8	83.1	78.8	75.2	72.2	66.6	65.4	63.2	34.1	6.5	0.3
	Lognormal	88.3	82.4	78.2	74.9	72.1	67.1	65.9	63.7	34.4	6.5	0.3
	Gompertz	89.2	82.1	77.1	73.6	71.1	67.4	66.1	63.9	34.5	6.6	0.3
	Generalised Gamma	88.0	82.1	78.0	74.8	72.1	67.3	66.1	63.8	34.5	6.5	0.3
	Gamma	89.4	84.0	79.8	76.2	72.9	66.7	65.5	63.3	34.2	6.5	0.3
External data	POSH study, TNBC subset, Copson et al [77]		85.9			77.02	71.15					
HER2/HR+												
Olaparib	Observed	93.5	89.3	86.0	83.1	81.6						



	Exponential	95.4	91.1	86.9	82.9	79.0	62.2	48.6	37.4	8.1	1.0	0.0
	Weibull	95.8	91.5	87.2	83.1	79.1	61.3	47.8	37.3	9.3	1.2	0.0
	Log-logistic	95.8	91.3	86.9	82.8	78.9	62.9	51.8	43.4	15.5	2.5	0.1
	Lognormal	95.7	90.7	86.2	82.1	78.5	64.7	54.9	47.1	18.0	3.0	0.1
	Gompertz	95.5	91.2	87.1	83.0	79.3	69.6	65.6	62.5	33.5	6.4	0.3
	Generalised Gamma	95.7	90.4	85.9	81.9	78.4	67.0	59.9	54.0	24.5	4.4	0.2
	Gamma	95.8	91.5	87.3	83.1	79.1	61.3	46.9	35.5	7.5	0.9	0.0
Watch and wait	Observed	88.2	81.3	77.5	75.3	73.5						
	Exponential	93.2	87.0	81.1	75.6	70.4	49.4	34.4	23.6	3.2	0.3	0.0
	Weibull	90.8	84.5	79.2	74.5	70.3	53.8	41.9	32.7	8.1	1.1	0.0
	Log-logistic	90.6	83.9	78.4	73.8	69.7	54.9	45.2	37.9	13.6	2.2	0.1
	Lognormal	90.5	83.4	77.9	73.4	69.6	56.3	47.7	40.8	15.6	2.6	0.1
	Gompertz	89.8	82.4	76.9	72.7	69.4	60.8	57.4	54.7	29.3	5.6	0.2
	Generalised Gamma	89.5	81.9	76.7	72.7	69.6	59.5	53.1	47.9	21.7	3.9	0.2
	Gamma	91.0	84.8	79.5	74.8	70.4	53.1	40.4	30.5	6.4	0.8	0.0
External data	Meta-analysis of long-term survival with adjuvant ET; subgroup with 4 or more nodes [78]					78%*	64%*	55%*	48%*			

*estimated based on 1-risk of disease recurrence (22%, 36%, 45%, 52%)



D.1.8 Adjustment of background mortality

See description in Section D.1.7

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

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, [53] 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 37 shows the all-cause mortality curve for the general population and with adjustment for BRCA status and Figure 38 shows the cause-specific hazard rate for TP3

D.2 Extrapolation of non-metastatic recurrence (TP4 and TP5)

D.2.1 Data input

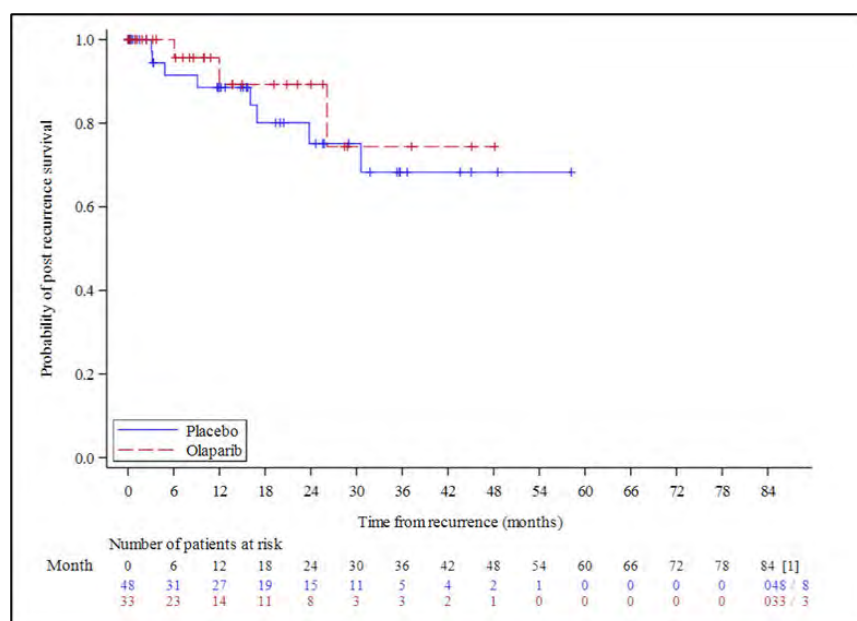
The transition probabilities for non-metastatic to metastatic breast cancer (TP4) and non-metastatic breast cancer to death (without metastatic diagnosis) (TP5) were modelled using data from the OlympiA trial.

At the interim OS analysis of OlympiA, 118 patients had experienced a non-metastatic recurrence. Of the 118 patients with non-metastatic recurrence, 25 had experienced a distant metastatic recurrence and 5 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 (Figure 39). 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 in the olaparib arm (Figure 63). 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 [39].

Figure 39. Post-recurrence survival of patients who had locoregional or contralateral invasive breast cancer in OlympiA (DCO2)



D.2.2 Model

A series of parametric survival models were fitted to the cause-specific time to event data for TP4 and TP5. The parametric models used for extrapolation were the following:

- Exponential
- Weibull
- Lognormal
- Log-logistic
- Generalised Gamma
- Gompertz
- Gamma



D.2.3 Proportional hazards

Not applicable.

D.2.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC statistics for each model, are shown in Table 70. For TP4 (-> mBC), the AIC and BIC scores favoured the exponential (best fitting according to AIC and BIC) and log-logistic (2nd best fitting according to AIC and BIC). For TP5 (-> death), the Generalised Gamma was the best fitting model according to AIC and the exponential was best fitting according to BIC.

Table 70. AIC and BIC values for the parametric survival models fitted to data on the time from non-distant metastatic recurrence to distant metastatic and time from non-distant metastatic to death (ITT) [TP4 and TP5]

Model	Rank on lowest AIC (A) and BIC (B)	Pooled treatment arms	
		AIC	BIC
Time from non-metastatic recurrence to distant metastatic recurrence (death censored) [TP4]			
Exponential	A: 1/7; B: 1/7	279.9	282.7
Weibull	A: 5/7; B: 5/7	281.7	287.2
Lognormal	A: 3/7; B: 3/7	281.5	287.1
Log-logistic	A: 2/7; B: 2/7	281.2	286.8
Gompertz	A: 6/7; B: 6/7	281.9	287.4
Generalised Gamma	A: 7/7; B: 7/7	283.2	291.5
Gamma	A: 4/7; B: 3/7	281.6	287.1
Time from non-metastatic recurrence to death [TP5]			
Exponential	A: 2/7; B: 1/7	76.0	78.8
Weibull	A: 6/7; B: 5/7	77.6	83.1
Lognormal	A: 4/7; B: 3/7	76.9	82.4
Log-logistic	A: 5/7; B: 4/7	77.5	83.0
Gompertz	A: 3/7; B: 2/7	76.1	81.6
Generalised Gamma	A: 1/7; B: 7/7	75.7	84.0
Gamma	A: 6/7; B: 5/7	77.6	83.1

D.2.5 Evaluation of visual fit

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 40 and



Figure 42, respectively. Observed time-to-event data and extrapolations of non-mBC to mBC (TP4) and non-mBC to death (TP5) for olaparib and watch and wait over the time horizon are presented in Figure 41 and Figure 43, 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.

Figure 40. Fit of parametric survival models to the Kaplan-Meier data for non-metastatic to metastatic recurrence in OlympiA, pooled arms (TP4)

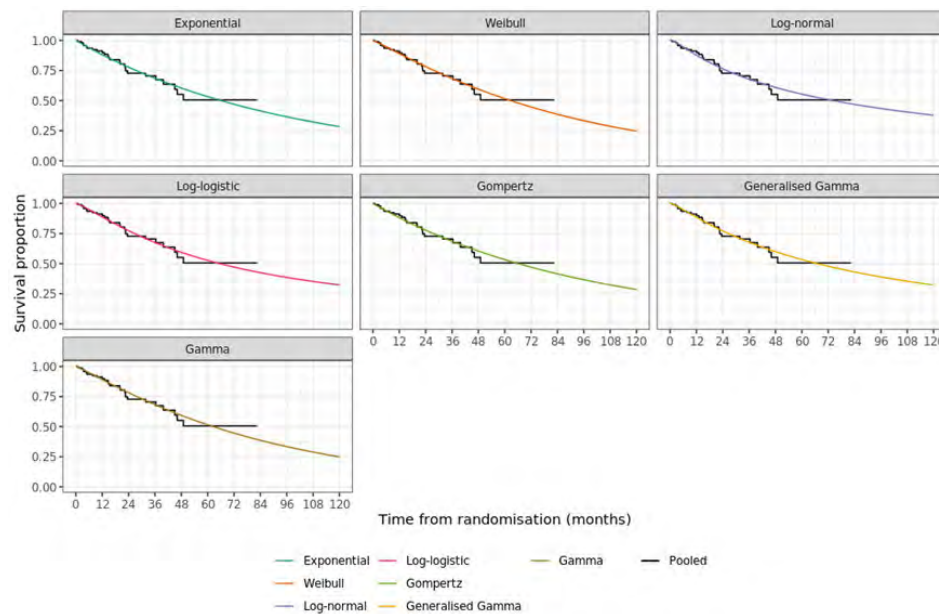


Figure 41. Observed time-to-event data and extrapolations of non-mBC to mBC (TP4) for olaparib and watch and wait over the time horizon

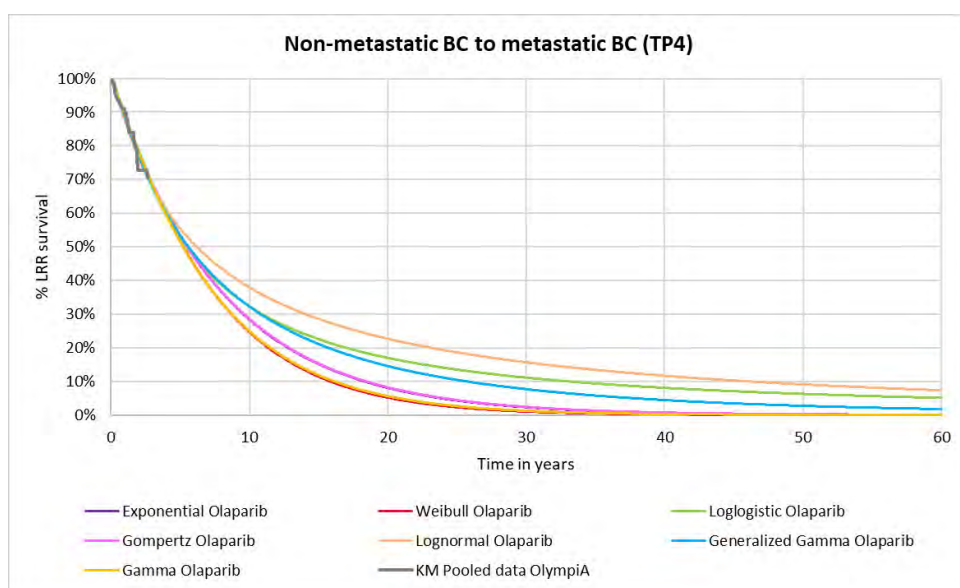




Figure 42. Fit of parametric survival model to the Kaplan-Meier data for non-metastatic to death in OlympiA, pooled arms (TP5)

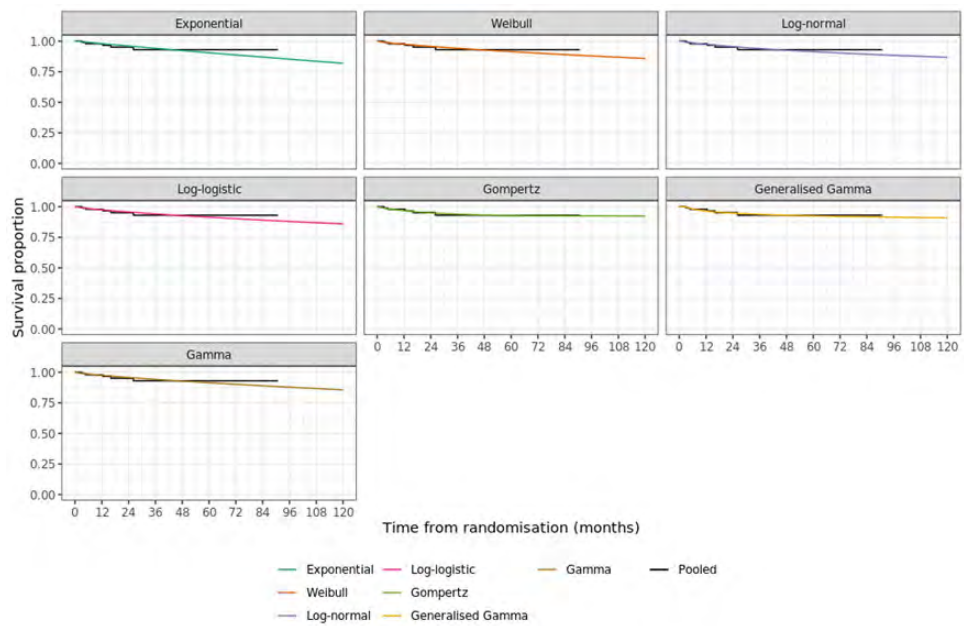
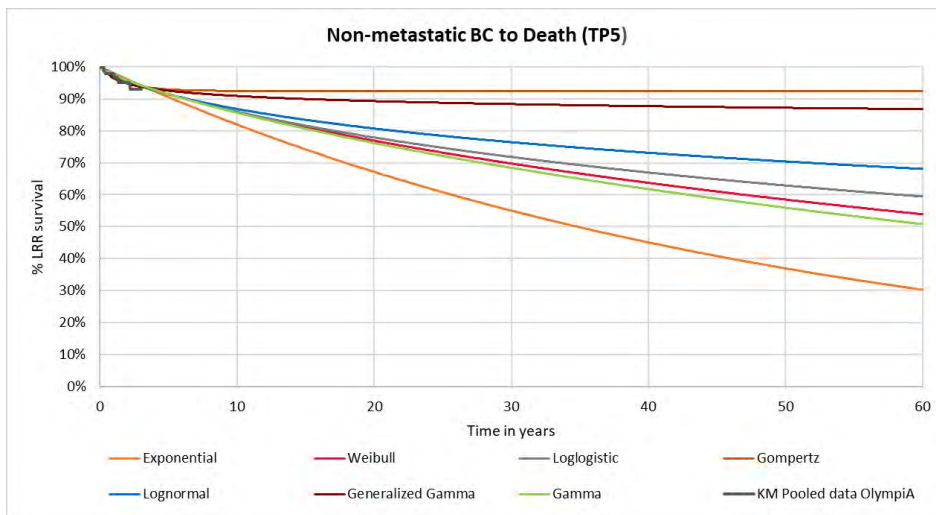


Figure 43. Observed time-to-event data and extrapolations of non-mBC to death (TP5) for olaparib and watch and wait over the time horizon



D.2.6 Evaluation of hazard functions

Figure 44 and Figure 45 present the predicted hazard versus the observed hazard for non-metastatic to mBC (TP4) and non-mBC to death (TP5). For TP4, the Weibull and



Gamma distributions fit the observed hazard well over the first year while the log-logistic have a better fit from about 24 months. For TP5, Gompertz or Generalised Gamma have the best visual fit to the observed data.

Figure 44. Predicted hazard versus the observed smoothed hazards by model for non-metastatic to metastatic disease (OlympiA, pooled across treatment arms) (TP4)

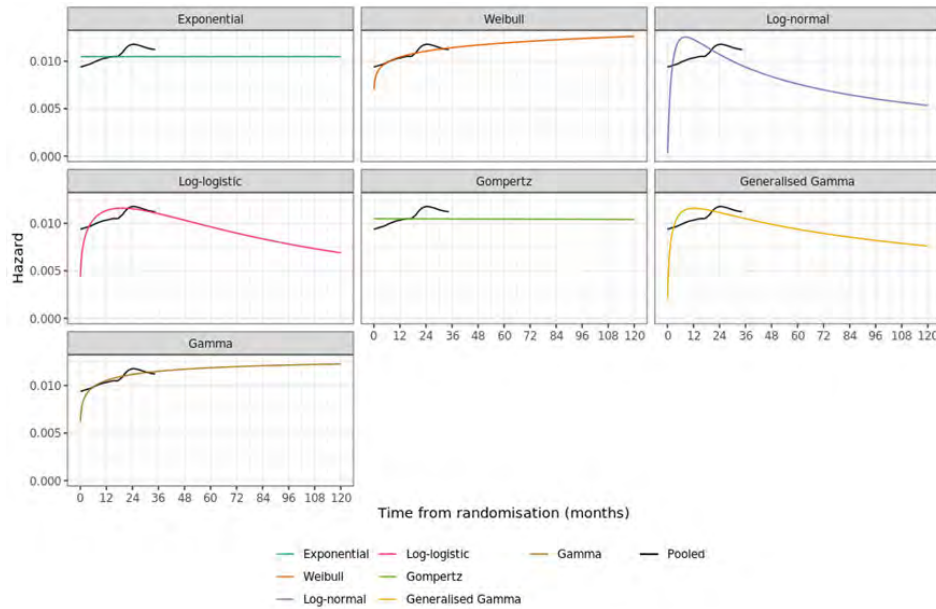
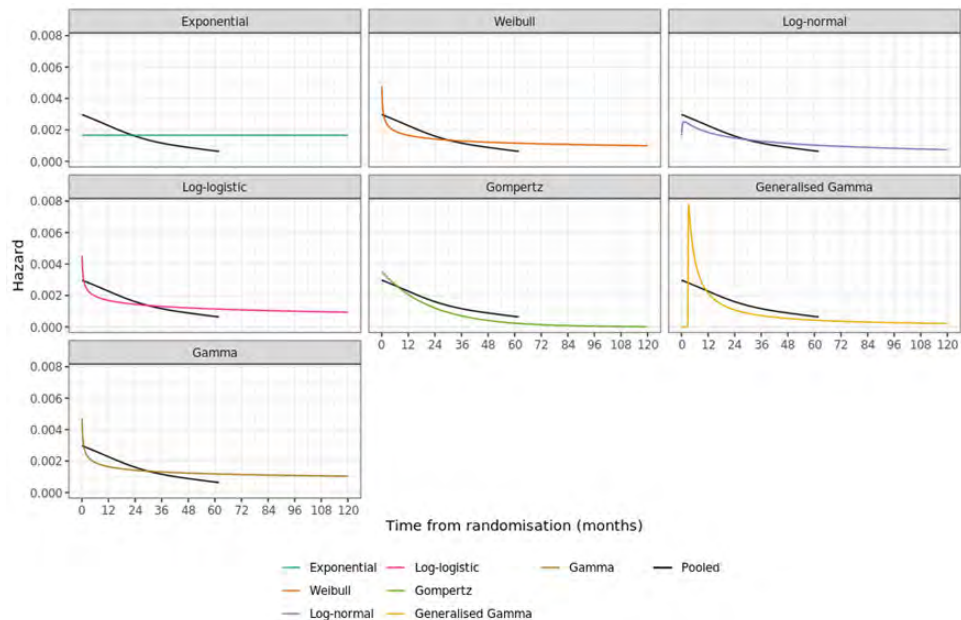


Figure 45. Predicted hazard versus the observed smoothed hazards by model for non-metastatic to death (OlympiA, pooled across treatment arms) (TP5)



D.2.7 Validation and discussion of extrapolated curves



For TP4, most survival models accurately predicted the Kaplan-Meier probabilities for non-metastatic to metastatic disease. 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 log-logistic models. Guided by the goodness of fit statistics, the log-logistic 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 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=5). 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.

D.2.8 Adjustment of background mortality

Not applicable.

D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

D.2.10 Waning effect

Not applicable.

D.2.11 Cure-point

Not applicable.

D.3 Extrapolation of early onset mBC to death (TP6)

D.3.1 Data input

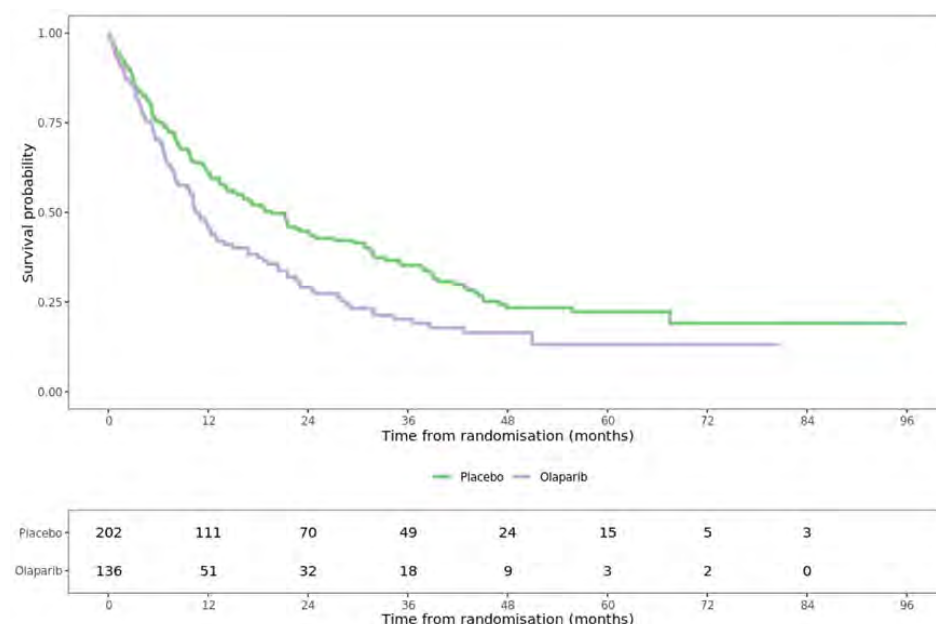
The transition probabilities for 'early onset mBC' to 'Death' (TP6) were modelled using data on the time from distant metastatic recurrence to death in the OlympiA trial. These data represent the survival outcomes of patients who had distant recurrence during the approximately 6.1 years of follow-up in OlympiA at DCO3.

At DCO3 of OlympiA, 136 patients from the olaparib arm and 202 patients from the placebo arm had experienced a distant metastatic recurrence. In total, there were 96 deaths after metastatic recurrence in the olaparib arm and 133 deaths after metastatic recurrence in the placebo arm. The median time to death was 10.5 [95% confidence



interval 8.0 to 14.0] months in the olaparib arm versus 19.6 [95% confidence interval 14.0 to 24.9] in the placebo arm. The Kaplan-Meier plot for post-distant metastatic recurrence survival by arm is shown in Figure 46.

Figure 46. Kaplan-Meier plot of distant metastatic recurrence survival by arm in OlympiA (ITT)



The median survival after distant recurrence in the olaparib arm (median 10.5 months) was numerically shorter than for placebo (median 19.6 months). This differences 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 randomized trials have demonstrated a median OS benefit for PARP inhibitors versus chemotherapy in BRCA-mutated mBC [50, 79].

For the base case, the transition probabilities for 'early onset mBC' to 'Death' (TP6) were modelled separately by treatment arm using data from the OlympiA trial. This approach was validated by Danish clinical experts [39]. 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.

D.3.2 Model

A series of parametric survival models were fitted to the time to event data for TP6. The parametric models used for extrapolation were the following:

- Exponential

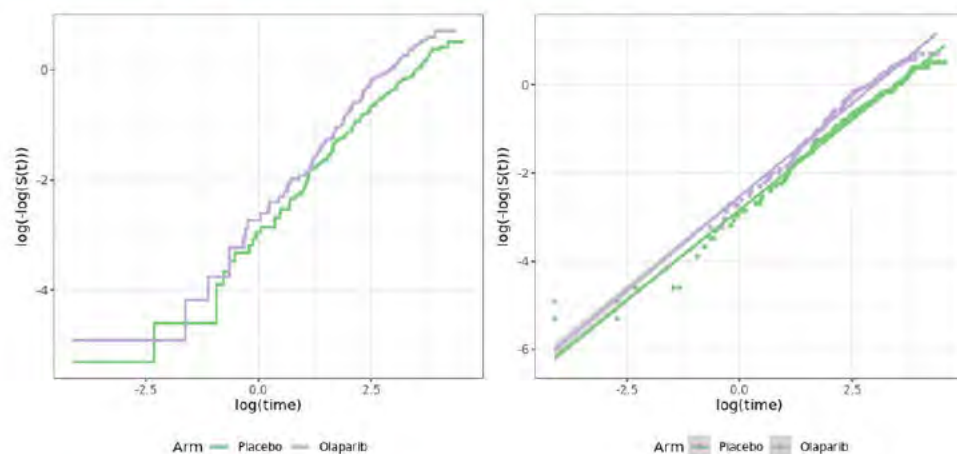


- Weibull
- Lognormal
- Log-logistic
- Generalised Gamma
- Gompertz
- Gamma

D.3.3 Proportional hazards

Due to evidence of non-PH from the overlapping of Kaplan-Meier probabilities across study arms at the beginning of the survival curve for TP6 (Figure 46), 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 survival curves (Figure 47).

