Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende olaparib i kombination med abirateron og prednisolon til behandling af metastatisk kastrationsresistent kræft i blærehalskirtlen

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. olaparib i kombination med abirateron og prednisolon
2. Forhandlingsnotat fra Amgros vedr. olaparib i kombination med abirateron og prednisolon
3. Ansøgers endelige ansøgning vedr. olaparib i kombination med abirateron og prednisolon

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

18.12.2023

Re: Assessment report. Lynparza (olaparib) plus abiraterone and prednisolone in prostate cancer

Thank you for the above assessment. AstraZeneca believes that many of the comments and conclusions are a fair summary of the available data but wish to highlight four comments for consideration:

Efficacy of olaparib + abiraterone beyond BRCAm:
AstraZeneca recognises Medicinrådet's conclusion that the efficacy of olaparib + abiraterone in BRCAm patients appears to have the greatest benefit, however, Medicinrådet concluded that only patients with BRCAm benefit from olaparib + abiraterone and not patients with non-BRCA HRRm on the basis that no OS benefit was observed, despite a median gain of 7.1 months of rPFS. Whilst the comment is made that the size of subgroups and the lack of stratification should be taken into consideration, it must be noted that the trial was not designed to assess a significant difference in OS even in the ITT population. Evidence from the PAOLA-1 study in advanced ovarian cancer showed that significant follow-up was needed to observe a difference in OS between olaparib + bevacizumab and placebo + bevacizumab in HRD positive/BRCA wild-type patients,[1] which may be an indication that a survival benefit for add-on olaparib in patients with defects in the HR pathway in prostate cancer is forthcoming. A post-authorisation study of olaparib + abiraterone in mCRPC is now enrolling in Europe. PARP inhibitors may also not have an equal effect on all HRR mutations,[2-4] and so further research may elicit a subset of HRR mutations beyond BRCA1/2 may who benefit from olaparib + abiraterone.

Looking at all non-BRCA patients enrolled in PROpel, subgroup analyses of the trial showed a clinically meaningful benefit in rPFS (median gain of 5.1 months) and prolonged time to subsequent treatment (median gain of 4.1 months) and time to initiation of cytotoxic chemotherapy (median gain 7.4 months).[5] OS data were immature but showed a trend for improved survival. In the subgroup of patients without BRCAm, there is a particularly positive trend for OS in patients younger than 65 years (HR 0.64), with good performance status (HR 0.86), who have previously received docetaxel (HR 0.82), or who had visceral metastases (HR 0.74).[5]

AstraZeneca believes that there might therefore be further subgroups of patients without BRCAm who benefit from olaparib + abiraterone.

Validity of the overall survival curves for olaparib + abiraterone:
Despite selecting the most pessimistic distribution for OS for olaparib + abiraterone, Medicinrådet comments that this still probably overestimates the survival because some patients die at the same rate as the general population and therefore olaparib is assumed to be curative. This is not strictly true. It is well known that most prostate cancer patients overall die *with* prostate cancer rather than *of* prostate cancer in general, at it is also a phenomenon in mCRPC. Evidence from a Swedish registry-based study shows that 5% of mCRPC patients die due to causes other than prostate cancer,[6] which could expected to be higher with life-prolonging therapies like olaparib. In the ITT population of the PROpel, 22 of the 176 deaths in the olaparib arm (12.5%) were due to causes other than prostate cancer or adverse events. As PROpel has the longest follow-up of first-line BRCAm patients with mCRPC, it is not possible to conclusively determine if the long-term survival for the olaparib arm as presented by AstraZeneca is valid and therefore taking a more conservative approach as per Medicinrådet's base case is plausible however this should be noted that it is a conservative approach and not an overestimation.

Subsequent treatments:
Medicinrådet has elected to reduce the number of BRCAm abiraterone-treated patients for whom olaparib is a subsequent therapy from 80.8% to 2.5%. Based on Medicinrådet's estimated patient numbers, this would suggest that of the 40 BRCAm patients starting abiraterone in year 1 in Denmark, 0.7 would receive olaparib as a subsequent therapy (after adjustment for those who do not receive active subsequent therapy). Despite the current reimbursement restriction for olaparib in BRCAm mCRPC patients who don't have other treatment options, it is believed that currently, more than one patient per year initiates olaparib monotherapy for mCRPC.

Terminal care costs:
Medicinrådet has elected to exclude terminal care costs for the assessment because it is unclear what palliative care entails and how many patients would receive this in practice. AstraZeneca would like to comment that Medicinrådet did include terminal care costs in their previous assessment for olaparib monotherapy for mCRPC with BRCA mutations, assuming that 10% of patients receiving active treatment will receive palliative care using a single hospitalisation to document the cost of palliative care. It is documented in the current submission from AstraZeneca as well as the report from Medicinrådet that only the costs of hospitalisation for palliative care are included, thus being in line with the required analytical perspective of cost-effective analyses and with Danish real-world evidence.

Concluding statement:
At net prices, we estimate olaparib in combination with abiraterone (+ prednisolone) to be cost-effective for BRCAm patients and we hope that this combined with the data in this group of patients will be seen as a new treatment option for prostate cancer patients within this subgroup.

We look forward to the outcome of the meeting in Medicinrådet on January 24th, 2024.

Kind Regards
AstraZeneca A/S

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References:

1. Ray-Coquard I, Leary A, Pignata S, Cropet C, Gonzalez-Martin A, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Ann Oncol. 2023;34(8):681-692.
2. De Bono JS, Matsubara N, Penel N, Mehra N, Kolinsky MP, et al. Exploratory gene-by-gene analysis of olaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): PROfound. J Clin Oncol. 2021;39(6):126.
3. Chi KN, Sandhu S, Smith MR, Attard G, Saad M, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. Ann Oncol. 2023;34(9):772-782.
4. Fizazi K, Azad AA, Matsubara N, Carles J, Fay AP, et al. TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment for patients with metastatic castration-resistant prostate cancer harboring homologous recombination repair gene alternations (HRR-deficient population). Presented at: 2023 ASCO Annual Meeting; 2023 Jun 2-6; Chicago, IL.
5. Mehra N, Clarke N, Armstrong A, Oya M, Shore N, et al. Efficacy of olaparib + abiraterone vs placebo + abiraterone in the non-BRCA mutation subgroup of patients with metastatic castration-resistant prostate cancer in the PROpel trial. Poster presented at: ESMO Congress 2023; 2023 Oct 20-24; Madrid, Spain.
6. Svensson J, Franck Lissbrant I, Gauffin O, Hjälm-Eriksson M, Kilany S, et al. Time spent in hormone-sensitive and castration-resistant disease states in men with advanced prostate cancer, and its health economic impact: registry-based study in Sweden. Scand J Urol. 2021;55(1):1-8.

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20.12.2023
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	24.01.2024
Leverandør	AstraZeneca
Lægemiddel	Lynparza (olaparib)
Ansøgt indikation	Olaparib i kombination med abirateron og prednisolon til behandling af metastatisk kastrationsresistent kræft i blærehalskirtlen (mCRPC)
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Lynparza (olaparib) og abirateron:

Tabel 1: Aftalepris

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP, (DKK)	SAIP (DKK) pr. 01.04.2024	Rabatprocent ift. AIP
Lynparza	100 mg	56 stk.	15.628,06	[redacted]	[redacted]	[redacted]
Lynparza	150 mg	56 stk.	15.688,70	[redacted]	[redacted]	[redacted]
Abirateron (Medical Valley)	500 mg	56 stk.	20.000	[redacted]	[redacted]	[redacted]

Aftaleforhold

Amgros har en igangværende aftale med leverandøren, som gælder til den 31.03.2024. En ny aftale vil starte den 01.04.2024, [redacted]. Abirateron er aftaledækket indtil den 31.03.2025.

Konkurrencesituationen

I dag er abirateron standardbehandling til patienter med mCRPC. Dermed er den ansøgte kombination et ekstra alternativ til patienterne.

Tabel 2: Lægemiddeludgifter pr. patient for et års behandling

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Lynparza	150 mg	56 stk.	600 mg daglig	[redacted]	[redacted]
Abirateron (Medical Valley)	500 mg	56 stk.	1000 mg daglig	[redacted]	[redacted]
Samlet udgift for behandling					[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

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

Konklusion

[redacted]

Application for the assessment of Lynparza (olaparib) in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Lynparza
Generic name	Olaparib
Marketing authorization holder in Denmark	AstraZeneca AB
ATC code	L01XK01
Pharmacotherapeutic group	Tablet
Active substance(s)	Olaparib
Pharmaceutical form(s)	Tablets 100 and 150 mg
Mechanism of action	Olaparib is an oral potent inhibitor of PARP1, PARP2, and PARP3. These PARP enzymes are required for the efficient repair of DNA single-strand breaks. During the repair process, after chromatin modification, PARP auto-modifies itself and dissociates from the DNA to facilitate access for base excision repair (BER) enzymes. Olaparib, when bound to the active site of DNA-associated PARP, prevents dissociation from DNA, blocking the repair of the single-strand break.
Dosage regimen	Lynparza is available in 100 mg and 150 mg tablets. Daily dose of 300 mg (two tablets 150 mg) twice daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.
Date of approval by EMA in this indication	16 December 2022: marketing authorisation from EMA/EC 10 November 2022: positive opinion from CHMP
Other approved therapeutic indications	**Ovarian cancer** • Lynparza is indicated as monotherapy for the: Maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Lynparza in combination with bevacizumab is indicated for the: maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with

Overview of the pharmaceutical	
	homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability. **Breast cancer** • 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. Monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with 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. **Adenocarcinoma of the pancreas** • Lynparza is indicated as monotherapy for the maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. **Prostate cancer** • As monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) that have progressed after prior treatment that included a new hormonal agent.
Will dispensing be restricted to hospitals?	Yes. Labelled BEGR
Combination therapy and/or co-medication	In the study and indication olaparib is administered in combination with abiraterone and prednisone or prednisolone
Packaging – types, sizes/number of units, and concentrations	100 mg and 150 mg packs each containing 56 tablets
Orphan drug designation	No

2. Abbreviations

ADT	Androgen depletion therapy
AE	Adverse event
ASCO	American Society of Clinical Oncology
BPI-SF	Brief pain inventory (short form)
CI	Confidence interval
CRPC	Castrate-resistant prostate cancer
CTC	Circulating tumour cell
DDR	DNA damage response and repair
DET	Data extraction table
EAU	European Association of Urology
EQ-5D	European quality of life-5 dimensions
ESMO	European Society for Medical Oncology
FACT-PC	Functional Assessment of Cancer Therapy - Prostate Cancer
G-CSF	Granulocyte colony stimulating factor
HRD	Homologous recombination deficiency
HRQoL	Health-related quality of life
HR	Hazard ratio
HRR	Homologous recombination repair
IQR	Interquartile range
mCRPC	Metastatic castration-resistant prostate cancer
nmCRPC	Non-metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
NE	Not estimable
NHA	Novel hormonal agent
NICE	National Institute for Health and Care Excellence
NR	Not reported
OS	Overall survival
PARP	Poly-(ADP ribose) polymerase
PARPi	PARP inhibitor
PFS	Progression-free survival
PROSPERO	International prospective register of systematic reviews
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	Radiographic progression-free survival
RoB	Risk of bias
SAE	Serious adverse event
SLR	Systematic literature review
SMDM	Society for Medical Decision Making
SRE	Skeletal-related event
SSRE	Time to symptomatic skeletal-related event
TRAE	Treatment-related adverse event
TTFST	Time to first subsequent therapy
TTD	Time to treatment discontinuation
TTTF	Time to treatment failure
TTPP	Time to pain progression

3. Tables and Figures

3.1 Figures

3.2 Tables

4. Summary

Efficacy and safety

AstraZeneca is applying for extended access for olaparib (in combination with abiraterone and prednisone/prednisolone) in mCRPC in whom chemotherapy is not clinically indicated. This application in based on the phase 3, randomised, double-blind, placebo-controlled, multicentre PROpel trial (ClinicalTrials.gov identifier: NCT03732820). The PROpel trial assessed the efficacy and safety of olaparib in combination with abiraterone in an all-comer population with mCRPC.[1] It enrolled 796 patients with mCRPC who had received no prior cytotoxic chemotherapy or NHAs at the mCRPC stage who were randomised 1:1 to olaparib 300 mg (2 × 150 mg tablets orally twice daily) plus abiraterone 1000 mg (once daily orally; with prednisone or prednisolone) or placebo plus abiraterone (once daily orally; with prednisone or prednisolone).[1]

Results presented are mainly from the third data cut-off (DCO3: 12th October 2022) as the latest published results, with supplemental results from DCO2 (14th March 2022) which represents the final formal analysis for radiographic progression free survival (rPFS), as well as DCO1 (30th July 2021) as the primary rPFS analysis.

PROpel met its primary endpoint, extending median rPFS by approximately 50% compared with placebo plus abiraterone (DCO1: 24.8 months vs 16.6 months; hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.54, 0.81; $p < 0.0001$). This effect was sustained to the final analysis (25.0 months vs. 16.5 months; HR 0.68; 95% CI 0.57, 0.81; $p < 0.0001$), including in the prespecified HRR and non-HRR subgroups (HRRm: 0.51; 95% CI 0.36, 0.70; and non-HRRm: 0.79; 95% CI 0.64, 0.98; testing conducted after randomisation).[1,2] Olaparib plus abiraterone showed a consistent positive trend towards improved OS compared with placebo plus abiraterone (HR 0.81; 95% CI 0.67, 1.00; p = 0.0544) in both patients with and without HRR mutations (HRRm: 0.66; 95% CI 0.45, 0.95; and non-HRRm: 0.89; 95% CI 0.70, 1.14), as well as towards second progression-free survival (PFS2; HR 0.76; 95% CI 0.59, 0.99; nominal $p = 0.0534$).[2,3] Nominally significant trends were also observed towards time to first subsequent therapy (24.6 months vs. 19.4 months; HR 0.76; 95% CI 0.64, 0.90; nominal $p = 0.0025$), supporting long-term benefit.[2] The safety profile of abiraterone was not adversely impacted by its combination with olaparib and most patients remained on study treatment (median relative dose intensity, olaparib, 98.2%; placebo, 99.7%; and abiraterone, 100%). The incidence of AEs was similar in the two treatment arms and was consistent with the known safety profile for olaparib and abiraterone.[1,4,5] The proportion of patients who experienced at least one AE of any grade was similar between treatment arms: olaparib plus abiraterone, 389 patients (97.7%) and placebo and abiraterone, 380 patients (96.0%), which generally manageable through dose interruptions and reductions.

Patients relevant for this application

Lynparza (olaparib) in combination with abiraterone is indicated for adult patients with mCRPC in whom chemotherapy is not clinically indicated. This is aligned with the patient group in the registrational PROpel trial and reflects the group of patients who would be treated with a new hormonal agent (NHA; abiraterone or enzalutamide) as their first line therapy for mCRPC. Patients who are indicated for chemotherapy in Denmark are those who have had a short response to androgen deprivation therapy in treatment settings prior to mCRPC or who have particularly symptomatic disease, as well as those patients who were treated with an NHA in the prior treatment setting as sequential use of NHAs is not recommended in clinical practice and therefore these patients would most likely be given chemotherapy. AstraZeneca estimates that approximately [redacted] patients per year will be treatment with olaparib in combination with abiraterone in Denmark.

Patients with mCRPC have a poor prognosis, with those patients receiving treatment with NHAs at first line today having a median survival of less than 3 years. Fewer than half of patients with mCRPC receive more than one line of therapy,

and disease progression after first line treatment is associated with the development of symptomatic pain, skeletal complications, and limited remaining effective treatment options.

Costs and QALY

The cost-utility analysis (CUA) for olaparib + abiraterone is performed with abiraterone and enzalutamide as the comparators, given these are the treatments which will be displaced in Danish clinical practice. The CUA is based on a partitioned survival analysis, extrapolating the primary and key secondary efficacy endpoints of rPFS and OS from the PROpel trial over a lifetime horizon.

For the labelled (ITT) population, olaparib + abiraterone is associated with an estimated gain of 1.37 QALYs compared to NHAs (assuming comparable efficacy between abiraterone and enzalutamide) and incremental costs (at drug list prices) of 1 021 255 DKK compared to abiraterone and 550 959 DKK compared to enzalutamide. As the majority of patients in Danish clinical practice are expected to be treated with abiraterone today, the resulting base case incremental cost-effectiveness ratio is 745 651 DKK/QALY. Both deterministic and probabilistic sensitivity analyses were performed and show that the cost-effectiveness estimates of olaparib + abiraterone are robust across sensitivity analyses.

It is estimated that between *** and *** patients will initiate treatment with olaparib combination therapy each year. The budget impact analysis shows that the introduction of olaparib combination therapy for 1L mCRPC is expected to be associated with an additional expenditure of ********** DKK by the fifth year after introduction (at ex-WHLS price, not including discounts). The increased budget impact is mainly driven by the increased costs of medication expenditure, with some costs savings in hospital care.

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

5.1 The medical condition and patient population

Approximately 4 500 men are diagnosed with prostate cancer (PC) each year in Denmark, and the prevalence in 2020 was nearly 46 000.[6] About one-third of diagnosed men can undergo curative treatment through surgery or radiotherapy. The remaining patients undergo observation, antiandrogen treatment, or castration. Prostate cancer is categorized into localized, locally advanced, and metastatic disease (see Figure 1 for an overview of disease stages and treatment modalities). Some patients are diagnosed with metastatic disease, whilst others progress following a recurrence of localised disease. At the first development of metastases the disease is assumed to be sensitive to castration (hormone sensitive prostate cancer; mHSPC), distinguished between high- (i.e., visceral metastasis and/or widespread bone metastasis) and low-volume (fewer than 4 bone metastases and no visceral metastases) disease.[7] In Danish practice, newly diagnosed high-volume mHSPC was typically treated with androgen deprivation therapy (ADT) + docetaxel, though triple therapy with ADT + docetaxel + abiraterone is becoming more standard practice, while a small group of patients unsuitable for docetaxel treatment is treated with ADT + abiraterone.[8] Patients with low volume disease are typically treated with ADT and radiotherapy. However, following castration some patients' disease progresses further and becomes resistant to castration and requires initiation of new therapy types. This phase of the disease is known as castration resistant disease (CRPC). A limited number of patients are castration resistant without metastases, having developed castration resistance due to therapy of a non-metastatic disease recurrence, though many of these patients ultimately develop metastases.

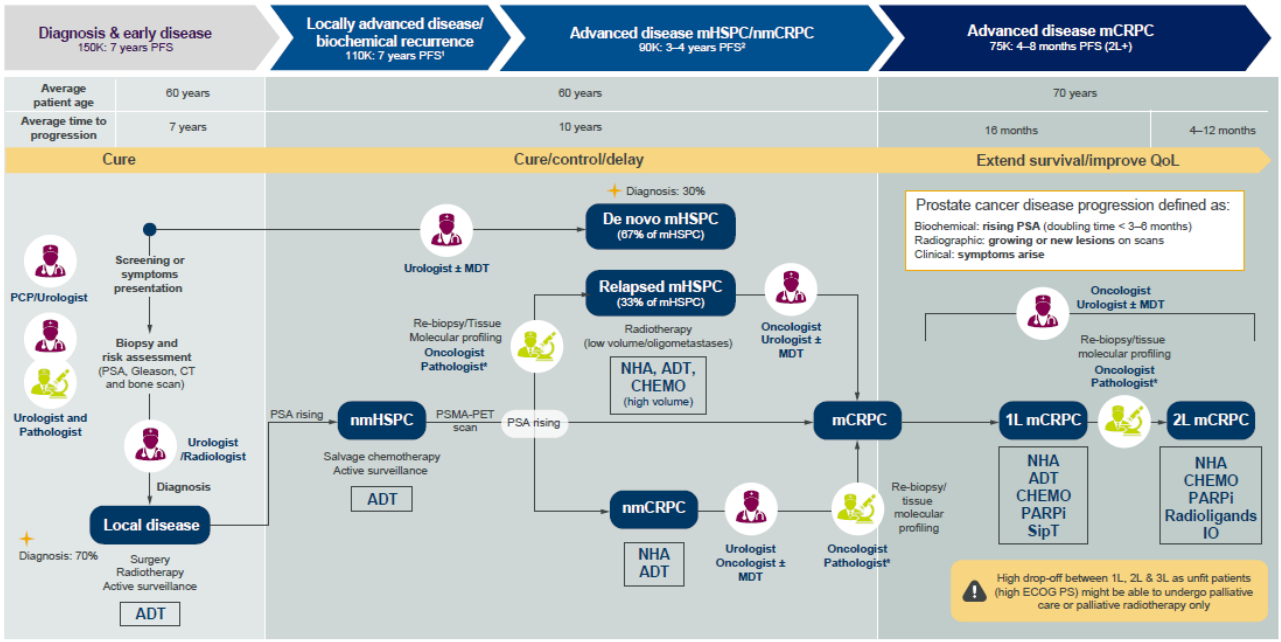
Table 1. Incidence and prevalence in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	4 450	4 674	4 516	4 560	4 620
Prevalence in Denmark	40 116	42 318	44 155	45 600	47 219

Metastatic castration-resistant prostate cancer (mCRPC) refers to PC with proven metastases involving either bone, lymph nodes outside the lesser pelvis, or parenchymatous organs that progress despite serum testosterone at castration level. mCRPC is defined as having serum testosterone < 1.7 nmol/l (< 50 ng/dl) plus either biochemical progression (three consecutive increases in PSA, measured at least one week apart, resulting in a 50% increase in two measurements) or radiological progression (two or more bone foci on bone scintigraphy or progression of soft tissue lesions according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1).[9]

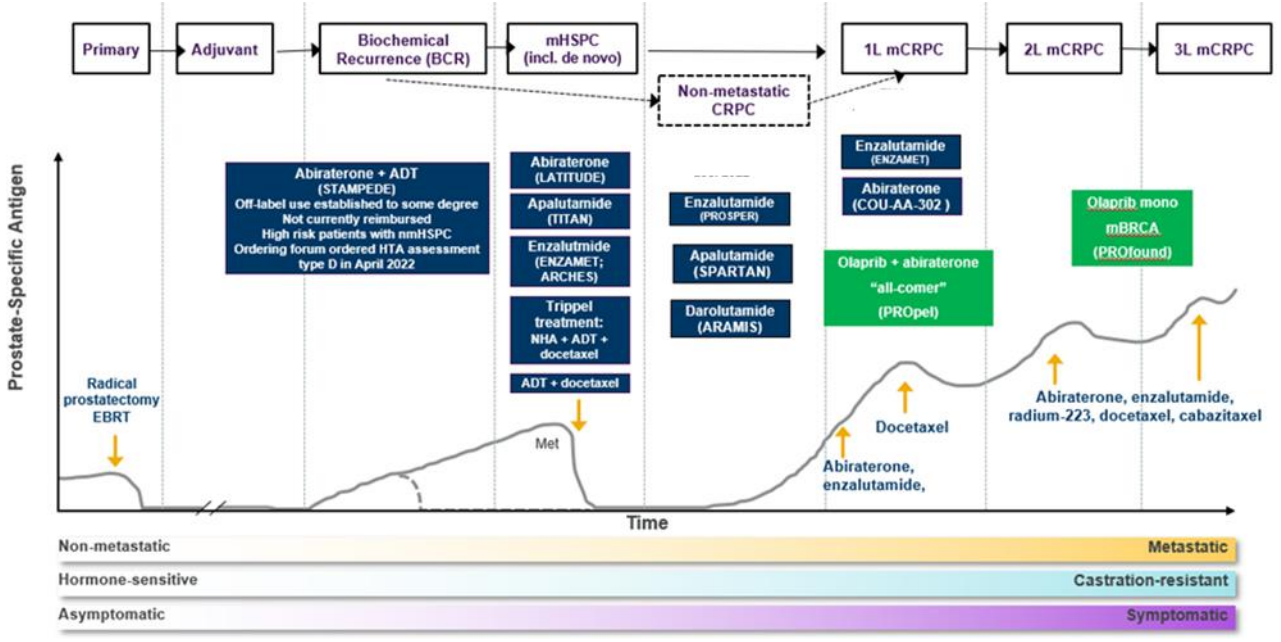
Despite an increase in the number of available therapies for patients with mCRPC, the 5-year survival rate remains only approximately 20%.[10] New hormonal agents (NHAs), such as abiraterone and enzalutamide, and the taxane-based chemotherapies, docetaxel and cabazitaxel, are widely available for patients with mCRPC.[9,11] Treatments including poly(adenosine diphosphate)-ribose phosphate (PARP) inhibitors, lutetium-177-labelled prostate-specific membrane antigen (177Lu-PSMA-617), and radium-223 are currently limited to specific populations. However, none of these treatments are curative, instead delaying progression and prolonging survival.[12-19] In current clinical practice, first-line treatment options fail within 10 months of initiation,[20] and only half of patients receive more than one line of life-prolonging therapy.[10,20,21] Median survival (mOS) for patients who receive NHA treatment in the first-line setting is approximately 35 months in the clinical trial setting and 33 months in real-world clinical practice.[10,17,22] There is therefore a substantial unmet need for effective treatments that are available early in the metastatic setting.

Figure 1. The treatment pathway in patients with prostate cancer



Strong evidence is lacking on the optimal sequence of treatments for mCRPC, but Danish practice indicates the following underlying principles: docetaxel is prioritized in the first line for symptomatic patients and patients with rapid progression on ADT in the HSPC phase. Cabazitaxel is only given to patients previously treated with docetaxel. New hormonal agents (NHAs), namely abiraterone and enzalutamide, are given in the first line to asymptomatic patients, but sequential treatment with NHAs (e.g., enzalutamide after abiraterone, or vice versa) is generally not recommended but may be used in a small number of patients under certain conditions. Radium-223 is used per indication only in third line or later, but can be given to a small number of patients with symptomatic bone metastases (and without visceral metastases) who are unsuitable for docetaxel treatment. Patients are not re-treated with the same drug.[9,23]

Figure 2. Clinical landscape for medical treatment of prostate cancer



5.1.1.1 Mutations in mCRPC

Some patients with mCRPC have mutations in genes associated with DNA repair. Some of these genes are linked to homologous recombination repair (HRR), which is a key mechanism for DNA repair. HRR is an important element of healthy cell function and wholeness, and mutations in genes in HRR can cause genomic instability and enhance tumour growth. HRR mutations are found in approximately 28% of patients with mCRPC.[24,25] The most well-known and well-defined mutations in the HRR are BRCA1 and BRCA2, which are prevalent in around 10% of patients overall.

Prostate cancer patients with HRR mutations are more likely to have more aggressive and advanced disease at the time of diagnosis and to progress more rapidly to metastatic disease.[26,27] Furthermore, a recent post hoc analysis of five trials of first line mCRPC patients with known mutation status, BRCA mutations (mPFS 7.1 months, mOS 19.4 months) or other non-BRCA HRR mutations (mPFS 9.0 months, mOS 21.9 months) were associated with poor progression-free and overall survival than unmutated patients (mPFS 10.3 months, mOS 27.9 months).[28]Patients harbouring defects in HRR pathway genes are unable to repair DNA damage effectively and are, therefore, particularly sensitive to certain therapies, including PARP inhibitors and therapies that exploit deficiencies in the HRR pathway.[26,29] However, there is evidence that suggests the benefits conveyed with the use of PARP inhibitors extend beyond patients with an HRR gene mutation.[30,31]

5.1.2 Patient populations relevant for this application

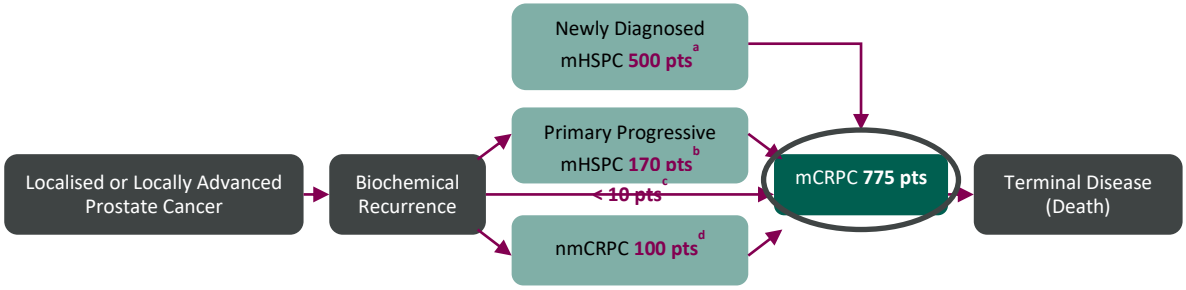
This application focuses on the indicated population for Lynparza (olaparib) in combination with abiraterone, namely adult patients with mCRPC in whom chemotherapy is not clinically indicated. In clinical practice, these are patients who today would be treated with new hormonal agents. This reflects the patient population who are expected to be candidates for olaparib in combination with abiraterone in Danish clinical practice, where olaparib would be used as an add-on therapy to abiraterone. A subgroup analysis is also presented for patients with mutations in the homologous recombination repair pathway (HRRm) as this was a pre-specified subgroup of the registrational PROpel trial and the mechanism of action of PARP inhibition may be of particular interest in patients with HRR mutations (see section 5.1.1.1 above), though olaparib combination therapy has shown effect in patients both with and without HRR mutations.[32]

5.1.3 Estimated patient numbers

In the RADS treatment algorithm for mCRPC, developed in 2015, it is estimated that the incidence of mCRPC is comparable to the mortality rate due to prostate cancer, based on the assumption that the majority of deaths due to prostate cancer would occur in patients with mCRPC.[33] However, this method can lead to significant overestimation of the number of patients being treated for mCRPC. The estimates presented by RADS indicate that approximately 720 patients per year would receive docetaxel treatment in the first two lines of therapy for mCRPC. [33] In addition, it was noted in Medicinrådet's assessment of apalutamide for mHSPC that around 300 patients would receive docetaxel for de novo mHSPC,[34] and some patients would also receive docetaxel for primary progressive mHSPC or at later lines of mCRPC. Therefore, over 1 000 advanced prostate cancer patients are expected to be treated with docetaxel each year in Danish clinical practice but, according to figures from the Danish Prostate Cancer Group (DaProCa), only ~600 patients per year initiate treatment with docetaxel.[6] Similarly, abiraterone is recommended by DaProCa for patients with de novo mHSPC, as well as in the treatment of mCRPC for both first line therapy or after docetaxel (along with enzalutamide), and therefore the estimated number of patients starting NHA treatment would be expected to be close to 2000 if the mCRPC incidence was comparable to the prostate cancer mortality rate. However, only 900-1000 patients per year initiate treatment with abiraterone or enzalutamide.[6] Therefore, the prostate cancer mortality rate does not appear to be a good indicator of estimates of the number of patients with mCRPC who are eligible for treatment.

Due to this discrepancy, AstraZeneca instead chooses to use estimates of those progressing from treatment settings prior to mCRPC to estimate the number of patients who may receive treatment for mCRPC. In Medicinrådet's assessments of apalutamide, it was reported that 500 patients per year would be diagnosed with de novo mHSPC and be eligible for apalutamide treatment,[34] in addition to 100 patients with nmCRPC at a high risk of developing metastatic disease.[35] As well as those patients with de novo mHSPC, patients can progress from localised/locally advanced disease at diagnosis to later mHSPC. In clinical trials and RWE studies that include both de novo and progressive mHSPC patients, 20-30% of patients had metastases at diagnosis.[36-38] It is therefore assumed that the 500 patients with de novo mHSPC would represent approximately 75% of the total mHSPC patient group. Feedback from Nordic clinical experts indicates that very few patients progress directly from nmHSPC to mCRPC. Real world evidence from Sweden shows that the mortality rate in the mHSPC and nmCRPC settings is low and most of these patients rather progress to mCRPC.[38] Therefore the total patient count from each setting prior to mCRPC is approximately equal to the number of patients progressing to mCRPC. AstraZeneca estimates this to be about 775 new mCRPC patients each year (Figure 3).

Figure 3. Number of patients treated in disease stages prior to mCRPC



[a] As reported in Medicinrådets anbefaling vedrørende apalutamid til behandling af metastatisk hormonfølsom kræft i blærehalskirtlen

[b] Calculated based on data showing that 20-30% of mHSPC patients did not have metastases at time of prostate cancer diagnosis

[c] Based on feedback from Danish clinical experts, very few patients progress directly to mCRPC from nmHSPC in Denmark

[d] As reported in Medicinrådets protokol for vurdering af apalutamid til behandling af højrisiko ikke-metastaserende kastrationsresistent prostatakræft

The validity of these estimates was retrospectively assessed by comparing the derived patient numbers with the number of patients initiating treatment from DaProCa. Combining the logic of the patient flow above with the treatment algorithm and pathways presented in Medicinrådet's algorithm for mCRPC treatment,[23] it is estimated that 1580 patients would commence treatment with docetaxel, abiraterone, or enzalutamide each year in the mHSPC, nmCRPC, or mCRPC (all lines) settings. This compares to 1488 patients in 2020 and 1677 in 2021, according to DaProCa,[6] implying that this alternative method of estimating patient numbers in mCRPC provides a good indicator of the number of patients being treated. Calculations can be made available upon request.

Of the approximately 775 patients who are estimated to be eligible for treatment in mCRPC each year, not all will be eligible or can be expected to be treated with olaparib + abiraterone in clinical practice. The combination is indicated for patients in whom chemotherapy is not clinically indicated, though some patients in this group may not be fit enough to be eligible for add-on therapy. The role of biomarkers and the presence of mutations may also influence the uptake. AstraZeneca have estimated the number of patients who may be eligible to use olaparib + abiraterone in clinical practice on the basis of existing treatment guidelines from Medicinrådet, as well as clinical input from Nordic physicians working in advanced prostate cancer.

Of mCRPC patients who are eligible for life-prolonging therapy, chemotherapy is typically clinically indicated for those with aggressive disease that has progressed within 12 months of beginning ADT (castration treatment) or who have significant symptoms that would not make them eligible for treatment with NHAs.[23] In developing the treatment guideline for mCRPC, the expert committee estimated that 13% of new mCRPC patients would have had < 12 months

response to ADT.[33] It was also assumed that 8% of patients would have symptoms making them ineligible for treatment with abiraterone or enzalutamide.[33] Whilst abiraterone and enzalutamide are indicated for patients who are asymptomatic or mildly symptomatic, clinical experts that AstraZeneca have consulted have reported that in clinical practice it is rare for a patient to be considered so symptomatic that they would not be a candidate for treatment with an NHA. It is therefore assumed that in total only ~17.5% of patients would be considered clinically indicated for chemotherapy on the basis of poor response to ADT or symptomatic disease, instead of 21%.

Clinicians have reported, however, that when evaluating whether a patient is indicated for chemotherapy what is more important to consider is the treatment received in the previous setting. Clinicians advised that a switch in mechanism of action is required and that sequencing different NHAs in clinical practice should be avoided. No NHAs have been recommended by Medicinrådet for use in mHSPC though a review is ongoing (including a range of NHAs),[8] however DaProCa recommends off-label use of the triple combination of docetaxel + abiraterone + ADT for patients with high volume disease. Medicinrådet estimates that around 300 patients per year have high volume mHSPC. Though historically these patients have just been treated with docetaxel + ADT, some patients may have received abiraterone in addition. As abiraterone is now available as a generic medication, it's use in settings prior to mCRPC is anticipated to increase. As these patients begin to progress into the mCRPC setting (with a median time to CRPC of 3.8 years with triple therapy),[39] a significant number of patients (200-250) may be NHA exposed in the mHSPC setting when they reach first line mCRPC in coming years. As the use of NHAs in the mHSPC setting increases, the number of patients eligible for NHA treatment for first line mCRPC is likely to decrease. In current clinical practice it is assumed only a modest number of patients have been previously exposed to NHAs but this will increase significantly over the next few years (see Table 2).

Daratolumide, enzalutamide, and apalutamide are also recommended for nmCRPC by Medicinrådet and DaProCa. As these therapies were recommended in 2021, the first patients to initiate these treatments are likely to be progressing to mCRPC in 2023/2024 (assuming 24-30 month time to progression), and therefore within the next few years most of the 100 nmCRPC patients progressing to mCRPC will be NHA exposed. These are reflected in the number of NHA-exposed patients in Table 2. [redacted]. Table 2 shows the estimated number of patients who may be candidates for treatment with olaparib + abiraterone if it is recommended to label.

Table 2. Estimated number of patients eligible for treatment if recommended to label

Year	2024	2025	2026	2027	2028
Patients progressing to mCRPC in Denmark	775	775	775	775	775
Patients receiving best supportive care only	39 (5%)	39 (5%)	39 (5%)	39 (5%)	39 (5%)
Patients for whom chemotherapy is indicated based on poor response to ADT or symptomatic disease	136 (17.5%)	136 (17.5%)	136 (17.5%)	136 (17.5%)	136 (17.5%)
Patients for whom chemotherapy is indicated based on prior exposure to a new hormonal agent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Year	2024	2025	2026	2027	2028
Patients with mCRPC receiving active treatment but for whom chemotherapy is not clinically indicated	*** (***%)	*** (***%)	*** (***%)	*** (***%)	*** (***%)
Of whom are anticipated to be candidates for olaparib + abiraterone in the coming years	*** (***%)	*** (***%)	*** (***%)	*** (***%)	*** (***%)

Given the mechanism of action of PARP inhibition and as a key subgroup of the PROpel trial, patients with HRR mutations may also be a relevant patient subgroup for assessment. On the basis of the eligibility screening of the PROfound trial and the prevalence of HRR mutations identified in the PROpel study, it is estimated that approximately 28% of patients would have a HRR mutation.[24,25] However, as HRRm testing is not currently standard practice in prostate cancer, and current standard testing methods (i.e., tumour tissue biopsy testing) more often result in failed tests compared to novel methods (e.g., ctDNA), the effective rate of known HRR mutations in the population is likely to be lower than this as testing capacity increases and methods improve. Table 3 shows the effective number of patients who may be eligible for olaparib + abiraterone if they have a known HRR mutation.

Table 3. Estimated number of patients with known HRR mutations eligible for treatment

Year	2024	2025	2026	2027	2028
Patients with mCRPC receiving active treatment but for whom chemotherapy is not clinically indicated	***	***	***	***	***
Prevalence of HRR mutations in population	28%	28%	28%	28%	28%
Testing rate for HRR mutations in Denmark	***	***	***	***	***
Successful test rate (i.e., provides conclusive result)	***	***	***	***	***
Patients with known HRR mutations for whom chemotherapy is not clinically indicated	***	***	***	***	***
Patients with known HRR mutations who may be candidates for olaparib + abiraterone	** (**%)	** (**%)	** (**%)	** (**%)	** (**%)

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The treatment landscape of metastatic prostate cancer is highly dynamic and has seen several new treatment options and standard treatments moving earlier in the disease course. However, the dynamic landscape has led to a situation with no established optimal sequencing of the current treatment options and a lack of concrete treatment guidance. Moreover, the increasing knowledge on cross-resistant mechanisms are further limiting the treatment options in mCRPC. Recommendations by DaProCa are largely aligned with those issued by ESMO and the European Association of Urology (EAU).[9,11,40] DaProCa guidelines advocate that treatment choice is based on performance status, symptoms, comorbidities, location and extent of the disease, genetic profile (e.g., BRCA/HRR mutations), and treatment receive for mHSPC, as well as patient preferences.[9]

Currently approved and recommended therapies for mCRPC in Denmark are the NHAs abiraterone and enzalutamide, taxane-based chemotherapy with docetaxel or cabazitaxel, as well as olaparib monotherapy or the radiopharmaceutical radium-223.[9] Lutetium-177 also recently received EU approval in PSMA-positive mCRPC patients previously treated with both androgen receptor pathway inhibitors and a taxane, but has not yet been assessed in Denmark. The main therapies

used for first-line mCRPC in Denmark today include chemotherapy (in the form of docetaxel) or NHA, which can be abiraterone with prednisolone or enzalutamide. These therapies are also recommended in Medicinrådet's treatment guideline.[23] With regards to selecting first line therapy, clinical expert feedback is that the choice of therapy is most often driven by what therapy the patient received in the previous setting. Back-to-back treatment with the same mode of action is not recommended neither for symptomatic or asymptomatic patients, and a new mode of action is preferred for all patients. The DaProCa guidelines recommend that sequential use of different NHAs should be avoided, and that chemotherapy should be offered to patients who have previously been treated with an NHA.[9] With the approvals for NHAs in the nmCRPC and mHSPC settings, treatment choices in these settings become pertinent when considering treatment options in first line mCRPC. Patients treated with docetaxel in the mHSPC stage are likely to receive NHA for first line mCRPC stage, whilst patients treated with a NHA in the mHSPC stage will primarily receive docetaxel if the patient is deemed to be able to tolerate chemotherapy. Patients who progress from nmCRPC will most likely have received an NHA in this stage and consequently be treated with docetaxel for first line mCRPC.

When abiraterone and enzalutamide were introduced to the market for first line mCRPC, the labelled indications were limited to asymptomatic or mildly symptomatic patients (though post-docetaxel this restriction was not applied). The DaProCa and Medicinrådet treatment guidelines also recommend abiraterone and enzalutamide to asymptomatic patients with good performance status.[9,23] However, the what defines asymptomatic or mildly symptomatic disease has not been clearly established. Cancer-related pain or the use of opioid analgesics have been posited as markers of symptomatic disease in clinical trials, though clinical experts who AstraZeneca have consulted have reported that some pain or opioid use are not explicitly barriers to NHA use in clinical practice, though particularly symptomatic disease (e.g., obstruction of urinary tract) may warrant more intensive therapy. The DaProCa guidelines highlight that there are broader clinical markers that would permit use of chemotherapy compared to NHAs (e.g., symptomatic disease and performance status 0-2), though clinical experts who AstraZeneca have spoken to have highlighted a preference to use NHAs over chemotherapy where possible. As both docetaxel and NHAs now also are used pre-mCRPC, most patients that have not received an NHA before are likely to receive this for first line mCRPC irrespective of symptom burden.

Therapies for second and third line mCRPC also focus on the sequence of treatment, with DaProCa and Medicinrådet treatment guidelines recommending a switch to chemotherapy for those treated with a NHA at first line mCRPC, and for those who receive docetaxel it is recommend they are given cabazitaxel at the next line. Olaparib is approved for mCRPC patients with BRCA mutations who have progressed on prior treatment with NHA (e.g., for mHSPC, mCRPC,and/or nmCRPC). In current Danish clinical guidelines it is recommended for patients who have received at least one line of therapy for mCRPC with an NHA.[9] Patients with symptomatic bone metastases without visercal metastases can be given radium-223 if they have received at least two lines of therapy mCPRC.

5.2.2 Choice of comparator(s)

5.2.3 Description of the comparator(s)

Brand name, approved name and therapeutic class

Zytiga (abiraterone). Generic versions are also available.

Pharmaceutical form

Abiraterone branded and generics are available as 500mg tablets for oral administration.

Administration and dosing

The recommended dose is 1 000 mg as a single daily dose that must not be taken with food. Taking the tablets with food increases systemic exposure to abiraterone. Abiraterone is combined with prednisone/prednisolone.

Mechanism of action

Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17).

Indication and proposed position in treatment sequence

ZYTIGA is indicated with prednisone or prednisolone for:

- the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)
- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

5.3 The intervention

Olaparib in combination with abiraterone has been evaluated as a first-line treatment for mCRPC compared to abiraterone alone. This is reflected in the marketing authorization whereby it is indicated for patients with mCRPC in whom chemotherapy is not clinically indicated (i.e., patients who would receive an NHA in clinical practice). As olaparib is used as an add-on therapy to a currently available therapy there are unlikely to be significant changes to the current treatment algorithm, though as use of genetic testing comes into clinical practice and further therapies in the same class (PARP inhibitors) are approved for use in mCRPC, more targeted use of the olaparib may be applied in clinical practice.

Brand name, approved name and therapeutic class

Lynparza (olaparib) is a PARP inhibitor.

Pharmaceutical form

Olaparib is available as 100 mg and 150 mg tablets for oral administration.

Administration and dosing

Olaparib is recommended at a dose of 300 mg (2 × 150 mg tablets) taken twice daily with or without food, equivalent to a total daily dose of 600 mg. The 100 mg tablet is available for dose reductions. Patients should also receive a gonadotrophin-releasing hormone (GnRH) analogue concurrently or should have had bilateral orchiectomy. For patients with moderate renal impairment (creatinine clearance, 31–50 mL/min), the dose should be reduced to 200 mg orally twice daily.

Mechanism of action

Olaparib is a potent inhibitor of human PARP enzymes (PARP-1, PARP-2 and PARP-3) that are required for the efficient repair of DNA single strand breaks.[41] Through binding to the active site of the PARP enzymes, olaparib prevents the dissociation of the PARP enzyme from the DNA, blocking repair and, in replicating cells, causing a double strand break (DSB). In normal cells, DSBs are efficiently repaired by the HRR pathway; however, in HRR-deficient cells e.g. HRR-mutated cancer cells, DSBs cannot be accurately or effectively repaired resulting in the activation of alternative and error-prone pathways. Following several rounds of replication, the genomic stability of cancerous cells becomes compromised leading to cellular death, in part due to the already high DNA damage load compared with normal cells.

Olaparib in combination with abiraterone together represent the first combination approach to deliver clinically meaningful activity in mCRPC, including patients with or without an HRRm.[1] Two additional mechanisms have been put forward to explain the biomarker independent activity of the olaparib−abiraterone combination based on observations

in vitro and *in vivo* preclinical models.[42,43] The first mechanism involves the transcriptional role of PARP-1 in the androgen receptor pathway that enhances the activity of NHAs, such as abiraterone.[42-45] This is supported by the observation that inhibition of PARP may suppress transcription of several AR targets accompanied by improved effectiveness of PARP inhibitors if combined with castration in a xenograft prostate tumours, compared with castration or PARP inhibitors alone.[43] The second mechanism involves the induction of an HRR-deficient phenotype via inhibition of AR signalling. Studies have shown downregulation of HRR transcripts and proteins in response to AR signalling in prostate cancer accompanied by deficiency in DNA repair and increased sensitivity to DNA damage and olaparib despite resistance to initial ADT.[42,44] Additionally, the improved anti-tumour effect observed with the combination of olaparib and abiraterone may reflect the well-recognised potentiation effect of radiotherapy and ADT in early prostate cancer.[45,46] Like the combined approach of olaparib and abiraterone, radiotherapy causes DNA damage and ADT inhibits DNA repair.[45,46]

Indication and proposed position in treatment sequence

Olaparib has previously been approved by the EMA[41] in the mCRPC setting as monotherapy for patients with a *BRCA 1* or *BRCA2* mutation who have progressed following prior therapy that included a new hormonal agent. The label was recently extended in the mCRPC setting to permit use in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Restrictions of use

The safety and efficacy of olaparib in children and adolescents have not been established.

6. Literature search and identification of efficacy and safety studies

A systematic literature search (SLR) was conducted to identify studies on the combination of olaparib and abiraterone, yielding two studies. However, one of these studies, Study08, was excluded as it only included patients who had progressed on docetaxel. As head-to-head evidence against the main comparator was available from PROpel, studies for the comparators were also excluded. The PROpel clinical trial was the study considered relevant to the decision problem, which investigated the use of Lynparza for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. This study was used to inform the health economic analysis. For more information on the SLR, refer to Appendix A - Literature search for efficacy and safety of intervention and comparator(s). Results of the study can be found in appendix B.

Table 4. Relevant studies included in the assessment

Reference	Trial Name	NCT Number	Dates of Study	Used in Comparison
Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evidence. 2022; 1 (9). Oya M, Armstrong AJ, Thiery-Vuillemin A, Shore N, Procopio G, Arslan C, et al. 157O Biomarker analysis and updated results from the phase III PROpel trial of abiraterone (abi) and olaparib (ola) vs abi and placebo (pbo) as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). Ann Oncol. 2022; 33 (Suppl. 9): S1495. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore ND, Procopio G, et al. Final overall survival (OS) in PROpel: Abiraterone (abi) and olaparib (ola) versus abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2023; 41 (6_Suppl): LBA16. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Procopio G, et al. PROpel: Efficacy of abiraterone + olaparib vs. abiraterone + placebo in the first-line treatment of patients with asymptomatic/mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC) at baseline. Eur Urology. 2023; 83 (Suppl 1): S1674-S1675. AstraZeneca. Clinical Study Report Addendum 1. A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer: Second Interim Analysis [Data on File]. 2022. AstraZeneca. Clinical Study Report Addendum 2. Tables and Figures: Final Analysis [Data on File]. 2022.	PROpel	NCT03732820	• Actual Study Start Date: October 31, 2018 • Actual Primary Completion Date: July 30, 2021 (median 21 months follow-up) • Second Data Cut-Off: March 14, 2022 (median 27 months follow-up) • Third Data Cut-Off: October 12, 2022 (median 33 months follow-up)	Olaparib + abiraterone + prednisone/prednisolone vs. abiraterone + prednisone/prednisolone

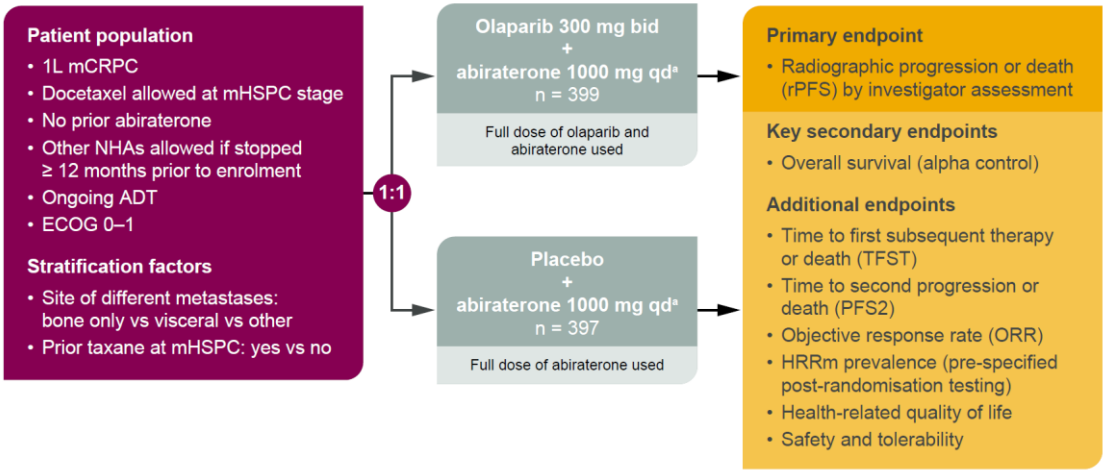
7. Efficacy and safety

7.1 PROpel: olaparib + abiraterone vs. placebo + abiraterone for mCRPC patients in whom chemotherapy is not clinically indicated

7.1.1 Study overview

PROpel (NCT03732820) is an ongoing randomised, double-blind, placebo-controlled, multicentre phase 3 study that is assessing the efficacy and safety of the combination of olaparib and abiraterone compared with placebo and abiraterone in patients with mCRPC who are previously untreated for mCRPC (Figure 4).

Figure 4. Study outline PROpel



[a]In combination with prednisone or prednisolone 5 mg twice daily. First patient randomised: November 2018. Last patient randomised: March 2020. Data cut-off: 30 July 2021 for interim analysis of rPFS and OS.

Following enrolment, all patients underwent prospective assessment of tissue to assess for HRR gene mutations to enable HRR status subgroup analysis on the primary endpoint (rPFS). The dosing information for olaparib and abiraterone is summarised in Table 5. All study treatments were given continuously until investigator-assessed radiographic disease progression, the patient discontinued treatment owing to AEs, or consent was withdrawn.

Table 5. Dosing information for the investigational product and comparators in PROpel

Study treatment	Formulation	Dosing information	Permitted dose reductions
Olaparib	100 mg tablets 150 mg tablets	300 mg (2 × 150 mg tablets) orally twice daily	Step 1: 250 mg twice daily Step 2: 200 mg twice daily No further dose reductions are permitted. Once the dose is reduced, escalation is not permitted
Abiraterone	250 mg tablets 500 mg tablets	1000 mg (4 × 250 mg or 2 × 500 mg tablets) orally once daily	In case dose reductions are necessary for abiraterone, the investigator should refer to abiraterone local prescribing information for further details
Prednisone/prednisolone	5 mg tablets	5 mg orally twice daily	N/A
Placebo	100 mg tablets 150 mg tablets	300 mg (2 × 150 mg tablets) orally twice daily	N/A

Source: PROpel Clinical Study Report version 1, 1 December 2021 and EPAR

The primary endpoint, investigator-assessed rPFS, was formally analysed at two planned data cuts (first and second data cut-offs [DCO1 and DCO2; final rPFS]) and OS has been analysed at three planned data cuts (Table 6), however following a protocol amendment patients are continuing to be followed up for OS. It was assumed that the true treatment effect will have an HR of 0.68, which corresponds to an increase in median rPFS from 16.5 months with placebo plus abiraterone to 24.3 months with olaparib plus abiraterone.

Table 6. Planned data cuts for PROpel

Data cut	Analysis
DCO1	**Interim rPFS and interim OS** At DCO1, the PROpel study had 94.1% power to detect a statistically significant difference in the primary endpoint at a one-sided alpha level of 0.025% based on 379 rPFS events (47.6% maturity) occurring in 796 patients who were randomised 1:1 to receive olaparib or placebo with abiraterone
DCO2	**Final rPFS and interim OS** At DCO2, the PROpel study will have a 98.2% power to detect a statistically significant difference in rPFS at a one-sided alpha level of 0.021 based on 453 rPFS events (56.9% maturity) occurring in 796 patients who were randomised 1:1 to receive olaparib or placebo with abiraterone
DCO3	**Final OS** DCO3 will occur after 360 OS events, approximately 48 months after the first patient is randomised, when a minimum follow-up of 30 months would be expected The smallest treatment difference that would be statistically significant at the final analysis is an HR of 0.81

7.1.2 Efficacy

7.1.2.1 Primary endpoint: investigator-assessed rPFS

PROpel met its primary endpoint of investigator-assessed rPFS for the ITT population at DCO1; a statistically significant improvement for olaparib + abiraterone vs. placebo + abiraterone was demonstrated with an rPFS of 24.8 months vs. 16.6 months (HR 0.66; 95% CI 0.54, 0.81; p < 0.001). This benefit was sustained through the final analysis with an 8.5-month rPFS gain at DCO3 (Table 7). These results are to be considered exploratory, but are presented below as they are from the latest data-cut.

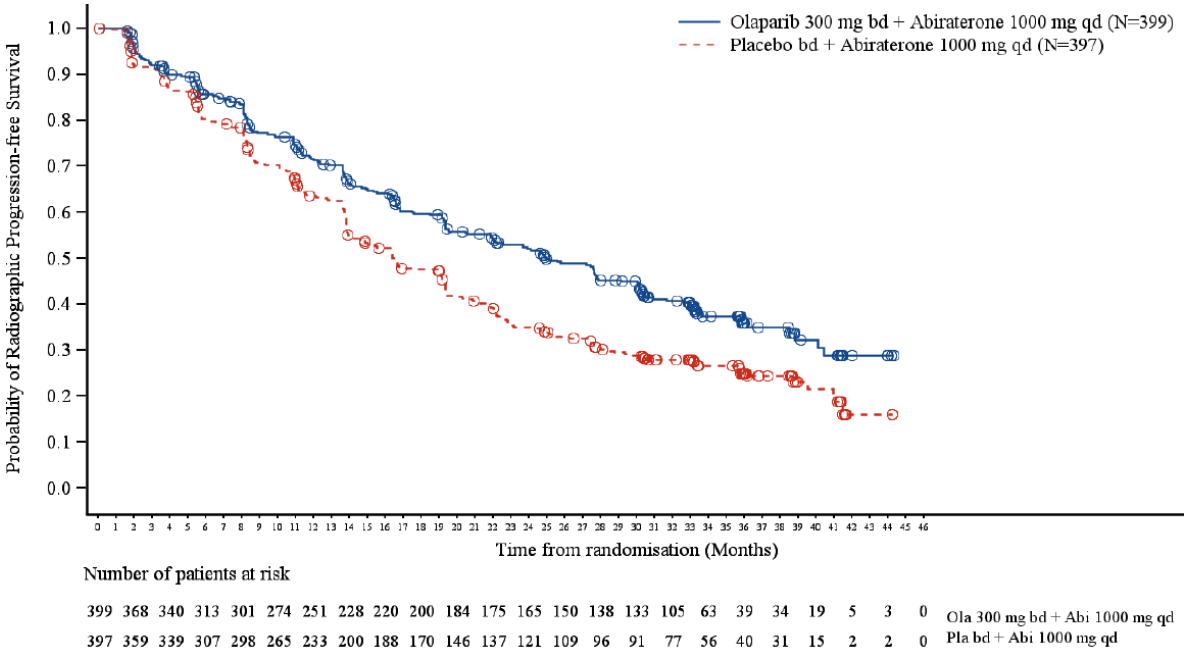
Table 7. Evolution of investigator-assessed rPFS results in PROpel

Data Cut-Off	Outcome	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
DCO1 (30 July 2021)	Events,[a] n (%)	168 (42.1)	226 (56.9)
	Median rPFS, months	24.8	16.6
	HR (95% CI)[b]	0.66 (0.54, 0.81); *p* < 0.0001	
DCO2 (14 March 2022)	Events,[a] n (%)	199 (49.9)	258 (65.0)
	Median rPFS, months	25.0	16.4
	HR (95% CI)[b]	0.67 (0.56, 0.81); *p* < 0.0001	
DCO3 (12 October 2022)	Events,[a] n (%)	219 (54.9)	277 (69.8)
	Median rPFS, months	25.0	16.5
	HR (95% CI)[b]	0.68 (0.57, 0.81); *p* < 0.0001	

[a]Progression defined by investigator assessment of RECIST 1.1 and PCWG-3 criteria. [b]HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: Metastases (bone only, visceral, other) and Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib plus abiraterone. The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy, using the Breslow method for handling ties.

The study demonstrated a statistically significant improvement in the risk of radiological disease progression or death for olaparib + abiraterone compared to placebo + abiraterone as assessed by the investigator at DCO3, supportive of the primary analysis (HR 0.68; 95% CI 0.57, 0.81; p<0.0001). The median rPFS was 25.0 months in the olaparib + abiraterone arm and 16.5 months in the placebo + abiraterone arm, resulting in an 8.5-month improvement which extends median rPFS by ≈50% for the compared to today's standard of care. This is the first time a median rPFS beyond 2 years seen in this setting.[1] The Kaplan–Meier plot demonstrates a clear and consistent separation of the curves in favour of the olaparib plus abiraterone arm from an early time point and throughout study follow-up.

Figure 5. Kaplan-Meier plot of radiological PFS based on investigator assessment



Data as of DCO3 (12 Oct 2022). Abi, abiraterone; DCO, data cut-off; FAS, full analysis set; Ola, olaparib; PCWG-3, Prostate Cancer Working Group-3; Pla, placebo; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiological progression-free survival.

7.1.2.1.1 Sensitivity analyses of rPFS based on BICR (DCO2, 14 March 2022)

As well as the primary analysis of rPFS based on investigator assessments, a sensitivity analysis by a blinded independent central review (BICR) committee was conducted for the first two data cuts of PROpel. The results of the sensitivity analysis using BICR data were consistent with the primary analysis of investigator-assessed rPFS and BICR-assessed rPFS. Olaparib plus abiraterone was associated with a nominally significant 11.1 month-improvement in rPFS compared with placebo plus abiraterone arm, which corresponds to a 38% reduction in the risk of radiographic or death (HR 0.62, 95% CI, 0.51, 0.75; nominal $p < 0.0001$; Table 8). The overall concordance rate between the investigator-assessed and BICR-assessed rPFS events was 86.6%, and supports the robustness of the analysis of the primary endpoint based on investigator-based assessment.

Table 8. Sensitivity analysis of the primary outcome: BICR-assessed rPFS (DCO2,14 March 2022)

Sensitivity analysis of the primary outcome: BICR-assessed rPFS[a]	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Event,[a] n (%)	182 (45.6)	242 (61.0)
Median rPFS, months (95% CI)[b]	27.6 (20.5, 30.2)	16.5 (13.8, 19.2)
HR (95% CI)	0.62 (0.51, 0.75); p < 0.0001[c]	

[a]Progression defined by BICR assessment of RECIST 1.1 and PCWG-3 criteria. [b]Calculated using the Kaplan-Meier technique. [c]HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: Metastases(bone only, visceral, other) and Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib plus abiraterone. [d]The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy, using the Breslow method for handling ties. DCO1 date: 30 July 2021. ***Source**: PROpel Clinical Study Report Addendum, 28 June 2022 and EPAR.*

7.1.2.1.2 Exploratory subgroup analyses of rPFS

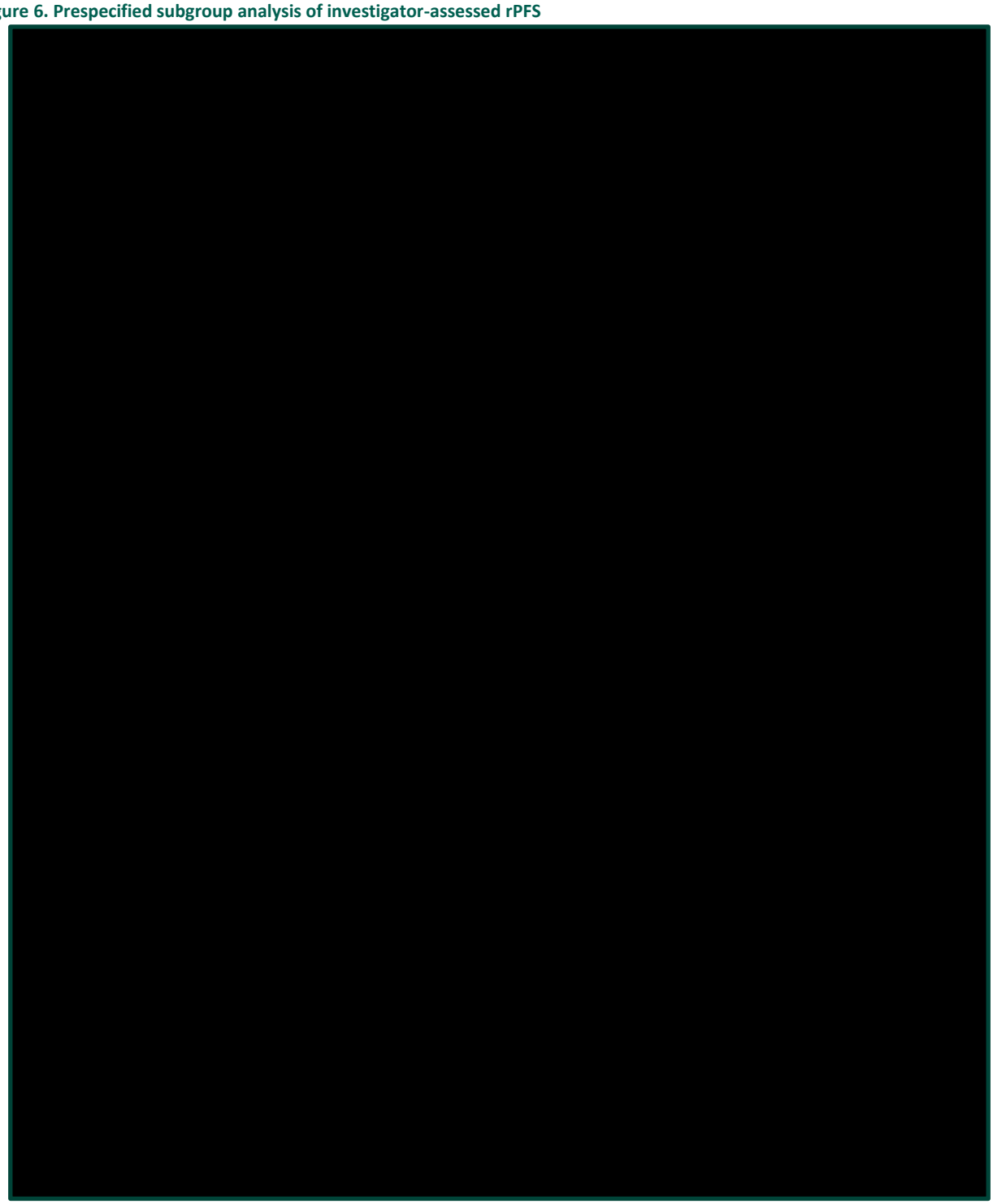
Exploratory subgroup analyses of the primary endpoint of rPFS based on investigator assessment were performed to investigate the consistency of the treatment effect across pre-defined subgroups based on the following:

- Site of distant metastases (bone only vs visceral vs other)
- Docetaxel treatment at mHSPC stage (yes vs no)
- HRR gene mutation status
- ECOG performance status
- Age at randomisation
- Region
- Race
- Baseline PSA

The study was not powered to assess efficacy within individual subgroups and given the large number of comparisons without control for multiplicity, the rPFS subgroup analyses should be interpreted with caution.

The benefit of olaparib over placebo in combination with abiraterone was maintained across all pre-defined subgroups, with clinically meaningful reductions in the risk of radiological disease progression or death in patients receiving olaparib plus abiraterone (Figure 6**;** note: the results for the aggregate HRRm group are presented separately). The global interaction test was not significant at the 10% level, indicating that there was no evidence that the treatment effect differed across the subgroups. There was a clinically meaningful rPFS improvement associated with olaparib plus abiraterone compared with placebo plus abiraterone in both the HRRm and non-HRRm subgroups. Patients' HRR gene mutation status was determined retrospectively by testing of ctDNA and tumour tissue samples provided at baseline. Assessment of HRRm in the real-world is evolving; HRRm can be determined by either a tissue or ctDNA test, both of which have limitations. Tissue and plasma ctDNA HRRm testing were combined in PROpel, to maximise the proportion of patients with assigned HRR status.

Figure 6. Prespecified subgroup analysis of investigator-assessed rPFS



[a]Analysis performed included the stratification factors selected in the primary pooling strategy as covariates. Each subgroup analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction. Grey band represents the 95% CI for the overall (all patients) hazard ratio. [b]Defined as any deleterious or suspected deleterious HRR gene mutation detected. [c]Defined as no deleterious or suspected deleterious HRR gene mutation detected. [d]Test failed/sample not analysed. [e]Excludes patients with no baseline assessment. DCO3 date: 12 Oct 2022.