Figure 47. Log-cumulative hazards versus log-time plot of n post-metastatic recurrence for the placebo arm and olaparib arms of OlympiA (ITT population)



D.3.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC statistics for the fitted models are shown in Table 71. For the olaparib arm, the Gompertz followed by log-logistic was the best fitting on both AIC and BIC. For the placebo arm, the log-logistic was the best fitting on both AIC and BIC.

Table 71. AIC and BIC values for the parametric survival models fitted to data on time from metastatic recurrence to death

Model	Rank on lowest AIC/BIC by arm	Olaparib (O)		Placebo (P)	
		AIC	BIC	AIC	BIC
Exponential	O: 7/6 P: 7/7	781.2	784.1	1199.6	1202.9



Weibull	O: 4/3 P: 4/3	776.2	782.1	1189.3	1195.9
Lognormal	O: 5/4 P: 6/6	777.4	783.2	1191.9	1198.6
Log-logistic	O: 2/2 P: 1/1	770.2	776.0	1186.0	1192.6
Gompertz	O: 1/1 P: 1/2	769.1	775.0	1186.0	1192.7
Generalised Gamma	O: 3/5 P: 3/5	774.8	783.5	1188.5	1198.5
Gamma	O: 6/7 P: 5/4	778.4	784.2	1191.5	1198.1

D.3.5 Evaluation of visual fit

The fit of the models to the Kaplan-Meier probabilities for TP6 are shown in Figure 48 for the olaparib arm and for the placebo arm.

Figure 48. Fit of parametric survival models to the Kaplan-Meier data for metastatic to death for the olaparib arm of OlympiA (ITT)

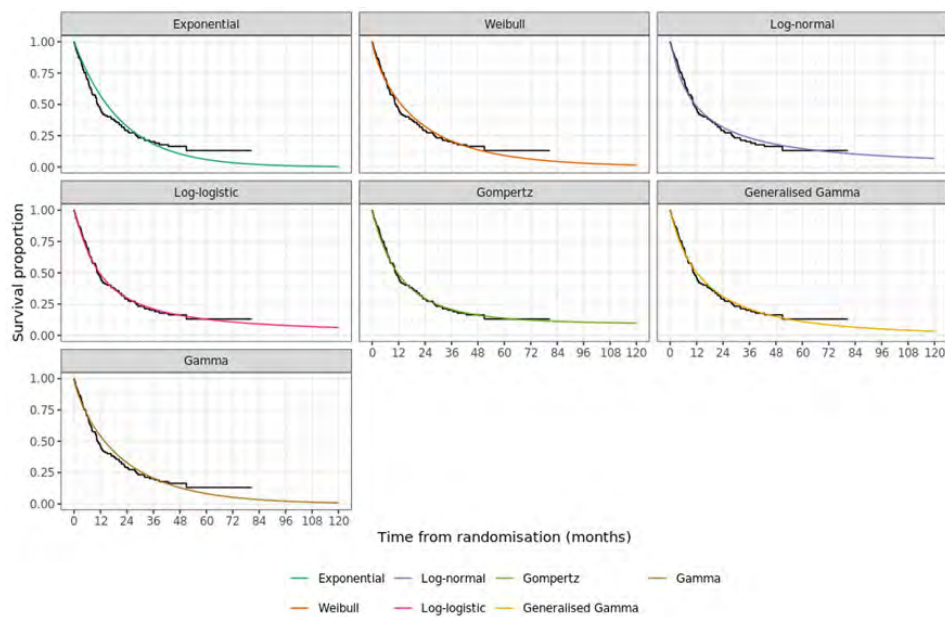




Figure 49. Fit of parametric survival models to the Kaplan-Meier data for metastatic to death for the placebo arm of OlympiA (ITT)

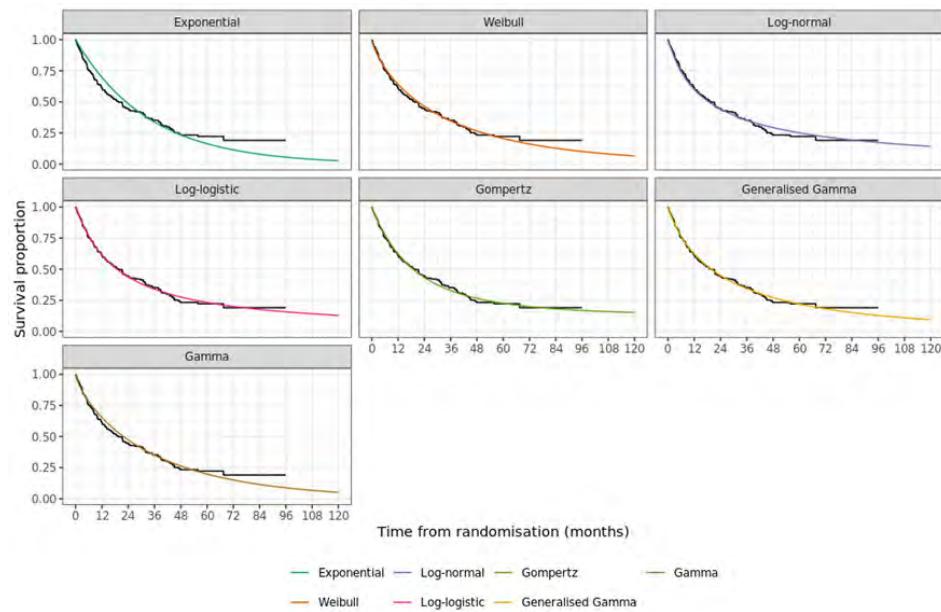
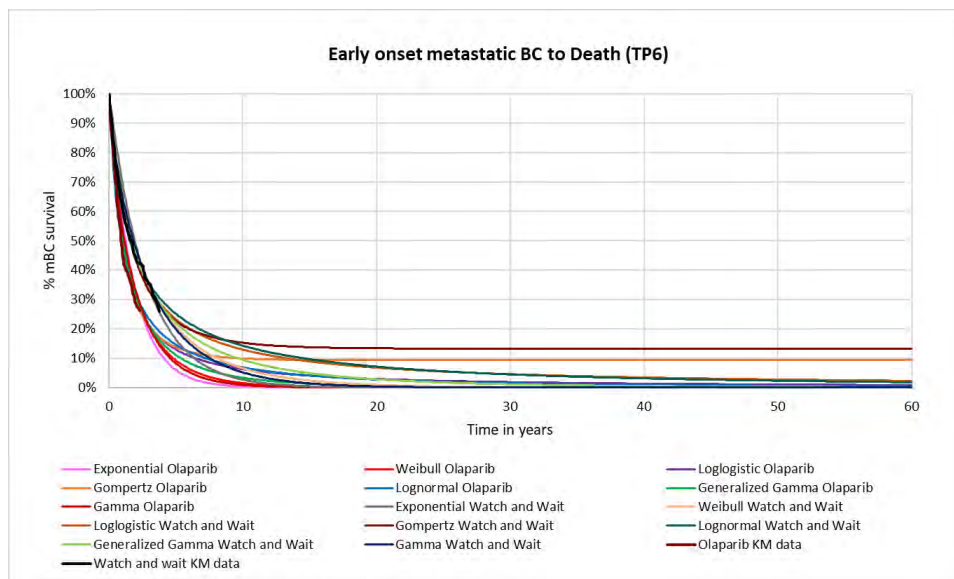


Figure 50. Observed time-to-event data and extrapolations of early onset non-mBC to death (TP6) for olaparib and watch and wait over the time horizon



D.3.6 Evaluation of hazard functions

For both the olaparib and placebo arm, the Gompertz and log-logistic models provided the closest visual fit of the observed hazards (Figure 51 and Figure 52). This is in line with the rankings of the best fitting models based on AIC and BIC. However, none of the fitted models accurately predicted the hazards observed.



Figure 51. Predicted hazard versus the observed smoothed hazards by model for early onset metastatic disease to death (OlympiA, olaparib arm)

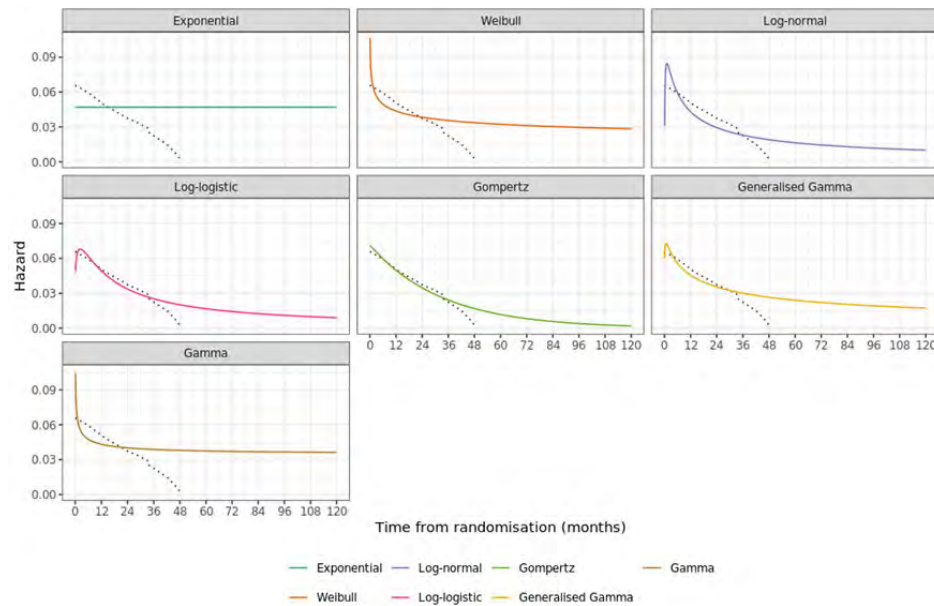
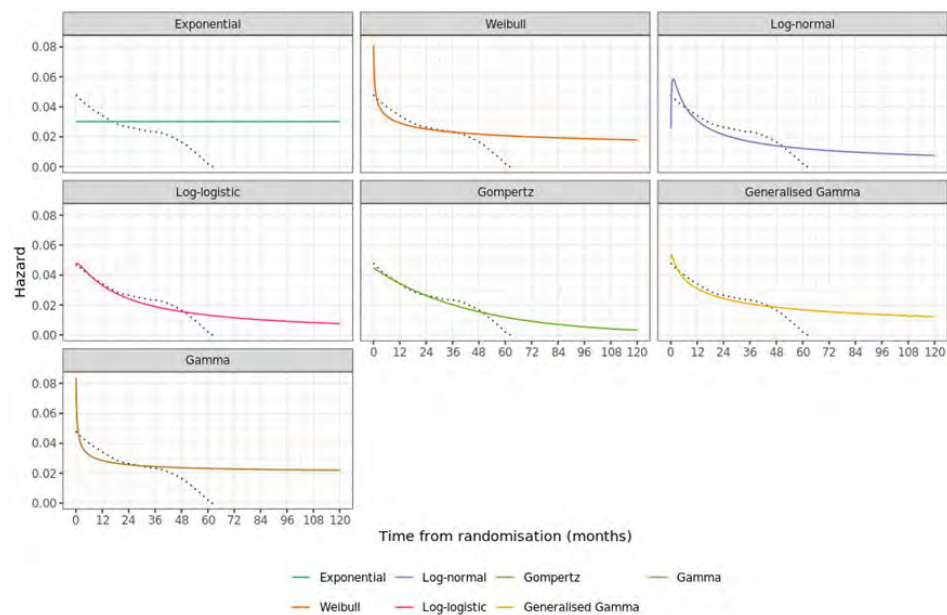


Figure 52. Predicted hazard versus the observed smoothed hazards by model for early onset metastatic disease to death (OlympiA, placebo arm)



D.3.7 Validation and discussion of extrapolated curves

For the placebo arm, all models yielded a similar and reasonable prediction of survival up to around 3 years. After this time point, there was divergence in the fit of the models to the Kaplan-Meier data. The Gompertz and log-logistic models tended to overestimate the survivorship towards the end of the study with extrapolated 10-year survival of 15.2% and 12.9%, respectively. The exponential, with extrapolated 10-year survival of



2.7%, was judged to provide the most plausible prediction when compared to literature estimates of post-distant recurrence survival in patient with 'early onset mBC' (~0% at 10 years) [58].

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 10-years after 'early onset mBC' was approximately 9.9% for the Gompertz and 0.4% 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 arm.

D.3.8 Adjustment of background mortality

Not applicable.

D.3.9 Adjustment for treatment switching/cross-over

Not applicable.

D.3.10 Waning effect

Not applicable.

D.3.11 Cure-point

Not applicable.

D.4 Extrapolation of late onset mBC to death (TP7)

D.4.1 Data input

The transition probabilities for 'late onset mBC' to death (TP7) were modelled using external data to the OlympiA trial.

To reflect the breadth of potential treatment options and associated outcomes after 'late onset mBC', the transition probabilities for TP7 were modelled as a 'weighted-average' of survival probabilities ($S(t)$) for first-line treatments of BRCA mBC. Following guidelines [80] and clinical expert input [39], the first-line treatment options available to patients with BRCA mBC in Denmark are:

- Single chemotherapy
- CDK4/6 inhibitor plus endocrine therapy (only relevant for HER2-/HR+)
- Atezolizumab plus nab-paclitaxel (TNBC and PD-L1 $\geq$ 10)

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

- Single chemotherapy: OlympiAD study [49, 50] (clinical trial)



- CDK 4/6 inhibitor plus endocrine therapy: Collins et al 2021 (Flatirone real world study) [60]
- Atezolizumab plus paclitaxel: BRCAm biomarker subgroup of the IMpassion 130 study [51] (clinical trial).

The OlympiAD study was a randomized, 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 [49, 50]. 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) [60]. 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 the 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 randomized, 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 substudy of IMpassion 130, the efficacy of treatment was evaluated based on immune biomarkers and BRCA1/2 alterations [51]. Of 612 patients tested, 89 (14.5%) had BRCA1/2 mutations [51]. Of these, approximately 50% (45 of 89) were PD-L1 positive and eligible for atezolizumab treatment based on its European marketing authorization [51]. 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 randomized clinical trials in gBRCA mutated mBC [81], 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 [28].

An overview of the clinical characteristics of the OlympiAD and Collins et al study populations is provided in Table 72. In both data sets, the mean time from diagnosis to randomization (OlympiAD) or start of CDK4/6 inhibitor treatment (Flatiron) was greater than 2 years indicating that patients in these studies were likely to have developed metastatic disease in a 'late onset' setting (ranged from 4.7 to 4.8 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).[49, 50, 60] 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 72. Summary of clinical characteristic for OlympiAD and Flatiron health database study

Characteristic	OlympiAD [49, 50] 1 st line subgroup, unless otherwise stated		Flatiron health database (all patients, 1 st line specific not available) N=85 [60]
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 both 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 the TNBC population. 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 CDK 4/6 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. 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 [51].

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 ⁷, and $\hat{S}(t)_i$ is the associated survival probability. The following sections detail the fitting of parametric 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.

As summary of the weights used to derive the ‘weighted-average’ survival probabilities for TP7 is provided in Table 73. The case mix was informed by Danish clinical experts [39]. 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 [39].

Table 73. Case mix of treatment in the ‘late onset’ mBC state based on clinical expert input

	Olaparib	Placebo	Efficacy data source
TNBC			
Single chemotherapy	85%	85%	TPC arm of the 1 st line subgroup of OlympiAD
Atezolizumab plus nab-paclitaxel	15%	15%	TPC arm of the 1 st line subgroup of OlympiAD, adjusted for the hazard ratio benefit of atezolizumab from IMpassion 130
HER2-/HR+			
Single chemotherapy	10%	10%	TPC arm of the 1 st 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

D.4.2 Model

A series of parametric survival models were fitted to the time to event data from OlympiAD and Collins et al. The parametric models used for extrapolation were the following:

- Exponential
- Weibull
- Lognormal

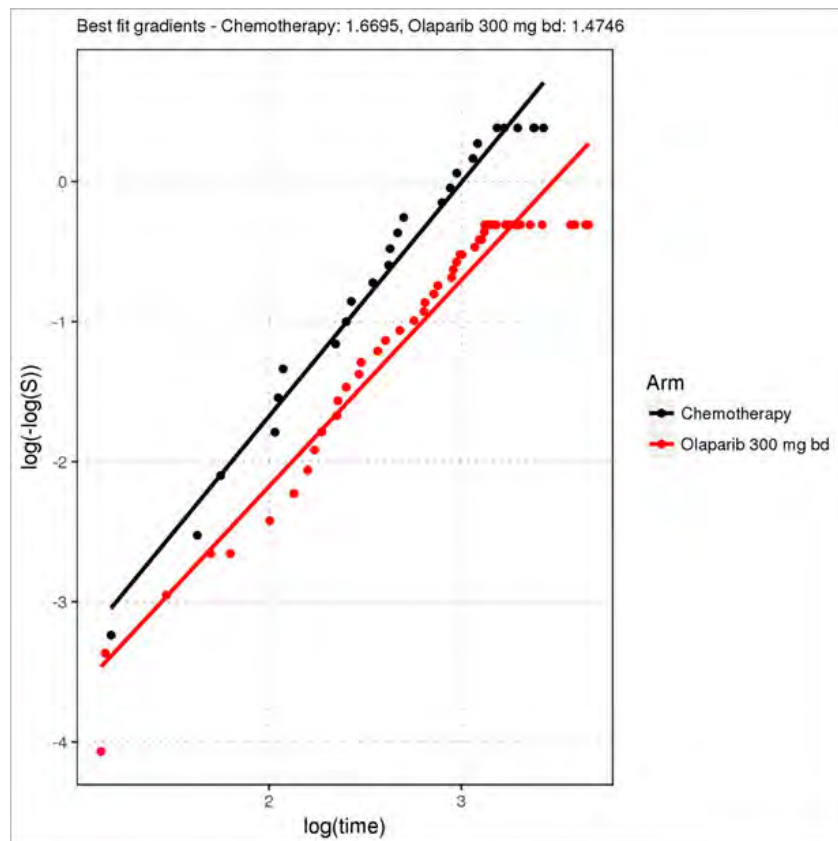


- Log-logistic
- Generalised Gamma
- Gompertz
- Gamma

D.4.3 Proportional hazards

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 53). This was used to inform the choice of survival model. The lack of proportionality in the curves for olaparib and TPC support the fitting of independent curves to each arm of the study population.

Figure 53. Log-cumulative hazards versus log-time plot for the first-line subgroup of OlympiAD



For Collins et al, the event time was defined as the time from the start date of first line CDK4/6 inhibitor treatment to death from any cause [60]. 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.

D.4.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC statistics for the models fitted independently to each treatment arm of OlympiAD and Collins et al are shown in Table 74. For both the olaparib and TPC arms of



OlympiAD, the lognormal was the best fitting model according to both AIC and BIC, with the log-logistic model having the second-best fit on both scores. For the CDK4/6 inhibitor group of Collins et al. the log-logistic was the best fitting according to AIC and BIC, and the lognormal was second best.

Table 74. 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

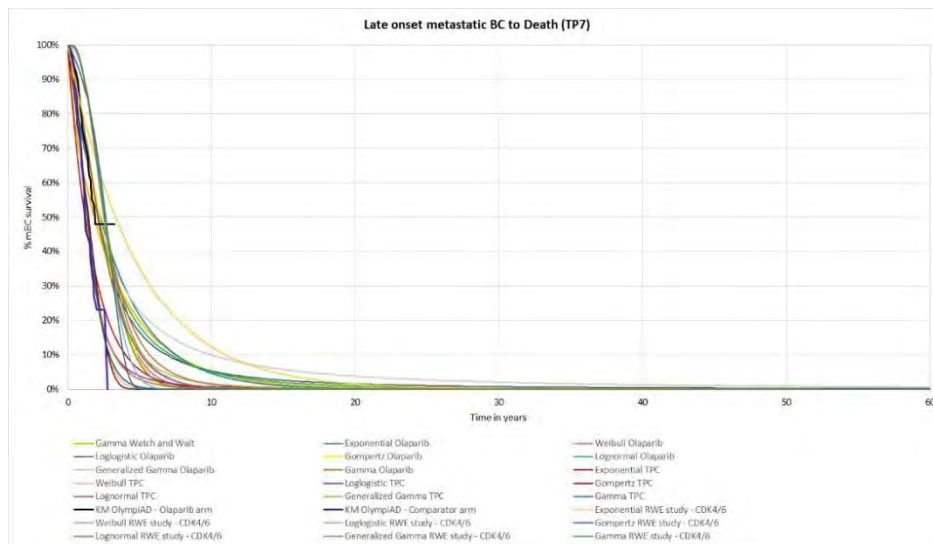
Model	Rank on lowest AIC/BIC by arm	Olaparib, N=59Placebo, N=28 CDK4/6 inhibitor N=36	
		AIC	BIC
Olaparib arm of first-line OlympiAD group (TP7)			
Exponential	6/6	281.91	283.98
Weibull	5/4	279.05	283.21
Log-logistic	2/2	276.49	280.65
Lognormal	1/1	275.64	279.80
Gompertz	7/7	282.67	286.82
Generalised Gamma	3/5	277.26	283.49
Gamma	4/3	277.88	282.04
TPC arm of first-line OlympiAD group (TP7)			
Exponential	6/6	171.69	173.02
Weibull	3/3	166.64	169.30
Log-logistic	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
First-line CDK4/6 inhibitor treatment in Flatiron study (TP7)			
Exponential	7/7	133.26	134.84
Weibull	4/4	125.04	128.2
Log-logistic	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



D.4.5 Evaluation of visual fit

The fit of the models to the Kaplan-Meier probabilities for TP7 are shown in Figure 54 for OlympiAD and Collins et al.

Figure 54. Observed time-to-event data and extrapolations of late onset non-mBC to death (TP7) for olaparib and watch and wait over the time horizon



For the TPC arm of OlympiAD, most models provided robust fit to the Kaplan-Meier data. The exponential model had 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 modes according to AIC and BIC (lognormal and log-logistic) provided similar levels of fit to the trial data and has 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 number 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 log-logistic (best on AIC and BIC) was used to model the outcomes of CDK4/6 inhibitor treatment on TP7,

D.4.6 Evaluation of hazard functions

Not available.

D.4.7 Validation and discussion of extrapolated curves

Weighted survival for TP7

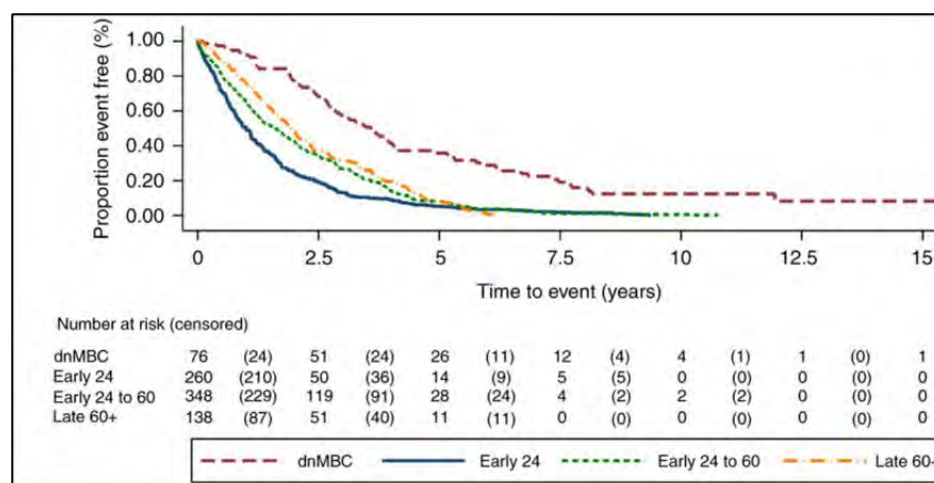


The weighted-average survival probabilities for TP7 were modelled using the survival parameters from the OlympiAD and Collins et al studies, the hazard ratio of OS from IMpassion 130 (0.55 [95% CI 0.21 to 1.41]), and the case mix probabilities from Table 73.

Figure 56 shows the weighted-average survival probabilities for TP7 in the TNBC and HER2-/HR+ populations. 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 a proxy for pembrolizumab plus paclitaxel or carboplatin). The median survival for TP7 is approximately 17 months, with approximately 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% [59]. 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, when using data from DCO3, predicts improved survival for those with 'late' versus 'early' disease up until about 1 year in the watch and wait arm (Figure 56). After this time point, patients with 'early' disease are predicted to have improved survival. This is to some extent in contradiction with the post-recurrence survival reported in the UK POSH study by McKenzie et al [58] (Figure 55). 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 the differences between the publication and the model prediction.

Figure 55. Post-distant recurrence survival for subjects with de novo and recurrent disease



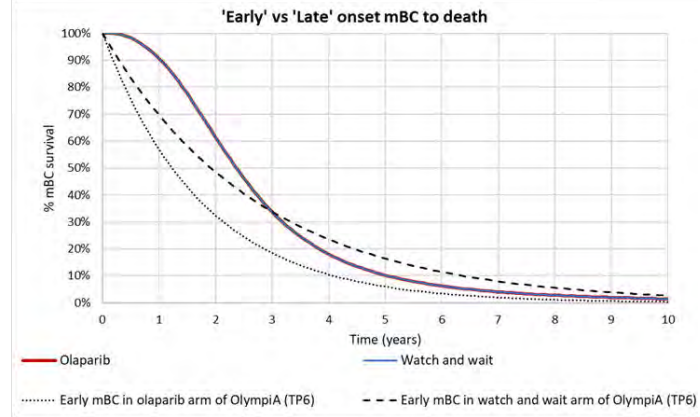
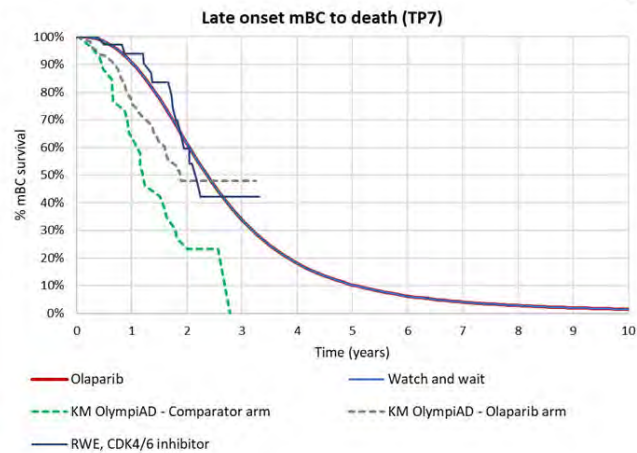
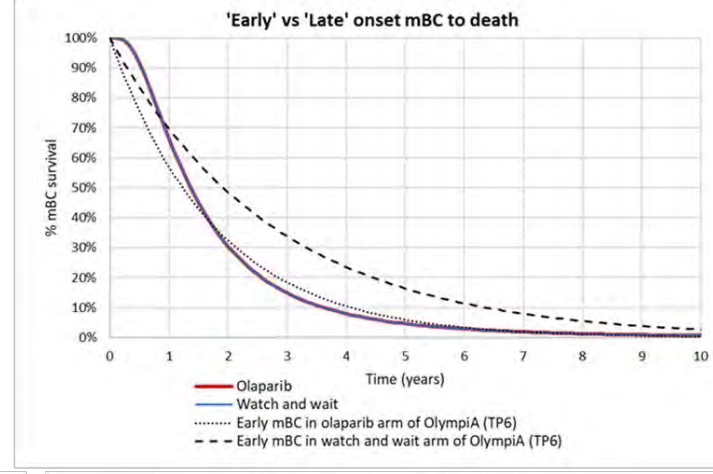
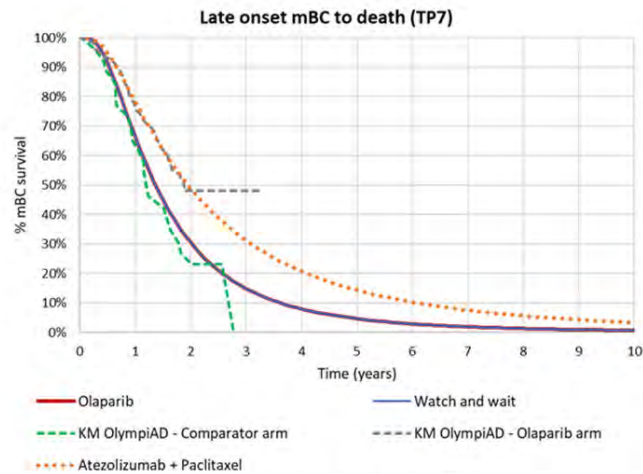
For HER-/HR+, TP7 is modelled using a case mix of survival probabilities for the TPC arm of OlympiAD and CDK4/6 inhibitor treatment from Collins et al. The resulting weighted-average survival probabilities for TP7 fall between the Kaplan-Meier estimates for each



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 56).



Figure 56. 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)





D.4.8 Adjustment of background mortality

Not applicable.

D.4.9 Adjustment for treatment switching/cross-over

Not applicable.

D.4.10 Waning effect

Not applicable.

D.4.11 Cure-point

Not applicable.



Appendix E. Serious adverse events

The most common (≥ 3 patients in either treatment arm) SAEs including those with an outcome of death from the OlympiA clinical trial [62] are listed in Table 75.

Table 75. SAEs by system organ class and preferred term (≥ 3 patients in either treatment arm)

System organ class/MedDRA preferred term	Number (%) of patients	
	Olaparib 300 mg bd (N=911)	Placebo (N=904)
Patients with any SAE	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
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)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (0.5)	21 (2.3)
Breast cancer	1 (0.1)	3 (0.3)
Malignant melanoma	1 (0.1)	4 (0.4)
Ovarian cancer	0	4 (0.4)
Gastrointestinal disorders	5 (0.5)	6 (0.7)
Abdominal pain	0	3 (0.3)
General disorders and administration site conditions	5 (0.5)	4 (0.4)
Pyrexia	1 (0.1)	3 (0.3)
Injury, poisoning and procedural complications	4 (0.4)	8 (0.9)
Wound dehiscence	1 (0.1)	4 (0.4)



Appendix F. Health-related quality of life

Not applicable.



Appendix G. Probabilistic sensitivity analyses

Table 76 presents the input parameters in the PSA. For parametric survival models, Cholesky decomposition was used to account for uncertainty in model parameters and their correlations (see the sheet “Efficacy parameters” in the health economic model).

Table 76. Overview of parameters in the PSA

Input parameter	Mean	SE	Alpha	Beta	Distribution
Settings - Patient Characteristics					
Patients' age at baseline (mean)	43.30	0.26			Normal
Mean weight	68.70	0.38			Normal
Body surface area	1.77	0.01			Normal
Settings - Efficacy					
Time separation point early/late progressors - ITT	24.00	2.40			Normal
Time point at which patients are considered cured - Olaparib arm	60.00	6.00			Normal
Probability of non-distant mets: Olap	0.27	106.00	28.69	77.31	Beta
Probability of non-distant mets: Control	0.27	178.00	48.17	129.83	Beta
SMR applied to general population mortality	1.46	0.59	0.30	0.39	Log-normal
Hazard ratio of atezolizumab + Pac vs Pac alone	0.55	0.31	-0.73	0.52	Log-normal
PARP inhibitor	0.00	89.00	0.00	1.00	Dirichlet
Single chemotherapy	0.75	89.00	66.75	1.00	Dirichlet
Atezolizumab + Paclitaxel	0.15	89.00	13.35	1.00	Dirichlet
PARP inhibitor	0.00	89.00	0.00	1.00	Dirichlet
Single chemotherapy	0.85	89.00	75.65	1.00	Dirichlet
Atezolizumab + Paclitaxel	0.15	89.00	13.35	1.00	Dirichlet
Treatment Shares					



Share receiving Olaparib 150 mg	0.60	65.67	39.40	26.27	Beta
non-mBC Rad Olap	0.16	81.00	12.96	68.04	Beta
non-mBC Surg Olap	0.62	81.00	49.98	31.02	Beta
non-mBC - Olaparib arm: Capecitabine market share	0.10	81.00	8.10	1.00	Dirichlet
non-mBC - Olaparib arm: Docetaxel + Cyclophosphamide market share	0.80	81.00	64.80	1.00	Dirichlet
non-mBC - Olaparib arm - Capecitabine - Duration	7.10	0.71	100.00	0.07	Gamma
non-mBC - Olaparib arm - Docetaxel + Cyclophosphamide - Duration	6.00	0.60	100.00	0.06	Gamma
non-mBC Rad WaW	0.16	81.00	12.96	68.04	Beta
non-mBC Surg WaW	0.62	81.00	49.98	31.02	Beta
non-mBC - WaW arm: Capecitabine market share	0.10	81.00	8.10	1.00	Dirichlet
non-mBC - WaW arm: Docetaxel + Cyclophosphamide market share	0.80	81.00	64.80	1.00	Dirichlet
non-mBC - WaW arm - Capecitabine - Duration	7.10	0.71	100.00	0.07	Gamma
non-mBC - WaW arm - Docetaxel + Cyclophosphamide - Duration	6.00	0.60	100.00	0.06	Gamma
emBC Rad Olap	0.31	105.00	32.03	72.98	Beta
emBC Surg Olap	0.26	105.00	26.99	78.02	Beta
emBC proportion treated beyond 1st line Olap	0.75	28.00	21.00	7.00	Beta
emBC number of subsequent lines	1.70	0.17	99.75	0.02	Gamma
emBC - Olaparib arm - Capecitabine - Share First	0.85	105.00	89.25	1.00	Dirichlet
emBC - Olaparib arm - Atezolizumab + Abraxane - Share First	0.15	105.00	15.75	1.00	Dirichlet
emBC - Olaparib arm - Capecitabine - Duration First	7.10	0.71	100.00	0.07	Gamma
emBC - Olaparib arm - Atezolizumab + Abraxane - Duration First	7.00	0.70	100.00	0.07	Gamma
emBC - Olaparib arm - Eribulin - Share Second plus	0.90	105.00	94.50	1.00	Dirichlet
emBC - Olaparib arm - Eribulin - Duration Second plus	7.10	0.71	100.00	0.07	Gamma
emBC Rad WaW	0.37	169.00	63.04	105.96	Beta
emBC Surg WaW	0.27	169.00	44.95	124.05	Beta



emBC proportion treated beyond 1st line WaW	0.75	28.00	21.00	7.00	Beta
emBC number of subsequent lines WaW	1.70	0.17	99.75	0.02	Gamma
emBC - WaW arm - Capecitabine - Share First	0.85	105.00	89.25	1.00	Dirichlet
emBC - WaW arm - Atezolizumab + Abraxane - Share First	0.15	105.00	15.75	1.00	Dirichlet
emBC - WaW arm - Capecitabine - Duration First	7.10	0.71	100.00	0.07	Gamma
emBC - WaW arm - Atezolizumab + Abraxane - Duration First	7.00	0.70	100.00	0.07	Gamma
emBC - WaW arm - Eribulin - Share Second plus	0.90	105.00	94.50	1.00	Dirichlet
emBC - WaW arm - Eribulin - Duration Second plus	7.10	0.71	100.00	0.07	Gamma
ImBC Rad Olap	0.35	105.00	36.44	68.57	Beta
ImBC Surg Olap	0.26	105.00	27.62	77.39	Beta
ImBC proportion treated beyond 1st line Olap	0.75	28.00	21.00	7.00	Beta
ImBC number of subsequent lines	1.70	0.17	99.75	0.02	Gamma
ImBC - Olaparib arm - Capecitabine - Share First	0.85	105.00	89.25	1.00	Dirichlet
ImBC - Olaparib arm - Atezolizumab + Abraxane - Share First	0.15	105.00	15.75	1.00	Dirichlet
ImBC - Olaparib arm - Capecitabine - Duration First	7.10	0.71	100.00	0.07	Gamma
ImBC - Olaparib arm - Atezolizumab + Abraxane - Duration First	7.00	0.70	100.00	0.07	Gamma
ImBC - Olaparib arm - Capecitabine - Share Second plus	0.03	105.00	2.63	1.00	Dirichlet
ImBC - Olaparib arm - Eribulin - Share Second plus	0.20	105.00	21.00	1.00	Dirichlet
ImBC - Olaparib arm - Paclitaxel - Share Second plus	0.43	105.00	44.63	1.00	Dirichlet
ImBC - Olaparib arm - Capecitabine - Duration Second plus	7.10	0.71	100.00	0.07	Gamma
ImBC - Olaparib arm - Eribulin - Duration Second plus	7.10	0.71	100.00	0.07	Gamma
ImBC - Olaparib arm - Paclitaxel - Duration Second plus	6.00	0.60	100.00	0.06	Gamma
ImBC Rad WaW	0.35	169.00	58.64	110.36	Beta
ImBC Surg WaW	0.26	169.00	44.45	124.55	Beta
ImBC proportion treated beyond 1st line WaW	0.75	28.00	21.00	7.00	Beta



ImBC number of subsequent lines	1.70	0.17	99.75	0.02	Gamma
ImBC - WaW arm - Capecitabine - Share First	0.85	169.00	143.65	1.00	Dirichlet
ImBC - WaW arm - Atezolizumab + Abraxane - Share First	0.15	169.00	25.35	1.00	Dirichlet
ImBC - WaW arm - Capecitabine - Duration First	7.10	0.71	100.00	0.07	Gamma
ImBC - WaW arm - Atezolizumab + Abraxane - Duration First	7.00	0.70	100.00	0.07	Gamma
ImBC - WaW arm - Capecitabine - Share Second plus	0.03	105.00	2.63	1.00	Dirichlet
ImBC - WaW arm - Eribulin - Share Second plus	0.20	105.00	21.00	1.00	Dirichlet
ImBC - WaW arm - Paclitaxel - Share Second plus	0.43	105.00	44.63	1.00	Dirichlet
ImBC - WaW arm - Capecitabine - Duration Second plus	7.10	0.71	100.00	0.07	Gamma
ImBC - WaW arm - Eribulin - Duration Second plus	7.10	0.71	100.00	0.07	Gamma
ImBC - WaW arm - Paclitaxel - Duration Second plus	6.00	0.60	100.00	0.06	Gamma
Administration Costs					
IV administration	1 625	162.50	7.39	0.10	Log-normal
Disease Management Costs					
Disease management - Oncology visit: frequency DFS	0.21	0.02	-1.57	0.10	Log-normal
Disease management - Cancer nurse: frequency DFS	0.17	0.02	-1.80	0.10	Log-normal
Disease management - CT scan: frequency DFS	0.04	0.00	-3.18	0.10	Log-normal
Disease management - Patient time: frequency DFS	0.15	0.01	-1.93	0.10	Log-normal
Disease management - Transport: frequency DFS	0.83	0.08	-0.19	0.10	Log-normal
Disease management - Oncology visit: frequency DFS years 2 to 5	0.02	0.00	-3.88	0.10	Log-normal
Disease management - Phone call: frequency DFS years 2 to 5	0.04	0.00	-3.18	0.10	Log-normal
Disease management - Mammogram: frequency DFS years 2 to 5	0.00	0.00	-5.49	0.10	Log-normal
Disease management - Patient time: frequency DFS years 2 to 5	0.01	0.00	-4.71	0.10	Log-normal
Disease management - Transport: frequency DFS years 2 to 5	0.05	0.01	-3.00	0.10	Log-normal
Disease management - MRI: frequency DFS years 2 to 5	0.00	0.00	-5.49	0.10	Log-normal



Disease management - Mammogram: frequency DFS year5 onwards	0.00	0.00	-5.77	0.10	Log-normal
Disease management - Patient time: frequency DFS year5 onwards	0.00	0.00	-6.47	0.10	Log-normal
Disease management - Transport: frequency DFS year5 onwards	0.01	0.00	-5.08	0.10	Log-normal
Disease management - MRI: frequency DFS year5 onwards	0.00	0.00	-5.77	0.10	Log-normal
Disease management - Oncology visit: frequency LR	0.25	0.03	-1.39	0.10	Log-normal
Disease management - CT scan2: frequency LR	0.25	0.03	-1.39	0.10	Log-normal
Disease management - Patient time: frequency LR	0.21	0.02	-1.57	0.10	Log-normal
Disease management - Transport: frequency LR	1.00	0.10	-0.00	0.10	Log-normal
Disease management - Full blood count: frequency LR	0.25	0.03	-1.39	0.10	Log-normal
Disease management - Oncology visit: frequency mBC	0.25	0.03	-1.39	0.10	Log-normal
Disease management - CT scan2: frequency mBC	0.25	0.03	-1.39	0.10	Log-normal
Disease management - Patient time: frequency mBC	0.21	0.02	-1.57	0.10	Log-normal
Disease management - Transport: frequency mBC	1.00	0.10	-0.00	0.10	Log-normal
Disease management - Full blood count: frequency mBC	0.25	0.03	-1.39	0.10	Log-normal
HCRU Costs					
Disease management - Complete blood count frequency: Olaparib (mono)	1.00	0.10	-0.00	0.10	Log-normal
Adverse events - Anemia: No. of events% - Olaparib	0.09	921.00	80.13	840.87	Beta
Adverse events - Leukopenia: No. of events% - Olaparib	0.03	921.00	27.63	893.37	Beta
Adverse events - Neutropenia: No. of events% - Olaparib	0.05	921.00	45.13	875.87	Beta
Adverse events - Anemia: Duration (days) - Olaparib	72.44	7.24	4.28	0.10	Log-normal
Adverse events - Leukopenia: Duration (days) - Olaparib	28.92	2.89	3.36	0.10	Log-normal
Adverse events - Neutropenia: Duration (days) - Olaparib	28.92	2.89	3.36	0.10	Log-normal
Adverse events - Anemia: No. of events% - W&W arm	0.00	915.00	2.75	912.26	Beta
Adverse events - Leukopenia: No. of events% - W&W arm	0.00	915.00	2.75	912.26	Beta
Adverse events - Neutropenia: No. of events% - W&W arm	0.01	915.00	7.32	907.68	Beta



Adverse events - Anemia: Duration (days) - W&W arm	35.92	3.59	3.58	0.10	Log-normal
Adverse events - Leukopenia: Duration (days) - W&W arm	31.05	3.11	3.43	0.10	Log-normal
Adverse events - Neutropenia: Duration (days) - W&W arm	31.05	3.11	3.43	0.10	Log-normal
Utilities					
Utility - Olaparib: DFS	0.87	0.00	23 751.29	3 580.46	Beta
Utility - Olaparib: non-mBC	0.87	0.00	23 751.29	3 580.46	Beta
Utility - Olaparib: mBC (Late)	0.69	0.03	171.05	78.66	Beta
Utility - Olaparib: mBC (Early)	0.69	0.03	171.05	78.66	Beta
Utility - Watch and wait arm: DFS	0.87	0.00	23 751.29	3 580.46	Beta
Utility - Watch and wait arm: LR	0.87	0.00	23 751.29	3 580.46	Beta
Utility - Watch and wait arm: mBC (Late)	0.69	0.03	171.05	78.66	Beta
Utility - Watch and wait arm: mBC (Early)	0.69	0.03	171.05	78.66	Beta
Utility - Intercept (for age adjustment)	0.95	0.10			Normal
Utility - Gender parameter (for age adjustment)	0.02	0.00			Normal
Utility - Age parameter (for age adjustment)	0.00	0.00			Normal
TDT for Olaparib					
TDT for olaparib	1.00		47.00	704.00	Beta
TDT for olaparib	0.94		23.00	681.00	Beta
TDT for olaparib	0.91		20.00	661.00	Beta
TDT for olaparib	0.88		18.00	643.00	Beta
TDT for olaparib	0.86		13.00	630.00	Beta
TDT for olaparib	0.84		13.00	617.00	Beta
TDT for olaparib	0.82		5.00	612.00	Beta
TDT for olaparib	0.81		12.00	600.00	Beta
TDT for olaparib	0.80		12.00	588.01	Beta



TDT for olaparib	0.78	10.00	578.00	Beta
TDT for olaparib	0.77	12.00	566.00	Beta
TDT for olaparib	0.75	225.00	341.00	Beta
TDT for olaparib	0.45	329.00	12.00	Beta
TDT for olaparib	0.02	8.00	4.00	Beta
TDT for olaparib	0.01	1.01	2.99	Beta
TDT for Abemaciclib				
TDT for abemaciclib	1.00	109.57	2445.43	Beta
TDT for abemaciclib	0.96	88.46	2466.54	Beta
TDT for abemaciclib	0.92	64.68	2490.32	Beta
TDT for abemaciclib	0.90	27.65	2527.35	Beta
TDT for abemaciclib	0.89	39.14	2515.86	Beta
TDT for abemaciclib	0.88	51.10	2503.90	Beta
TDT for abemaciclib	0.86	40.56	2514.44	Beta
TDT for abemaciclib	0.85	35.32	2519.68	Beta
TDT for abemaciclib	0.83	29.85	2525.15	Beta
TDT for abemaciclib	0.82	42.28	2512.72	Beta
TDT for abemaciclib	0.81	24.57	2530.43	Beta
TDT for abemaciclib	0.80	43.41	2511.59	Beta
TDT for abemaciclib	0.79	12.62	2542.38	Beta
TDT for abemaciclib	0.79	25.36	2529.64	Beta
TDT for abemaciclib	0.78	38.42	2516.58	Beta
TDT for abemaciclib	0.77	6.50	2548.50	Beta
TDT for abemaciclib	0.76	32.59	2522.41	Beta
TDT for abemaciclib	0.75	13.20	2541.80	Beta



TDT for abemaciclib	0.75	19.91	2535.09	Beta
TDT for abemaciclib	0.74	20.07	2534.93	Beta
TDT for abemaciclib	0.74	26.97	2528.03	Beta
TDT for abemaciclib	0.73	34.07	2520.93	Beta
TDT for abemaciclib	0.72	110.49	2444.51	Beta
TDT for abemaciclib	0.69	2 143.60	411.40	Beta
TDT for abemaciclib	0.11	2 241.23	313.77	Beta
TDT for abemaciclib	0.1	1 825.00	730.00	Beta



Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

Objectives

The SLR was conducted to identify RCTs reporting the efficacy and safety of interventions of interest, including targeted therapies, endocrine therapy, immune-oncology drugs, and capecitabine, for patients with non-metastatic, primary, invasive HER2-negative breast cancer.

Methods

The SLR eligibility criteria initially aligned with the OlympiA population. However, owing to a paucity of data, the criteria were broadened beyond germline BRCA and high-risk studies only. The final eligibility criteria included RCTs conducted in adult patients (≥18 years) with non-metastatic primary invasive HER2-negative adenocarcinoma of the breast receiving treatment in the post-surgical adjuvant setting. In the original review (up to Jan 2022), interventions of interest were immune-oncology drugs (atezolizumab and pembrolizumab), cyclin-dependent kinase (CDK) 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib), olaparib, capecitabine, and endocrine therapy. In the 2022-2025 update, the focus is only on treatments for patients with TNBC.

The following sources were used to identify potentially relevant publications:

- Electronic databases
- Reference lists of eligible studies
- Conference proceedings
- Global HTA bodies
- Additional relevant websites
- Clinical trial registries

The original search was conducted up to January 2022, but has been complemented with a search in Medline/PubMed up to September 2025 (Table 77).

Table 77. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 – Jan 2022	12.01.2022
Medline	Ovid	1946 – Sep 2025	15.09.2025



Database	Platform/source	Relevant period for the search	Date of search completion
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EBM Reviews*	Ovid	Up to Jan 2022	12.01.2022
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*Includes the HTA database, the National Health Service Economic Evaluation Database (NHS EED), Cochrane Central register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews

Table 78. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Early breast cancer AND (TNBC OR HER2 negative)	
SMC	www.scottishmedicines.org.uk	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
CADTH/CDA-AMC	www.cda-amc.ca	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
PBAC	www.pbs.gov.au/pbs/home	Early breast cancer AND (TNBC OR HER2 negative)	
US National Institutes of Health registry & results database	https://clinicaltrials.gov	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
WHO International Clinical Trials Registry Platform registry	http://apps.who.int/trialsearch/	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022

Table 79. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://meetinglibrary.asco.org/	Abstracts were identified by searching keywords in the ASCO meeting library, 2018-2021	Early breast cancer AND "HER2 negative" AND breast NOT "HER2 positive" AND TNBC	21.01.2022



Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ESMO	https://oncologypro.esmo.org/meeting-resources/esmo-congress ; https://www.journals.evsier.com/annals-of-oncology	Abstracts were identified by searching keywords in the ESMO congress meeting resources and Annals of Oncology, 2018-2021	Early breast cancer AND (TNBC OR HER2 negative)	21.01.2022
AACR	https://www.abstractsonline.com/pp8/#!/9325/sessions/early%20breast%20cancer/1 ; https://cancerres.aacrjournals.org/content/	Abstracts were identified by searching categories in the AACR annual meetings 2018-2021 via Cancer Research.	HSUV, Early breast cancer, AND (TNBC OR triple negative OR HER2 negative)	21.01.2022
SABCS	https://www.abstractsonline.com/pp8/#!/10462 ; https://www.abstractsonline.com/pp8/#!/9223	abstracts were identified by searching the San Antonio Breast Cancer Symposium 2019-2021 using keywords	EQ-5D OR HSUV OR ("Early breast cancer" AND "HSUV") OR ("Early breast cancer" AND utility)	21.01.2022
EBCC	https://conferences.eortc.org/ebcc12/wp-content/uploads/sites/4/2020/10/EBCC_2020_Abstract_Book.pdf	Abstracts were identified by searching the European Breast Cancer Conference abstract book for 2020 using keywords	Early breast cancer AND (HER2 negative OR TNBC) OR Triple negative breast cancer OR Operable breast cancer	11.01.2021

H.1.1 Search strategies

Eligibility criteria applied in the review are summarised in Table 80.