7.1.2.2 Analysis by HRRm status

HRRm status was established for 535 (67.2%) patients using tumour tissue testing, 734 (92.2%) patients using ctDNA testing, permitting the majority of patients in the study (778 patients; 97.7%) to have their HRRm status determined using aggregated tumour tissue and ctDNA testing results. Patients were assigned to the HRRm subgroup if a HRR gene mutation was detected by either test, the non-HRRm subgroup if no HRR gene mutation was detected by either test, or the HRRm unknown subgroup if neither test produced a valid HRR test result. The aggregate HRRm population included 226 patients (90 positive both by tumour tissue and ctDNA, 28 positive by tumour tissue only, and 108 positive by ctDNA only) and the non-HRRm population included 552 patients (328 negative both by tumour tissue and ctDNA, 38 negative by tumour tissue only with no ctDNA result obtained, and 186 negative by ctDNA only with no tumour tissue result obtained).[1,24] For more information on testing in PROpel, please see Armstrong *et al*. (2022).[24]

All hazard ratios for the aggregate HRRm and non-HRRm populations favoured the combination of olaparib + abiraterone compared to placebo + abiraterone across both DCO2 and DCO3 (see Table 9 and Table 10). Median rPFS results with olaparib + abiraterone in both the HRRm and non-HRRm populations were broadly consistent with the ITT population and exceeded 2 years suggestive of a clinically meaningful improvement in rPFS in both of these populations, though outcomes are considerably worse for placebo + abiraterone treated patients if they have HRR mutations (Table 10 and Figure 7). Results were consistent regardless whether HRRm status was determined by tumour tissue testing or ctDNA testing (see Figure 6). In their assessment of the clinical documentation from DCO2, the EMA concluded that "*the combination olaparib + abiraterone shows a benefit in all HRR mutation subgroups (based on tissue test, ctDNA, aggregate analysis, BRCAm, or non-BRCAm/BRCAm unknown), without detrimental effect and were overall consistent with the FAS (ITT). These data, although considered with caution due to the exploratory character of the data as there were no control by multiplicity, demonstrate a potential benefit in the non-BRCAm/ BRCAm unknown status and non-HRRm/HRRm unknown subgroups and do not preclude use in these subpopulations*".[47]

Table 9. Summary of investigator-assessed rPFS for subgroups by HRRm status (DCO2, 14 Mar 2022)

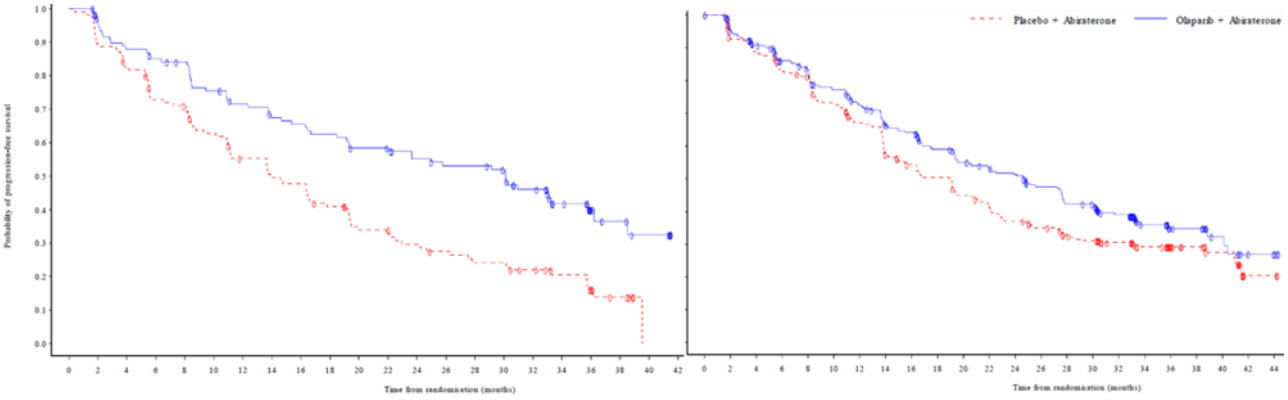
Investigator-assessed rPFS	Olaparib + Abiraterone	Placebo + Abiraterone
HRRm	**(n = 111)**	**(n = 115)**
Events, n (%)	51 (45.9)	82 (71.3)
HR (95% CI)	0.49 (0.35, 0.70)	
Median rPFS, months (95% CI)	30.1 (19.3, NC)	13.9 (11.0, 19.2)
Non-HRRm	**(n = 279)**	**(n = 273)**
Events, n (%)	142 (50.9)	171 (62.6)
HR (95% CI)	0.79 (0.63, 0.98)	
Median rPFS, months (95% CI)	24.8 (19.4, 27.6)	19.0 (14.3, 20.9)

Table 10. Summary of investigator-assessed rPFS for subgroups by HRRm status (DCO3, 12 Oct 2022)

Investigator-assessed rPFS	Olaparib + Abiraterone	Placebo + Abiraterone
HRRm	**(n = 111)**	**(n = 115)**
Events, n (%)	60 (54.1)	89 (77.4)
HR (95% CI)	0.51 (0.36, 0.70)	
Median rPFS, months (95% CI)	30.1 (19.3, 36.2)	13.9 (11.0, 19.2)

Non-HRRm	(n = 279)	(n = 273)
Events, n (%)	152 (54.5)	182 (66.7)
HR (95% CI)	0.79 (0.64, 0.98)	
Median rPFS, months (95% CI)	24.6 (19.4, 27.8)	19.0 (14.9, 20.9)

Figure 7. Kaplan-Meier plot of radiographic PFS based on investigator assessment at DCO3 by aggregate HRRm status



Left panel shows rPFS for patients with HRRm mCRPC and right panel shows rPFS for patients with non-HRRm mCRPC

7.1.2.3 Key secondary endpoint: OS

PROpel was not powered to detect a statistically significant OS gain. However, results from the three consecutive data cut-offs show an ongoing trend for an improvement in OS with olaparib + abiraterone beyond placebo + abiraterone with a 7.4-month difference in median OS at the final pre-planned data cut-off (Table 11).

At DCO3, OS data were 47.9% mature with approximately 33 months of follow-up in the ITT population. A numerical improvement was observed with olaparib + abiraterone over placebo + abiraterone, with a median OS of 42.1 months vs. 34.7 months (HR 0.81; 95% CI 0.67, 1.00; p = 0.0544) for the ITT population, suggesting a continued trend towards improved OS in patients receiving olaparib plus abiraterone. Figure 8 shows the Kaplan−Meier curves for OS as of DCO3, where it can be seen that the benefit of add-on olaparib begins after approximately 22 months.

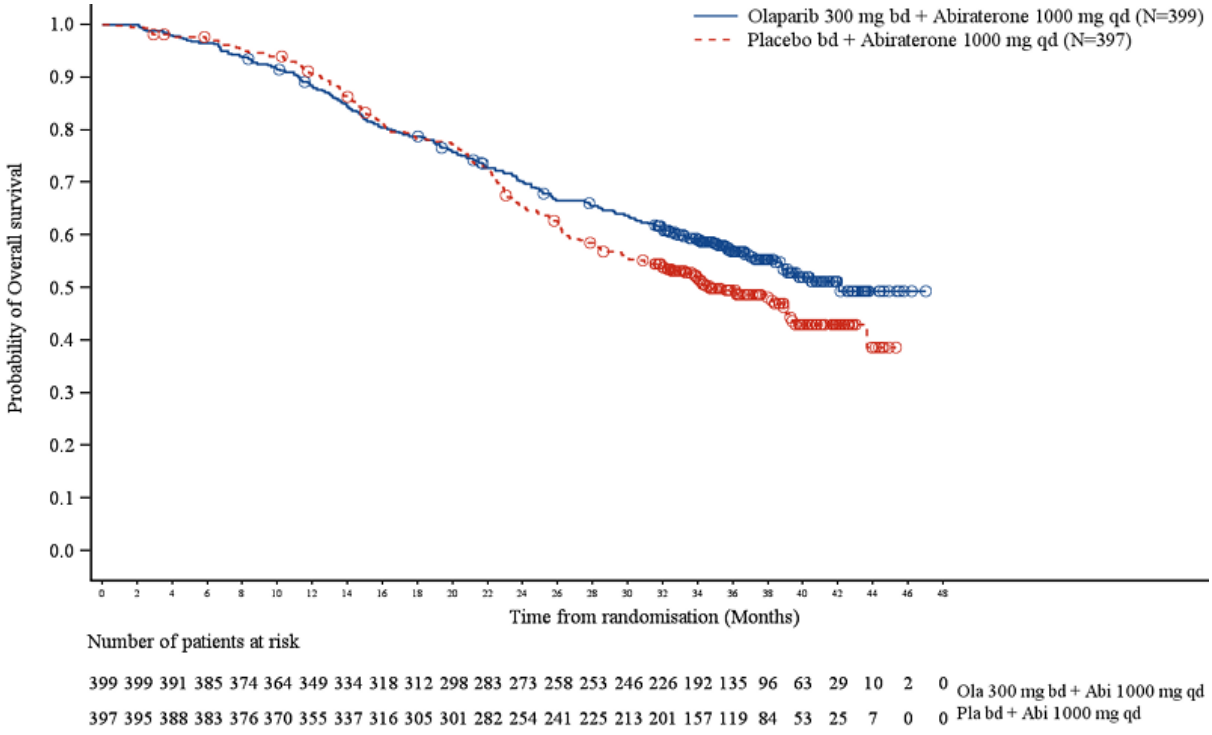
Table 11. Evolution of OS results in PROpel

Data Cut-Off	Outcome	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
DCO1 (30 July 2021)	Deaths, n (%)	107 (26.8)	121 (30.5)
	Median follow-up (range), months	20.8 (0.0, 32.6)	20.6 (0.1, 30.9)
	Median OS, months	NR	NR
	HR (95% CI)[a]	0.86 (0.66, 1.12); *p* = 0.2923	
DCO2 (14 March 2022)	Deaths, n (%)	148 (37.1)	171 (43.1)
	Median follow-up (range), months	27.6 (0.0, 40.0)	26.3 (0.4, 38.3)
	Median OS, months	NR	NR
	HR (95% CI)[a]	0.83 (0.66, 1.03); *p* = 0.1126	
DCO3 (12 October 2022)	Deaths, n (%)	176 (44.1)	205 (51.6)
	Median follow-up (range), months	33.6 (2.0, 47.0)	32.1 (0.4, 45.3)

Data Cut-Off	Outcome	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
	Median OS, months	42.1	34.7
	HR (95% CI)[a]	0.81 (0.67, 1.00); *p* = 0.0544	

[a]HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: Metastases (bone only, visceral, other) and Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib plus abiraterone. The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy, using the Breslow method for handling ties.

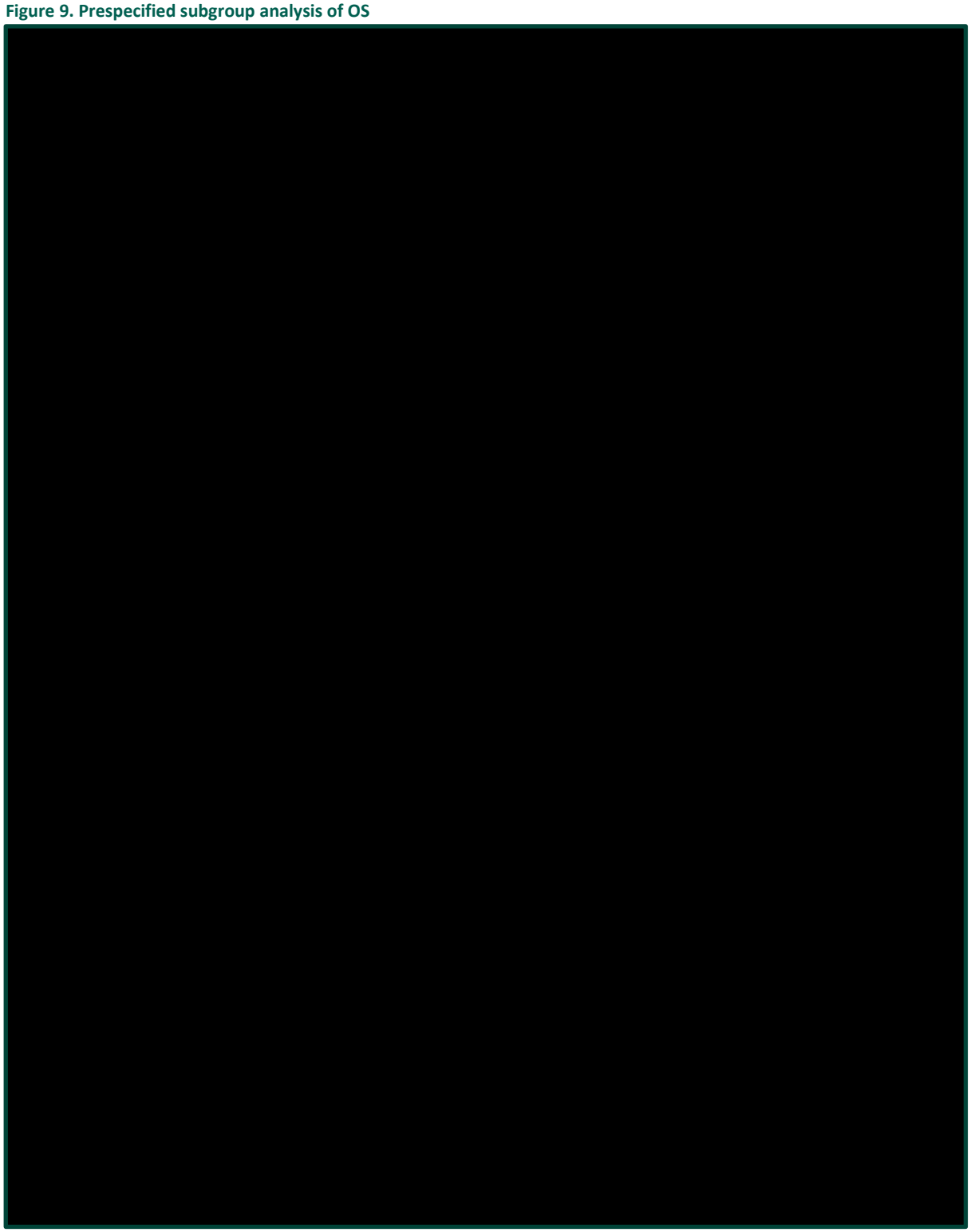
Figure 8. Kaplan-Meier plot of OS at DCO3 (12 October 2022)



7.1.2.3.1 Exploratory subgroup analyses of OS

The results of the exploratory analyses of OS subgroups were generally consistent with the ITT population, but are not powered to assess efficacy and should be considered exploratory. The results presented in Figure 9 show that the relative benefit of olaparib + abiraterone over placebo + abiraterone was consistent across the pre-specified subgroups.

Figure 9. Prespecified subgroup analysis of OS



OS by HRR status

Hazard ratios for the both HRRm and non-HRRm populations favoured the combination of olaparib + abiraterone compared to placebo + abiraterone in both DCO2 and DCO3 (see Table 12 and Table 13). As of DCO3, olaparib + abiraterone reduced the risk of death by 34% (HR 0.66; 95% CI 0.45, 0.95) in patients with HRRm. In their assessment

of olaparib + abiraterone based on OS as of DCO2, the EMA concluded that the OS benefit remained uncertain in non-HRRm patients and requested the final OS data, but that the data demonstrate "*a potential benefit and do not preclude use in this subpopulation*". As can be seen from Table 12 and Table 13, an increase in OS maturity in the non-HRRm population from 38.9% at DCO2 to 46.2% permitted median OS values to be reached and showed that olaparib + abiraterone treated patients had 3.2 months additional survival and a marginal improvement in the hazard ratio. As with the ITT population, OS curves in the non-HRRm population begin to separate after approximately 22 months, therefore it is plausible that an additional survival benefit would be observed with longer follow-up. Following DCO3, an extension of OS follow-up has been implemented in PROpel and investigators are now being unblinded to treatment received and HRRm status, with patients able to continue on abiraterone ± olaparib until study discontinuation.

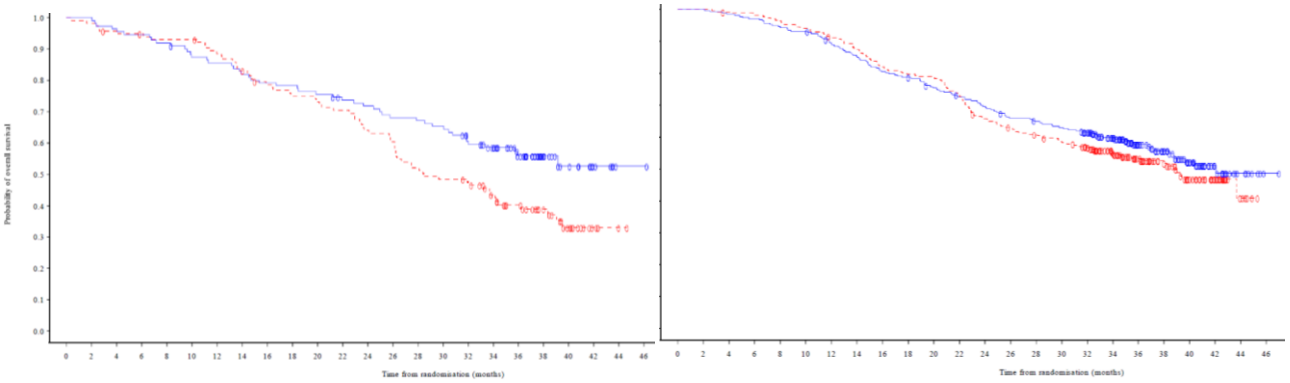
Table 12. Summary of OS outcomes by aggregate HRRm status at DCO2 (14 March 2022)

Outcome	Olaparib + Abiraterone	Placebo + Abiraterone
HRRm	**(n = 111)**	**(n = 115)**
Deaths, n (%)	41 (36.9)	57 (49.6)
Median OS, months (95% CI)	NC (NC, NC)	28.4 (26.2, NC)
HR (95% CI)[a]	0.69 (0.46, 1.03)	
Non-HRRm	**(n = 279)**	**(n = 273)**
Deaths, n (%)	104 (37.3)	111 (40.7)
Median OS, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[a]	0.90 (0.69, 1.18)	

Table 13. Summary of OS outcomes by aggregate HRRm status at DCO3 (12 October 2022)

Outcome	Olaparib + Abiraterone	Placebo + Abiraterone
HRRm	**(n = 111)**	**(n = 115)**
Deaths, n (%)	48 (43.2)	69 (60.0)
Median OS, months (95% CI)	NC (32.0, NC)	28.5 (26.2, 34.4)
HR (95% CI)[a]	0.66 (0.45, 0.95)	
Non-HRRm	**(n = 279)**	**(n = 273)**
Deaths, n (%)	123 (44.1)	132 (48.4)
Median OS, months (95% CI)	42.1 (37.3, NC)	38.9 (32.5, NC)
HR (95% CI)[a]	0.89 (0.70, 1.14)	

Figure 10. Kaplan-Meier plot of OS based on investigator assessment at DCO3 by aggregate HRRm status



Left panel shows OS for patients with HRRm mCRPC and right panel shows OS for patients with non-HRRm mCRPC

7.1.2.4 Other secondary endpoint: TFST

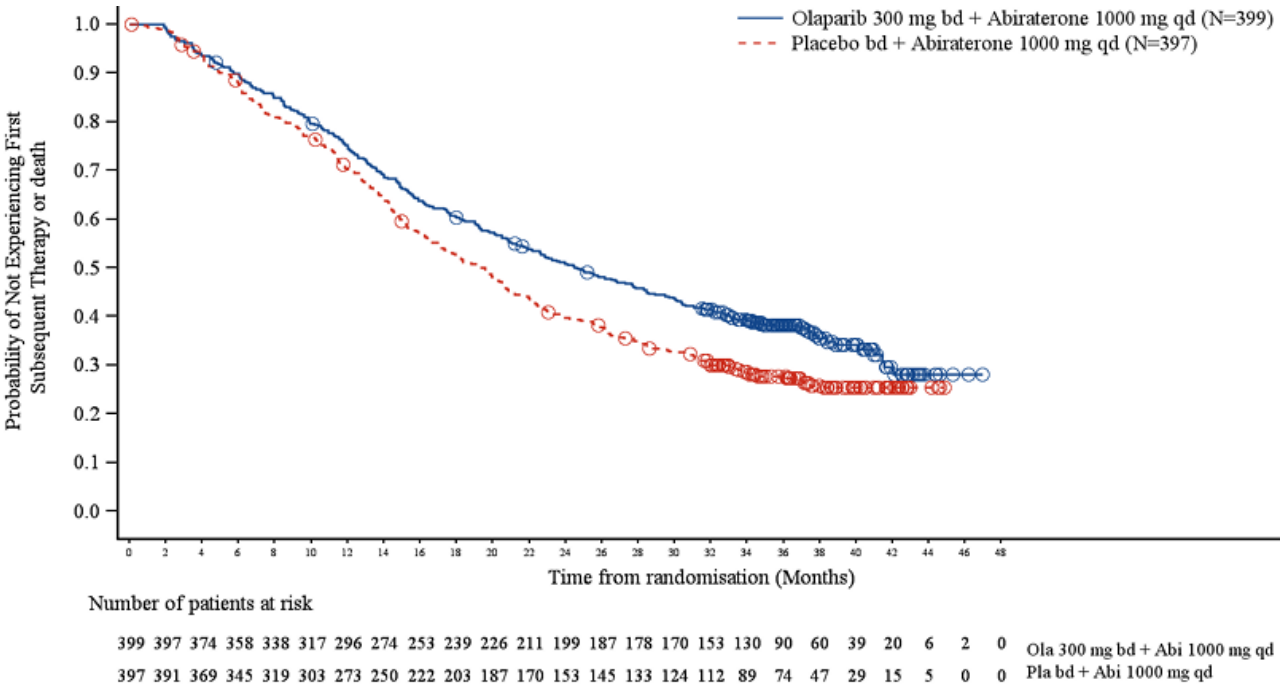
At DCO3, the time to first subsequent therapy or death (TFST) data were 67.8% mature. Olaparib + abiraterone was associated with a nominally statistically significant and clinically meaningful 5.2-month improvement in TFST versus placebo + abiraterone (HR 0.76, 95% CI 0.64, 0.90; p = 0.0025; Table 14; Figure 11).

Table 14. Summary of investigator-assessed TFST (DCO3, 12 Oct 2022)

Time to first subsequent therapy or death	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Events,[a] n (%)	255 (63.9)	285 (71.8)
HR (95% CI)[b]	0.76 (0.64, 0.90); *p* = 0.0025	
Median TFST, months (95% CI)	24.6 (21.1, 28.5)	19.4 (17.0, 21.1)

[a]Defined start of first subsequent anticancer therapy after discontinuation of randomized treatment or death from any cause. [b]HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: Metastases (bone only, visceral, other) and Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy, using the Breslow method for handling ties.

Figure 11. Kaplan-Meier plot of TFST (DCO3, 12 Oct 2022)



The post-discontinuation anticancer therapies received are summarised in Table 15. As of DCO3, 179 patients (44.9%) in the olaparib + abiraterone arm and 216 (54.4%) patients in the placebo + abiraterone arm had received anticancer therapy following discontinuation. Most subsequent therapies received in PROpel were aligned with therapies approved and used in Danish clinical practice and balanced between treatment arms, with patients predominantly receiving docetaxel (29.6%), cabazitaxel (13.2%), or enzalutamide (10.9%). There was some limited use of abiraterone rechallenge and radiopharmaceuticals. The use of subsequent PARPis was limited in both arms.

Table 15. Post-discontinuation anticancer therapies recorded in PROpel

Anticancer therapy[a]	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Any post-discontinuation anticancer therapy	179 (44.9)	216 (54.5)
Hormonal Therapy	**67 (16.8)**	**75 (18.9)**
Abiraterone[b]	28 (7.0)	24 (6.0)
Enzalutamide	39 (9.8)	49 (12.3)[c]
GnRH agonists	2 (0.5)	8 (2.0)
Cytotoxic Chemotherapy	**123 (30.8)**	**167 (42.1)**
Cabazitaxel	43 (10.8)	62 (15.6)
Carboplatin	9 (2.3)	10 (2.5)
Docetaxel	95 (23.8)	144 (36.3)[cd]
Immunotherapy	**23 (5.8)**	**23 (5.8)**
Nivolumab	5 (1.3)	3 (0.8)
Pembrolizumab	5 (1.3)	7 (1.8)

PARP Inhibitors	**2 (0.5)**	**5 (1.3)**
Targeted Therapy	**20 (5.0)**	**29 (7.3)**
Lutetium (Lu177)	9 (2.3)	4 (1.0)
Radium (Ra223)	10 (2.5)	15 (3.8)

Only specific treatments where at least 1% of the overall study population received the treatment are reported [a]Patients can be counted in > 1 anticancer therapy. [b]Includes abiraterone acetate. [c]Also includes patients counted under the Targeted Therapy category instead of Hormonal Therapy. [d]Aslo includes patients counted under the Systemic Therapy category instead of Cytotoxic Chemotherapy.

7.1.2.5 Other secondary endpoint: PFS2

PFS2 was defined as the time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression, or death. Patients who had not initiated a subsequent anticancer therapy (i.e., due to death before second line therapy, still remaining on first line therapy, or had not yet had their first disease progression) were censored at the date last known alive and not having received a subsequent therapy. Patients experiencing second disease progression or death immediately after at least two missing assessments for second disease progression were also censored at the date of the prior evaluable PFS2 assessment. At DCO3, the PFS2 data were 28.8% mature. Due to prespecified censoring of patients with missing visit assessments for PFS2 (106 patients in each arm) or had not yet initiated a subsequent anticancer therapy as of data cut-off (31 patients in each arm), PFS2 is less mature than the OS data. Despite this, olaparib + abiraterone shows some benefits beyond first disease progression, with a trend for improved outcomes compared with placebo plus abiraterone (HR 0.76; 95% CI 0.59, 0.99; Table 16).

Table 16. Summary of investigator-assessed PFS2 (DCO3, 12 Oct 2022)

Investigator-assessed PFS2	Olaparib + Abiraterone (n = 399)	Placebo + Abiraterone (n = 397)
Events,[a] n (%)	103 (25.8)	126 (31.7)
HR (95% CI)[b]	0.76 (0.59, 0.99); p = 0.0534	
Median PFS2, months (95% CI)	NC (NC, NC)	NC (NC, NC)

[a]Progression defined by investigator assessment of radiological progression (RECIST 1.1 and PCWG-3 criteria), clinical symptomatic progression (initiation of a new anticancer therapy, cancer pain requiring initiation of opioids, or deterioiration in ECOG performance status to ≥ 3), or PSA progression (two rising PSA levels with an interval of ≥1 week between each determination). [b]HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: Metastases (bone only, visceral, other) and Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib plus abiraterone. The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy, using the Breslow method for handling ties.

7.1.2.6 Other secondary endpoint: TTPP, time to opiate use, and time to an SSRE

In PROpel, time to pain progression (TTPP) (based on the BPI-SF worst pain [Item 3] and opiate use), time to opiate use for cancer-related pain, and time to first symptomatic skeletal-related event (SSRE) were not mature at DCO3. There was no difference in TTPP, time to opiate use, or time to first SSRE in the olaparib + abiraterone arm vs. the placebo + abiraterone arm (Table 17).

Table 17. Summary of TTPP, time to opiate use, and time to SSRE (DCO3, 12 Oct 2022)

Outcome	Olaparib + Abiraterone	Placebo + Abiraterone
Time to pain progression	**(n = 399)**	**(n = 397)**
Events,[a] n (%)	68 (17.0)	60 (15.1)

Outcome	Olaparib + Abiraterone	Placebo + Abiraterone
Time to pain progression	**(n = 399)**	**(n = 397)**
Median TTPP, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[b]	1.06 (0.75, 1.50); *p* = 0.7456[c]	
Time to opiate use for cancer-related pain	**(n = 344)[d]**	**(n = 353)[d]**
Events, n (%)	58 (16.9)	45 (12.7)
Median time to opiate use, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[b]	1.21 (0.82, 1.79); *p* = 0.3099[c]	
Time to first symptomatic skeletal-related event	**(n = 399)**	**(n = 397)**
Events,[e] n (%)	46 (11.5)	51 (12.8)
Median time to SSRE, months (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)[b]	0.82 (0.55, 1.22); *p* = 0.3212[c]	

[a]1) For patients who were asymptomatic at baseline, a ≥2 point change from baseline in the average (4-7 days) BPI-SF Item 3 (worst pain in 24 hours) score at 2 consecutive evaluations (with ≥2 weeks between the end of the initial visit and start of the subsequent visit) OR initiation of opioid use for pain; 2) for patients who are symptomatic at baseline (average BPI-SF Item 3 score > 0 and/or currently taking opioids), a ≥2 point change from baseline in the average BPI-Sf Item 3 score observed at 2 consecutive visits and average worst pain score ≥4, and no decrease in average opioid use (≥1-point change in AQA score from starting value of 2 or higher) OR any increase in opioid use (e.g., 1-point change in AQA score) at 2 consecutive follow-up visits (with ≥2 weeks between the end of initial visit and start of subsequent visit). Any patient who had >2 consecutive visits that were not evaluable for pain progression was to be censored at the last evaluable assessment. [b]HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: Metastases (bone only, visceral, other) and Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib plus abiraterone. [c]The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy, using the Breslow method for handling ties. [d]Only patients who are not on opiates at baseline are included. [e]Defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrenceof new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting form minimal or no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention.

7.1.2.7 Other secondary endpoint: HRQoL using FACT-P

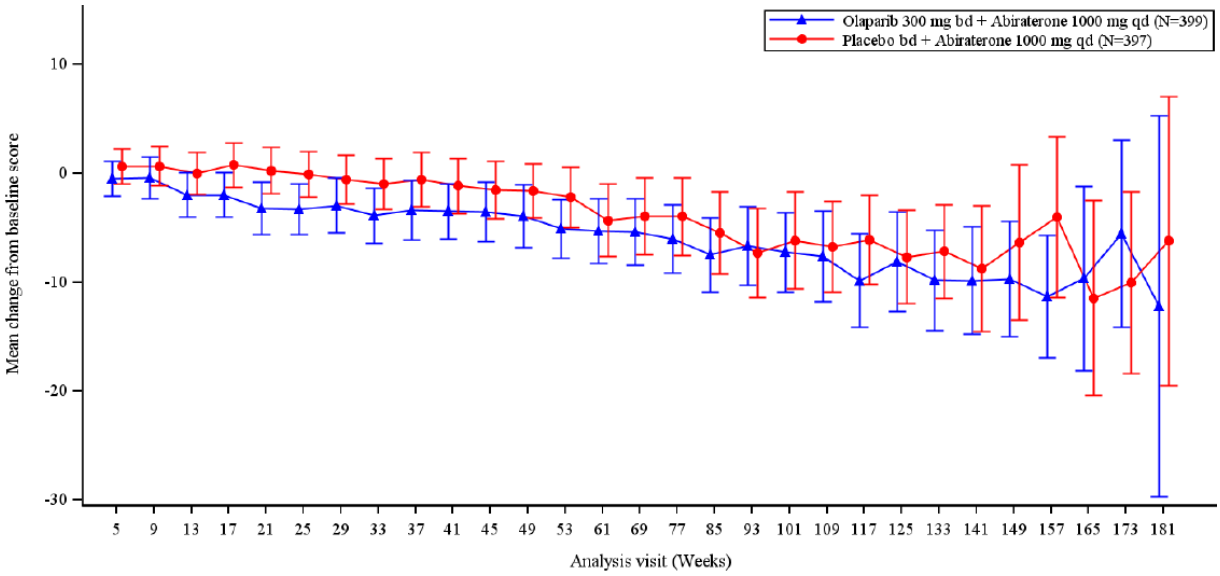
Health-related quality of life (HRQoL) results as applied in the model, using the EQ-5D, are reported in section 8.5 below. In addition, HRQoL data in the form of the FACT-P (Functional Assessment of Cancer Therapy – Prostate) was a specified secondary endpoint in PROpel. FACT-P is a 39-item, multidimensional instrument with 12 cancer site specific items, designed to assess physical and functional HRQoL specifically in patients with prostate cancer. For the FACT-P total score, scores range from 0 to 156 with higher scores indicating better quality of life. In PROpel, the FACT-P was collected every 4 weeks in the first year and then every 8 weeks thereafter until 12 weeks after confirmed progressive disease.

Change from baseline scores for each time point and treatment group were calculated on the FACT-P total score and subscales. Change from baseline was analysed until there are less than one third of patients with evaluable data. Assessment in the change from baseline was performed using a MMRM with treatment, visit, treatment by visit interaction, baseline FACT-P score, baseline by visit interaction, site of metastases, and docetaxel treatment at mHSPC stage as fixed effects. The overall treatment effect across visits is reported here. In addition, deterioration in FACT-P score was defined as the first worsening (a visit with a decrease from baseline of at least 10 points) that is confirmed at a subsequent visit at least 3 weeks apart with no improvement (increase in score of at least 10 points) in between the visits, except if it was the patient's last available assessment, or death. Patients with missing baseline data or FACT-P total scores less than 10 at baseline were censored for the analysis. Patients with at least two missing visits were

censored at their last evaluable assessment. Time to deterioration was analyses using a Cox proportional hazards model, adjusting for the trial stratification factors.

Compliance rates for the completion of the FACT-P at baseline and overall were 70.9% and 69.8%, and 75.6% and 74.5% for the olaparib + abiraterone and placebo + abiraterone arms, respectively. The adjusted mean change from baseline in the FACT-P total score showed no detriment for the olaparib + abiraterone compared with placebo + abiraterone by DCO3 (difference in least squares mean -0.54; 95% CI -3.00, 1.92; *p* = 0.6675; Figure 12). There was also no detriment observed in any of the subscales/indices of the FACT-P (data not shown, available on request). There was also no overall HRQoL detriment in the time to deterioration in FACT-P total score between the olaparib + abiraterone arm and the placebo + abiraterone arm (HR 1.01; 95% CI 0.81, 1.27; *p* = 0.9910). Therefore, mCRPC patients treated with abiraterone do not experience any worsening of their HRQoL when olaparib is added to their treatment regimen.

Figure 12. Mean change from baseline in FACT-P Total Score



Given that many patients with mCRPC treated with NHAs today report good quality of life with a low symptom burden, the lack of detriment in quality of life with the addition of olaparib is clinically meaningful.

7.1.2.8 Exploratory endpoints: tumour response, disease control rate, and duration of response

In total, 321 patients (40.3%) had measurable disease at baseline. The analysis of radiological ORR at DCO2 based on investigator assessment showed that ORR was numerically higher in the olaparib plus abiraterone arm than in the placebo plus abiraterone (59.0% vs 48.1%; OR, 1.64 [95% CI 1.05−2.59]). The results for BICR-assessed tumour response were consistent with the investigator-assessed tumour response. Overall radiological ORR based on BICR was higher in the olaparib + abiraterone arm than in the placebo + abiraterone arm (59.3% vs. 48.0%; OR 1.62 [95% CI 1.03, 2.56]).

Seven patients (4.3%) in the olaparib + abiraterone arm and 11 (6.9%) in the placebo + abiraterone arm had a complete response (CR). Partial response was reported for 88 (54.7%) and 66 patients (41.3%) in the olaparib + abiraterone and placebo + abiraterone arms, respectively. The proportion of patients with stable disease for 11 weeks or longer was similar between the two treatment arms: 25.5% and 28.1% in in the olaparib + abiraterone and placebo + abiraterone, respectively. The disease control rate (DCR) at 24 weeks was higher in the olaparib + abiraterone arm compared with the placebo + abiraterone arm: 132 patients (82.0%) compared with 121 (75.6%), respectively. Median duration of response (DoR) was 11.3 months longer in the olaparib plus abiraterone arm than in the placebo + abiraterone arm

(24.2 months vs 12.9 months), with a similar median time to onset of response in both arms: 2.3 months (95% CI, 1.9–3.7) and 2.0 months (95% CI, 1.9–3.7) in the olaparib + abiraterone and placebo + abiraterone arms, respectively.

7.1.3 Safety and tolerability

The median total duration of exposure to olaparib was 564 days by DCO3. The median total duration of exposure to abiraterone was 1.3 times longer in the olaparib + abiraterone arm compared to the placebo + abiraterone arm (612 days vs. 477 days), supporting the notion of a synergistic effect between olaparib and abiraterone in delaying progression and permitting patients to remain on treatment for longer. The incidence of adverse events (AEs) was similar in the two treatment arms and was consistent with the known safety profile for olaparib and abiraterone. The safety profile of abiraterone was not adversely impacted by its combination with olaparib. Pharmacokinetic analyses from PROpel confirmed that combination treatment of olaparib and abiraterone had no clinically significant effect on the pharmacokinetic profiles of either drugs.

7.1.3.1 Adverse events

The proportion of patients who experienced at least one AE of any grade was similar between treatment arms, and AEs were generally manageable through dose interruptions and reductions. A summary of the main safety outcomes is provided in Figure 13. The most frequently reported AEs in the olaparib + abiraterone arm were anaemia, fatigue/asthenia, and nausea, and these were also the AEs most frequently reported to be treatment-related. In the placebo + abiraterone arm, the most frequently reported AEs were fatigue/asthenia, back pain, and arthralgia, where fatigue, anaemia, and nausea were the AEs most frequently reported to be treatment-related.

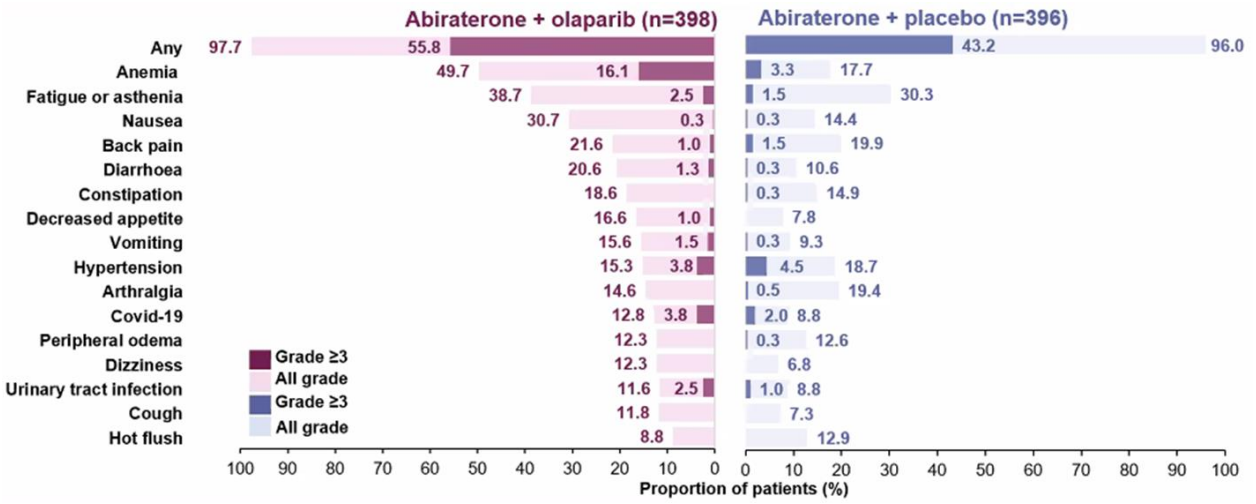
As of DCO3, AEs of Grade ≥3 were reported in 56% of patients treated with olaparib + abiraterone and 43% treated with placbeo + abiraterone. At the system organ class level, the most commonly reported AEs of Grade ≥3 that were more prevalent in patients treated with olaparib + abiraterone compared to placebo + abiraterone were: blood and lymphatic system disorders (18.3% vs 5.8%), respiratory, thoracic and mediastinal disorders (9.3% vs. 3.3%), infections and infestations (14.8% vs. 10.1%), and investigations (11.8% vs. 8.6%).

Table 18. Adverse events in any category (safety analysis set) at DCO3 (12 Oct 2022)

Category of adverse event	Olaparib + Abiraterone (n = 398)	Placebo + Abiraterone (n = 396)
Any AE	389 (97.7)	380 (96.0)
Any AE causally related to study treatment	339 (85.2)	279 (70.5)
Any AE of CTCAE Grade 3 or higher	222 (55.8)	171 (43.2)
Any AE of CTCAE Grade 3 or higher, causally related to study treatment	122 (30.7)	65 (16.4)
Any AE with outcome of death	26 (6.5)	20 (5.1)
Any AE with outcome of death, causally related to study treatment	0	1 (0.3)
Any SAE (including events with outcome of death)	161 (40.5)	126 (31.8)
Any SAE (including events with outcome of death), causally related to study treatment	56 (14.1)	24 (6.1)
Any AE leading to discontinuation of study treatment	71 (17.8)	43 (10.9)
Any AE leading to discontinuation of study treatment, causally related to study treatment	41 (10.3)	27 (6.8)

Patients with multiple events in the same category are counted only once in that category. Patients with events in > 1 category are counted in each of those categories. 'Study treatment' refers to olaparib/placebo, and/or abiraterone, and/or prednisone/prednisolone.

Figure 13. Most common adverse events (in ≥10% of patients) at DCO3 (12 Oct 2022)



Safety was assessed through the reporting of AEs according to the NCI CTCAE version 4.03 and laboratory assessments*Anaemia category includes anaemia, decreased haemoglobin level, decreased red cell count, decreased haematocrit level, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia and normocytic anaemia, NCI, National Cancer Institute

Table 19 shows AEs grade ≥ 3 by preferred term occurring in at least 2% of patients as of DCO3. The included AEs in the health economic model are based on AEs with this severity and frequency. Specific adverse events of Grade ≥3 that were more prevalent in patients treated with olaparib + abiraterone compared to placebo + abiraterone were: anaemia, decreased levels of different types of white blood cell, and pulmonary embolism. Despite grade ≥3 COVID-19 occurring in more than 2% of patients in PROpel, this is not expected to be a significant concern in future and therefore was excluded from the economic model.

Table 19. Adverse events CTCAE grade 3 or higher, occurring in at least 2% of patients in either treatment arm (DCO3; 12 Oct 2022)

Adverse event	Olaparib + Abiraterone (n = 398)	Placebo + Abiraterone (n = 396)
Anaemia	64 (16.1)	13 (3.3)
Pulmonary embolism	29 (7.3)	9 (2.3)
Hypertension	15 (3.8)	18 (4.5)
COVID-19	15 (3.8)	8 (2.0)
Lymphocyte count decreased	15 (3.8)	6 (1.5)
Neutrophil count decrease	11 (2.8)	3 (0.8)
Pneumonia	10 (2.5)	4 (1.0)
Urinary tract infection	10 (2.5)	4 (1.0)
White blood cell count decrease	9 (2.3)	2 (0.5)
Hyperglycaemia	8 (2.0)	6 (1.5)
Alanine aminotransferase increased	4 (1.0)	9 (2.3)

Serious AEs (SAEs) were reported in 40.5% and 31.8% of patients treated with olaparib + abiraterone and placebo + abiraterone, respectively. The most commonly occurring SAEs (≥2% of patients in either arm) were anaemia, COVID-19, pulmonary embolism, pneumonia, and urinary tract infection. Anaemia was the most frequently reported SAE and more common in patients treated with olaparib + abiraterone (5.8%) compared to placebo + abiraterone (0.8%). The incidence of pulmonary embolism was also greater in the olaparib + abiraterone arm (3.8% vs. 0.8%). The rates of specific serious infections were not dissimilar between arms, though slightly more common in olaparib + abiraterone treated patients than in placebo + abiraterone treated patients (COVID-19: 3.8% vs. 2.5%; pneumonia: 2.8% vs. 1.3%; urinary tract infection: 2.3% vs. 0.8%).

7.1.3.2 Dose interruptions, reductions and modifications

The proportions of dose interruptions, reductions and modifications are summarised in Table 20. Treatment interruptions occurred more frequently with olaparib than with placebo (52.3% vs 33.6%), and a higher proportion of patients required abiraterone interruptions in the olaparib combination arm than in the placebo + abiraterone arm (39.9% vs 27.3%). Similarly, dose reductions of olaparib were required more frequently than dose reductions of placebo (25.1% vs 8.1%), but the proportion of abiraterone dose reductions was similar in the combination and placebo arms (3.8% vs 5.1%). The most frequently reported reason for treatment interruption or dose reduction was AEs. The proportion of patients with AEs leading to dose reduction or dose interruption of olaparib or placebo was higher in the olaparib plus abiraterone arm than the placebo plus abiraterone arm (interruption: 40.5% vs 21.7%; reduction, 22.1% vs 5.3%). However, most AEs did not lead to discontinuation of study treatment.

The median relative dose intensities (RDI) were high for olaparib, placebo, and abiraterone, suggesting that dose intensity was not affected by dose interruptions or reductions during treatment, though a marginally lower percentage intended dose for patients receiving olaparib indicates that some patients discontinued before progression.

Table 20. Treatment interruptions and dose reductions in PROpel

Number of Patients, n (%)	Olaparib plus Abiraterone		Placebo plus Abiraterone	
	Olaparib (n = 398)	Abiraterone (n = 398)	Placebo (n = 396)	Abiraterone (n = 396)
Received planned starting dose	387 (97.2)	396 (99.5)	390 (98.5)	394 (99.5)
Interruptions				
Patients with any interruption	208 (52.3)	159 (39.9)	133 (33.6)	108 (27.3)
Dose reductions				
Patients with a dose reduction	100 (25.1)	15 (3.8)	32 (8.1)	20 (5.1)
Relative Dose Intensity (RDI)[a]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	98.2 (88.5, 100.0)	100.0 (97.1, 100.0)	99.7 (97.0, 100.0)	100.0 (98.6, 100.0)
Percentage Intended Dose (PID)[b]				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	96.5 (77.0, 100.0)	99.6 (92.5, 100.0)	99.4 (91.9, 100.0)	100.0 (95.0, 100.0)

[a]Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation.
[b]Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression.

7.1.4 Summary of efficacy and safety

PROpel demonstrated a statistically significant 8.5-month improvement in the risk of rPFS for olaparib + abiraterone compared to placebo + abiraterone (HR 0.68; 95% CI 0.57, 0.81; p < 0.0001), extending median rPFS by nearly 50%. These data are clinically relevant, with PROpel being the first study to show a PFS longer than two years in the mCRPC setting. A numerical improvement was observed for olaparib + abiraterone over placebo + abiraterone, with a median OS of 42.1 months vs. 34.7 months (HR 0.81; 95% CI, 0.67, 1.00; p = 0.0544): a 7.4-month improvement. With this, data suggests that the OS gain is approaching the PFS gain (8.5 months).

EMA assessed during the MA process that "the results are consistent with FAS (ITT) and demonstrate a potential benefit of the association abiraterone + olaparib for all the populations eligible, i.e. in whom the chemotherapy is not clinically indicated at mCRPC, regardless of symptomatic disease status or previous treatment with docetaxel in mHSPC".[47] A higher proportion of patients had AEs considered related to study treatment in the olaparib + abiraterone than in the placebo plus abiraterone arm (85.2% vs 70.5%). The most frequently reported treatment-related AEs reported in the olaparib + abiraterone arm were anaemia (40.7%), nausea (20.4%), and fatigue (19.3%); and in the placebo + abiraterone arm were fatigue (12.9%), anaemia (10.6%), and nausea (6.1%). The incidence of AEs was consistent with the known safety profile for olaparib and abiraterone.[1,5,30]

The median total duration of exposure to olaparib was 1.2 times longer than the duration of exposure to placebo (564 days versus 476.5 days), and the median total duration of exposure to abiraterone was 1.3 times longer on the olaparib plus abiraterone arm compared with the placebo plus abiraterone arm (612.0 days vs 477.0 days), suggesting that combining olaparib with abiraterone did not reduce the planned administration of abiraterone.

8. Health economic analysis

8.1 Scope

The health economic analysis is designed to assess the incremental cost-effectiveness of Lynparza® (olaparib) in Denmark within its licensed indication in combination with abiraterone and prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. As olaparib + abiraterone is demonstrated to improve patients outcomes in terms of progression-free survival and overall survival compared to abiraterone alone (standard of care in Denmark today), a cost-utility analysis has been developed, with results presented as cost per QALY gained. The analysis takes a limited societal perspective. This includes the costs of drug acquisition including subsequent therapies, costs of administering any hospital drugs, routine medical care costs, costs of adverse events and skeletal-related events, end of life care costs, and the costs to the patient in terms of time and transport.

The cost-effectiveness model was developed in Microsoft Excel® 365 (macro-enabled workbook). All macros have been signed with a security certificate from AstraZeneca.

8.1.1 Patient population

The patient population in the economic analysis is aligned with the indicated patient population and therefore the patients expected to the treated with olaparib + abiraterone in Danish clinical practice, and is informed by the ITT population of the PROpel trial. A scenario analysis is also presented based on the subgroup of patients from the PROpel trial with HRR mutations. As there were no significant or meaningful differences in the patient characteristics between the ITT population of the trial and the HRRm subgroup, the patient characteristics applied in the model are derived from the ITT population (Table 21).

Table 21. Patient baseline characteristics applied in the model

Patient Characteristics	Mean (SD)	Source / Rationale
Age, years	69.1 (8.24)	ITT population from PROpel
Weight (kg)	82.7 (16.08)	ITT population from PROpel
Height (cm)	174.9 (7.7)	COU-AA-302 (NICE TA387) – height data not collected in PROpel
Body surface area (m^2)	1.98	Derived from height and weight using the Du Bois formula

8.1.2 Intervention

The intervention in the analysis is olaparib (Lynparza®) tablets 300 mg (2 x 150 mg) BID (i.e., 600 mg/day) given in combination with abiraterone 1000 mg QD and prednisolone 5 mg BID (i.e., 10 mg/day), in line with the dosing regimen studied in the PROpel trial and included in the SmPC.

8.1.3 Comparator(s)

The treatment landscape of mCRPC and the relevant comparator in Danish clinical practice is described in section 5.2. Based on Danish and European treatment guidelines and feedback from clinical experts, current treatment options available for mCRPC patients in whom chemotherapy is not clinically indicated are primarily new hormonal agents (NHAs), namely abiraterone or enzalutamide. These two therapies are considered sufficiently clinically equivalent and a tendered for mCRPC in Denmark, with generic abiraterone (Abirateron Medical Valley) as the current tender winner for asymptomatic or mildly symptomatic patients with a performance status < 2 and without visceral metastases. The stratification to create a separate category for patients with or without visceral metastases was due to the lack of

documented effect of abiraterone in the pre-chemotherapy setting in patients with visceral metastases when the initial RADS guidance was developed. Feedback from clinical experts is that this stratification is not strictly applied in clinical practice as subsequent evidence and experience has shown abiraterone to have effect in patients with visceral metastases. Results from the PROpel trial also show that the relative efficacy of olaparib + abiraterone compared to placebo + abiraterone is comparable between patients with and without visceral metastases. Consequently, abiraterone is considered the primary comparator given that as a generic treatment it is likely to be preferred in practice in future. However, as enzalutamide (Xtandi) is the tender winner amongst patients with visceral metastases a comparison to this treatment this is considered as a scenario analysis.

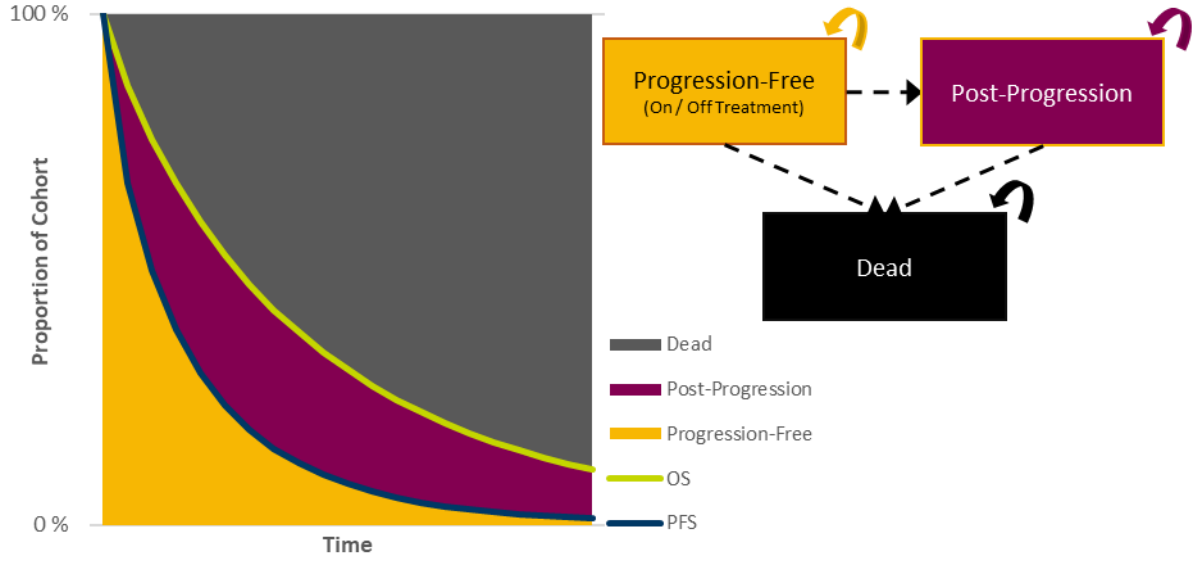
Abiraterone tablets (2 x 500 mg) are taken as a single daily dose in combination with 10 mg/day prednisone or prednisolone (taken as 5 mg BID in the PROpel and COU-AA-302 clinical trials – the registrational trial for abiraterone in this indication).[1,5,48] Enzalutamide tablets (4 x 40 mg) are taken as a single daily dose.[49]

8.2 Model

8.2.1 Model structure

A three-state partitioned-survival (or area under the curve) model is used to evaluate the cost-effectiveness of olaparib with abiraterone in the mCRPC setting. The model uses extrapolated survival curves based on observed time to event outcomes from the PROpel clinical trial, namely radiological progression-free survival (rPFS) and overall survival (OS). Consequently, the model structure captures the primary and key secondary endpoints of the trial. Using these curves, the model can estimate the proportion of patients in a cohort who are in any of one three mutually exclusive and fully exhaustive health states at any given time: progression-free, post-progression, or dead. Costs and utilities are assigned to each health state. All patients are assumed to be alive and progression-free at baseline and therefore occupy this health state. Figure 14 shows an example of the implementation of the model structure and the conceptual underlying transitions between health states that it is assumed to represent.

Figure 14. Illustration of the partitioned survival model structure



The model structure is designed to reflect the natural progression of mCRPC and capture the benefits of treatment with olaparib with abiraterone in terms of delayed disease progression (and in turn the need for subsequent lines of therapy) as well as prolonged survival. The progression status of the cohort was used to model the health-related quality of life of patients over time, with the progression-free state representing the period of relatively high quality of life while the

disease is under control and progressed disease representing the period with new and worsening symptoms. The utility weights for progression-free and progressed disease states were based on data from PROpel.

In addition to the extrapolation of the OS and rPFS curves, time to discontinuation of treatment has also been extrapolated. Whilst in the PROpel study, treatment was planned to be continued until objective imaging-based progressive disease as assessed by the investigator, unacceptable toxicity, or withdrawal of consent, As can be seen from Figure 15, time on treatment in the trial was shorter than progression-free survival. Time on treatment was therefore extrapolated independently of disease progression. No explicit restrictions were applied in the model to limit time on treatment to be less than PFS, however time on treatment was capped so that it could not exceed overall survival and a restriction was applied in the model so that the hazard of treatment discontinuation was at least as high as the risk of death in the general population. Therefore, patients can be progression-free and on first line treatment or progression-free having discontinued treatment, as well as potentially continuing first line treatment beyond disease progression should the clinical data indicate this. Time on treatment was extrapolated independently for time to discontinuation of abiraterone (TDA) and for time to discontinuation of study treatment (TDT), i.e., olaparib. This was as patients were observed to discontinue olaparib prior to abiraterone during the trial.

Figure 15. Kaplan-Meier curves of time on treatment and rPFS in the olaparib + abiraterone arm of PROpel

8.2.2 Time horizon, cycle length, and discounting

In the base case a time horizon of 30 years is applied. This is assumed to reflect a lifetime perspective and capture all relevant costs and health outcomes. In the base case, after 30 years all patients in the comparator arm are assumed to have died and 1% of those in the olaparib + abiraterone arm were still alive. Both future costs and benefits were discounted by 3.5% per annum over the duration of the model time horizon, as recommended by the Danish Ministry of Finance. In scenarios using longer time horizons (i.e., up to 40 years), the discount rate in the years after 35 years from baseline were discounted at 2.5% per annum.

A cycle length of one calendar month (30.44 days) is applied in the model. This enabled adequate granularity to capture the model costs and outcomes measurements in the PROpel trial. Half-cycle correction has been applied using a lifetable approach to the calculation of cost and health outcome results, where required. The key exceptions were drug acquisition and administration costs, which were assumed to be administered at the start of each cycle to capture the costs of discarded medication in patients that stop treatment before the next cycle. Additionally, adverse event-related

disutilities for each first line treatment were incurred as a one-time application during the first cycle of the model based on observed incidence rates and were not half-cycle adjusted.

8.2.3 Model validation

Model validation was pursued considering four different aspects of validity: face validity, technical validation, external validation, and cross validation.

- **Face validity**: the patient population used and comparator therapies included in the analysis were discussed with Danish clinical experts to discuss their relevance to the expected population to be potentially considered as candidates for olaparib + abiraterone in Norwegian clinical practice. In addition, the face validity of the model results were evaluated.
- **Technical validation**: a comprehensive review of the model programming was performed by an internal peer reviewer not involved with the original programming. The review included a detailed inspection of the formulae and sequence of calculations, a quality check and functional assessment of any VBA programming, extreme value testing to identify and correct potential inconsistencies in model behaviour, and checking data inputs against references and sources.
- **External validation**: survival extrapolations in the model were compared to published data on PFS and OS from other trials and real-world evidence. Further details can be found in section 8.4 above.
- **Cross validation**: outcomes for the comparator arm were compared with those reported as preferred by the HTA agency in the NICE (TA387), NoMA (ID2013_036), and TLV (Dnr 4774/2014) assessments of abiraterone in the same setting. The estimated discounted life years gained with abiraterone treatment were similar between the current models and those conducted in Sweden and Norway (a difference of 3-4 months between models). This difference was assumed acceptable given that at the time of the abiraterone assessment, survival data were less mature than the more recent publications, and the discounted QALYs gained with abiraterone were near identical to the current model (Δ0.02), and several treatments which can be used after abiraterone have been approved since the registrational trial for abiraterone was conducted (e.g., cabazitaxel for patients who have previously received docetaxel, olaparib for patients with BRCA 1/2 mutations, radium-223 for patients with bone metastases). When applying Norwegian and Swedish prices as per the time of the initial abiraterone assessments, total estimated costs for the abiraterone arm in the model were within 0.4% and 8% of the reported values in Norway and Sweden, respectively. Modelled time on treatment with abiraterone was similar between the current model and the NICE submission, with median time differing by 0.3 months and the proportion of patients continuing treatment beyond two years being similar (31% vs. 33%).

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

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

The majority of clinical inputs in the model were obtained from the PROpel clinical trial data as of DCO3 (final planned OS analysis) from the ITT population. As the PROpel trial reflects the labelled patient population and treated, as well as a relevant comparator for Denmark, the use of trial data was deemed appropriate for the analysis and applicable to Danish clinical practice. Exceptions to this were patients height (for estimating body surface area for use in the calculations of doses of subsequent therapies as this was not collected in PROpel), estimates for disutilities due to adverse events, and inputs related to the scenario analysis compared to enzalutamide, which were obtained from published literature from the source considered most appropriate. Table 22 provides an overview of the sources of the inputs into the model.

Table 22. Input data used in the model

Parameter	Source	Results in Source	Value Used in Model	How Value was Obtained/Estimated
Patient Characteristics				
Age at baseline, years	PROpel ITT	69.1	69.1	Direct use of trial data
Patient weight, kg	PROpel ITT	82.7	82.7	Direct use of trial data
Patient height, cm	COU-AA-302[50]	174.9	174.9	Direct use of source data
Body surface area, m^2	N/A	N/A	1.98	Derived from height and weight data using Du Bois formula
Efficacy Inputs & Time to Event Outcomes				
rPFS	PROpel ITT	See 7.1.2	See 8.4	Parametric extrapolation of patient level data using lognormal distribution
Proportion of rPFS events which are progression	PROpel ITT	Ola: 81.2% Abi: 88.1% Enz: 88.1%	Ola: 81.2% Abi: 88.1% Enz: 88.1%	From observed rPFS events as of DCO3 (219 for olaparib and 277 for placebo) and the number of deaths pre-progression (41 for olaparib and 33 for placebo), the proportion of progression events was estimated to determine the proportion of patients potentially moving to next line of therapy. Assumed equivalency between abiraterone and enzalutamide.
Overall survival	PROpel ITT	See 7.1.2	See 8.4	Parametric extrapolation of patient level data using generalised gamma distribution
Time to discontinuation of abiraterone	PROpel ITT	See 8.4	See 8.4	Parametric extrapolation of patient level data using loglogistic distribution
Time to discontinuation of olaparib	PROpel ITT	See 8.4	See 8.4	Parametric extrapolation of patient level data using generalised gamma distribution
Relative effectiveness of enzalutamide	N/A	N/A	HR 1.00	Assumed equivalency of rPFS and OS on the basis of clinical feedback, Medicinrådet tenders, real-world evidence, and trial evidence. Time on treatment also assumed to be equivalent.
Safety Inputs				
Incidence: ALAT Increased	PROpel ITT / Xtandi EPAR	Ola: 1.0% Abi: 2.3% Enz: NR	Ola: 1.0% Abi: 2.3% Enz: 0.0%	Direct use of trial data for treatments in PROpel. Safety results reported in EPAR used for enzalutamide given the comparable duration of treatment exposure and follow-up. Where an adverse event was not reported in the source, the incidence was assumed to be 0%.
Incidence: Anaemia		Ola: 16.1% Abi: 3.3% Enz: 3.3%	Ola: 16.1% Abi: 3.3% Enz: 3.3%	
Incidence: Back Pain		Ola: 1.0% Abi: 1.5% Enz: 2.5%	Ola: 1.0% Abi: 1.5% Enz: 2.5%	
Incidence: General Physical Health Deterioration		Ola: 0.3% Abi: 0.3% Enz: 2.1%	Ola: 0.3% Abi: 0.3% Enz: 2.1%	

Parameter	Source	Results in Source	Value Used in Model	How Value was Obtained/Estimated
Incidence: Hyperglycaemia		Ola: 2.0% Abi: 1.5% Enz: 4.0%	Ola: 2.0% Abi: 1.5% Enz: 4.0%	
Incidence: Hypertension		Ola: 3.8% Abi: 4.5% Enz: 3.8%	Ola: 3.8% Abi: 4.5% Enz: 3.8%	
Incidence: Lymphocyte Count Decreased		Ola: 3.8% Abi: 1.5% Enz: NR	Ola: 3.8% Abi: 1.5% Enz: 0.0%	
Incidence: Neutrophil Count Decreased		Ola: 2.8% Abi: 0.8% Enz: 0.9%	Ola: 2.8% Abi: 0.8% Enz: 0.9%	
Incidence: Pneumonia		Ola: 2.5% Abi: 1.0% Enz: 2.5%	Ola: 2.5% Abi: 1.0% Enz: 2.5%	
Incidence: Pulmonary Embolism		Ola: 7.3% Abi: 2.3% Enz: NR	Ola: 7.3% Abi: 2.3% Enz: 0.0%	
Incidence: Urinary Tract Infection		Ola: 2.5% Abi: 1.0% Enz: 1.5%	Ola: 2.5% Abi: 1.0% Enz: 1.5%	
Incidence: White Blood Cell Count Decreased		Ola: 2.3% Abi: 0.5% Enz: NR	Ola: 2.3% Abi: 0.5% Enz: 0.0%	
QALY Loss: ALAT Increased	N/A	N/A	-0.000	Assumed to have no detrimental impact on QALYs in the absence of hepatitis or cirrhosis
QALY Loss: Anaemia	Sullivan 2011[51]	-0.022	-0.001	Assumed 10.5 days duration
QALY Loss: Back Pain	Sullivan 2011[51]	-0.087	-0.002	Assumed 10.5 days duration
QALY Loss: General Physical Health Deterioration	Swinburn 2010[52]	-0.204	-0.051	Assumed 3 months duration
QALY Loss: Hyperglycaemia	N/A	N/A	-0.000	Assumed to have no detrimental impact on QALYs in the absence of peripheral neuropathy or ketoacidosis
QALY Loss: Hypertension	Sullivan 2011[51]	-0.046	-0.001	Assumed 10.5 days duration
QALY Loss: Lymphocyte Count Decreased	N/A	N/A	-0.000	Assumed to have no detrimental impact on QALYs in the absence of a lymphocytopenia-related infection
QALY Loss: Neutrophil Count Decreased	Nafees 2008[53]	-0.090	-0.003	Assumed 10.5 days duration
QALY Loss: Pneumonia	Tolley 2013[54]	-0.061, -0.195	-0.004	Average of reported severe infection disutilities over assumed 10.5 days duration

Parameter	Source	Results in Source	Value Used in Model	How Value was Obtained/Estimated
QALY Loss: Pulmonary Embolism	Locadia 2004[55]	-0.31	-0.009	Assumed 10.5 days duration
QALY Loss: Urinary Tract Infection	Sullivan 2011[51]	-0.005	-0.000	Assumed 10.5 days duration
QALY Loss: White Blood Cell Count Decreased	N/A	N/A	-0.003	Assumed equal to neutropenia
Probability of experiencing SSRE upon disease progression	PROpel ITT	Ola: 25.8% Abi: 20.9% Enz: 20.9%	Ola: 25.8% Abi: 20.9% Enz: 20.9%	From observed progression events as of DCO3 (178 for olaparib and 244 for placebo) and the number of SSREs occuring in patients (46 for olaparib and 51 for placebo), the proportion of patients experiencing an SSRE relative progression events was estimated to determine the incidence of SSREs in the model. Assumed equivalence between abiraterone and enzalutamide.
QALY Loss: SSRE	NICE TA831[56]	-0.013	-0.013	Assumed one month duration of SSRE and a distribution of different SSREs with individual disutilities
Health State Utility Values				
Pre-Progression	PROpel ITT	0.8800	0.8800	Based on a MMRM of all EQ-5D-5L data collected from the trial, using the Danish value set, where progression was the only significant explored predictor of utility
Post-Progression	PROpel ITT	0.8428	0.8428	

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

8.3.2.1 Patient population

The Danish patient population: adult patients with mCRPC in whom chemotherapy is not clinically indicated.

Patient population in the clinical documentation submitted: patients with mCRPC in the first-line setting who are candidates for abiraterone therapy and who have not received any systemic chemotherapy within 3 weeks prior to study treatment.

Patient population in the health economic analysis submitted: adult patients with mCRPC in whom chemotherapy is not clinically indicated.

As the patient population in Denmark is expected to be aligned with the labelled population, and this label was derived from the perceived risks and benefits in patients in the PROpel trial, it is assumed that the population in the clinical evidence is aligned with patients in Danish clinical practice. With respect to specific baseline characteristics, there is limited published real-world information on Danish mCRPC patients. Therefore insights have been drawn from selected publications, as well as the overall Danish prostate cancer population, estimates from the expert committee reported in Medicinrådet and RADS documentation, and data from the Swedish prostate cancer registry. Table 23 shows the population parameters in the model or relevant to the decision problem based on the trial data and those in Danish clinical practice.

Table 23. Patient population in the evidence compared to Danish clinical practice

Patient Characteristic	Clinical Documentation from PROpel Trial	Value Used in the Model	Danish Clinical Practice for 1L mCRPC Treated with NHA-Based Therapy
Patient characteristics applied in the model			
Age (years), median	69	Mean (SD): 69.1 (8.24)	In previous studies patients receiving abiraterone or enzalutamide in Danish clinical practice were aged between 71 and 76 years at treatment initiation.[57,58]
Patient weight (kg), mean (SD)	82.7 (16.1)	82.7 (16.1)	No identified studies report the weight of Danish mCRPC patients, however Medicinrådet's assessments of apalutmide for mHSPC and nmCRPC report an average patient weight of 78-87kg.[34,59]
Body surface area (m^2)	N/A (not collected in trial)	1.98 (derived from weight and assuming height of 174.9cm from COU-AA-302 trial using Du Bois formula)	The RADS expert committee estimated that the average body surface area of mCRPC is $2m^2$.[33]
Prevalence of HRR mutations	28.4%	28.4%	The prevalence of different HRR mutations has not been reported in Denmark, however results from the PROpel study are aligned with the largest study screening for different HRR mutations in prostate cancer patients to date.[25]
Prevalence of BRCA1/2 mutations	10.7%	10.7%	
Additional patient characteristics relevant to decision problem			
ECOG performance status < 2*	100%	N/A (not explicitly included in model, but performance status is considered in evaluating eligible number of patients)	The Medicinrådet algorithm states that all patients eligible for treatment with NHAs would have a performance status < 2,[23] however in a real-world study including Danish patients, as well as Swedish registry data, 84-91% of patients had ECOG PS 0-1 when initiating NHA treatment.[57,60]
Any visceral metastases	13%	N/A (not explicitly included in model, but accounted for in comparison with enzalutamide)	In Medicinrådet's algorithm for mCRPC treatment it is estimated that 13% of patients eligible for NHA treatment would have visceral metastases.[23] This is supported by a real-world study of mCRPC patients treated with NHAs, including those from Denmark, where 12% has visceral metastases at baseline.[57]

* Excludes missing values

In a study of mCRPC patients treated with abiraterone or enzalutamide in Denmark, France, or the UK, the median age at the start of treatment was 76 years,[57] though in a group of patients treated with abiraterone for mCRPC before

chemotherapy at Rigshospitalet, the median age at treatment initiation was 71.3 years.[58] In the economic base case, the age is aligned with that in the PROpel trial, which is slightly younger than in these studies, but a scenario analysis is considered with an average age at baseline of 76 years. For costing calculations related to drug doses, no specific weight for Danish mCRPC patients could be identified. However, the derived body surface area from the patient weight in PROpel is aligned with the estimated value from the expert committee when developing mCRPC treatment guidelines in Denmark ($2m^2$).[33] Therefore, the weight is assumed to also be representative.

For the subgroup analysis for patients with HRR mutations, no published data was identified for the prevalence of HRR mutations in Danish mCRPC patients. However, in the PROfound study (which included sites in Denmark, Sweden, and Norway), of the 4 426 screened patients a qualifying HRR mutation was detected in 27.9% of patients with an interpretable result.[25] This value is similar to other studies investigating the prevalence of HRR mutations in prostate cancer.[61] Therefore the prevalence of HRR mutations in PROpel (28.4%) was assumed to be representative. As some patients are eligible for olaparib monotherapy as a subsequent therapy, the prevalence of BRCA mutations is also relevant to the analysis. In the PROpel population the prevalence of BRCA mutations was 10.7%, which is aligned with the results of the PROfound screening (11.0%). However, in the assessment of olaparib monotherapy for mCRPC it is reported that the expert committee estimated that only 5% of mCRPC patients would have BRCA mutations, but this estimate lacks references.[62] Therefore in the base case the estimate of 10.7% from PROpel is preferred.