Table 80. Eligibility criteria for the clinical SLR

CRITERIA	INCLUSION CRITERIA	EXCLUSION CRITERIA
POPULATION	OlympiA included adult female and male patients (≥18 years) with germline BRCA mutations (BRCA1 and/or BRCA2) 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)	Studies where the HER2 status is not reported



CRITERIA	INCLUSION CRITERIA	EXCLUSION CRITERIA
	Criteria for the current SLR were adult female and male patients (≥18 years) with non-metastatic primary invasive HER2-negative adenocarcinoma of the breast who are receiving treatment in the post-surgical adjuvant setting. Further, studies that randomised patients during the neoadjuvant period and studies with mixed HER2-/+ status were considered for inclusion	
INTERVENTION	The interventions of interest were restricted to the adjuvant setting for the following: • Immuno-oncology drugs, to include: ○ Atezolizumab ○ Pembrolizumab • CDK4/6 inhibitors, including ○ Abemaciclib ○ Palbociclib ○ Ribociclib • Olaparib • Capecitabine • Endocrine therapy	• Interventions not of interest include: • Immuno-oncology drugs not listed for inclusion • Chemotherapy • Routine surveillance • Palliative radiotherapy
OUTCOMES	Studies reporting at least one outcome of interest (to include efficacy/safety outcomes reported in the OlympiA study), including: <i>Efficacy:</i> • iDFS • OS • DDFS • DFS • RFS • Time to first subsequent therapy • Time to treatment failure • Time to treatment discontinuation • Response rates (measured via RECIST criteria), to include pathological complete response • Rate of recurrence • Site of recurrence • Time to recurrence <i>Safety:</i> • All grade AEs • All-grade treatment-related AEs	-



CRITERIA	INCLUSION CRITERIA	EXCLUSION CRITERIA
	• Treatment-related Grade 3 or 4 AEs • All-grade SAEs • Treatment-related SAEs • Tolerability: Dose reductions and interruptions, discontinuation (any reason), discontinuation (due to AEs) • Individual AEs associated with PARP inhibitors • Mortality • Mortality due to AEs •	
STUDY DESIGN	• Eligible study designs include: • Prospective RCTs (Phase 2–4) with active or placebo or best supportive care controls with no restriction on blinding • Systematic reviews/meta-analyses	-
TERRITORY OF INTEREST	No restriction	-
DATE OF PUBLICATION	No restriction	-
LANGUAGE OF PUBLICATION	No restriction, although the primary focus is English language publications or non-English language publications with an English abstract	-

Abbreviations: AE, adverse event; BRCA1, breast cancer gene 1; BRCA2, breast cancer gene 2; CDK, cyclin dependent kinase; DDFS, distant disease-free survival; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HRQoL, health-related quality of life; iDFS, invasive disease-free survival; OS, overall survival; PARP, Poly (ADP-ribose) polymerase; PRO, patient-reported outcome; RCT, randomised controlled trial; RFS, recurrence-free survival; SAE, serious adverse event; SLR, systematic literature review.



Table 81 summaries the searches conducted in Embase (Ovid) for the years 1974 to 2022, accessed on January 11th, 2022.

Table 81 of search strategy table for Embase (Ovid)

#	Searches	Results
1	exp breast cancer/	514264
2	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp.	685925
3	1 or 2	690790
4	exp epidermal growth factor receptor/	91781
5	exp epidermal growth factor receptor 2/	65999
6	(epidermal growth factor receptor or HER*).mp.	3629875
7	4 or 5 or 6	3629875
8	(negative or -ve).mp.	1781560
9	7 and 8	250144
10	3 and 9	46350
11	exp triple negative breast cancer/	27301
12	(triple negative adj5 (tumour* or tumor* or cancer* or adenocarcinoma* or carcinoma* or adenoma* or neoplas* or malignan* or sarcoma*)).mp.	33372
13	(TNBC* or TNMBC* or mTNBC*).mp.	16078
14	11 or 12 or 13	33697
15	10 or 14	61933
16	(early or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*).ab,ti,kw.	2705579
17	(primary adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$ or TNBC\$)).mp.	308793
18	16 or 17	2956391
19	15 and 18	20149
20	random*.ti,ab.	1740654
21	factorial*.ti,ab.	42715
22	(crossover* or cross over*).ti,ab.	115857
23	((doubl* or singl*) adj blind*).ti,ab.	252575
24	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1144188
25	crossover procedure/	69077
26	double blind procedure/	191223
27	single blind procedure/	44794
28	randomized controlled trial/	690250
29	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	2602501
30	19 and 29	2863



31 limit 30 to yr="2020 -Current"

613

Table 82 summaries the searches conducted in Ovid MEDLINE(R) and includes Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations, Daily and Versions(R) for the years 1946 to January 10, 2022 (accessed January 11th, 2022).

Table 82 of search strategy table for Ovid MEDLINE(R)

#	Searches	Results
1	exp Breast Neoplasms/	318362
2	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	459769
3	1 or 2	459776
4	exp Receptor, ErbB-2/ or exp Receptor, Epidermal Growth Factor/	68135
5	(epidermal growth factor receptor or HER*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2855504
6	4 or 5	2876791
7	(negative or -ve).mp.	1242904
8	6 and 7	156900
9	3 and 8	21326
10	exp Triple Negative Breast Neoplasms/	7243
11	(triple negative adj5 (tumour* or tumor* or cancer* or adenocarcinoma* or carcinoma* or adenoma* or neoplas* or malignan* or sarcoma*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	15502
12	(TNBC* or TNMBC* or mTNBC*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8405
13	10 or 11 or 12	15878
14	9 or 13	29709
15	(early or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*).ab,ti,kw.	1956335
16	(primary adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$ or TNBC*)).mp.	237007



17	15 or 16	2157368
18	14 and 17	8164
19	randomized controlled trial.pt.	555367
20	controlled clinical trial.pt.	94632
21	randomi#ed.ab.	653615
22	placebo.ab.	224654
23	randomly.ab.	373690
24	clinical trials as topic.sh.	198760
25	trial.ti.	254427
26	19 or 20 or 21 or 22 or 23 or 24 or 25	1460337
27	18 and 26	990
28	limit 27 to yr="2020 -Current"	279

Table 83 summaries the searches conducted in BM Reviews (Ovid) including ACP Journal Club 1991 to December 2021, Cochrane Central Register of Controlled Trials December 2021, Cochrane Database of Systematic Reviews 2005 to January 5, 2022, and Cochrane Clinical Answers December 2021 (accessed January 11th, 2022).

Table 83 of search strategy table for BM Reviews (Ovid)

#	Searches	Results
1	exp Breast Neoplasms/	14088
2	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	44848
3	1 or 2	44848
4	exp Receptor, ErbB-2/ or exp Receptor, Epidermal Growth Factor/	952
5	(epidermal growth factor receptor or HER*).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	93621
6	4 or 5	93715
7	(negative or -ve).mp.	94660
8	6 and 7	12134
9	3 and 8	4263
10	exp Triple Negative Breast Neoplasms/	330
11	(triple negative adj5 (tumour* or tumor* or cancer* or adenocarcinoma* or carcinoma* or adenoma* or neoplas* or malignan* or sarcoma\$)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	1729
12	(TNBC* or TNMBC* or mTNBC*).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	1066
13	10 or 11 or 12	1777
14	9 or 13	5175
15	(early or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*).ab,ti,kw.	189693



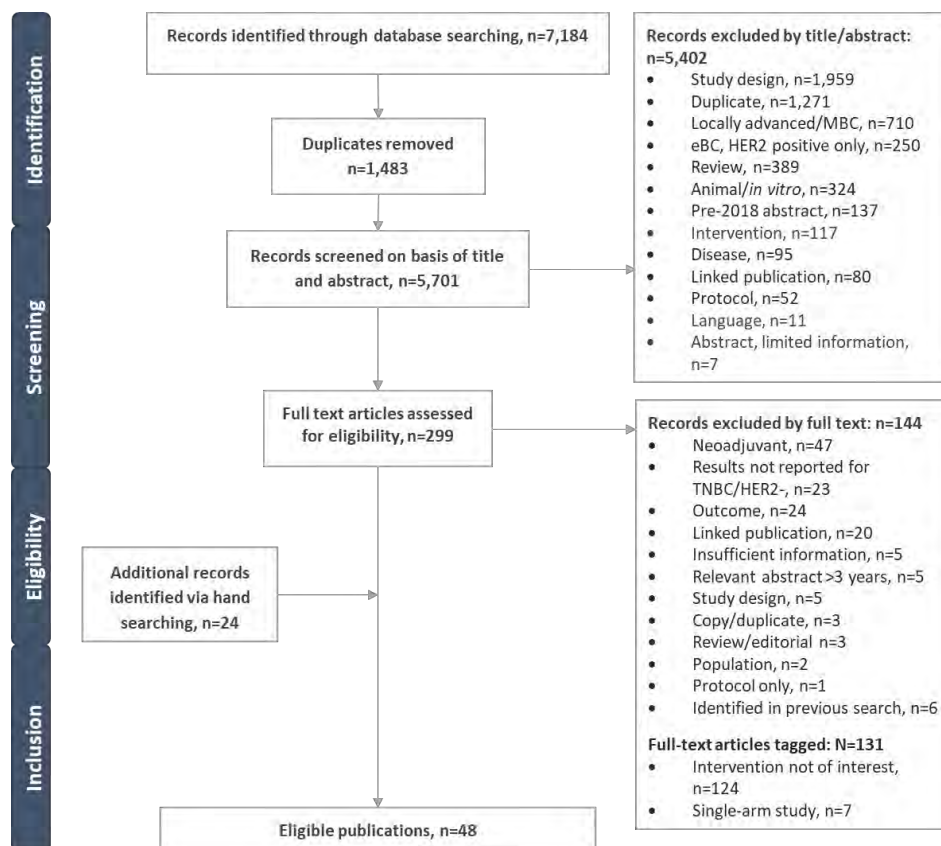
16	(primary adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$ or TNBC*)).mp.	27403
17	15 or 16	208800
18	14 and 17	2833
19	limit 18 to yr="2020 -Current"	493

PRISMA diagram including 2022 update

In total, 48 publications reporting on 32 studies were eligible for inclusion in the SLR. The majority of publications reported data for the adjuvant setting, with one study reporting data for the post-neoadjuvant setting and another study reporting data at both the neoadjuvant and adjuvant stages.

The flow of studies through review is summarised in the PRISMA flow diagram in Figure 57

Figure 57. PRISMA flow diagram (original clinical SLR plus 2022 update)



Abbreviations: EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TNBC, triple negative breast cancer.



Out of the 48 relevant publications, only 9 focused on TNBC patients, which is the population relevant for this application.

As a complement to the original clinical SLR and the Jan 2022 update we have conducted a further review to cover the time span up to September 2025. This was more limited in scope and included only Medline and no search for conference abstracts. We still expect that Medline should capture most of the relevant new studies in the area.

Data base: <https://pubmed.ncbi.nlm.nih.gov/>

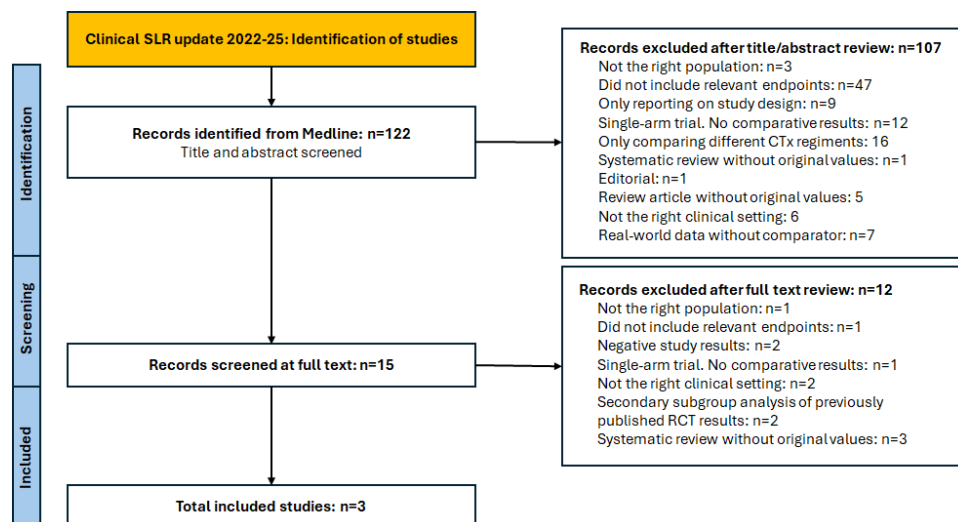
Search terms: "breast cancer" AND (adjuvant OR neoadjuvant) AND ("triple negative" OR TNBC) AND ("clinical trial" OR "phase iii trial" OR "phase ii trial" OR "clinical study") AND (progression OR overall OR survival OR "event-free" OR "disease-free") AND (2022 OR 2023 OR 2024 OR 2025)

Date: 18.09.2025

We also tested variations of the search string above, but these did not generate more relevant search results.

The flow of studies in the 2022-2025 update is summarised in the PRISMA flow diagram in Figure 58.

Figure 58. PRISMA flow diagram for the clinical SLR 2025 update.



The primary aim of this SLR was to evaluate the efficacy and safety of intervention in HER2-negative breast cancer. Accordingly, although the protocol allowed for studies with mixed populations, but only data relating to outcomes among patients with HER2-negative breast cancer were considered for inclusion. This re-application is even more restricted and is focused on the TNBC population. Hence, only studies including TNBC will be considered. The design of the TNBC studies eligible for inclusion is shown in Table 84. There are also some other studies that include TNBC subgroups, but with the exception of OlympiA these are studies including chemotherapy.



Table 84. Summary of the design of eligible TNBC studies (n=9) by type of intervention

Publication	Population	Intervention (Sample size)	High-risk breast cancer
Capecitabine (N=6)			
Li (2020), CBCSG010 (NCT01642771), China [82]	Females aged 18 to 70 years with newly diagnosed, unilateral, invasive, histologically-confirmed TNBC after primary surgery with a clear margin	Docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide (N=302) or capecitabine and docetaxel followed by capecitabine, epirubicin, and cyclophosphamide (N=308)	No
Lluch (2020), GEICAM/2003-11_CIBOMA/2004-01, eight countries (Spain, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, and Venezuela) [14]	Patients with triple-negative, operable breast cancer with histologically-confirmed invasive adenocarcinoma	Capecitabine (N=448) or observation (N=428)	No
Lluch (2020), GEICAM/2003-11_CIBOMA/2004-01, eight countries (Spain, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, and Venezuela) [15]	Patients with high-risk, triple-negative, operable breast cancer with histologically-confirmed invasive adenocarcinoma	Capecitabine (NR) or observation (NR)	Yes
Mayer 2021, ECOG-ACRIN EA1131 (NCT02445391), US [83]	Patients with stage II or III TNBC with residual disease after neoadjuvant chemotherapy	Capecitabine (N=213) or platinum therapy (N=199)	Yes
Schneider (2021), BRE12-158 (NCT02101385), US [84]	Patients with non-metastatic TNBC with residual disease at time of definitive surgical intervention	Capecitabine (N=74), olaparib (N=12), pembrolizumab (N=18), or observation (N=38)	Yes
Wang (2021), SYSUCC-001 (NCT01112826), China [85]	Patients with early-stage TNBC who had completed standard adjuvant chemotherapy	Capecitabine (N=222) or observation (N=221)	No
Immuno-oncology (N=3)			



Publication	Population	Intervention (Sample size)	High-risk breast cancer
Dent (2020), KEYNOTE-522 (NCT03036488), 21 countries [86]	Asian subgroup from KEYNOTE-522	Neoadjuvant: pembrolizumab plus chemotherapy (N=136) or placebo plus chemotherapy (N=79) Adjuvant: pembrolizumab plus radiotherapy (N=136) or placebo plus radiotherapy (N=79)	No
Schmid (2020), KEYNOTE-522 (NCT03036488), 21 countries [18]	Patients aged ≥18 years with centrally confirmed TNBC in all foci	Neoadjuvant: pembrolizumab plus chemotherapy (N=784) or placebo plus chemotherapy (N=390) Adjuvant: pembrolizumab plus radiotherapy (N=784) or placebo plus radiotherapy (N=390)	No
Schmid (2021), KEYNOTE-522 (NCT03036488), 21 countries [87]	Patients aged ≥18 years with centrally confirmed TNBC in all foci	Neoadjuvant: pembrolizumab plus chemotherapy (N=784) or placebo plus chemotherapy (N=390) Adjuvant: pembrolizumab plus radiotherapy (N=784) or placebo plus radiotherapy (N=390)	No

Abbreviations: HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.



Table 85. Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
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KEYNOTE-522	This study has been described in detail elsewhere. Please see section 6 (e.g., Table 13) and Appendix A.
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H.1.2 Excluded full text references

Table 86 includes a list of the studies that fulfilled the criteria in the original SLR but were excluded from this application.



Table 86. Summary of the design of excluded studies by hormone-receptor status and intervention

Publication	Population	Intervention (Sample size)	TNBC subgroup	Hormone-receptor-positive subgroup [†]	High-risk breast cancer
Hormone-receptor positive (N=24)					
CDK4/6 inhibitors (N=10)					
Gnant (2021), PALLAS (NCT02513394), 21 countries [88]	Patients with hormone-receptor-positive, HER2-negative eBC	Endocrine therapy plus palbociclib (N=2,884) or endocrine therapy plus placebo (N=2,877)	No	NA	No
Harbeck (2021), monarchE (NCT03155997), 38 countries [20]	Female and male patients aged ≥18 years with hormone-receptor-positive, HER2-negative breast cancer	Endocrine therapy alone (N=2,829) or endocrine therapy plus abemaciclib (N=2,808)	No	NA	Yes
Harbeck (2022), monarchE (NCT03155997), 38 countries [89]	Female and male patients aged ≥18 years with hormone-receptor-positive, HER2-negative breast cancer	Endocrine therapy alone (N=2,829) or endocrine therapy plus abemaciclib (N=2,808)	No	NA	Yes
Johnston (2020), monarchE (NCT03155997), 38 countries [21]	Female and male patients aged ≥18 years with hormone-receptor-positive, HER2-negative breast cancer	Endocrine therapy alone (N=2,829) or endocrine therapy plus abemaciclib (N=2,808)	No	NA	Yes
Loibl (2021), Penelope-B (NCT01864746), 11 countries [90]	Patients with high-risk residual disease for early hormone-receptor-positive, HER2-negative breast cancer	Endocrine therapy plus palbociclib (N=631) or endocrine therapy plus placebo (N=619)	No	NA	Yes
Mayer (2021), PALLAS (NCT02513394), 21 countries [91]	Patients with hormone-receptor-positive, HER2-negative eBC	Endocrine therapy plus palbociclib (N=2,883) or endocrine therapy plus placebo (N=2,877)	No	NA	No
Mayer (2022), PALLAS (NCT02513394), 21 countries [92]	Patients with hormone-receptor-positive, HER2-negative eBC	Endocrine therapy plus palbociclib (N=2,840) or endocrine therapy plus placebo (N=2,903)	No	NA	No



Publication	Population	Intervention (Sample size)	TNBC subgroup	Hormone-receptor-positive subgroup [†]	High-risk breast cancer
O'Shaughnessy (2020), monarchE (NCT03155997), 38 countries [93]	Patients with hormone-receptor-positive, HER2-negative, high-risk eBC	Endocrine therapy (NR) or endocrine therapy plus abemaciclib (NR)	No	NA	Yes
Spring (2020), LEADER (NCT03285412) [94]	Patients with localised stage I–III ER-positive (≥10%), HER2-negative breast cancer who had completed surgery and were on adjuvant endocrine therapy with at least one year or more of treatment remaining	Aromatase inhibitor plus continuous ribociclib (N=41) or aromatase inhibitor plus intermittent ribociclib (N=40)	No	NA	No
Zhimin (2021), monarchE (NCT03155997), 38 countries [95]	Subgroup of Chinese patients enrolled in monarchE	Endocrine therapy alone (N=242) or endocrine therapy plus abemaciclib (N=259)	No	NA	Yes
Endocrine therapy/chemo-endocrine therapy (N=14)					
Albain (2021), TAILORx (NCT00310180), four countries (USA, Canada, Ireland, Peru) [96]	Women aged 18 to 75 years with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer	Endocrine therapy (N=3,458) or chemo-endocrine therapy (N=3,449)	No	NA	No
Colleoni (2018), SOLE (NCT00553410), 22 countries [97]	Post-menopausal women with unilateral, lymph node-positive, steroid hormone receptor-positive operable breast cancer	Continuous letrozole (N=2,441) or intermittent letrozole (N=2,443)	No	NA	No
Dar (2021), STO-3, Sweden [98]	Post-menopausal women with lymph node-negative breast cancer	Tamoxifen (N=298) or control (N=267)	No	NA	No
Derks (2017), TEAM (NCT00279448 and NCT00032136), nine countries [99]	Post-menopausal women with histologically confirmed breast adenocarcinoma and locally assessed oestrogen receptor-positive or progesterone receptor-positive disease	Tamoxifen followed by exemestane (N=4,875) or exemestane (N=4,905)	No	NA	No



Publication	Population	Intervention (Sample size)	TNBC subgroup	Hormone-receptor-positive subgroup [†]	High-risk breast cancer
Kalinsky (2020), SWOG S1007 (RxPonder) (NCT01272037) [100]	Women aged >18 years with hormone-receptor-positive, HER2-negative breast cancer	Chemo-endocrine therapy (NR) vs endocrine therapy (NR)	No	NA	No
Ruiz-Borrego (2019), GEICAM/2006–10 (NCT00543127), Spain [101]	Post-menopausal women with centrally confirmed histological diagnosis of hormone-receptor-positive (ER-positive and/or PgR-positive) HER2-negative eBC	Anastrozole (N=437) or fulvestrant plus anastrozole (N= 433)	No	NA	No
Schochter (2018), SUCCESS C (NCT00847444), Germany [102]	Women with histologically confirmed HER2-negative, high-risk primary breast cancer with an indication for adjuvant chemotherapy	Tamoxifen plus exemestane (N=54) or exemestane (N=54)	No	NA	Yes
Smith (2017), FACE (NCT00248170) [103]	Post-menopausal women with hormone-receptor positive and node-positive eBC (stage IIA to IIIC invasive cancer)	Letrozole (N=2,061) or anastrozole (2,075)	No	NA	No
Smith (2020), POETIC (NCT02338310), UK [104]	Post-menopausal women with ER-positive or PgR - positive, HER2-positive or HER2-negative, operable primary breast cancer and no evidence of metastatic spread	Aromatase inhibitors (N=2,606) or control (N=1,316) [HER2-negative subgroup]	No	NA	No
Sparano (2018), TAILORx (NCT00310180), four countries (USA, Canada, Ireland, Peru) [105]	Women aged 18 to 75 years with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer	Endocrine therapy (N=3,458) or chemo-endocrine therapy (N=3,449)	No	NA	No
Sparano (2020), TAILORx (NCT00310180), four countries (USA, Canada, Ireland, Peru) [106]	Women aged 18 to 75 years with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer	Endocrine therapy (N=3,458) or chemo-endocrine therapy (N=3,449)	No	NA	No



Publication	Population	Intervention (Sample size)	TNBC subgroup	Hormone-receptor-positive subgroup [†]	High-risk breast cancer
Toi (2021), POTENT, Japan [107]	Women aged 20 to 75 years with histologically diagnosed stage I–IIIA and stage IIIB invasive breast cancer with an intermediate to high-risk of recurrence	Endocrine therapy (N=980) or endocrine therapy plus S-1 (N=979)	No	NA	No
Wagner (2020), TAILORx (NCT00310180), four countries (USA, Canada, Ireland, Peru) [108]	Women aged 18 to 75 years with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer	Endocrine therapy (N=3,458) or chemo-endocrine therapy (N=3,449)	No	NA	No
Yanez (2021), TAILORx (NCT00310180), four countries (USA, Canada, Ireland, Peru) [105, 109]	Women aged 18 to 75 years with hormone-receptor-positive, HER2-negative, axillary node-negative breast cancer	Endocrine therapy (N=3,458) or chemo-endocrine therapy (N=3,449)	No	NA	No
Mixed receptor status (N=15)					
Olaparib (N=1)					
Tutt (2021), OlympiA (NCT02032823), 23 countries [29]	Patients with HER2-negative eBC with BRCA1 or BRCA2 germline pathogenic or likely pathogenic variants and high-risk clinicopathological factors who had received local treatment and neoadjuvant or adjuvant chemotherapy	Olaparib (N=921) or placebo (N=915)	Yes	Yes	Yes
Capecitabine (N=8)					
Delaloge (2020), MINDACT (NCT00433589), nine countries [110]	Women aged 18 to 70 years with histologically proven primary non-metastatic (M0) invasive breast cancer (clinical T1, T2, or operable T3), initially lymph node negative only and, as of August 2009, with up to three positive axillary lymph nodes, and with a frozen tumour sample available	Anthracycline-based regimens with or without taxanes (N=566) or docetaxel plus capecitabine (N=574) [HER2-negative subgroup]	No	No	No