With respect to patients eligible to receive abiraterone-based therapy in Denmark, according to the current treatment algorithm from Medicinrådet, performance status, whether the patient has symptomatic disease, and the presence of visceral metastases are of relevance. According to the committee who developed the treatment algorithm for mCRPC, patients who are eligible for active first line treatment for mCRPC would have a performance status of 0-1,[23] in line with the PROpel inclusion criteria. Of patients who are considered eligible for NHA treatment, 13% were estimated to have visceral metastases by the expert committee.[23] This is aligned with a real world evidence study including Danish patients, where 12% had visceral metastases at treatment baseline regardless of whether they were treated with abiraterone or enzalutamide.[57] This is also aligned with the prevalence of visceral metastases in the PROpel trial. As patients in clinical practice appear to receive abiraterone despite having visceral metastases, the full trial population and results are considered relevant for the comparison with abiraterone. As in clinical practice, stratification by the presence of visceral metastases does not make a patient ineligible for abiraterone (and thus receive enzalutamide), the scenario analysis compared to enzalutamide is also based on the full population and not just the subgroup with visceral metastases.

8.3.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 5.3): olaparib 300 mg (two 150 mg tablets) taken twice daily in combination with abiraterone 1000 mg taken orally once daily and prednisolone 5 mg taken orally twice daily.

Intervention in the clinical documentation submitted: olaparib 300 mg (two 150 mg tablets) taken twice daily in combination with abiraterone 1000 mg taken orally once daily and prednisone/prednisolone 5 mg taken orally twice daily.

Intervention as in the health economic analysis submitted: olaparib 300 mg (two 150 mg tablets) taken twice daily in combination with abiraterone 1000 mg taken orally once daily and prednisolone 5 mg taken orally twice daily. The duration of abiraterone/prednisolone was modelled independently of the duration of olaparib given the difference in treatment duration observed in the PROpel trial.

Table 24. Intervention in the evidence compared to Danish clinical practice

Intervention	Clinical Documentation from PROpel Trial	Value Used in the Model	Expected Use in Danish Clinical Practice
Posology	Olaparib 300 mg BID + Abiraterone 1000 mg QD + Prednisone / Prednisolone 5 mg BID	Olaparib 300 mg BID + Abiraterone 1000 mg QD + Prednisolone* 5 mg BID	Olaparib 300 mg BID + Abiraterone 1000 mg QD + Prednisolone* 5 mg BID
Length of treatment	Median duration was 18.5 months for olaparib and 20.1 months for abiraterone.	Parametric time to event modelling fitted to trial data using generalized gamma distribution for olaparib discontinuation (median 17.3 months) and loglogistic for abiraterone discontinuation (median 19.4 months).	No available data on usage in Denmark, but anticipated to be aligned with trial data given validation of other time to event outcomes.
Criteria for discontinuation	Progression of the underlying disease or unacceptable toxicity.	Progression of the underlying disease or unacceptable toxicity.	Progression of the underlying disease or unacceptable toxicity.
The pharmaceutical's position in Danish clinical practice	First line mCRPC	First line mCRPC	First line mCRPC

* Prednisolone is the glucocorticoid mentioned in the Medicinrådet guidance for mCRPC

8.3.2.3 Comparators

The current Danish clinical practice (as described in section 5.2): abiraterone 1000 mg taken orally once daily and prednisolone 5 mg taken orally twice daily, or enzalutamide 160 mg (four 40 mg tablets) taken orally once daily.

Comparator(s) in the clinical documentation submitted: abiraterone 1000 mg taken orally once daily and prednisone/prednisolone 5 mg taken orally twice daily.

Comparator(s) in the health economic analysis submitted: abiraterone 1000 mg taken orally once daily and prednisolone 5 mg taken orally twice daily, or enzalutamide 160 mg (four 40 mg tablets) taken orally once daily.

Both abiraterone and enzalutamide are used in clinical practice to treat mCRPC patients which may have a broader application than applied in the initial registrational trials for the products. The NHAs are indicated for "the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated", but in modern clinical practice NHA-eligible patients may have been indicated for chemotherapy in the mHSPC setting and a level of symptoms which would make a patient ineligible for NHA treatment is not clearly established. Feedback from Danish clinicians is that very few patients are symptomatic to a degree where it influences treatment choice in such a way that NHAs would not be indicated, and NHAs are the first choice in 1L mCRPC for all NHA naïve patients. The submitted model uses the data directly from the PROpel trial, in accordance with the clinical documentation submitted and is consider to be in line with current clinical practice.

Table 25. Comparator in the evidence compared to Danish clinical practice

Comparator	Clinical Documentation from PROpel Trial	Value Used in the Model	Expected Use in Danish Clinical Practice
Posology	Abiraterone 1000 mg QD + Prednisone / Prednisolone 5 mg BID	Abiraterone 1000 mg QD + Prednisolone* 5 mg BID; or, Enzalutamide 160 mg QD	Abiraterone 1000 mg QD + Prednisolone* 5 mg BID; or, Enzalutamide 160 mg QD
Length of treatment	Median duration was 15.7 months and 21% were still on treatment after 3 years.	Parametric time to event modelling fitted to trial data using loglogistic distribution (median 15.4 months, 21% on treatment after 3 years).	Older Danish data in a limited number of patients suggests median duration of 5.3 months on abiraterone, though more recent Swedish registry data suggests a median 1L NHA treatment duration of 13.8 months and 24% are on treatment after 3 years.[60]
Criteria for discontinuation	Progression of the underlying disease or unacceptable toxicity.	Progression of the underlying disease or unacceptable toxicity.	Progression of the underlying disease or unacceptable toxicity.
The comparator's position in the Danish clinical practice	First line mCRPC	First line mCRPC	First line mCRPC (as well as for third line therapy for patients who receive docetaxel as first line therapy)

* Prednisolone is the glucocorticoid mentioned in the Medicinrådet guidance for mCRPC

Although enzalutamide was not investigated in the PROpel trial, it is generally accepted that abiraterone and enzalutamide have comparable efficacy in patients with mCRPC, as was commented by the expert committee in developing the Danish treatment guidance for mCRPC.[33] Therefore, the efficacy and time on treatment of abiraterone and enzalutamide are likely to be comparable in clinical practice and the observed results from abiraterone in the PROpel trial are considered applicable to enzalutamide (with only potential differences in safety and costs).

8.3.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: the primary endpoint in the PROpel trial was radiological progression-free survival (rPFS), with overall survival (OS) as a key secondary endpoint. Other secondary endpoints included time to first sequent therapy, time to pain progression, time to opiate use, time to a symptomatic skeletal-related event (SSRE), and time to second progression or death (PFS2). Results are discussed in section 7.1.2.

Relevance of the documentation for Danish clinical practice: DaProCa guidelines for mCRPC treatment place emphasis on that treatment should be life-extending and focus on the relief of symptoms, but highlight that significant effects in terms of postponement of disease progression are relevant. As disease progression is associated with the development of symptoms (e.g., pain progression, opiate use, SSREs), PFS can be a relevant proxy for patient-relevant outcomes.

The relative efficacy outcomes in the submitted health economic analysis: the economic model is primarily informed by the rPFS and OS data from PROpel, though considerations related to subsequent therapy use and SSREs are also included.

Table 26. Efficacy results applied in the model

Clinical efficacy outcome	Results from PROpel Trial*	Value Used in the Model
Primary endpoint: Progression-free survival (PFS)	Olaparib + Abiraterone: median 25.0 mths, 3-year PFS 35.9% Placebo + Abiraterone: median 16.5 mths, 3-year PFS 25.0%	Olaparib + Abiraterone: median 23.7 mths, 3-year PFS 37.0% (lognormal) Placebo + Abiraterone: median 16.4 mths, 3-year PFS 25.0% (lognormal)
Key secondary endpoint: Overall survival (OS)	Olaparib + Abiraterone: median 42.1 mths, 3-year OS 56.9% Placebo + Abiraterone: median 34.7 mths, 3-year OS 49.5%	Olaparib + Abiraterone: median 43.3 mths, 3-year OS 56.8% (generalized gamma) Placebo + Abiraterone: median 35.4 mths, 3-year OS 49.1% (generalized gamma)
Other secondary endpoint: Time to start of first subsequent anticancer therapy or death (TFST)	Olaparib + Abiraterone: median 24.6 mths, 3-year TFST 38.1% Placebo + Abiraterone: median 19.4 mths, 3-year OS 27.7%	Derived from time to treatment discontinuation curve and the number of patients receiving post-discontinuation anticancer therapy Olaparib + Abiraterone: 62.2% of patients who discontinued first line treatment received subsequent therapy Placebo + Abiraterone: 67.8% of who discontinued first line treatment received subsequent therapy
Other secondary endpoint: Time to a symptomatic skeletal-related event (SSRE)	Olaparib + Abiraterone: median not reached, SSRE free at 3 years 80.8% Placebo + Abiraterone: median not reached, SSRE free at 3 years 78.5%	Derived from PFS curve assuming SSREs would occur after progression. Estimated proportions of patients experiencing SSRE upon progression were derived from number of patients experiencing SSRE and the number of patients surviving beyond disease progression. Olaparib + Abiraterone: 25.8% of patients experience an SSRE after progression Placebo + Abiraterone: 20.9% of patients experience an SSRE after progression

* As of the third data cut-off (12 Oct 2022)

Table 27. Relevance of endpoints applied in the model to Danish clinical practice

Clinical efficacy outcome	Method of Assessment in PROpel Trial	Relevance of Outcome in Danish Clinical Practice	Relevance of Method of Assessment to Danish Clinical Practice
Primary endpoint: Progression-free survival (PFS)	Defined as the time from randomization to 1) radiological progression, assessed by the investigator per RESCIST 1.1 (soft tissue)	Disease progression is a relevant assessment as it is a proxy for a deterioration in the patients condition and a worsening of quality of life.	Disease progression will be assessed by the treating physician (equivalent to investigator). Diagnostic imaging (using PCWG criteria)

Clinical efficacy outcome	Method of Assessment in PROpel Trial	Relevance of Outcome in Danish Clinical Practice	Relevance of Method of Assessment to Danish Clinical Practice
	and PCWG-3 criteria (bone), or 2) death from any cause, whichever occurs first	The EAU guidelines, on which the DaProCa guidelines are based, also comment that a symptomatic progression of metastatic disease warrants a change of treatment, and therefore PFS is relevant in terms of clinical decision making and patient outcomes	every 2-4 months is recommended in the Medicinrådet guidelines for mCRPC treatment. Radiological progression is one method of assessment mentioned in the DaProCa guidelines, along with PSA progression. PSA progression results in PROpel were not dissimilar to rPFS results (median 24.1 months vs. 12.0 months; HR 0.59). Therefore, the rPFS results are considered applicable to Danish clinical practice.
Key secondary endpoint: Overall survival (OS)	Defined as the time from randomization to death from any cause	The prolongation of survival is noted as one of the key treatment goals in the DaProCa guidelines for the management of mCRPC	Assumed to be relevant to Danish clinical practice.
Other secondary endpoint: Time to start of first subsequent anticancer therapy or death (TFST)	Time from randomization to 1) the start of the first subsequent anticancer therapy following study treatment discontinuation, or 2) death from any cause	The sequencing of treatments in mCRPC is a key clinical topic in order to optimize benefits for patients. Given the costs associated with further lines of anticancer treatment, the assessment of subsequent treatment is deemed relevant.	Assumed to be relevant to Danish clinical practice.
Other secondary endpoint: Time to a symptomatic skeletal-related event (SSRE)	Time from randomization to the first SSRE, defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal to no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention	The prevention of SSREs is mentioned as a treatment goal in the DaProCa guidelines. SSREs have been considered clinically relevant costs in previous Medicinrådet assessments.	Assumed to be relevant to Danish clinical practice.

8.3.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: Safety and tolerability was one of the secondary endpoints in the PROpel trial and all adverse events, serious adverse events, physical examination findings, vital signs, ECG findings, and laboratory test results were recorded.

Adverse reaction outcomes in the health economic analysis submitted: All adverse-events (by preferred term) of CTCAE grade 3 or higher occurring in at least 2% of patients in either arm of the PROpel trial or in at least 2% of patients treated with enzalutamide in the PREVAIL trial. Despite Grade ≥3 COVID-19 occuring in more than 2% of patients in PROpel this is not expected to be a significant concern in future and therefore was excluded from the economic model.

Table 28. Adverse reaction outcomes included in the model

Adverse Events	Olaparib + Abiraterone	Abiraterone	Enzalutamide
Alanine Aminotransferase Increased	1.0%	2.3%	0.0%
Anaemia	16.1%	3.3%	3.3%
Back Pain	1.0%	1.5%	2.5%
General Physical Health Deterioration	0.3%	0.3%	2.1%
Hyperglycaemia	2.0%	1.5%	4.0%
Hypertension	3.8%	4.5%	6.8%
Lymphocyte Count Decreased	3.8%	1.5%	0.0%
Neutrophil Count Decreased	2.8%	0.8%	0.9%
Pneumonia	2.5%	1.0%	1.3%
Pulmonary Embolism	7.3%	2.3%	0.0%
Urinary Tract Infection	2.5%	1.0%	1.5%
White Blood Cell Count Decreased	2.3%	0.5%	0.0%

The choice to include only events of CTCAE grade ≥3 was determined was informed by the definitions of the grades, where grade 3 or 4 events require medical intervention and can impact activities of daily living (and therefore quality of life), whereas grade 1 or 2 events are only indicated for minimal intervention and a limited impact on quality of life. This is assumed to be representative of Danish clinical practice where grade 1 or 2 adverse events which occurred more commonly in olaparib-treated patients (e.g., anaemia, nausea, diarrhoea) would be managed primarily by the patient with a limited impact on costs or health-related quality of life.

The incidence of adverse events in the enzalutamide arm were sourced from those reported for the PREVAIL trial in the EPAR for Xtandi for first line mCRPC. This source was chosen over other published sources given that the duration of exposure to enzalutamide (median 16.6 months) was the most similar to that of the duration of exposure to abiraterone in PROpel (median 15.7 months), thereby reducing confounding.

In addition to adverse events, SSREs were included in the analysis as adverse outcomes. SSREs are common complications of bone metastases and have serious negative consequences for patients with mCRPC. SSREs pose a significant health and economic burden and have historically been included in cost-effectiveness assessment of treatments in mCRPC. For application in the model, SSREs are assumed to occur at the time of disease progression to avoid the complexities of extrapolating an additional endpoint, but also SSREs are somewhat correlated with the

progression of disease. In the ITT population of PROpel, the hazard ratio between olaparib + abiraterone and abiraterone alone for time to first SSRE was 0.76, which is somewhat aligned with the PFS hazard ratio of 0.67. As not all patients who have a PFS event experience an SSRE, this was adjusted in the model. For patients treated with olaparib + abiraterone in PROpel, there were 46 patients experiencing an SSRE and 178 patients had a disease progression event (25.8%), and for abiraterone there were 51 patients with SSREs compared to 244 progression events (20.9%). Although patients may have more than one SSRE during disease progression, the model uses the proportion of patients who have had at least one SSRE occurred as a proxy for the proportion experiencing SSRE. Due to the lack of mature data on rPFS events for enzalutamide compared to SSREs an accurate proportion could not be calculate and therefore was assumed to be equal to abiraterone. The SSREs included in the model are spinal cord compression, radiation to the bone, surgery to the bone, or a pathological bone fracture. The distribution of SSREs applied based on the incidence of any SSRE are derived from the average of those reported in the ALSYMPCA trial (radium-223 dichloride versus placebo/best supportive care),[63] COU-AA-301 (abiraterone plus prednisone versus placebo plus prednisone in a post-docetaxel setting),[64] and AFFIRM (enzalutamide versus placebo in a post-docetaxel setting),[65,66] as reported in the NICE appraisal of olaparib monotherapy for mCRPC with BRCA mutations.[56]

Table 29. Probability of experiencing an SSRE upon progression by treatment and the distribution of SSREs

SSRE	Distribution	Olaparib + Abiraterone	Abiraterone	Enzalutamide
Spinal Cord Compression	15.5%	25.8%	20.9%	20.9%
Radiation to Bone	67.7%			
Surgery to Bone	4.1%			
Pathological Bone Fracture	12.9%			
Source	NICE TA831[56]	PROpel	PROpel	Equal to abiraterone

8.4 Extrapolation of relative efficacy

All time to event outcomes for use in the model were extrapolated from the patient-level data from the PROpel trial following the Medicinrådet's guidelines on the extrapolation of efficacy as well as the guidance from the NICE Decision Support Unit's Technical Support Document 14,[67] with consideration to the statistical and visual fit to the trial data and the plausibility of the long-term extrapolations. All extrapolations are based on the final planned data cut-off (DCO3) of PROpel (12 October 2022) after a median follow-up of 33 months. For each endpoint the following steps were followed:

1. Generate Kaplan-Meier plots and various diagnostic plots (log cumulative hazards, log odds, log normal, quantile-quantile, Schoenfeld residual, empirical and smoothed hazards) to assess whether or not the proportional hazards or accelerated failure time assumptions have been violated and assess potential functional forms of the data.
2. Fit parametric survival models using standard distributions (exponential, Weibull, Gompertz, gamma, lognormal, loglogistic, and generalised gamma) to the individual arms of the trial and joint models (where appropriate). The Generalised F distribution is included, where it can converge, to help inform diagnostic selection of other parametric fits.
3. Evaluate the best fitting parametric curve(s) to each arm on the basis of statistical fit to the trial data (Akaike's Information Criterion [AIC] and Bayesian Information Criterion [BIC]), visual fit of the extrapolated curve to the trial Kaplan-Meier curve, visual fit of the hazard function of the extrapolated curve to the smoothed hazards from the patient-level data, comparison of the extrapolated portion of the curves to empirical longer term survival data or conditional survival estimates, and feedback from AstraZeneca medical advisors and external clinical experts on the plausibility of long-term survival.

For each endpoint a preferred statistical fit was selected based on the above criteria, but in cases where the choice was subject to some uncertainty which has a meaningful impact on results, alternative distributions were explored in scenario analyses. Comprehensive reporting of survival analysis results and methods can be found in Appendix G Extrapolation.

As is standard practice in oncology models, rPFS and TDT/TDA were constrained by the OS curve, such that the proportion of patients who are in the progression-free state or currently receiving treatment could not exceed the proportion of patients alive. In addition, all time to event outcomes were constraint so that the mortality rate, the rate of progression or death, or the rate of treatment discontinuation due to death, as components of the OS, rPFS, and TDT/TDA endpoints, respectively could not be lower than the all-cause mortality rate observed in the general Danish population. Mortality rates were obtained from life tables from Danmarks Statistik.[68] The selected rates were for males only from the past five years (2018 to 2022). The choice to use the past five years rather than a single year was to mediate any potential impacts of excess mortality during the COVID-19 pandemic. Mortality rates per cycle in the model were derived based on the distribution of ages of the cohort at model baseline.

8.4.1 Summary of time to event data

Full reporting on the extrapolations can be found in Appendix G Extrapolation. A brief summary of the rationale for each extrapolation model is provided under the headings below.

Table 30. Base case parametric models selected for each arm in the economic analysis

Endpoint	Olaparib + Abiraterone	Abiraterone
Radiological Progression-Free Survival	Lognormal	Lognormal
Overall Survival	Generalised Gamma	Generalised Gamma
Time to Discontinuation of Abiraterone	Loglogistic	Loglogistic
Time to Discontinuation of Olaparib	Generalised Gamma	N/A

8.4.1.1 Radiological progression-free survival

Separate curves were fitted to each arm of PROpel, as an assessment of the trial data indicated that the proportional hazards assumption was violated. On the basis of statistical fit (AIC and BIC), and visual inspection of the fitted curves and the hazard functions, parametric fits with non-monotonic hazards (lognormal, loglogistic, or generalised gamma) had the best fit to the trial data.

In terms of external validation and clinically plausibility of the long-term extrapolation, the PROpel trial reports the longest follow-up for rPFS data for randomised trials. Despite this, the plausibility of a slowing of the hazard rate of disease progression, as well as potential landmark estimates for rPFS, were assessed using external data. The conditional survival estimates for rPFS were derived from the reported data from the COU-AA-302 trial of abiraterone and the PREVAIL trial of enzalutamide, and these indicate that a declining hazard of progression in the long-term may be plausible in this setting, as there is rapid decline in rPFS in the early months but the longer patients remain progression-free the lower the probability of progression.[48,69] With regards to absolute estimates, there is a lack of long-term data on rPFS for NHAs, however real-world evidence is available for time on treatment, time to next treatment (TTNT), and PSA-based progression for NHA treated patients from both Sweden and Finland, and it is anticipated that these

outcomes are strongly correlated with rPFS. In a real-world cohort of 348 Finnish patients treated with an NHA for first line mCRPC, PSA-based PFS at 4-years was ~9% and TTNT was ~10%.[10] However, data from the Individual Patient Overview (IPÖ) of the National Prostate Cancer Registry (NPCR) of Sweden shows that for patients treated with an NHA for first line mCRPC, ~21% remain on treatment at 4 years and ~17% at 5 years.[70] These estimates from Sweden represent higher values that observed in PROpel, but the data show a slowing of the hazard rate (conditional probability of treatment discontinuation of 38%, 27%, 19%, and 16% in the second, third, fourth, and fifth years of treatment, respectively), indicating that a longer tail with a non-monotonic functional form may be plausible.[70]

Based on the best statistical fit as well as a good visual fit to the Kaplan-Meier and smoothed hazards plots, and providing statistically plausible long-term outcomes, the lognormal distribution is selected for placebo + abiraterone arm in the base case. As this distribution also had the best statistical fit to the olaparib + abiraterone arm and provides plausible long-term outcomes, it was also selected for use this arm.

Figure 16. Fitted independent parametric models vs. Kaplan-Meier for rPFS in the placebo + abiraterone arm

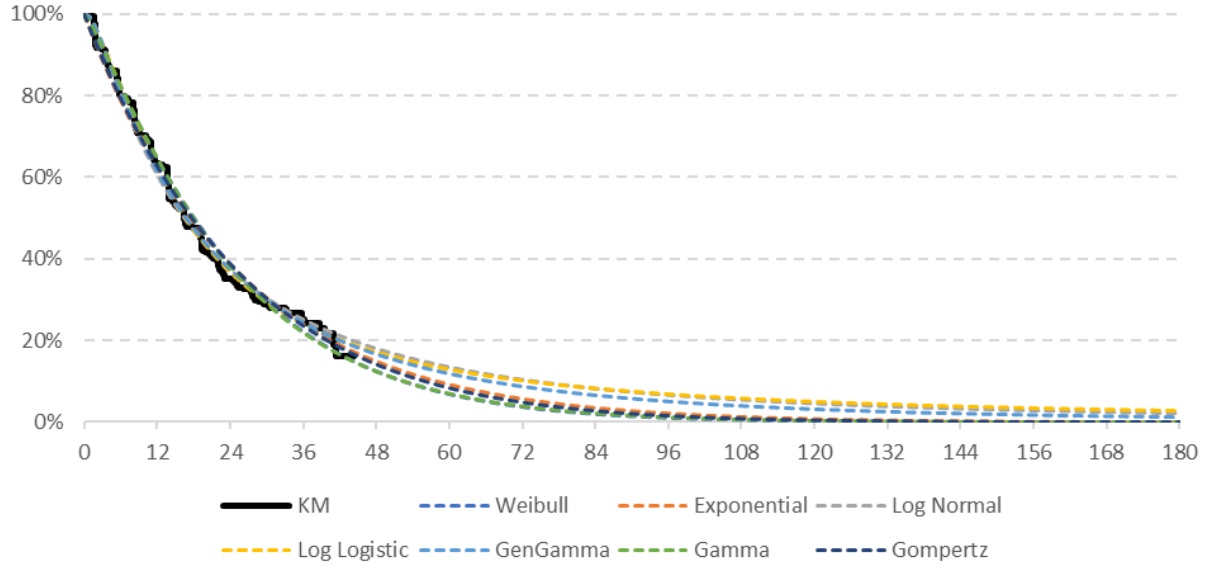


Figure 17. Fitted independent parametric models vs. Kaplan-Meier for rPFS in the olaparib + abiraterone arm

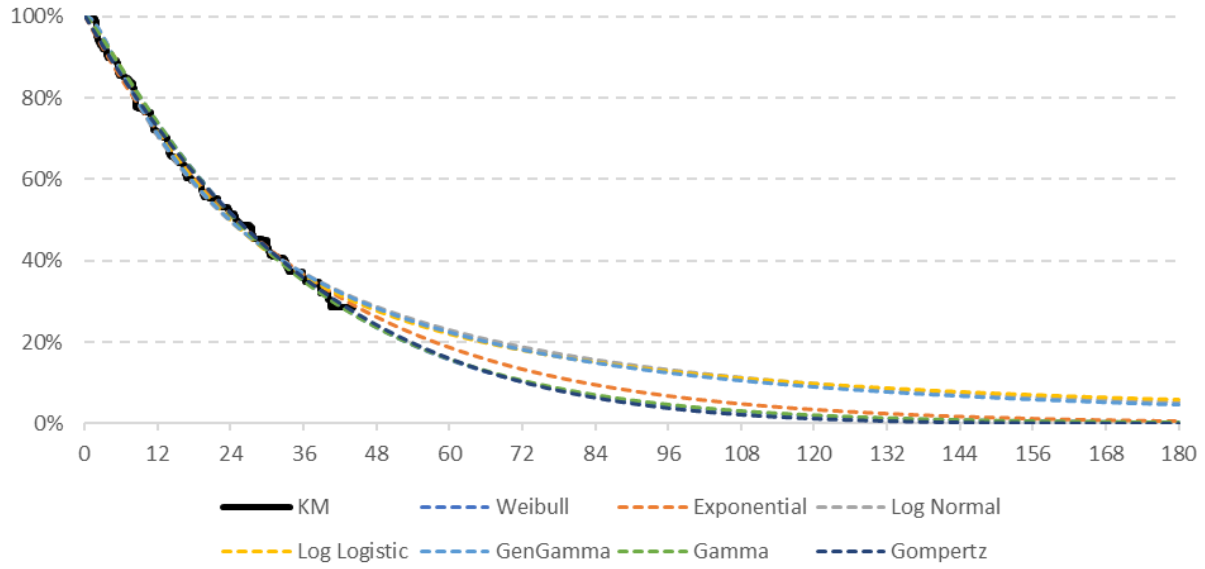


Table 31. Landmark analysis of rPFS comparing modelled outcomes with trial results

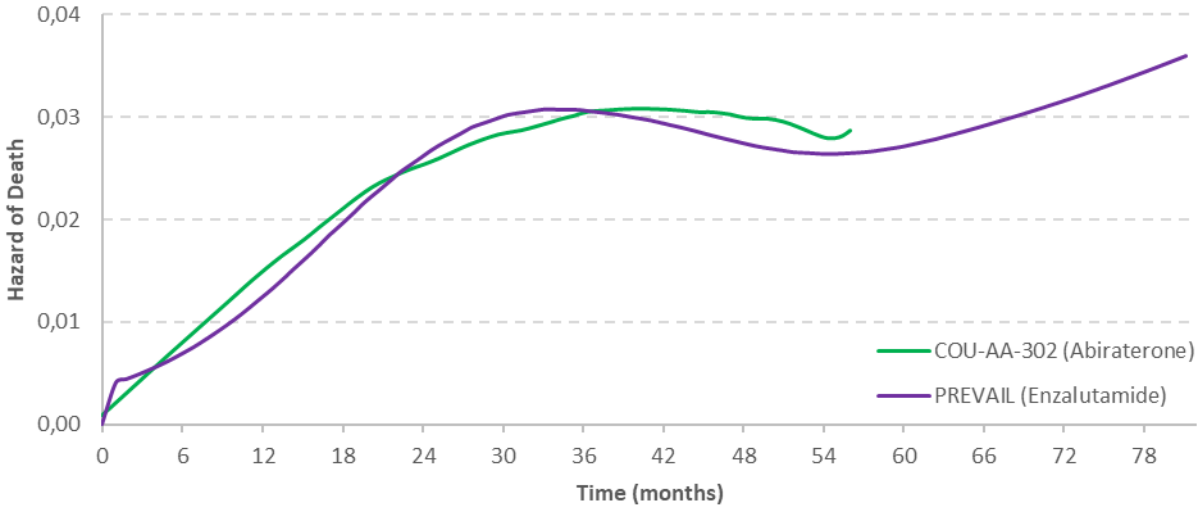
Treatment Arm	Source	6 months	12 months	18 months	24 months	30 months	36 months	Median
Olaparib + Abiraterone	Model	86.2 %	70.5 %	58.7 %	49.6 %	42.6 %	37.0 %	23.7
	Trial	85.6 %	71.7 %	59.7 %	52.1 %	44.9 %	35.9 %	25.0
Abiraterone	Model	80.6 %	60.6 %	46.9 %	37.2 %	30.3 %	25.0 %	16.4
	Trial	80.0 %	63.5 %	47.6 %	35.0 %	28.9 %	25.0 %	16.5

8.4.1.2 Overall survival

No adjustment for treatment crossover were made to the overall survival data from PROpel as crossover from placebo to olaparib in combination with abiraterone was not allowed in the trial. As of DCO3, five patients in the placebo arm received a PARP inhibitor (including olaparib) after discontinuation. Given the low usage and as olaparib as monotherapy is recommended in Denmark for selected mCRPC patients it was deemed that no adjustment was necessary. Given the delayed separation of the OS curves and clear violation of the proportional hazards assumption, separate curves were fitted to each arm of PROpel.

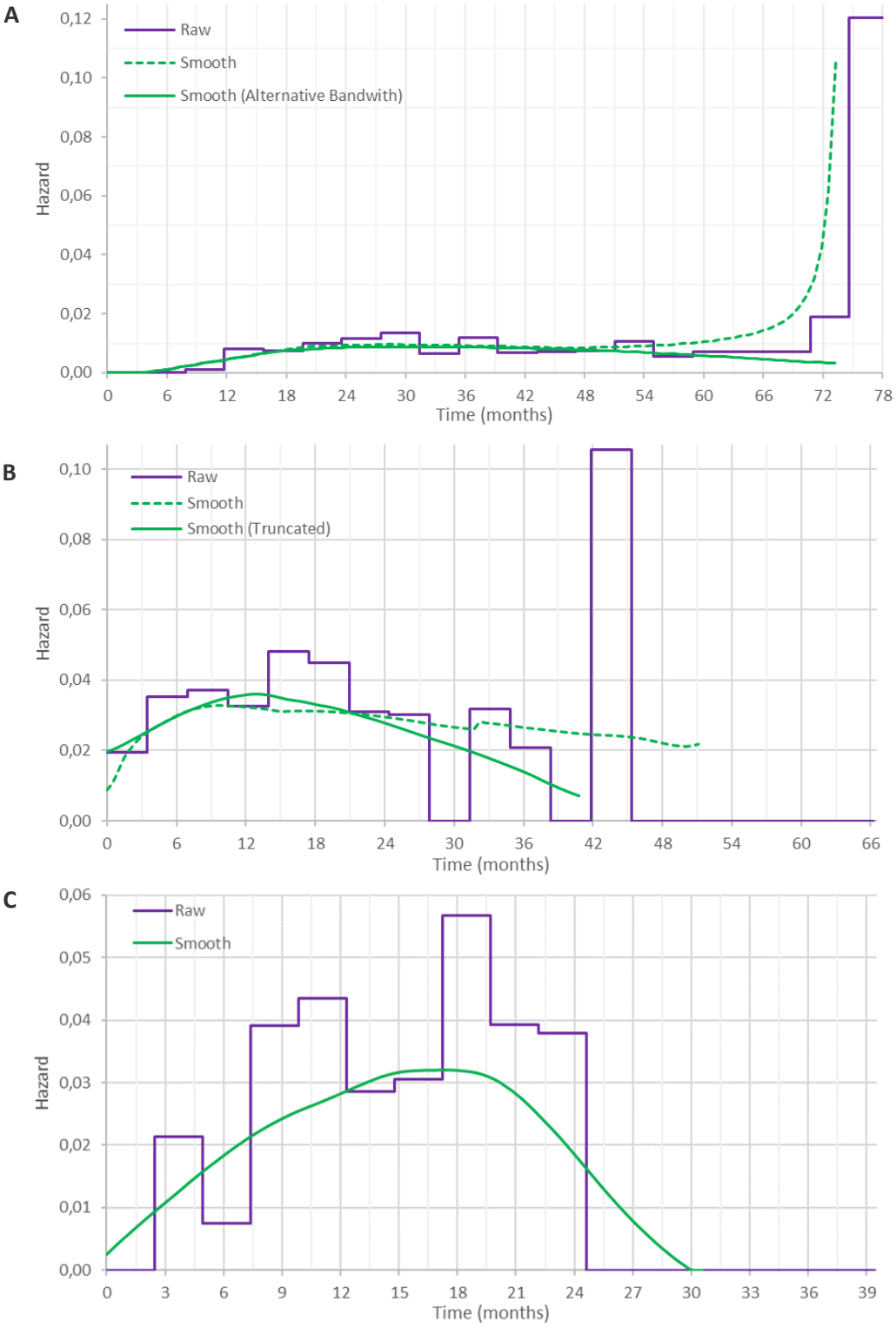
Based on statistical and visual fit, the loglogistic, generalized gamma, gamma and Weibull distributions had a good fit to the placebo + abiraterone arm, and the lognormal, generalized gamma, loglogistic, and gamma distributions fitted well to the olaparib + abiraterone arm. Based on an inspection of the empirical hazards from the trial data, the Weibull distributions was rejected as it resulted in a constantly increasing hazard of death. This was not supported by external data from COU-AA-302 for abiraterone or PREVAIL or enzalutamide, where the hazard of death appears to plateau after approximately 3 years and potential decrease slightly in the longer term (Figure 18). Therefore the loglogistic and generalized gamma distributions (taking a similar functional form to the gamma) were considered plausible for the placebo + abiraterone arm. Data from first line NHA-treated patients for mCRPC in Finland supports this, where the 5- and 7-year survival to be 24% and 12%, respectively.[10] The respective 5- and 7-year survival with the generalized gamma and loglogistic distributions are 23% and 10% and 26% and 15%, implying both are aligned with external evidence. Comparison to the final OS analysis of COU-AA-302,[17] where abiraterone data were 65% mature, showed that fitting the generalized gamma distribution to the PROpel data was more aligned with the observed OS data from COU-AA-302 than the loglogistic. However, when applying the generalized gamma distribution, this results in the truncation of the preferred rPFS and time to discontinuation extrapolations, such that 4.5% of patients would die prior to radiological disease progression and whilst still on first line treatment (curves converge after 105 months). In the PROpel trial, 12% of rPFS events and 4% of causes of treatment discontinuations in the placebo + abiraterone arm were deaths, indicating that death before disease progression whilst on treatment is clinically plausible. This is further supported by evidence from Sweden which shows that ~10% of deaths in mCRPC are due to causes other than prostate cancer.[71] Despite this, a scenario analysis is presented applying the loglogistic distribution for overall survival where the rPFS and OS curves do not converge within the model time horizon.

Figure 18. Smoothed hazards of death from previous trials of first-line NHA treatments for mCRPC



Based on the guidance from the NICE DSU's Technical Support Document 14, it recommends that similar types of parametric model should be fitted to each arm to avoid different models from following very differently shaped distributions.[67] The report highlights that the lognormal and loglogistic distributions are similar, and in addition the generalised gamma distribution can follow a non-monotonic form similar to the lognormal.[67] Accordingly, these distributions were considered as potential options for extrapolating the olaparib + abiraterone arm, given the plausible options in the placebo + abiraterone arm. In order to select preferred fit, consideration was given to the clinically plausibility of the magnitude and duration of the treatment effect. In both PROpel and COU-AA-302, a delayed separation of the overall survival curves was also observed. In COU-AA-302 it was proposed that this was related to the use of a control arm with some effect (prednisone), to which a number of patients responded.[17] The later separation in PROpel could be attributed to the use of a more effective control arm (abiraterone + prednisone). The observed survival data from PROpel shows that the addition of olaparib to abiraterone adds a 7-8% survival benefit over abiraterone alone from month ~27 to the end of follow up, and the results of COU-AA-302 show that following separation the benefit of abiraterone was sustained over the subsequent 3 years of follow-up. It was therefore considered plausible that the treatment benefit of olaparib could continue for further years. Previous evidence of olaparib in other tumours has shown it to have a prolonged effect on overall survival (beyond treatment discontinuation). Evidence from the PAOLA1 trial with a median follow-up of over 5 years shows that treatment with up to two years of olaparib (in combination with bevacizumab) demonstrated a non-monotonic functional form for overall survival in patients with newly diagnosed advanced ovarian cancer (Figure 19a). This non-monotonic form for survival with olaparib treatment has also been observed in the metastatic setting in patients with pancreatic cancer and breast cancer (Figure 19b and c).

Figure 19. Smoothed hazards of death from previous trials of olaparib in (A) advanced ovarian cancer (PAOLA1), (B) metastatic pancreatic cancer (POLO), and (C) chemotherapy naïve metastatic breast cancer (OlympiAD)



Use of non-monotonic distributions results in the hazard of death declining over time. With the lognormal distribution, the hazard in olaparib-treated patients would be equal to the general population after 18 years when 7.6% of patients

remain alive. With the loglogistic this is 7.4% after 17 years, and with the generalised gamma distribution, this is 6.0% after 19 years. The notion that 6-7% of patients would have a risk of death similar to the general population is potentially plausible. Evidence from the Norwegian Prostate Cancer Registry shows that in patients diagnosed with primary metastatic disease (representing most patients who progress to mCRPC), a considerable proportion (20-25% after 10 years) die due to causes other than prostate cancer and that this proportion grows over time (i.e., the risk of death due to none prostate cancer causes is not just due to comorbidities at diagnosis).[72] This is aligned with the Swedish evidence showing that ~10% of deaths in mCRPC are due to causes other than prostate cancer.[71]

For the base case analysis, the generalised gamma distribution is selected for both arms. This is justified by the good statistical and visual fit to both arms during trial follow-up, as well as having a functional form which aligns well with the smoothed hazards. In addition, this distribution is well aligned with observed historical data from the COU-AA-302 trial and Nordic RWE. The generalised gamma distribution also shows a plausible long-term benefit when adding olaparib, in line with the observed benefit following separation of the survival curves in the trial. This also follows NICE DSU guidance that similar functional forms should be used when extrapolating curves independently.

Figure 20. Fitted independent parametric models vs. Kaplan-Meier for OS in the placebo + abiraterone arm

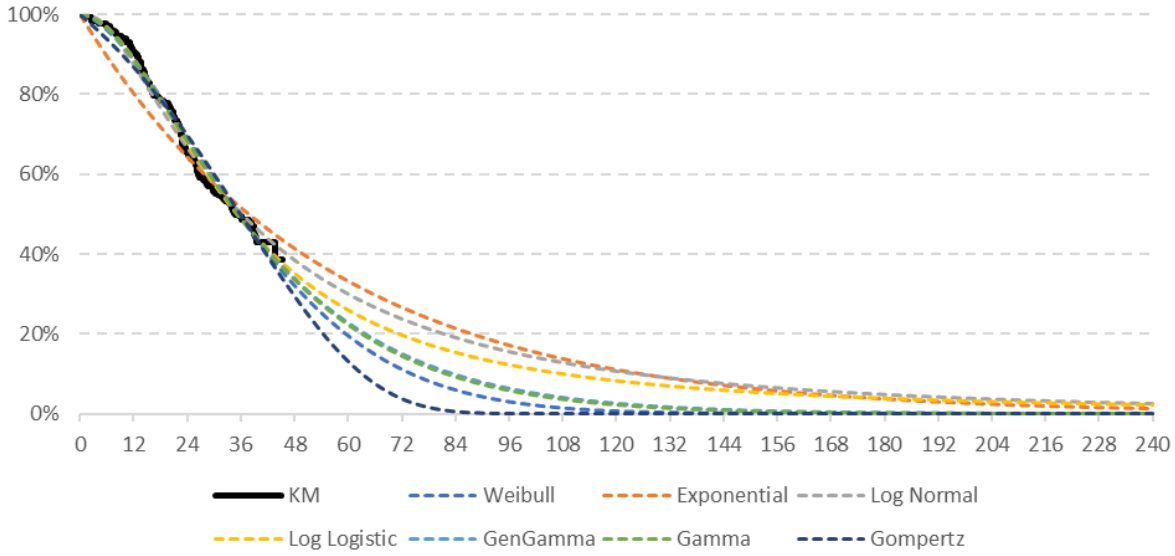
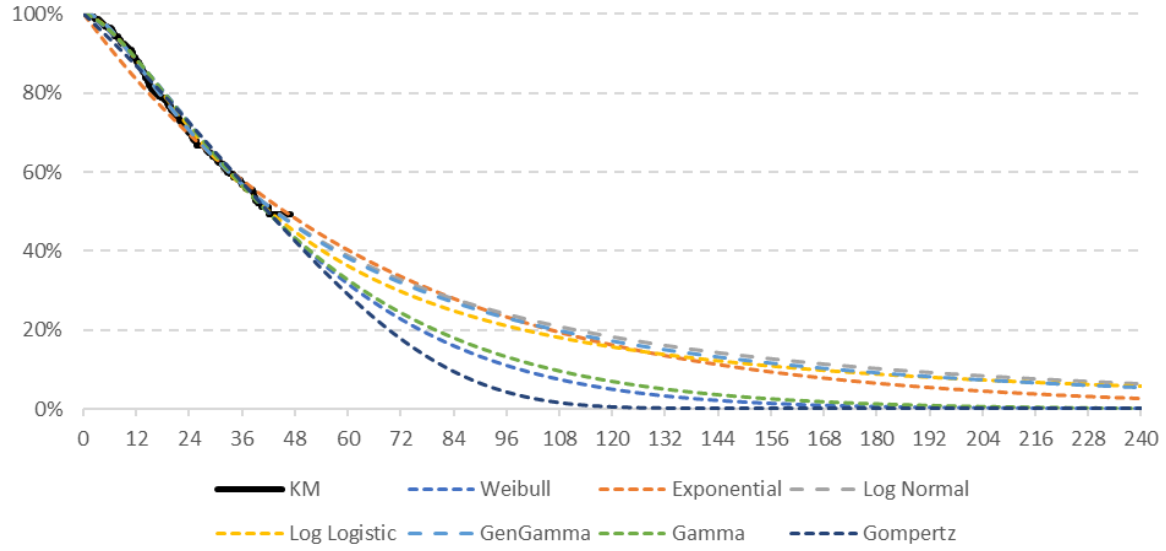


Table 32. Landmark analysis of OS comparing modelled outcomes with trial results

Treatment Arm	Source	6 months	12 months	18 months	24 months	30 months	36 months	Median
Olaparib + Abiraterone	Model	96.2 %	87.7 %	78.8 %	70.5 %	63.2 %	56.8 %	43.3
	Trial	96.5 %	88.2 %	78.8 %	70.2 %	63.7 %	56.9 %	42.1
Abiraterone	Model	96.7 %	88.7 %	78.8 %	68.3 %	58.3 %	49.1 %	35.4
	Trial	97.2 %	90.6 %	78.3 %	65.5 %	55.6 %	49.5 %	34.7

Figure 21. Fitted independent parametric models vs. Kaplan-Meier for OS in the olaparib + abiraterone arm



8.4.1.3 Time to discontinuation of abiraterone

Based on an assessment of the proportional hazards, it was considered preferable to fit independent models to each arm of the trial, in line with rPFS. The lognormal, loglogistic, and generalised gamma distributions provided the best visual and statistical fit to the data for both arms. Looking to external data, in the NICE assessment of abiraterone for first line mCRPC the committee preferred the loglogistic distribution for the endpoint “time from starting to stopping first treatment with abiraterone", and therefore this was considered plausible when extrapolating the PROpel data.

Given the relative maturity of the data on this endpoint (76.0%), greater weight can be applied to statistical and visual fit in selecting curves for the base case. The maturity of the data also means there is little difference in the long-term extrapolations. Given the good statistical and visual fit of the loglogistic distribution to the placebo + abiraterone arm, this is selected for the base case. The loglogistic distribution also a good visual fit to the olaparib + abiraterone arm. As NICE DSU guidance recommends applying similar functional forms between both extrapolated arms, the loglogistic distribution is selected for this arm as well. This follows a similar functional form to the models for rPFS.

Figure 22. Fitted independent parametric models vs. Kaplan-Meier for TDA in the placebo + abiraterone arm

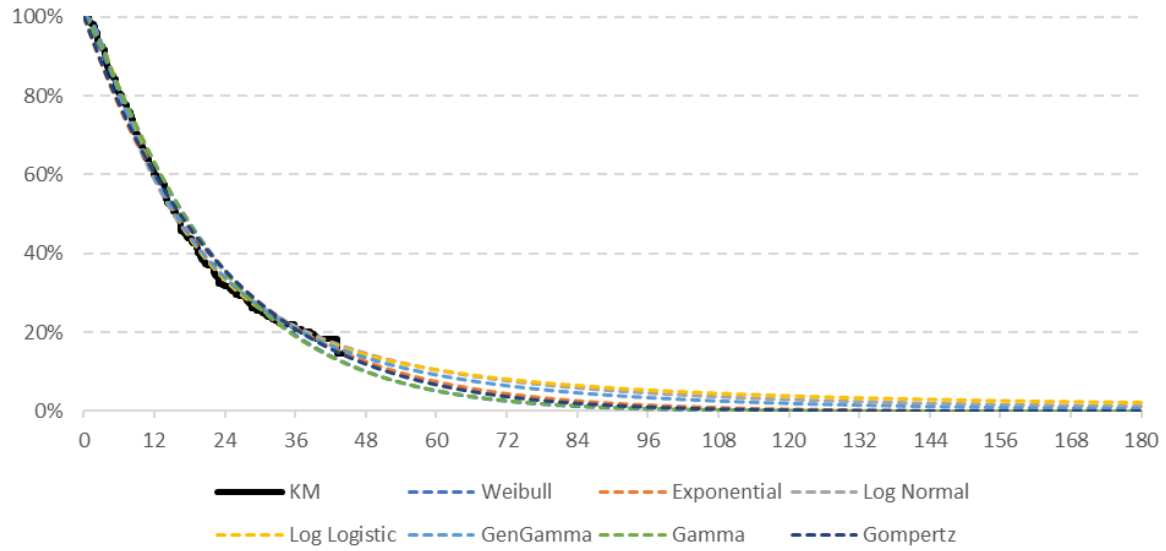


Figure 23. Fitted independent parametric models vs. Kaplan-Meier for TDA in the olaparib + abiraterone arm

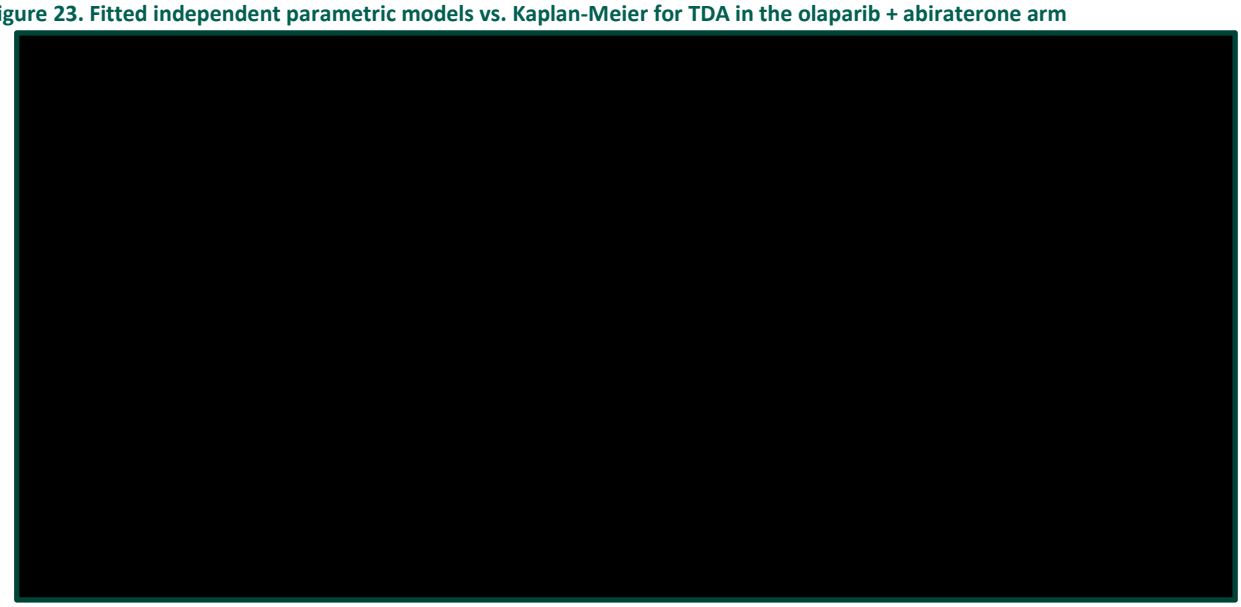


Table 33. Landmark analysis of TDA comparing modelled outcomes with trial results

Treatment Arm	Source	6 months	12 months	18 months	24 months	30 months	36 months	Median
Olaparib + Abiraterone	Model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Trial	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	Model	81.8 %	59.8 %	43.9 %	33.1 %	25.8 %	20.6 %	15.4
	Trial	80.8 %	60.1 %	43.7 %	31.6 %	25.5 %	21.0 %	15.7

8.4.1.4 Time to discontinuation of olaparib

For time to discontinuation of olaparib (TDT), the lognormal and generalised gamma distributions both had a reasonable statistical fit and given the relative maturity of the data (73.9%) all parametric fits had a reasonable visual fit to the within trial data. The plausibility of the long-term outcome was therefore considered with respect to other time to event endpoints.

When extrapolating the lognormal curve, after approximately 7 years this converges to be equal to the time on abiraterone curve. As evidence from the trial suggests that patients discontinue olaparib prior to abiraterone this was considered unlikely. With the generalised gamma distribution, the modelled time on olaparib is marginally less than the modelled time on abiraterone, in line with the trial data.

Based on having a good statistical and visual fit and the most clinically plausible long-term outcomes in terms of other time to event endpoints, the generalised gamma distribution is selected for time to discontinuation of olaparib in the base case.

Figure 24. Fitted parametric model vs. Kaplan-Meier for time to discontinuation of olaparib

Table 34. Landmark analysis of TDT comparing modelled outcomes with trial results

Treatment Arm	Source	6 months	12 months	18 months	24 months	30 months	36 months	Median
Olaparib + Abiraterone	Model	****	****	****	****	****	****	****
	Trial	****	****	****	****	****	****	****

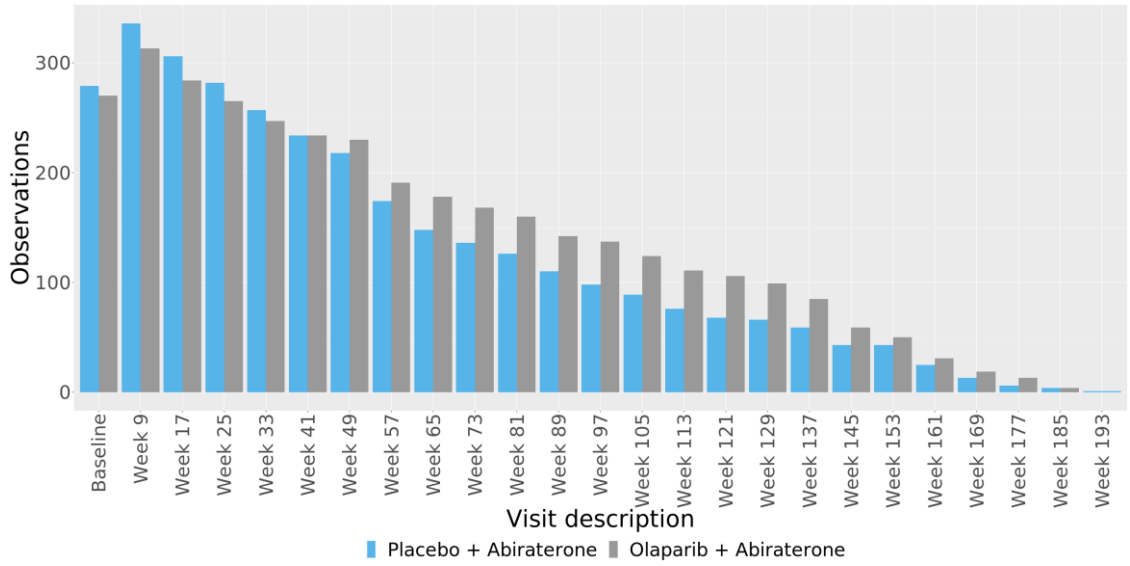
8.5 Documentation of health-related quality of life (HRQoL)

As HRQoL data were available from the key clinical trial (PROpel), the trial data was utilized in the health economic analysis. To supplement and validate results from the trial, a systematic literature search was conducted to identify relevant published utility values for health states relating to patients with mCRPC in the first-line setting (original search in April 2021, updated in April 2022). Details on the literature search are presented in
Appendix H Literature search for HRQoL data. In addition, previous assessments in prostate cancer by Medicinrådet were screened for utility values relevant to mCRPC.

8.5.1 Overview of health state utility values (HSUV)

The EQ-5D-5L was collected every 8 weeks in PROpel until 12 weeks after confirmed disease progression. The overall compliance rate was 65.1% in the olaparib + abiraterone arm and 67.7% in the placebo + abiraterone arm and the maximum follow-up time for the EQ-5D was 200 weeks after baseline in the olaparib + abiraterone arm and 192 weeks in the placebo + abiraterone arm. A summary of the available data are presented in Figure 25. Of all completed EQ-5D-5L questionnaires, 542 observations (8.1%) from 229 patients were recorded after radiological disease progression (7.4% of all observations in the olaparib + abiraterone arm and 8.8% in the placebo + abiraterone arm).

Figure 25. The number of EQ-5D observations per treatment arm over time



Utility weights from the EQ-5D-5L were estimated on the Danish value set.[73] To estimate utility values for use in the economic model, mixed effects models for repeated measures (MMRM) were performed. Details on the MMRM analysis can be found in Appendix I Analysis of HRQoL data. The best fitting model was judged based on Akaike Information Criterion (AIC). According to AIC, the best fitting model included only progression status. Consistent with the analysis of FACT-P in PROpel (see section 7.1.2.7), utilities were not significantly or meaningfully different between treatment arms. These data showed no detriment in utility from the addition of olaparib to abiraterone (Table 35), and so the same health state utility values were applied to both arms in the model.

Table 35. Utilities by treatment arm in PROpel

	Utility Value	95% CI	Source
Placebo + Abiraterone	0.882	0.867, 0.896	MMRM using treatment arm as fixed effect based on EQ-5D-5L data from PROpel (Danish value set)
Olaparib + Abiraterone	0.870	0.851, 0.888	

The only utilities identified for mCRPC patients using the EQ-5D-5L and Danish value sets were obtained from Medicinrådet's assessment of apalutamide in mHSPC.[34] The presented utility for the mCRPC health state (i.e., after disease progression in mHSPC) was 0.852 for low volume disease and 0.793 for high volume disease. The utilities in PROpel are slightly higher, though this may be reflective of the fact that after disease progression when treated with apalutamide for mHSPC these patients are likely to receive docetaxel for mCRPC. Chemotherapy treatment is associated with a toxicity burden and a requirement for travelling to hospital for infusions, which can impact HRQoL. Additionally patients treated with NHA-based therapy for mCRPC have a lower symptom burden (historically asymptomatic or mildly symptomatic) and therefore would be expected to have a better quality of life. Compared to the utilities for the mHSPC health state in the same model (0.911 for low-volume disease and 0.873 for high volume disease), the results in PROpel are not dissimilar. The utility values in both health states were accepted by Medicinrådet. Given that both the mHSPC population in the apalutamide trial (TITAN) and the first line mCRPC population in PROpel reflect patients treated with NHA-based therapy for metastatic prostate cancer, it may be easier to draw parallels. Therefore, the fact that utilities in PROpel are within the range of utilities for NHA-treated patients for metastatic prostate cancer as well as general utilities for mCRPC patients suggests that these are also valid.

The PROpel results indicate that only a modest decline in HRQoL would be observed upon disease progression. Feedback from a Swedish clinical expert collected by TLV is that disease progression is not strongly associated with quality of life, with many patients remaining asymptomatic through second and third line treatment.

8.5.2 Health state utility values used in the health economic model

The economic model uses the EQ-5D-5L data collected from the PROpel study to estimate the health state utility values in the economic model. For input to the cost-effectiveness model, the mean health state utility was derived from the regression analysis using the least squares mean (i.e., marginal mean). The model utilities were applied to the progression-free and progressed disease states. Utility values associated with each health state are displayed in Table 36. Health state utility values are also age-adjusted in the model using the multiplicative method based on the Danish standard utility values reported by Medicinrådet and the average age of the modelled cohort across the time horizon.

Table 36. Summary of utility values used in the model

	Utility Value	95% CI	Source
Health State			
Progression-Free	0.8800	0.8683, 0.8917	MMRM using EQ-5D-5L data from PROpel (Danish value set)
Progressed Disease	0.8428	0.8211, 0.8646	
Adverse Reaction			
Alanine Aminotransferase Increased	0.0000	N/A	Assumed to have no impact on utility in the absence of hepatitis or cirrhosis.
Anaemia	-0.0219	-0.0428, -0.0078	Sullivan 2011[51] (ICD-9: 285 Other anaemias). Assumed duration of 10.5 days in model.
Back Pain	-0.0866	-0.1051, -0.0697	Sullivan 2011[51] (ICD-9: 724 Other and unspecified disorders of back). Assumed duration of 10.5 days.
General Physical Health Deterioration	-0.2040	-0.2661, -0.1482	Swinburn 2010[52] (equal to fatigue). Assumed duration of 3 months.
Hyperglycaemia	0.0000	N/A	Assumed to have no impact on utility in the absence of peripheral neuropathy or ketoacidosis.
Hypertension	-0.0460	-0.1569, -0.0016	Sullivan 2011[51] (ICD-9: 401 Essential hypertension). Assumed duration of 10.5 days.
Lymphocyte Count Decreased	0.0000	N/A	Assumed to have no detrimental impact on utility in the absence of a lymphocytopenia-related infection
Neutrophil Count Decreased	-0.0897	-0.1159, -0.0665	Nafees 2008[53] (equal to neutropenia). Assumed duration of 10.5 days.

	Utility Value	95% CI	Source
Pneumonia	-0.1280	-0.1363, -0.1200	Tolley 2012[54] (Severe infection). Assumed duration of 10.5 days.
Pulmonary Embolism	-0.3100	-0.3322, -0.2883	Locadia 2004[55] (Pulmonary embolism). Assumed duration of 10.5 days.
Urinary Tract Infection	-0.0054	-0.0318, -0.0000	Sullivan 2011[51] (ICD-9: 599 Other disorders of urinary tract). Assumed duration of 10.5 days.
White Blood Cell Count Decreased	-0.0897	-0.1082, -0.0728	Nafees 2008[53] (equal to neutropenia). Assumed duration of 10.5 days.
Symptomatic Skeletal-Related Events			
Pathologic Bone Facture	-0.1300		Fassler 2011[74] (pathologic bone fractures). Assumed duration of 1 month.
Radiation to Bone	-0.0700		Fassler 2011[74] (radiation to bone). Assumed duration of 1 month.
Spinal Cord Compression	-0.5550		Fassler 2011[74] (spinal cord compression). Assumed duration of 1 month.
Surgery to Bone	-0.1300		Fassler 2011[74] (equal to bone fracture). Assumed duration of 1 month.

In the base case, the utility values associated with the progression-free and progressed disease health states were 0.880 and 0.843, respectively, prior to age-adjustment. The pre-progression utility is somewhat aligned with published values for asymptomatic or mildly symptomatic mCRPC patients or those ineligible for or pre-chemotherapy identified in the literature using a range of different measurement instruments and value sets (0.70 – 0.87),[75-79] as well as the HSUV applied to the mCRPC state after progression from mHSPC applied in Medicinrådet's assessment of apalutamide using the Danish value set on the EQ-5D-5L (0.793 – 0.852).[34] All identified studies showed either a modest decline in utility upon disease progression or lower utilities for patients treated with chemotherapy (a likely next line of therapy for patients treated with NHA-based therapy at first line), and therefore the slight decline in utility on disease progression is considered plausible given that the age-adjustment for utility will reflect future decline in the patient's condition.

Two scenario analyses are conducted on health state utility values in the model to explore the impact of different value sets and data sources. The first of these uses the EQ-5D data from PROpel but using utility weights estimated on the UK value set for the EQ-5D-3L using the mapping algorithm developed by Hernández-Alava and Pudney.[80,81] The second scenario sources utility values from the Norwegian Medicines Agency's assessment of abiraterone for first line mCRPC based on the COU-AA-302 trial.[82]

To account for decrements in quality of life and the loss of QALYs due to adverse events or SSREs, disutilities are applied in the model. Disutilities were obtained from published sources and the duration for which the event was considered to impact HRQoL were sourced from prior health technology assessments in mCRPC. The total QALY loss was applied as a one-off, either in the first model cycle for adverse events or upon disease progression for SSREs, and was estimated as the weighted sum of disutility, duration, and incidence of the event specific to the treatment of interest. Note that

the impact of adverse events due to subsequent treatments are not included. The incidence of adverse events as applied in the model are presented in Table 28. As no specific sources were identified for disutilities for adverse events assessed using the EQ-5D-5L and the Danish value set, disutilities were sourced from the literature and primarily assessed using the EQ-5D-3L and the UK value set, though some were obtained from other sources. However, as adverse events contribute to very little of the overall QALY gain in the analysis, any potential bias is assumed to be limited. Disutilities for adverse events were sourced from the catalogue of EQ-5D scores for the United Kingdom where disutilities for different ICD-9 codes are reported,[51] or publications assessing HRQoL changes due to adverse events in advanced cancers.[52-55] For example, the disutilities for general physical health deterioration, the included cytopenias, and pneumonia were obtained from vignettes assessed using the time trade-off or standard gamble designed to develop UK societal utility values for health states in metastatic renal cell carcinoma, non-small cell lung cancer, or late-stage chronic lymphocytic leukaemia, respectively.[52-54] The disutility for pulmonary embolism was derived from a vignette study assessing various utilities for venous thromboembolism in Dutch patients who had a history of venous thromboembolism (either current or previous).[55]

The duration of adverse events were obtained from clinical expert interviews reported in the Evidence Review Group report for the evaluation of abiraterone in mCRPC in the UK submission to NICE.[50] The experts estimated that most adverse events would impact HRQoL for between 7 and 14 days, and so the midpoint was selected (10.5 days) for implementation in the model, but that a general deterioration in physical health would last approximately 3 months. Disutilities for SSREs were obtained from a published systematic review reporting on utility decrements associated with SSREs in patients with CRPC.[74] No specific disutility for surgery to the bone was reported and so this was assumed to be equal to experiencing a pathological bone fracture. The duration of the HRQoL loss for each SSRE was assumed to be one month, in line with previous cost-effectiveness analyses and HTAs including the impact of SSREs in cancer.[65,83,84] Disutilities for SSREs are applied as a one-off at the time of disease progression as noted in section 8.3.2.5 above.

8.6 Resource use and costs

The costs for managing patients with mCRPC are described below. Included costs are reported in 2023 Danish kroner (DKK). Costs from previous years were inflated using the subgroup of the net price index excluding energy.[85] In line with the Danish limited societal perspective, the model includes the following costs:

- Initial treatment costs (drug acquisition, and where relevant, treatment administration)
- Subsequent treatment costs (drug acquisition and administration)
- Costs of adverse events and SSREs
- Routine medical care and follow-up costs
- End of life care costs
- Costs of genetic testing, where relevant in the assessment of patients with HRR mutations and for patients with BRCA mutations receiving olaparib as a subsequent treatment
- Patients costs related to travel to the hospital and time used for hospital visits

8.6.1 Initial treatment costs

As noted above, the included initial treatments for patients with mCRPC where chemotherapy is not clinically indicated are olaparib + abiraterone, abiraterone, and enzalutamide. Unit costs of drugs, at the pharmacy purchase price (AIP) reported in Medicinpriser.dk (accessed 27 April 2023), are reported in Table 37. As olaparib is dosed at 600 mg per day, it is assumed that the 150 mg tablets rather than the 100 mg tablets would be provided to patients to minimise the number of tablets taken. The current Medicinrådet treatment guidelines (at the time on submission) recommend Abirateron “Medical Valley” as the preferred provider of abiraterone. As abiraterone is now available as a generic

product, it is assumed this treatment has the lowest net price in Denmark. However, as it is not the product with the lowest public price for abiraterone, the manufacturer with the cheapest public price for abiraterone (Abirateron "Accord") was used as a placeholder to more accurately represent the effective price in Denmark. For prednisolone, as the drug is given as a 5mg dose twice a day, the cheapest 5 mg tablet was included.

Monthly costs (aligned with model cycles) of drug acquisition were calculated based on the prices in Table 37 and the posology reported in the SmPC or within the trial protocol. Dose interruptions or reductions which would result in reduced tablet consumption fewer packs used have been captured using the relative dose intensity (RDI) reported in PROpel (for olaparib and abiraterone) or from a real-world retrospective study in Sweden for enzalutamide.[86] The RDI for abiraterone in PROpel was comparable to the observed value in the Swedish study.[86] The monthly cost for each first line regimen is shown in Table 38. Patients were assumed to continue on treatment until discontinuation as modelled by the time on treatment curves. Time on abiraterone, prednisolone, and enzalutamide followed the modelled curve based on time to discontinuation of abiraterone (TDA), and for olaparib this was based on the time to discontinuation of treatment curve (TDT). As all treatments are delivered orally, no treatment administration costs were included.

Table 37. Unit costs of first line medications

Drug	Dose per Tablet	Tablets per Pack	Cost per Pack (AIP)	Cost per Tablet (AIP)
Olaparib (LYNPARZA)	150 mg	56	15 688.70	280.16
	100 mg	56	15 682.06	280.04
Abiraterone (Abirateron "Accord")	500 mg	56	1 525.00	27.23
Prednisolone (Prednisolon "EQL Pharma")	5 mg	100	33.50	0.34
Enzalutamide (XTANDI)	40 mg	112	19 960.66	178.22

AIP, pharmacy purchase price (apotekernes indkøpspris). Obtained from medicinpriser.dk (27th April 2023)

Table 38. Monthly costs of treatment for first line regimens

Regimen	Drug	Intended Daily Dose	RDI	Dose per Month	Tablets per Month	Cost per Month (AIP)
Olaparib + Abiraterone	Olaparib	600 mg (300 mg bid)	[redacted]	[redacted] mg	[redacted]	[redacted]
	Abiraterone	1000 mg	[redacted]	[redacted] mg	[redacted]	[redacted]
	Prednisolone	10 mg (5 mg bid)	100%	304 mg	60.9	20.39
Abiraterone	Abiraterone	1000 mg	95.8%	29 585 mg	59.2	1 611.34
	Prednisolone	10 mg (5 mg bid)	100%	304 mg	60.9	20.39
Enzalutamide	Enzalutamide	160 mg	95%	4 627 mg	115.7	20 613.39

AIP, pharmacy purchase price (apotekernes indkøpspris); RDI, relative dose intensity

8.6.2 Subsequent therapies

As noted in section 0, there were 255 patients in the olaparib + abiraterone arm and 285 patients in the placebo + abiraterone arm who received subsequent therapy or died after first line treatment discontinuation by the time of data cut-off. Of these events, 179 patients in the olaparib + abiraterone arm and 215 patients in the placebo + abiraterone arm received a subsequent therapy, with the remainder being deaths. There were 288 treatment discontinuations in the olaparib + abiraterone arm and 317 in the placebo + abiraterone arm. It was therefore assumed that 62.2% (179/288) of patients discontinuing first line treatment in the olaparib + abiraterone arm would receive subsequent therapy, and 67.8% (215/317) of patients discontinuing first line abiraterone would receive subsequent therapy (with

an equal proportion in the modelled enzalutamide arm). All patients who survive beyond first line treatment discontinuation but who do not receive subsequent anticancer therapy are assumed to receive best supportive care.

Given the paucity of data on longer term treatment sequences in the trial, and real-world evidence from Swedish and Finnish studies shows that only approximately 20-25% of patients reach third line treatment for mCRPC,[10,21] only two lines of therapy are modelled.

Of patients receiving further treatment, the distribution of therapies received was estimated based on feedback from four Nordic clinical experts (two from Norway and two from Sweden) on how treatments are sequenced in clinical practice. Treatments approved and available for use in Denmark at second or later lines in patients with mCRPC are abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223, and olaparib monotherapy. Table 39 shows the distribution of subsequent therapies applied in the base case. This is largely consistent with Medicinrådet's preferred assumptions on subsequent treatments from the assessment of apalutamide, darolutamide, and enzalutamide for nmCRPC and apalutamide for mHSPC, where NHA treated patients for first line mCRPC are likely to be treated with a taxane at the next line of therapy, with this mostly being docetaxel though a considerable proportion would receive cabazitaxel given docetaxel-based treatment for high volume mHSPC. Despite advice in treatment guidelines, most clinical experts noted that a small number of patients would be sequenced between NHAs. A scenario analysis was also considered assumed all patients would receive docetaxel as their subsequent therapy based on the current treatment guidelines for mCRPC from Medicinrådet.