Publication	Population	Intervention (Sample size)	TNBC subgroup	Hormone-receptor-positive subgroup [†]	High-risk breast cancer
Joensuu (2009), FinXX (NCT00114816), multinational (Finland and Sweden) [111]	Patients aged 18 to 65 years with histologically confirmed invasive breast cancer and either regional lymph nodes containing cancer or node-negative cancer with diameter 20 mm or larger and negative progesterone receptor expression	Docetaxel followed by cyclophosphamide plus epirubicin plus fluorouracil (N=607) or docetaxel plus capecitabine followed by cyclophosphamide plus epirubicin plus capecitabine (N=606) [HER2-negative subgroup]	No	No	No
Joensuu (2012), FinXX (NCT00114816), multinational (Finland and Sweden)	Patients aged 18 to 65 years with histologically confirmed invasive breast cancer and either regional lymph nodes containing cancer or node-negative cancer with diameter 20 mm or larger and negative progesterone receptor expression	Docetaxel followed by cyclophosphamide plus epirubicin plus fluorouracil (N=607) or docetaxel plus capecitabine followed by cyclophosphamide plus epirubicin plus capecitabine (N=606) [HER2-negative subgroup]	Yes	Yes	No
Joensuu (2017), FinXX (NCT00114816), multinational (Finland and Sweden) [112]	Patients aged 18 to 65 years with histologically confirmed invasive breast cancer and either regional lymph nodes containing cancer or node-negative cancer with diameter 20 mm or larger and negative progesterone receptor expression	Docetaxel followed by cyclophosphamide plus epirubicin plus fluorouracil (N=607) or docetaxel plus capecitabine followed by cyclophosphamide plus epirubicin plus capecitabine (N=606) [HER2-negative subgroup]	Yes	Yes	No
Joensuu (2022), FinXX (NCT00114816), multinational (Finland and Sweden) [113]	Patients aged 18 to 65 years with histologically confirmed invasive breast cancer and either regional lymph nodes containing cancer or node-negative cancer with diameter 20 mm or larger and negative progesterone receptor expression	Docetaxel followed by cyclophosphamide plus epirubicin plus fluorouracil (N=607) or docetaxel plus capecitabine followed by cyclophosphamide plus epirubicin plus capecitabine (N=606) [HER2-negative subgroup]	Yes	Yes	No
Martin (2015), GEICAM/2003-10 (NCT00129389), Spain [114]	Women aged 18 to 70 years with a histological diagnosis of invasive HER2-negative breast cancer with axillary involvement (T1–3/N1–3), who had undergone primary surgery	Epirubicin plus cyclophosphamide followed by docetaxel (N=592) or epirubicin plus docetaxel followed by capecitabine (N=637) [HER2-negative subgroup]	Yes	Yes	No
Masuda (2017), CREATE-X, multinational (Japan and South Korea) [16]	Patients with HER2-negative, stage I–IIIB breast cancer and pathologically assessed residual cancer cells after	Endocrine therapy/radiotherapy (N=443) or endocrine therapy/radiotherapy plus capecitabine (N=444)	Yes	Yes	Yes



Publication	Population	Intervention (Sample size)	TNBC subgroup	Hormone-receptor-positive subgroup [†]	High-risk breast cancer
O'Shaughnessy (2015), NCT00089479 [115]	neoadjuvant chemotherapy with anthracycline, taxane, or both Women aged 18 to 70 years with high-risk (T1–3, N1–2, M0; or T>2 cm, N0, M0; or T>1 cm, N0, M0 and both ER- and PgR-negative), operable, histologically confirmed adenocarcinoma of the breast	Doxorubicin plus cyclophosphamide followed by docetaxel (N=1,124) or doxorubicin plus cyclophosphamide followed by docetaxel and capecitabine (N=1,137) [HER2-negative subgroup]	Yes	No	Yes
Endocrine therapy (N=6)					
Bramwell (2010), MA.12, Canada [116]	Pre-menopausal women with stage I–III breast cancer of any receptor status who completed adjuvant chemotherapy	Tamoxifen (N=338) or placebo (N=334)	No	Yes [‡]	No
De Placido (2003), GUN, Italy [117]	Patients aged ≤80 years with histologically confirmed, non-inflammatory, stages I–III (T3a) operable breast cancer	Tamoxifen (N=114) or no tamoxifen (N=127) with or without cyclophosphamide-methotrexate-fluorouracil [HER2-negative subgroup]	No	No	No
Ejlertsen (2013), DBCG 82-C, Denmark [118]	Post-menopausal women with complete resection of a unilateral invasive carcinoma of the breast who were high-risk patients without signs of distant metastases	Tamoxifen (N=367) or tamoxifen plus cyclophosphamide-methotrexate-fluorouracil (N=416) [HER2-negative subgroup]	Yes	Yes	Yes
Francis (2018), SOFT & TEXT (NCT00066690), 24 countries [119]	Women with documented pre-menopausal status and operable breast cancer that expressed oestrogen or progesterone receptors in at least 10% of cells	Tamoxifen (N=860), tamoxifen plus ovarian suppression (N=868), exemestane plus ovarian suppression (N=858) [HER2-negative subgroup]	No	No	No
Knoop (2014), DBCG 77C, Denmark [120]	Post-menopausal women with breast cancer and no malignant disease	Tamoxifen (N=868) or observation (N=848)	Yes	Yes	Yes
Rasmussen (2008), BIG 1-98 (NCT00004205) [121]	Post-menopausal women with eBC whose tumours were assessed by local pathologists as either ER-positive, PgR-positive, or both	Letrozole (N=1,648) or tamoxifen (N=1,646) [HER2-negative subgroup]	No	Yes	No



Abbreviations: BRCA1, breast cancer gene 1; BRCA2, breast cancer gene 2; eBC, early breast cancer; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; TNBC, triple-negative breast cancer; UK, United Kingdom.

† Only labelled 'yes' if the hormone-receptor-positive subgroup was also HER2-negative; HER2-positive, hormone-receptor-positive subgroups were not of interest to this SLR.

‡ Subgroup data were reported for patients with mixed HER2 status and are of limited relevance to this SLR.



The results from the 2025 clinical SLR update are included in Table 87.

Table 87. Eligible clinical studies identified in the 2022-2025 update

Authors	Clinical setting	Treatments	Main ITT results	Regulatory status
Schmid et al. [42]	Neoadjuvant and adjuvant tx of newly diagnosed, previously untreated, nonmetastatic (stage II/III) TNBC	Neoadjuvant pembro + CTx followed by adjuvant pembro vs. neoadjuvant PBO + CTx followed by adjuvant placebo	EFS HR: 0.65 (95% CI: 0.51-0.83); OS HR: 0.66 (95% CI: 0.50-0.87)	Approved in the EU
Mittendorf et al. [122]	Neoadjuvant and adjuvant tx in tx naïve patients with stage II/III TNBC	Neoadjuvant atezo + CTx followed by adjuvant atezo vs. neoadjuvant PBO + CTx followed by adjuvant placebo	EFS HR: 0.76 (95% CI: 0.47-1.21); OS HR: 0.56 (95% CI: 0.30-1.04)	Not approved in the EU
Conte et al. [123]	Adjuvant avelumab tx for 1-year vs PBO in high-risk, early TNBC following neoadjuvant/adjuvant CTX	Neoadjuvant avelumab + CTx followed by adjuvant avelumab vs. neoadjuvant PBO + CTx followed by adjuvant placebo	DFS HR: 0.81 (95% CI: 0.61-1.09); OS HR: 0.66 (95% CI: 0.45-0.97)	Not approved in the EU

Only three studies fulfilled the search criteria for the 2022-25 update of the clinical SLR [42, 122, 123]. However, two of these treatments are not approved in the neoadjuvant setting in the EU. Avelumab has no approved breast cancer indications, and atezolizumab is approved in combination with nab-paclitaxel for the treatment of unresectable locally advanced or metastatic TNBC whose tumours have PD-L1 expression $\geq 1\%$ and who have not received prior chemotherapy for metastatic disease, but not for neoadjuvant/adjuvant treatment. Hence, pembrolizumab is the only approved IO treatment in this clinical setting.

H.1.3 Quality assessment

The quality assessment suggested that studies included in the SLR were generally well reported and described results of the intention-to-treat analysis. Most studies used an appropriate method of randomisation and adequately concealed the intervention allocation. Baseline characteristics were generally similar between treatment arms. Outcome data were consistently analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis. Blinding was inadequate in most studies; however, where an open-label design was used, most patients did not deviate from their intended treatment due to the trial context.

H.1.4 Unpublished data

Not relevant.



Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

Objectives

A systematic literature review (SLR) was completed to identify the available health state utility values (HSUVs) for health states relating to patients with early breast cancer (EBC).

Due to the expected paucity of utility data available specifically for the HER2-negative primary BC population, the inclusion criteria were broadened to include all patients with early breast cancer regardless of their histology subtype. Therefore, this would include patients with HER2+ disease.

Research question

What are the available HSUVs associated with patients with early BC?

Sources

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 original search was conducted up to January 2022, but has been complemented with a search in Medline/PubMed up to September 2025 (Table 88).

Table 88. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 – Jan 2022	12.01.2022
Medline	Ovid	1946 – Sep 2025	15.09.2025
EBM Reviews*	Ovid	Up to Jan 2022	12.01.2022
EconLit	<u>Ovid</u>	Up to Jan 2022	12.01.2022



*Includes the HTA database, the National Health Service Economic Evaluation Database (NHS EED), Cochrane Central register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), the Cochrane Database of Systematic Reviews

Abbreviations: EBM: Evidence-Based Medicine

Table 89. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
SMC	www.scottishmedicines.org.uk	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
CADTH/CDA-AMC	www.cda-amc.ca	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
CEA Reg	https://cevr.tuftsmedicalcenter.org/databases/cea-registry	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
PBAC	www.pbs.gov.au/pbs/home	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
RePEc	http://repec.org/	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
EuroQoL	https://euroqol.org/	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
MAPI Institute	https://mapi-trust.org/	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
NIHR HTA	www.hta.ac.uk	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
INAHTA	www.inahta.org	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022
ScHARRHUD	www.scharrhud.org	Early breast cancer AND (TNBC OR HER2 negative)	12.01.2022

Table 90. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://meetinglibrary.asco.org/	Abstracts were identified by searching keywords in the ASCO meeting	Early breast cancer AND "HER2 negative" AND breast NOT	21.01.2022



Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
		library, 2018-2021	"HER2 positive" AND TNBC	
ESMO	https://oncology.pro.esmo.org/meeting-resources/esmo-congress ; https://www.journals.elsevier.com/annals-of-oncology	Abstracts were identified by searching keywords in the ESMO congress meeting resources and Annals of Oncology, 2018-2021	Early breast cancer AND (TNBC OR HER2 negative)	21.01.2022
AACR	https://www.abstractsonline.com/pp8/#!/9325/sessions/early%20breast%20cancer/1 ; https://cancerres.aacrjournals.org/content/	Abstracts were identified by searching categories in the AACR annual meetings 2018-2021 via Cancer Research.	HSUV, Early breast cancer, AND (TNBC OR triple negative OR HER2 negative)	21.01.2022
SABCS	https://www.abstractsonline.com/pp8/#!/10462 ; https://www.abstractsonline.com/pp8/#!/9223	abstracts were identified by searching the San Antonio Breast Cancer Symposium 2019-2021 using keywords	EQ-5D OR HSUV OR ("Early breast cancer" AND "HSUV") OR ("Early breast cancer" AND utility)	21.01.2022
EBCC	https://conferences.eortc.org/ebcc12/wp-content/uploads/sites/4/2020/10/EBCC_2020_Abstract_Book.pdf	Abstracts were identified by searching the European Breast Cancer Conference abstract book for 2020 using keywords	Early breast cancer AND (HER2 negative OR TNBC) OR Triple negative breast cancer OR Operable breast cancer	11.01.2021
ISPOR	https://www.ispor.org/heor-resources/presentations-database/search	Relevant conference abstracts were identified by searching the ISPOR presentations database using	(Early breast cancer OR Operable breast cancer) AND (HER2 negative OR TNBC OR triple negative)	21.01.2022



Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
		keywords 2018-2021		
HTAi	https://htai.org/wp-content/uploads/2021/06/HTAi_A_M21_Full-Program.pdf ; https://htai.even-tsair.com/htai Beijing2020/ ; https://htai.org/wp-content/uploads/2019/08/htai_A_M19_abstracts_20190812.pdf	Abstracts were identified by searching the HTAi online annual meeting abstract book 2018-2020	(Early breast cancer OR Operable breast cancer) AND (HER2 negative OR TNBC OR Triple negative breast cancer)	21.01.2022
SMDM	https://smdm.com/nfex.com/smdm/17bec/meetingapp.cgi/Session/2772 ; https://smdm.com/nfex.com/smdm/16BEC/webprogram/ata glance.html	Relevant conference abstracts were identified using the SMDM online resource 2016-2018	("Early breast cancer" OR Operable breast cancer) AND ("HER2 negative" OR "Triple negative" OR TNBC)	12.01.2021

I.1.1 Search strategies

Eligibility criteria applied in the review are summarised in Table 91.



Table 91. Eligibility criteria

CRITERIA	INCLUSION CRITERIA	EXCLUSION 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	-
DATE OF PUBLICATION	No limitation	-
LANGUAGE OF PUBLICATION	English abstracts of foreign publications will be considered. Studies published in a non-English language will be flagged, and their inclusion will be decided on a case-by-case basis.	-

Abbreviations: AE, adverse event; EQ-5D, European Quality of Life-5 Dimensions; HSUV, health state utility value; HUI, Health Utilities Index; HRQOL, health related quality of life; ICER, incremental cost-effectiveness ratio; LYG, life year gained; PRO, patient reported outcome; QALY, quality adjusted life year; QOL, quality of life; RCT, randomized controlled trial; SAE, serious adverse event; SF-6D, Short Form-6 Dimensions; SG, standard gamble; SLR, systematic literature review; TTO, time trade off; TRAE, treatment-related adverse event; US, United States.

The search strategies for the original and update SLRs are shown below.

Original review (December 2020)

Table 92 summaries the searches conducted in Embase for the years 1974 to 2020 (December 23). The database was access on December 24th, 2020.



Table 92 Search strategy for Embase

#	Searches	Results
1	quality adjusted life year/	27956
2	(quality adjusted or adjusted life year\$).ti,ab,kw.	26419
3	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab,kw.	21532
4	(illness state\$1 or health state\$1).ti,ab,kw.	11895
5	(hui or hui1 or hui2 or hui3).ti,ab,kw.	2430
6	(multiattribute\$ or multi attribute\$).ti,ab,kw.	1224
7	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab,kw.	25643
8	utilities.ti,ab,kw.	12344
9	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab,kw.	22815
10	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab,kw.	6732
11	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab,kw.	39428
12	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab,kw.	2911
13	"quality of life"/ and ((quality of life or qol) adj (score\$1 or measure\$1)).ti,ab,kw.	26636
14	"quality of life"/ and ec.fs.	44459
15	"quality of life"/ and (health adj3 status).ti,ab,kw.	16900
16	(quality of life or qol).ti,ab,kw. and "cost benefit analysis"/	5702
17	(qol or hrqol or quality of life).ti,kw.	147930
18	"quality of life"/	490037
19	((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab.	173096
20	18 and 19	134563
21	"cost benefit analysis"/ and (cost-effectiveness ratio\$ and (perspective\$ or life expectanc\$)).ti,ab,kw. and (quality of life or qol).ti.	4
22	"quality of life"/ and (quality of life or qol).ti.	104198
23	"quality of life"/ and ((quality of life or qol) adj3 (improv\$ or chang\$)).ti,ab,kw.	79502
24	"quality of life"/ and health-related quality of life.ti,ab,kw.	61368
25	economic model/	2282
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 20 or 21 or 22 or 23 or 24 or 25	372105
27	exp breast cancer/	482039
28	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp.	644213



#	Searches	Results
29	27 or 28	648731
30	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*) adj4 (breast or mammary or tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).ab,ti,kw.	228222
31	29 and 30	57432
32	26 and 31	2351

Table 93 summaries the searches conducted in Ovid MEDLINE®, including Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions®, from 1946 to December 23, 2020 (accessed December 24th, 2020).

Table 93 Search strategy for Ovid MEDLINE®

#	Searches	Results
1	exp Breast Neoplasms/	297616
2	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp.	433097
3	1 or 2	433104
4	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*) adj4 (breast or mammary or tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).ab,ti,kw.	146988
5	3 and 4	34809
6	Quality-Adjusted Life Years/	12717
7	(quality adjusted or adjusted life year\$).ti,ab,kf.	17862
8	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab,kf.	11335
9	(illness state\$1 or health state\$1).ti,ab,kf.	6788
10	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1588
11	(multiattribute\$ or multi attribute\$).ti,ab,kf.	957
12	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab,kf.	15966
13	utilities.ti,ab,kf.	7486
14	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab,kf.	12423
15	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab,kf.	4402
16	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab,kf.	22845
17	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab,kf.	1961



#	Searches	Results
18	quality of life/ and ((quality of life or qol) adj (score\$1 or measure\$1)).ti,ab,kf.	12102
19	quality of life/ and ec.fs.	10324
20	quality of life/ and (health adj3 status).ti,ab,kf.	9316
21	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	13201
22	(qol or hrqol or quality of life).ti,kf.	90621
23	((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab.	102946
24	*"Quality of Life"/	91968
25	23 and 24	29210
26	Cost-Benefit Analysis/ and (cost-effectiveness ratio\$ and (perspective\$ or life expectanc\$)).ti,ab,kf.	3706
27	(quality of life or qol).ti.	72562
28	24 and 27	55539
29	quality of life/ and ((quality of life or qol) adj3 (improv\$ or chang\$)).ti,ab,kf.	28726
30	quality of life/ and health-related quality of life.ti,ab,kf.	33462
31	models,economic/	10363
32	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 25 or 26 or 28 or 29 or 30 or 31	190266
33	5 and 32	957

Table 94 summaries the searches conducted in EBM Reviews (see details in table notes).

Table 94. Search strategy for EBM Reviews*

#	Searches	Results
1	exp Breast Neoplasms/	14130
2	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp.	44615
3	1 or 2	44615
4	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*) adj4 (breast or mammary or tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).ab,ti,kw.	26816
5	3 and 4	9727
6	Quality-Adjusted Life Years/	4538
7	(quality adjusted or adjusted life year\$).ti,ab,kf.	5030
8	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab,kf.	4039
9	(illness state\$1 or health state\$1).ti,ab,kf.	1317
10	(hui or hui1 or hui2 or hui3).ti,ab,kf.	280



#	Searches	Results
11	(multiattribute\$ or multi attribute\$).ti,ab,kf.	82
12	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab,kf.	5176
13	utilities.ti,ab,kf.	1236
14	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab,kf.	9988
15	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab,kf.	3306
16	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab,kf.	12017
17	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab,kf.	311
18	quality of life/ and ((quality of life or qol) adj (score\$1 or measure\$1)).ti,ab,kf.	2757
19	quality of life/ and ec.fs.	2782
20	quality of life/ and (health adj3 status).ti,ab,kf.	1043
21	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	1815
22	(qol or hrqol or quality of life).ti,kf.	20714
23	((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab.	42056
24	Cost-Benefit Analysis/ and (cost-effectiveness ratio\$ and (perspective\$ or life expectanc\$)).ti,ab,kf.	524
25	(quality of life or qol).ti.	20536
26	quality of life/ and ((quality of life or qol) adj3 (improv\$ or chang\$)).ti,ab,kf.	7105
27	quality of life/ and health-related quality of life.ti,ab,kf.	4478
28	models,economic/	1569
29	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	81470
30	5 and 29	782

*EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 17, 2020; EBM Reviews - ACP Journal Club 1991 to November 2020; EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016; EBM Reviews - Cochrane Clinical Answers November 2020; EBM Reviews - Cochrane Central Register of Controlled Trials November 2020; EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012; EBM Reviews - Health Technology Assessment 4th Quarter 2016; EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016: accessed December 24th 2020

January 2022 update

Table 95 summaries the updated searched conducted in Embase (Ovid) for the years 1974 to 2022 January 11. The database was searched 12.01.22.



Table 95 Search strategy for Embase (Ovid)

#	Searches	Results
1	quality adjusted life year/	30494
2	(quality adjusted or adjusted life year\$).ti,ab,kw.	28744
3	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab,kw.	23448
4	(illness state\$1 or health state\$1).ti,ab,kw.	12789
5	(hui or hui1 or hui2 or hui3).ti,ab,kw.	2699
6	(multiattribute\$ or multi attribute\$).ti,ab,kw.	1310
7	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab,kw.	27364
8	utilities.ti,ab,kw.	13239
9	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab,kw.	25779
10	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab,kw.	7492
11	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab,kw.	41814
12	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab,kw.	3107
13	"quality of life"/ and ((quality of life or qol) adj (score\$1 or measure\$1)).ti,ab,kw.	28952
14	"quality of life"/ and ec.fs.	49815
15	"quality of life"/ and (health adj3 status).ti,ab,kw.	17641
16	(quality of life or qol).ti,ab,kw. and "cost benefit analysis"/	6129
17	(qol or hrqol or quality of life).ti,kw.	154933
18	"quality of life"/	536543
19	((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab.	191014
20	18 and 19	148237
21	"cost benefit analysis"/ and (cost-effectiveness ratio\$ and (perspective\$ or life expectanc\$)).ti,ab,kw. and (quality of life or qol).ti.	5
22	"quality of life"/ and (quality of life or qol).ti.	112799
23	"quality of life"/ and ((quality of life or qol) adj3 (improv\$ or chang\$)).ti,ab,kw.	87415
24	"quality of life"/ and health-related quality of life.ti,ab,kw.	67382
25	economic model/	2600
26	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 20 or 21 or 22 or 23 or 24 or 25	405387
27	exp breast cancer/	514306



#	Searches	Results
28	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp.	685978
29	27 or 28	690843
30	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*) adj4 (breast or mammary or tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).ab,ti,kw.	242196
31	29 and 30	60776
32	26 and 31	2503
33	limit 32 to yr="2020 -Current"	354

Table 96 summaries the updated searches conducted in Ovid MEDLINE(R), including Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations, Daily and Versions(R), from 1946 to January 11, 2022. The database was searched 12.01.22.

Table 96 Search strategy for Ovid MEDLINE(R)

#	Searches	Results
1	exp Breast Neoplasms/	318489
2	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	459945
3	1 or 2	459952
4	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*) adj4 (breast or mammary or tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).ab,ti,kw.	157298
5	3 and 4	36956
6	Quality-Adjusted Life Years/	14257
7	(quality adjusted or adjusted life year\$).ti,ab,kf.	20040
8	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab,kf.	12683
9	(illness state\$1 or health state\$1).ti,ab,kf.	7437
10	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1767
11	(multiattribute\$ or multi attribute\$).ti,ab,kf.	1065
12	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab,kf.	17672
13	utilities.ti,ab,kf.	8264
14	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro qual or	14336



#	Searches	Results
	euroqol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab,kf.	
15	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab,kf.	5016
16	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab,kf.	24424
17	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab,kf.	2121
18	quality of life/ and ((quality of life or qol) adj (score\$1 or measure\$1)).ti,ab,kf.	13625
19	quality of life/ and ec.fs.	10814
20	quality of life/ and (health adj3 status).ti,ab,kf.	10451
21	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/	15031
22	(qol or hrqol or quality of life).ti,kf.	101370
23	((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab.	114761
24	*"Quality of Life"/	103007
25	23 and 24	33349
26	Cost-Benefit Analysis/ and (cost-effectiveness ratio\$ and (perspective\$ or life expectanc\$)).ti,ab,kf.	4427
27	(quality of life or qol).ti.	79357
28	24 and 27	60443
29	quality of life/ and ((quality of life or qol) adj3 (improv\$ or chang\$)).ti,ab,kf.	34074
30	quality of life/ and health-related quality of life.ti,ab,kf.	38597
31	models,economic/	10893
32	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 25 or 26 or 28 or 29 or 30 or 31	213066
33	5 and 32	1044
34	limit 33 to yr="2020 -Current"	182

Table 97 summaries the updated searches conducted in EBM Reviews (Ovid) (further details are presented in table notes).