Table 39. Distribution of subsequent treatments in ITT population

Second Line Therapy Received	After Olaparib + Abiraterone	After Abiraterone	After Enzalutamide
Abiraterone	0%	0%	3.3%
Cabazitaxel	20.0%	17.2%	16.6%
Docetaxel	60.4%	59.6%	59.6%
Enzalutamide	7.2%	3.0%	0%
Olaparib	0%	8.6%	9.0%
Radium-223	12.4%	11.6%	11.6%

In the scenario analysis for the subgroup of patients with HRR mutations, adjustments were made to the clinical feedback obtained. The clinical experts consulted reported that approximately 9% of patients treated with NHAs at first line for mCRPC would receive olaparib monotherapy as a subsequent therapy. As olaparib monotherapy is only approved for patients with BRCA mutations it is assumed that all those treated with olaparib would be patients with BRCA mutations. The prevalence of known BRCA mutations in the PROpel trial was 10.7% as a proportion of the ITT population, with BRCA mutations prevalent in 37.6% of patients with any HRR mutation. It is therefore assumed that the proportion of patients with HRR mutations who could receive olaparib monotherapy as a subsequent therapy is upweighted accordingly. Table 40 shows the estimated distribution of subsequent treatments, with the increased use of olaparib monotherapy but the distribution of all other treatments remaining proportional to the ITT population.

Table 40. Distribution of subsequent treatments in HRRm subgroup

Second Line Therapy Received	After Olaparib + Abiraterone	After Abiraterone	After Enzalutamide
Abiraterone	0%	0%	2.4%
Cabazitaxel	20.0%	13.1%	12.4%
Docetaxel	60.4%	45.4%	44.8%

Second Line Therapy Received	After Olaparib + Abiraterone	After Abiraterone	After Enzalutamide
Enzalutamide	7.2%	2.3%	0%
Olaparib	0%	30.4%	31.7%
Radium-223	12.4%	8.8%	8.7%

The unit costs of additional medications included as subsequent therapies are shown in Table 41. No cost was identified for radium-223 from public sources in Denmark. In line with the approach taken in the apalutamide assessment in mHSPC this was derived from the Swedish price and converted to Danish kroner. The dosing schedules of subsequent therapies were based on the recommended regimes reported in the SmPC of the product and Medicinrådet's preferred assumptions on dosing as reported in their assessment of olaparib for mCRPC with BRCA1/2 mutations. The estimated costs per month for each subsequent treatment regimen are shown in Table 42. For intravenously administered drugs (cabazitaxel, docetaxel, and radium-223) a cost of drug administration was included for each infusion. The cost of drug administration was based on the DRG code identified by searching for an outpatient hospitalization with the ICD-10 code C61.9Z (Kastrationsresistent prostatakræft (CRPC)) and the procedure BWAA62 (Medicingivning ved intravenøs infusion) using the Interaktiv DRG tool.[i] In addition, wastage was included for drugs with a weighted dose where unused portions of vials incur a cost despite not being used.

Table 41. Unit costs of additional medications used as subsequent therapies

Drug	Form	Dose/Unit	Units/Pack	Cost per Pack (AIP)	Cost per Unit (AIP)
Cabazitaxel (Cabazitaxel "Ever Pharma")	Conc. Inf	60 mg	1	1 712.00	1 712.00
Pre-medication:					
Promethazine (Phenergan)	Film C. Tab	25 mg	100	198.00	1.98
Domperidone (Domperidon "Alternova")	Tablet	10 mg	30	110.21	3.67
Methylprednisone (Depo-Medol)	Sus. Inj	40 mg	25	427.74	17.11
Clemastine (Clemastin "Paranova")	Sol. Inj	2 mg	5	471.00	94.20
Filgrastim (Accofil)	Conc. Inf	48 MU	5	1 900.00	380.00
Docetaxel (Docetaxel "Accord")	Conc. Inf	160 mg	1	309.00	309.00
Radium-223 (XOFIGO)	Sol. Inj	6 600 kBq	1	26 459.59	26 459.59
Morphine (Morfin "DAK")	Tablet	10 mg	100	83.10	0.83
Denosumab (XGEVA)	Sol. Inj	120 mg	1	1 899.44	1 899.44

Conc. Inf, concentrate for solution for infusion; Film C. Tab, film-coated tablet; Sol, solution for injection; Sus. Inj, suspension for injection. Obtained from medicinpriser.dk (27th April 2023), excepted XOFIGO which was obtained from TLV and converted to DKK.

Table 42. Monthly costs of treatment for subsequent treatment regimens

Regimen	Drug	Intended Dose	Dose per Month†	Units per Month	Cost per Month (AIP)
Abiraterone	Abiraterone	1000 mg	29 585 mg	59.2	1 611.34
	Prednisolone	10 mg	304 mg	60.9	20.39
Cabazitaxel	Cabazitaxel	20 mg/m^2	57 mg	1.4	2 481.38

[i] https://interaktivdrg.sundhedsdata.dk/

Regimen	Drug	Intended Dose	Dose per Month†	Units per Month	Cost per Month (AIP)
	Prednisolone	10 mg	304 mg	60.9	20.39
	Promethazine	25 mg	761 mg	30.4	60.27
	Domperidone	30 mg	913 mg	91.3	335.45
	Meythlprednisone	40 mg	58 mg	1.4	24.80
	Clemastine	2 mg	3 mg	1.4	136.53
	Filgrastim	0.5 MU/kg	30 MU‡	0.7	275.39
Docetaxel	Docetaxel	75 mg/m^2	216 mg	1.4	447.87
	Prednisolone	10 mg	304 mg	60.9	20.39
Enzalutamide	Enzalutamide	160 mg	4 627 mg	115.7	20 613.39
Olaparib	Olaparib	600 mg	16 710 mg	111.4	31 209.66
Radium-223	Radium-223	55 kBq/kg	4 944 kBq	1.1	28 762.99
Best Supportive Care	Prednisolone	10 mg	304 mg	60.9	20.39
	Morphine	10 mg	304 mg	30.4	25.29
	Denosumab	120 mg	130 mg	1.1	2 064.79

† Includes adjusted for relative dose intensity. ‡ Only half of patients are assumed to require G-CSF.

The total costs per regimen (including drug administration for intravenously administered treatments) with the estimated durations are reported in Table 43. In addition, the cost of olaparib monotherapy as a subsequent therapy includes the costs of genetic testing to identify patients eligible for treatment for patients with unknown mutation status (i.e., the subgroup of patients with HRR mutations treated with olaparib + abiraterone for first line mCRPC are assumed to have their BRCA mutation status known, for all other patients this must be established prior to commencing olaparib monotherapy). This is derived by estimating the number needed to test to identify one patient eligible for treatment (the inverse of the prevalence of BRCA mutations, assumed to be 10.7% based on the PROpel population) by the unit cost of genetic testing. The total cost of BRCA mutation testing was reported to be 11 000 DKK in Medicinrådet's assessment of olaparib for patients with BRCA mutations. When multiplying the cost per regimen by the treatment distribution estimates for the ITT population shown in Table 39, the average costs of subsequent treatment per first line regimen are derived. These values are shown in Table 44.

Table 43. Average costs of subsequent treatment regimens

Regimen	Duration (Months)	Source	Total Drug Costs	Total Admin. Costs
Abiraterone	3.60	Reported median time on second line abiraterone after receiving enzalutamide at first line[87]	5 874.24	0.00
Cabazitaxel	4.83	Median of 7 treatment cycles given in the CARD trial[14]	16 102.80	11 032.00
Docetaxel	5.52	Medicinrådet estimated that a median of 8 cycles given in clinical practice[34]	2 584.56	12 608.00
Enzalutamide	4.60	Reported median time on second line enzalutamide after receiving abiraterone at first line[87]	94 821.60	0.00
Olaparib	[redacted]	Medicinrådet's base case in the scenario for olaparib after NHA in patients with BRCA mutations[84]	[redacted]	0.00

Regimen	Duration (Months)	Source	Total Drug Costs	Total Admin. Costs
Radium-223	4.69	Total number of injections given in the ALSYMPCA trial[88]	134 943.91	8 037.60
Best Supportive Care	3.50	Medicinrådet's base case in the scenario for comparator when there are no other treatment options[84]	7 386.68	5 996.19

Table 44. Average subsequent treatment costs per patient applied in the model for the ITT population

First Line Therapy Received	Drug Acquisition	Drug Administration	Genetic Testing
Olaparib + Abiraterone	30 689.96	12 693.33	0.00
Abiraterone	64 400.06	12 026.46	8 884.76
Enzalutamide	63 366.11	11 957.51	9 271.06

8.6.3 Adverse events

The total costs of adverse events for each treatment were calculated based on the per event unit costs (Table 45), and the probability of experiencing adverse events (see Table 28 in section 8.3.2.5). The costs of adverse events are applied as a one-off cost in the first cycle of the model. The unit costs of adverse events in the model were estimated based on DRG costs or previously published estimates. Certain adverse events, particularly those related to investigations (e.g., alanine aminotransferase increased) were assumed to have very limited costs and treated with a single outpatient visit given the routine monitoring and in the absence of a clinical adverse event would typically result in a dose reduction as captured in the relative dose intensities.

Table 45. Unit costs of adverse events applied in the model

Event	Cost (DKK)	Description / Source
ALAT Increased	1 638.00	DRG 23MA98 (MDC23 1-dagsgruppe, pat. mindst 7 år) based on ICD-10 R74.8A (Abnorm serumamylase)
Anaemia	5 901.00	DRG 16PR01 (Transfusion af plasma og/eller behandlet blod)
Back Pain	1 510.00	DRG 08MA98 (MDC08 1-dagsgruppe, pat. mindst 7 år) based on ICD-10 M54.8 (Andre rygsmerter)
General Physical Health Deterioration	4 728.00	DRG 23MA03 (Symptomer og fund, u. kompl. bidiag.) based on ICD-10 R53.9E (Sygdomsfølelse)
Hyperglycaemia	4 728.00	DRG 23MA03 (Symptomer og fund, u. kompl. bidiag.) based on ICD-10 R73.9 (Hyperglykæmi UNS)
Hypertension	17 304.00	DRG 05MA11 (Hypertension)
Lymphocyte Count Decreased	2 240.00	DRG 16MA98 (MDC16 1-dagsgruppe, pat. mindst 7 år) based on ICD-10 D72.8D (Lymfopeni)
Neutrophil Count Decreased	1 858.00	DRG 12MA98 (MDC12 1-dagsgruppe, pat. mindst 7 år)
Pneumonia	41 804.00	DRG 04MA13 (Lungebetændelse og pleuritis, pat. mindst 60 år)
Pulmonary Embolism	31 555.00	DRG 04MA04 (Lungeemboli)
Urinary Tract Infection	28 523.00	DRG 11MA07 (Infektioner i nyrer og urinvej, pat. mindst 16 år)
White Blood Cell Count Decreased	1 858.00	Assumed equal to neutrophil count decreased

SSRE costs are calculated as a weighted average using the unit cost of each SSRE (Table 46), which were sourced based on the DRG codes applied for SSREs in Medicinrådet's assessment of olaparib for mCRPC patients with BRCA mutations. This cost is then applied to the proportion of patients who progress on treatment who are assumed to experience an SSRE, as reported in Table 29 above. The assumption was applied as SSRE is one of the key markers of bone progression and it is only expected to occur once a patient progresses.

Table 46. Unit costs of SSREs applied in the model

Event	Weight	Cost (DKK)	Description / Source
Pathological Bone Fracture	12.9%	92 113.00	DRG 08MP22 (Frakturkirurgi, ryg/hals)
Radiation to Bone	67.7%	40 193.00	DRG 27MP05 (Strålebehandling, konventionel, mindst 5 fraktioner)
Spinal Cord Compression	15.5%	39 320.00	DRG 01MA02 (Sygdomme og skader på rygmarven)
Surgery to Bone	4.1%	32 887.00	Average of DRGs 08MP63 (Øvrige kirurgiske procedurer, overekstremitet, store led) and 08MP65 (Øvrige kirurgiske procedurer, underekstremitet, store led)
Total	**100%**	**46 433.95**	

8.6.4 Routine healthcare and monitoring

The cost of patient follow-up in the model was calculated by multiplying resource use (e.g., number of occasions a component of care was accessed in a cycle) by the unit cost for each resource item. A summary of unit costs used in this analysis is presented in Table 47. Whilst certain laboratory tests are recommended to be routinely conducted in Danish clinical guidelines (e.g., PSA, alkaline phosphatase, lactate dehydrogenase), it has previously been reported by Medicinrådet that the cost of these would be captured in outpatient visits and so no further costs were included.[84]

Table 47. Unit costs of healthcare resources

Healthcare Resource	Unit Cost (DKK)	Source
Outpatient visit	1 858.00	DRG 12MA98 (MDC12 1-dagsgruppe, pat. mindst 7 år)
CT scan	2 440.00	DRG 30PR06 (CT-scanning, kompliceret)
Bone scan	3 441.00	DRG 30PR17 (Røntgenundersøgelse (alm), kompliceret)
Genetic testing (HRRm / BRCAm)	11 000.00	Medicinrådet 2021 (reported cost for BRCA mutation testing)

The resource use data were estimated based on the frequency of tests and scans recommended in Medicinrådet's treatment guideline for mCRPC as well as those reported in Medicinrådet's assessment of olaparib for mCRPC in patients with BRCA mutations (Table 48).[23,84] The frequency of use of healthcare resources was assumed to be independent of treatment used and disease progression/treatment status. Clinical expert feedback suggested there would be no increase in monitoring and visits with the addition of olaparib to abiraterone.

Table 48. Frequency of healthcare resource use per month

Healthcare Resource	Olaparib + Abiraterone	Abiraterone	Enzalutamide	Off Therapy / Progressed Disease
Outpatient visit	1.00	1.00	1.00	1.00
CT scan	0.33	0.33	0.33	0.33

Healthcare Resource	Olaparib + Abiraterone	Abiraterone	Enzalutamide	Off Therapy / Progressed Disease
Bone scan	0.33	0.33	0.33	0.33
Monthly cost (DKK)	3 818.33	3 818.33	3 818.33	3 818.33

For the biomarker-related subgroup of patients with HRR mutations, the model includes the one-off cost of testing for the genetic mutations. The cost of testing is calculated as unit cost of the test multiplied by the number needed to test to identify a positive case who would be eligible for treatment with olaparib + abiraterone. The number needed to test was calculated as the inverse of the prevalence of known HRR mutations in the PROpel trial. Of the 796 patients treated in PROpel, 226 had a HRR mutation based on either tumour tissue testing or ctDNA.[24] Although 18 patients in the trial did not have a successful assessment for mutations, it is assumed that some test failures would occur in clinical practice as well and therefore these patients are still included in the denominator in order to estimate confirmed HRRm rates. Therefore, the prevalence of HRR mutations was 28.4%, with a number needed to test of 3.5. The unit cost of mutation testing was estimated to be 11 000 DKK based on the reported cost of testing for BRCA mutations in Medicinrådet's previous assessment of olaparib and assumed to be equal for testing other HRR mutations. The cost of HRR mutation testing in the model was 38 743.36 DKK and this was applied to the olaparib + abiraterone arm only in the evaluation of the HRRm subgroup. No initial costs of genetic testing were applied in the ITT population. As noted above, costs of mutation testing for BRCA were also included for patients receiving olaparib monotherapy as a subsequent therapy in both the ITT and HRRm populations.

8.6.5 Patient costs

Patient costs in the model were related to the frequency and duration of healthcare visits related to ongoing monitoring of mCRPC, given that initial treatments are all taken orally and therefore patients do not need to have to travel to the hospital for treatment administration.

The unit costs of patients time and transport were taken from Medicinrådet's unit costs list, assuming 181 DKK/hour for patient time and 3.51 DKK per km travelled. Based on published sources, the average distance travelled to the nearest hospital is 19.6 km each way, and the average travel time to the hospital was estimated to be approximately 25 minutes each way based on figures from Eurostat. The duration of patient time used in different healthcare processes (outpatient visit, CT scan, or bone scan) were taken from the preferred durations in Medicinrådet's assessment of olaparib for patients with mCRPC with BRCA mutations.[84]

Resource	Use per Visit	Frequency of Use per Treatment			
		Olaparib + Abiraterone	Abiraterone	Enzalutamide	Off Therapy / Progressed Disease
Outpatient visit	20 mins	1.00	1.00	1.00	1.00
CT scan	30 mins	0.33	0.33	0.33	0.33
Bone scan	30 mins	0.33	0.33	0.33	0.33
Travel time (per visit)	50 mins	1.00	1.00	1.00	1.00
Travel distance (per visit)	39.2 km	1.00	1.00	1.00	1.00
Monthly cost (DKK)		409.09	409.09	409.09	409.09

8.6.6 End of life care

Estimates of the use of palliative / end of life care for mCRPC patients were derived from published literature in Denmark. A registry-based analysis of adult patients dying from cancer in Denmark determined that patients with prostate cancer were more often admitted to hospital-based palliative care but not to hospices.[89] It was therefore assumed that most end of life care for mCRPC patients would be conducted in hospitals. A retrospective study on Danish registries showed that patients dying of cancer had a median of 2 hospital admissions in the last 6 months of life (i.e., some patients have none and some have more) with the median length of stay per admission of 4 days.[90] Feedback from one clinical expert consultant was that patients who receive a more effective treatment for mCRPC would be less likely to require palliative care for their disease. Given the demonstrated prolonged rPFS when treating with olaparib + abiraterone it was therefore assumed that the average number of palliative care hospitalization for patients treated with olaparib + abiraterone would be 1.5 instead of 2.

An appropriate DRG code and costs for a palliative care hospitalization was sourced from the Interaktiv DRG tool using the ICD-10 code C61.9Z (Kastrationsresistent prostatakreft (CRPC)) and the procedure code BXBA (Specialiseret palliativ indsats), with a length of stay of 4 days.

Table 49. Costs of end of life care

	Olaparib + Abiraterone	Abiraterone	Enzalutamide
Unit cost of one palliative care hospitalisation (DRG 11MA08 Sygdomme i prostata, ondartet sygdom, pat. mindst 18 år)	31 486.00	31 486.00	31 486.00
Palliative care hospitalisations in last 6 months of life	1.5	2.0	2.0
Cost of end of life care (DKK)	47 229.00	62 972.00	62 972.00

8.7 Results

8.7.1 Base case overview

An overview of the main scope of the base case analysis is presented in Table 50.

Table 50. Base case overview

Setting/Parameter	Value
Population	Adult patients with mCRPC in whom chemotherapy in not clinically indication
Comparator	Abiraterone in combination with prednisolone
Type of model	Partitioned survival analysis
Time horizon	30 years (lifetime)
Treatment line	1st line, with costs of first subsequent anticancer therapy also included
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in the PROpel study with health state utilities derived using Danish population weights based on progression status
Included costs	Pharmaceutical costs (first line and subsequent therapy) Hospital costs related to routine monitoring Costs of adverse events and skeletal-related events End of life costs Patient costs

Dosage of pharmaceutical	600 mg (2 x 150 mg tablets BID) taken orally
Average time on treatment	**Olaparib + Abiraterone** Olaparib: 17.3 months (median) and 34.7 months (mean) Abiraterone: 18.5 months (median) and 39.1 months (mean) **Abiraterone**: 20.1 months (median) and 26.6 months (mean)
Parametric function for rPFS	Olaparib + Abiraterone: Lognormal Abiraterone: Lognormal
Parametric function for OS	Olaparib + Abiraterone: Generalised Gamma Abiraterone: Generalised Gamma

8.7.2 Base case results

The results from the base case analysis comparing olaparib + abiraterone to abiraterone alone in patients with mCRPC in whom chemotherapy is not clinically indicated are detailed in Table 51. Over the lifetime horizon, treatment with olaparib + abiraterone was associated with higher costs than with abiraterone alone and was also associated with longer survival and a greater number of QALYs gained. The resulting discounted incremental cost per QALY for olaparib + abiraterone versus abiraterone alone at the pharmacy purchase price was 745 651 DKK.

Table 51. Base case cost-effectiveness results

Per patient	Olaparib + Abiraterone	Abiraterone	Difference
Life Years Gained (Undiscounted)			
Total life years gained	5.88	3.55	2.33
Progression-free life years	3.99	2.38	1.61
Post-progression life years	1.89	1.17	0.72
QALYs (Discounted)			
Total QALYs	4.22	2.85	1.37
Progression-free QALYs	2.97	1.94	1.03
Post-progression QALYs	1.26	0.91	0.34
Adverse event QALYs	-0.00	-0.00	-0.00
Symptomatic skeletal-related event QALYs	-0.00	-0.00	-0.00
Costs (Discounted)			
Total costs	[redacted]	[redacted]	1 021 255
Drug acquisition costs (first line)	[redacted]	[redacted]	[redacted]
Drug acquisition costs (subsequent lines)	[redacted]	[redacted]	[redacted]
Drug administration costs (subsequent lines)	[redacted]	[redacted]	[redacted]
Genetic testing	0	5 909	- 5 909
Hospital costs and ongoing monitoring	225 205	151 143	74 062
Adverse event costs	5 984	2 609	3 375
Symptomatic skeletal-related event costs	8 736	7 617	1 119

Per patient	Olaparib + Abiraterone	Abiraterone	Difference
End of life care costs	39 776	56 835	- 17 059
Patient time and transport costs	24 128	16 193	7 935
Incremental Cost-Effectiveness (Discounted)			
ICER (per QALY)	745 651		

8.7.3 Comparison with enzalutamide

The comparison with enzalutamide is provided as a supplement to the base case, given that it is expected that most patients with mCRPC in whom chemotherapy is not clinically indicated are expected to receive abiraterone in future given the availability of generic alternatives. As noted above, the comparison with enzalutamide assumes equal efficacy and time on treatment for abiraterone and enzalutamide, and only differs in terms of costs and adverse events. Compard to enzalutamide, olaparib + abiraterone has an incremental cost-effectiveness ratio of 402 044 DKK.

Per patient	Olaparib + Abiraterone	Enzalutamide	Difference
Life Years Gained (Undiscounted)			
Total life years gained	5.88	3.55	2.33
QALYs (Discounted)			
Total QALYs	4.22	2.85	1.37
Costs (Discounted)			
Total costs	[redacted]	[redacted]	550 959
Drug acquisition costs (first line)	[redacted]	[redacted]	[redacted]
Drug acquisition costs (subsequent lines)	[redacted]	[redacted]	[redacted]
Drug administration costs (subsequent lines)	[redacted]	[redacted]	[redacted]
Hospital costs and ongoing monitoring	225 205	151 143	74 062
Adverse event costs	5 984	2 665	3 318
Symptomatic skeletal-related event costs	8 736	7 617	1 119
End of life care costs	39 776	56 835	- 17 059
Patient time and transport costs	24 128	16 193	7 935
Incremental Cost-Effectiveness (Discounted)			
ICER (per QALY)	402 044		

8.8 Sensitivity analyses

The model explored structural and parameter uncertainty in a variety of ways, namely:

- Scenario analyses were conducted to assess the impact of changes in a number of key model parameters on results. Parameters explored were: time horizon, discount rates, treatment costs, subsequent treatment distributions, patient population under evaluation, and assumptions regardless efficacy/survival extrapolations.

- Deterministic (one-way) sensitivity analyses were used to assess the one-way sensitivity of results on a range of model parameters, including utility values, healthcare resource use and costs, adverse events, subsequent treatment durations, and relative dose intensities for initial treatments.
- Probability sensitivity analysis was also performed to assess the joint parameter uncertainty within the model by sampling multiple parameters simultaneously from pre-specified probability distributions (e.g., normal, lognormal, beta, gamma).

8.8.1 Scenario analyses

A number of additional scenarios were considered compared to the base case analysis. These scenarios considered some potential uncertainties on structural choices or assumptions in the model. The results of these scenarios are presented in Table 52. The only scenarios that potentially influence cost-effectiveness conclusions are those related to the functional form of the overall survival extrapolation. Assuming that the OS extrapolation follows the loglogistic distribution in both arms resulted in a higher ICER compared to the base case.

Changing the source of utilities or adjusting the baseline values for age to result in lower health state utility values in both cases only had a modest impact on the ICER. However, as the majority of mCRPC patients who would be candidates for NHA-based treatment are asymptomatic or mildly symptomatic prior to mCRPC disease progression, it is plausible that there is limited impact on their quality of life at this time and therefore their health state utility could be higher than the general population aged over 70 years whose health may be burdened by other diseases and conditions. Results were not especially sensitive to time on treatment distributions applied or assumptions subsequent treatments.

Table 52. Summary of scenario analyses on the base case results

	Change	Reason / Rational / Source	Incremental Cost (DKK)	Incremental QALYs	ICER (DKK/QALY)
Base case	-	-	1 021 255	1.37	745 651
Overall survival distribution	Loglogistic in both arms	Plausible alternative fit for abiraterone arm, and assuming similar functional form for olaparib	985 516	0.83	1 180 627
	Loglogistic for abiraterone, lognormal for olaparib	Best statistical fits for each arm with similar functional forms	997 138	1.03	968 254
Time to treatment discontinuation distributions	Lognormal for time to discontinuation of abiraterone (both arms) and olaparib	Plausible alternative distributions	1 044 188	1.37	762 396
Drug costs of abiraterone	- 10%	Current tender winner has higher max. AIP than lowest public AIP and therefore a negotiated net price is assumed to exist	1 019 821	1.37	744 604
	- 20%		1 018 386	1.37	743 557
Discounting	0 %	To assess the impact of alternative discounting rate given recent changes in cost inflation and health investment	1 185 231	1.96	606 027
	5 %		968 961	1.19	811 497

	Change	Reason / Rational / Source	Incremental Cost (DKK)	Incremental QALYs	ICER (DKK/QALY)
Subsequent treatment distributions	In all arms: 80% docetaxel, 15% cabazitaxel, 5% radium-223	An approximation of the current treatment guideline from Medicinrådet with regards to subsequent therapy after NHA for first line mCRPC	1 048 307	1.37	765 403
Utility weight source	PF: 0.814 PD: 0.775	Using PROpel dataset but UK value set for EQ-5D to generate utilities lower than population norms for Denmark	1 021 255	1.27	807 023
	PF: 0.851 PD: 0.625	Using utility data from abiraterone trial (COU-AA-302) as adding olaparib was shown to lead to no detriment in HRQoL compared to abiraterone, but COU-AA-302 data suggests greater impact of disease progression on HRQoL	1 021 255	1.25	819 088
Adjusted utility values	PF: 0.818	Utility value for the progression-free health state proportionally reduced to be in line with general population values	1 021 255	1.27	802 211

8.8.1.1 Patients with HRR mutations

As a pre-specified subgroup of the PROpel trial, given its association with poor prognosis in mCRPC status, the cost-effectiveness of olaparib + abiraterone in patients with HRR mutations was also evaluated. This analysis is based on the 111 patients in the olaparib + abiraterone arm and 115 patients in the placebo + abiraterone arm in PROpel who were identified to have a HRR mutation on either the tumour tissue test or ctDNA-based test. Survival curves were fitted to the data as appropriate (see Appendix G Extrapolation), the cost of genetic testing was applied to the olaparib + abiraterone arm (see section 8.6.4 above), and subsequent treatment distributions were modified as appropriate (see section 8.6.2), however all other model assumptions remained equal to the base case.

The main results from the subgroup analysis are summarised in Table 53. The resulting discounted incremental cost per QALY for olaparib + abiraterone versus abiraterone alone was 566 630 DKK. This incremental cost per QALY compared to enzalutamide was 402 358 DKK (detailed results not shown).

Table 53. Cost-effectiveness results for the subgroup of patients with HRR mutations

Per patient	Olaparib + Abiraterone	Abiraterone	Difference
Life Years Gained (Undiscounted)			
Total life years gained	6.27	2.75	3.51
Progression-free life years	4.75	1.68	3.07
Post-progression life years	1.52	1.08	0.44
QALYs (Discounted)			
Total QALYs	4.44	2.27	2.18
Progression-free QALYs	3.42	1.42	2.00

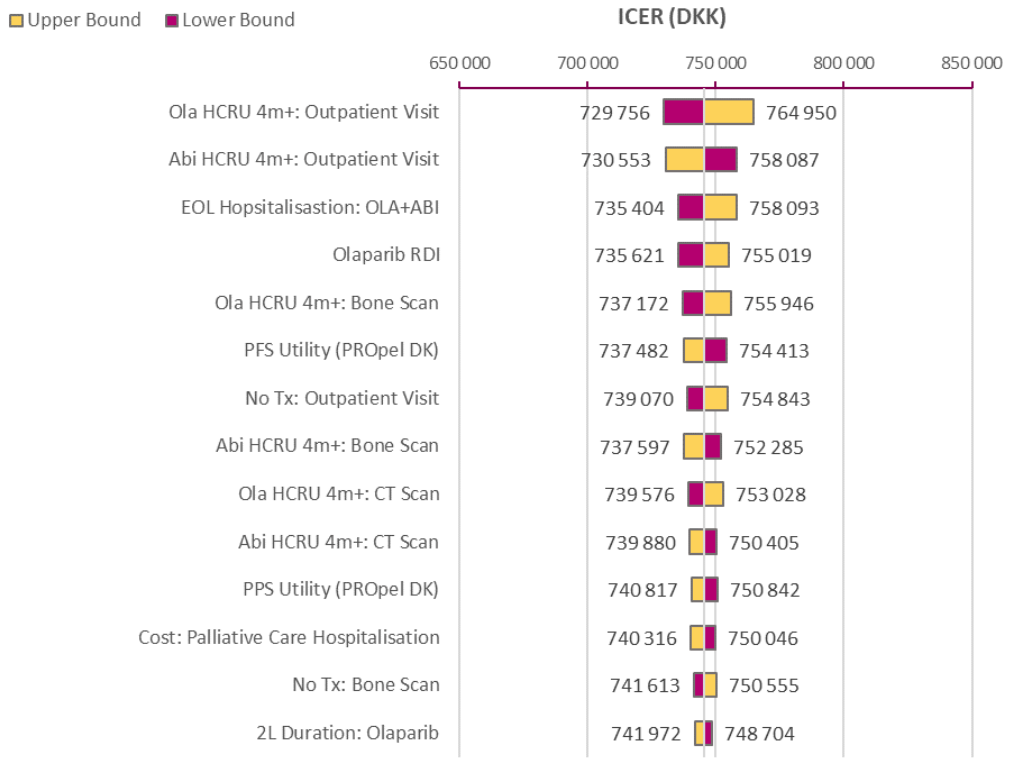
Per patient	Olaparib + Abiraterone	Abiraterone	Difference
Post-progression QALYs	1.03	0.85	0.18
Adverse event QALYs	-0.00	-0.00	-0.00
Symptomatic skeletal-related event QALYs	-0.00	-0.00	-0.00
Costs (Discounted)			
Total costs	[redacted]	[redacted]	1 232 606
Drug acquisition costs (first line)	[redacted]	[redacted]	[redacted]
Drug acquisition costs (subsequent lines)	[redacted]	[redacted]	[redacted]
Drug administration costs (subsequent lines)	[redacted]	[redacted]	[redacted]
Genetic testing	38 743	5 687	33 056
Hospital costs and ongoing monitoring	236 643	120 441	116 202
Adverse event costs	5 984	2 609	3 375
Symptomatic skeletal-related event costs	8 540	7 906	634
End of life care costs	39 315	58 276	- 18 961
Patient time and transport costs	25 354	12 904	12 450
Incremental Cost-Effectiveness (Discounted)			
ICER (per QALY)	566 630		

8.8.2 Deterministic sensitivity analyses

Figure 26 shows the one-way sensitivity analyses (OWSA) on the ICER, as a result of varying certain parameter values across their confidence intervals or plausible ranges (based on an appropriate distribution, such as gamma for healthcare resource use, with a standard error equal to 20% of the mean). Parameters explored were patient characteristics, utility values and disutilities, frequency of tests and scans, adverse event rates, the probability of experiencing an SSRE, drug relative dose intensities, the proportion of PFS events that were progression and the proportion of progressed patients starting subsequent therapy, and the durations of subsequent treatments.

As can be seen from the figures, the parameters with the greatest impact on the ICER were the frequency of outpatient visits (ranging from 0.6 to 1.4 per month), the number of hospitalisations at the end of life for patients treated with olaparib + abiraterone (ranging from 1.0 to 2.1), and the relative dose intensity of olaparib (ranging from 90% to 93%). However, despite having the greatest impact on the ICER of explored parameters, the variability was still modest with a range of ±19 000 DKK compared to the base case.

Figure 26. Tornado diagram of the OWSA comparing olaparib + abiraterone to abiraterone in the labelled population



Estimates of the impact on the ICER of discounted price of olaparib compared to current practice are presented in Figure 27. Note that the ICER never crosses the x-axis (drops below zero) because the addition of olaparib extends the time during which patients are able to receive abiraterone and therefore these patients still accumulate treatment costs, as well as prolonging survival which is associated with further hospital and patient costs.

Figure 27. Estimated ICERs across different prices of olaparib

8.8.3 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed to assess the impact on the model outputs of parameter uncertainty and stochasticity in the parameter estimates used. Parameter values and distributions applied in the PSA are given in Appendix J Probabilistic sensitivity analyses. In general, the parameters tested in the PSA along with their selected distributions were:

- **Time to event inputs**: rPFS, OS, and time to treatment discontinuation (multivariate normal distributions on the Cholesky decomposition)
- **Safety inputs**: incidence of adverse events (beta distribution), probability of experiencing an SSRE upon progression (beta distribution)
- **Cost-related inputs**: patient height and weight for treatment dosing (normal distribution), proportion of patients receiving subsequent therapy (beta distribution), relative dose intensities of initial treatments (beta distribution), duration of subsequent treatments (lognormal distribution), frequency of healthcare resource use (gamma distribution), costs of adverse events or SSREs (gamma distribution)
- **Utility inputs**: health state utility values (beta distribution), disutilities due to adverse events or SSREs (beta distribution), duration of adverse events (lognormal distribution)

The PSA was run using 1000 iterations. Convergence plots show the ICER stabilising after approximately 100 iterations. The mean ICER of olaparib + abiraterone vs. abiraterone over the sampled PSA iterations was 765 568 DKK/QALY (Table 54), which is highly aligned with the deterministic base case results. The probabilistic sampling showed that treatment with olaparib + abiraterone was consistently associated with a health gain over treatment with abiraterone (ΔQALYs 1.35; 95% Credible Interval [CrI] 0.55, 2.22).

Table 54. Results of the probabilistic sensitivity analysis

Treatment	Mean (95% CrI)		Incremental (95% CrI)		ICER (95% CrI)
	Costs (DKK)	QALYs	Costs (DKK)	QALYs	
Olaparib + Abiraterone	[redacted]	4.23 (3.47, 5.11)			
Abiraterone	[redacted]	2.89 (2.58, 3.25)	1 031 070 (876 481, 1 217 314)	1.35 (0.55, 2.22)	765 568 (470 447, 1 851 699)
Enzalutamide	[redacted]	2.89 (2.58, 3.25)	559 187 (387 835, 753 737)	1.35 (0.55, 2.22)	414 939 (248 769, 921 380)

The cost-effectiveness plane for the probabilistic comparison of olaparib + abiraterone to abiraterone alone or enzalutamide, including the 95% credible ellipse, is shown in Figure 28. The cost-effectiveness acceptability curves (CEAC) for the comparisons are presented in Figure 29.

Figure 28. Scatterplot of probabilistic sensitivity analysis results including 95% credible ellipses

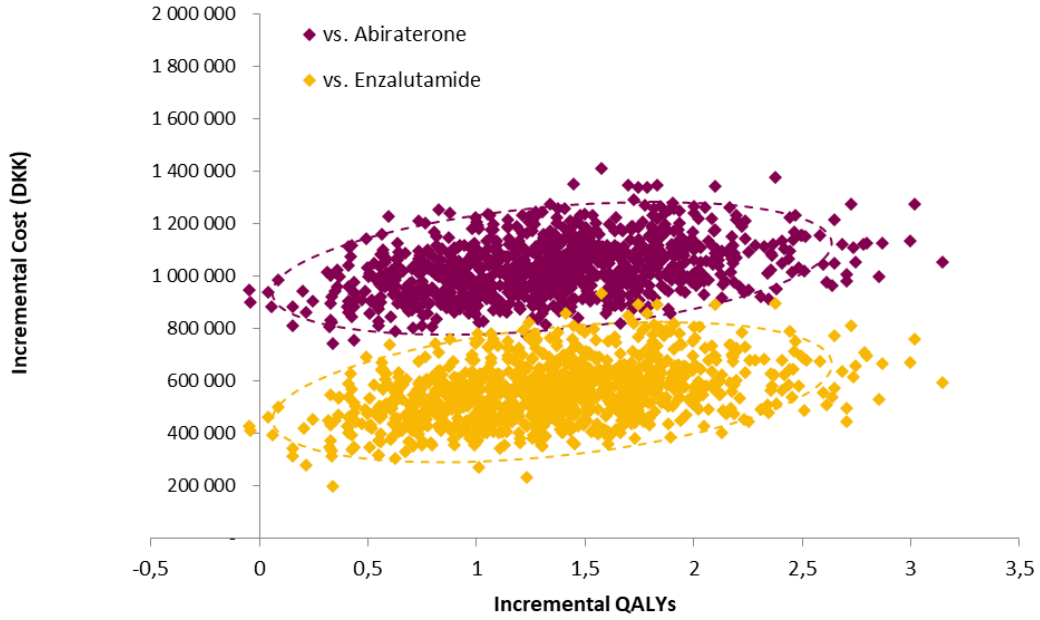
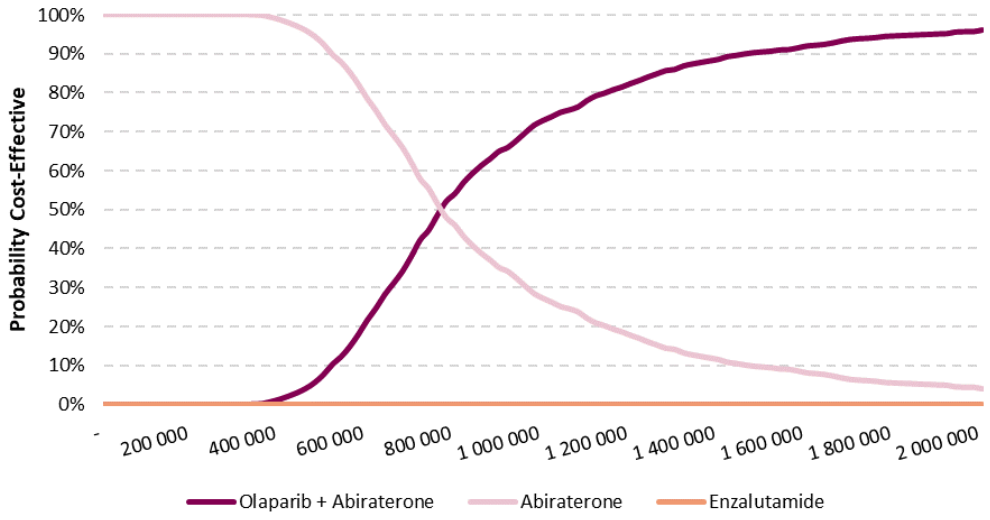


Figure 29. Cost-effectiveness acceptability curves



9. Budget impact analysis

Budget impact analysis was conducted to estimate the additional expenditure to the Danish Healthcare system as a consequence of recommending olaparib in combination with abiraterone in adult patient with mCRPC in whom chemotherapy is not clinically indicted. This analysis is conducted on two patient populations: the labelled population and the subgroup of patients with HRR mutations. Within both of these scenarios, the analysis assumes that NHA-based therapies (olaparib + abiraterone, abiraterone, and enzalutamide) are available treatment options.

The estimated budget impact of introducing olaparib + abiraterone is based on the costs to the healthcare services (i.e., excludes patient costs), derived from the cost-effectiveness model, and the estimated number of patients eligible for treatment presented in section 5.1.3 above. The estimates include assumptions on the current size of NHA market within the mCRPC setting and the expected changes in the market over the coming five years. The analysis start in the year 2024, assuming this is the first full year where patients will be eligible to receive treatment with olaparib in combination with abiraterone, following a recommendation from Medicinrådet. As reported above, it is estimated that the number of patients eligible for NHA-based treatment in Denmark is *** in 2024 and declines to *** in 2028. The calculations can be found in the Excel model along with the cost-effectiveness analysis.

9.1 Number of patients

9.1.1 Base case (biomarker unselected patients)

As reported in Table 2 (section 5.1.3), *** to *** mCRPC patients per year will be eligible for NHA-based treatment (i.e., in whom chemotherapy is not clinically indicated) in Denmark, with the number declining each year due to an increase in the exposure to NHAs at prior treatment lines. In the scenario where olaparib + abiraterone is not recommended, it is assumed that no patients will receive the combination. The current Medicinrådet guideline recommends that at least 80% of NHA-eligible patients without visceral metastases receive abiraterone and that at least 80% of NHA-eligible patients with visceral metastases receive enzalutamide.[23] Given that abiraterone is available as a generic medication it is assume to be preferred wherever possible. Medicinrådet estimate that 13.3% of NHA-eligible patients have visceral metastases. It is therefore assumed that in current practice around 12% would receive enzalutamide and the remaining 88% receive abiraterone.

In the scenario where olaparib + abiraterone is recommended it is assumed that, at the peak of its growth, 65% of patients in this setting will be treated with olaparib + abiraterone. This is based on market research across the European Union and from clinical feedback from Nordic physicians where add-on olaparib is likely to be preferred for younger and/or fitter patients or those with HRR mutations, given the greater marginal benefit in these populations. Uptake is expected to grow over the first two to three years to reflect this patient prioritization. At the peak year, 291 patients are expected to start treatment with olaparib + abiraterone. Olaparib + abiraterone is expected to displace both abiraterone and enzalutamide in clinical practice, however it may displace relatively more potential abiraterone patients than potential enzalutamide patients as it is assumed that some patients may be at greater risk for steroid-related complications and therefore enzalutamide is a preferred treatment.

Table 55. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	2024	2025	2026	2027	2028
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	2024	2025	2026	2027	2028
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	***	***	***	***	***

Table 56. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	2024	2025	2026	2027	2028
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	***	***	***	***	***

9.1.2 Scenario analysis (HRR mutated patients)

As a scenario to the base case, the budget impact is also estimated if olaparib + abiraterone is only used in Denmark for patients with HRR mutations. As reported in Table 3 (section 5.1.3), the number of patients with known HRR mutations is contingent on three factors: the prevalence of HRR mutations in the mCRPC population, the number of patients who are tested for HRR mutations, and the proportion of tests which return a conclusive results (HRR mutated or not). The prevalence of HRR mutations in the 778 patients in PROpel with a conclusive result was 29%. In the screening for the PROfound study, of the 2793 patients with interpretable results, a qualifying HRR mutated was detected in 28% of patients. It is therefore assumed that the prevalence of HRR mutations in approximately 28%. The proportion of tests which return conclusive results is largely based on the testing method. In the PROpel study, only 535 patients (67.2%) obtained valid results from tumour tissue testing, whereas 734 patients (92.2%) obtained valid results from ctDNA-based tests. Overall, 97.7% of patients managed to obtained a valid test result from either method. Currently in Danish clinical practice, tumour tissue testing is used. However there is an impetus in the Nordics for developing and validating ctDNA assays. Therefore, in estimating the number of successful tests we have chosen to assume a gradual increase in test success rates from 67% in 2024 up to 92% in 2028. With regards to testing practices, it is already recommended in the DaProCa guidelines that patients should be offered a BRCA mutation test if this is relevant for treatment,[9] and the EAU guidelines state that all metastatic patients should be offered genomic testing for HRR defects.[11] It is therefore assumed some testing already exists in practice and will increase regardless of whether olaparib + abiraterone is recommended. AstraZeneca estimates that around 10% of mCRPC patients are tested today and this will increase to up to 25% over the next five years. It is expected that if olaparib is recommended for HRR mutated patients then testing will increase, with half of mCRPC patients being tested in 2024 and up to 80% in 2028.

Table 57. Estimates on the number of patients with known HRR mutations in Denmark

Year	2024	2025	2026	2027	2028
Patients with mCRPC receiving active treatment but for whom chemotherapy is not clinically indicated	***	***	***	***	***
Proportion of patients being tested for HRR mutations if olaparib is recommended	50%	60%	70%	80%	80%
Proportion of patients being tested for HRR mutations if olaparib is NOT recommended*	10%	15%	20%	25%	25%

Year	2024	2025	2026	2027	2028
Proportion of patients with a successful test	67%	73%	80%	86%	82%
Prevalence of HRR mutations	28%	28%	28%	28%	28%
Patients with known HRR mutations who may be candidates for olaparib + abiraterone	**	**	**	**	**

* Note that this proportion is only used to estimate differences in the total costs of testing to the Danish healthcare system should olaparib be recommended, but not to estimate different patient group sizes so that the budget impact is calculated on the same number of patients

Based on these patients numbers, in the scenario where olaparib + abiraterone is not recommended, it is assumed that no patients will receive the combination and the distribution of abiraterone and enzalutamide is equal to the base case. In the scenario where olaparib + abiraterone is recommended, it is assumed that in the peak year 80% of patients with known HRR mutations will be treated with olaparib + abiraterone based on market research from different EU countries. Uptake is expected to grow as clinical experience and knowledge of target mutations develops. At the peak year, ** patients with HRR mutations are expected to start treatment with olaparib + abiraterone.

Table 58. Number of patients with known HRR mutations expected to be treated over the next five-year period - if the pharmaceutical is introduced

	2024	2025	2026	2027	2028
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	***	***	***	***	***

Table 59. Number of patients with known HRR mutations expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	2024	2025	2026	2027	2028
Olaparib + Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	***	***	***	***	***

9.2 Expenditure per patient

The tables below show the costs to the healthcare system per patient per year after treatment initiation for olaparib + abiraterone, abiraterone, and enzalutamide. Patients who initiate treatment in 2024 will accrue five years of costs within the five-year time horizon of the budget impact analysis, but those who initiate treatment in 2028 only initiate the first year of treatment costs within the horizon.

9.2.1 Base case (biomarker unselected patients)

Table 60. Costs per patient per year for patients treated with olaparib + abiraterone

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which are olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which are abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which are subsequent therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration Costs	2 509	1 975	1 083	629	395
Hospital Costs	49 149	44 330	35 593	28 510	23 115
Adverse Event Costs	5 984	-	-	-	-
Skeletal Related Event Costs	2 759	2 089	1 252	816	566
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 61. Costs per patient per year for patients treated with abiraterone

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug Costs	33 092	21 033	10 844	6 308	4 087
Of which are abiraterone	*16 261*	*8 983*	*5 223*	*3 397*	*2 399*
Of which are subsequent therapies	*16 830*	*12 050*	*5 620*	*2 912*	*1 687*
Administration Costs	3 143	2 250	1 050	544	329
Hospital Costs	50 543	48 850	38 974	28 525	19 904
Adverse Event Costs	2 609	-	-	-	-
Skeletal Related Event Costs	3 248	2 058	1 069	625	397
Total Costs	**94 957**	**75 854**	**52 712**	**36 403**	**24 949**

Table 62. Costs per patient per year for patients treated with enzalutamide

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug Costs	221 987	125 342	71 513	45 774	31 970
Of which are enzalutamide	*205 427*	*113 486*	*65 983*	*42 909*	*30 309*
Of which are subsequent therapies	*16 560*	*11 856*	*5 530*	*2 865*	*1 660*
Administration Costs	3 125	2 237	1 044	541	313
Hospital Costs	50 543	48 850	38 974	28 525	19 904
Adverse Event Costs	2 665	-	-	-	-
Skeletal Related Event Costs	3 248	2 058	1 069	625	397
Total Costs	**283 991**	**180 222**	**113 409**	**75 883**	**52 827**

9.2.2 Scenario analysis (HRR mutated patients)

Table 63. Costs per patient per year for patients treated with olaparib + abiraterone

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which are olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which are abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which are subsequent therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration Costs	2 520	1 705	941	586	400
Hospital Costs	49 435	43 077	35 027	28 689	23 798
Adverse Event Costs	5 984	-	-	-	-
Skeletal Related Event Costs	2 702	1 880	1 146	769	550
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64. Costs per patient per year for patients treated with abiraterone

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug Costs	64 123	37 095	17 850	9 099	4 887
Of which are abiraterone	*15 368*	*7 699*	*3 956*	*2 142*	*1 212*
Of which are subsequent therapies	*48 755*	*29 396*	*13 894*	*6 957*	*3 675*
Administration Costs	2 937	1 771	837	419	233
Hospital Costs	51 674	47 942	38 108	26 135	14 990
Adverse Event Costs	2 609	-	-	-	-
Skeletal Related Event Costs	3 737	2 244	1 116	592	332
Total Costs	**127 808**	**90 969**	**58 689**	**36 634**	**20 647**

Table 65. Costs per patient per year for patients treated with enzalutamide

	Year 1	Year 2	Year 3	Year 4	Year 5
Drug Costs	244 038	127 351	64 194	34 184	19 067
Of which are enzalutamide	*194 136*	*97 264*	*49 973*	*27 063*	*15 305*
Of which are subsequent therapies	*49 902*	*30 087*	*14 221*	*7 120*	*3 762*
Administration Costs	2 885	1 739	822	412	217
Hospital Costs	51 674	47 942	38 108	26 135	14 990
Adverse Event Costs	2 665	-	-	-	-
Skeletal Related Event Costs	3 737	2 244	1 116	592	332
Total Costs	**307 845**	**180 992**	**105 051**	**61 728**	**34 820**

9.3 Costs of diagnostic testing

Testing for BRCA and HRR mutations in metastatic prostate cancer is recommended but not fully implemented in Denmark. Currently, only olaparib monotherapy is recommended for patients with BRCA mutations in Denmark. Therefore patients must have been tested to receive this treatment, though a number of patients are routinely tested for genetic mutations upon diagnosis of mCRPC. As a nationwide testing scheme is starting to be implemented, the costs of mutation testing as standard practice upon diagnosis of mCRPC as opposed to on-demand testing (i.e., the number needed to test to identify a single patient eligible for olaparib) should be estimated. However, as not all patients are tested for mutations at first line the total costs of mutation testing were derived based on the number of tests at first line plus the number of patients with unknown BRCA status still requiring BRCA testing at subsequent lines to determine eligibility for olaparib monotherapy.

With regards to the number of tests at first line, this is assumed to follow the trajectory reported in Table 57 above, with 10% of all first line mCRPC patients being tested in 2024 and increasing to 25% by 2028. If olaparib in combination with abiraterone is recommended for a biomarker unselected population it is assumed that there will be no differences in testing rates and the costs of first line testing. These are reported in Table 66. However, differences in costs may exist with respect to testing at subsequent treatment lines. As reported in section 8.6.2, olaparib monotherapy is unlikely to be a subsequent therapy after olaparib + abiraterone at first line but may be used after abiraterone and/or enzalutamide.

Of patients who are tested, 10.7% are assumed to be positive for BRCA mutations (based on the prevalence in the PROpel and PROfound studies),[24,25] and therefore between ** and ** patients are assumed to be identified as having BRCA mutations at first line. Based on the modelled initiation of subsequent treatments and the proportion of patients starting subsequent therapy with olaparib (see section 8.6.2 for details) and the market shares for different first line treatments (see section 9.1) it is possible to estimate the number of patients who will receive second line olaparib in the future (shown in Table 66). As an example, if olaparib + abiraterone is recommended ** patients who start first line mCRPC treatment in 2024 will receive olaparib monotherapy as a subsequent treatment. Given that ** patients have their BRCA status known at first line, ** patients would need to have their BRCA status determined at second line. Therefore it can be assumed that ***% (****) of subsequent BRCA testing costs as estimated in the cost-effectiveness model (103 012 DKK assuming a testing cost of 11 000 DKK and a number needed to test of 9.4) could be applied at second line.

Table 66. Estimating population-level costs of genetic mutation testing

Year	2024	2025	2026	2027	2028
Patients with mCRPC receiving active treatment but for whom chemotherapy is not clinically indicated	***	***	***	***	***
Patients being tested for genetic mutations at first line	** (**%)	** (**%)	** (**%)	** (**%)	** (**%)
Cost of mutation testing at first line (DKK)	*******	*******	*******	*******	*******
Patients testing positive for BRCA mutations at first line	**	**	**	**	**
Number of patients estimated to start olaparib at second if olaparib in combination with abiraterone is recommended for patients with mCRPC	**	**	**	**	**
Number of patients estimated to start olaparib at second if olaparib in combination with abiraterone is NOT recommended for patients with mCRPC	**	**	**	**	**

For the subgroup analysis in patients with HRR mutations, if further PARP inhibitors and combinations are recommended for biomarker-selected population in mCRPC this may lead to changes in the use of diagnostic testing in clinical practice. As noted in Table 57 above, the proportion of first line mCRPC patients expected to be tested for genetic mutations as part of standard practice is expected to increase from the current trajectory of 10-25% of patients to up to 50-80% of patients. With a greater proportion of patients having their mutation status known at first line, fewer patients would require BRCA testing at subsequent lines.

9.4 Budget impact

9.4.1 Base case (biomarker unselected patients)

The overall budget impact estimate to the healthcare service if olaparib + abiraterone is introduced for mCRPC is presented in Table 67. The budget impact in the fifth year after introduction is estimated to be [redacted] DKK. The budget impact is driven by the additional costs of drug acquisition, though there are some modest cost savings in terms of drug administration, hospital care for routine monitoring, and skeletal-related events. If olaparib + abiraterone is recommended for a biomarker unselected population (i.e., to the product label) there is also the potential for cost savings with regards to diagnostic testing.

Table 67. Expected budget impact of recommending olaparib in combination with abiraterone for ITT mCRPC patient

	2024	2025	2026	2027	2028
Olaparib in combination with abiraterone is recommended for mCRPC patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	1 640 651	2 687 577	3 038 637	3 106 092	2 949 423
Of which: Hospital costs	28 124 871	52 634 546	69 682 868	79 996 040	83 360 895
Of which: Adverse event costs	2 131 748	2 248 956	2 245 560	2 141 109	1 768 742
Of which: Skeletal-related event costs	1 728 677	2 733 633	3 152 448	3 307 329	3 208 726
Of which: Diagnostic testing costs	1 220 585	1 556 109	1 475 833	1 432 617	1 125 263
Minus: Olaparib in combination with abiraterone is NOT recommended for mCRPC patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	1 764 758	2 906 514	3 287 013	3 342 850	3 134 192
Of which: Hospital costs	28 399 105	53 888 262	71 935 445	82 601 008	85 359 170
Of which: Adverse event costs	1 469 660	1 368 304	1 266 948	1 165 593	962 881
Of which: Skeletal-related event costs	1 824 770	2 855 391	3 250 328	3 354 335	3 180 128
Of which: Diagnostic testing costs	1 680 047	2 496 088	2 745 461	2 747 576	2 344 858
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.4.2 Scenario analysis (HRR mutated patients)

If olaparib + abiraterone is recommended for mCRPC patients with HRR mutations, the overall budget impact in the fifth year after introduction is estimated to be [redacted] DKK (Table 68). Similar to the base case, the additional expenditure

is mostly attributable to drug acquisition, and the cost savings with regards to drug administration, hospital care for routine monitoring, and skeletal-related events are also presented. In addition, the recommendation for the HRR mutated population would result in approximately 2.5 million DKK per year for increase diagnostic testing.

Table 68. Expected budget impact of recommending the pharmaceutical for patients with HRR mutations

	2024	2025	2026	2027	2028
Olaparib in combination with abiraterone is recommended for mCRPC patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	145 019	265 949	360 412	445 163	473 202
Of which: Hospital costs	2 704 235	5 706 973	8 695 503	11 550 363	13 305 156
Of which: Adverse event costs	239 520	325 588	407 493	462 043	409 439
Of which: Skeletal-related event costs	169 823	306 784	414 163	514 341	552 751
Of which: Diagnostic testing costs	3 090 313	3 452 625	3 729 688	3 921 500	3 239 500
Minus: Olaparib in combination with abiraterone is NOT recommended for mCRPC patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	157 103	286 565	385 309	467 642	483 525
Of which: Hospital costs	2 770 235	5 952 978	9 146 664	12 070 638	13 594 166
Of which: Adverse event costs	140 224	171 233	200 711	227 580	201 670
Of which: Skeletal-related event costs	200 353	364 972	493 535	602 192	625 604
Of which: Diagnostic testing costs	683 685	968 577	1 194 131	1 373 082	1 171 341
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10. Discussion on the submitted documentation

mCPRC is an incurable disease where there still exists a large unmet need for effective treatments for all patients. Survival remains poor with currently available treatments (docetaxel or NHAs). For those patients who are candidates for active therapy, median survival is approximately 2.5 years and the 5-year survival is approximately 20%.[10] Existing treatments are consistently being moved earlier in the disease path, leading to very limited treatment options when the patients reach mCPRC stage.

The PROpel clinical trial is a phase III randomised, double-blind, multicentre study evaluating the combined effect of olaparib and abiraterone versus placebo and abiraterone as first-line therapy for patients with mCRPC. PROpel demonstrated a statistically and clinically significant improvement in rPFS for olaparib + abiraterone compared to placebo + abiraterone (HR 0.68; 95% CI 0.57, 0.81), with an 8.5-months (~50%) improvement in median rPFS. PROpel is the first study to show a PFS longer than 2 years in the mCRPC setting. A numerical improvement in median OS was also observed for olaparib + abiraterone (42.1 months) over placebo + abiraterone (34.7 months), showing a 7.4 month improvement (HR 0.81; 95% CI 0.67, 1.00), suggesting that the OS gain is approaching the PFS gain. The study results show clinically significant improvements when adding olaparib to abiraterone across subgroups and regardless of biomarker status (HRRm/non-HRRm), symptom burden, and prior exposure to chemotherapy. The addition of olaparib to abiraterone results in limited additional risk of adverse events (all grades: 97.7% vs. 96.0%; grade ≥3: 55.8% vs. 43.2%). The main excess grade ≥3 event (anaemia and pulmonary embolism) were managed with olaparib dose reductions or temporary interruptions (no discontinuations) and no adverse events of anaemia with fatal outcome were reported. EMA have evaluated that olaparib in combination with abiraterone has a positive benefit/risk balance.

The evidence from PROpel is applicable to Danish mCRPC patients considered candidates for first line therapy with NHAs today, as olaparib + abiraterone is restricted to patients in whom chemotherapy is not indicated. In current clinical practice, many mCRPC patients who have already received docetaxel-based therapy in prior lines will receive a new hormonal agent for first line mCRPC, as treatment guidelines recommend the introduction of a new mechanism of action. This makes the comparator from PROpel directly relevant for Danish clinical practice as this is expected to be the most widely used NHA in first line mCRPC given the availability of generic alternative. This permits PROpel study data to be used directly in the relative efficacy and cost-effectiveness assessments. Approximately one-quarter of patients in PROpel were previously exposed to docetaxel, whilst most patients eligible for abiraterone ± olaparib in Denmark will be docetaxel-exposed. However, this discrepancy does not introduce any negative uncertainties about the transferability of PROpel results to Danish practice as subgroup analyses show that both taxane-exposed and naïve patients have clinically significant benefits with olaparib + abiraterone. According to Nordic clinicians AstraZeneca have consulted, baseline patient characteristics from the PROpel trial are representative for Nordic clinical practice. Notably, age, site of metastases, and cancer-related pain are comparable to the Nordic population given the range of presenting symptoms and that combination therapy is likely to be used in patients with the greatest marginal benefit (e.g., slightly younger patients).

The economic model was developed in line with the recommendations from Medincinrådet. For the labelled (ITT) population, a gain of 1.37 QALYs and an incremental cost (at AIP) of 1 021 255 DKK is estimated for olaparib + abiraterone compared to abiraterone in the base case, resulting in an ICER of 745 651 DKK/QALY. These results were largely robust across sensitivity and scenario analyses, though there is some uncertainty on the magnitude of overall survival benefit whilst data collection still continues, as well as the starting utility weight of these patients where minimal symptoms are reported but quality of life remains high despite metastatic disease. However, the additional benefits and costs of adding olaparib to abiraterone is plausible given the observed efficacy from the trial. This may be driven by both the addition of olaparib, but also that olaparib-treated patients are able to stay on abiraterone treatment for 30% longer which has further added benefits. There is also empirical evidence showing that the hazards of progression and death in mCRPC

decrease with time (i.e., the longer you are progression-free/alive, the longer you are expected to continue to remain progression-free/alive), and therefore longer observed survival is likely to relate to longer unobserved survival beyond the trial horizon.

It is estimated that up to [redacted] patients per year will initiate treatment with olaparib + abiraterone. The estimates of patient numbers reflect the expected decline in patients eligibility for NHA-based treatments for first line mCRPC due to increased used of the therapies in earlier prostate cancer settings. The budget impact analysis estimates that the introduction of olaparib combination therapy in first mCRPC will result in additional expenditure of [redacted] DKK within five years of a positive recommendation. The increased budget impact is mainly driven by the increased costs of drugs.

There remains a large unmet need for effective therapies with new modes of action and acceptable safety profiles for all patients with mCRPC. mCRPC is an aggressive cancer which reduces patients' survival and leads to declining HRQoL. PROpel is the first randomised phase III clinical trial to demonstrate significant and clinically meaningful efficacy of the combination of olaparib plus abiraterone in the first line treatment of mCPRC, irrespective of various patient characteristics and independent of tumour biomarker status, offering substantial benefits for patients who would be treated with NHAs today. The base case results from the health economic analysis demonstrate the value of olaparib + abiraterone in this indication compared to today's standard of care, and that there are economically justifiable benefits of add-on olaparib regardless of biomarker status. Further, the study showed the longest progression-free survival of any approved treatment for mCRPC to date, as well as showing a trend towards improved survival. The prolongation of progression-free survival, contributing to preserving HRQoL, and extending survival in mCPRC show that olaparib has the potential to fill an important unmet need.

11. List of experts

[redacted]

12. References

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

Objective of the literature search: The SLR aims to understand efficacy of the intervention and comparator among patients relevant to this application.

Databases: The following electronic databases were searched via the OVID platform from inception, on the 8th April 2021 and updated on 7th June 2022.