Table 97 Search strategy for EBM Reviews (Ovid)

#	Searches	Results
1	exp Breast Neoplasms/	14088
2	((breast or mammary) adj5 (tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$)).mp. [mp=ti, ab, tx, kw, ct, ot, sh, hw]	44848
3	1 or 2	44848
4	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*))	28083



#	Searches	Results
	adj4 (breast or mammary or tumour\$ or tumor\$ or cancer\$ or neoplasm\$ or adenocarcinoma\$ or carcinoma\$).ab,ti,kw.	
5	3 and 4	9997
6	Quality-Adjusted Life Years/	1419
7	(quality adjusted or adjusted life year\$).ti,ab.	5609
8	(qaly\$ or qald\$ or qale\$ or qtime\$).ti,ab.	4486
9	(illness state\$1 or health state\$1).ti,ab.	1401
10	(hui or hui1 or hui2 or hui3).ti,ab.	287
11	(multiattribute\$ or multi attribute\$).ti,ab.	86
12	(utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain or gains or index\$)).ti,ab.	4961
13	utilities.ti,ab.	1307
14	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$ quality of life or european qol).ti,ab.	11356
15	(euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or 5domain\$)).ti,ab.	3743
16	(sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab.	13092
17	(time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab.	310
18	quality of life/ and ((quality of life or qol) adj (score\$1 or measure\$1)).ti,ab.	3066
19	quality of life/ and ec.fs.	1685
20	quality of life/ and (health adj3 status).ti,ab.	1177
21	(quality of life or qol).ti,ab. and Cost-Benefit Analysis/	1861
22	(qol or hrqol or quality of life).ti.	21868
23	((qol or hrqol\$ or quality of life) adj2 (increas\$ or decrease\$ or improv\$ or declin\$ or reduc\$ or high\$ or low\$ or effect or effects or worse or score or scores or change\$1 or impact\$1 or impacted or deteriorat\$)).ab.	47008
24	Cost-Benefit Analysis/ and (cost-effectiveness ratio\$ and (perspective\$ or life expectanc\$)).ti,ab.	620
25	(quality of life or qol).ti.	21788
26	quality of life/ and ((quality of life or qol) adj3 (improv\$ or chang\$)).ti,ab.	8038
27	quality of life/ and health-related quality of life.ti,ab.	5077
28	models,economic/	263
29	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	84231
30	5 and 29	779
31	limit 30 to yr="2020 -Current"	113



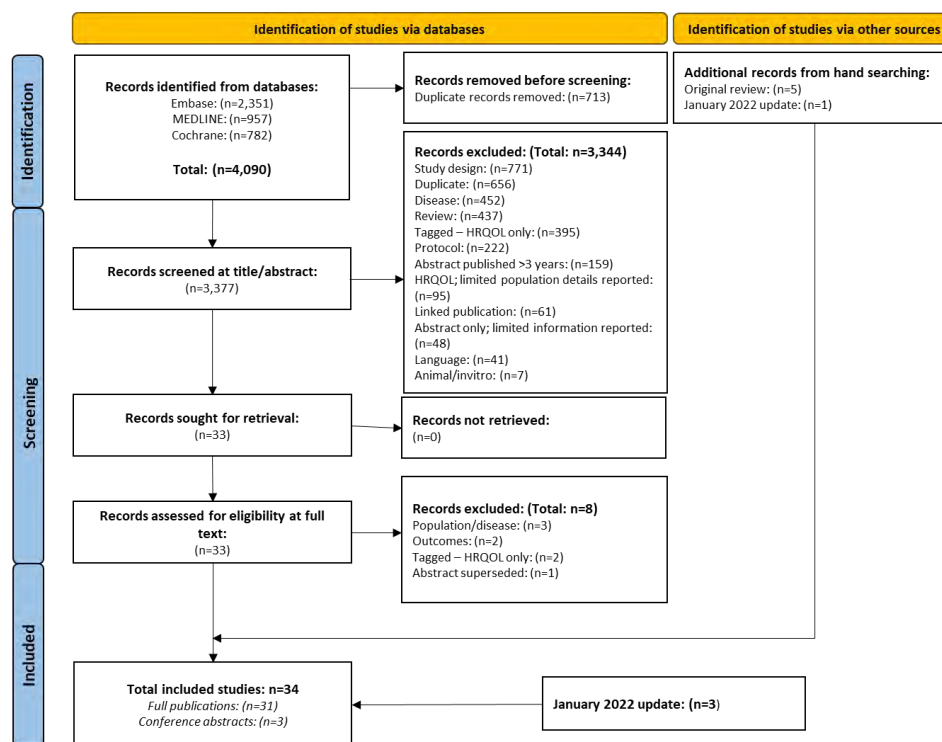
*ACP Journal Club 1991 to December 2021, Cochrane Central Register of Controlled Trials December 2021, Cochrane Database of Systematic Reviews 2005 to January 5, 2022, Cochrane Clinical Answers December 2021: searched 12.01.22

PRISMA diagram including 2022 update

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). 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 59.

Figure 59. PRISMA flow diagram for the HSUV review



Abbreviations: HRQoL, health related quality of life.

As a complement to the original SLR and the Jan 2022 update we have conducted a further review to cover the time span up to September 2025. This was more limited in scope and included only Medline and no search for conference abstracts. We still expect that Medline should capture most of the relevant new studies in the area.

Data base: <https://pubmed.ncbi.nlm.nih.gov/>

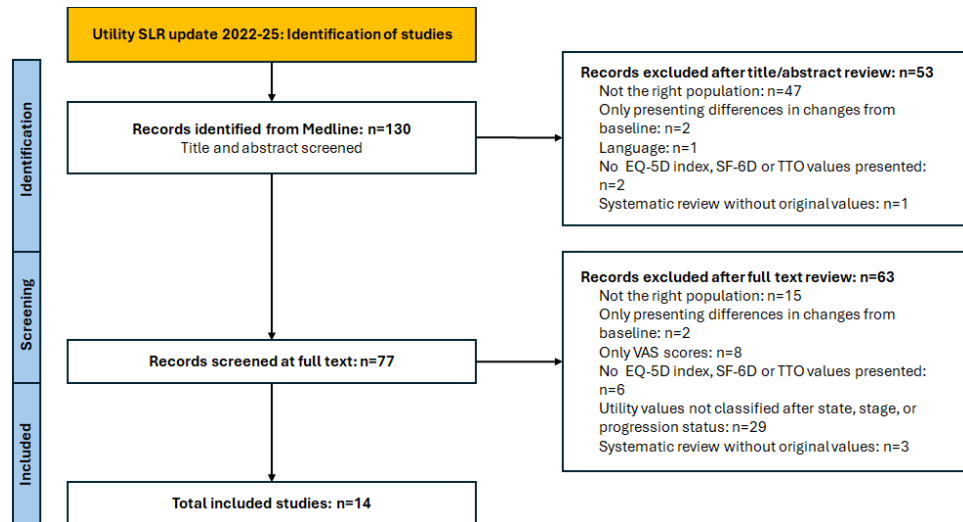
Search terms: breast cancer AND (eq-5d OR SF-6 OR TTO) AND “quality of life” AND (2022 OR 2023 OR 2024 OR 2025)

Date: 15.09.2025



We also tested variations of the search string above, such as: "breast cancer" AND (eq-5d OR SF-6 OR SF-8 OR SF-12 OR TTO OR "time trade-off" OR "standard gamble") AND ("quality of life" OR utility OR "index score") AND (2022 OR 2023 OR 2024 OR 2025). However, these did not generate more relevant search results.

Figure 60. PRISMA flow diagram for the HSUV 2025 update



In the original SLR, the selection of studies for inclusion in the health economic model was primarily based on how the methods and results aligned with the references cases from CADTH in Canada, NICE in England, SMC in Scotland, and PBAC in Australia. In Table 98 the HTA relevance of published HSUVs associated with EBC is outlined.



Table 98. Summary of HTA relevance of published HSUVs associated with EBC (N=34)

Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Bernhard, 2008 [124]	No – TTO	Yes – patients with operable BC	NA	NA	NICE	✗	1/3/4
					SMC	✗	1/3/4
					CADTH	✗	1/3/4
					PBAC	✗	1/3/4
Blankensteijn, 2020 [125]	No – TTO	No – members of the Canadian general population	NA	NA	NICE	✗	1/3/4
					SMC	✗	1/3/4
					CADTH	✗	1/3/4
					PBAC	✗	1/3/4
Cheng, 2012 [126]	No – SG	Yes – patients with stages Ia-IIIa EBC	NA	NA	NICE	✗	1/3/4
					SMC	✗	1/3/4
					CADTH	✗	1/3/4
					PBAC	✗	1/3/4
Conner-Spady 2001 [127]	Yes – EQ-5D-3L	Yes – patients with stages II/III EBC	Yes – UK tariff	Yes – TTO	NICE	✓	NA
					SMC	✓	NA
					CADTH	✓	NA
					PBAC	✓	NA



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Conner-Spady, 2005 [128]	Yes – EQ-5D-3L	Yes – patients with stages II/III EBC	Yes – UK tariff	Yes – TTO	NICE	✓	NA
					SMC	✓	NA
					CADTH	✓	NA
					PBAC	✓	NA
Criscitiello, 2021 [129]	Yes – EQ-5D-5L	Yes – patients with stages I-III HR+/HER2- EBC	Yes – country-specific societal tariffs including van Hout et al (2012) [130] for the UK [†]	Methods varied by value set used ^{††}	NICE	✓	NA
					SMC	✓	NA
					CADTH	✓	NA
					PBAC	✓	NA
Delaloge, 2019 [131]	Yes – EQ-5D-3L	Yes – patients with stage I-III EBC	NR	NR	NICE	Unclear	3/4
					SMC	Unclear	3/4
					CADTH	Unclear	3/4
					PBAC	Unclear	3/4
Elkin, 2005 [132]	No – arbitrary values were used in the model	Yes – patients with ER+ operable BC	NA	NA	NICE	✗	1/3/4
					SMC	✗	1/3/4
					CADTH	✗	1/3/4
					PBAC	✗	1/3/4
	Yes – EQ-5D-3L	Yes – patients with stages 0-II EBC			NICE	✗	3/4



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Freedman, 2010 [133]			Yes – US societal tariff (assumed)	Unclear – it is unclear whether TTO/SG was used to value health states as the data sets used were not clearly specified	<i>SMC</i>	Unclear	4
					<i>CADTH</i>	✓	NA
					<i>PBAC</i>	✓	NA
					<i>NICE</i>	✗	1/3/4
Grimison, 2009 [134]	No – UBQ-C	Yes – patients with advanced or early BC	NA	NA	<i>SMC</i>	✗	1/3/4
					<i>CADTH</i>	✗	1/3/4
					<i>PBAC</i>	✗	1/3/4
					<i>NICE</i>	✗	1/3/4
Hayman, 1997 [135]	No – SG	Yes – patients with stage I/II BC	NA	NA	<i>SMC</i>	✗	1/3/4
					<i>CADTH</i>	✗	1/3/4
					<i>PBAC</i>	✗	1/3/4
					<i>NICE</i>	✗	1/3/4
Hillner, 1991 [136]	No – survey of oncology staff	No – oncology staff who treated patients with EBC	NR	NR	<i>SMC</i>	✗	1/2/3/4
					<i>CADTH</i>	✗	1/2/3/4
					<i>PBAC</i>	✗	1/2/3/4
	No – TTO and SG	Yes – patients with EBC	NA	NA	<i>SMC</i>	✗	1/2/3/4
					<i>CADTH</i>	✗	1/2/3/4
					<i>NICE</i>	✗	1/3/4



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Jansen, 1998 [137]	No – TTO, SG, and VAS	Yes – patients with EBC	NA	NA	SMC	✗	1/3/4
					CADTH	✗	1/3/4
					PBAC	✗	1/3/4
NICE					✗	1/3/4	
SMC					✗	1/3/4	
CADTH					✗	1/3/4	
PBAC					✗	1/3/4	
NICE					✗	1/3/4	
SMC					✗	1/3/4	
CADTH					✗	1/3/4	
PBAC					✗	1/3/4	
NICE					✗	2/3/4	
SMC					✗	2/3/4	
CADTH					✗	2/3/4	
PBAC					✗	2/3/4	
Jeruss, 2006 [140]	Yes – EQ-5D-3L	No – surgeons on behalf of patients with invasive BC	NR	NR	NICE	✗	2/3/4
					SMC	✗	2/3/4
					CADTH	✗	2/3/4
Kim, 2017 [141]	No – SG and VAS	No – members of the South Korean general population	NA	NA	PBAC	✗	2/3/4
					NICE	✗	1/2/3/4
					SMC	✗	1/2/3/4
					CADTH	✗	1/2/3/4



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Knuttel, 2017 [142]	No – TTO and VAS	Yes – patients with BC and healthy controls without BC	NA	NA	PBAC	✗	1/2/3/4
					NICE	✗	1/3/4
					SMC	✗	1/3/4
					CADTH	✗	1/3/4
					PBAC	✗	1/3/4
Koskinen, 2019 [143]	No – 15D and EQ-5D-3L. EQ-5D results were not reported for BC patients only.	Yes – patients with BC	NR	NR	NICE	✗	1/3/4
					SMC	✗	1/3/4
					CADTH	Unclear	3/4
					PBAC	Unclear	3/4
					NICE	Unclear	3/4
Lagendijk, 2018 [144]	Yes – EQ-5D-5L	Yes – patients with stage pTis-3N0-3M0 EBC	NR	NR	SMC	Unclear	3/4
					CADTH	Unclear	3/4
					PBAC	Unclear	3/4
					NICE	Unclear	3/4
					SMC	Unclear	3/4
Law, 2020 [145]	Yes – EQ-5D-5L	Yes – patients with stage I-III HR+/HER2- EBC	Unclear – available country specific data sets were used but these were not specified	Unclear – it is unclear whether TTO/SG was used to value health states as the data sets used were not specified	CADTH	Unclear	3/4
					NICE	Unclear	3/4
					SMC	Unclear	3/4
					PBAC	Unclear	3/4
					CADTH	Unclear	3/4



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Lidgren, 2007 [43]	Yes – EQ-5D-3L and TTO	Yes – patients with BC	Yes – UK tariff	Yes – TTO	PBAC	Unclear	3/4
					NICE	✓	NA
					SMC	✓	NA
					CADTH	✓	NA
					PBAC	✓	NA
Lovrics, 2008 [146]	Yes – HUI3	Yes – patients with EBC	NR	NR	NICE	✗	1/3/4
					SMC	✗	1/3/4
					CADTH	Unclear	3
					PBAC	Unclear	3
Mahal, 2020 [147]	Yes – SF-6D	Yes – patients EBC were included in the total population	NR	No – utilities were derived from SF-12 and SF-36 surveys [148, 149]	NICE	✗	3/4
					SMC	✗	3/4
					CADTH	✗	3/4
					PBAC	✗	3/4
Mortimer, 2017 [150]	Yes – EQ-5D (version not specified)	Yes – patients with stages I-III HER2+ EBC	NR	NR	NICE	Unclear	3/4
					SMC	Unclear	3/4
					CADTH	Unclear	3/4
					PBAC	Unclear	3/4



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Ochi, 2021 [151]	Yes – EQ-5D (version not specified)	Yes – patients with stages I-II EBC	NR	NR	NICE	Unclear	1/3/4
					SMC	Unclear	3/4
					CADTH	Unclear	3/4
					PBAC	Unclear	3/4
Ring, 2021 [152]	Yes – EQ-5D-5L	Yes – patients with EBC, TNM stages: T1-3, N0-1, M0	NR	NR	NICE	Unclear	3/4
					SMC	Unclear	3/4
					CADTH	Unclear	3/4
					PBAC	Unclear	3/4
Rukminingsih, 2018 [153]	Yes – EQ-5D-5L	Yes – patients with EBC	NR	NR	NICE	Unclear	3/4
					SMC	Unclear	3/4
					CADTH	Unclear	3/4
					PBAC	Unclear	3/4
Schleinitz, 2006 [154]	No – TTO and SG	Unclear – women from primary care clinics and the community	NA	NA	NICE	✗	1/2/3/4
					SMC	✗	1/2/3/4
					CADTH	✗	1/2/3/4
					PBAC	✗	1/2/3/4
			Yes – UK tariff [66]	Yes – TTO	NICE	Unclear	1



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
Seferina, 2017 [155]	Yes – EQ-5D (version not specified)	Yes – patients with different stages of BC			<i>SMC</i>	✓	NA
					<i>CADTH</i>	✓	NA
					<i>PBAC</i>	✓	NA
Stout, 2006 [156]	Yes – EQ-5D (version not specified)	No – hypothetical utilities for BC health states	NA	NA	<i>NICE</i>	✗	2/3/4
					<i>SMC</i>	✗	2/3/4
					<i>CADTH</i>	✗	2/3/4
					<i>PBAC</i>	✗	2/3/4
Verrill, 2020 [157]	Yes –EQ-5D-5L	Yes – patients with EBC and metastatic BC	Yes – UK tariff by Devlin et al (2016) and van Hout et al (2012)	Yes – TTO (Devlin, 2016)	<i>NICE</i>	✓	NA
					<i>SMC</i>	✓	NA
					<i>CADTH</i>	✓	NA
					<i>PBAC</i>	✓	NA
Vos, 2018 [158]	Yes – EQ-5D (version not specified)	No – utilities were calculated for BC health states taken from Freedman et al (2010) [133], Vos et al (2015) [159], and Jagsi et al (2015) [160]	NR	Yes - TTO	<i>NICE</i>	✗	2/3
					<i>SMC</i>	✗	2/3
					<i>CADTH</i>	✗	2/3
					<i>PBAC</i>	✗	2/3
Wang, 2018 [161]	Yes – EQ-5D-3L	Yes – patients with BC and patients with pre-cancer	Yes – Chinese scoring algorithm [162]	Yes - TTO	<i>NICE</i>	✗	3
					<i>SMC</i>	✓	NA



Study	(1) Was a generic preference-based instrument used to describe health states?	(2) Did patients describe the health states?	(3) Were appropriate societal preferences used to value health states?	(4) Was the TTO/SG method used to value health states?	Is the study consistent with HTA body reference cases?		
					HTA body	Consistent with reference case (✓/✗/unclear)	If ✗/unclear, specify reason(s)
					CADTH	✗	3
					PBAC	✗	3

Abbreviations: BC, breast cancer; CADTH, Canadian Agency of Drugs and Technologies in Health; EBC, early breast cancer; EQ-5D (-3L/-5L), European Quality of Life Questionnaire – 5 Dimensions (-3 Level version/ -5 Level version); HSUV, health state utility value; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; NA, not applicable/available; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; SF-12, Short Form 12; SF-36, Short Form 36; SF-6D, Short Form 6-Dimensions; SG, standard gamble; SMC, Scottish Medicines Consortium; TTO, time trade-off; UK, United Kingdom; US, United States.

†The following value sets were used by country: US, Pickard et al (2019) [163]; Japan, Shiroiwa et al (2016) [164]; France, Andrade et al (2020) [165]; Germany, Ludwig et al (2018) [166]; Spain, Ramos-Goni et al (2018) [167]; UK, van Hout et al (2012) [130]; Italy, van Hout et al (2012) [130].

††The following country-specific value sets used direct methods of valuation (TTO/SG): US, Pickard et al (2019) [163]; France, Andrade et al (2020) [165]; Germany, Ludwig et al (2018) [166]; Spain, Ramos-Goni et al (2018) [167].



The results from the 2025 HSUV update are included in Table 99.

Table 99. Eligible HSUV studies identified in the 2022-2025 update.

Authors	Typology	HRQoL Instrument	Utility values
Rugo et al. [168]	HR+/HER2-; advanced	EQ-5D-5L, crosswalk UK EQ-5D-3L tariff by the van Hout et al.	aBC: 0.72 (SD: 0.20)
Wadasadawala et al. [169]	All adult histologically confirmed BC patients of stage I-IV	EQ-5D-5L, Indian value set	S I: 0.884±0.093, S II: 0.884±0.094, S III: 0.866±0.126, S IV: 0.836±0.187
Park et al. [170]	Metastatic	EQ-5D-5L, South Korean value set	mBC: 0.79 ± 0.13
Torres et al. [171]	Stage I-IV; HR+: 69%, HER2+: 17%, TNBC: 12%	EQ-5D-5L, Canadian value set	S I-III: 0.84 (SD: 0.14), S IV: 0.78 (0.14)
Milovic et al. [172]	(1) 1st year after primary BC, (2) 2nd and following years after primary BC or recurrence, and (3) metastatic disease	EQ-5D-3L, Slovenian value set	S I-III: 0.777 (SD: 0.191), S IV: 0.646 (SD: 0.224)
Kleijburg et al. [173]	eBC: primary ER+ breast cancer indicated for adjuvant tamoxifen	EQ-5D-5L, Dutch value set	S I: 0.81 ± 0.17, S II: 0.81 ± 0.18
Miret et al. [174]	Stage 0-III; 85% receiving hormonal tx	EQ-5D-5L, Spanish value set	S I-III: 0.86 (SD: 0.14)
Vrancken et al. [175]	Invasive BC indicated for surgical treatment with curative intention. Most in stage I and II at diagnosis (83%).	EQ-5D-5L, Dutch value set	S I-III: 0.852 (SD: 0.143)
Kwong et al. [176]	High-risk early TNBC	EQ-5D-5L, crosswalk UK EQ-5D-3L tariff by the van Hout et al.	EF on tx: 0.859, EF off tx: 0.862, LR: 0.80, DM: 0.697
Luu et al. [177]	HER2-positive BC. Stage I, II, or III: 66%. Stage IV (metastatic): 34%	EQ-5D-5L, Vietnamese value set	S I-III: 0.89 ± 0.13, S IV: 0.79 ± 0.21
Ndirangu et al. [178]	HER2- aBC; stage IIIb-IV	EQ-5D-5L, not clear what value set was used.	aBC: 1L: 0.77, 2L: 0.70; 3L+: 0.65
Mahtani et al. [179]	HER2- BRCa aBC.	EQ-5D-5L, country-specific value sets, except for Israel where the crosswalk UK EQ-5D-3L tariff by the van Hout et al. was used	aBC: PARPi vs CTx: 0.83 ± 0.02 vs 0.75 ± 0.04
Aguiar-Ibáñez et al. [180]	Early-stage TNBC	EQ-5D-5L, US value set	LR: Pre: 0.80, Post: 0.59; DM recurrence: Pre: 0.86; Post: 0.57
Crafoord et al. [181]	Before and after neoadjuvant treatment.	EQ-5D-3L, Swedish value set	Before tx: Intervention: 0.86, Control: 0.87; After tx: Intervention: 0.84, Control: 0.80



Abbreviations: aBC: Advanced breast cancer, BC: Breast cancer, CTx: Chemotherapy, DM: Distant metastatic, eBC: Early breast cancer, EF: Event-free, ER+: Estrogen-receptorpositive, HER2: Human epidermal growth factor receptor 2, HR+: Hormon-receptor positive, LR: Locoregional recurrence, S: Stage, tx: treatment.

Literature search results included in the model/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 gBRCA, HER2 -negative, high-risk eBC. In terms of health status, only Lidgren et al [43] 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 (gBRCA, HER2-negative, high-risk).

The 2022-25 update of HSUV literature search was more inclusive than previously in the sense that early breast cancer was not specified in the search. In addition, metastatic recurrence is also a state used in the health economic model.

In the model, we are using the OlympiA data for HSUs as it represents the only source of HSU for patients with gBRCAm, HER2-negative, high-risk early breast cancer. That is not affected by the updated literature search, but the results are confirming that the utility weights are reasonable. For IDFS and non-metastatic BC, the EQ-5D index score is 0.869 in the model. This is comparable with stage I-III results from other studies using EQ-5D, e.g. Wadasadawala et al. [169] (S I-II: 0.884, S III: 0.866), Torres et al. [171] (S I-III: 0.84), Kleijburg et al. [173] (S I-II: 0.81), Miret et al. [173] (S I-III: 0.86), Vrancken et al. [174] (S I-III: 0.852), Kwong et al. [175] (event-free: 0.86), and Luu et al. [176] (S I-III: 0.89). The studies are quite mixed regarding HR and HER2 status, but there does not seem to be a clear pattern with differences in HRQoL depending on molecular subtype.

A review of previous HTA submissions in eBC also indicated that Lidgren et al. [43] was one of the most frequently used studies for health economic modelling.

Table 100. Summary of literature estimates of HSUs in early BC (Lidgren et al.) [43]

Population, country, sample size	Method used to derive utilities	Health states	HSUV (95% CI)
Population: patients with a prior diagnosis of BC in Sweden Sample size: N=345	Instrument: EQ-5D-3L and TTO (not included in table)	Patients in the first year after primary BC, mean EQ-5D-3L score (N=72; 21%)	0.696 (0.634; 0.747)
	Tariff: EQ-5D-3L: UK tariff - Dolan (1997) [66]	Patients in the first year after recurrence, mean EQ-5D-3L scores (N=21; 6%)	0.779 (0.700; 0.849)
	TTO: NA	Patients in the second and following years after primary BC/recurrence,	0.779



		mean EQ-5D-3L score (N=177; 53%)	(0.745; 0.811)
		Patients in the metastatic disease state, mean EQ- 5D-3L score (N=65; 19%)	0.685 (0.620; 0.735)

I.1.2 Quality assessment and generalizability of estimates

Strengths of the study by Lidgren et al. [43] include that the utilities were derived from patients with BC, including patients with non-metastatic BC as separate health states. The number of patients who responded to each section of the EQ-5D questionnaire were also reported. A weakness with the study by Lidgren et al. is that the number of subjects contacted is not stated, only the number of enrolled patients. Another weakness is that it is not stated how missing data were handled. The generalizability for Denmark is limited by the use of the EQ-5D-3L questionnaire. The HSUV estimate of 0.685 is still in line with international HSUV estimates for advanced, metastatic and stage IV breast cancer in Table 99 above.

I.1.3 Unpublished data

Not relevant.



Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A, no literature search conducted for input to HE model.

Table 101 Sources included in the search – N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	N/A	N/A	N/A
Medline	N/A	N/A	N/A
CENTRAL	N/A	N/A	N/A

Table 102 Sources included in the targeted literature search – N/A

Source name/ database	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A



Appendix K. Mapping of HRQoL data

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 EORTC 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 randomization. No EQ-5D-3L or EQ-5D-5L data were collected in the study.

In the absence of EQ-5D-3L or EQ-5D-5L data, HSU values were estimated by mapping from the EORTC QLQ-C30 data collected at DCO1 of OlympiA using published algorithms. These data were considered 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.

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 [182]. To ensure comparability with OlympiA, the general population normative data were based on scores from females aged 40-49 years old.

Figure 61 and Figure 62 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) difference in mean scores between OlympiA and the population norms, Figure 61.

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 [65]. 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 generally comparable symptom burden to the age- and gender-matched general population.