Table 69. Bibliographic databases included in the literature search

Bibliographic databases
Embase, 1974 to present
MEDLINE, 1946 to present, including: **MEDLINE Epub Ahead of Print** **MEDLINE In-Process & Other Non-Indexed Citations** **MEDLINE Daily**
EBM Reviews, incorporating: • **The HTA database** • **The National Health Service Economic Evaluation Database** • **Cochrane Central register of Controlled Trials (CENTRAL)** • **Database of Abstracts of Reviews of Effects** • **The Cochrane Database of Systematic Reviews**

Table 70. Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov		8th April 2021 and updated on 7th June 2022
WHO ICTRP registry	https://apps.who.int/trialsearch/		8th April 2021 and updated on 7th June 2022
EU Clinical Trials Register	EU Clinical Trials Register		8th April 2021 and updated on 7th June 2022

Abbreviations:

The following conference abstracts and proceedings were searched for the last 3 years and additionally it acted as supplementary sources (* indicates conferences that were included in the databases search):

Table 71. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
Advanced Prostate Cancer Consensus Conference	state website	Manual search	
American Society of Clinical Oncology (ASCO)*		Search by individual words in the congress material	
ASCO Genitourinary Cancers Symposium European Society for Medical Oncology (ESMO)*			
American Urological Association*			
European Association of Urology			
ESMO*			
International Society for Pharmacoeconomics and Outcomes Research (ISPOR): European and International Congresses*			
Society for Medical Decision Making			
Society of Urologic Oncology			

Search strategy

Table 72. Embase (Ovid): 1974 to 7 April 2021

#	Searches	Results
1	castration resistant prostate cancer/	14827
2	(CRPC or mCRPC or HRPC or AIPC).ti,ab.	13190

3	1 or 2	19441
4	exp prostate cancer/	228977
5	exp prostate tumor/	254921
6	prostatic intraepithelial neoplasia/	2928
7	(prostat$ adj4 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial or adeno$)).ti,ab,ot.	230592
8	or/4-7	284732
9	(castrat$ resist$ or hormone refrac$ or hormone resist$ or androgen independ$ or androgen insensit$ or androgen in-sensit$ or androgen resist$).ti,ab,ot.	30048
10	8 and 9	25801
11	3 or 10	29656
12	enzalutamide/	6713
13	(enzalutamide or xtandi$).ti,ab,ot,rn.	6971
14	abiraterone/	4936
15	(abiraterone or zytiga$ or cb 7598 or cb7598).ti,ab,ot,rn.	6987
16	sipuleucel T/	1942
17	(sipuleucel$ or provenge$ or apc 8015 or apc8015).ti,ab,ot,rn.	2250
18	docetaxel/	61777
19	(Docetaxel or daxotel$ or dexotel$ or docefrez$ or taxespira$ or taxoter$).ti,ab,ot,rn.	63857
20	cabazitaxel/	3105
21	(cabazitaxel or jevtana$).ti,ab,ot,rn.	3273
22	(radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,ot,rn.	1850
23	flutamide/	8440
24	(flutamid$ or apimid$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or flutamex$ or flutamin$ or flutan$ or	9408

	flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or niphtholid$ or novoflutamide$ or odyne$ or prostamid$ or prostica$ or prostogenat$ or sebatrol$ or tafenil$ or testac$).ti,ab,ot,rn.	
25	bicalutamide/	6573
26	(bicalutamid$ or casodex$ or cosudex$ or calutide$ or kalumid$ or lutamidal$ or raffolutil$).ti,ab,ot,rn.	6778
27	nilutamide/	1447
28	(nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$).ti,ab,ot,rn.	1480
29	apalutamide/	737
30	(apalutamid$ or erleada$).ti,ab,ot,rn.	764
31	darolutamide/	302
32	(darolutamid$ or nubeqa$).ti,ab,ot,rn.	312
33	olaparib/	5866
34	(Olaparib or lynparza$).ti,ab,ot,rn.	6031
35	niraparib/	1312
36	(Niraparib or zejula$).ti,ab,ot,rn.	1337
37	rucaparib/	1429
38	(Rucaparib or rubraca$).ti,ab,ot,rn.	1436
39	veliparib/	1958
40	(veliparib or abt888 or abt 888).ti,ab,ot,rn.	2136
41	talazoparib/	1039
42	(talazoparib or talzenna$).ti,ab,ot,rn.	1051
43	pamiparib/	64
44	(pamiparib or bgb 290 or bgb290).ti,ab,ot,rn.	76
45	carboplatin/	72726

46	(Carboplat$ or blastocarb or carbosin or carbotec or carplan or cbdca or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or oncocarb or paraplatin$).ti,ab,ot,rn.	75556
47	mitroxantrone/	23981
48	(mitoxantrone or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthron$ or mitoxgen or neotalem or norexan or novanthron$ or novantron$ or oncotron or onkotrone or ralenova).ti,ab,ot,rn.	24648
49	Cisplatin/	191726
50	(Cisplatin$ or abiplatin or biocisplatinum or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or cis diamine$ or cis diammine$ or cis dichloridiam$ or cis dichloroadiam$ or cis cis dichlorodiam$ or cis platinous diamino dichloride or cis platinum or cisplatyl or citoplatino or diamine dichloroplatinum or diaminodichloroplatinum or diamminodichloroplatinum or dichlorodiamine platinum or dichlorodiammineplatinum or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platamine or platinex or platinil or platinol or platinoxan or (platinum adj2 diamin$) or platiran or platisil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,ot,rn.	200959
51	or/12-50	319425
52	random$.ti,ab.	1661764
53	factorial$.ti,ab.	40997
54	(crossover$ or cross over$).ti,ab.	112538
55	((doubl$ or singl$) adj blind$).ti,ab.	245220
56	(assign$ or allocat$ or volunteer$ or placebo$).ti,ab.	1103199
57	crossover procedure/	66869
58	double blind procedure/	183947
59	single blind procedure/	42653
60	randomized controlled trial/	656955
61	or/52-60	2496487
62	11 and 51 and 61	2784

Table 73. Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R): 1946 to 7 April 2021

#	Searches	Results
1	Prostatic Neoplasms, Castration-Resistant/	4313
2	(CRPC or mCRPC or HRPC or AIPC).ti,ab.	5822
3	1 or 2	7776
4	Prostatic Neoplasms/	128442
5	Prostatic Intraepithelial Neoplasia/	1373
6	(prostat$ adj4 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial or adeno$)).ti,ab,ot.	155721
7	or/4-6	177567
8	(castrat$ resist$ or hormone refrac$ or hormone resist$ or androgen independ$ or androgen insensit$ or androgen in-sensit$ or androgen resist$).ti,ab,ot.	18540
9	7 and 8	15344
10	3 or 9	16336
11	(enzalutamide or xtandi$).ti,ab,ot,rn.	1975
12	Abiraterone Acetate/	493
13	(abiraterone or zytiga$ or cb 7598 or cb7598).ti,ab,ot,rn.	2352
14	(sipuleucel$ or provenge$ or apc 8015 or apc8015).ti,ab,ot,rn.	728
15	Docetaxel/	10952
16	(Docetaxel or daxotel$ or dexotel$ or docefrez$ or taxespira$ or taxoter$).ti,ab,ot,rn.	17544
17	(cabazitaxel or jevtana$).ti,ab,ot,rn.	991
18	(radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,ot,rn.	789
19	Flutamide/	2663
20	(flutamid$ or apimid$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or flutamex$ or flutamin$ or flutan$ or flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or	4354

	niphtholid$ or novoflutamide$ or odyne$ or prostamid$ or prostica$ or prostogenat$ or sebatrol$ or tafenil$ or testac$).ti,ab,ot,rn.	
21	(bicalutamid$ or casodex$ or cosudex$ or calutide$ or kalumid$ or lutamidal$ or raffolutil$).ti,ab,ot,rn.	1894
22	(nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$).ti,ab,ot,rn.	323
23	(apalutamid$ or erleada$).ti,ab,ot,rn.	232
24	(darolutamid$ or nubeqa$).ti,ab,ot,rn.	108
25	(Olaparib or lynparza$).ti,ab,ot,rn.	1657
26	(Niraparib or zejula$).ti,ab,ot,rn.	264
27	(Rucaparib or rubraca$).ti,ab,ot,rn.	312
28	(veliparib or abt888 or abt 888).ti,ab,ot,rn.	440
29	(talazoparib or talzenna$).ti,ab,ot,rn.	236
30	(pamiparib or bgb 290 or bgb290).ti,ab,ot,rn.	5
31	Carboplatin/	11943
32	(Carboplat$ or blastocarb or carbosin or carbotec or carplan or cbdca or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or oncocarb or paraplatin$).ti,ab,ot,rn.	18501
33	Mitoxantrone/	4291
34	(mitoxantrone or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthron$ or mitoxgen or neotalem or norexan or novanthron$ or novantron$ or oncotron or onkotrone or ralenova).ti,ab,ot,rn.	6434
35	Cisplatin/	53353
36	(Cisplatin$ or abiplatin or biocisplatinum or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or cis diamine$ or cis diammine$ or cis dichloridiam$ or cis dichloroadiam$ or cis cis dichlorodiam$ or cis platinous diamino dichloride or cis platinum or cisplatyl or citoplatino or diamine dichloroplatinum or diaminodichloroplatinum or diamminodichloroplatinum or dichlorodiamine platinum or dichlorodiammineplatinum or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platamine or platinex or platinil or platinol or platinoxan or (platinum adj2 diamin$) or platiran or platisil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,ot,rn.	80466

37	or/11-36	122104
38	randomized controlled trial.pt. or "randomized controlled trials as topic"/	662872
39	controlled clinical trial.pt.	94118
40	random$.ti,ot.	246646
41	placebo.ab.	216842
42	clinical trials as topic.sh.	195389
43	randomly.ab.	354777
44	trial.ti.	237653
45	or/38-44	1299116
46	10 and 37 and 45	1208

Table 74. EBM Reviews - ACP Journal Club 1991 to March 2021, EBM Reviews - Cochrane Central Register of Controlled Trials March 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to 8 April 2021, EBM Reviews - Cochrane Clinical Answers March 2021

#	Searches	Results
1	Prostatic Neoplasms, Castration-Resistant/	270
2	(CRPC or mCRPC or HRPC or AIPC).ti,ab.	1744
3	1 or 2	1865
4	Prostatic Neoplasms/	5831
5	Prostatic Intraepithelial Neoplasia/	48
6	(prostat$ adj4 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial or adeno$)).ti,ab,ot.	15487
7	or/4-6	16037
8	(castrat$ resist$ or hormone refrac$ or hormone resist$ or androgen independ$ or androgen insensit$ or androgen in-sensit$ or androgen resist$).ti,ab,ot.	3044
9	7 and 8	2932

10	3 or 9	3090
11	(enzalutamide or xtandi$).ti,ab,ot.	752
12	Abiraterone Acetate/	162
13	(abiraterone or zytiga$ or cb 7598 or cb7598).ti,ab,ot.	867
14	(sipuleucel$ or provenge$ or apc 8015 or apc8015).ti,ab,ot.	163
15	Docetaxel/	2139
16	(Docetaxel or daxotel$ or dexotel$ or docefrez$ or taxespira$ or taxoter$).ti,ab,ot.	7404
17	(cabazitaxel or jevtana$).ti,ab,ot.	298
18	(radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,ot.	265
19	Flutamide/	343
20	(flutamid$ or apimid$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or flutamex$ or flutamin$ or flutan$ or flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or niphtholid$ or novoflutamide$ or odyne$ or prostamid$ or prostica$ or prostogenat$ or sebatrol$ or tafenil$ or testac$).ti,ab,ot.	546
21	(bicalutamid$ or casodex$ or cosudex$ or calutide$ or kalumid$ or lutamidal$ or raffolutil$).ti,ab,ot.	511
22	(nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$).ti,ab,ot.	73
23	(apalutamid$ or erleada$).ti,ab,ot.	145
24	(darolutamid$ or nubeqa$).ti,ab,ot.	64
25	(Olaparib or lynparza$).ti,ab,ot.	554
26	(Niraparib or zejula$).ti,ab,ot.	152
27	(Rucaparib or rubraca$).ti,ab,ot.	111
28	(veliparib or abt888 or abt 888).ti,ab,ot.	216
29	(talazoparib or talzenna$).ti,ab,ot.	85
30	(pamiparib or bgb 290 or bgb290).ti,ab,ot.	12

31	Carboplatin/	2441
32	(Carboplat$ or blastocarb or carbosin or carbotec or carplan or cbdca or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or oncocarb or paraplatin$).ti,ab,ot.	6980
33	Mitoxantrone/	529
34	(mitoxantrone or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthron$ or mitoxgen or neotalem or norexan or novanthron$ or novantron$ or oncotron or onkotrone or ralenova).ti,ab,ot.	1286
35	Cisplatin/	5128
36	(Cisplatin$ or abiplatin or biocisplatinum or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or cis diamine$ or cis diammine$ or cis dichloridiam$ or cis dichloroadiam$ or cis cis dichlorodiam$ or cis platinous diamino dichloride or cis platinum or cisplatyl or citoplatino or diamine dichloroplatinum or diaminodichloroplatinum or diamminodichloroplatinum or dichlorodiamine platinum or dichlorodiammineplatinum or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platamine or platinex or platinil or platinol or platinoxan or (platinum adj2 diamin$) or platiran or platisil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,ot.	14154
37	or/11-34	18600
38	10 and 37	2125

Below are the update searches.

Table 75. Embase (Ovid): 1974 to 6 June 2022

#	Searches	Results
1	castration resistant prostate cancer/	15776
2	(CRPC or mCRPC or HRPC or AIPC).ti,ab.	14585
3	1 or 2	21379
4	exp prostate cancer/	244789
5	exp prostate tumor/	272351
6	prostatic intraepithelial neoplasia/	2987
7	(prostat$ adj4 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial or adeno$)).ti,ab,ot.	245258
8	or/4-7	304017

9	(castrat$ resist$ or hormone refrac$ or hormone resist$ or androgen independ$ or androgen insensit$ or androgen in-sensit$ or androgen resist$).ti,ab,ot.	32239
10	8 and 9	27856
11	3 or 10	32088
12	enzalutamide/	8007
13	(enzalutamide or xtandi$).ti,ab,ot,rn.	8344
14	abiraterone/	5735
15	(abiraterone or zytiga$ or cb 7598 or cb7598).ti,ab,ot,rn.	7980
16	sipuleucel T/	2081
17	(sipuleucel$ or provenge$ or apc 8015 or apc8015).ti,ab,ot,rn.	2400
18	docetaxel/	66732
19	(Docetaxel or daxotel$ or dexotel$ or docefrez$ or taxespira$ or taxoter$).ti,ab,ot,rn.	68877
20	cabazitaxel/	3534
21	(cabazitaxel or jevtana$).ti,ab,ot,rn.	3698
22	(radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,ot,rn.	1975
23	flutamide/	8655
24	(flutamid$ or apimid$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or flutamex$ or flutamin$ or flutan$ or flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or niphtholid$ or novoflutamide$ or odyne$ or prostamid$ or prostica$ or prostogenat$ or sebatrol$ or tafenil$ or testac$).ti,ab,ot,rn.	9673
25	bicalutamide/	7070
26	(bicalutamid$ or casodex$ or cosudex$ or calutide$ or kalumid$ or lutamidal$ or raffolutil$).ti,ab,ot,rn.	7297
27	nilutamide/	1486
28	(nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$).ti,ab,ot,rn.	1519
29	apalutamide/	1058
30	(apalutamid$ or erleada$).ti,ab,ot,rn.	1110
31	darolutamide/	504
32	(darolutamid$ or nubeqa$).ti,ab,ot,rn.	524
33	olaparib/	7551
34	(Olaparib or lynparza$).ti,ab,ot,rn.	7776
35	niraparib/	1859
36	(Niraparib or zejula$).ti,ab,ot,rn.	1896
37	rucaparib/	1920

38	(Rucaparib or rubraca$).ti,ab,ot,rn.	1938
39	veliparib/	2265
40	(veliparib or abt888 or abt 888).ti,ab,ot,rn.	2449
41	talazoparib/	1479
42	(talazoparib or talzenna$).ti,ab,ot,rn.	1496
43	pamiparib/	97
44	(pamiparib or bgb 290 or bgb290).ti,ab,ot,rn.	108
45	carboplatin/	78885
46	(Carboplat$ or blastocarb or carbosin or carbotec or carplan or cbdca or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or oncocarb or paraplatin$).ti,ab,ot,rn.	81829
47	mitroxantrone/	24793
48	(mitoxantrone or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthron$ or mitoxgen or neotalem or norexan or novanthron$ or novantron$ or oncotron or onkotrone or ralenova).ti,ab,ot,rn.	25504
49	Cisplatin/	203382
50	(Cisplatin$ or abiplatin or biocisplatinum or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or cis diamine$ or cis diammine$ or cis dichloridiam$ or cis dichloroadiam$ or cis cis dichlorodiam$ or cis platinous diamino dichloride or cis platinum or cisplatyl or citoplatino or diamine dichloroplatinum or diaminodichloroplatinum or diamminodichloroplatinum or dichlorodiamine platinum or dichlorodiammineplatinum or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platamine or platinex or platinil or platinol or platinoxan or (platinum adj2 diamin$) or platiran or platisil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,ot,rn.	213213
51	or/12-50	341831
52	random$.ti,ab.	1795359
53	factorial$.ti,ab.	43960
54	(crossover$ or cross over$).ti,ab.	118292
55	((doubl$ or singl$) adj blind$).ti,ab.	257490
56	(assign$ or allocat$ or volunteer$ or placebo$).ti,ab.	1172862
57	crossover procedure/	70524
58	double blind procedure/	195478
59	single blind procedure/	46318
60	randomized controlled trial/	711212
61	or/52-60	2676690
62	11 and 51 and 61	3069
63	limit 62 to dc=20210407-20220607	332

Table 76. Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to 6 June 2022

#	Searches	Results
1	Prostatic Neoplasms, Castration-Resistant/	5579
2	(CRPC or mCRPC or HRPC or AIPC).ti,ab.	6726
3	1 or 2	9151
4	Prostatic Neoplasms/	137935
5	Prostatic Intraepithelial Neoplasia/	1399
6	(prostat$ adj4 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial or adeno$)).ti,ab,ot.	166714
7	or/4-6	189420
8	(castrat$ resist$ or hormone refrac$ or hormone resist$ or androgen independ$ or androgen insensit$ or androgen in-sensit$ or androgen resist$).ti,ab,ot.	20160
9	7 and 8	16845
10	3 or 9	18020
11	(enzalutamide or xtandi$).ti,ab,ot,rn.	2607
12	Abiraterone Acetate/	607
13	(abiraterone or zytiga$ or cb 7598 or cb7598).ti,ab,ot,rn.	2714
14	(sipuleucel$ or provenge$ or apc 8015 or apc8015).ti,ab,ot,rn.	759
15	Docetaxel/	11749
16	(Docetaxel or daxotel$ or dexotel$ or docefrez$ or taxespira$ or taxoter$).ti,ab,ot,rn.	18757
17	(cabazitaxel or jevtana$).ti,ab,ot,rn.	1098
18	(radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,ot,rn.	890
19	Flutamide/	2699
20	(flutamid$ or apimid$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or flutamex$ or flutamin$ or flutan$ or flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or niphtholid$ or novoflutamide$ or odyne$ or prostamid$ or prostica$ or prostogenat$ or sebatrol$ or tafenil$ or testac$).ti,ab,ot,rn.	4448
21	(bicalutamid$ or casodex$ or cosudex$ or calutide$ or kalumid$ or lutamidal$ or raffolutil$).ti,ab,ot,rn.	2019
22	(nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$).ti,ab,ot,rn.	331
23	(apalutamid$ or erleada$).ti,ab,ot,rn.	348
24	(darolutamid$ or nubeqa$).ti,ab,ot,rn.	173
25	(Olaparib or lynparza$).ti,ab,ot,rn.	2173
26	(Niraparib or zejula$).ti,ab,ot,rn.	374

27	(Rucaparib or rubraca$).ti,ab,ot,rn.	414
28	(veliparib or abt888 or abt 888).ti,ab,ot,rn.	504
29	(talazoparib or talzenna$).ti,ab,ot,rn.	321
30	(pamiparib or bgb 290 or bgb290).ti,ab,ot,rn.	13
31	Carboplatin/	12626
32	(Carboplat$ or blastocarb or carbosin or carbotec or carplan or cbdca or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or oncocarb or paraplatin$).ti,ab,ot,rn.	19609
33	Mitoxantrone/	4370
34	(mitoxantrone or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthron$ or mitoxgen or neotalem or norexan or novanthron$ or novantron$ or oncotron or onkotrone or ralenova).ti,ab,ot,rn.	6598
35	Cisplatin/	56455
36	(Cisplatin$ or abiplatin or biocisplatinum or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or cis diamine$ or cis diammine$ or cis dichloridiam$ or cis dichloroadiam$ or cis cis dichlorodiam$ or cis platinous diamino dichloride or cis platinum or cisplatyl or citoplatino or diamine dichloroplatinum or diaminodichloroplatinum or diamminodichloroplatinum or dichlorodiamine platinum or dichlorodiammineplatinum or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platamine or platinex or platinil or platinol or platinoxan or (platinum adj2 diamin$) or platiran or platisil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,ot,rn.	85033
37	or/11-36	130087
38	randomized controlled trial.pt. or "randomized controlled trials as topic"/	720138
39	controlled clinical trial.pt.	94896
40	random$.ti,ot.	275917
41	placebo.ab.	228865
42	clinical trials as topic.sh.	200049
43	randomly.ab.	383996
44	trial.ti.	263868
45	or/38-44	1383662
46	10 and 37 and 45	1358
47	limit 46 to dt=20210407-20220607	115

Table 77. EBM Reviews (Ovid): ACP Journal Club 1991 to May 2022, Cochrane Central Register of Controlled Trials May 2022, Cochrane Database of Systematic Reviews 2005 to 1 June 2022, Cochrane Clinical Answers May 2022

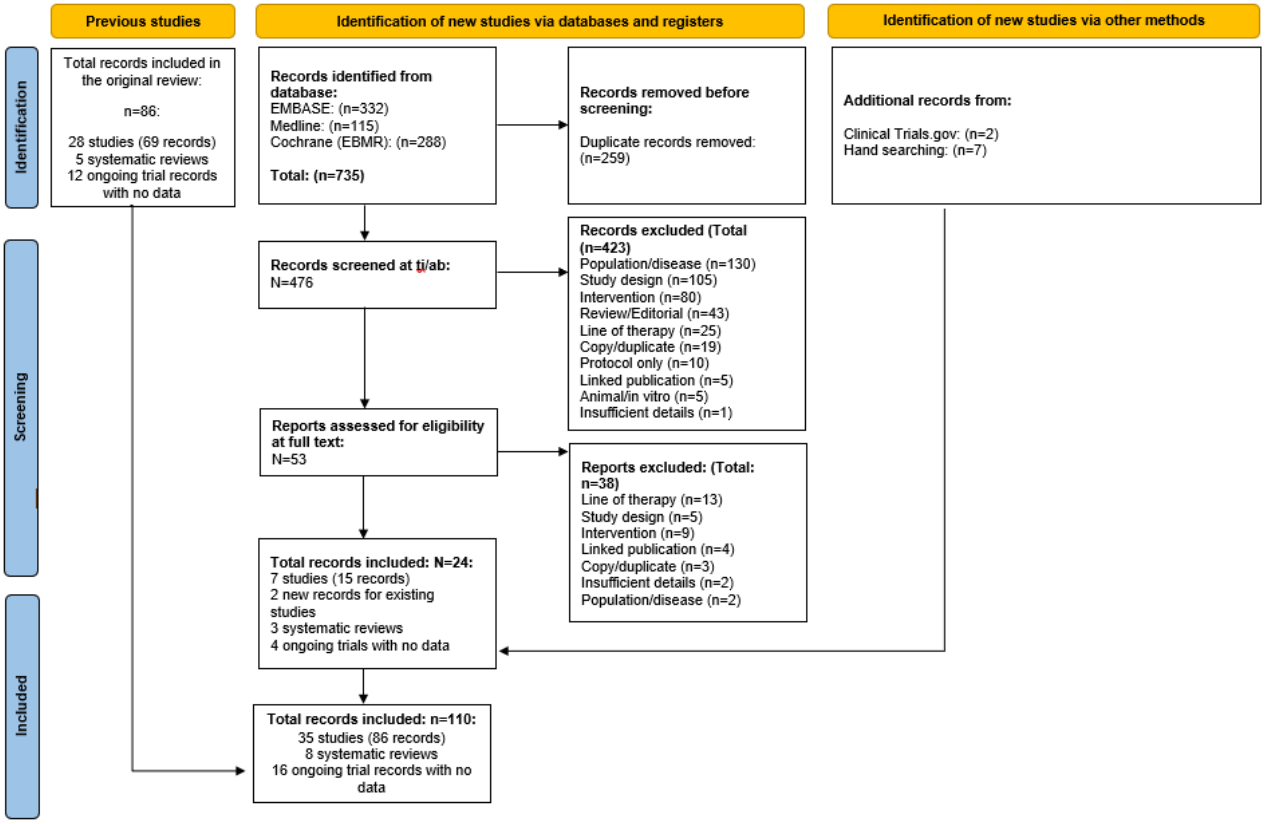
#	Searches	Results
1	Prostatic Neoplasms, Castration-Resistant/	342

2	(CRPC or mCRPC or HRPC or AIPC).ti,ab.	1928
3	1 or 2	2073
4	Prostatic Neoplasms/	5866
5	Prostatic Intraepithelial Neoplasia/	47
6	(prostat$ adj4 (cancer$ or carcinoma$ or malignan$ or tumo?r$ or neoplas$ or intraepithelial or adeno$)).ti,ab,ot.	15578
7	or/4-6	16121
8	(castrat$ resist$ or hormone refrac$ or hormone resist$ or androgen independ$ or androgen insensit$ or androgen in-sensit$ or androgen resist$).ti,ab,ot.	3207
9	7 and 8	3111
10	3 or 9	3299
11	(enzalutamide or xtandi$).ti,ab,ot.	889
12	Abiraterone Acetate/	186
13	(abiraterone or zytiga$ or cb 7598 or cb7598).ti,ab,ot.	999
14	(sipuleucel$ or provenge$ or apc 8015 or apc8015).ti,ab,ot.	157
15	Docetaxel/	2294
16	(Docetaxel or daxotel$ or dexotel$ or docefrez$ or taxespira$ or taxoter$).ti,ab,ot.	7573
17	(cabazitaxel or jevtana$).ti,ab,ot.	319
18	(radium-223 or ra223 or ra-223 or xofigo$ or alpharadin$).ti,ab,ot.	283
19	Flutamide/	340
20	(flutamid$ or apimid$ or cytamid$ or drogenil$ or etaconil$ or euflex$ or eulexin$ or flucinom$ or fludinom$ or flugerel$ or fluken$ or flulem$ or flumid$ or flutamex$ or flutamin$ or flutan$ or flutaplex$ or flutax$ or flutexin$ or flutol$ or fluxus$ or fugerel$ or grisetin$ or niftolid$ or niphtholid$ or novoflutamide$ or odyne$ or prostamid$ or prostica$ or prostogenat$ or sebatrol$ or tafenil$ or testac$).ti,ab,ot.	555
21	(bicalutamid$ or casodex$ or cosudex$ or calutide$ or kalumid$ or lutamidal$ or raffolutil$).ti,ab,ot.	526
22	(nilutamid$ or anadron$ or anandron$ or canandron$ or nilandron$ or nitulamide$).ti,ab,ot.	73
23	(apalutamid$ or erleada$).ti,ab,ot.	207
24	(darolutamid$ or nubeqa$).ti,ab,ot.	114
25	(Olaparib or lynparza$).ti,ab,ot.	714
26	(Niraparib or zejula$).ti,ab,ot.	205
27	(Rucaparib or rubraca$).ti,ab,ot.	141
28	(veliparib or abt888 or abt 888).ti,ab,ot.	235
29	(talazoparib or talzenna$).ti,ab,ot.	107
30	(pamiparib or bgb 290 or bgb290).ti,ab,ot.	12

31	Carboplatin/	2591
32	(Carboplat$ or blastocarb or carbosin or carbotec or carplan or cbdca or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or oncocarb or paraplatin$).ti,ab,ot.	7350
33	Mitoxantrone/	520
34	(mitoxantrone or dhad or dhaq or domitrone or elsep or formyxan or genefadrone or misostol or mitoxanthron$ or mitoxgen or neotalem or norexan or novanthron$ or novantron$ or oncotron or onkotrone or ralenova).ti,ab,ot.	1289
35	Cisplatin/	5260
36	(Cisplatin$ or abiplatin or biocisplatinum or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or cis diamine$ or cis diammine$ or cis dichloridiam$ or cis dichloroadiam$ or cis cis dichlorodiam$ or cis platinous diamino dichloride or cis platinum or cisplatyl or citoplatino or diamine dichloroplatinum or diaminodichloroplatinum or diamminodichloroplatinum or dichlorodiamine platinum or dichlorodiammineplatinum or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platamine or platinex or platinil or platinol or platinoxan or (platinum adj2 diamin$) or platiran or platisil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,ot.	14668
37	or/11-36	31074
38	10 and 37	2351
39	limit 38 to yr="2021 -Current"	288

Systematic selection of studies

Figure 30. PRISMA diagram for the clinical SLR



Of the 110 of total included identified records only XX were used in the application due to relevance. All of the excluded studies can be found in the enclosed document named Excluded studies.

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
PROpel **Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer, Noel W. Clarke, M.B.B.S. et. al., NEJM Evid 2022**	Evaluate the efficacy and safety of the combination of olaparib and abiraterone vs. placebo and abiraterone in mCRPC who have received no prior cytotoxic chemotherapy	PROpel is a randomized, double-blind, placebo-controlled, multicentre phase III study	mCRPC. See table below for inclusion/exclusion criteria	Olaparib + abiraterone: 399 and Placebo + abiraterone: 397	See table below	See table below

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
NCT03732820	or NHAs at mCRPC stage					

Quality assessment

Strengths

Extensive literature searches were conducted to maximise the retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of conference abstracts and professional websites to identify unpublished studies.

Clear inclusion criteria were specified in the protocol for this review, the eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for exclusion for all the studies on assessment of the full publication. Independent screening methods and data checking methods were used to limit reviewer bias.

Limitations

Overall, the reporting of baseline characteristics was minimal in the included studies, and it was frequently difficult to ascertain whether the studies were first line treatments. Of the included studies, 19 (54%) studies had inclusion criteria that was unclear regarding previous treatments, line of therapy, or stage of disease. A conservative approach to the inclusion of studies was taken to ensure all relevant studies were included when the reporting of details around treatment line was vague.

None of the studies were judged to have low ROB. This was predominantly due to insufficient reporting details, which prevented clear judgements from being made. In addition, many included studies were conference abstracts or trial registries, reflecting that this is an evolving area of research, but one that currently provides limited data.

Unpublished data

This application mentions unpublished data in the form of data on file from AstraZeneca.

Appendix B Main characteristics of included studies

Trial name: PROpel	NCT number: NCT03732820
Objective	The purpose of this study is to evaluate the efficacy and safety (including evaluating side effects of the combination of olaparib and abiraterone versus placebo and abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) who have received no prior cytotoxic chemotherapy or new hormonal agents (NHAs) at metastatic castration-resistant prostate cancer (mCRPC) stage. PROpel is a randomized, double-blind, placebo-controlled, multicentre phase III study
Publications – title, author, journal, year	Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer, Noel W. Clarke, M.B.B.S. et. al., NEJM Evid 2022; 1 (9), DOI:https://doi.org/10.1056/EVIDoa2200043, Published June 3, 2022
Study type and design	Interventional Clinical Trial with 796 participants in total. Randomized, Parallel Assignment with Masking of Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Sample size (n)	Olaparib + abiraterone: 399 and Placebo + abiraterone: 397

Main inclusion and exclusion criteria

Inclusion criteria:

1. Histologically or cytologically confirmed prostate adenocarcinoma.
2. Metastatic status is defined as at least 1 documented metastatic lesion on either a bone scan or a computed tomography(CT)/ magnetic resonance imaging (MRI) scan.
3. First-line metastatic castration-resistant prostate cancer (mCRPC).
4. Ongoing androgen deprivation with gonadotropin-releasing hormone analog or bilateral orchiectomy, with serum testosterone <50 nanograms per decilitre (ng/dL) (<2.0 nanomoles per liter (nmol/L)) within 28 days before randomization. Patients receiving androgen deprivation therapy (ADT) at study entry should continue to do so throughout the study.
5. Candidate for abiraterone therapy with documented evidence of progressive disease.
6. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0-1, with no deterioration over the previous 2 weeks.

Exclusion criteria:

1. Patients with myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) or with features suggestive of myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML).
2. Clinically significant cardiovascular disease Association Class II-IV heart failure or cardiac ejection fraction measurement of <50% during screening as assessed by echocardiography or multi gated acquisition scan.
3. Uncontrolled hypertension (systolic blood pressure (BP) ≥160 millimeters of mercury (mmHg) or diastolic blood pressure (BP) ≥95 millimeters of mercury (mmHg)).
4. History of uncontrolled pituitary or adrenal dysfunction.
5. Active infection or other medical condition that would make prednisone/prednisolone use contraindicated.
6. Any chronic medical condition requiring a systemic dose of corticosteroid >10 milligrams (mg) of prednisone/prednisolone per day.
7. Persistent toxicities (Common Terminology Criteria for Adverse Events [CTCAEs] grade >2) caused by previous cancer therapy, excluding alopecia.
8. Patients with brain metastases. A scan to confirm the absence of brain metastases is not required.
9. Patients with spinal cord compression are excluded unless they are considered to have received definitive treatment for this and have evidence of clinically stable disease for 4 weeks.
10. Immunocompromised patients
11. Patients with known active hepatitis infection (ie, hepatitis B or C).
12. Any previous treatment with Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase (PARP) inhibitor, including olaparib.
13. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. Patients who receive palliative radiotherapy need to stop radiotherapy 1 week before randomisation.
14. Any previous exposure to a Cytochrome P450 (CYP) 17 (17α-hydroxylase/C17,20-lyase) inhibitor (eg, abiraterone, orteronel).
15. Concomitant use of known strong Cytochrome P450 (CYP) 3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate

Trial name: PROpel	NCT number: NCT03732820
	CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment is 2 weeks. 16. Concomitant use of known strong Cytochrome P450 (CYP) 3A inducers (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine or St John's wort) or moderate Cytochrome P450 (CYP) 3A inducers (eg, bosentan, efavirenz or modafinil). The required period prior to starting study treatment is 5 weeks for phenobarbital and enzalutamide and 3 weeks for other agents.
Intervention	Olaparib orally at a dose of 300 milligrams (mg) twice daily (bid). The initial dosage of 300 milligrams (mg) twice daily will be composed of 2 x 150 milligrams (mg) tablets per dose. The 100 milligrams (mg) and 150 milligrams (mg) tablets will be used to manage dose reductions during the study. Abiraterone acetate with prednisone or prednisolone will be sourced locally as commercially available materials. Subjects will be administered abiraterone orally at a dose of 1000 milligrams (mg) once daily, in combination with prednisone or prednisolone 5 milligrams (mg) administered orally twice daily. N= 399
Comparator(s)	Abiraterone acetate with prednisone or prednisolone will be sourced locally as commercially available materials. Subjects will be administered abiraterone orally at a dose of 1000 milligrams (mg) once daily, in combination with prednisone or prednisolone 5 milligrams (mg) administered orally twice daily. N=397
Follow-up time	• Actual Study Start Date: October 31, 2018 • Actual Primary Completion Date: July 30, 2021 (median 21 months follow-up) • Second Data Cut-Off: March 14, 2022 (median 27 months follow-up) • Third Data Cut-Off: October 12, 2022 (median 33 months follow-up)
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Primary Outcome Measures:

1. Radiological progression free survival (rPFS) [Time Frame: From date of randomization to study completion (up to 4 years)]
   Radiological progression free survival (rPFS) - defined as the time from randomisation to
   a) radiological progression, assessed by investigator per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (soft tissue) and Prostate Cancer Working Group-3 (PCWG-3) criteria (bone), or
   b) death from any cause, whichever occurs first

Secondary Outcome Measures:

1. Overall survival (OS)
   - Time from randomisation to death from any cause
2. Time to first subsequent anticancer therapy or death (TFST)
   - Time from randomisation to the earlier of the first subsequent anticancer therapy start date following study treatment discontinuation or death from any cause
3. Time to pain progression (TTPP)
   - Time to pain progression (TTPP) is defined as the time from randomisation to pain progression based on the Brief Pain Inventory-Short Form (BPI-SF) Item 3 "worst pain in 24 hours" and opiate analgesic use (analgesic quantification algorithm [AQA] score)
4. Time to opiate use
   - Time from randomisation to the first opiate use for cancer-related pain
5. Time to a Symptomatic Skeletal-Related Event (SSRE) [Time Frame: From date of randomization to study completion (up to 4 years)]
   - A Symptomatic Skeletal-Related Event (SSRE) is defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention.
6. Time to second progression or death (PFS2)
   - Time from randomisation to second progression or clinical progression or death
   - Brief Pain Inventory-Short Form (BPI-SF) To assess progression in pain severity domain, change in pain interference domain, and pain palliation
7. Functional Assessment of Cancer Therapy- Prostate Cancer (FACT-P)
   - Functional Assessment of Cancer Therapy- Prostate Cancer (FACT-P) total score, Functional Assessment of Cancer Therapy- General (FACT-G) total score, trial outcome index, functional well-being, physical well-being, prostate cancer subscale, and Functional Assessment of Cancer Therapy (FACT) Advanced Prostate Symptom Index-6 (FAPSI-6)
8. Homologous Recombination Repair (HRR) gene status
   - Tumour and blood samples for mutations in Breast Cancer 1 gene (BRCA1), or Breast Cancer 2 gene (BRCA2), Ataxia-telangiectasia mutated (ATM) and 12 other Homologous Recombination Repair (HRR) genes will be evaluated.

Trial name: PROpel	NCT number: NCT03732820
	The rest of the secondary outcome meseasurements is referered to clinicaltrial.gov
Method of analysis	The PROpel study used a multiplicity strategy for the statistical testing of primary and secondary endpoints. Once statistical significance was reached in the primary endpoint (rPFS), sequential testing of the secondary endpoints was performed using the two-sided 5% alpha-level recycled from the primary endpoint. All analyses were conducted in accordance with the corresponding final pooling strategy for stratification factors: if there were fewer than five rPFS events within each stratum, the levels of the strata were collapsed until the minimum five-event criterion was achieved for the primary rPFS endpoint. Unstratified analyses were conducted for secondary endpoints that still did not conform to the five-event rule per stratum and were supported by unstratified sensitivity analyses of the primary endpoint. Additional sensitivity analyses were conducted as required.
Subgroup analyses	**Pre-specified subgroups:** • Age: <65yrs or ≥65yrs • ECOG: 0 or 1 • Metastases: bone only, visceral, other • Docetaxel at mHSPC stage: yes or no • Baseline PSA: below median or above/equal to median **HRRm status (aggregated between tumour tissue and ctDNA):** • HRRm or non-HRRm HRRm status (ctDNA test): HRRm, non-HRRm, or unknown • HRRm status (tumour tissue): HRRm, non-HRRm, or unknown • Region: Asia, Europe, North and South America • Race: White, Black/African American, Asian, other
Other relevant information	No

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

PROpel study

Baseline characteristics were generally well balanced between treatment arms in PROpel, and were also in line with expectations based on real-world evidence.[10,20] Enrolled patients included those with bone and visceral metastases, asymptomatic and symptomatic disease, and patients were stratified by metastases (bone only vs visceral vs other) and docetaxel treatment at mHSPC stage (yes vs no). Approximately one-quarter of patients (23.0%; olaparib plus abiraterone, 25.8%; placebo plus abiraterone, 20.2%) had symptomatic disease at baseline, and therefore would not meet the criteria for abiraterone as per the EMA label.[5] The proportion of patients in PROpel with an HRRm was similar between treatment arms (olaparib plus abiraterone, 27.8%; placebo plus abiraterone, 29.0%), and was consistent with what has been observed in real-world data and previous datasets, including the PROfound study.[25]

A single patient (olaparib plus abiraterone arm) had received previous treatment with a second-generation new hormonal agent (enzalutamide).

Patient characteristics for PROpel.

Baseline characteristic	Olaparib plus abiraterone (n = 399)	Placebo plus abiraterone (n = 397)
Age		
Median (range) age, years	68.5 (43–91)	69.8 (46–88)
< 65 years, n (%)	130 (32.6)	97 (24.4)
≥ 65 years, n (%)	269 (67.4)	300 (75.6)
Median time from mCRPC to randomisation (range), months	2.1 (0–101)	2.3 (0–108)
Prior treatment with second-generation antiandrogen agents prior to mCRPC stage		
Yes (Enzalutamide)	1 (0.3)	0
ECOG performance status, n (%)		
0	286 (71.7)	272 (68.5)
1	112 (28.1)	124 (31.2)
Symptomatic,[a] n (%)	103 (25.8)	80 (20.2)
Baseline pain score (BPI-SF Item 3 worst pain score)		
0 (no pain)	133 (33.3)	137 (34.5)
> 0 - < 4 (mild pain)	151 (37.8)	173 (43.6)
4 - < 6 (moderate pain)	53 (13.3)	36 (9.1)
≥ 6 (severe pain)	32 (8.0)	28 (7.1)
Missing	30 (7.5)	23 (5.8)
Site of metastases, n (%)		
Bone	349 (87.5)	339 (85.4)
Distant lymph nodes	113 (33.3)	119 (30.0)
Locoregional lymph nodes	82 (20.6)	89 (22.4)
Lung/Respiratory	40 (10.0)	42 (10.6)
Liver	15 (3.8)	18 (4.5)
Docetaxel treatment at mHSPC stage,[b] n (%)	90 (22.6)	90 (22.7)

Median PSA, ug/L (min–max)		17.90 (0.07–1869.5)	16.81 (0.01–1888.0)
Prior treatment with second-generation antiandrogen agents prior to mCRPC stage			
Yes (enzalutamide)		1 (0.3)	0
No		398 (99.7)	397 (100)
HRRm status[c]			
HRRm		111 (27.8)	115 (29.0)
Non-HRRm		279 (69.9)	273 (68.8)
Stratification factors at randomisation			
Site of distant metastases	**Docetaxel treatment at mHSPC stage**	**Number of patients, (%)**	
		Olaparib + abiraterone (n = 399)	**Placebo + abiraterone (n = 397)**
As randomised (IWRS)			
Bone only	Yes	55 (13.8)	54 (13.6)
	No	162 (40.6)	163 (41.4)
Visceral	Yes	12 (3.0)	12 (3.0)
	No	41 (10.3)	40 (10.1)
Other	Yes	28 (7.0)	28 (7.1)
	No	101 (25.3)	100 (25.2)
Derived from eCRF data:			
Bone only	Yes	52 (13.0)	57 (14.4)
	No	161 (40.4)	169 (42.6)
Visceral	Yes	12 (3.0)	17 (4.3)
	No	55 (13.8)	56 (14.1)
Other	Yes	26 (6.5)	16 (4.0)
	No	93 (23.3)	82 (20.7)

[a]Patients with symptomatic pain at baseline: BPI-SF item #3 score ≥4 and/or opiate use at baseline [b]As long as no signs of failure or disease progression occurred during or immediately after docetaxel treatment [c]The HRRm status of patients in PROpel was determined retrospectively using results from tumour tissue and plasma ctDNA HRRm tests. Patients were classified as HRRm if (one or more) HRR gene mutation was detected by either test; patients were classified as non-HRRm patients if no HRR gene mutation was detected by either test; patients were classified as unknown HRRm if no valid HRR test result from either test was achieved

Comparability of patients across studies

As described in section 8.3, the main study used to obtain clinical inputs for the ITT population was PROpel of DCO3. PROpel study is assessed to be the most appropriate study trial reflecting the labelled patient population and treated, as well as a relevant comparator. Although, there were some exceptions with data patients heights to estimate body surface area, estimates for disutilities due to adverse events and inputs related to the scenario analysis compared to enzalutamide, which were obtained from published literature from the source considered most appropriate. Table 22 gives an overview on patient characteristics.

Comparability of the study populations with Danish patients eligible for treatment

As described in section 8.3.2.1 the patient population in Denmark is expected to be aligned with the labelled population in Europe, and this label was derived from the perceived risks and benefits in patients included in the registrational PROpel trial, it is therefore assumed that the population in the clinical evidence is largely aligned with patients in Danish clinical practice.

With respect to specific baseline characteristics, there is limited published real-world information on Danish patients with mCRPC. Therefore insights have been drawn from selected publications, as well as the overall Danish prostate cancer population, estimates from the expert committee reported in Medicinrådet and RADS documentation, and data from the Swedish prostate cancer registry. Table 23 shows the key population parameters in the model.

Appendix D Efficacy and safety results per study

Definition of included outcome measures

Outcome		Definition	Statistical analysis (as described in the SAP)
Primary outcome	rPFS (investigator assessed)	Time from randomisation until the date of objective disease progression (as assessed by the investigator using RECIST 1.1 or PCWG3) or death (by any cause in the absence of progression)	Primary analysis using a stratified log-rank test to calculate *p* value. The HR and CI were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates). Estimated rPFS rates at 6 and 12 months were summarised using the KM plot
	rPFS (BICR-assessed; sensitivity analysis)	Time from randomisation until the date of objective disease progression (as assessed by BICR using RECIST 1.1 or PCWG3) or death (by any cause in the absence of progression)	Key sensitivity analyses: Stratified log-rank test assessed for all patients by BICR per RECIST 1.1 and PCWG3 criteria. Subgroup analyses: HR and CI were estimated using Cox proportional hazards model (with ties = Efron and the stratification variables as covariates) and summarised in a forest plot
Secondary outcomes	PFS2	Time from randomisation to second progression on next-line anti-cancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression or death	PFS2 was analysed using the methods employed for analysis of the rPFS primary endpoint. The HR and corresponding 95% CI were based on the Cox model
	OS	Time from randomisation to death from any cause	Interim OS was analysed at the time of the primary rPFS analysis with approximately 47.6% maturity in Cohort A (approximately 230 events). Analysis using a log-rank test stratified to calculate *p* value. The HR and CI were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates). Estimated rPFS rates at 6 and 12 months were summarised using the KM plot
	TFST	Time from randomisation to the earlier of: start of the first subsequent anti-cancer therapy death from any cause	Analysed using the methods employed for analysis of the rPFS primary endpoint. The HR and corresponding 95% CI were based on the Cox model
	TTPP	Time from randomisation to the time point at which worsening in pain was observed as assessed by BPI-SF item 3 and opiate analgesic use (AQA score)	TTPP was analysed at the time of the primary rPFS analysis using the methods employed in the rPFS analysis. The *p* value was based on the stratified log-rank test and HR and 95% CI were based on the Cox model
	Time to opiate use for cancer pain	Time from randomisation to opiate use for cancer-related pain	Time to opiate use was analysed at the time of the primary rPFS analysis using the methods employed for rPFS analysis. The *p* value was based on the stratified log-rank test and HR and 95% CI were based on the Cox model

Outcome		Definition	Statistical analysis (as described in the SAP)
	Time to first SSRE	Time from randomisation to first SSRE, defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention	Time to first SSRE was analysed using the methods employed for analysis of the primary endpoint (rPFS)
	DoR	Time from first confirmed response by investigator- and BICR-assessed RECIST 1.1 and PCWG3 until BICR-assessed disease progression or death	Descriptive data are provided for DoR in patients who responded to treatment, including KM curves, without any formal comparison or *p* value attached
	PSA_{50} response	Proportion of patients achieving a ≥ 50% decrease in PSA level from baseline to the lowest post-baseline PSA result confirmed by the result of a second consecutive PSA assessment ≥ 3 weeks later	The proportion of patients achieving a PSA response and that of patients with a confirmed PSA response are presented with 95% CIs
PROs	TTPP	Time from randomisation to 'pain severity' progression as determined from the mean score of four items of the BPI-SF pain severity domain/subscale	Continuous PRO endpoints were summarised using mean, SD, median and range by treatment group for each visit until fewer than one-third of patients have evaluable data. Absolute and change from baseline scores for each time point were calculated for each treatment group. TTPP was analysed using MMRM
	Pain interference	Absolute and change from baseline scores of BPI-SF pain interference	Continuous PRO endpoints were summarised using mean, SD, median and range by treatment group for each visit until fewer than one-third of patients have evaluable data. Absolute scores and change from baseline scores for each time point were calculated for each treatment group

Outcome		Definition	Statistical analysis (as described in the SAP)
	FACT-P	Absolute and change from baseline scores in FACT-P total score, TOI, FAPSI-6, PCS, PWB and FWB subscales	FACT-P is multidimensional, self-report instrument designed to assess HRQoL in patients with prostate cancer. It comprises 27 core items across four domains: physical, social/family, emotional and functional wellbeing, and is supplemented by 12 site-specific items relating to prostate-related symptoms. Higher scores represent better HRQoL. Continuous PRO endpoints were summarised using mean, SD, median and range by treatment group for each visit until fewer than one-third of patients have evaluable data. Absolute scores and change from baseline scores for each time point were calculated for each treatment group. The proportion of patients with the best responses of 'improve', 'no change' and 'worsened' on FACT-P and subscale scores including TOI were compared between treatments using logistic regression, adjusting for metastases and docetaxel treatment at mHSPC stage
	EQ-5D-5L	Unique EQ-5D health states were converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (UK base case with other country value sets applied in the scenario analyses). Where values are not available, the EQ-5D-5L to EQ-5D-3L crosswalk was applied	Descriptive statistics are reported for health state utility index values and visual analogue scale by visits as well as for change in these scores from baseline. To support future economic evaluations of olaparib, additional appropriate analyses may be undertaken; for example, mean health state utility pre- and post-treatment, and pre- and post-progression
Safety	Safety and tolerability	Safety and tolerability were assessed in terms of AEs including SAEs, deaths, collection of vital signs (including BP and pulse), ECG, laboratory data (clinical chemistry and haematology) and physical examination	Safety analyses were presented using the SAS using descriptive statistics

Results per study

Table A3a Results of Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer, Noel W. Clarke, M.B.B.S. et. al., NEJM Evid 2022; 1 (9), June 3, 2022

				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**		
rPFS (INV assessed)	Olaparib plus abiraterone	399	Median: 24.97 (20.57, 30.06) 3 year: 35.8% (30.3, 41.5)	Median: 8.51 3 year: 10.9%	4.45, 13.35 3.6%, 18.2%	NA	HR: 0.68	0.57, 0.81	<0.0001	DCO3. 62.2% maturity (496 events). Primary analysis using a stratified log-rank test to calculate *p* value. The HR and CI were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates). Estimated rPFS rates at 6 and 12 months were summarised using the KM plot	AstraZeneca Data on File (DCO3 Clinical Study Report)
	Placebo plus abiraterone	397	Median: 16.46 (13.98, 19.22) 3 year: 25.0% (20.4, 29.9)								
rPFS (BICR assessed)	Olaparib plus abiraterone	399	Median: 27.60 (20.47, 30.16) 2 year: 54.3% (48.9, 59.5)	Median: 11.14 2 year: 18.8%	6.31, 16.99 11.4%, 26.2%	NA	HR: 0.62	0.51, 0.75	<0.0001	DCO2. 53.3% maturity (424 events). Key sensitivity analyses: Stratified log-rank test assessed for all patients by BICR per RECIST 1.1 and PCWG3 criteria. Subgroup analyses: HR and CI were estimated using Cox proportional hazards model (with ties = Efron and the stratification variables as covariates) and summarised in a forest plot	AstraZeneca Data on File (DCO2 Clinical Study Report)
	Placebo plus abiraterone	397	Median: 16.46 (13.80, 19.15) 2 year: 35.5% (30.4, 40.6)								

Table A3a Results of Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer, Noel W. Clarke, M.B.B.S. et. al., NEJM Evid 2022; 1 (9), June 3, 2022											
OS	Olaparib plus abiraterone	399	Median: 42.05 (38.41, NC) 3 year: 56.9% (51.7, 61.7)	Median: 7.36 3 year: 7.3%	-0.31, 16.74 0.2%, 14.5%	NA	0.81	0.67, 1.00	0.0544	DCO3. 47.7% maturity (381 events). Analysis using a log-rank test stratified to calculate p value. The HR and CI were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates)	AstraZeneca Data on File (DCO3 Clinical Study Report)
	Placebo plus abiraterone	397	Median: 34.69 (30.95, 39.29) 3 year: 49.5% (44.3, 54.5)								
PFS2	Olaparib plus abiraterone	399	Median: NC (NC, NC) 3 year: 67.9% (62.2, 72.9)	Median: NC 3 year: 8.6%	NC, NC 0.9%, 16.4%	NA	0.76	0.59, 0.99	0.0534	DCO3. 28.7% maturity (229 events). Analysis using a log-rank test stratified to calculate p value. The HR and CI were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates)	AstraZeneca Data on File (DCO3 Clinical Study Report)
	Placebo plus abiraterone	397	Median: NC (NC, NC) 3 year: 59.3% (53.4, 64.6)								
TFST	Olaparib plus abiraterone	399	Median: 24.6 (21.1, 28.5) 3 year: 38.1%	Median: 5.2 3 year: 10.4%	1.4, 9.7 3.8%, 17.0%	NA	0.76	0.64, 0.90	0.0025	DCO3. 67.7% maturity (540 events). Analysis using a log-rank test stratified to calculate p value. The HR and CI were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates)	AstraZeneca Data on File (DCO3 Clinical Study Report)
	Placebo plus abiraterone	397	Median: 19.4 (17.0, 21.1)								

Table A3a Results of Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer, Noel W. Clarke, M.B.B.S. et. al., NEJM Evid 2022; 1 (9), June 3, 2022											
			3 year: 27.7%								
rPFS (INV assessed) – HRRm subgroup	Olaparib plus abiraterone	111	Median: 30.13 (19.32, 36.21) 3 year: 39.9% (29.6, 50.0)	Median: 16.27 3 year: 23.8%	7.86, 27.94 11.0%, 36.5%	NA	0.51	0.36, 0.70	NA	DCO3. 62.1% maturity (483 events). The analysis was performed using a Cox proportional hazards model that contains a term for treatment, subgroup factor and a treatment by subgroup interaction. CIs calculated using profile likelihood method.	AstraZeneca Data on File (DCO3 Clinical Study Report - Addendum)
	Placebo plus abiraterone	115	Median: 13.86 (10.97, 19.19) 3 year: 16.1% (9.3, 24.6)								
rPFS (INV assessed) – non-HRRm subgroup	Olaparib plus abiraterone	279	Median: 24.64 (19.35, 27.76)	Median: 5.68	0.91, 11.60	NA	0.79	0.64, 0.98	NA		
	Placebo plus abiraterone	273	Median: 18.96 (14.88, 20.86)								
OS – HRRm subgroup	Olaparib plus abiraterone	111	Median: NC (NC, NC) 3 year: 56.0% (45.9, 64.9)	Median: NA 3 year: 15.8%	NA 2.5%, 29.0%	NA	0.66	0.45, 0.95	NA	DCO3. 47.8% maturity (372 events). The analysis was performed using a Cox proportional hazards model that contains a term for treatment, subgroup factor and a treatment by subgroup interaction. CIs calculated using profile likelihood method.	AstraZeneca Data on File (DCO3 Clinical Study Report - Addendum)
	Placebo plus abiraterone	115	Median: 28.45 (26.15, 34.40) 3 year: 40.2% (30.8, 49.4)								

Table A3a Results of Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer, Noel W. Clarke, M.B.B.S. et. al., NEJM Evid 2022; 1 (9), June 3, 2022											
OS – non-HRRm subgroup	Olaparib plus abiraterone	279	Median: 42.05 (37.29, NC)	Median: 3.15	-6.01, 14.86	NA	0.89	0.70, 1.14	NA		
	Placebo plus abiraterone	273	Median: 38.90 (32.53, NC)								
Any AEs	Olaparib plus abiraterone	398	97.7%	1.8%	-0.6%, 4.2%	NA	RR: 1.03	1.00, 1.05	NA	DCO3. Unstratified (naïve) analysis of observed AE incidence.	AstraZeneca Data on File (DCO3 Clinical Study Report)
	Placebo plus abiraterone	396	96.0%								
Any AE of CTCAE Grade 3 or higher	Olaparib plus abiraterone	398	55.8 %	12.6%	5.7%, 19.5%	NA	RR: 1.29	1.12, 1.49	NA	DCO3. Unstratified (naïve) analysis of observed AE incidence.	AstraZeneca Data on File (DCO3 Clinical Study Report)
	Placebo plus abiraterone	396	43.2 %								
FACT-P (Least squares mean change from baseline)	Olaparib plus abiraterone	278	-5.84 (-7.86, -3.81)	-0.54	-3.00, 1.92	0.6675	NA	NA	NA	DCO3. 27 core items across four domains: physical, social/family, emotional and functional wellbeing, and is supplemented by 12 site-specific items relating to prostate-related symptoms. Higher scores represent better HRQoL. Analysis was performed using a mixed model for repeated measures (MMRM) with treatment, visit, treatment by visit interaction, baseline FACT-P total score, baseline score by visit	AstraZeneca Data on File (DCO3 Clinical Study Report)
	Placebo plus abiraterone	295	-5.30 (-7.38, -3.22)								

Table A3a Results of Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer, Noel W. Clarke, M.B.B.S. et. al., NEJM Evid 2022; 1 (9), June 3, 2022	
	interaction, metastases, and docetaxel treatment at mHSPC stage as fixed effects. A Toeplitz with heterogeneity covariance matrix is used to model the within-patient error. The Kenward-Roger approximation is used to estimate degrees of freedom.

Appendix E Safety data for intervention and comparator(s)

Category of adverse event	Olaparib + Abiraterone (n = 398)	Placebo + Abiraterone (n = 396)
Any AE	389 (97.7)	380 (96.0)
Any AE causally related to study treatment	339 (85.2)	279 (70.5)
Any AE of CTCAE Grade 3 or higher	222 (55.8)	171 (43.2)
Any AE of CTCAE Grade 3 or higher, causally related to study treatment	122 (30.7)	65 (16.4)
Any AE with outcome of death	26 (6.5)	20 (5.1)
Any AE with outcome of death, causally related to study treatment	0	1 (0.3)
Any SAE (including events with outcome of death)	161 (40.5)	126 (31.8)
Any SAE (including events with outcome of death), causally related to study treatment	56 (14.1)	24 (6.1)
Any AE leading to discontinuation of study treatment	71 (17.8)	43 (10.9)
Any AE leading to discontinuation of study treatment, causally related to study treatment	41 (10.3)	27 (6.8)

Patients with multiple events in the same category are counted only once in that category. Patients with events in > 1 category are counted in each of those categories. 'Study treatment' refers to olaparib/placebo, and/or abiraterone, and/or prednisone/prednisolone.

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Appendix F Comparative analysis of efficacy and safety

Given that a single head-to-head study formed the basis of the application, no meta-analysis or indirect treatment comparisons were used in the submission.

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Appendix G Extrapolation

Introduction

The following report includes all supplementary figures, tables, and analyses to support the fitting and selection of survival curves for inclusion in the economic model for the various subgroups as reported in the documentation for the single technology assessment for Lynparza® (olaparib) in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.
All time to event outcomes for use in the model were extrapolated from the patient-level data from the PROpel trial following the guidance from the NICE Decision Support Unit's Technical Support Document 14 and the Norwegian Medicines Agency's guidelines on the extrapolation of efficacy. All extrapolations are based on the final analysis (third data cut-off; DCO3) of the PROpel trial, dated 12 October 2022 after a median follow-up of 33 months. For each endpoint the following outputs are generated:

1. Summary statistics, Kaplan-Meier plots, and various diagnostic plots (log cumulative hazards, log odds, log normal, quantile-quantile, Schoenfeld residual, empirical and smoothed hazards) to assess whether or not the proportional hazards or accelerated failure time assumptions have been violated and assess potential functional forms of the data.
2. Parametric survival models using standard distributions (exponential, Weibull, Gompertz, gamma, lognormal, loglogistic, and generalised gamma) to the individual arms of the trial and joint models (where appropriate). The Generalised F distribution is included, where it can converge, to help inform diagnostic selection of other parametric fits.
3. Statistical fit of the fitted models to the trial data in terms of Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC)
4. Comparison of the visual fit of the extrapolated curve to the trial Kaplan-Meier curve and the visual fit of the hazard function of the extrapolated curve to the smoothed hazards from the patient-level data.

Additional consideration should be given to the plausibility of long-term extrapolations as included in the health economic model, as well as the statistical analyses presented in this report based on the observed trial data.

ITT Population

Radiological Progression-Free Survival

Number of subject and events for rPFS in the ITT population

Arm	N	Events	Maturity
Placebo + Abiraterone	397	277	69.8%
Olaparib + Abiraterone	399	219	54.9%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last time point where each arm has observations, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

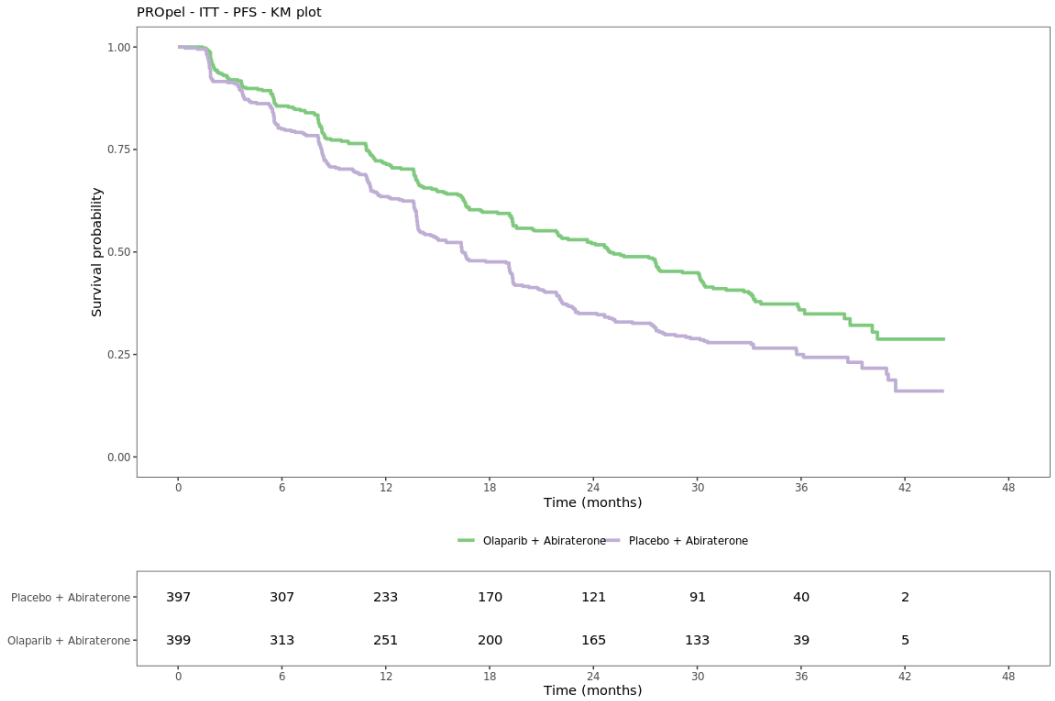
Restricted mean survival times and median survival times for rPFS in the ITT population

Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	20.8 (19.3, 22.3)	16.5 (13.9, 19.2)
Olaparib + Abiraterone	25.4 (23.8, 27.1)	25.0 (20.6, 30.1)

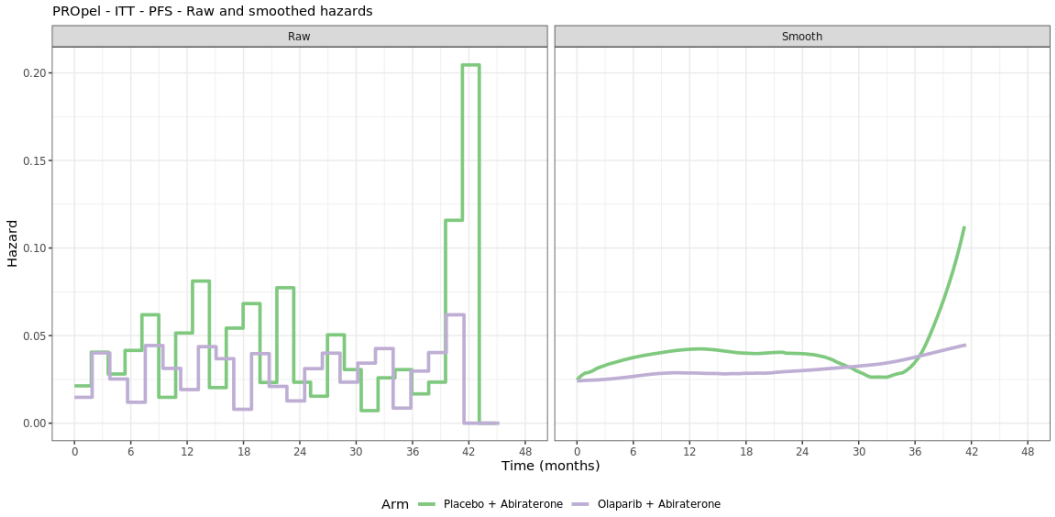
CI, confidence interval; RMST, restricted mean survival time

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

Kaplan-Meier survival plot for rPFS in the ITT population



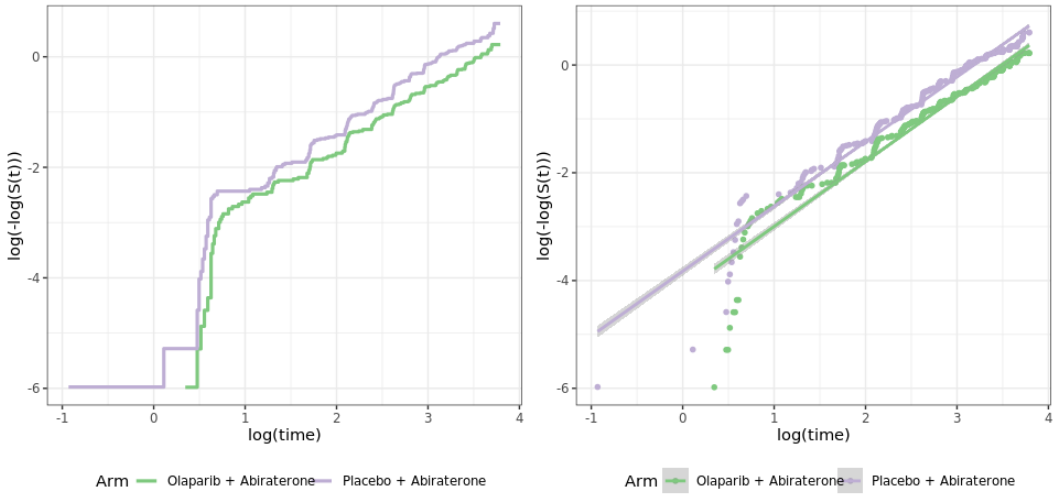
Smoothed and empirical hazards for rPFS in the ITT population



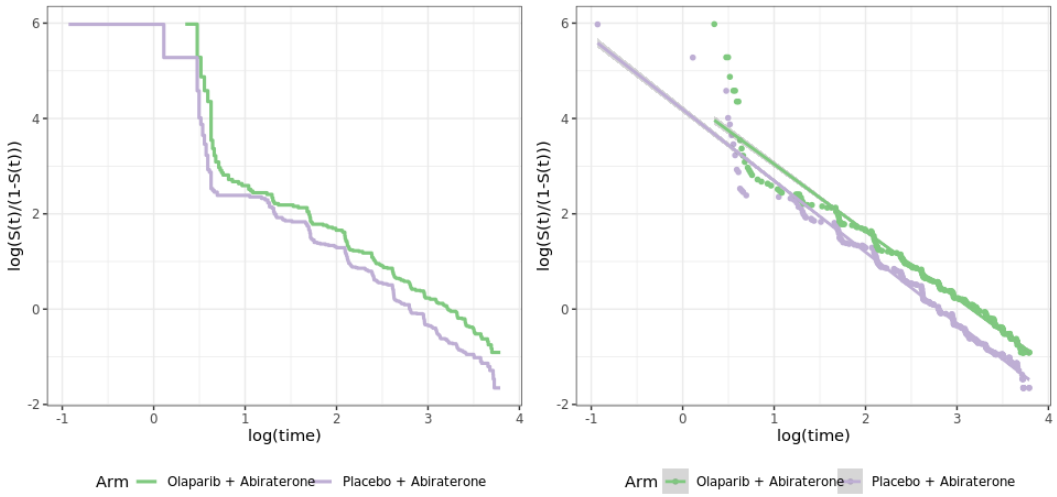
The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log-cumulative hazards (Weibull) plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds (loglogistic) diagnostic plot, parallel lines indicate proportional odds and in the lognormal diagnostic plot, parallel lines indicate constant acceleration.

Diagnostic plots for rPFS in the ITT population

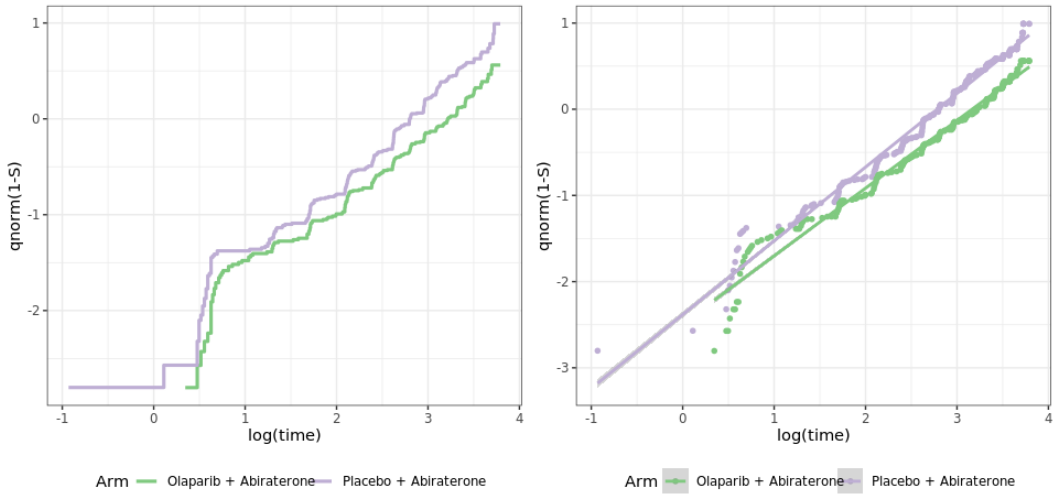
Log cumulative hazards vs. log time



Log odds vs. log time



Log normal vs. log time



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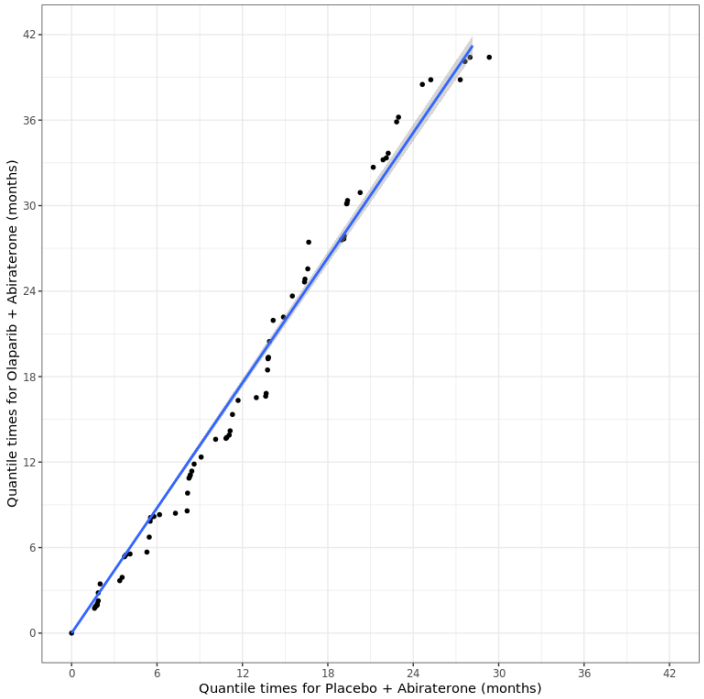
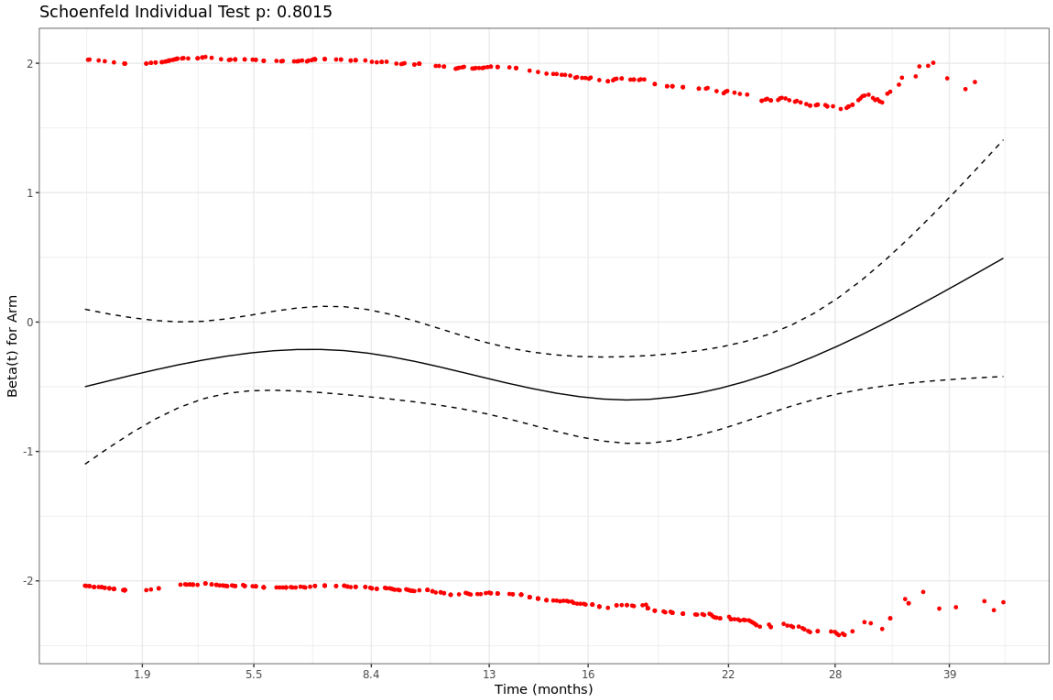
Quantile-quantile plot for rPFS in the ITT population



A straight line in the quantile-quantile plot indicates that an accelerated failure time model may fit the data well.

Schoenfeld residuals plot for rPFS in the ITT population



Schoenfeld residuals have been calculated using the KM transform. The Schoenfeld residuals can be used to test the proportional hazard assumption. If hazards are proportion, the plot of the residuals against time should show a linear trend with slope=0. A significant value on the Schoenfeld individual test indicates that the proportional hazards assumption has been violated. The visual inspection of this plot is more important than the test, however, a p-value is also outputted as the result of a test of non-negative slope (Therneau and Grambsch).