Figure 61. Comparison of EORTC QLQ-C30 functioning scores in OlympiA (from mapping report) versus the population norms

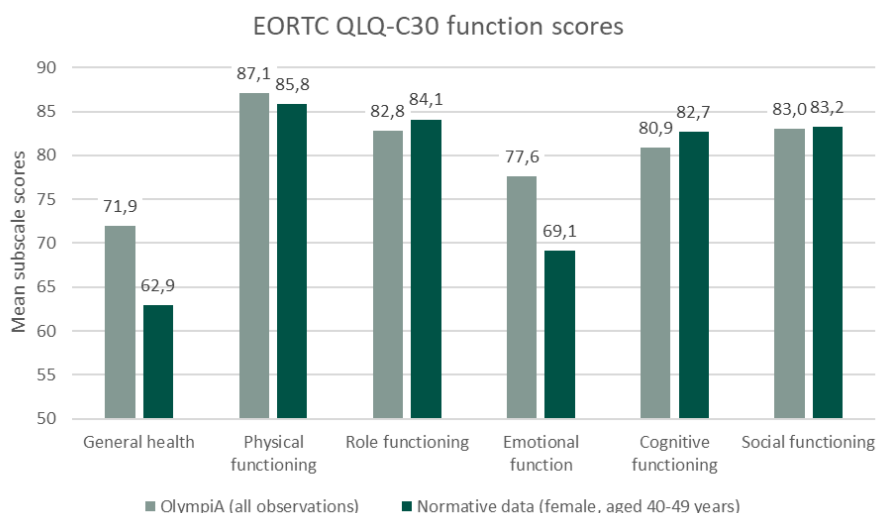
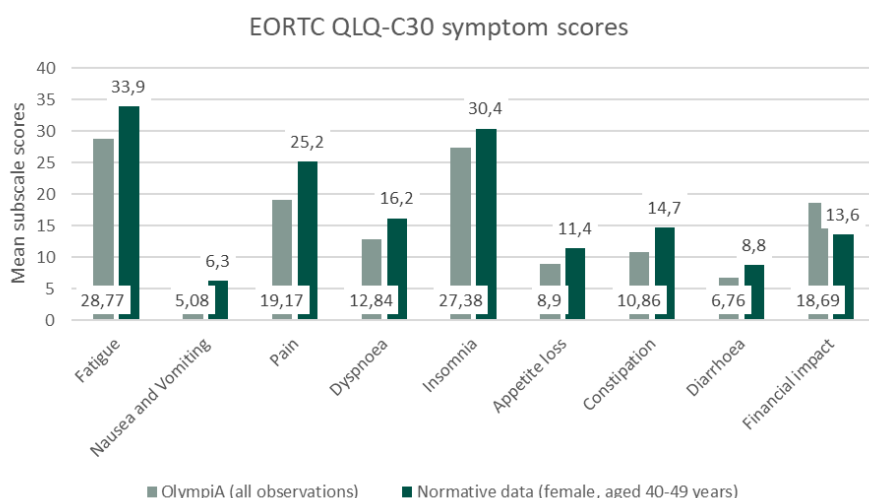


Figure 62. Comparison of EORTC QLQ-C30 symptom scores in OlympiA (from mapping report) versus the population norms



Mapping analysis

Published 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 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 [65, 183].

The algorithm by Crott and Briggs 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. HSUs based on the mapping by Longworth et al 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. A summary of the mean HSUs based on Crott and Briggs is presented by arm and follow-up period in Table 103.

Table 103. 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	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	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	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 EORT QLQ-C30 in OlympiA, 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. 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 104



Table 104. 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) 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% CI 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 10.3.4.

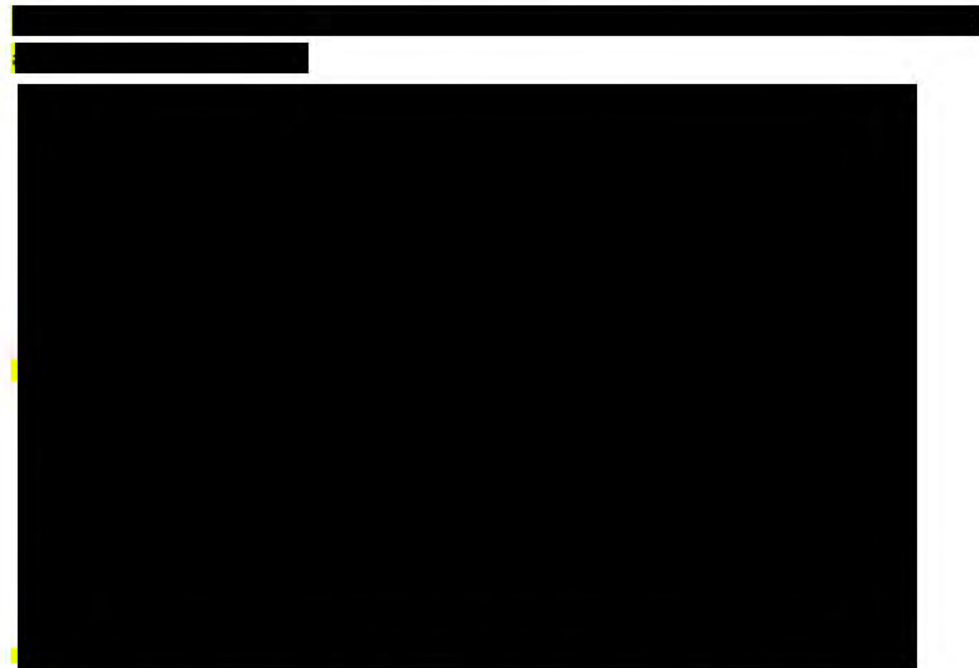
Additional regression analyses were performed to assess the impact of hormone receptor status on HSU. There was no significant or meaningful impact of HR+ versus TNBC on HSU (-0.001, p=0.895). Further, there was no impact of receptor status on the HSU of post versus pre-recurrence (interaction term -0.016,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



Appendix L. Validation of model clinical extrapolations

Figure 63 shows the long-term model projections of IDFS and OS for the TNBC and HER-/HR+ populations. The Kaplan-Meier graphs for DCO3 are overlaid on the projections.

The long-term projections illustrate the modelled risk profile for the TNBC and HER-/HR+ patients. For TNBC, the risk of recurrence was assumed to plateau at year 7 (Section D.1.7). 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 IDFS and OS curves. The trends are consistent with the literature evidence discussed previously in Section 4.



Overall, the model accurately predicts the Kaplan-Meier curves for both IDFS and OS across both TNBC and HER-/HR+ (Figure 63). This is further supported by the comparison of landmark OS probabilities in Table 105.

For TNBC, the model projections of OS at year 1 to 5 are within a margin of 1.5% and 3.5% points of all observed landmark probabilities in the olaparib and watch and wait arm, respectively. Beyond 5 years, the OS model projections and the KM landmarks are not as close for TNBC. However, the differences in area under the curve, measured as restricted mean survival time (RMST), for OS are similar up to 114 months, with a difference in RMST of 4.66 months based on the base-case modelling versus 4.43 months based on the observed landmark KM OS data for TNBC. [REDACTED]

[REDACTED] [77], with the model versus observed estimates of 74.0% versus 72% at 10 years



For HER2-/HR+, it is only the olaparib arm that is of interest given that the olaparib and abemaciclib are assumed equal in terms of efficacy and a cost-minimisation analysis is conducted (the abemaciclib efficacy is set equal to olaparib). For the olaparib arm, the model projections are within a margin of 2.8% points of the observed landmarks in OlympiA.

Table 105. 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 [77])						
1			1.0%			2.2%
2			1.4%			3.4%
3			1.2%			3.3%
4			1.1%			0.8%
5			0.9%	85.8%**		2.3%
10			-	72%*		-
HR+ (***)landmark from Pan et al and based on 1 minus risk of death from breast cancer)						
1			1.3%			2.4%
2			2.0%			3.8%
3			2.1%			4.4%
4			2.8%			3.1%
5			1.0%			0.5%
10			-	71%***		-
15			-	60%***		-
20			-	51%***		-

**The value in Copson et al was 81% at 5 years



Appendix M. The modelled treatment pathway

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.

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

- TP1: develop a locoregional recurrence or contralateral breast cancer and enter the non-mBC state.
- TP2: develop a distant metastatic recurrence or second primary non-breast invasive malignancy and enter the disease states for mBC.
- 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-mBC are described below.

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 mBC' state. After 2 years, patients that develop a distant metastatic recurrence enter the 'late onset mBC' state. Patients can enter the metastatic state from the disease-free state or the non-metastatic state. From the metastatic state, 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.

The model includes an option to set the time point for 'early' versus 'late' onset mBC 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 106). The alternative time points 1 and 3 years were considered in sensitivity analysis.



For both ‘early’ and ‘late’ onset mBC, 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 mBC was necessary to OlympiA data to inform the risk of death for ‘early onset’ mBC. 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.

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* mBC (median post-recurrence survival of 9.8-14.3 months in OlympiA (data on file), see Figure 46 in Appendix D.3) 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).

Table 106. Summary of literature evidence on the impact of time to recurrence on survival after diagnosis of metastatic breast cancer

Study	Population	Definition (early vs. late)	Post-recurrence survival for early vs. late
McKenzie et al. [58]. Prospective outcomes in sporadic vs. hereditary breast cancer (POSH) cohort study	Young women (aged <40 years) with initially localized disease from 127 hospitals in the United Kingdom	Recurrence time: <24 months 24-60 months 60+ months	2-year post-recurrence survival <24 months: 25% 24-60 months: 43% 60+ months: 49%
Lobbezoo et al. [184]	Consecutive patients diagnosed with mBC from 8 hospitals in the Netherlands	Metastatic free interval: <2 years >2years	Median survival from recurrence: <2 years: 9.1 months >2years: 27.9 months
Dawood et al. [185]	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	Median survival from recurrence: <6 months: 17.4 months 6-24 months: 17.3 months 2-5 years: 30.4 months 5+ years: 47.4 months



Non-metastatic recurrence pathway

Patients that enter the non-mBC health state remain in this state until the onset of distant mBC (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 mBC' state and those that have recurrence after 2 years enter the 'late onset mBC' 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 mBC or death after a locoregional event (see Figure 39 in Appendix D.2). 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.



Appendix N. Safety

N.1 Safety data from the clinical documentation

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 [62]. 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. [11, 62]

Grade AE ≥ 3 (OlympiA 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 $\geq 5\%$ of patients (8.7% of olaparib-treated patients vs 0.3% of placebo-treated patients) [62].

AEs of special interest (OlympiA DCO2)

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 [62]. 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%).



Dose reductions (OlympiA DCO2)

A summary of all dose reductions, dose interruptions and treatment discontinuations can be seen in Table 107. At DCO2, dose interruptions of olaparib or placebo due to AEs occurred in a higher proportion of patients in the olaparib arm (36.2%) compared to the placebo arm (14.2%). AEs leading to both dose reduction and interruption occurred in 16.9% of patients in the olaparib arm and 2.5% of patients in the placebo arm. Anaemia, decreased neutrophil count and nausea were the most common AEs leading to olaparib dose reduction, interruption or discontinuation:

- **Nausea:** In the olaparib arm, 4.7% and 5.5% of patients experienced nausea leading to dose reductions and interruptions, respectively. In the placebo arm, 0.2% and 0.7% of patients experienced nausea leading to dose reductions and interruptions, respectively.
- **Anaemia:** In the olaparib arm, 8.0% and 11.4% of patients experienced anaemia leading to dose reductions and interruptions, respectively. In the placebo arm, 0.2% and 0% of patients experienced anaemia leading to dose reductions and interruptions, respectively.
- **Decreased neutrophil count:** In the olaparib arm, 4.6% and 5.9% of patients experienced decreased neutrophil count leading to dose reductions and interruptions, respectively. In the placebo arm, 0.7% and 0.7% of patients experienced decreased neutrophil count leading to dose reductions and interruptions, respectively.

Table 107. Dose interruptions, reductions, and discontinuations due to AEs, DCO2 (SAS)

	n (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
Dose interruption due to AEs ^a	286 (31.4)	99 (11.0)
Dose reduction due to AEs ^b	213 (23.4)	33 (3.7)
Discontinuation due to AEs ^c	98 (10.8)	42 (4.6)

Footnotes: DCO2: 12 July 2021. ^aDose interruption is an AE leading to temporary discontinuation of olaparib or placebo. ^bDose reduction is an AE leading to dose reduction of olaparib or placebo. Patients may have had more than one AE leading to dose reduction. ^cOlaparib or placebo permanently stopped. CTCAE Version 4.03. MedDRA Version 24.0. **Source:** AstraZeneca Data on File (OlympiA: Primary Safety Analysis DCO2) [62]

Table 108. Overview of safety events, DCO 12 July 2021

	Olaparib (N=911) (OlympiA)	Comparator (N=907) (OlympiA)	Difference,% (95% CI)
Number of adverse events, n	NA	NA	
Number and proportion of patients with ≥1 adverse events, n (%)	836 (91.8)	758 (83.8)	8.0% (5.5 – 11.5%)
Number of serious adverse events*, n	NA	NA	



	Olaparib (N=911) (OlympiA)	Comparator (N=907) (OlympiA)	Difference,% (95% CI)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	79 (8.7)	78 (8.6)	0.1% (-2.5 – 2.7%)
Number of CTCAE grade ≥ 3 events, n	NA	NA	
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events [§] , n (%)	223 (24.5)	102 (11.3)	13.2% (9.8 – 16.7%)
Number of adverse reactions, n	NA	NA	
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	736 (80.8%)	482 (53.1%)	27.7% (23.5 – 31.8%)
Number and proportion of patients who had a dose reduction, n (%)	228 (25.0)	47 (5.2)	19.8% (16.7 – 23.0%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	236 (25.9%) ^a	187 (20.7%) ^a	5.2% (1.4 – 9.2%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	98 (10.8)	42 (4.6)	6.2% (3.7 – 8.6%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available.^a DCO March 27, 2020. CI calculated by AstraZeneca



No SAEs occurred with a frequency of $\geq 5\%$ in either treatment arm during the follow-up period. Anaemia was the most common SAE in the olaparib arm occurring in 15 patients (1.6%).

Table 109. Serious adverse events $\geq 5\%$ OlympiA

Adverse events	Olaparib (N = 911)		Placebo (N = 909)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	0	NA	0	NA

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the [ICH's complete definition](#)).

Table 110 presents the AEs of grade ≥ 3 occurring in $>1\%$ of patients in either treatment arm of the KEYNOTE-522 clinical trial, which were included in the health economic analysis for the health technology assessment of the indication in Denmark [55].

Table 110. Adverse events, grade ≥ 3 , with an incidence of $>1\%$ in either arm, Keynote-522

Adverse events	Pembrolizumab + chemotherapy		Chemotherapy	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Anaemia	19.5%	NA	15.7%	NA
Febrile neutropenia, n (%)	18.4%	NA	74.6%	NA
Increase in alanine aminotransferase, n (%)	6.4%	NA	0.0%	NA

Table 111 presents the AEs of grade ≥ 3 occurring in $>1\%$ of patients in either treatment arm of the CREATE-X clinical trial for capecitabine vs. control group.



Table 111. Adverse events, grade ≥ 3 , with an incidence of $>1\%$ in either arm, CREATE-X

Adverse events	Capecitabine (N=443)		Control group (N=459)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Neutropenia, n (%)	28 (6.3%)	NA	0 (0%)	NA
Leukopenia, n (%)	7 (1.6%)	NA	1 (0.2%)	NA
Diarrhoea, n (%)	13 (2.9%)	NA	0 (0%)	NA
Fatigue, n (%)	5 (1.1%)	NA	0 (0%)	NA
Hand-foot syndrome, n (%)	49 (11.1%)	NA	0 (0%)	NA

Table 112 presents the AEs of grade ≥ 3 occurring in $>3\%$ of patients in either treatment arm of the MonarchE clinical trial for abemaciclib + ET vs. ET.

Table 112. Adverse events, grade ≥ 3 , with an incidence of $>1\%$ in either arm, MonarchE

Adverse events	Abemaciclib + ET (N=2 791)		ET (N=2 800)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Diarrhoea, n (%)	219 (7.8%)	NA	6 (0.2%)	NA
Fatigue, n (%)	80 (2.9%)	NA	4 (0.1%)	NA
Abdominal pain, n (%)	39 (1.4%)	NA	9 (0.3%)	NA



Adverse events	Abemaciclib + ET (N=2 791)		ET (N=2 800)	
Leukopenia, n (%)	318 (11.4%)	NA	11 (0.4%)	NA
Neutropenia, n (%)	548 (19.6%)	NA	24 (0.9%)	NA
Arthralgia, n (%)	9 (0.3%)	NA	29 (1.0%)	NA
Anaemia, n (%)	58 (2.1%)	NA	12 (0.4%)	NA
Thrombocytopenia, n (%)	36 (1.3%)	NA	4 (0.1%)	NA
Aspartate aminotransferase increased, n (%)	53 (1.9%)	NA	15 (0.5%)	NA
Alanine aminotransferase increased, n (%)	77 (2.8%)	NA	19 (0.7%)	NA
Lymphopenia, n (%)	151 (5.4%)	NA	14 (0.5%)	NA
Hypertension, n (%)	30 (1.1%)	NA	49 (1.8%)	NA
Hypokalaemia, n (%)	32 (1.1%)	NA	7 (0.3%)	NA
Gamma-glutamyltransferase increased, n (%)	39 (1.4%)	NA	6 (0.2%)	NA
Venous thromboembolic event, n (%)	38 (1.4%)	NA	9 (0.3%)	NA
Pulmonary embolism, n (%)	28 (1.0%)	NA	4 (0.1%)	NA



Table 113 presents the frequency of AEs applied by treatment arm in the cost-effectiveness analysis and cost-minimisation analyses. AEs included in the analysis had a severity grade of ≥ 3 and an incidence of $\geq 3\%$ in either treatment arm. For pembrolizumab, capecitabine and abemaciclib, the user has the option to set the frequency of AEs to the same as for olaparib or to apply the frequency of grade ≥ 3 AEs with an incidence of $\geq 3\%$ in KEYNOTE 522, CREATE-X or MonarchE clinical trials, respectively, as reported in Schmid et al 2024, Masuda et al 2017 and Johnston et al 2023. AEs that did not meet the inclusion criteria (grade ≥ 3 AEs with an incidence of $\geq 3\%$) were set to 0% in the health economic model.



Table 113. Frequency of adverse events used in the health economic model

Adverse events	Olaparib	Watch and wait	Pembrolizumab	Capecitabine	Abemaciclib	Source
Anaemia, n (%)	8.70%	0.30%	18.00%	-	-	OlympiA CSR, data on file, KN 522, CREATE-X, MonarchE
Leukopenia, n (%)	3.00%	0.30%	-	-	318 (11.39%)	
Neutropenia, n (%)	4.90%	0.80%	34.50%	28 (6.32%)	548 (19.36%)	
Nausea	-	-	3.40%	-	-	
Fatigue	-	-	3.60%	-	-	
Elevated alanine aminotransferase level	-	-	5.50%	-	-	
Asthenia	-	-	3.60%	-	-	
Decreased neutrophil count	-	-	18.60%	-	-	
Severe skin reaction	-	-	4.70%	-	-	
Diarrhoea	-	-	-	-	219 (7.85%)	
Lymphopenia	-	-	-	-	151 (5.41%)	
Hand-foot syndrome	-	-	-	49 (11.06%)	-	



N.2 Safety data from external literature applied in the health economic model

See Section N.1 above.



Table 114. Adverse events that appear in more than X% of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference,% (95% CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	NA	NA	NA	NA	NA	NA	NA	NA



Appendix O. Surgery and radiotherapy costs in non-mBC and mBC health states

O.1 Non-mBC

A summary of the surgery and radiotherapy costs for non-mBC is provided in Table 115. In line with the clinical inputs for non-mBC (see Appendix D.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 [3]. 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 27 722.99DKK.

Table 115. Probabilities and costs (DKK) of radiotherapy and surgery for non-mBC (TNBC and HER2-/HR+)

Treatment	Proportion	N	Unit costs (DKK)
Radiotherapy	16.0%	81	7 905.00
Surgery	61.7%	81	42 882.00

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 117 and Table 118, respectively. The doses and treatment durations are validated, and the shares of treatments are informed by clinical expert input [39].

The one-off total costs of drug treatment for non-mBC in TNBC and HER2-/HR+ were 10 282.58 DKK (2 482.58 DKK ‘acquisition’ plus 7 800.00 DKK ‘administration’) and 7 364.44 DKK (1 839.44 DKK ‘acquisition’ plus 5 525.00 DKK ‘administration’), respectively as presented in Table 116.

Table 116. Summary of total one-off costs (DKK) for non-mBC

Population	Health state	Total per patient cost (DKK)
TNBC	Drug acquisition	2 482.58
	Drug administration	7 800.00



	Surgery/radiotherapy	27 722.99
HER2-/HR+	Drug acquisition	1 839.44
	Drug administration	5 525.00
	Surgery/radiotherapy	27 722.99

Table 117. Costs (DKK) and market shares of treatment for non-mBC (TNBC)

Treatment	Regimen	Number of cycles (21 days) of treatment	Sources for treatment duration	Market share	Treatment cost per cycle (DKK)	Administration costs per cycle (DKK)
Capecitabine	2000,g per m ² ‡ per day on days 1 to 14 followed by 7 days rest <u>Administration type:</u> Oral	7.1	Mean number of cycles of chemotherapy in the OlympiAD trial [50], data on file	10%	445.21	0.00
Docetaxel plus cyclophosphamide	Docetaxel: 75mg per m ² and Cyclophosphamide: 600mg per m ² once every 21 days [www.lmk.dk] <u>Administration type:</u> IV	E+C:6	Clinical expert input [39]	80%	D+C: 451.35	D+C: 1 625.00

‡ The body surface area is estimated to be 1.77 m², using the Cornell University Body Surface Area calculator [186]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).



Table 118. Costs (DKK) and market shares of treatment for non-mBC (HR+)

Treatment	Regimen	Number of cycles (21 days) of treatment	Sources for treatment duration	Market share	Treatment cost per cycle (DKK)	Administration costs per cycle (DKK)
Capecitabine	2000,g per m ² ± per day on days 1 to 14 followed by 7 days rest <u>Administration type:</u> Oral	7.1	Mean number of cycles of chemotherapy in the OlympiAD trial [50], data on file	5%	445.21	0.00
Docetaxel plus cyclophosphamide	Docetaxel: 75mg per m ² and Cyclophosphamide: 600mg per m ² once every 21 days [www.lmk.dk] <u>Administration type:</u> IV	E+C:6	Clinical expert input [39]	50%	D+C: 451.35	D+C: 1 625.00
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	C + E: 4 P: 4 (21-day cycles)	Clinical expert input [39]	5%	P + C + E: 993.75	P + C + E: 3 250.00



Administra
tion type:
IV

Letrozole	2.5 mg daily tablet.	13.9 (monthly cycles)	Median exposure to anastrozol e in the phase 3 FALCON study [187]	90%	10.28	0.00
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Administra
tion type:
oral

‡ The body surface area is estimated to be 1.77 m², using the Cornell University Body Surface Area calculator [186]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).

0.2 Early onset mBC

A summary of the surgery and radiotherapy costs for ‘early onset mBC’ is provided in Table 119. 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 D.3), the proportion 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 [62] (Table 119).

The one-off total costs of radiotherapy and surgical procedures per patient for ‘early’ mBC are 29 635.16 DKK, for the olaparib arm and 31 126.08 DKK for the watch and wait arm (Table 120).

Table 119. Probabilities and costs (DKK) of radiotherapy and surgery for ‘early’ mBC (pooled across TNBC and HER-/HR+)

Arm	Treatment	Probability of procedure	N*	Unit costs (DKK)
Olaparib	Radiotherapy	30.5%	105	7 905.00
	Surgery	25.7%	105	105 930.50
Watch and wait	Radiotherapy	37.3%	169	7 905.00
	Surgery	26.6%	169	105 930.50

*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 [50]. The mean number of subsequent treatment lines is equal to 1.70 based on data from OlympiAD [50]. 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 121 and Table 122. The doses and treatment durations are validated and the share of first and second-line treatments informed by clinical expert input [39]. 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 is 173 244.48 DKK in the olaparib arm and the watch and wait arm. The one-off total costs of drug treatment (all lines) per patient for 'early mBC' in HER2-/HR+ is 239 254.99 DKK in the olaparib arm (the same cost is applied to abemaciclib in the cost-minimisation analysis). A summary of the total per patient costs for 'early' mBC by arm and receptor status is provided in Table 120.

Table 120. Summary of total per patient costs (DKK) for 'early' mBC by arm and receptor status

Population	Arm	Health state	Total one-off cost (DKK)
TNBC	Olaparib	Drug acquisition (all treatment lines)	173 244.48
		Drug administration (all treatment lines)	28 184.81
		Procedure (surgery or radiotherapy)	29 635.16
	Watch and wait	Drug acquisition (all treatment lines)	173 244.48
		Drug administration (all treatment lines)	28 184.81
		Procedure (surgery or radiotherapy)	31 126.08
HER2-/HR+	Olaparib	Drug acquisition (all treatment lines)	239 254.99
		Drug administration (all treatment lines)	0.00
		Procedure (surgery or radiotherapy)	29 635.16
		Drug acquisition (all treatment lines)	239 254.99



Watch and wait	Drug administration (all treatment lines)	0.00
	Procedure (surgery or radiotherapy)	31 126.08



Table 121. Costs (DKK) 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 (DKK)	Administration costs per cycle (DKK)
				Market share of treatment at 1 st line	Market share of treatment at 2 nd line	Market share of treatment at 1 st line	Market share of treatment at 2 nd line		
Capecitabine (or single chemotherapy in general)*	2000mg per m ² ‡ per day on days 1 to 14 followed by 7 days rest <u>Administration type:</u> Oral	7.1 (21-day cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [50], data on file	85%	0%	85%	0%	445.21	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 <u>Administration type:</u> IV	7 (21-day cycles)	Median number of cycles in IMpassion 130 trial [51]	15%	0%	15%	0%	48 360.68	1 625.00
Eribulin	1.23mg per m ² ‡ on days 1 and 8 of a 21-day cycle <u>Administration type:</u> IV	7.1 (21-day cycles)	As for capecitabine (Mean number of cycles of chemotherapy in the OlympiAD trial [50], data on file)	0%	90%	0%	90%	14 701.76	3 250.00

* 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 m², using the Cornell University Body Surface Area calculator [186]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).