The diagnostic plots show that the curves are somewhat parallel but not straight lines. The lognormal or loglogistic plots show a slightly better fit to the data, but the quantile-quantile plot suggests that an accelerated failure time model would not fit the data well. The Schoenfeld residuals plot indicates that proportional hazards has been violated. Therefore, independent extrapolations of the survival curves is favoured.

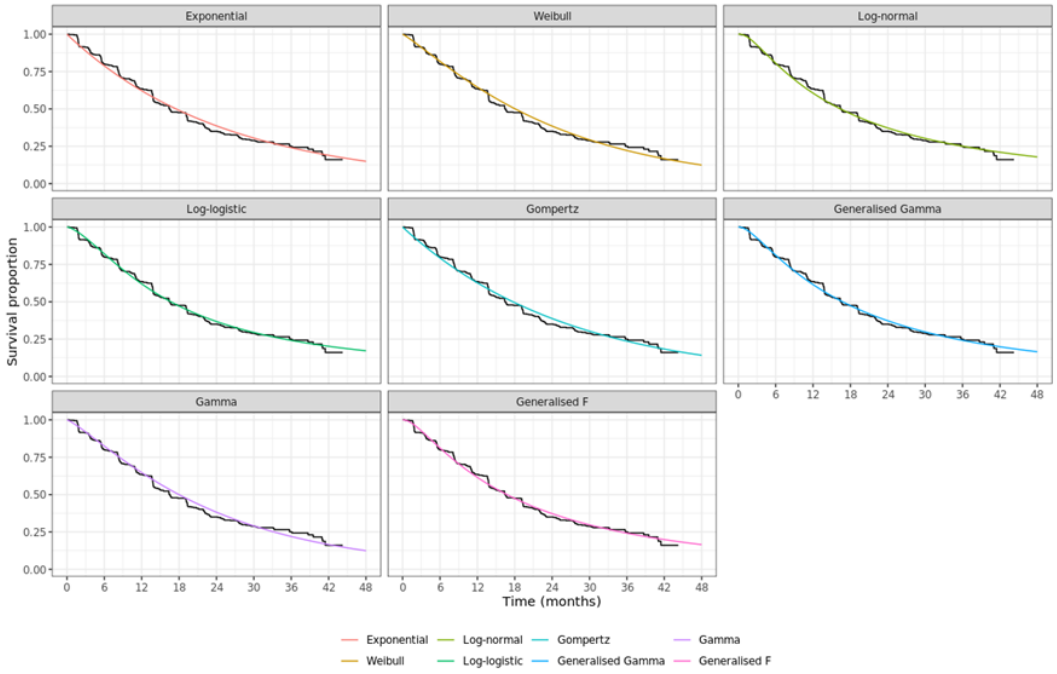
Goodness of fit statistics for independent models fitted to rPFS in the ITT population

Olaparib + Abiraterone			Placebo + Abiraterone		
Distribution	AIC	BIC	Distribution	AIC	BIC
Lognormal	1997.7	2005.7	Lognormal	2330.6	2338.6
Generalised Gamma	1999.6	2011.6	Generalised Gamma	2331.6	2343.6
Loglogistic	2002.3	2010.3	Loglogistic	2331.9	2339.9
Gamma	2004.5	2012.5	Gamma	2339.3	2347.3
Weibull	2005.8	2013.7	Weibull	2341.9	2349.8
Exponential	2007.6	2011.5	Exponential	2345.1	2349.0
Gompertz	2008.9	2016.8	Gompertz	2346.9	2354.9

For the placebo + abiraterone arm, the lognormal distribution has the best statistical fit. The generalised gamma and loglogistic distributions were also good fits (ΔAIC < 5). For the olaparib + abiraterone arm, the lognormal distribution has the best statistical fit. The generalised gamma and loglogistic distributions were also good fits (ΔAIC < 5).

The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

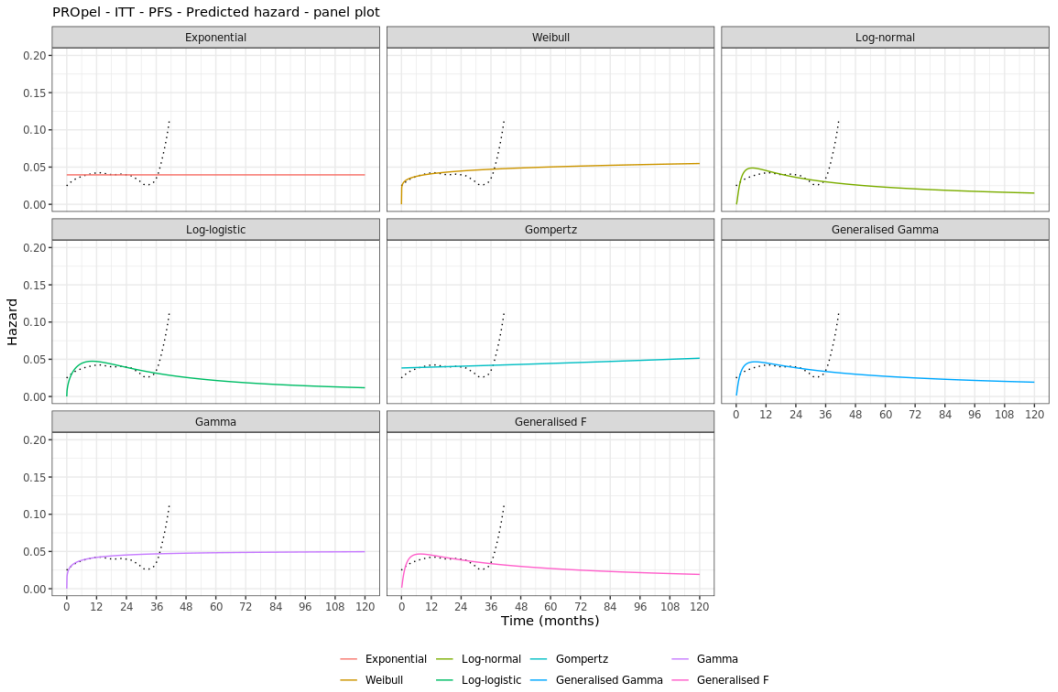
Fitted independent parametric models vs. Kaplan-Meier for rPFS in the placebo + abiraterone arm in the ITT population



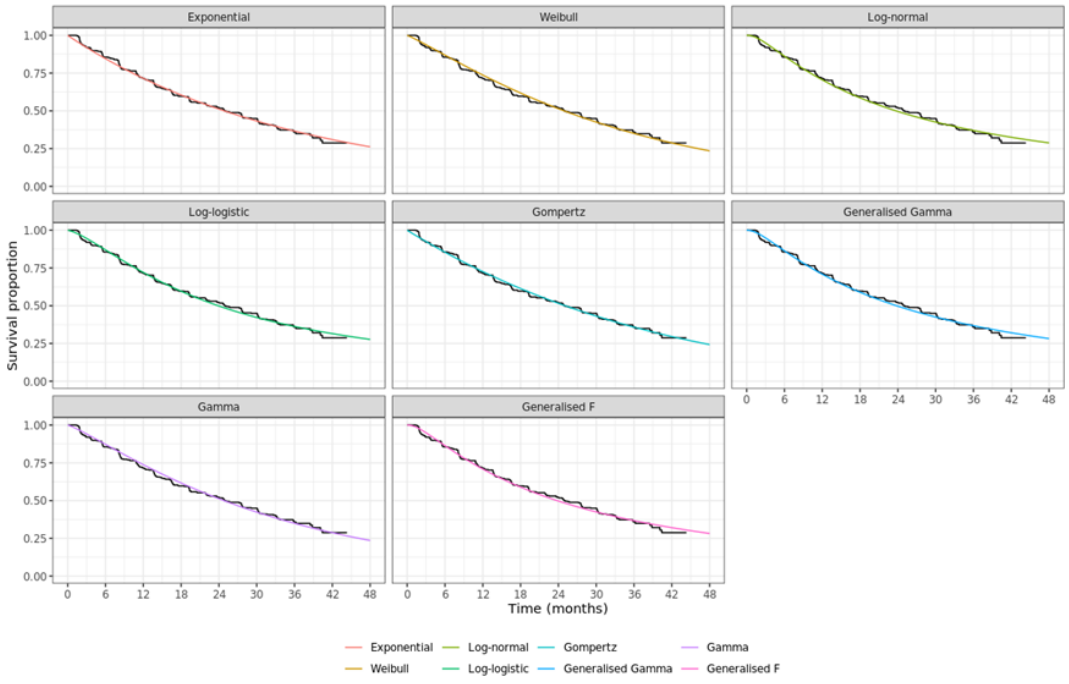
All curves provided a reasonable visual fit to the placebo + abiraterone arm during trial follow-up. The gamma and Gompertz distributions provide a more pessimistic long-term outcome, whilst potentially overestimating short-term survival. In line with the AIC and BIC criteria, the lognormal,

loglogistic, and generalised gamma distributions provided the best visual fit. Up to around 32 months (after which point the number at risk is declining rapidly due to censoring), the smoothed hazards indicate a non-monotonic hazard function in line with the lognormal, generalised gamma, and loglogistic distributions. This is supported by the flexible fits of the generalised F distribution.

Hazard functions of fitted parametric models to the placebo + abiraterone arm compared to smoothed hazards for rPFS in the ITT population



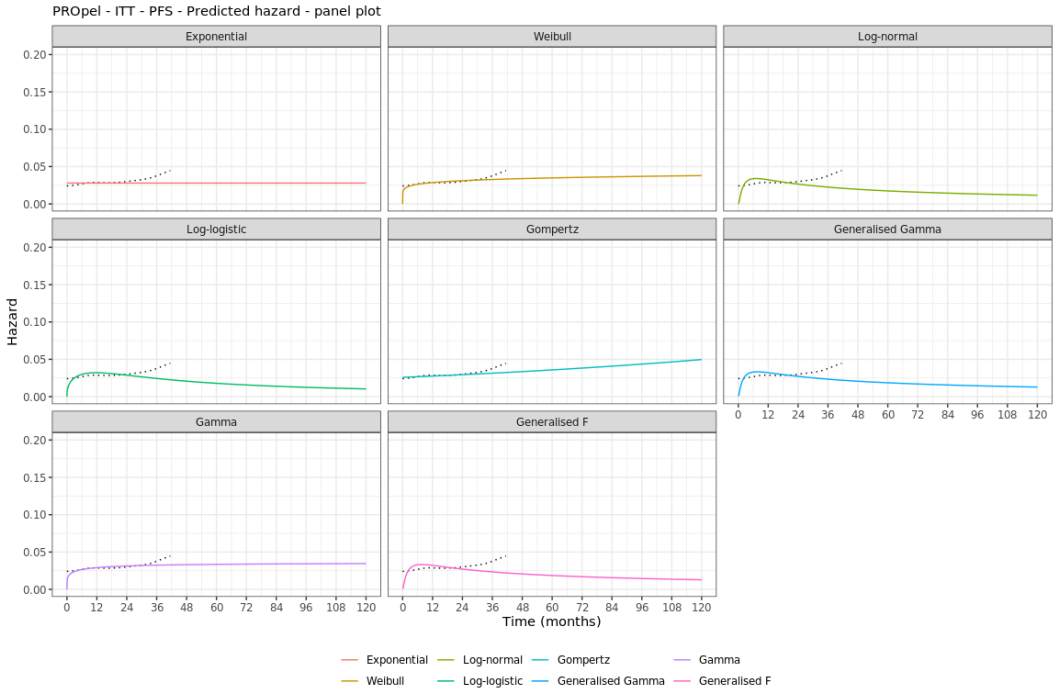
Fitted independent parametric models vs. Kaplan-Meier for rPFS in the olaparib + abiraterone arm in the ITT population



In the olaparib + abiraterone arm, all curves provided a reasonable fit during the trial follow-up, with little evidence to dismiss any parametric model based on visual fit. The greater immaturity of the data makes the smoothed hazards less informative about the shape of the underlying hazards

of the data, though during trial follow-up (up to around 24 months) the hazards are similar between functional forms.

Hazard functions of fitted parametric models to the olaparib + abiraterone arm compared to smoothed hazards for rPFS in the ITT population



On the basis of the best statistical fit, good fit to the observed trial data, and alignment with the observed smoothed hazards of the trial data, the lognormal distribution is selected for the placebo + abiraterone arm. As this distribution also provides the best statistical fit and a good visual fit to the trial data for the olaparib + abiraterone arm, it is also selected here. This is aligned with NICE DSU guidance that survival curves for different arms should follow similar functional forms.

Overall Survival

Number of subject and events for OS in the ITT population

Arm	N	Events	Maturity
Placebo + Abiraterone	397	205	51.6%
Olaparib + Abiraterone	399	176	44.1%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last time point where each arm has observations, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

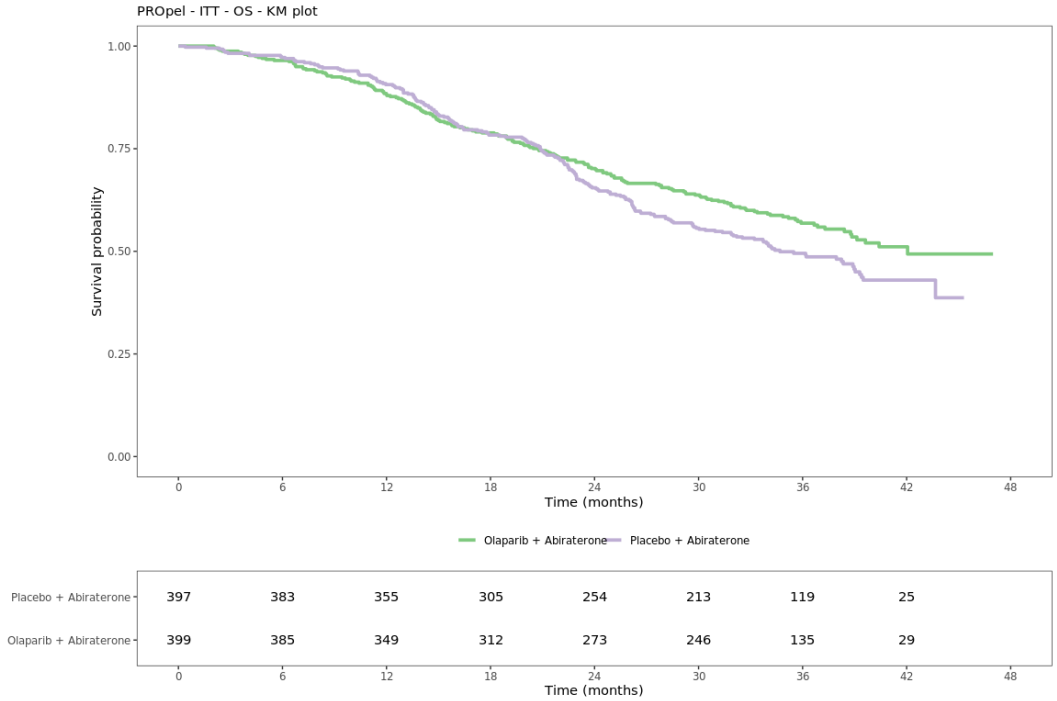
Restricted mean survival times and median survival times for OS in the ITT population

Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	31.9 (30.5, 33.3)	34.7 (30.9, 39.3)
Olaparib + Abiraterone	33.4 (32.0, 34.8)	42.1 (38.4, NR)

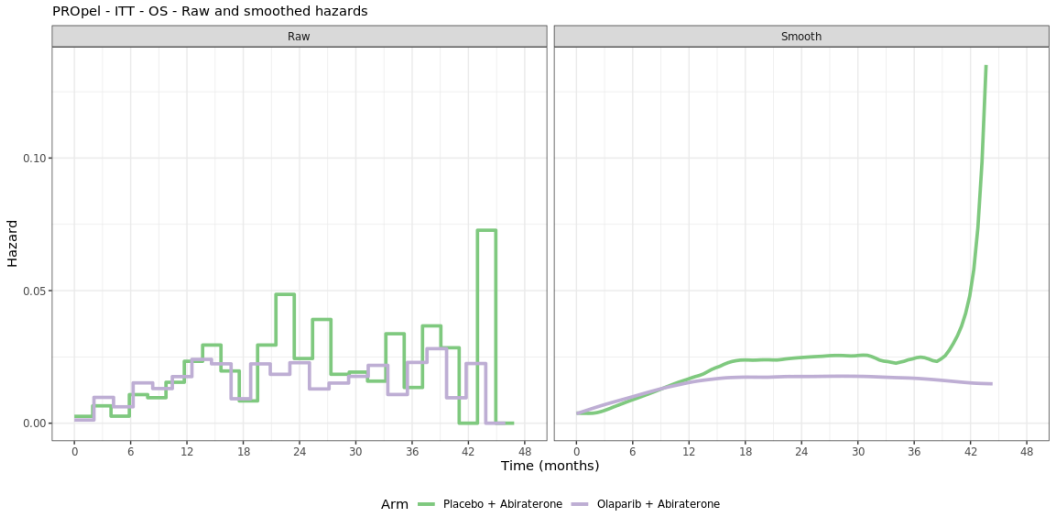
CI, confidence interval; NC, not calculable; RMST, restricted mean survival time

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

Kaplan-Meier survival plot for OS in the ITT population



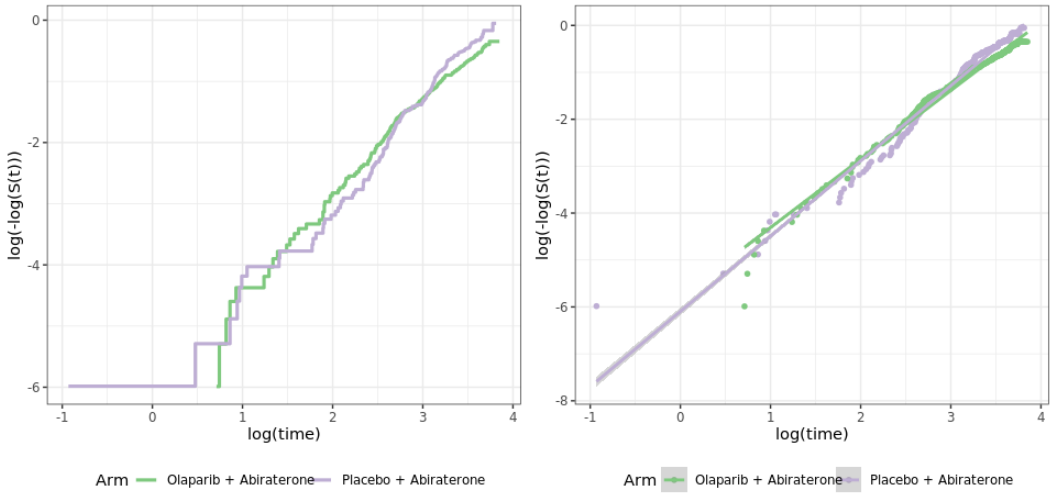
Smoothed and empirical hazards for OS in the ITT population



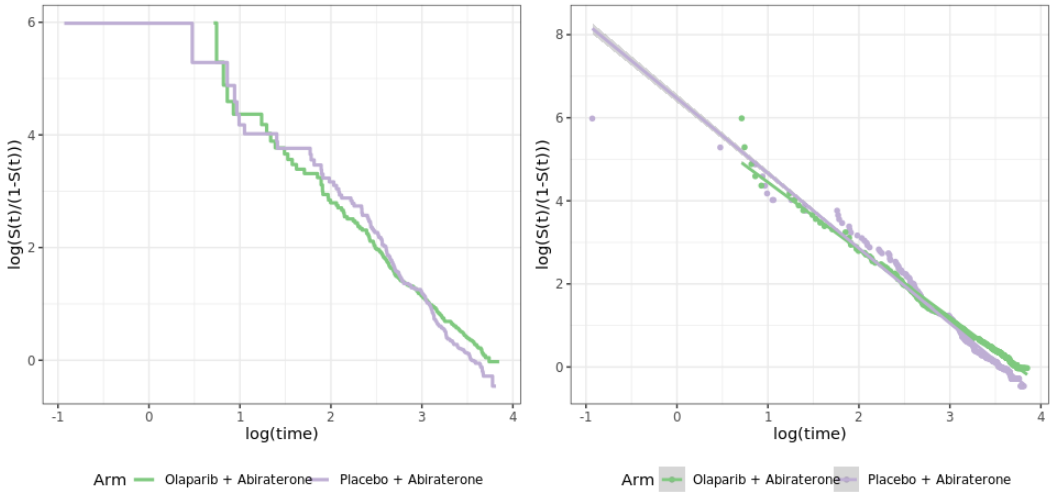
The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log-cumulative hazards (Weibull) plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds (loglogistic) diagnostic plot, parallel lines indicate proportional odds and in the lognormal diagnostic plot, parallel lines indicate constant acceleration.

Diagnostic plots for OS in the ITT population

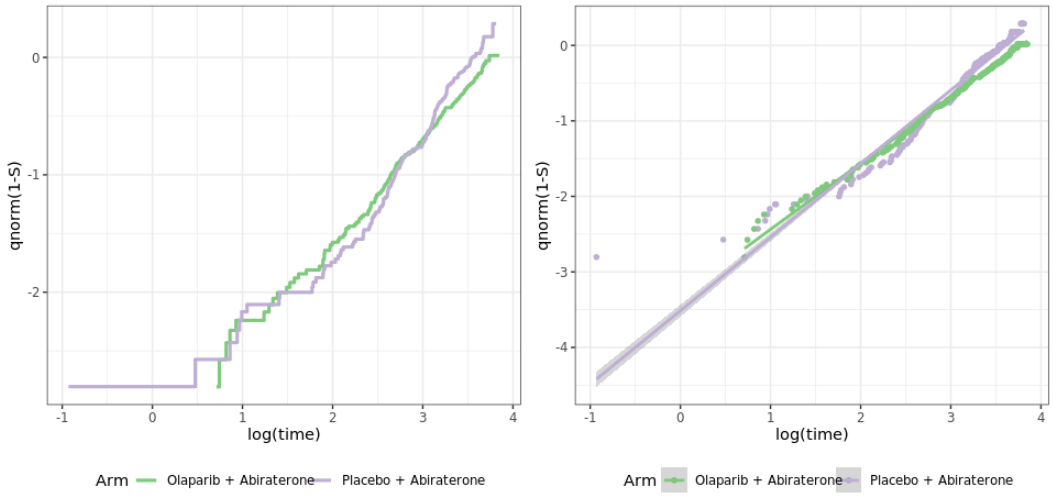
Log cumulative hazards vs. log time



Log odds vs. log time



Log normal vs. log time



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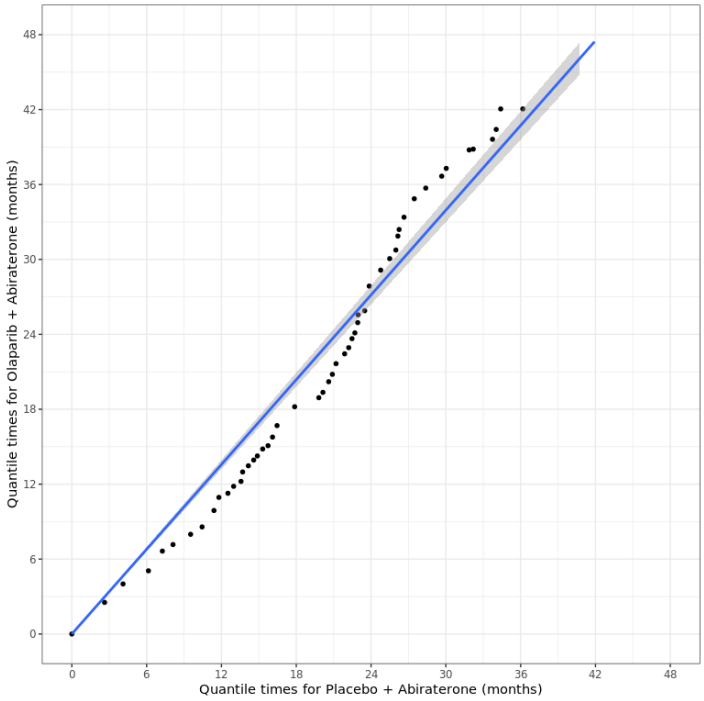
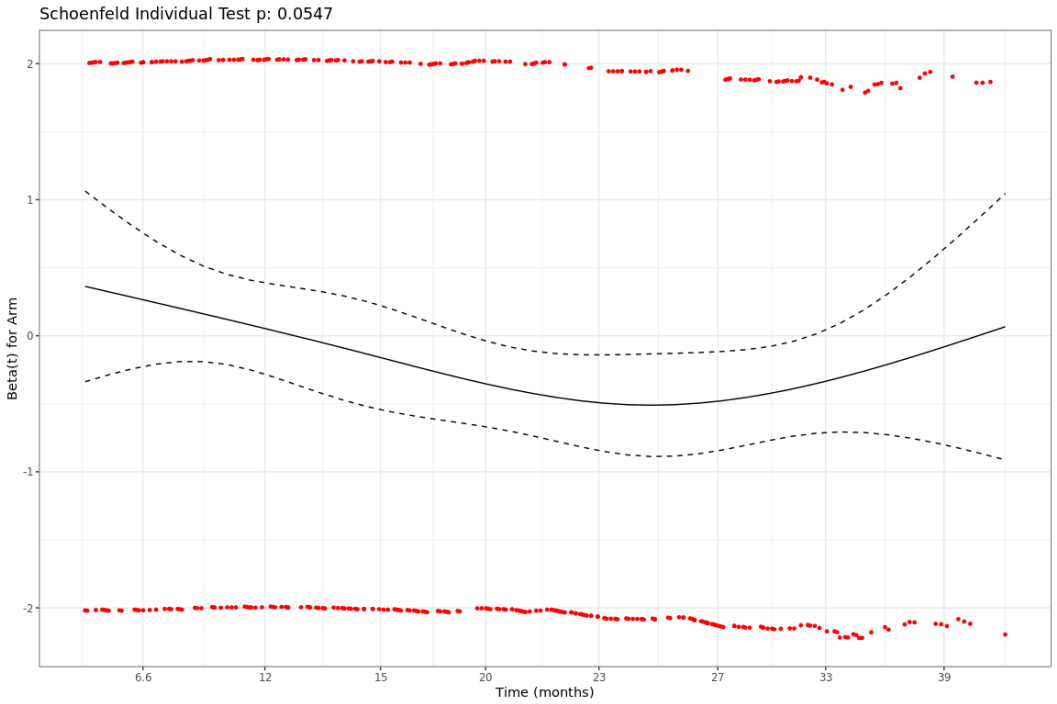
Quantile-quantile plot for OS in the ITT population



A straight line in the quantile-quantile plot indicates that an accelerated failure time model may fit the data well.

Schoenfeld residuals plot for OS in the ITT population



Schoenfeld residuals have been calculated using the KM transform. The Schoenfeld residuals can be used to test the proportional hazard assumption. If hazards are proportion, the plot of the residuals against time should show a linear trend with slope=0. A significant value on the Schoenfeld individual test indicates that the proportional hazards assumption has been violated. The visual inspection of this plot is more important than the test, however, a p-value is also outputted as the result of a test of non-negative slope (Therneau and Grambsch).

The diagnostic plots show that the curves cross during the initial period before separating, indicating the proportional hazards is not plausible. The Schoenfeld residuals plot indicates that

proportional hazards has been violated, consistent with the quantile-quantile plot showing a poor fit to an accelerated failure time model. Therefore, independent extrapolations of the survival curves is favoured.

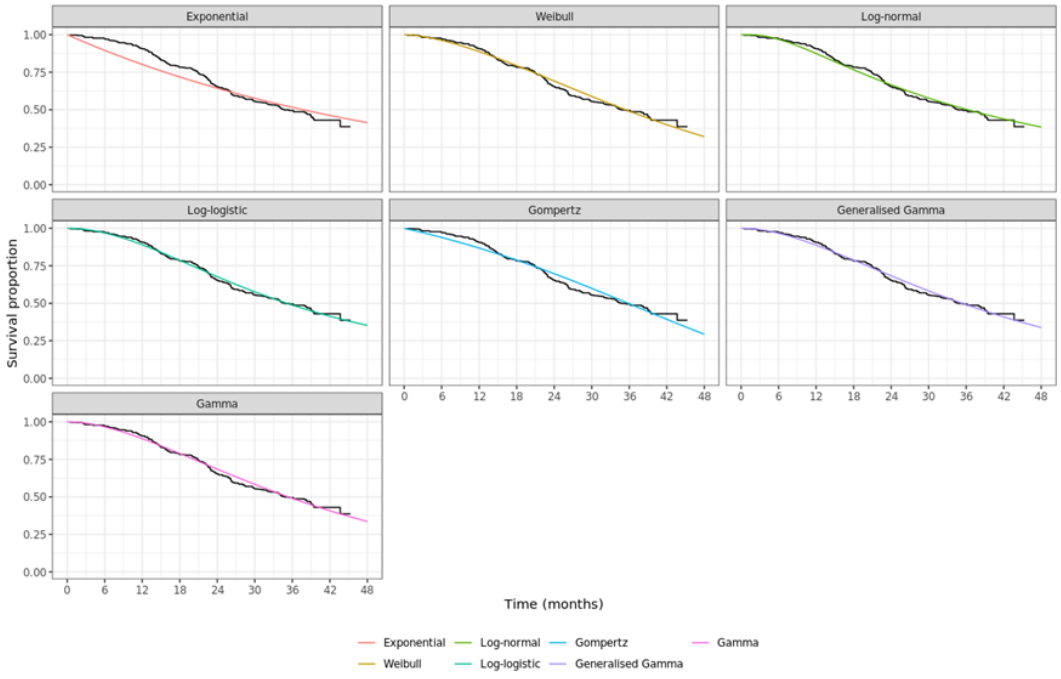
Goodness of fit statistics for independent models fitted to OS in the ITT population

Olaparib + Abiraterone			Placebo + Abiraterone		
Distribution	AIC	BIC	Distribution	AIC	BIC
Lognormal	1803.3	1811.3	Loglogistic	1998.8	2006.8
Generalised Gamma	1805.2	1817.2	Gamma	2001.3	2009.3
Loglogistic	1805.8	1813.7	Weibull	2003.2	2011.2
Gamma	1807.6	1815.6	Generalised Gamma	2003.3	2015.2
Weibull	1810.0	1818.0	Lognormal	2012.2	2020.2
Gompertz	1820.5	1828.5	Gompertz	2019.7	2027.7
Exponential	1827.9	1831.9	Exponential	2050.5	2054.5

For the placebo + abiraterone arm, the loglogistic distribution has the best statistical fit. The gamma, Weibull, and generalised gamma distributions were also good fits (ΔAIC < 5). For the olaparib + abiraterone arm, the lognormal distribution has the best statistical fit. The generalised gamma, loglogistic, and gamma distributions were also good fits (ΔAIC < 5).

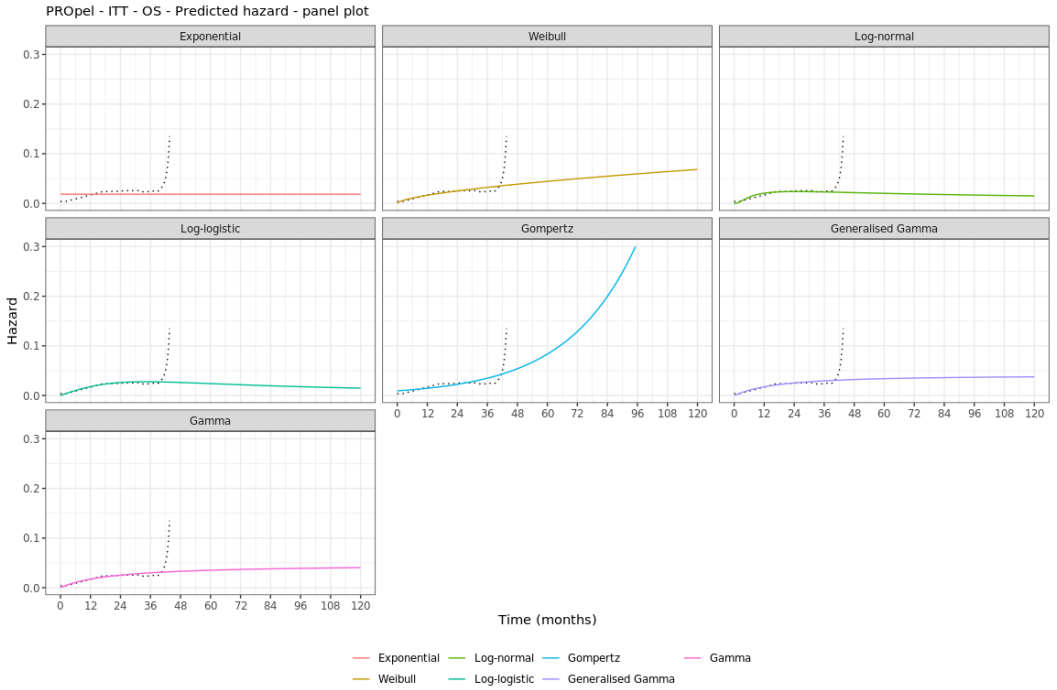
The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

Fitted independent parametric models vs. Kaplan-Meier for OS in the placebo + abiraterone arm in the ITT population

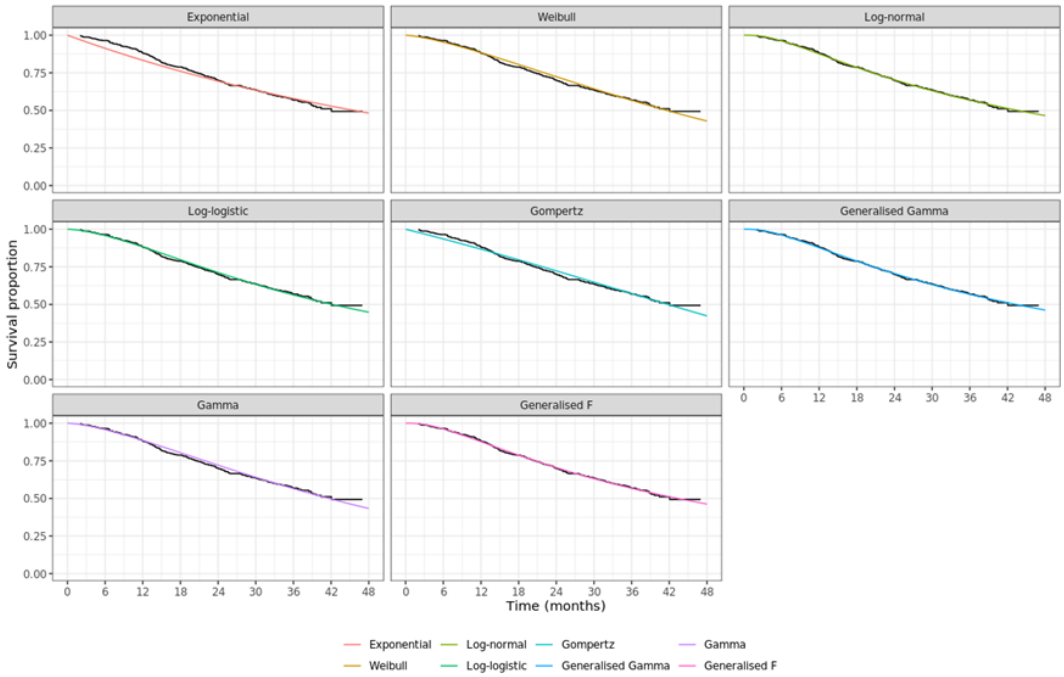


The exponential and Gompertz distributions provided a poor fit to the placebo + abiraterone arm during trial follow-up. Amongst distributions with an acceptable visual fit, the lognormal distribution provides the most optimistic long-term outcomes and the Weibull the most pessimistic. The smoothed hazards are aligned with the AIC criteria, with the lognormal, loglogistic, generalised gamma, and gamma distributions fitting well.

Hazard functions of fitted parametric models to the placebo + abiraterone arm compared to smoothed hazards for OS in the ITT population

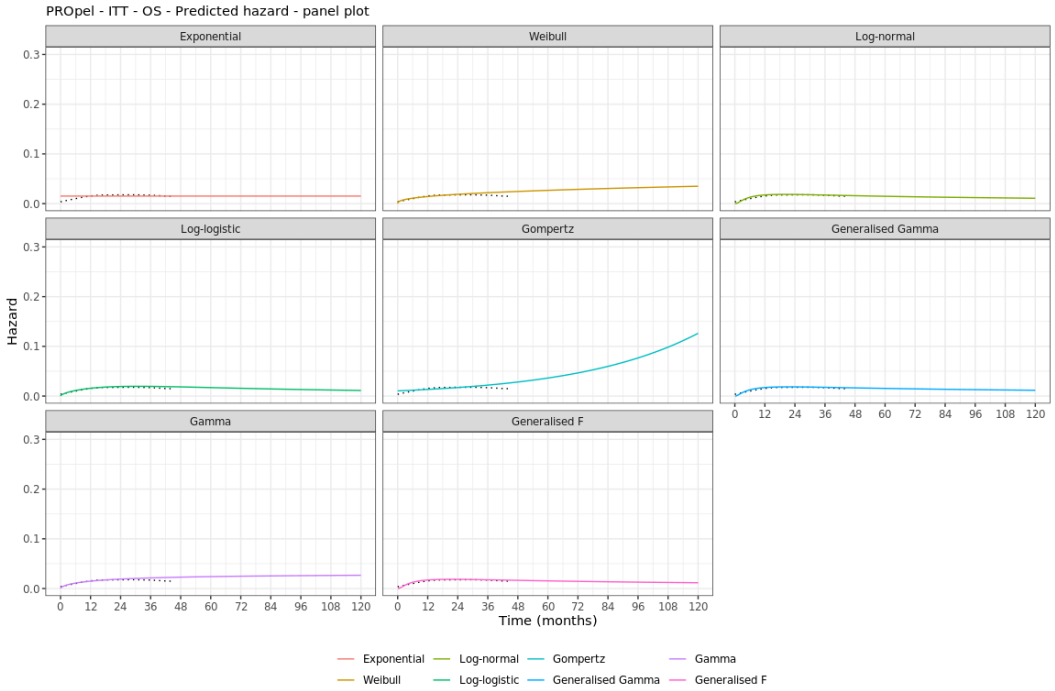


Fitted independent parametric models vs. Kaplan-Meier for OS in the olaparib + abiraterone arm in the ITT population



In the olaparib + abiraterone arm, the exponential and Gompertz distributions also provided a poor fit. The lognormal distribution provides a very aligned visual fit, with the loglogistic and generalised gamma also fitting well. These distributions also appear to fit well to the smoothed hazards.

Hazard functions of fitted parametric models to the olaparib + abiraterone arm compared to smoothed hazards for OS in the ITT population



In favour of selecting the distributions with similar functional forms for both arms, despite the convergence of the curves, statistical and visual fit indicates that the lognormal, loglogistic, and generalised gamma distributions are plausible. Given the relative immaturity of the data, clinical insight on long-term outcomes was obtained were 5-year survival was estimated to be around 25% with patients treated with NHAs, and 10-year survival being 5-10%. On this basis, the lognormal distribution was considered to overestimate long-term outcomes in the placebo + abiraterone arm, though both the loglogistic and generalised gamma distributions were aligned with these assumptions. With regards to the magnitude and duration of the relative effect of adding olaparib, the more flexible form of the generalised gamma distribution permits modelling of the relatively equal hazards during the first 2 years of follow-up, followed by the progressive divergence of the risk of death as observed in the diagnostic plots. Therefore, the generalised gamma distribution is selected in the base case for both arms.

Time to Discontinuation of Abiraterone

Number of subject and events for TDA in the ITT population

Arm	N	Events	Maturity
Placebo + Abiraterone	397	317	79.8%
Olaparib + Abiraterone	399	288	72.2%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last time point where each arm has observations, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

Restricted mean survival times and median survival times for TDA in the ITT population

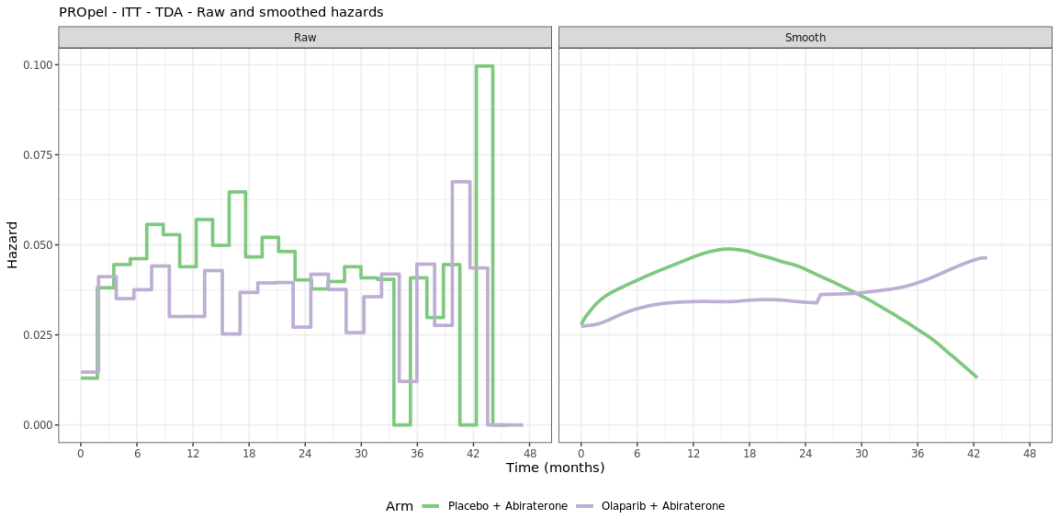
Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	19.8 (18.4, 21.3)	15.7 (13.8, 17.1)
Olaparib + Abiraterone	[redacted]	[redacted]

CI, confidence interval; RMST, restricted mean survival time

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

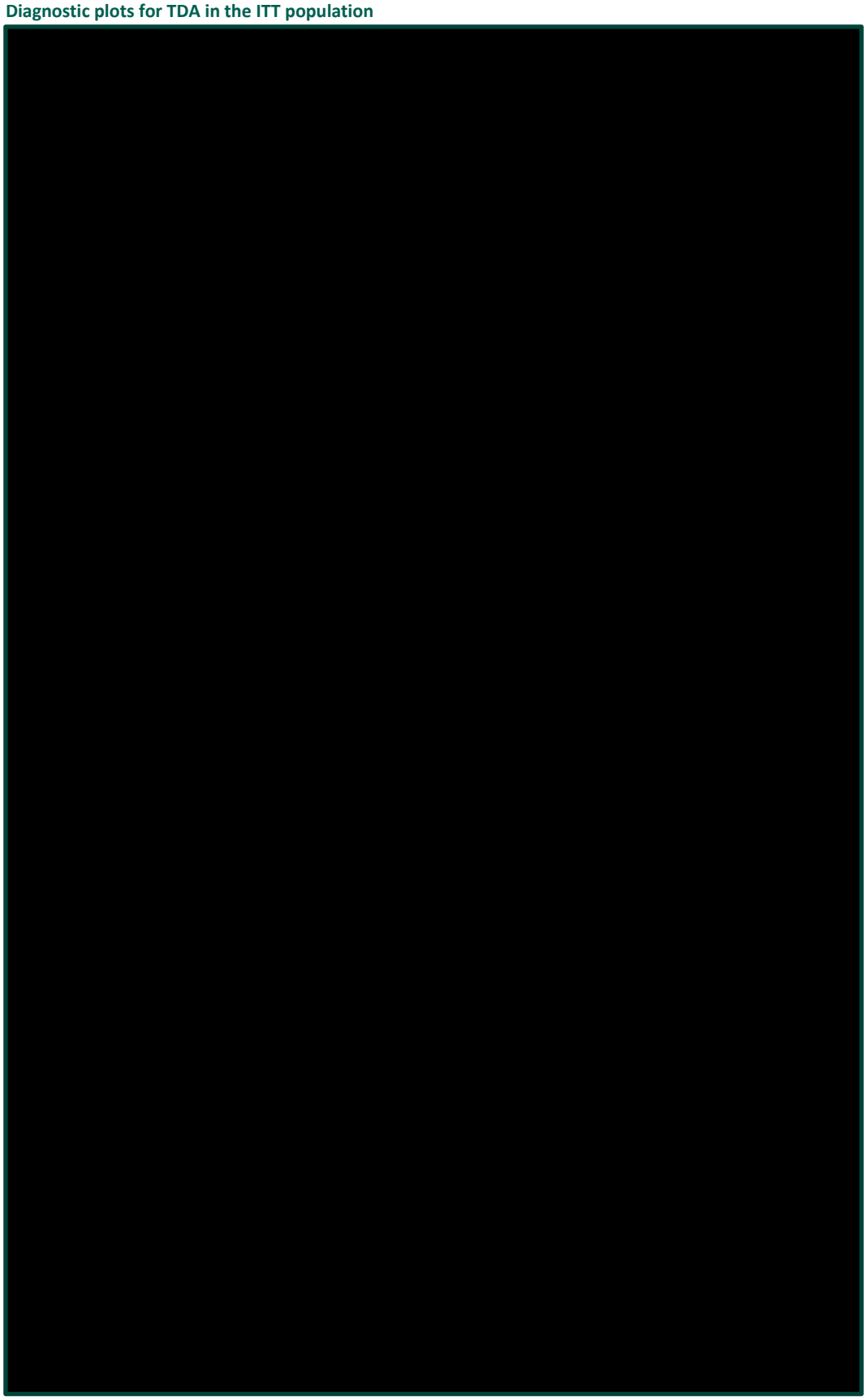
Kaplan-Meier survival plot for TDA in the ITT population

Smoothed and empirical hazards for TDA in the ITT population



The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log-cumulative hazards (Weibull) plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds (loglogistic) diagnostic plot, parallel lines indicate proportional odds and in the lognormal diagnostic plot, parallel lines indicate constant acceleration.

Diagnostic plots for TDA in the ITT population



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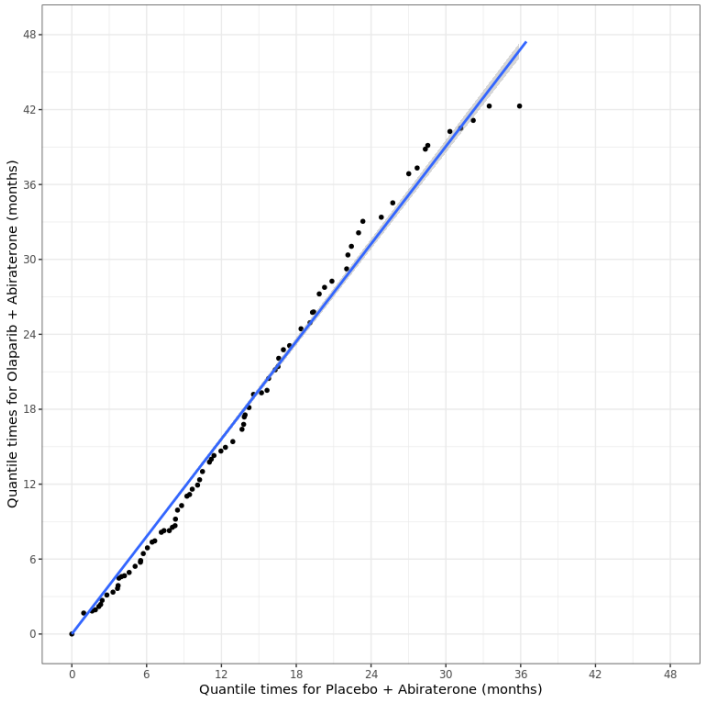
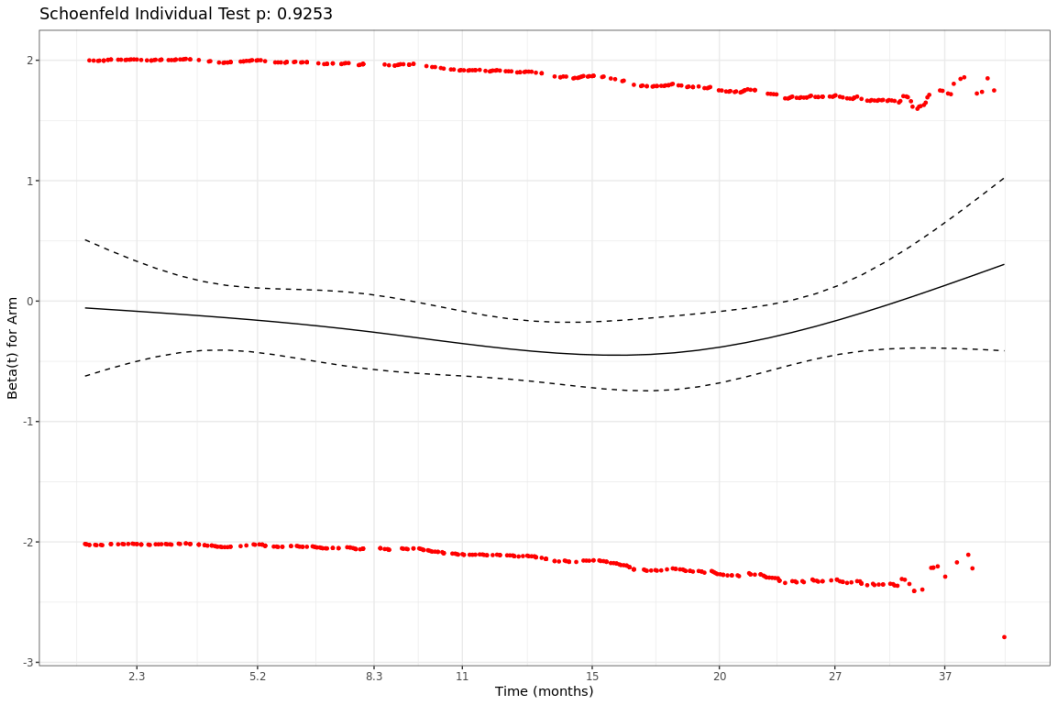
Quantile-quantile plot for rPFS in the ITT population



A straight line in the quantile-quantile plot indicates that an accelerated failure time model may fit the data well.

Schoenfeld residuals plot for TDA in the ITT population



Schoenfeld residuals have been calculated using the KM transform. The Schoenfeld residuals can be used to test the proportional hazard assumption. If hazards are proportion, the plot of the residuals against time should show a linear trend with slope=0. A significant value on the Schoenfeld individual test indicates that the proportional hazards assumption has been violated. The visual inspection of this plot is more important than the test, however, a p-value is also outputted as the result of a test of non-negative slope (Therneau and Grambsch).

The diagnostic plots show some clear crossing of the lines during the early period, followed by a progressing separation. This is supported by the Schoenfeld residuals plot and the Q-Q plot where

it shows that a proportional hazards model or accelerated failure time model does not fit the data well in the later period. Therefore, independent extrapolations of the survival curves is favoured.

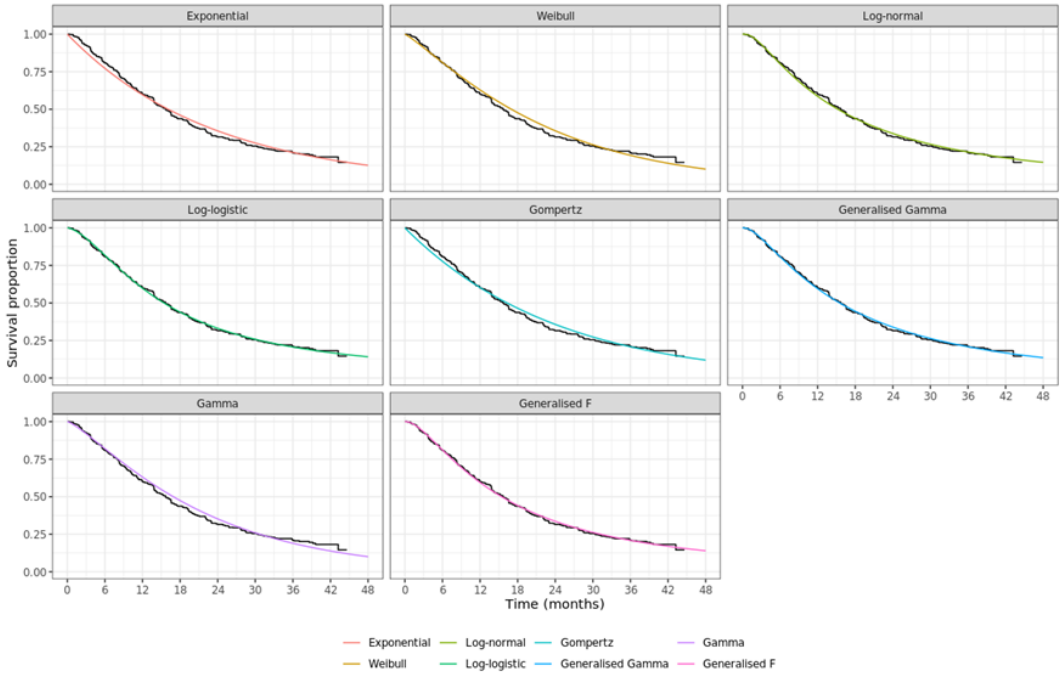
Goodness of fit statistics for independent models fitted to TDA in the ITT population

Olaparib + Abiraterone			Placebo + Abiraterone		
Distribution	AIC	BIC	Distribution	AIC	BIC
Lognormal	2508.2	2516.2	Loglogistic	2605.7	2613.7
Generalised Gamma	2510.2	2522.1	Lognormal	2606.3	2614.2
Loglogistic	2514.7	2522.7	Generalised Gamma	2607.2	2619.2
Gamma	2502.2	2528.2	Gamma	2619.1	2627.1
Weibull	2522.5	2530.5	Weibull	2623.5	2631.5
Exponential	2525.4	2529.4	Exponential	2629.8	2633.8
Gompertz	2527.0	2534.9	Gompertz	2631.6	2639.6

For the placebo + abiraterone arm, the loglogistic distribution has the best statistical fit. The lognormal and generalised gamma distributions were also good fits (ΔAIC < 5). For the olaparib + abiraterone arm, the lognormal distribution has the best statistical fit. The generalised gamma distribution was also a good fit (ΔAIC < 5).

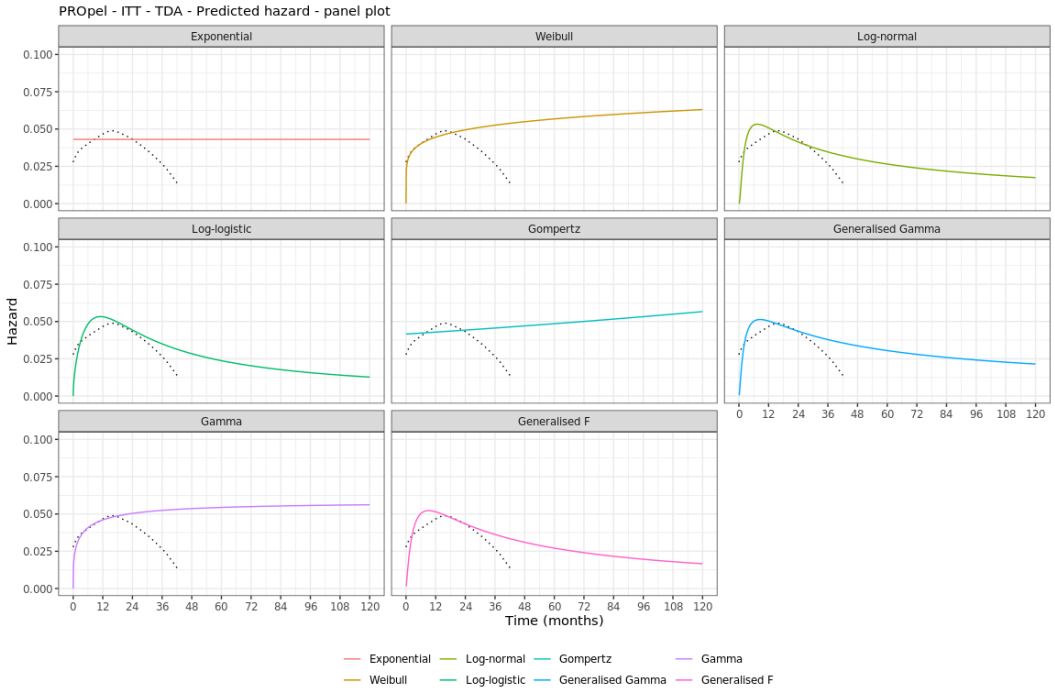
The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

Fitted independent parametric models vs. Kaplan-Meier for TDA in the placebo + abiraterone arm in the ITT population



Most curves provided a reasonable visual fit to the placebo + abiraterone arm during trial follow-up, though the exponential, Weibull, Gompertz, and gamma curves less closely followed the Kaplan-Meier. The smoothed hazards indicate a non-monotonic functional form, and flexible fits with the generalised F distribution support this. The visual fit of the smoothed hazards and Kaplan-Meier indicate that the loglogistic, lognormal, or generalised gamma would be plausible, in line with the goodness fit statistics.

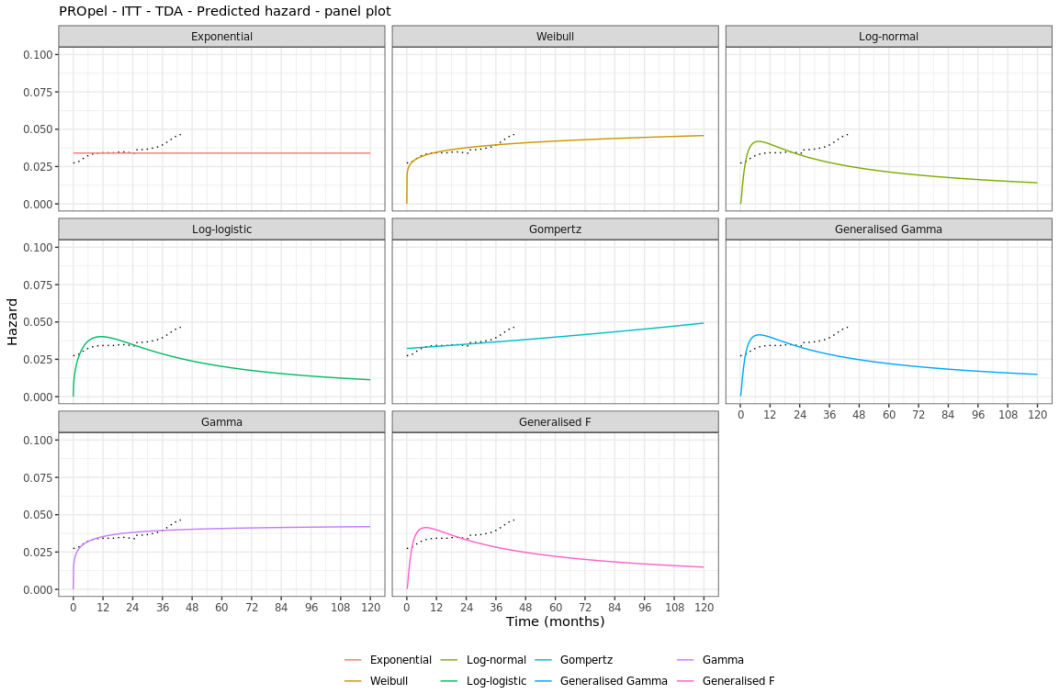
Hazard functions of fitted parametric models to the placebo + abiraterone arm compared to smoothed hazards for TDA in the ITT population



Fitted independent parametric models vs. Kaplan-Meier for TDA in the olaparib + abiraterone arm in the ITT population

In the olaparib + abiraterone arm, all curves provided a reasonable visual fit to the observed trial period, though the exponential distribution underestimates early survival and the Weibull and gamma distributions slightly overestimating mid-term survival. The shape of the smoothed hazards is not especially aligned with any distribution, though considering the empirical hazards in the figures above there is some added stochasticity in the data from around 33 months (after which point the impact of censoring can bias inferences on events/underlying hazard). Prior to this time, the exponential and Gompertz distributions could be dismissed based on their poor fits to the underlying hazards.

Hazard functions of fitted parametric models to the olaparib + abiraterone arm compared to smoothed hazards for TDA in the ITT population



Given the relative maturity of the data, there is very little difference in the long-term extrapolations. On the basis of the best statistical best, as well as having a good visual fit to the observed trial data and matching the smoothed hazards, the loglogistic distribution is selected for the placebo + abiraterone arm. Given that this distribution also had a good statistical and visual fit to the olaparib + abiraterone, and the NICE DSU guidance to apply similar functional forms between both extrapolated treatment arm, the loglogistic distribution is selected for this arm as well. This also follows a similar functional form than the selected models for rPFS.

Time to Discontinuation of Olaparib

Number of subject and events for TDT in the ITT population

Arm	N	Events	Maturity
Olaparib + Abiraterone	399	295	73.9%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last observed time point, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

Median survival times for TDT in the ITT population

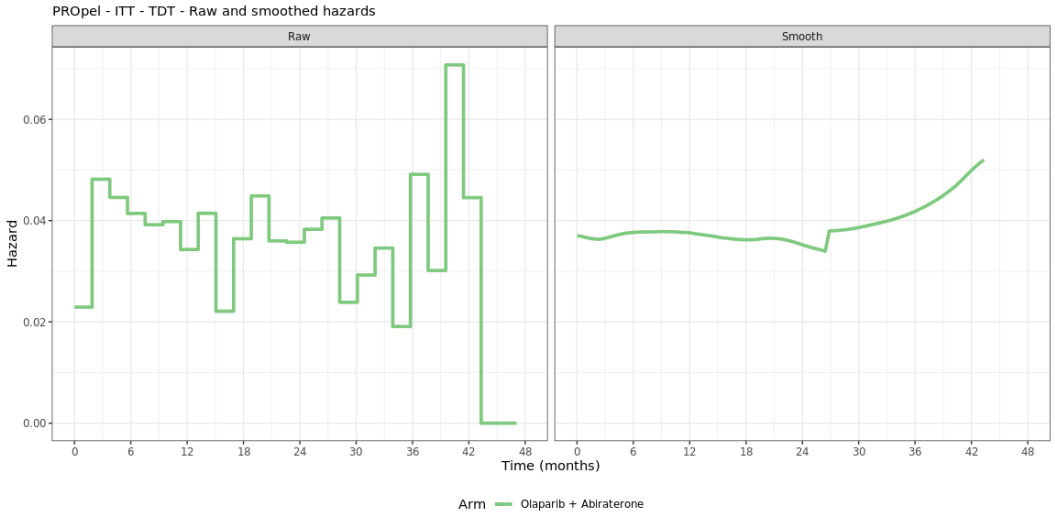
Arm	RMST (95% CI)	Median (95% CI)
Olaparib + Abiraterone	[redacted]	[redacted]

CI, confidence interval

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

Kaplan-Meier survival plot for TDT in the ITT population

Smoothed and empirical hazards for TDT in the ITT population



The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution.

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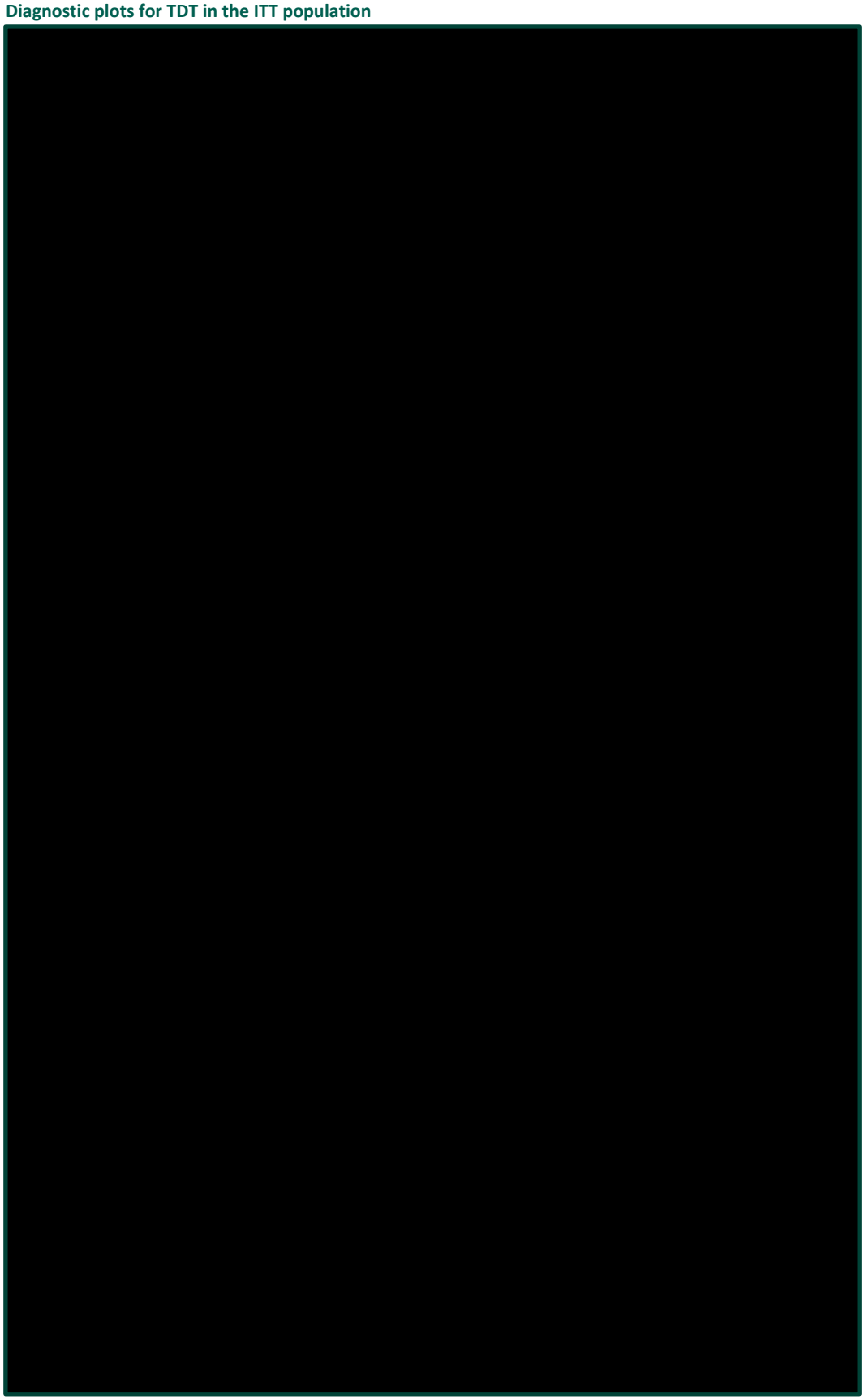
Diagnostic plots for TDT in the ITT population



Goodness of fit statistics for models fitted to TDT in the ITT population

Olaparib + Abiraterone		
Distribution	AIC	BIC
Lognormal	2527.3	2535.3

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Olaparib + Abiraterone		
Distribution	AIC	BIC
Generalised Gamma	2529.1	2541.1
Loglogistic	2533.7	2541.7
Exponential	2540.3	2544.3
Gamma	2540.5	2548.4
Weibull	2541.6	2549.5
Gompertz	2542.0	2550.0

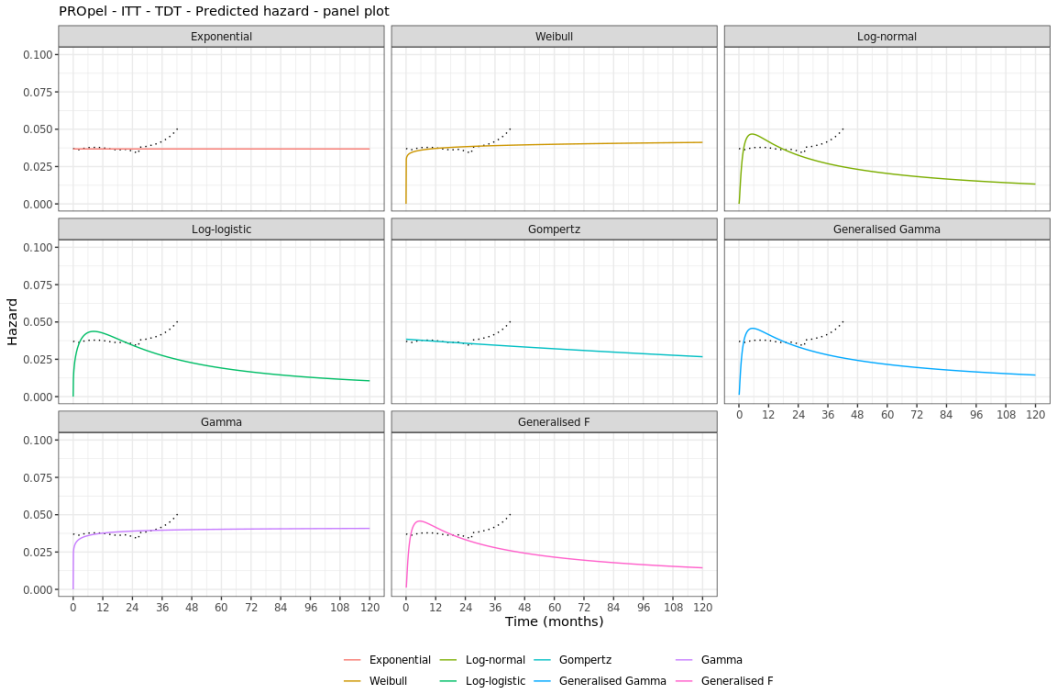
The lognormal distribution has the best statistical fit. The generalised gamma distribution was also a good fit (ΔAIC < 5).