Table 122. Costs (DKK) 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 (DKK)	Administration costs per cycle (DKK)
				Market share of treatment at 1 st line	Market share of treatment at 2 nd line or later	Market share of treatment at 1 st line	Market share of treatment at 2 nd line or later		
Capecitabine	2000mg per m2 ± per day on days 1 to 14 followed by 7 days rest <u>Administration type:</u> Oral	7.1 (21-day cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [50], data on file	12.5%	27.5%	12.5%	27.5%	445.21	0.00
Letrozole	L: 2.5mg daily <u>Administration type:</u> Oral	13.9 (28-day cycles)	Median exposure to anastrozole in the phase 3 FALCON study [187]	0.0%	20.0%	0.0%	20.0%	10.28	0.00
Anastrozole	1mg daily <u>Administration type:</u> Oral	13.9 (28-day cycles)	Median exposure to anastrozole in the phase 3 FALCON study [187]	0.0%	30.0%	0.0%	30.0%	37.74	0.00
Fulvestrant		1 (loading dose) + 15.0 (subsequent months)	Median exposure to anastrozole in the phase 3 FALCON study [187]	0.0%	17.5%	0.0%	17.5%	1 004.44 (loading), 502.22 (subsequent)	0.00
Abemaciclib + letrozole	A: 150mg twice daily L: 2.5mg daily	16 (28-day cycles)	Median number of abemaciclib treatment	85%	0%	85%	0%	17 334.94	0.00



Administration type: Oral

cycles in the phase 3
MONARCH3 study [188]

* 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 m², using the Cornell University Body Surface Area calculator [186]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg).



O.3 Late onset mBC

A summary of the surgery and radiotherapy costs for 'late mBC' is provided in Table 123. 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 [3] (Table 123).

The one-off total costs of radiotherapy and surgical procedures per patient for 'late mBC' is 30 602.76 DKK for both arms of the model (Table 124).

Table 123. Probabilities and costs (DKK) of radiotherapy and surgery for 'late' mBC (TNBC and HER2-/HR+)

Arm	Treatment	Probability of procedure	N*	Unit costs (DKK)
Olaparib	Radiotherapy	34.7%	105	7 905.00
	Surgery	26.3%	105	105 930.50
Watch and wait	Radiotherapy	34.7%	169	7 905.00
	Surgery	26.3%	169	105 930.50

*based on the number of patients with distant recurrence in OlympiA

As for 'early onset mBC', patients in the 'late onset mBC' 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) [50].

The summary of the systemic drug therapy costs for 'late mBC' in TNBC and HER2-/HR+ are provided in Table 125 and Table 126. The doses and treatment durations are validated and the shares of first and second-line treatments by subgroup are informed by clinical expert input [39].

The share of first-line treatment is based on the case mix used to model the weighted-average survival after 'late onset mBC' as described in Table 73 (Appendix D.4). For single chemotherapy (60% of use in TNBC and 40% in HER2-/HR+), 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 [39]. 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 80 860.29 DKK and 264 436.18 DKK, respectively (Table 124).

Table 124. Summary of total one-off costs (DKK) for 'late' mBC by arm and receptor status

Population	Arm	Health state	Total one-off cost (DKK)
TNBC	Olaparib	Drug acquisition (all treatment lines)	80 860.29
		Drug administration (all treatment lines)	12 873.66
		Procedure (surgery or radiotherapy)	30 602.76
	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)	264 436.18
		Drug administration (all treatment lines)	4 410.74
		Procedure (surgery or radiotherapy)	30 602.76
	Watch and wait	Drug acquisition (all treatment lines)	Same as olaparib arm
		Drug administration (all treatment lines)	
		Procedure (surgery or radiotherapy)	



Table 125. Costs (DKK) and market shares of treatment for 'late onset mBC' (TNBC)

Treatment	Regimen	Number of cycles of treatment	Source for treatment duration	Olaparib and placebo arm		Treatment costs per cycle (DKK)	Administration costs per cycle (DKK)
				Market share of treatment at 1 st line	Market share of treatment at 2 nd line or later		
Capecitabine	2000mg per m ² ‡ per day on days 1 to 14 followed by 7 days rest <u>Administration type: Oral</u>	7.1 (21-day cycles)	Mean number of cycles of chemotherapy in the OlympiAD trial [50], data on file	85%	2.5%	445.21	0.00
Eribulin	1.23mg per m ² ‡ on days 1 and 8 of a 21-day cycle <u>Administration type: IV</u>	7.1 (21-day cycles)	As for capecitabine (Mean number of cycles of chemotherapy in the OlympiAD trial [50], data on file)	0%	20%	14 701.76	3 250.00
Paclitaxel	175mg per m ² ‡ on day 1 of each 21-day cycle <u>Administration type: IV</u>	6 (21-day cycles)	Maximum of 6 cycles	0%	42.5%	208.05	1 625.00
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 <u>Administration type: IV</u>	7 (21-day cycles)	Median number of cycles in IMpassion 130 trial [51]	15%	0%	48 360.68	1 625.00

‡ The body surface area is estimated to be 1.77 m², using the Cornell University Body Surface Area calculator [186]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg)



Table 126. Costs (DKK) and market shares of treatment for 'late onset mBC' (HER2-/HR+)

Treatment	Regimen	Number of cycles of treatment	Source for treatment duration	Olaparib and placebo arm		Treatment costs per cycle (DKK)	Administration costs per cycle (DKK)
				Market share of treatment at 1 st line	Market share of treatment at 2 nd 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 [57], data on file	5%	26%	445.21	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%	14 701.76	3 250.00
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%	208.05	1 625.00
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%	232.31	1 625.00



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 [188]	90%	0%	17 334.94	0.00
Anastrozole	1mg daily Administration type: Oral	13.9 (28-day cycles)	Median exposure to anastrozole in the phase 3 FALCON study	0.0%	30.0%	37.74	0.00

‡ The body surface area is estimated to be 1.77 m², using the Cornell University Body Surface Area calculator [186]. The calculation is based on the average height for Danish women (167cm) and the mean weight reported in the OlympiA trial (68.7kg)



Appendix P. Disease management costs

A summary of the disease management costs by health state is presented in Table 127.

Table 127. Disease management costs used in the model

Activity	Frequency per month*	Unit cost [DKK]	DRG code	Reference
Oncologist visits	IDFS (0-12 months): 0.21	1 605.00	DRG: 23MA04 Kontrolundersøgelse	DRG 2026
	IDFS (12-60 months): 0.02			
	IDFS (year 5+): -			
	Non-MBC (0-60 months): 0.25			
	mBC: 0.25			
Cancer nurse visit	IDFS (0-12 months): 0.17	462.00		Visit + preparation and documentation. Sygeplejersker, Timeløn [DKK]. Værdisætning af enhedsomkostninger [68]
	IDFS (12-60 months): -			
	IDFS (year 5+): -			
	Non-MBC (0-60 months): -			
	mBC: -			
Cancer nurse phone call	IDFS (0-12 months): -	608.07	DRG: 65TE01 Telefon- og videokonsultation	DRG 2022, inflated to January 2026 value
	IDFS (12-60 months): 0.04			
	IDFS (year 5+): -			
	Non-mBC (0-60 months): -			
	mBC: -			
Computed tomography (CT) scan – thoracic	IDFS (0-12 months): 0.04	2 677.00	DRG: 30PRO7 CT-scanning, ukompliceret	DRG 2026
	IDFS (12-60 months): -			
	IDFS (year 5+): -			
	Non-mBC (0-60 months): -			
	mBC: -			



Activity	Frequency per month*	Unit cost [DKK]	DRG code	Reference
Computed tomography (CT) scan – thoracic and abdomen	IDFS (0-12 months): -		DRG: 30PRO7 CT-scanning, ukompliceret	DRG 2026
	IDFS (12-60 months): -			
	IDFS (year 5+): -	2 677.00		
	Non-mBC (0-60 months): 0.25 mBC: 0.25			
Mammogram	IDFS (0-12 months): -		DRG: 30PR14 Mammografi, ukompliceret	DRG 2026
	IDFS (12-60 months): 0.0042	703.00		
	IDFS (year 5+): 0.0031			
	Non-mBC (0-60 months): - mBC: -			
Full blood count	IDFS (0-12 months): -			As proposed for Kadcyła (HER2+ eBC) submission – Medicinrådet 2020 p.16, inflated to January 2026 value [70]
	IDFS (12-60 months): -			
	IDFS (year 5+): -	408.20		
	Non-mBC (0-60 months): 0.25 mBC: 0.25			
Total cost (DKK)	IDFS (0-12 months):	778.26		
	IDFS (12-60 months):	36.37		
	IDFS (year 5+):	2.20		
	Non-mBC (0-60 months):	1 172.55		
	mBC:	1 172.55		
* Based on estimates on average frequency of visits from two clinical experts				



Appendix Q. Sensitivity analysis

Q.1 Deterministic sensitivity analysis – TNBC population

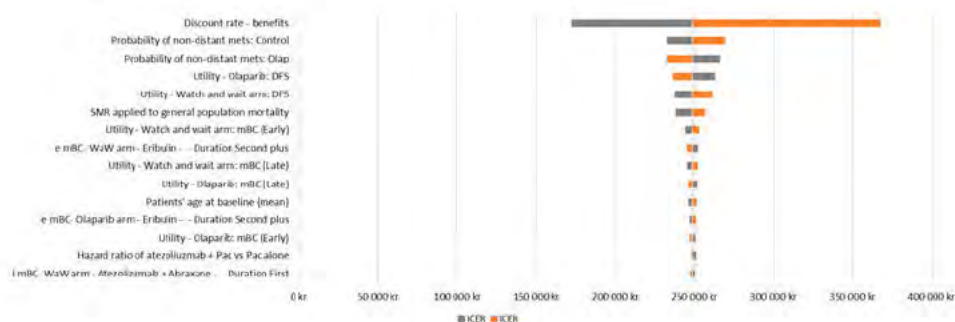
Results of the deterministic sensitivity analysis is presented in Table 128 and Figure 64. The parameter with the greatest impact on the ICER was the discount rate assigned to benefits. Excluding the variation as a result of the discount rate, and given the variation of additional included parameters, the deterministic sensitivity analysis indicated that the results of the cost-effectiveness analysis were robust. The parameter with the second greatest impact on the ICER was the conditional probability of a non-mBC event in the watch and wait arm.

Table 128. One-way sensitivity analyses results of the cost-effectiveness analysis (olaparib vs. watch and wait) – TNBC population

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Discount rate – benefits	±10%	Assumption	306 148	1.78	172 312
			306 148	0.83	367 656
Conditional probability of non- mBC event: watch and wait	±10%	Assumption	306 583	1.32	232 847
			305 678	1.14	268 961
Conditional probability of non- mBC event: olaparib	±10%	Assumption	305 451	1.15	266 128
			306 916	1.32	232 401
Utility – Olaparib: DFS	±10%	Assumption	306 148	1.16	263 114
			306 148	1.30	236 306
Utility – watch and wait: DFS	±10%	Assumption	306 148	1.29	237 456
			306 148	1.17	261 346
SMR applied to general population mortality	±10%	Assumption	306 134	1.29	237 978
			306 158	1.20	255 964



**Figure 64. Tornado diagram of ICER, cost-effectiveness analysis (olaparib vs. watch and wait).
TNBC population**



Q.2 Probabilistic sensitivity analysis

Cost-effectiveness analysis of olaparib versus watch and wait, TNBC population

Table 129 presents the results of the probabilistic sensitivity analysis for olaparib versus watch and wait, when running 1000 Monte Carlo simulations. Over the lifetime time horizon, the deterministic ICER was 248 905 DKK to be compared with the probabilistic ICER of 239 304 DKK.

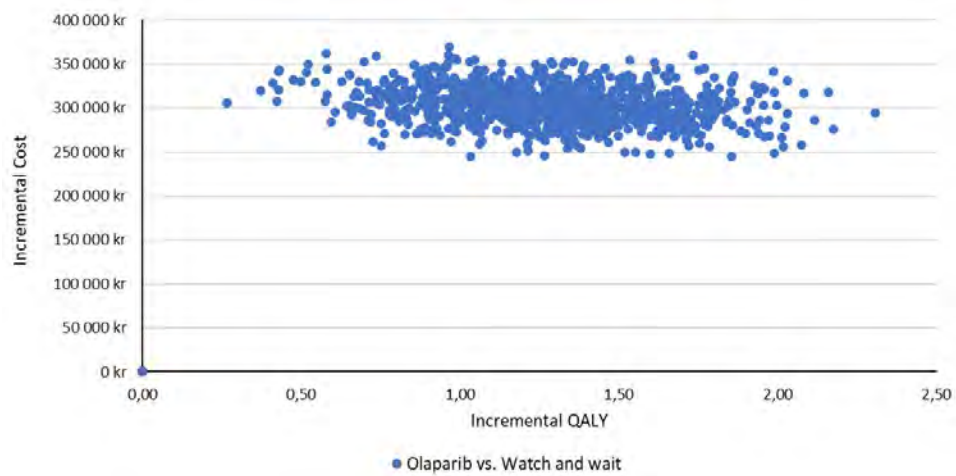
Table 129. Deterministic and probabilistic results of olaparib versus watch and wait, TNBC population

	Inc. costs	Inc. QALYs	ICER
Deterministic results			
(olaparib vs. watch and wait)	306 147	1.23	248 905
Probabilistic results			
(olaparib vs. watch and wait)	303 962	1.28	237 477

Figure 65 presents the cost-effectiveness plane for the probabilistic sensitivity analysis of olaparib versus watch and wait. The results of the 1000 simulations end up in the northeast quadrant of the cost-effectiveness plane, indicating that olaparib results in higher costs and QALYs gained compared with watch and wait.

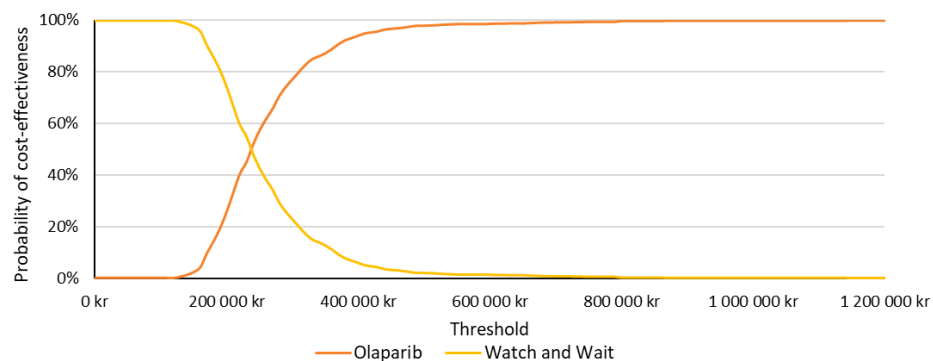


Figure 65. Cost-effectiveness plane (olaparib vs watch and wait), TNBC population



The cost-effectiveness acceptability curve, presented in Figure 66, indicate that the probability of olaparib being cost-effective compared with watch and wait is 99% at a willingness to pay (WTP) threshold of 600 000 DKK, and 100% at WTP thresholds of 800 000 DKK and 1 000 000 DKK.

Figure 66. Cost-effectiveness acceptability curve (olaparib vs watch and wait), TNBC population



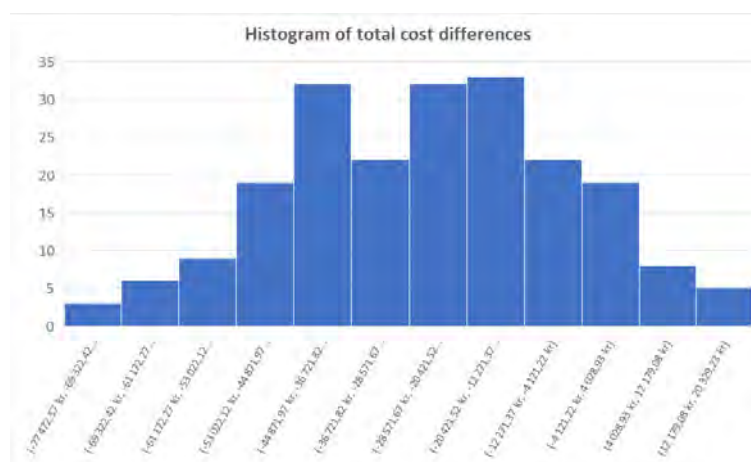
Cost-minimisation analysis of olaparib versus pembrolizumab/capecitabine, TNBC population

The PSA for the cost-minimisation analysis of olaparib versus pembrolizumab/capecitabine was run for 1 000 simulations and resulted in a probabilistic incremental cost of -27 181 DKK which can be compared with the deterministic incremental cost of -26 715 DKK.

The results are illustrated as a histogram in Figure 67, which shows how the cost differences were distributed in the PSA simulations.



Figure 67. Distribution of total cost differences for olaparib vs. pembrolizumab/capecitabine

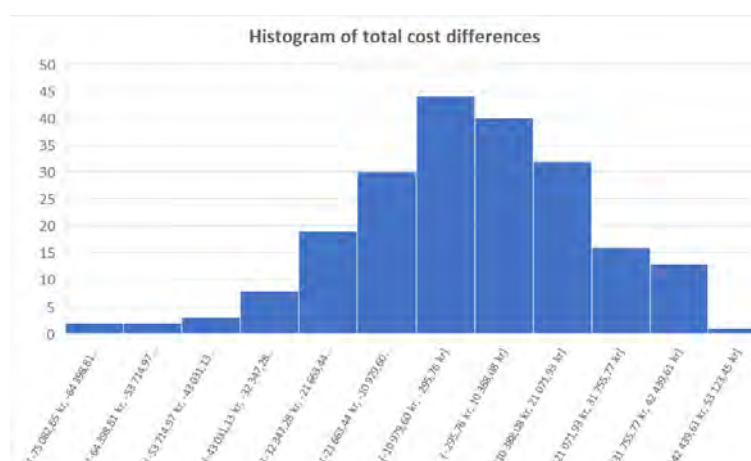


Cost-minimisation analysis of olaparib versus abemaciclib, HR+ population

The PSA for the cost-minimisation analysis of olaparib versus abemaciclib in the HR+ population was run for 1 000 simulations and resulted in a probabilistic incremental cost of -1 669 DKK which can be compared with the deterministic incremental cost of -2 050 DKK.

The results are illustrated as a histogram in Figure 68, which shows how the cost differences were distributed in the PSA simulations

Figure 68. Distribution of total cost differences for olaparib vs. abemaciclib



Q.3 Scenario analysis

Cost-effectiveness analysis of olaparib versus watch and wait – TNBC population

Table 130 provides a summary of the results of the scenario analysis run for the cost-effectiveness analysis of olaparib versus watch and wait that had an absolute change of >3% impact on the ICER. The scenario with the greatest impact on the ICER (+19.0%) was



when the time horizon was set to 30 years, followed by when the Gompertz distribution was applied to the placebo arm for TP6 (+14.9%). In general, the scenarios resulted in small changes of the ICER indicating robust results of the cost-effectiveness analysis. In additional scenario analysis run for the comparison of olaparib versus watch and wait, as mentioned in Section 11.8, costs of palliative care were included and in a second scenario the costs were applied to all patients. These scenarios had a minor impact on the results with ICERs of 243 621 DKK (a reduction of 2.1% compared with the base case) and 245 494 DKK (a reduction of 1.4% compared with the base case), respectively.

Table 130. Scenario analysis of the cost-effectiveness analysis of olaparib vs. watch and wait

Scenario	Inc. cost (DKK)	Inc. QALY	ICER (DKK/QALY)	% change from base case
Base case	306 147	1,23	248 905	NA
Time horizon - 30 years	306 232	1.03	296 311	19,0%
TP6 distribution (Placebo) - Gompertz	301 881	1.06	286 048	14,9%
Utility source (Lidgren et al. 2007 for all health states)	306 147	1.08	282 345	13,4%
TP1/TP2 distribution - Generalized Gamma	307 990	1.12	274 873	10,4%
Utility source - OlympiA Longworth mapping	306 147	1.12	272 973	9,7%
TP6 distribution (Placebo) - Lognormal	303 300	1.11	272 545	9,5%
TP6 distribution (Placebo) - Loglogistic	303 577	1.12	269 997	8,5%
TP1/TP2 distribution - Exponential	308 256	1.33	231 198	-7,1%
TP6 distribution (Olap) - Gompertz	307 939	1.30	236 252	-5,1%
TP6 distribution (Placebo) - Generalised Gamma	304 876	1.18	258 916	4,0%
Time horizon - 40 years	306 163	1.18	258 748	4,0%
Time point at which patients are no longer at risk of recurrence (5 years)	305 592	1.27	240 176	-3,5%
Patients' age at baseline: 45	306 155	1.19	257 167	3,3%
Utility source (using Lloyd et al for the mBC states)	306 147	1.27	240 810	-3,3%
Time point at which patients are no longer at risk of recurrence (15 years)	306 650	1.19	256 745	3,1%
TP6 - Assume the same risk of death across arms	307 172	1.27	241 292	-3,1%



Cost-minimisation analysis of olaparib versus pembrolizumab/capecitabine – TNBC population

Table 131 provides a summary of the results of the scenario analysis run for the cost-minimisation analysis of olaparib versus pembrolizumab/capecitabine in the TNBC population.

Applying AEs and frequencies for the pembrolizumab and capecitabine arm derived from the KEYNOTE 522 trial (as reported in Schmid et al 2024) and CREATE-X trial (as reported in Masuda et al 2017), respectively, only had a limited impact on the incremental costs. The total cost of the pembrolizumab/capecitabine arm increased from 413 639 DKK to 414 846 DKK causing the incremental costs to change from -26 715 to -27 922.

A scenario was run where the cost of neoadjuvant pembrolizumab was added to the olaparib arm. This had a large impact on the incremental cost since the total cost for olaparib increased from 386 924 DKK to 611 099 DKK (incremental cost of 197 460 DKK versus the base case of -26 715 DKK). However, the basic assumption behind a cost-minimisation analysis is that the clinical effect is the same or at least very similar for the treatments compared. In this scenario, it could be questioned whether the same efficacy can be assumed since the setting compared with the clinical trial setting for olaparib in OlympiA has changed. The total efficacy could be higher by first adding neoadjuvant pembrolizumab to chemotherapy. Hence, it is a conservative scenario to add neoadjuvant pembrolizumab treatment costs to the olaparib arm without assuming any impact on the efficacy.

The fixed dose of pembrolizumab was used in a scenario analysis, as that is the dose used in KN522 and also reflected in the indication for pembrolizumab as neo- and adjuvant treatment in early TNBC. This caused the total cost of the comparator arm to increase to 563 940 DKK and the resulting incremental cost was -177 016 DKK in favour of olaparib. In addition, a scenario only including pembrolizumab in the comparator arm by setting the weight of capecitabine to 0% was also run. The total cost of the comparator arm increased to 444 622 DKK vs 413 639 DKK in the base case causing the incremental cost to be -57 698 DKK in favour of olaparib.

Table 131. Scenario analysis of the cost-minimisation analysis of olaparib vs. pembrolizumab/capecitabine, TNBC population

Scenario	Total cost olaparib	Total cost pembrolizumab /capecitabine	Inc. cost (DKK)	% change from base case
Base case	386 924	413 639	-26 715	NA
AEs in pembrolizumab/capecitabine arm based on KN 522 and CREATE-X	386 924	414 846	-27 922	-5%



Cost of neoadjuvant pembrolizumab applied to the olaparib arm	611 099	413 639	197 460	+839%
Fixed 200 mg dose for pembrolizumab as in KN522	386 924	563 940	-177 016	-563%
Comparator arm set to 100% pembrolizumab, 0% capecitabine	386 924	444 622	-57 698	-116%

Cost-minimisation analysis of olaparib versus abemaciclib – HR+ population

Table 132 provides a summary of the results of the scenario analysis run for the cost-minimisation analysis of olaparib versus abemaciclib in the HR+ population.

Applying AEs and frequencies for the abemaciclib arm derived from the MonarchE clinical trial (as reported in Johnston et al 2023), only had a limited impact on the incremental costs. The total cost of the abemaciclib arm increased from 531 289 DKK to 531 371 DKK causing the incremental costs to change from -2 050 to -2 131.

In a second scenario, the cost of gBRCA testing was excluded from the olaparib arm. This cost the difference in total costs to increase to – 30 841 DKK in favour of olaparib. In the base case assumption, it was assumed that 65% of patients are currently tested, this was varied in a scenario analysis to 85% causing the number needed to test to decrease from 7 to 3. This caused a difference in total costs of DKK -18 502 in favour of olaparib.

Table 132. Scenario analysis of the cost-minimisation analysis of olaparib vs. abemaciclib, HR+ population

Scenario	Total cost olaparib	Total cost abemaciclib	Inc. cost (DKK)	% change from base case
Base case	529 239	531 289	-2 050	NA
AEs in abemaciclib arm based on MonarchE	529 239	531 371	-2 131	-4%
Excluding testing costs	500 448	531 289	-30 841	-1 405%
Assume that 85% are currently being tested	512 787	531 289	-18 502	-803%

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