The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

Fitted independent parametric models vs. Kaplan-Meier for TDT in the ITT population

Most curves provided a good visual fit to the placebo + abiraterone arm during trial follow-up, with the potential exception of the Weibull and gamma distributions. As with the time to discontinuation of abiraterone curve for this arm, there is an increase in the smoothed hazards after around 26 months, potentially informed by the increase in empirical hazards observed around the same time. Were the hazards truncated at around 36 months, then it is plausible that the smooth hazards would decrease from around month 3 onwards. This could explain the favourable statistical fit of the lognormal, loglogistic, and generalised gamma curves and the alignment with the smoothed hazards during the first 26 months.

Hazard functions of fitted parametric models compared to smoothed hazards for TDT in the ITT population



On the basis of the good statistical fit and visual fits, as well as the linear diagnostic plots, only the lognormal, loglogistic, and generalised gamma distributions were considered potentially plausible, in line with the time to discontinuation of abiraterone curve. The base case curve was selected based on the plausibility of long-term extrapolations. Assuming a loglogistic distribution for time to discontinuation of abiraterone, time to discontinuation of olaparib would exceed this after approximately 8 years when using the loglogistic distribution. As this contradicts with the trial evidence, the loglogistic distribution for this endpoint was considered implausible. Despite having the best statistical fit, the time on treatment using the lognormal distribution converges to be approximately equal to the time to discontinuation of abiraterone curve. For these curves to converge, it implicitly assumes that the hazard of olaparib discontinuation must at some point be greater than the hazard of abiraterone discontinuation. As this contradicts with the observed data, the generalised gamma distribution is selected for the base case.

Patients with HRR mutations

Radiological Progression-Free Survival

Number of subject and events for rPFS in the HRRm population

Arm	N	Events	Maturity
Placebo + Abiraterone	115	89	77.4%
Olaparib + Abiraterone	111	60	54.1%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last time point where each arm has observations, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

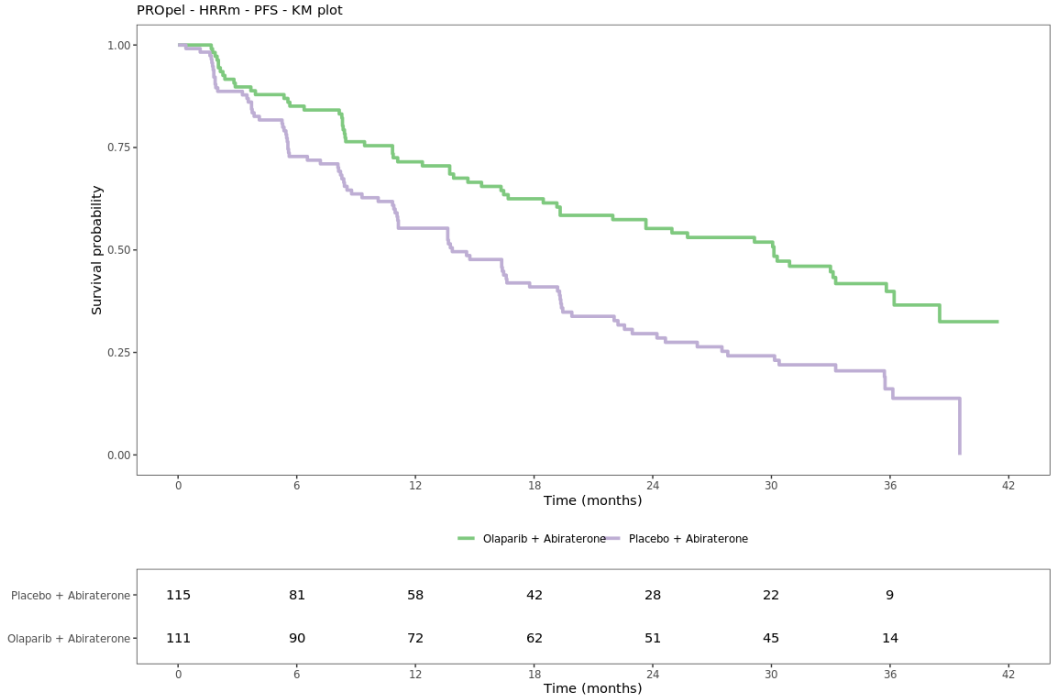
Restricted mean survival times and median survival times for rPFS in the HRRm population

Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	17.5 (15.0, 20.0)	13.9 (11.0, 19.2)
Olaparib + Abiraterone	24.9 (22.1, 27.7)	30.1 (19.3, 36.2)

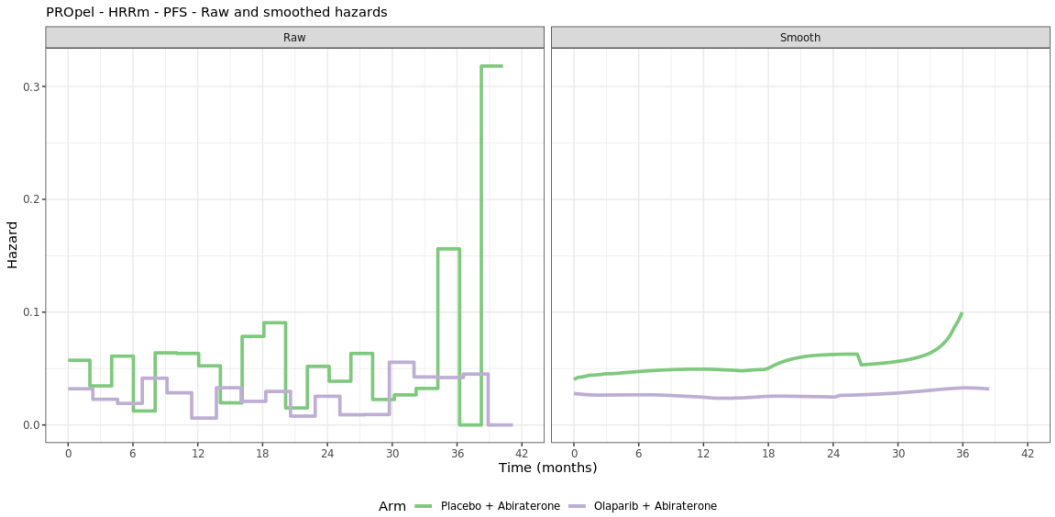
CI, confidence interval; NC, not calculable; RMST, restricted mean survival time

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

Kaplan-Meier survival plot for rPFS in the HRRm population



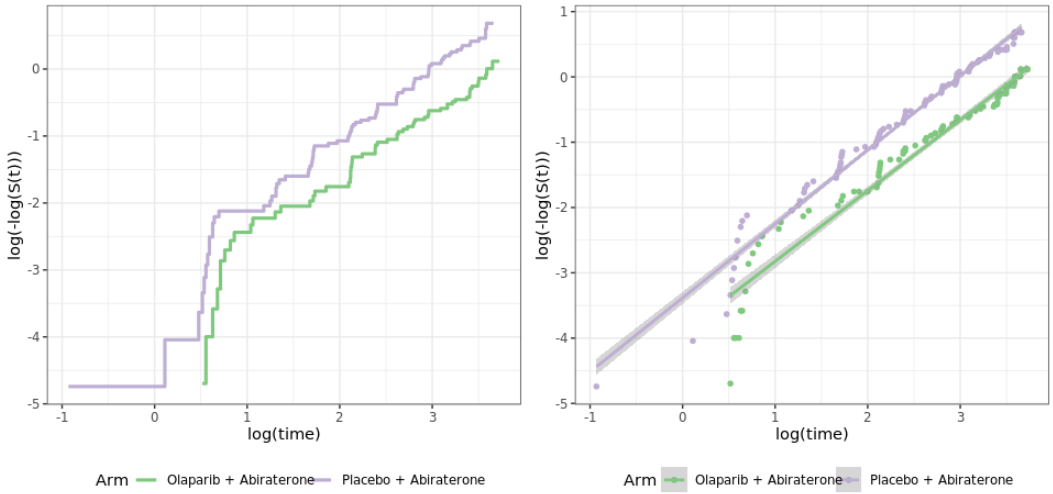
Smoothed and empirical hazards for rPFS in the HRRm population



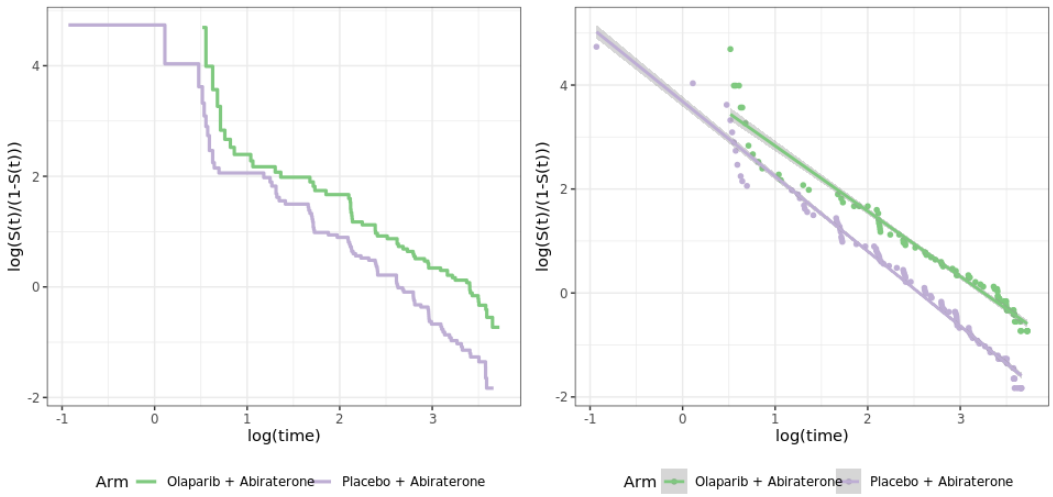
The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log-cumulative hazards (Weibull) plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds (loglogistic) diagnostic plot, parallel lines indicate proportional odds and in the lognormal diagnostic plot, parallel lines indicate constant acceleration.

Diagnostic plots for rPFS in the HRRm population

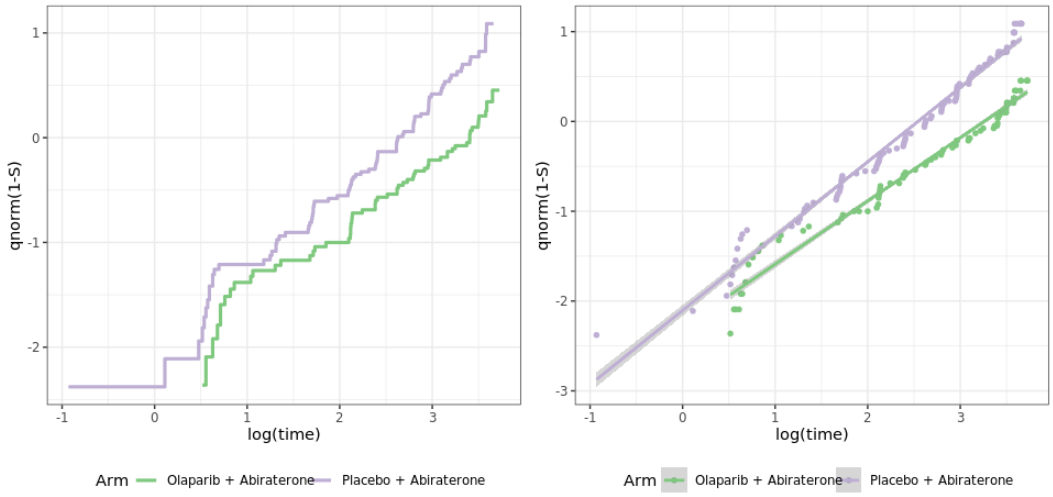
Log cumulative hazards vs. log time



Log odds vs. log time



Log normal vs. log time



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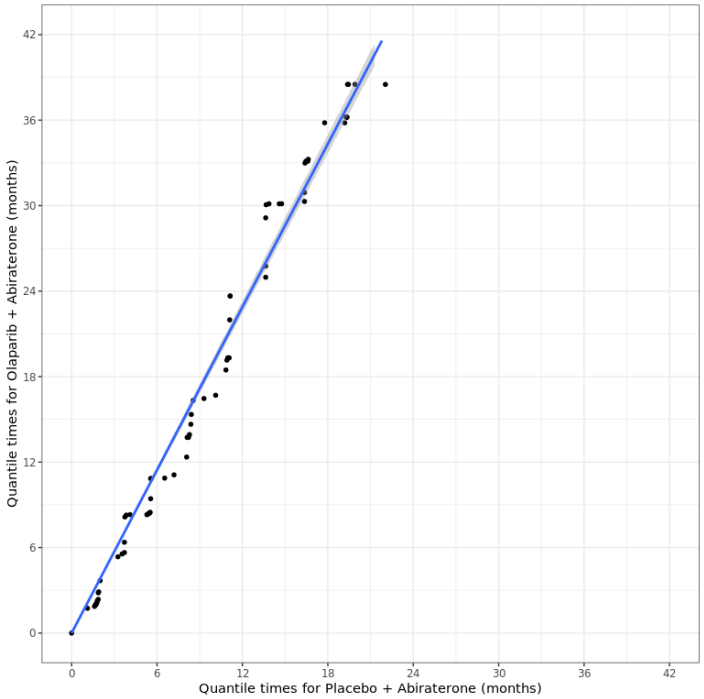
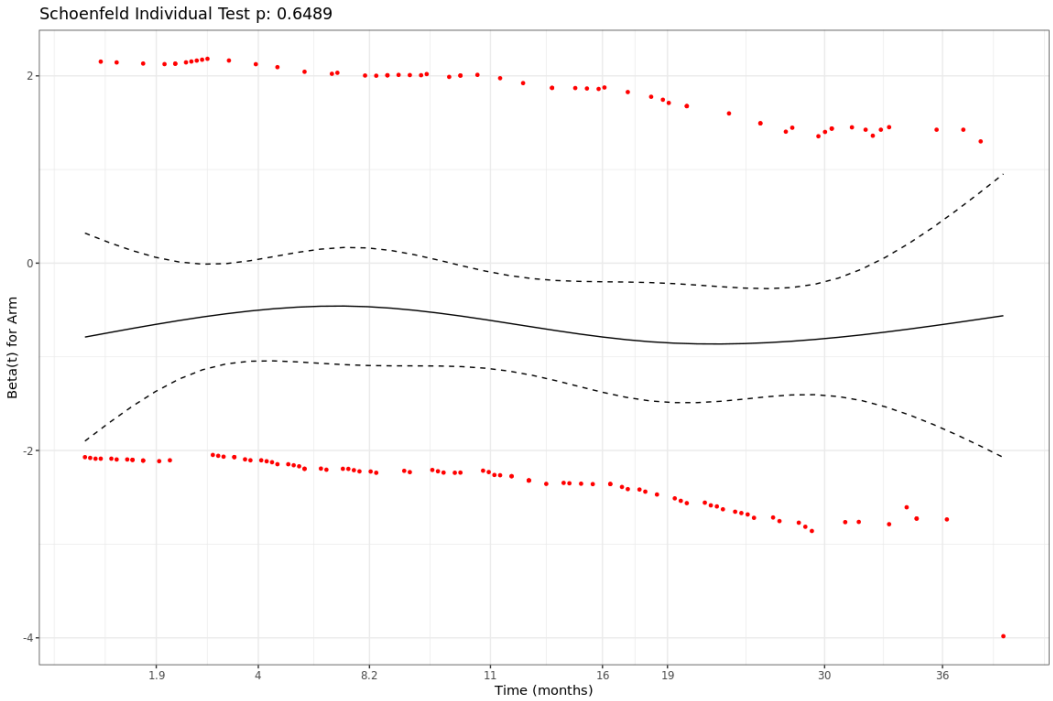
Quantile-quantile plot for rPFS in the HRRm population



A straight line in the quantile-quantile plot indicates that an accelerated failure time model may fit the data well.

Schoenfeld residuals plot for rPFS in the HRRm population



Schoenfeld residuals have been calculated using the KM transform. The Schoenfeld residuals can be used to test the proportional hazard assumption. If hazards are proportion, the plot of the residuals against time should show a linear trend with slope=0. A significant value on the Schoenfeld individual test indicates that the proportional hazards assumption has been violated. The visual inspection of this plot is more important than the test, however, a p-value is also outputted as the result of a test of non-negative slope (Therneau and Grambsch).

The Kaplan-Meier plot shows a clear progression of the benefit of olaparib, the smoothed hazards are somewhat proportional, and the diagnostic plots show that the lines do not cross but diverge

slightly over time but that the lognormal or loglogistic plot is a slightly better fit to the data. Despite this, the quantile-quantile plot indicates than an accelerated failure time model is not an exact fit to the data. The Schoenfeld residuals plots has an almost horizontal slope but a slight negative trend in the plotted residuals. The evidence indicates that independent extrapolation of the curves would be preferable, but as the evidence is not conclusive joint models are also considered.

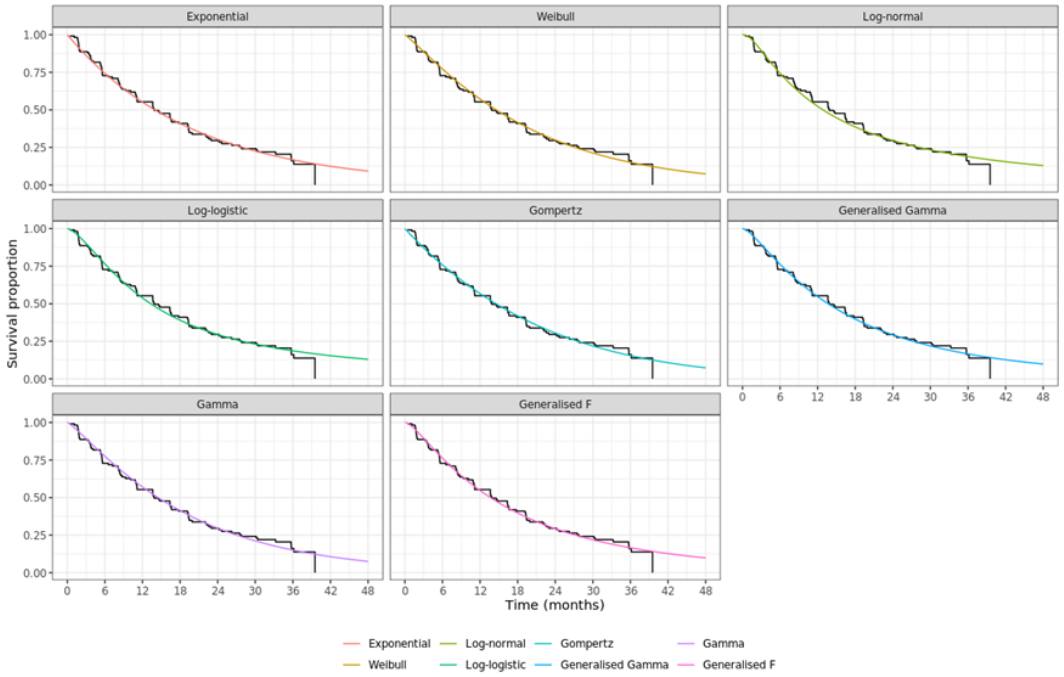
Goodness of fit statistics for independent models fitted to rPFS in the HRRm population

Olaparib + Abiraterone			Placebo + Abiraterone		
Distribution	AIC	BIC	Distribution	AIC	BIC
Lognormal	561.8	567.2	Exponential	714.7	717.4
Exponential	562.1	564.8	Gamma	714.9	720.4
Loglogistic	563.7	569.1	Weibull	715.3	720.8
Generalised Gamma	563.8	571.9	Lognormal	715.7	721.1
Gamma	563.9	569.3	Generalised Gamma	715.8	724.0
Weibull	564.0	569.4	Gompertz	716.2	721.7
Gompertz	564.1	569.5	Loglogistic	716.4	721.9

For the placebo + abiraterone arm, the exponential distribution has the best statistical fit. All other distributions also provided good statistical fits (ΔAIC < 5). For the olaparib + abiraterone arm, the lognormal distribution has the best statistical fit. All other distributions also provided good statistical fits (ΔAIC < 5).

The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

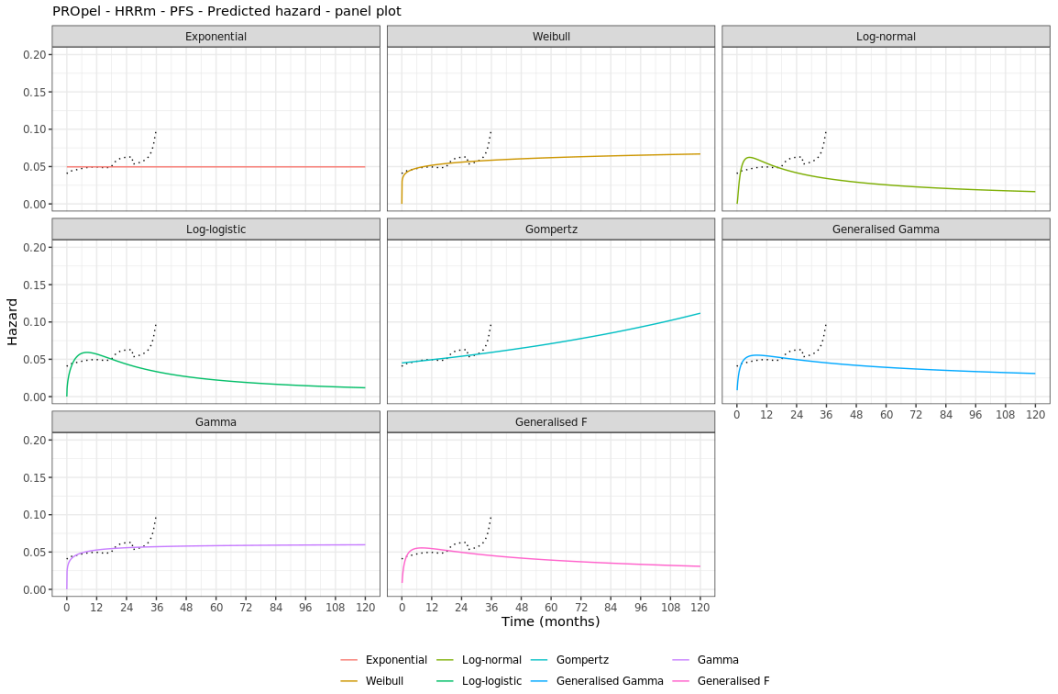
Fitted independent parametric models vs. Kaplan-Meier for rPFS in the placebo + abiraterone arm in the HRRm population



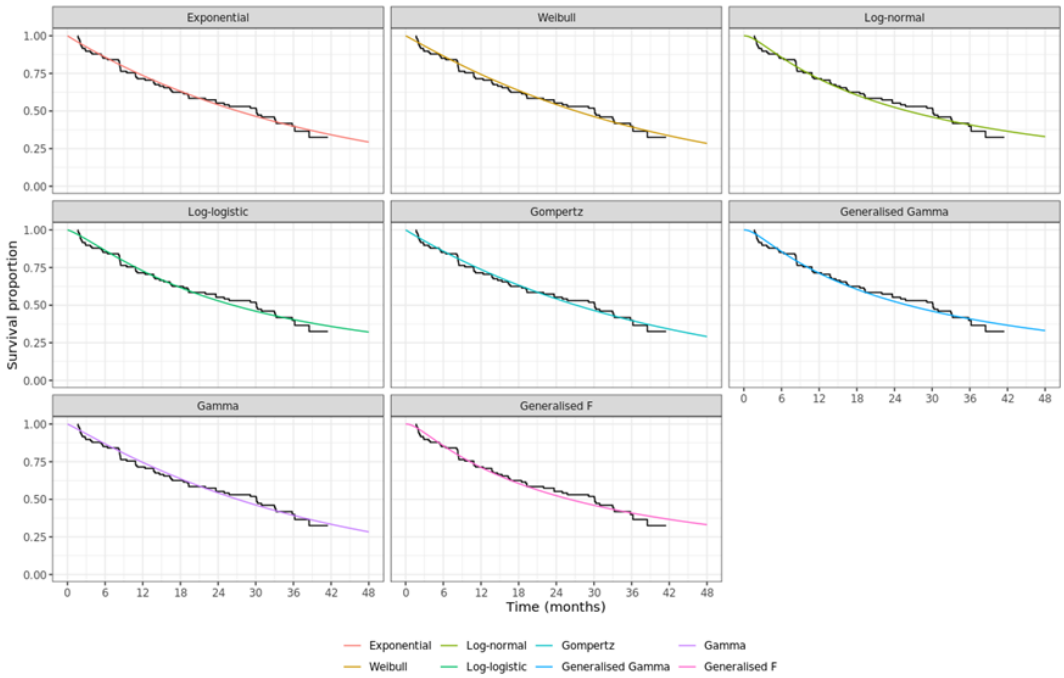
All curves provided a reasonable visual fit to the placebo + abiraterone arm during trial follow-up. The lognormal distribution underestimated mid-term survival slightly in favour of a longer tail. Outcomes with the gamma, Gompertz, and Weibull distributions were more or less identical, supported by their similar hazard functions. The underlying data do not particularly favour any particular functional form, though on the basis of the log-cumulative hazard and Schoenfeld

residuals plot, a pure proportional hazards model doesn't seem plausible and so the exponential is rejected.

Hazard functions of fitted parametric models to the placebo + abiraterone arm compared to smoothed hazards for rPFS in the HRRm population

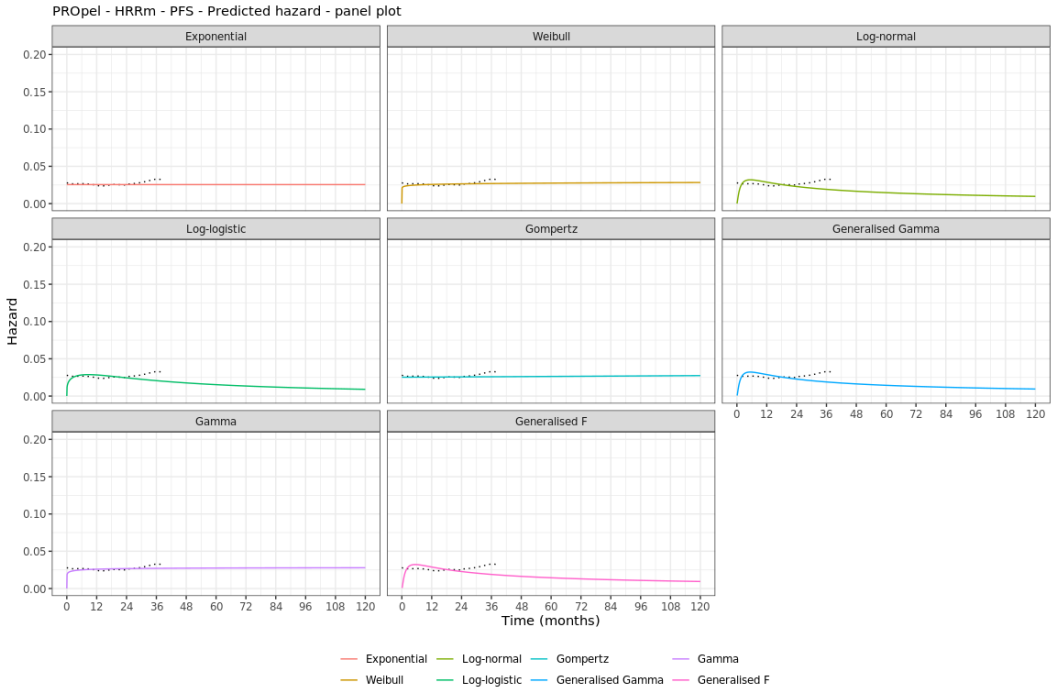


Fitted independent parametric models vs. Kaplan-Meier for rPFS in the olaparib + abiraterone arm in the HRRm population



In the olaparib + abiraterone arm, all curves provided a reasonable fit to the observed data with the exception of the slight underestimation of survival between months 22 and 32. In terms of functional form, all curves provided a reasonable fit to the underlying hazards in the data.

Hazard functions of fitted parametric models to the olaparib + abiraterone arm compared to smoothed hazards for rPFS in the HRRm population



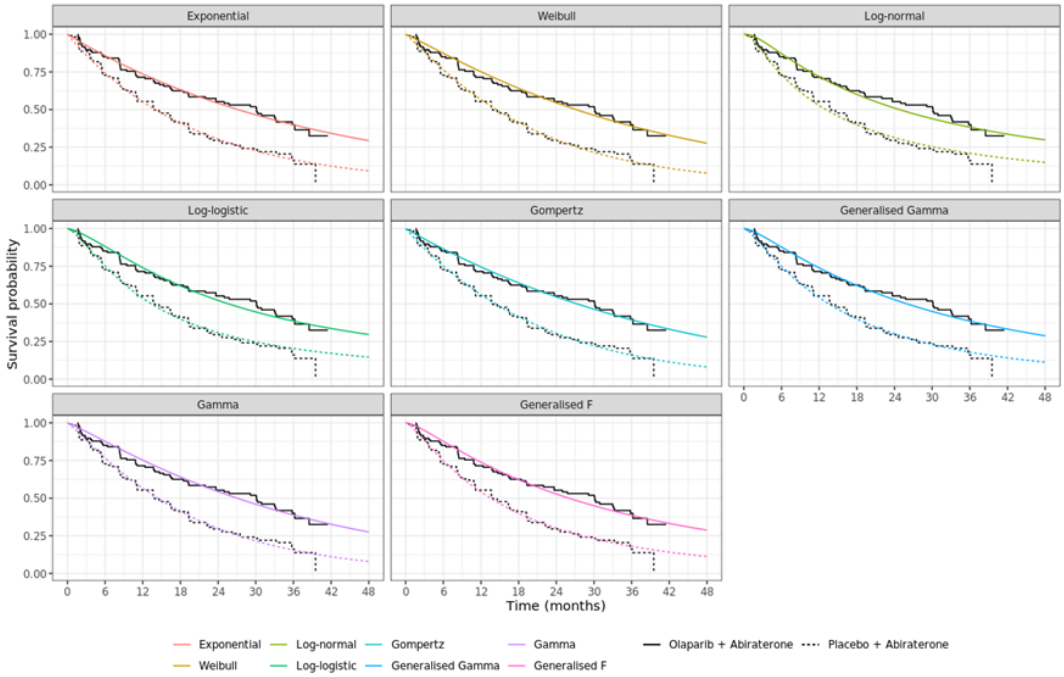
Goodness of fit statistics for joint models fitted to rPFS in the HRRm population

Distribution	AIC	BIC
Exponential	1276.8	1283.7
Gamma	1277.0	1287.3
Generalised Gamma	1277.2	1290.9
Lognormal	1277.3	1287.6
Weibull	1277.5	1287.8
Gompertz	1278.5	1288.8
Loglogistic	1279.6	1289.9

The exponential distribution has the best statistical fit. All other distributions also provided good statistical fits (ΔAIC < 5).

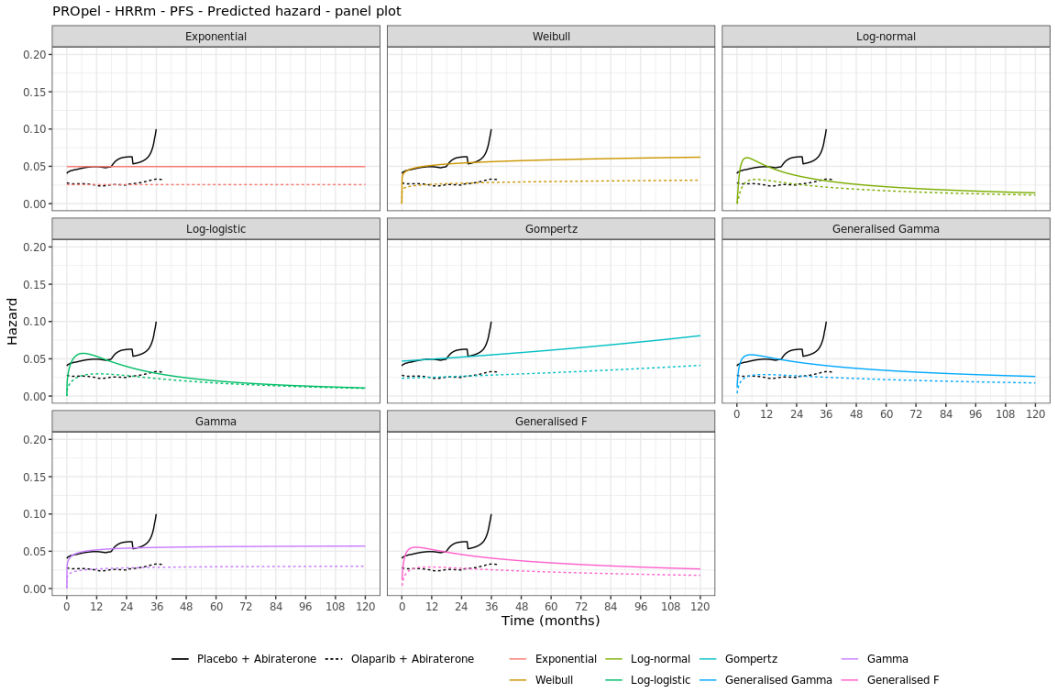
The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

Fitted joint parametric models vs. Kaplan-Meier for rPFS in the HRRm population



Most models provided a reasonable visual fit to the observed data, but the joint lognormal and loglogistic models provided a poor fit to one or both arms. This is supported by the quantile-quantile plot presented above. The smoothed hazards plots also indicate a poor fit to these curves. However, despite the flexibility of the generalised gamma and generalised F distributions to follow the exponential, Weibull, or gamma distributions (as well as the lognormal or loglogistic distributions), both of these forms converged showing a non-monotonic hazards, suggesting that these models may be preferable to monotonically increasing or decreasing models, despite the poor fit of the joint models.

Hazard functions of fitted parametric models compared to smoothed hazards for rPFS in the HRRm population



On the basis of the log-cumulative hazards and Schoenfeld residuals plot, the exponential distribution is dismissed as this would result in a constant proportional hazards model in either

independent or joint modelling. The lognormal and loglogistic diagnostic plots show a slightly better fit to the data, despite the smoothed hazards not explicitly suggesting a non-monotonic form. However, joint models using the lognormal or loglogistic distribution resulted in a poor fit compared to the trial data, supported by the quantile-quantile plot which indicates that the assumption of an accelerated failure time is unlikely to hold.

As models with montonically increasing or decreasing hazards, such as the gamma or Weibull (both with similar results) would result in a progression-free survival which is shorter than the modelled time on treatment (where the data is more mature), it is assumed that a non-monotonic hazard model is required. As joint models on these curves did not fit the data well, independent extrapolation is considered. The lognormal, loglogistic, and generalised gamma distributions produce similar results. The generalised gamma distribution provides survival estimates which may be expected based on real-world outcomes in the overall population, as well as not significantly overestimating rPFS compared to time on treatment, it is preferred distribution for this endpoint.

Overall Survival

Number of subject and events for OS in the HRRm population

Arm	N	Events	Maturity
Placebo + Abiraterone	115	69	60.0%
Olaparib + Abiraterone	111	48	43.2%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last time point where each arm has observations, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

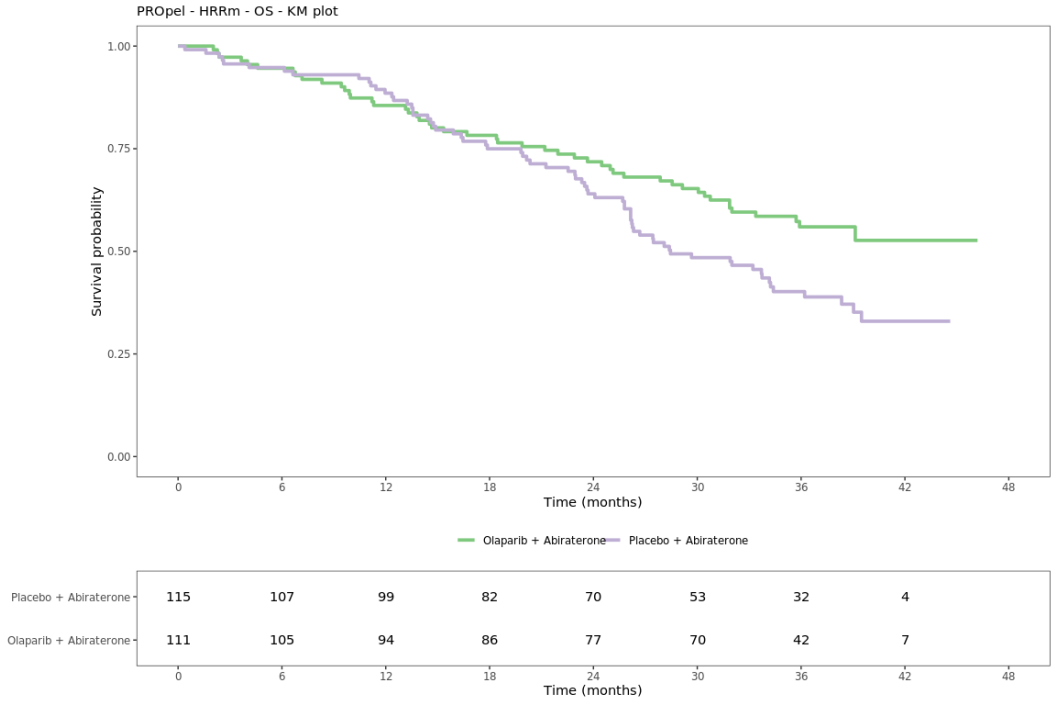
Restricted mean survival times and median survival times for OS in the HRRm population

Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	29.6 (27.0, 32.1)	28.5 (26.2, 34.4)
Olaparib + Abiraterone	33.0 (30.2, 35.7)	NR (32.0, NR)

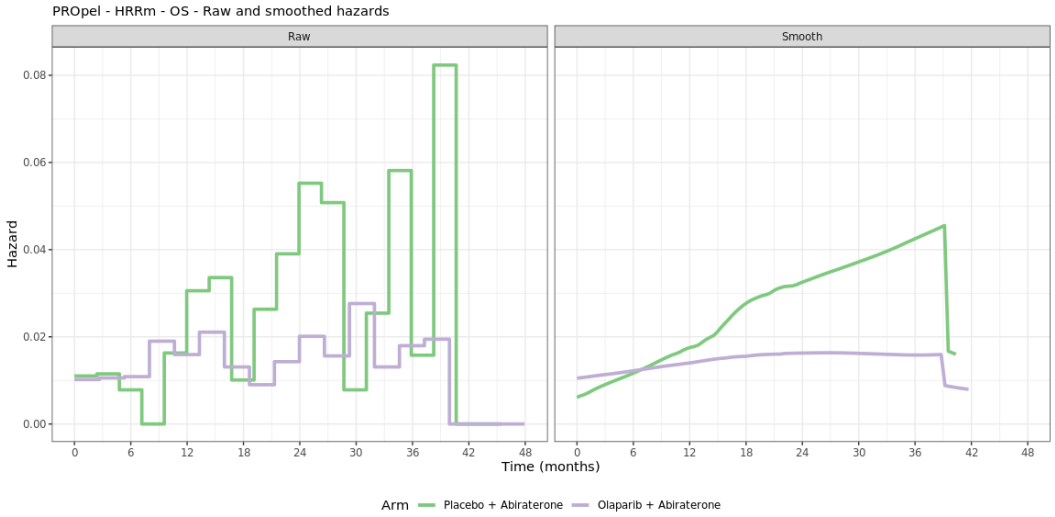
CI, confidence interval; NC, not calculable; RMST, restricted mean survival time

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

Kaplan-Meier survival plot for OS in the HRRm population



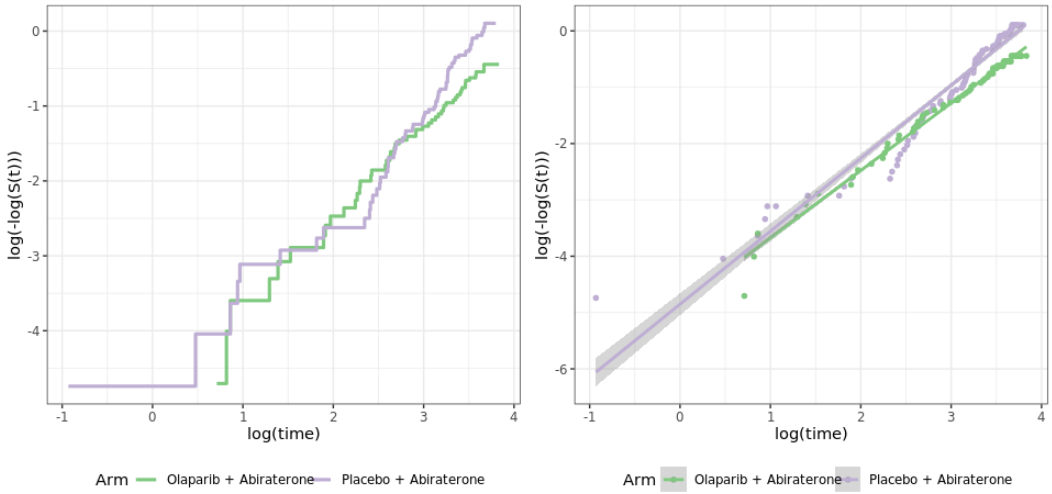
Smoothed and empirical hazards for OS in the HRRm population



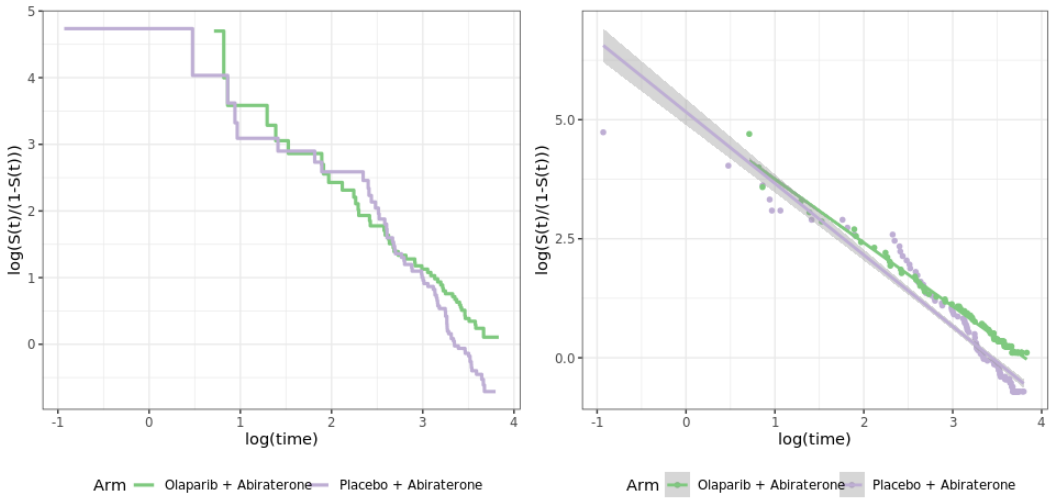
The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log-cumulative hazards (Weibull) plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds (loglogistic) diagnostic plot, parallel lines indicate proportional odds and in the lognormal diagnostic plot, parallel lines indicate constant acceleration.

Diagnostic plots for OS in the HRRm population

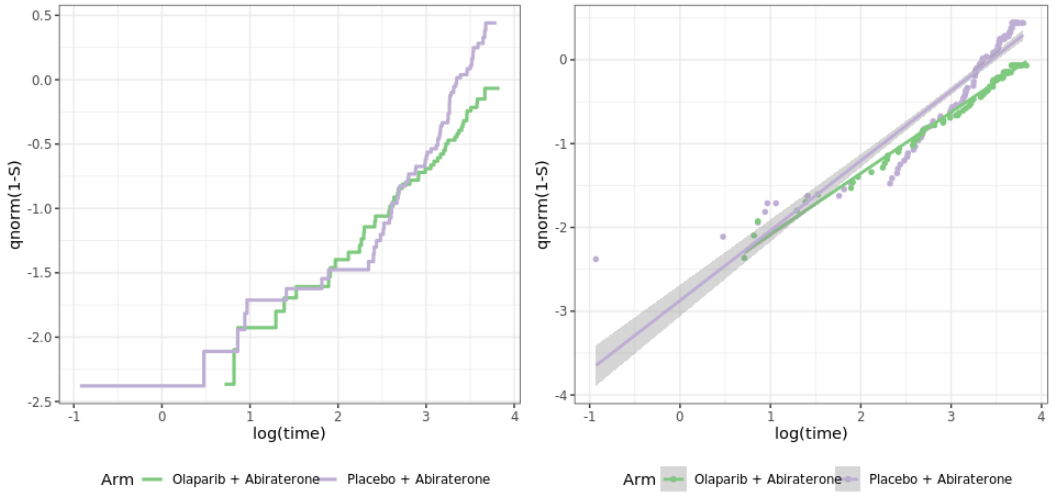
Log cumulative hazards vs. log time



Log odds vs. log time



Log normal vs. log time



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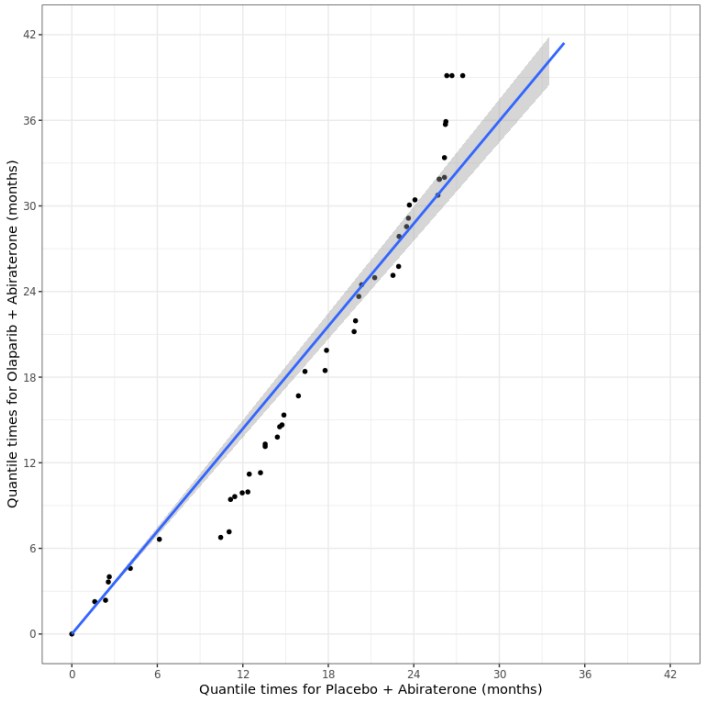
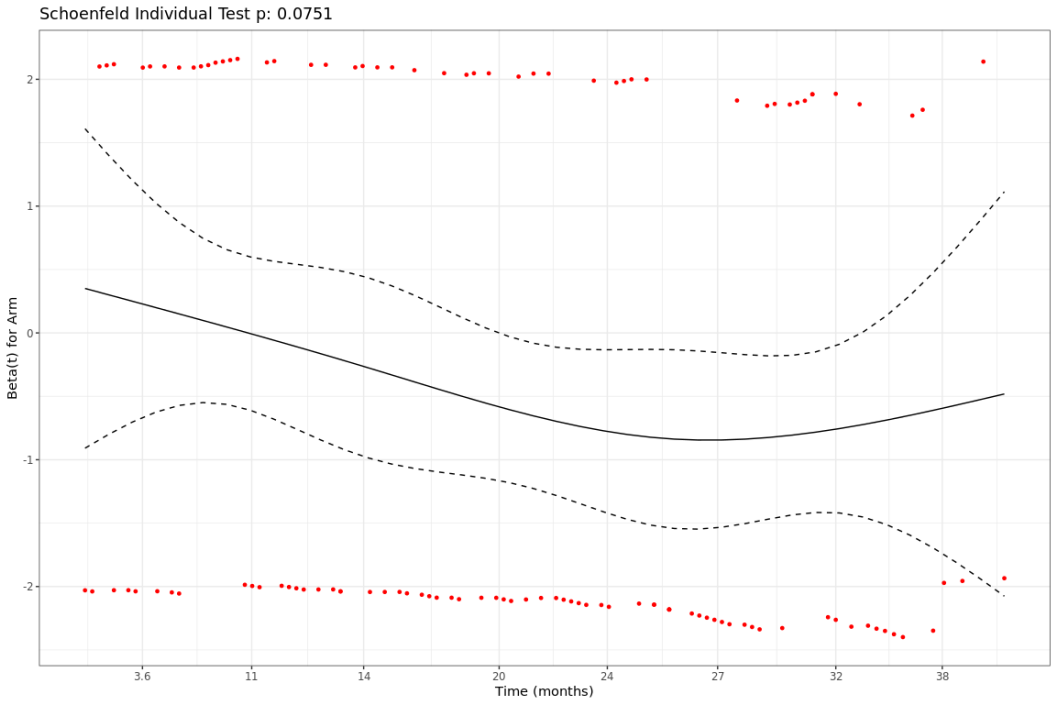
Quantile-quantile plot for OS in the HRRm population



A straight line in the quantile-quantile plot indicates that an accelerated failure time model may fit the data well.

Schoenfeld residuals plot for OS in the HRRm population



Schoenfeld residuals have been calculated using the KM transform. The Schoenfeld residuals can be used to test the proportional hazard assumption. If hazards are proportion, the plot of the residuals against time should show a linear trend with slope=0. A significant value on the Schoenfeld individual test indicates that the proportional hazards assumption has been violated. The visual inspection of this plot is more important than the test, however, a p-value is also outputted as the result of a test of non-negative slope (Therneau and Grambsch).

The diagnostic plots show that the curves cross during the initial period before a period of growing divergence, indicating the proportional hazards is not plausible. The Schoenfeld residuals plot

indicates that proportional hazards has been violated and the Q-Q plot shows that an accelerated failure time model would not fit the data well. Therefore, independent extrapolations of the survival curves is performed.

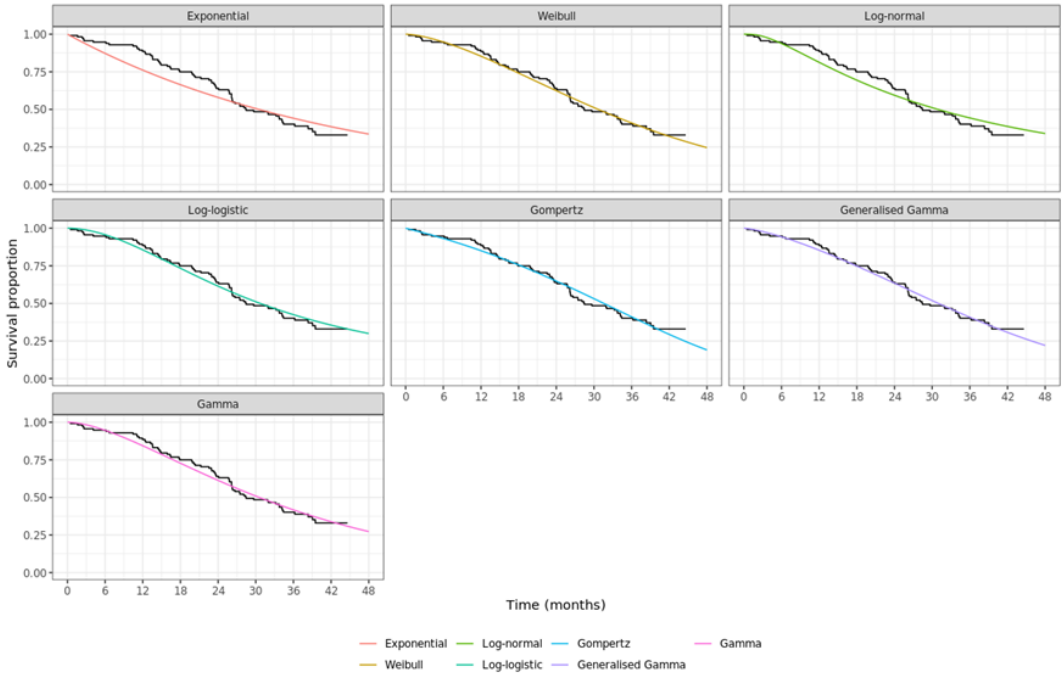
Goodness of fit statistics for independent models fitted to OS in the HRRm population

Olaparib + Abiraterone			Placebo + Abiraterone		
Distribution	AIC	BIC	Distribution	AIC	BIC
Lognormal	499.8	505.2	Gompertz	648.8	654.3
Loglogistic	500.1	505.5	Weibull	649.3	654.7
Gamma	500.3	505.8	Generalised Gamma	650.4	658.6
Weibull	500.6	506.0	Gamma	651.3	656.7
Exponential	500.9	503.6	Loglogistic	652.7	658.2
Generalised Gamma	501.6	509.8	Exponential	662.2	665.0
Gompertz	501.8	507.2	Lognormal	664.6	670.1

For the placebo + abiraterone arm, the Gompertz distribution has the best statistical fit. The Weibull, generalised gamma, gamma, and loglogistic distributions were also good fits (ΔAIC < 5). For the olaparib + abiraterone arm, the lognormal distribution has the best statistical fit. All other distributions provided good statistical fits (ΔAIC < 5).

The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

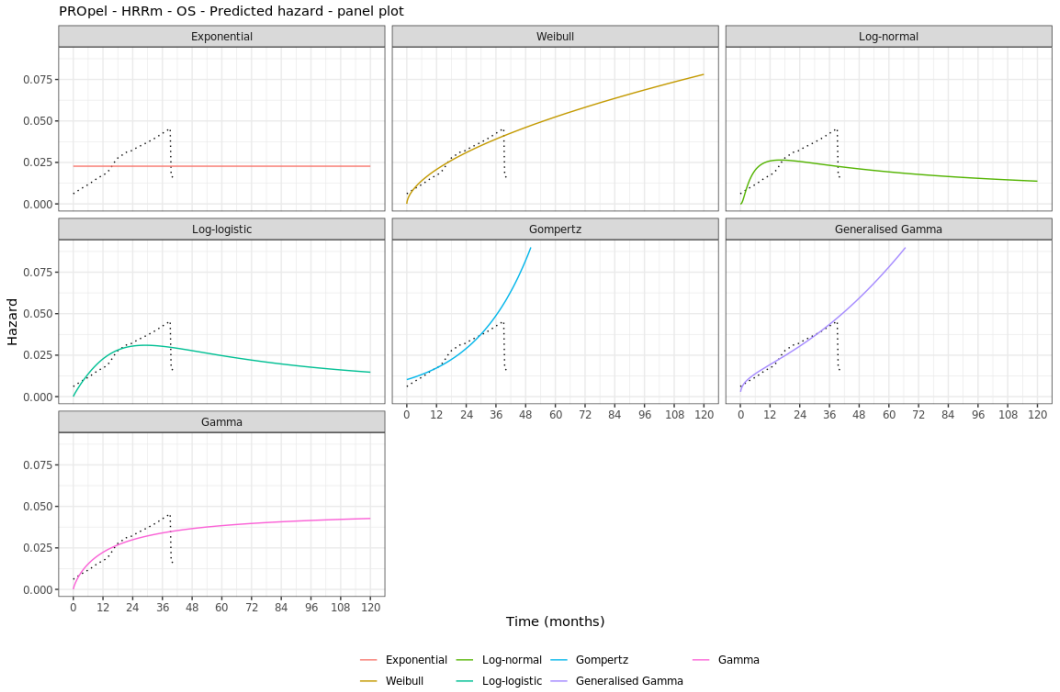
Fitted independent parametric models vs. Kaplan-Meier for OS in the placebo + abiraterone arm in the HRRm population



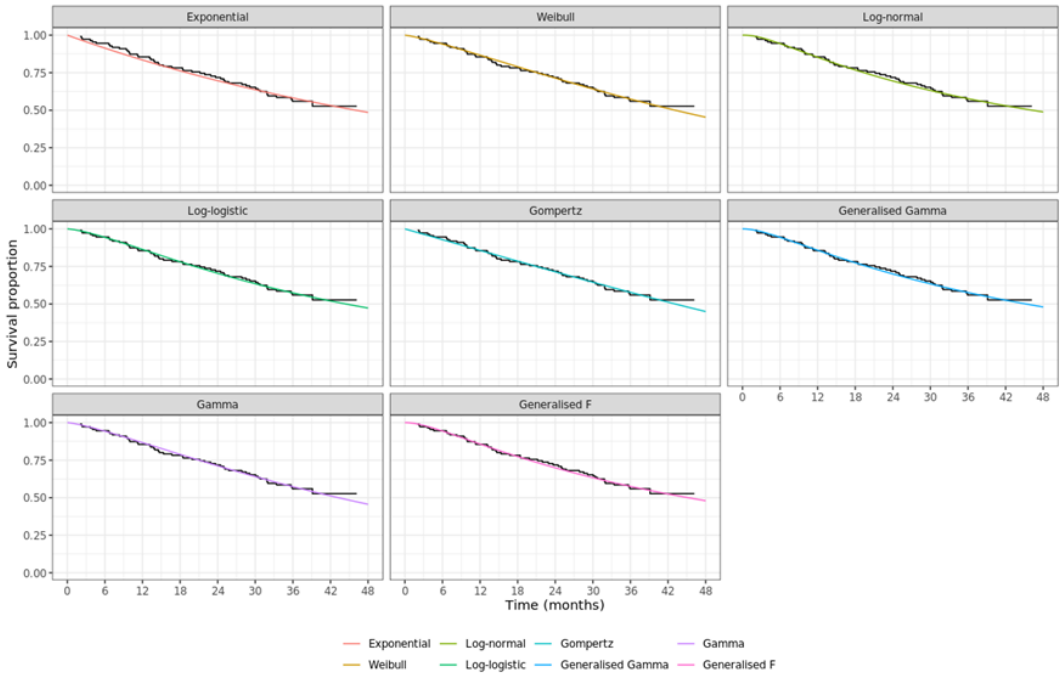
The exponential and lognormal distributions provided a poor fit to the placebo + abiraterone arm. The Gompertz distribution showed particularly poor survival outcomes after trial follow-up, though patients with HRR mutations are known to have a poor prognosis on new hormonal agents alone. Of fits that provided a good fit during follow-up, the loglogistic has a potentially optimistic tail and shows a slowing of the hazards. Whilst the smoothed hazards show a dramatic drop in the hazards towards the end of follow-up, the low number at risk at this time makes this somewhat uninformative. The Weibull, Gompertz, and generalised gamma follow similar functional forms

during follow-up, though the rate of growth of the hazard differs between the distributions, though all three are well aligned to the observed smoothed hazards.

Hazard functions of fitted parametric models to the placebo + abiraterone arm compared to smoothed hazards for OS in the HRRm population

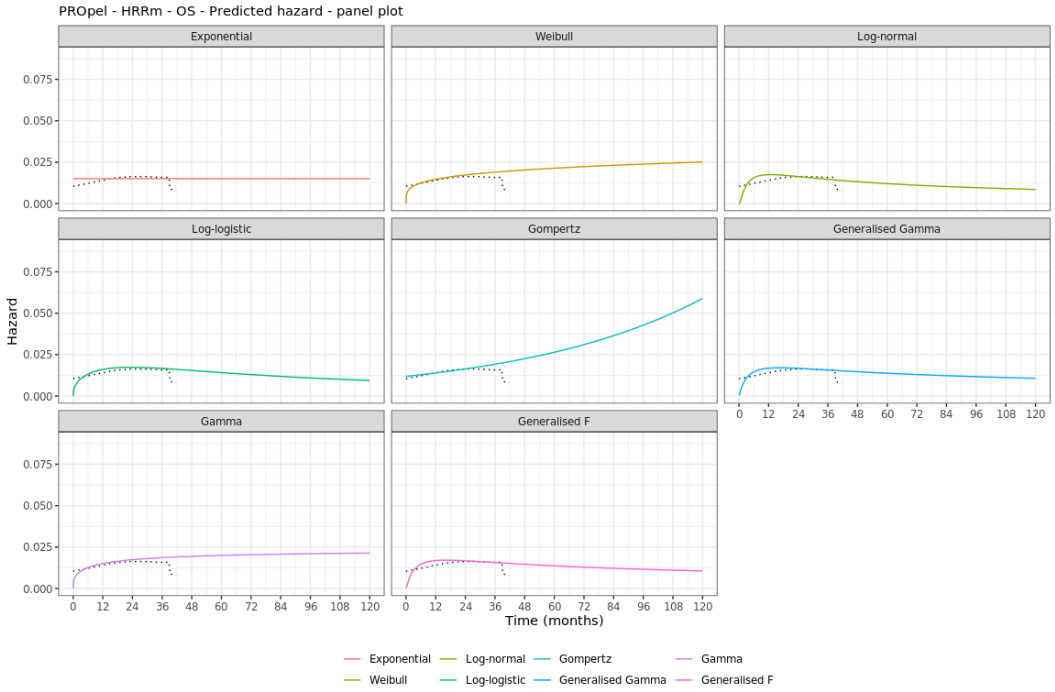


Fitted independent parametric models vs. Kaplan-Meier for OS in the olaparib + abiraterone arm in the HRRm population



In the olaparib + abiraterone arm, most curves provided a reasonable visual fit, except for the exponential distribution which tended to underestimate survival. With regards to functional form compared to the underlying hazard, only the exponential and lognormal distributions provided a less plausible fit. Given the immaturity of the data, it is not possible to dismiss a model using non-monotonic hazards, though one with a shallower peak and trough such as the loglogistic or generalised gamma seems more plausible.

Hazard functions of fitted parametric models to the olaparib + abiraterone arm compared to smoothed hazards for OS in the HRRm population



In the absence of real-world data to validate survival in patients with HRR mutations, assumptions are required. Estimates of the 5-year and 10-year survival with new hormonal agents from clinical experts are approximately 25% and 5-10%. Patients with HRR mutations are known to have a worse prognosis than those without, and therefore survival in the abiraterone arm would be expected to be worse for HRRm patients. The Gompertz distribution may be too pessimistic given that OS would drop below expected rPFS only a year after trial follow-up. The Weibull and generalised gamma provide more realistic estimates, whereas the loglogistic distribution would put survival at similar levels to all-comers (including patients without HRR mutations). For the olaparib + abiraterone arm, 5-year survival was assumed to have to be at least as good as in the ITT population, given the increased efficacy observed in HRRm patients during follow-up. Therefore, the Gompertz and Weibull distributions were considered implausible. The loglogistic and generalised gamma distributions provided similar results to the ITT population and were therefore considered relatively conservative, though the lognormal distribution provides more optimistic outcomes. Whilst the underlying hazard functions differ slightly given the flexibility of the models, the generalised gamma is selected for both arms given the plausibility of the outcomes. The NICE DSU guidance outlines that different functional forms can be used when justified. On the basis of the smoothed hazards showing very different forms within the observed data, and the lack of clinical plausibility of the long-term outcomes when applying other distributions to both arms, it can be justified in this case.

Time to Discontinuation of Abiraterone

Number of subject and events for TDA in the HRRm population

Arm	N	Events	Maturity
Placebo + Abiraterone	115	100	87.0%
Olaparib + Abiraterone	111	75	67.6%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last time point where each arm has observations, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

Restricted mean survival times and median survival times for TDA in the HRRm population

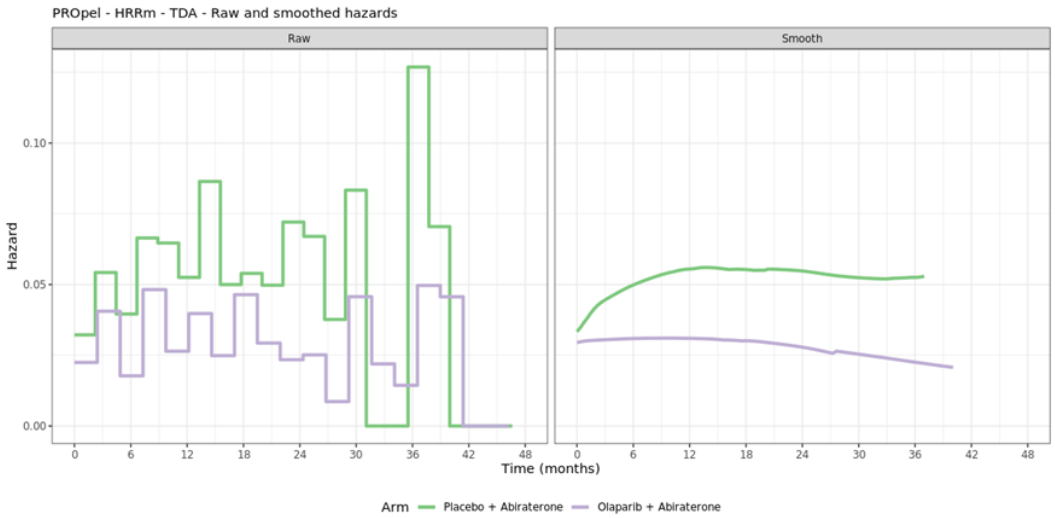
Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	17.1 (14.7, 19.6)	13.7 (10.1, 15.7)
Olaparib + Abiraterone	[redacted]	[redacted]

CI, confidence interval; RMST, restricted mean survival time

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

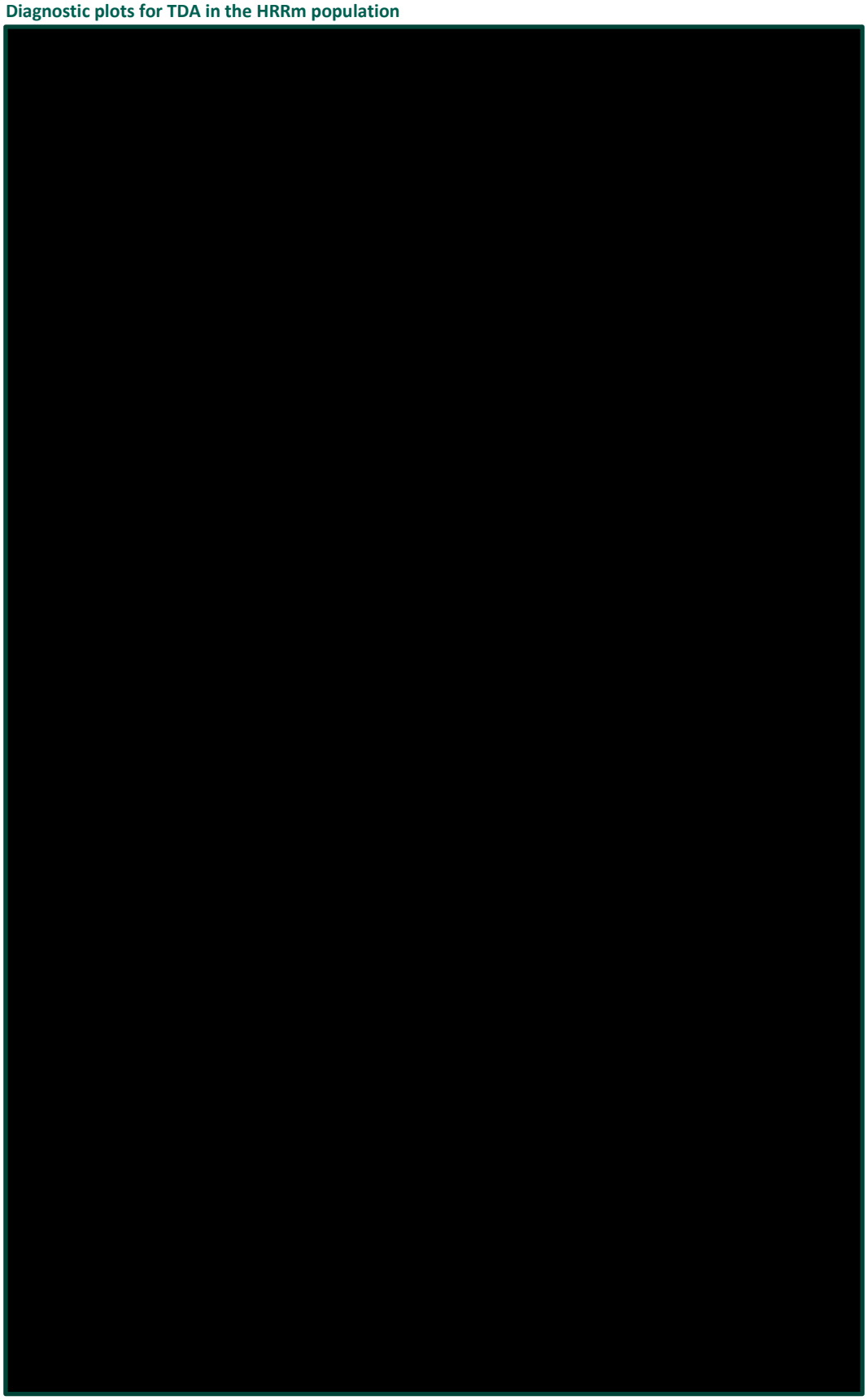
Kaplan-Meier survival plot for TDA in the HRRm population

Smoothed and empirical hazards for TDA in the HRRm population



The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log-cumulative hazards (Weibull) plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds (loglogistic) diagnostic plot, parallel lines indicate proportional odds and in the lognormal diagnostic plot, parallel lines indicate constant acceleration.

Diagnostic plots for TDA in the HRRm population



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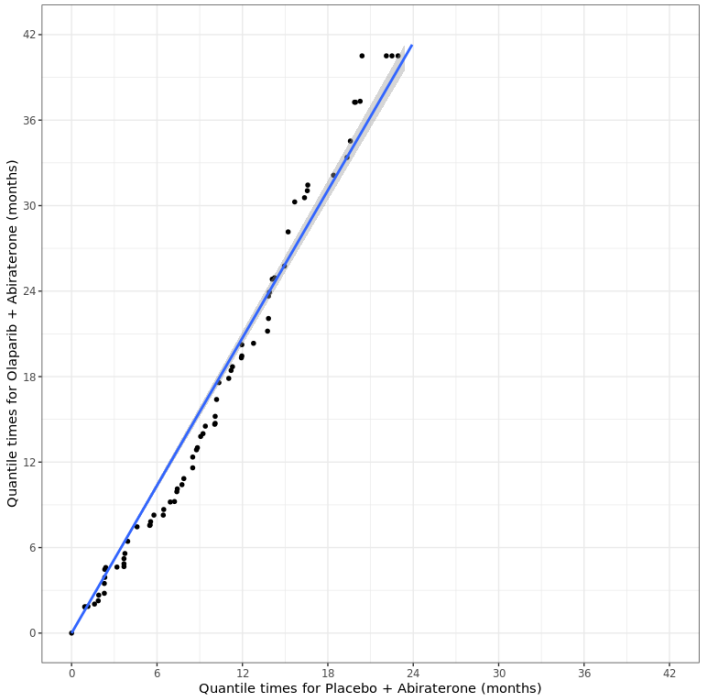
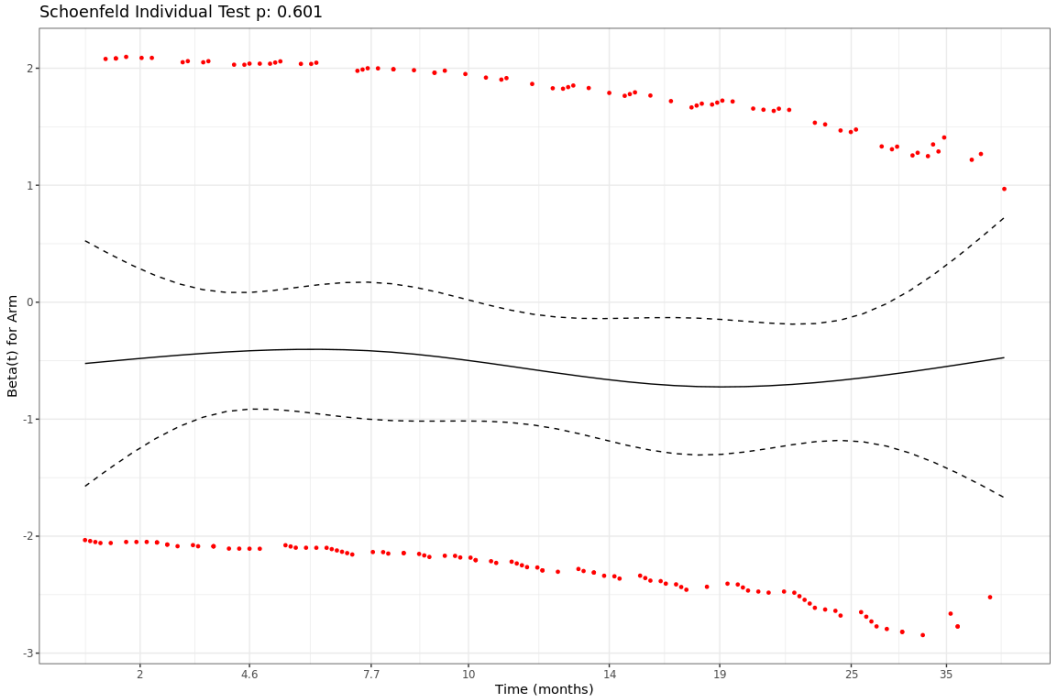
Quantile-quantile plot for TDA in the HRRm population



A straight line in the quantile-quantile plot indicates that an accelerated failure time model may fit the data well.

Schoenfeld residuals plot for TDA in the HRRm population



Schoenfeld residuals have been calculated using the KM transform. The Schoenfeld residuals can be used to test the proportional hazard assumption. If hazards are proportion, the plot of the residuals against time should show a linear trend with slope=0. A significant value on the Schoenfeld individual test indicates that the proportional hazards assumption has been violated. The visual inspection of this plot is more important than the test, however, a p-value is also outputted as the result of a test of non-negative slope (Therneau and Grambsch).

The Kaplan-Meier and diagnostic plots shows clear separation of the curves, and the smoothed hazards indicate that after approximately 12 months they could be proportional, but that overall,

they follow slightly different forms. The lines on the diagnostic plots could be considered to be largely parallel, but with a slight narrowing in the middle of follow-up. The Schoenfeld residuals plot indicates that hazards could be proportional, but the Q-Q plot does not necessarily favour an accelerated failure time model. Joint models should be considered, but in line with other endpoints independent extrapolations are also performed.

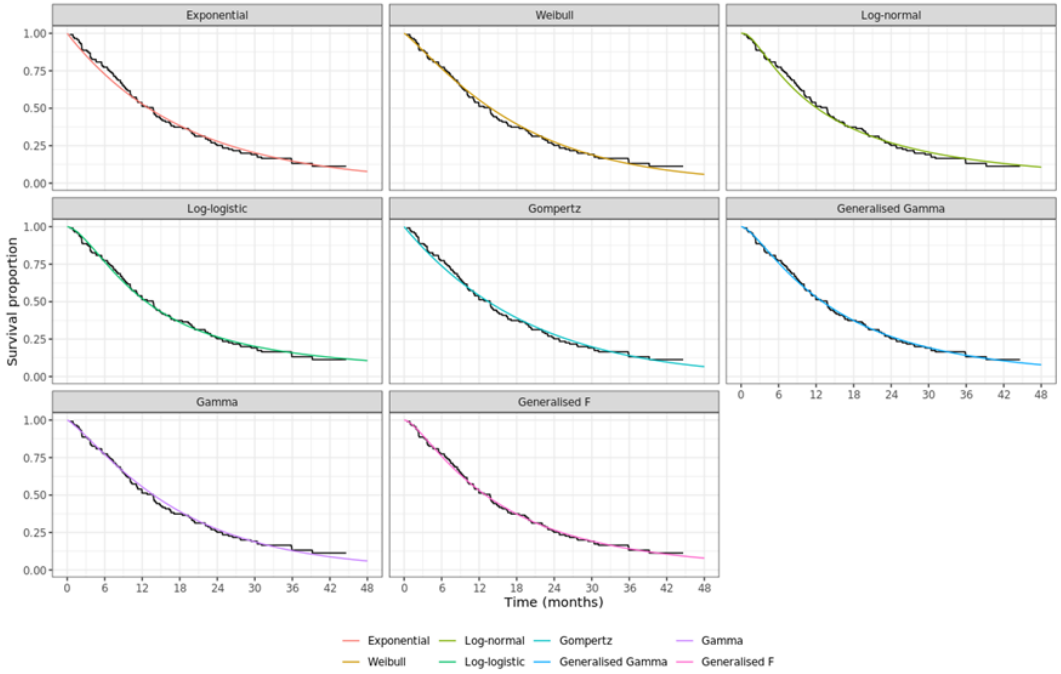
Goodness of fit statistics for independent models fitted to TDA in the HRRm population

Olaparib + Abiraterone			Placebo + Abiraterone		
Distribution	AIC	BIC	Distribution	AIC	BIC
Lognormal	671.9	677.3	Loglogistic	787.5	793.0
Generalised Gamma	673.6	681.7	Gamma	787.8	793.2
Loglogistic	674.3	679.7	Generalised Gamma	788.2	796.4
Exponential	676.1	678.8	Weibull	788.6	794.1
Gamma	677.2	682.6	Exponential	788.8	791.6
Weibull	677.7	683.1	Lognormal	789.0	794.5
Gompertz	678.0	683.4	Gompertz	790.5	796.0

For the placebo + abiraterone arm, the loglogistic distribution has the best statistical fit. All other distributions also provided good fits (ΔAIC < 5). For the olaparib + abiraterone arm, the lognormal distribution has the best statistical fit. The generalised gamma, loglogistic, and exponential distributions are also good fits (ΔAIC < 5).

The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

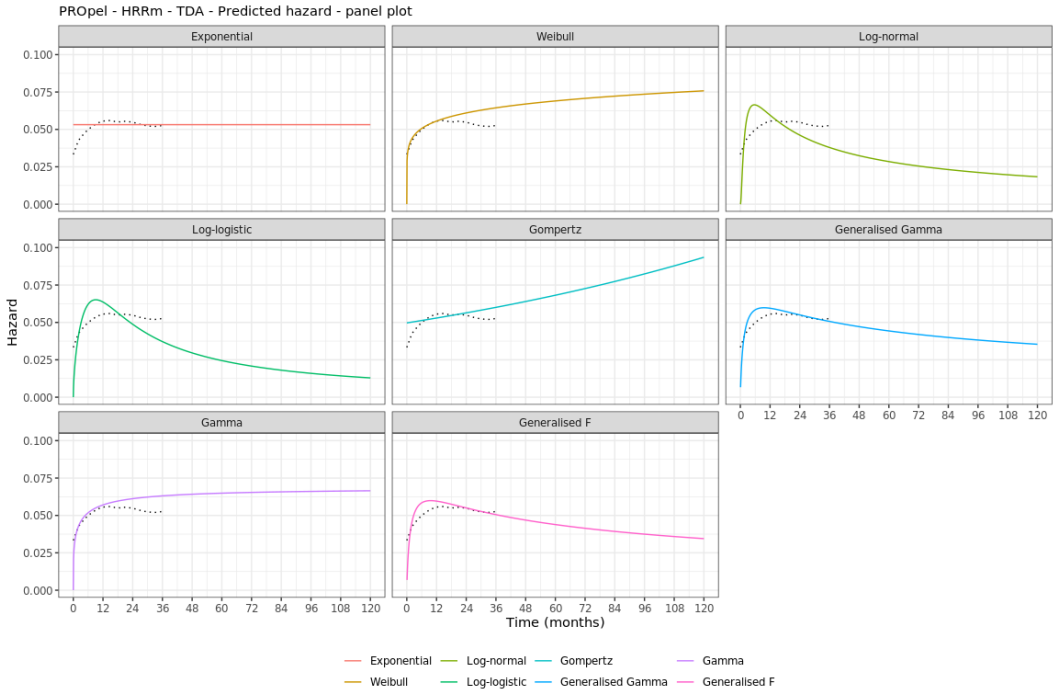
Fitted independent parametric models vs. Kaplan-Meier for TDA in the placebo + abiraterone arm in the HRRm population



All curves provided a generally good fit to the placebo + abiraterone arm during trial follow-up, though the exponential distribution was a less clear match to the Kaplan-Meier. Outcomes on other distributions were similar, with the gamma and Gompertz being more pessimistic, and the lognormal and loglogistic being more optimistic. With regards to smoothed hazards, the Weibull, gamma, and Gompertz may overestimate the long-term hazard. The shape of the curve also

indicates that a slightly decline in the hazard in the long-term is plausible, in line with the modelled generalised gamma curve.

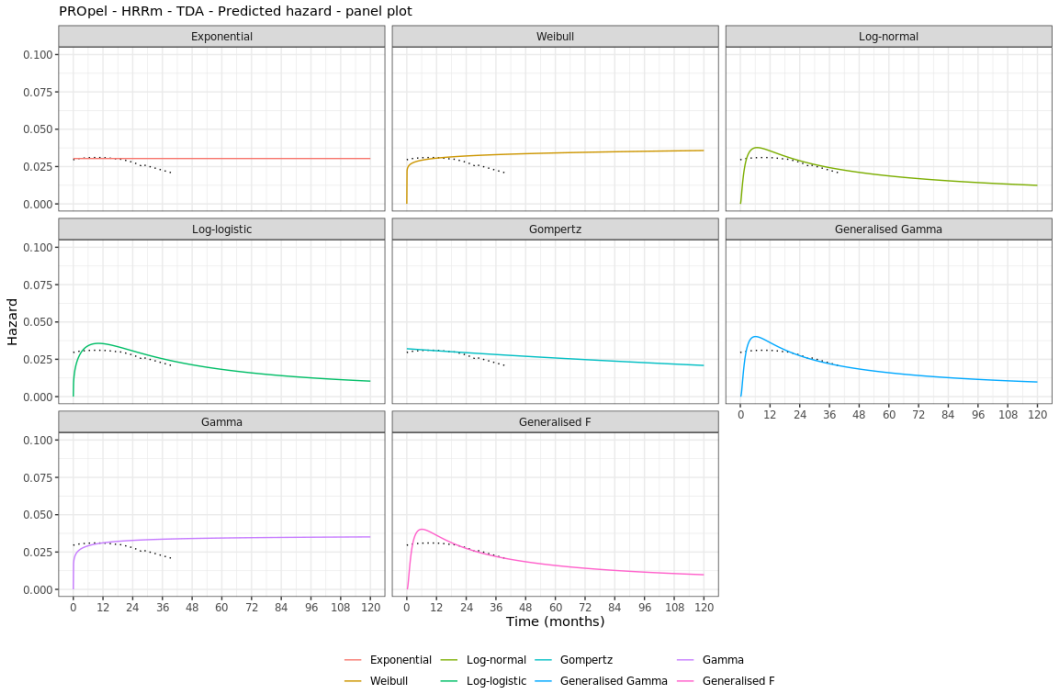
Hazard functions of fitted parametric models to the placebo + abiraterone arm compared to smoothed hazards for TDA in the HRRm population



Fitted independent parametric models vs. Kaplan-Meier for TDA in the olaparib + abiraterone arm in the HRRm population

In the olaparib + abiraterone arm, all curves provided a reasonable visual fit to the trial data during follow-up. The exponential, Weibull, and gamma distributions tended to slightly overestimate survival between months 9 and 24, supported by the hazard plots showing an initial underestimation compared to the smoothed hazard, followed by an overestimation in the long-term. The smoothed hazards plots indicate that a non-monotonic functional form is plausible, with the lognormal, loglogistic, and generalised gamma distributions showing a comparable hazard function to the smoothed hazards.

Hazard functions of fitted parametric models to the olaparib + abiraterone arm compared to smoothed hazards for TDA in the HRRm population



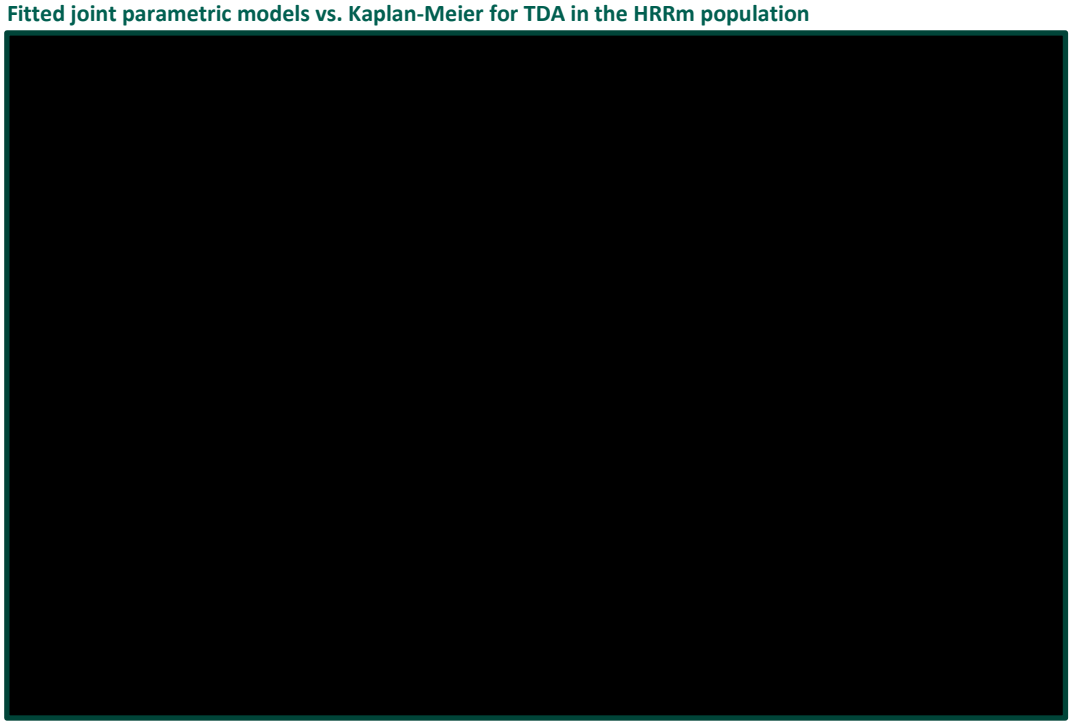
Goodness of fit statistics for joint models fitted to TDA in the HRRm population

Distribution	AIC	BIC
Lognormal	1459.9	1470.1
Generalised Gamma	1460.4	1474.1
Loglogistic	1461.3	1471.5
Gamma	1463.2	1473.5
Weibull	1464.5	1478.8
Exponential	1464.9	1471.7
Gompertz	1466.9	1477.1

The lognormal distribution has the best statistical fit. The generalised gamma, loglogistic, gamma, and Weibull distributions are also good fits (ΔAIC < 5).

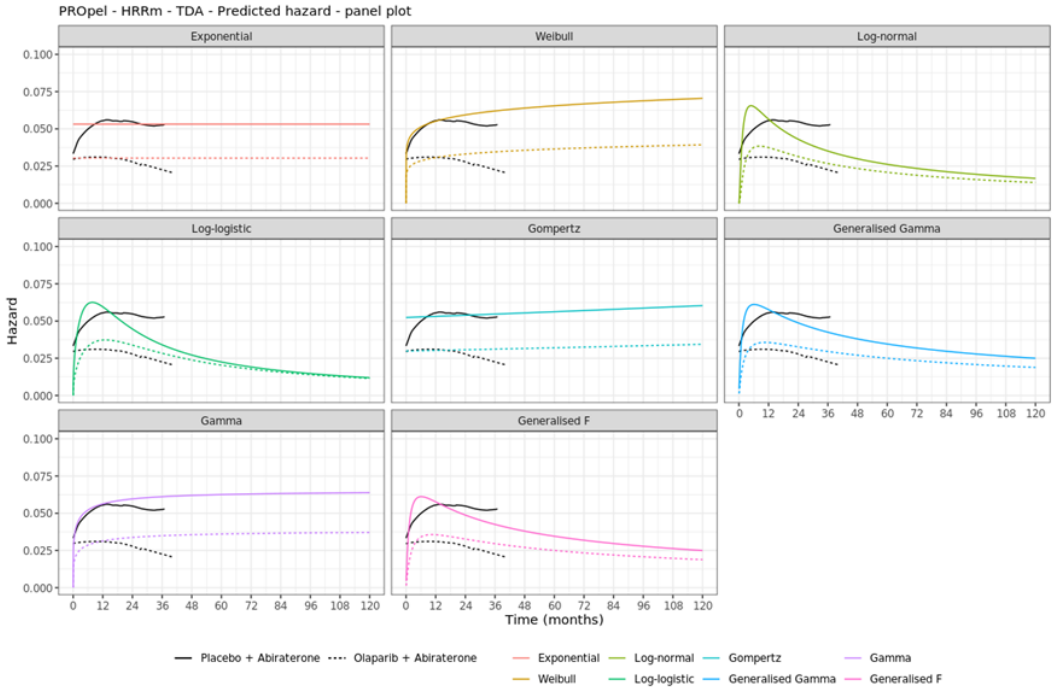
The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

Fitted joint parametric models vs. Kaplan-Meier for TDA in the HRRm population



All curves followed the generally trajectory of the observed data, though fits were dubious. The exponential and Gompertz distributions underestimate survival in the placebo arm during the first 9 months. The Weibull and gamma distributions overestimate survival in the olaparib arm during the first 24 months. The lognormal and loglogistic curves underestimate outcomes in the olaparib arm but overestimate outcomes in the placebo arm from around 26 months onwards. The generalised gamma provides the best visual fit to both arms. However, the slightly different shapes of the smoothed hazards between arms means none of the functional forms perfectly align when considering joint models.

Hazard functions of fitted parametric models compared to smoothed hazards for TDA in the HRRm population



As statistical fit was not generally informative in either independent models or joint extrapolations, visual fit to the Kaplan-Meier curve, the shape of the underlying hazard, and the

diagnostic plots inform choices on preferred curve fit. The smoothed hazard plots potentially indicate that hazards for this endpoint are non-monotonic for both arms, and this is somewhat supported by the AIC values where non-monotonic functional forms had the best statistical fit in both independent and joint models. However, the Q-Q plot indicates joint accelerated failure time not possible. Therefore, independent extrapolation using a non-monotonic functional form is preferred. This is aligned with the assumptions in the ITT population. The inadequate visual fit of joint parametric curves compared to the Kaplan-Meier further supports using independent models for the base case.

The generalised gamma was considered statistically plausible in independent extrapolations and had a better visual fit to the data and aligned with the smoothed hazards in both arms. As patients with HRRm are expected to have a better prognosis with olaparib-based treatment, despite being the most optimistic the generalised gamma was considered plausible for time on abiraterone. Should a joint model be considered, the generalised gamma provided the best fit to the observed data and can be considered in scenario analyses.

Time to Discontinuation of Olaparib

Number of subject and events for TDT in the HRRm population

Arm	N	Events	Maturity
Olaparib + Abiraterone	111	78	70.3%

A summary of the median and mean time to event is shown below. Restricted means are calculated until the last time point where each arm has observations, using the area under Kaplan-Meier curve with confidence interval at the 95% level.

Median survival times for TDT in the HRRm population

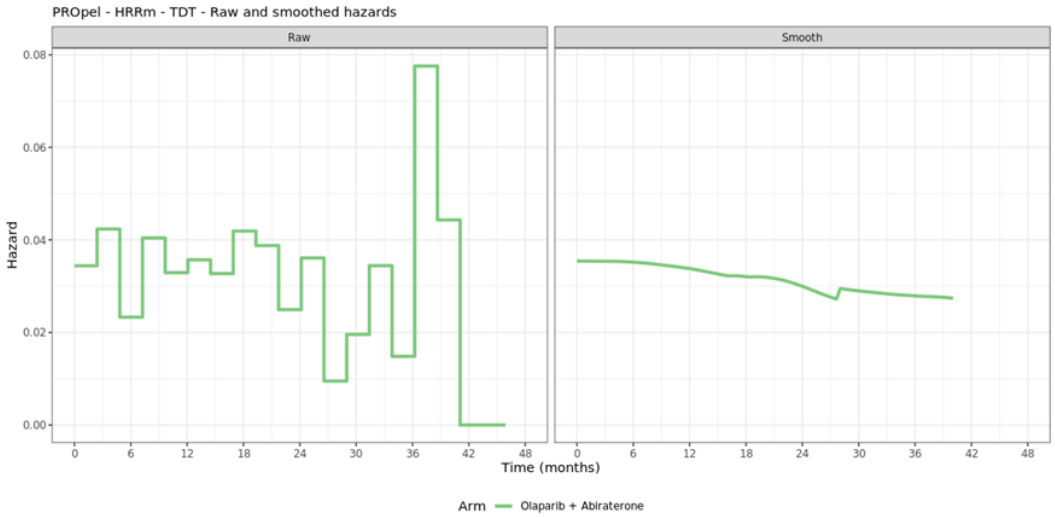
Arm	RMST (95% CI)	Median (95% CI)
Olaparib + Abiraterone	[redacted]	[redacted]

CI, confidence interval

The Kaplan-Meier survival plot for each arm and the smoothed and empirical hazards derived from the trial data are shown in the figures below.

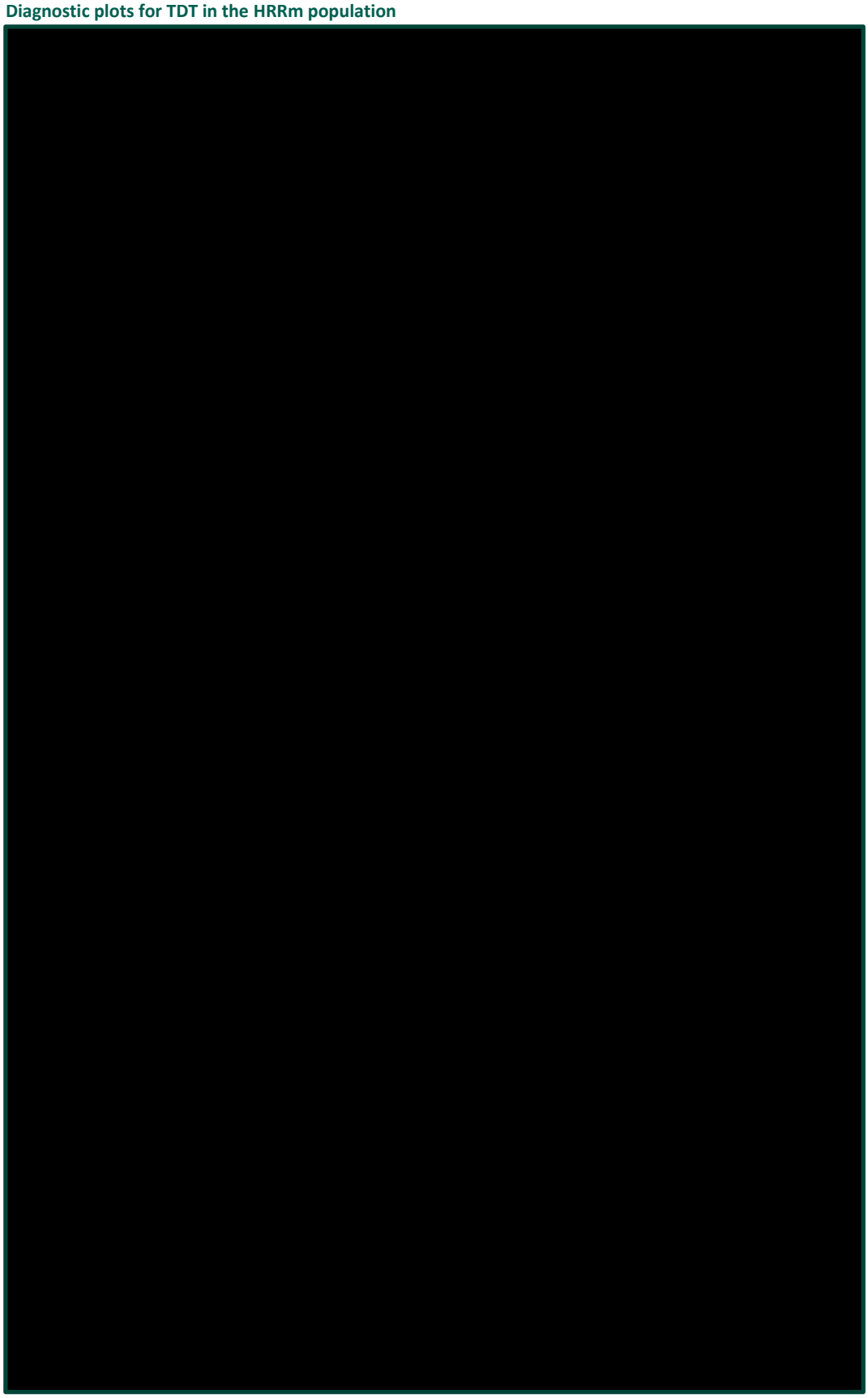
Kaplan-Meier survival plot for TDT in the HRRm population

Smoothed and empirical hazards for TDT in the HRRm population



The following are diagnostic plots to check assumptions. Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution.

Diagnostic plots for TDT in the HRRm population



Goodness of fit statistics for models fitted to TDT in the HRRm population

Olaparib + Abiraterone		
Distribution	AIC	BIC
Lognormal	687.8	693.2

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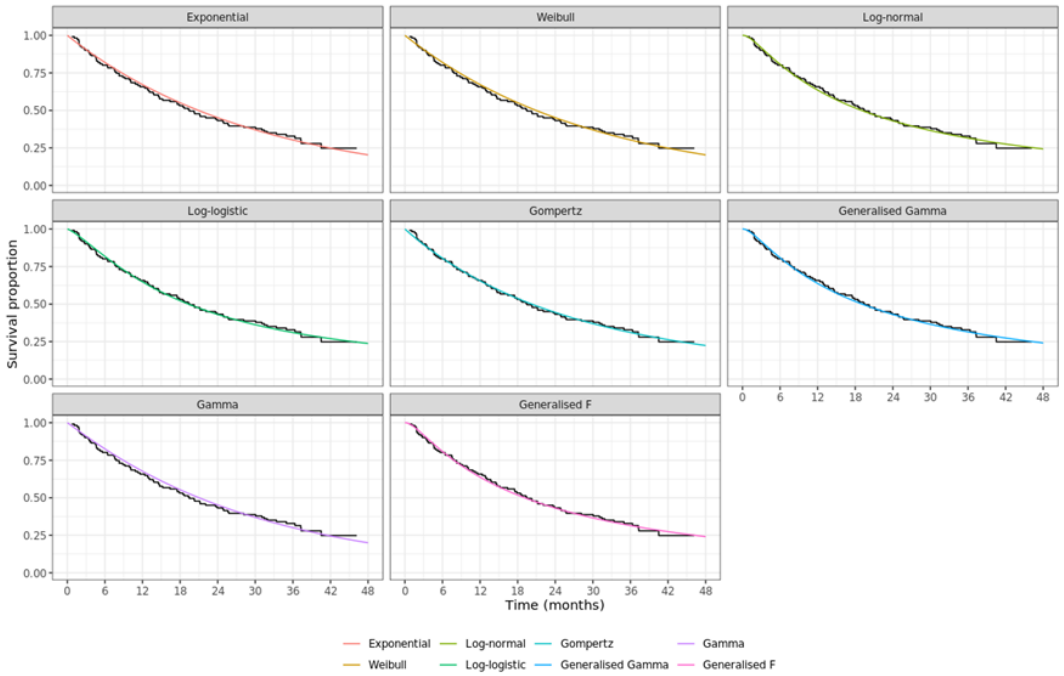
Olaparib + Abiraterone		
Distribution	AIC	BIC
Loglogistic	689.5	694.9
Exponential	689.6	692.3
Generalised Gamma	689.8	697.9
Gompertz	691.1	696.5
Gamma	691.5	696.9
Weibull	691.6	697.0

The lognormal distribution has the best statistical fit. All other distributions provided good fits (ΔAIC < 5).

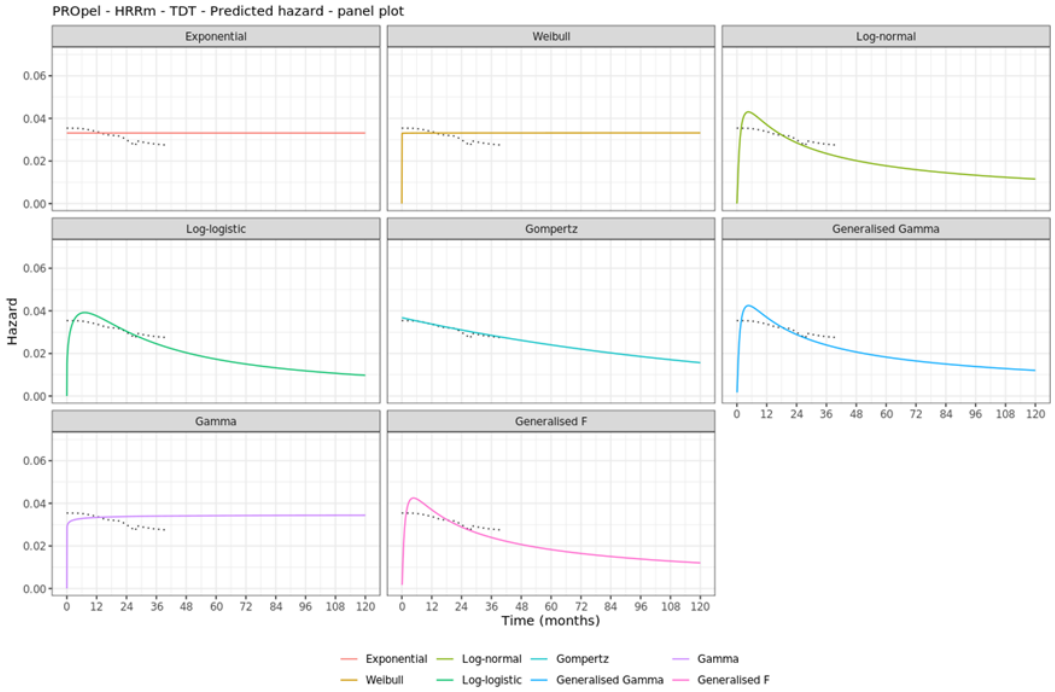
The fitted models are plotted against the Kaplan-Meier curve below in order to illustrate how well they capture the within trial trends, as well as a comparison of the long-term hazard function of the fitted curves versus the smoothed hazards of the trial data.

Fitted independent parametric models vs. Kaplan-Meier for TDT in the HRRm population



All curves provided a good fit to the Kaplan-Meier during trial follow-up, with the Gompertz and loglogistic being slightly better aligned. This is supported by the smoothed hazards where these two distributions seem to follow the functional form well.

Hazard functions of fitted parametric models compared to smoothed hazards for TDT in the ITT population



Given the preferred fits on time to discontinuation of abiraterone, the smoothed hazards, and goodness of fit statistics, plausible distributions were assumed to be the lognormal, loglogistic, and generalised gamma. All three curves produce plausible results, with time on olaparib being shorter than time on abiraterone – as was observed in the trial. As there is no substantial difference in modelled results between these curves, the lognormal was chosen for the initial scenario given the best AIC.

Appendix H Literature search for HRQoL data

As the EQ-5D-5L was collected in PROpel, utility values could be generated directly using the Danish value set. Therefore the use of published HRQoL data were very limited, but the below text describes the literature search that was done for HRQoL data.

The following electronic databases were interrogated via the Ovid platform on the 13th April, 2021: Embase, MEDLINE (In-Process, In-Data-Review & Other Non-Indexed Citations, Epub Ahead of Print, and Daily), and EBM Reviews (incorporating the Health Technology Assessment [HTA] database, 4th Quarter 2016 and the National Health Service Economic Evaluation Database [NHS EED] 1st Quarter 2016). In addition, the University of York, Centre for Reviews and Dissemination (CRD) website was searched to identify records from HTA, NHS EED, and DARE from 2016 to 2021. The original electronic database searches were updated on the 27th April 2022. The searches in EBM Reviews (HTA and NHS EED) and CRD were not re-run as the databases had not been updated since the original search in April 2021. Supplementary searches were also completed, covering relevant conference proceedings and additional websites (e.g. EuroQoL website), as well as reference checks of relevant reviews and included studies.

A total of 20 publications reporting HSUVs associated with patients with mCRPC were identified for final inclusion in the review (full publications, N=18; post-2018 conference abstracts, N=2) (4-23). Countries from which the utility data were derived included: the US (N=5) (4, 5, 17, 19, 20); the UK (N=2) (10, 13); Canada (N=1) (11); Japan (N=1) (15); Italy (N=1) (23) and the Netherlands (N=1) (12). The remaining studies were multi-national and considered patients enrolled across multiple sites globally (N=9) (6-9, 14, 16, 18, 21, 22). No identified studies reported including Danish patients nor applied the Danish value set of the EQ-5D-5L. Studies included patients in various prostate cancer states (not specifically mCRPC patients who are ineligible for chemotherapy), no published studies specifically reported utilities by pre- or post-progression status in a relevant population for the economic analysis. Some utilities from prior NICE submissions were in first line chemotherapy-naïve mCRPC patients but derived using the UK value set for the EQ-5D. Therefore, as the most relevant source the Danish reference case, values from PROpel were used in the model.

Below is the PRSMA flow diagram for the HSUV review. If of interest, the complete SLR can be shared upon request.

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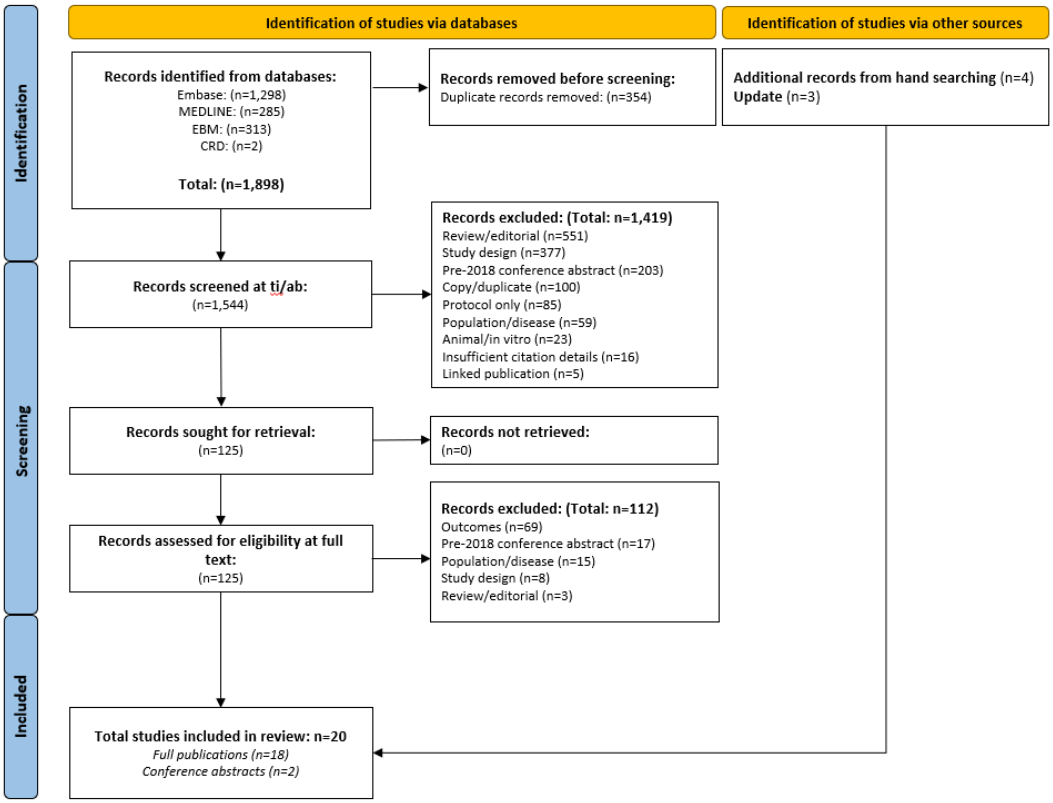
Figure 31. Overall PRISMA flow diagram for the HSUV review



Appendix I Analysis of HRQoL data

As the EQ-5D-5L was collected in PROpel, utility values could be generated directly using the Danish value set. Therefore no mapping of HRQoL data was conducted.

Utility weights from the EQ-5D-5L were estimated on the Danish value set. To estimate utility values for use in the economic model, mixed effects models for repeated measures (MMRM) analysis were performed. The MMRM analysis provides valid estimates of the mean and standard error of repeated measures data that considers the correlation that exists between the repeated measurements of utility values by subject, and allows for the exploration of predictors of changes in the health state utility. It provides valid results under the assumption that missing data are missing at random. All completed EQ-5D-5L measures were used to estimate health state utility values for the model.

The MMRM analysis was used to determine the impact of randomised treatment group and progression status (investigator-assessed rPFS) on the utility of patients in PROpel, according to the following specifications:

- **Model 1:** Utility ~ Treatment Arm
- **Model 2:** Utility ~ Progression State
- **Model 3:** Utility ~ Treatment Arm + Progression State
- **Model 4:** Utility ~ Treatment Arm * Progression State + Treatment Arm + Progression State

To allow for the correlation over time of the repeated utility measurements within subjects, covariance structures were specified. All models converged when specifying an autoregressive – order 1 with heterogeneity covariance structure (i.e., each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are).

The best fitting model was judged based on Akaike Information Criterion (AIC) score, with lower scores indicating an improved (and more parsimonious) fit to the trial data. According to AIC score, the best fitting MMRM was the model including only progression status (model 2). Across models, only progression status was consistently and significantly ($p < 0.001$) associated with utility values.

Parameter	β (Std Err)			
	Model 1	Model 2	Model 3	Model 4
Intercept	0.8816 (0.0073)	0.8800 (0.0060)	0.8871 (0.0073)	0.8884 (0.0072)
Treatment: Olaparib (vs. Placebo)	-0.0120 (0.0118) $p = 0.3114$	-	-0.0135 (0.0118) $p = 0.2526$	-0.0161 (0.0118) $p = 0.1731$
Progressed Disease (vs. Progression-Free)	-	-0.0372 (0.0101) $p = 0.0002$	-0.0376 (0.0100) $p = 0.0002$	-0.0470 (0.0137) $p = 0.0006$
Interaction Term (Olaparib * Progressed Disease)	-	-	-	0.0221 (0.0200) $p = 0.2697$
AIC	-8908.8	**-8929.5**	-8922.1	-8915.6

Appendix J Probabilistic sensitivity analyses

The table below shows all sampled variables, distributions, and parameters of the distributions in the model applied in the probabilistic sensitivity analysis. In addition to those presented here, parameters for the fitting of survival curves were also probabilistically sampled using multivariate normal distributions on the Cholesky decomposition of the covariance matrix for each selected survival curves. Certain parameters in the model (e.g., unit costs of acquiring medications) were not probabilistically sampled on the assumption that there is no uncertainty in the value of the parameter applied in the model, though parameters related to these (e.g., relative dose intensities or duration of treatment) have been sampled to adequately reflect uncertainty.

	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
Patient Characteristics							
Weight (kg)	82.7	0.57	PROpel	Normal	μ: 82.7	σ: 0.57	'General Model Parameters'!E19
Height (cm)	174.9	7.7	COU-AA-302	Normal	μ: 174.9	σ: 7.7	'General Model Parameters'!E21
Prevalence of BRCA mutations	0.11	0.01	PROpel	Beta	α: 84.9	β: 710.1	'Medical & Mortality Costs'!H50
Prevalence of HRR mutations	0.28	0.02	PROpel	Beta	α: 225.7	β: 569.3	'Medical & Mortality Costs'!H51
Probabilities							
Proportion of PFS events which are progression: olaparib + abiraterone	0.81	0.03	PROpel	Beta	α: 135.7	β: 31.3	'General Model Parameters'!E60
Proportion of PFS events which are progression: abiraterone	0.88	0.02	PROpel	Beta	α: 198.2	β: 26.8	'General Model Parameters'!E61
Proportion of PFS events which are progression: enzalutamide	0.88	0.02	Equal to abiraterone	Beta	α: 198.2	β: 26.8	'General Model Parameters'!E62
Proportion of treatment discontinuation events which are deaths: olaparib + abiraterone	0.07	0.01	PROpel	Beta	α: 18.9	β: 269.1	'General Model Parameters'!E81
Proportion of treatment discontinuation	0.04	0.01	PROpel	Beta	α: 13.0	β: 303.0	'General Model Parameters'!E82

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
events which are deaths: abiraterone							
Proportion of treatment discontinuation events which are deaths: enzalutamide	0.04	0.01	Equal to abiraterone	Beta	α: 13.0	β: 303.0	'General Model Parameters'!E83
Proportion of patients receiving subsequent therapy upon treatment discontinuation: olaparib + abiraterone	0.62	0.04	PROpel	Beta	α: 110.0	β: 67.0	'Therapy Options & Costing'!F59
Proportion of patients receiving subsequent therapy upon treatment discontinuation: abiraterone	0.68	0.03	PROpel	Beta	α: 164.8	β: 78.2	'Therapy Options & Costing'!H59
Proportion of patients receiving subsequent therapy upon treatment discontinuation: enzalutamide	0.68	0.03	Equal to abiraterone	Beta	α: 164.8	β: 78.2	'Therapy Options & Costing'!J59
Probability of SSRE upon Progression: olaparib + abiraterone	0.26	0.04	PROpel	Beta	α: 32.3	β: 92.7	'Medical & Mortality Costs'!F86
Probability of SSRE upon Progression: abiraterone	0.21	0.04	PROpel	Beta	α: 26.1	β: 98.9	'Medical & Mortality Costs'!G86
Probability of SSRE upon Progression: enzalutamide	0.21	0.04	Equal to abiraterone	Beta	α: 26.1	β: 98.9	'Medical & Mortality Costs'!H86
AE: ALAT Increased (olaparib + abiraterone)	0.01	0.00	PROpel	Beta	α: 4.0	β: 393.0	'Appendix AEs'!D17
AE: ALAT Increased (abiraterone)	0.02	0.01	PROpel	Beta	α: 9.0	β: 386.0	'Appendix AEs'!E17
AE: Anaemia (olaparib + abiraterone)	0.16	0.02	PROpel	Beta	α: 63.8	β: 333.2	'Appendix AEs'!D18

	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
AE: Anaemia (abiraterone)	0.03	0.01	PROpel	Beta	α: 13.0	β: 382.0	'Appendix AEs'!E18
AE: Anaemia (enzalutamide)	0.03	0.01	Xtandi EPAR	Beta	α: 29.0	β: 841.0	'Appendix AEs'!F18
AE: Back Pain (olaparib + abiraterone)	0.01	0.00	PROpel	Beta	α: 4.0	β: 393.0	'Appendix AEs'!D19
AE: Back Pain (abiraterone)	0.02	0.01	PROpel	Beta	α: 6.0	β: 391.0	'Appendix AEs'!E19
AE: Back Pain (enzalutamide)	0.03	0.01	Xtandi EPAR	Beta	α: 10.0	β: 387.0	'Appendix AEs'!F19
AE: General Deterioration (olaparib + abiraterone)	0.00	0.00	PROpel	Beta	α: 1.0	β: 396.0	'Appendix AEs'!D20
AE: General Deterioration (abiraterone)	0.00	0.00	PROpel	Beta	α: 1.0	β: 396.0	'Appendix AEs'!E20
AE: General Deterioration (enzalutamide)	0.02	0.01	Xtandi EPAR	Beta	α: 8.2	β: 388.8	'Appendix AEs'!F20
AE: Hyperglycaemia (olaparib + abiraterone)	0.02	0.01	PROpel	Beta	α: 8.0	β: 389.0	'Appendix AEs'!D21
AE: Hyperglycaemia (abiraterone)	0.02	0.01	PROpel	Beta	α: 6.0	β: 389.0	'Appendix AEs'!E21
AE: Hyperglycaemia (enzalutamide)	0.04	0.01	Xtandi EPAR	Beta	α: 35.0	β: 835.0	'Appendix AEs'!F21
AE: Hypertension (olaparib + abiraterone)	0.04	0.0	PROpel	Beta	α: 15.0	β: 382.0	'Appendix AEs'!D22
AE: Hypertension (abiraterone)	0.05	0.01	PROpel	Beta	α: 18.0	β: 377.0	'Appendix AEs'!E22
AE: Hypertension (enzalutamide)	0.07	0.01	Xtandi EPAR	Beta	α: 58.9	β: 811.1	'Appendix AEs'!F22
AE: Lymphocyte Count Decreased (olaparib + abiraterone)	0.04	0.01	PROpel	Beta	α: 15.0	β: 382.0	'Appendix AEs'!D23

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
AE: Lymphocyte Count Decreased (abiraterone)	0.02	0.01	PROpel	Beta	α: 6.0	β: 377.0	'Appendix AEs'!E23
AE: Neutrophil Count Decreased (olaparib + abiraterone)	0.03	0.01	PROpel	Beta	α: 11.0	β: 386.0	'Appendix AEs'!D24
AE: Neutrophil Count Decreased (abiraterone)	0.01	0.00	PROpel	Beta	α: 6.0	β: 389.0	'Appendix AEs'!E24
AE: Neutropenia (enzalutamide)	0.01	0.00	Xtandi EPAR	Beta	α: 8.0	β: 862.0	'Appendix AEs'!F24
AE: Pneumonia (olaparib + abiraterone)	0.03	0.01	PROpel	Beta	α: 10.0	β: 387.0	'Appendix AEs'!D25
AE: Pneumonia (abiraterone)	0.01	0.01	PROpel	Beta	α: 3.0	β: 392.0	'Appendix AEs'!E25
AE: Pneumonia (enzalutamide)	0.01	0.00	Xtandi EPAR	Beta	α: 11.0	β: 859.0	'Appendix AEs'!F25
AE: Pulmonary Embolism (olaparib + abiraterone)	0.07	0.01	PROpel	Beta	α: 28.9	β: 368.1	'Appendix AEs'!D26
AE: Pulmonary Embolism (abiraterone)	0.02	0.01	PROpel	Beta	α: 4.0	β: 391.0	'Appendix AEs'!E26
AE: Urinary Tract Infection (olaparib + abiraterone)	0.03	0.01	PROpel	Beta	α: 10.0	β: 387.0	'Appendix AEs'!D27
AE: Urinary Tract Infection (abiraterone)	0.01	0.01	PROpel	Beta	α: 4.0	β: 391.0	'Appendix AEs'!E27
AE: Urinary Tract Infection (enzalutamide)	0.01	0.00	Xtandi EPAR	Beta	α: 13.0	β: 857.0	'Appendix AEs'!F27
AE: WBC Count Decreased (olaparib + abiraterone)	0.02	0.01	PROpel	Beta	α: 9.0	β: 388.0	'Appendix AEs'!D28
AE: WBC Count Decreased (abiraterone)	0.01	0.00	PROpel	Beta	α: 2.0	β: 393.0	'Appendix AEs'!E28
HSUV							
Progression-Free	0.88	0.01	PROpel	Beta	α: 2008.8	β: 273.9	Utility!D17

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
Post-Progression	0.84	0.01	PROpel	Beta	α: 843.5	β: 157.3	Utility!D18
Anaemia Disutility	- 0.02	0.01	Sullivan 2011	Beta	α: 5.7	β: 254.5	Utility!F30
Anaemia Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H30
Back Pain Disutility	- 0.09	0.01	Sullivan 2011	Beta	α: 83.5	β: 881.0	Utility!F31
Back Pain Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H31
General Health Deterioration Disutility	- 0.20	0.03	Swinburn 2010	Beta	α: 36.2	β: 141.3	Utility!F32
General Health Deterioration Duration	91.25	20% of mean	NICE TA387	Lognormal	μ: 4.51	σ: 0.18	Utility!H32
Hypertension Disutility	- 0.05	0.04	Sullivan 2011	Beta	α: 1.1	β: 22.8	Utility!F34
Hypertension Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H34
Neutrophil Count Decreased Disutility	- 0.09	0.01	Nafees 2008	Beta	α: 45.9	β: 465.5	Utility!F36
Neutrophil Count Decreased Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H36
Pneumonia Disutility	- 0.13	0.00	Tolley 2013	Beta	α: 825.0	β: 5620.6	Utility!F37
Pneumonia Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H37
Pulmonary Embolism Disutility	- 0.31	0.01	Locadia 2004	Beta	α: 528.3	β: 1175.9	Utility!F38
Pulmonary Embolism Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H38
Urinary Tract Infection Disutility	- 0.01	0.01	Sullivan 2011	Beta	α: 0.3	β: 64.0	Utility!F39
Urinary Tract Infection Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H39
WBC Count Decreased Disutility	- 0.09	0.01	Nafees 2008	Beta	α: 45.9	β: 465.5	Utility!F40
WBC Count Decreased Duration	10.5	20% of mean	NICE TA387	Lognormal	μ: 2.35	σ: 0.18	Utility!H40

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
Spinal Cord Compression Disutility	- 0.56	20% of mean	Fassler 2011	Beta	α: 10.6	β: 8.5	Utility!F50
Spinal Cord Compression Duration	30.44	20% of mean	NICE TA831	Lognormal	μ: 3.42	σ: 0.18	Utility!H50
Radiation to Bone Disutility	- 0.07	20% of mean	Fassler 2011	Beta	α: 23.2	β: 308.0	Utility!F51
Radiation to Bone Duration	30.44	20% of mean	NICE TA831	Lognormal	μ: 3.42	σ: 0.18	Utility!H51
Surgery to Bone Disutility	- 0.13	20% of mean	Fassler 2011	Beta	α: 21.6	β: 144.7	Utility!F52
Surgery to Bone Duration	30.44	20% of mean	NICE TA831	Lognormal	μ: 3.42	σ: 0.18	Utility!H52
Pathological Bone Fracture Disutility	- 0.13	20% of mean	Fassler 2011	Beta	α: 21.6	β: 144.7	Utility!F53
Pathological Bone Fracture Duration	30.44	20% of mean	NICE TA831	Lognormal	μ: 3.42	σ: 0.18	Utility!H53
Costs							
Relative dose intensity: olaparib (first line)	0.92	0.01	PROpel	Beta	α: 1681.3	β: 152.2	'Therapy Options & Costing'!Q25
Relative dose intensity: abiraterone (+ olaparib)	0.96	0.01	PROpel	Beta	α: 1644.5	β: 63.2	'Therapy Options & Costing'!Q26
Relative dose intensity: abiraterone (monotherapy)	0.97	0.00	PROpel	Beta	α: 1656.5	β: 47.7	'Therapy Options & Costing'!Q28
Relative dose intensity: enzalutamide	0.95	0.00	Fallara 2020	Beta	α: 4306.4	β: 226.7	'Therapy Options & Costing'!Q30
Relative dose intensity: olaparib (second line)	0.92	0.01	PROfound	Beta	α: 1065.8	β: 99.0	'Therapy Options & Costing'!Q41
Duration of 2L treatment: olaparib	14.70	10% of mean	Medicinrådet PROfound assessment	Lognormal	μ: 2.69	σ: 0.10	'Therapy Options & Costing'!E78

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
Duration of 2L treatment: abiraterone	3.60	10% of mean	Khalaf 2019	Lognormal	μ: 1.28	σ: 0.10	'Therapy Options & Costing'!E79
Duration of 2L treatment: docetaxel	5.52	10% of mean	Medicinrådet apalutamide for mHSPC assessment	Lognormal	μ: 1.71	σ: 0.10	'Therapy Options & Costing'!E80
Duration of 2L treatment: enzalutamide	4.60	10% of mean	Khalaf 2019	Lognormal	μ: 1.53	σ: 0.10	'Therapy Options & Costing'!E81
Duration of 2L treatment: cabazitaxel	4.83	10% of mean	de Wit 2019	Lognormal	μ: 1.57	σ: 0.10	'Therapy Options & Costing'!E82
Duration of 2L treatment: radium-223	4.69	10% of mean	Parker 2013	Lognormal	μ: 1.55	σ: 0.10	'Therapy Options & Costing'!E83
Duration of 2L treatment: best supportive care	3.50	10% of mean	Medicinrådet PROfound assessment	Lognormal	μ: 1.25	σ: 0.10	'Therapy Options & Costing'!E84
Olaparib HCRU (Mth 0-3): Outpatient Visit	1.00	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.04	'Medical & Mortality Costs'!F35
Olaparib HCRU (Mth 0-3): CT Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!F37
Olaparib HCRU (Mth 0-3): Bone Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!F38
Olaparib HCRU (Mth 4+): Outpatient Visit	1.00	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.04	'Medical & Mortality Costs'!H35
Olaparib HCRU (Mth 4+): CT Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!H37
Olaparib HCRU (Mth 4+): Bone Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!H38
Abiraterone HCRU (Mth 0-3): Outpatient Visit	1.00	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.04	'Medical & Mortality Costs'!J35
Abiraterone HCRU (Mth 0-3): CT Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!J37

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
Abiraterone HCRU (Mth 0-3): Bone Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!J38
Abiraterone HCRU (Mth 4+): Outpatient Visit	1.00	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.04	'Medical & Mortality Costs'!L35
Abiraterone HCRU (Mth 4+): CT Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!L37
Abiraterone HCRU (Mth 4+): Bone Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!L38
Enzalutamide HCRU (Mth 0-3): Outpatient Visit	1.00	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.04	'Medical & Mortality Costs'!N35
Enzalutamide HCRU (Mth 0-3): CT Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!N37
Enzalutamide HCRU (Mth 0-3): Bone Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!N38
Enzalutamide HCRU (Mth 4+): Outpatient Visit	1.00	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.04	'Medical & Mortality Costs'!P35
Enzalutamide HCRU (Mth 4+): CT Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!P37
Enzalutamide HCRU (Mth 4+): Bone Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!P38
2L HCRU: Outpatient Visit	1.00	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.04	'Medical & Mortality Costs'!R35
2L HCRU: CT Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!R37
2L HCRU: Bone Scan	0.33	20% of mean	Medicinrådet PROfound assessment	Gamma	α: 25	β: 0.01	'Medical & Mortality Costs'!R38
Cost of Palliative Care Hospitalisation	31486	20% of mean	DRG for prostate cancer with palliative	Gamma	α: 25	β: 1259.4	'Medical & Mortality Costs'!F100

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
			care procedure				
No of Hospitalisation at End of Life: Olaparib + Abiraterone	1.5	20% of mean	Assumption	Gamma	α: 25	β: 0.06	'Medical & Mortality Costs'!F103
No of Hospitalisation at End of Life: Abiraterone	2	20% of mean	Vestergaard 2020	Gamma	α: 25	β: 0.08	'Medical & Mortality Costs'!H103
No of Hospitalisation at End of Life: Enzalutamide	2	20% of mean	Vestergaard 2020	Gamma	α: 25	β: 0.08	'Medical & Mortality Costs'!J103
AE Cost: ALAT Increased	1638	20% of mean		Gamma	α: 25	β: 65.52	'Medical & Mortality Costs'!E65
AE Cost: Anaemia	5901	20% of mean		Gamma	α: 25	β: 236.04	'Medical & Mortality Costs'!E66
AE Cost: Back Pain	1510	20% of mean		Gamma	α: 25	β: 60.4	'Medical & Mortality Costs'!E67
AE Cost: General Health Deterioration	4728	20% of mean		Gamma	α: 25	β: 189.12	'Medical & Mortality Costs'!E68
AE Cost: Hyperglycaemia	4728	20% of mean		Gamma	α: 25	β: 189.12	'Medical & Mortality Costs'!E69
AE Cost: Hypertension	17304	20% of mean		Gamma	α: 25	β: 692.16	'Medical & Mortality Costs'!E70
AE Cost: Lymphocyte Count Decreased	2240	20% of mean		Gamma	α: 25	β: 89.6	'Medical & Mortality Costs'!E71
AE Cost: Neutrophil Count Decreased	1858	20% of mean		Gamma	α: 25	β: 74.32	'Medical & Mortality Costs'!E72
AE Cost: Pneumonia	41804	20% of mean		Gamma	α: 25	β: 1672.16	'Medical & Mortality Costs'!E73
AE Cost: Pulmonary Embolism	31555	20% of mean		Gamma	α: 25	β: 1262.2	'Medical & Mortality Costs'!E74

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	Expected Value	Standard Error	Source / Rationale	Probability Distribution	Parameter A (Name: Value)	Parameter B (Name: Value)	Cell Reference
AE Cost: Urinary Tract Infection	28523	20% of mean		Gamma	α: 25	β: 1140.92	'Medical & Mortality Costs'!E75
AE Cost: WBC Count Decreased	1858	20% of mean		Gamma	α: 25	β: 74.32	'Medical & Mortality Costs'!E76
SSRE Cost: Spinal Cord Compression	39320	20% of mean		Gamma	α: 25	β: 1572.8	'Medical & Mortality Costs'!I87
SSRE Cost: Radiation to Bone	40193	20% of mean		Gamma	α: 25	β: 1607.72	'Medical & Mortality Costs'!I88
SSRE Cost: Surgery to Bone	32887	20% of mean		Gamma	α: 25	β: 1315.48	'Medical & Mortality Costs'!I89
SSRE Cost: Pathologic Bone Fracture	92113	20% of mean		Gamma	α: 25	β: 3684.52	'Medical & Mortality Costs'!I90

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Supplementary documentation for the assessment of Lynparza in combination with abiraterone and prednisolone for metastatic castration-resistant prostate cancer

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

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Table of contents

Tables and Figures

Abbreviations

Abi	Abiraterone
AE	Adverse event
AIC	Akaike information criteria
BIC	Bayesian information criteria
BICR	Blinded independent central review
BPI-SF	Brief Pain Inventory – Short Form
BRCA[m]	Breast Cancer gene [mutation]
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DKK	Danish kroner
FACT-P	Functional Assessment of Cancer Therapy –Prostate
HR	Hazard ratio
HRR[m]	Homologous recombination repair [mutation]
INV	Investigator-assessed
KM	Kaplan-Meier
mCRPC	Metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone-sensitive prostate cancer
N/A	Not applicable
NC	Not calculable
NHA	New hormonal agent
NR	Not reported
OS	Overall survival
PS	Performance status
PSA	Prostate specific antigen
QALY	Quality-adjusted life year
RMST	Restricted mean survival time
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAS	Safety analysis set
TDA	Time to discontinuation of abiraterone
TDT	Time to discontinuation of investigational treatment

1. Background

On Wednesday 16 August, AstraZeneca received a request from Medicinrådet for supplemental information pertaining to their ongoing assessment of olaparib (Lynparza) in combination with abiraterone and prednisolone for metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. Specifically, the expert committee and council have requested further information on the subset of patients with BRCA mutations:

Ansøgningen er blevet vendt med fagudvalget og rådet, og der er et ønske om, at effekten af olaparib+abirateron+prednison/prednisolon beskrives for patienter med BRCAm, herunder om effekten som ses for patienter med HRRm er drevet af patienterne med BRCA-mutationer. Derfor skal effekten for HRRm opdelt på BRCAm og non-BRCAm beskrives. Hvis effekten i de to grupper ikke er sammenlignelig, ønsker vi, at der redegøres for omkostningseffektiviteten med en sundhedsøkonomisk model i populationen af patienter med BRCAm.

Whilst the clinical trial was not designed or powered to assess differences in effects by biomarker subgroups, interaction tests indicate that treatment effects are greater for patients positive for a biomarker (BRCAm or HRRm) as opposed to in patients testing negative for the biomarker. A trend is also observed for treatment effects to be greater in patients with BRCA mutations as opposed to other (non-BRCA) HRR mutations. Therefore, the cost-effectiveness and budget impact of treating patients with mCRPC and BRCA mutations in whom chemotherapy is not clinically indicated with olaparib + abiraterone is presented.

2. Summary table

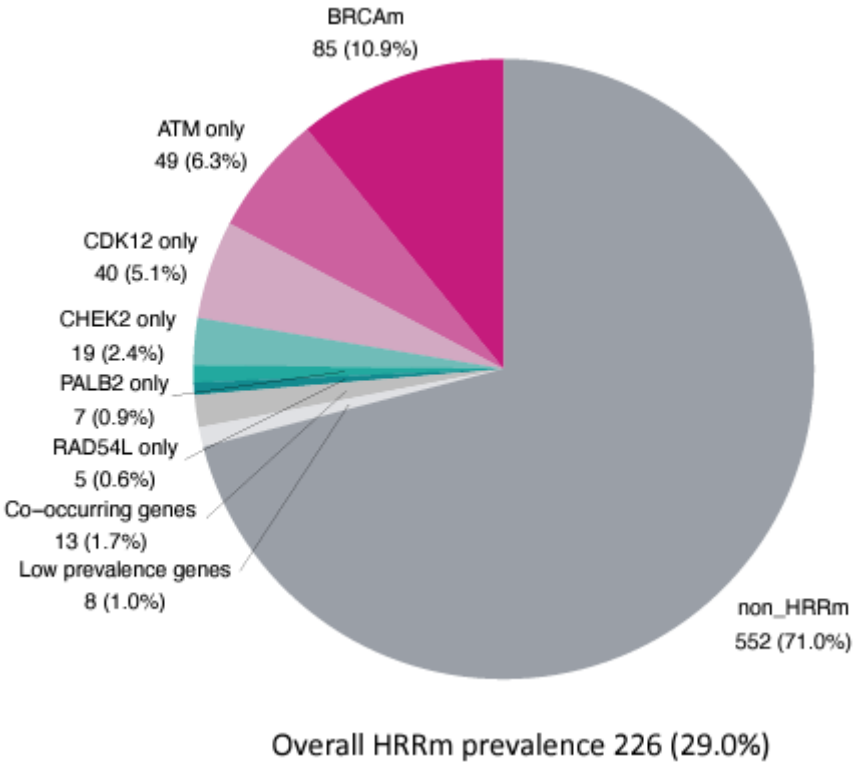
Summary	
Therapeutic indication presented	Adult patients with mCRPC and BRCA1/2-mutations in whom chemotherapy is not clinically indicated
Dosage regiment and administration:	Olaparib: 300 mg (two tablets 150 mg) twice daily Abiraterone: 1000 mg daily Prednisolone: 5 mg twice daily
Choice of comparator	Abiraterone in combination with prednisolone, as the most commonly used treatment in Denmark for patients in whom chemotherapy is not clinically indicated Abiraterone: 1000 mg daily Prednisolone: 5 mg twice daily
Prognosis with current treatment (comparator)	mCRPC has a poor prognosis with limited survival. Median survival for first-line patients treated with NHAs (abiraterone or enzalutamide) in the Nordics is approximately 2.5 years and 5-year survival is ~20%. Patients with BRCA mutations have been observed to have poorer survival than patients without.

Summary	
	First line patients generally have good quality of life considering that they have metastatic cancer, however toxicities associated with chemotherapy and events associated with disease progression (e.g., skeletal complications) negatively impact quality of life.
Type of evidence for the clinical evaluation	Post hoc subgroup analysis from head-to-head study
Subgroup impact on efficacy endpoints	OS: median NR vs. 23.0 months (HR 0.29; 95% CI 0.14, 0.56) PFS: * FACT-P total score: least squares change from baseline 2.43 vs. -1.21 (Difference 3.64; 95% CI -4.05, 11.33) *Substantially improved progression-free and overall survival, with no detriment to quality of life*
Subgroup impact on safety endpoints	*No meaningful differences in safety were observed between the full safety analysis set (ITT population) and the BRCAm subgroup*
Type of economic analysis that is submitted	Cost-utility analysis based on a partitioned survival model
Data sources used to model the clinical effects	PROpel clinical trial (registrational study): OS and rPFS
Data sources used to model the health-related quality of life	PROpel clinical trial (registrational study): EQ-5D-5L data mapped by health state to Danish algorithm. Data from the ITT population of the trial are used.
Life years gained	6.11 years (undiscounted) / 5.18 (discounted)
QALYs gained	3.82 QALY (discounted)
Incremental costs	1 462 586 DKK (discounted)
ICER (DKK/QALY)	382 563 DKK/QALY
Uncertainty associated with the ICER estimate	Parametric model selected for OS in the olaparib arm
Number of eligible patients in Denmark	~30 mCRPC patients per year would be identified as having BRCAm mutations at first line in Denmark
Budget impact (in year 5)	15 793 747 DKK

3. Supplementary clinical data

All clinical data presented here is based on the endpoints as previously presented in the initial application and are from the PROpel clinical trial. Data on radiographic progression-free survival (rPFS) are derived from the primary analysis (30 July 2021), unless otherwise stated. Data on overall survival (OS) and other endpoints are primary derived from the third data cut-off (DCO3; 12 October 2022).

Figure 1. Distributions of genetic mutations in the PROpel trial population



The non-BRCA HRR mutations included in the subgroup are ATM, CDK12, CHEK1, CHEK2, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, BARD1, BRIP1, and FANCL (Figure 1). Selected baseline characteristics for the HRRm subgroup, the BRCAm subgroup, and the non-BRCA HRRm subgroup are presented in Table 1. In both the BRCAm and non-BRCA HRRm subgroups, there were a greater number of older patients in the placebo arm. However, in both subgroups there were a greater number of patients with symptomatic pain at baseline in the olaparib arm. In the BRCAm subgroup, performance status was more favourable in the olaparib arm but was similar in the non-BRCA HRRm subgroup. Patients had a similar burden of adversely prognostic sites of metastases in the BRCAm subgroup, though in the non-BRCA HRRm subgroup more patients had non-skeletal metastases in the olaparib arm.

Table 1. Baseline characteristics of biomarker subgroups in PROpel

	HRRm (Overall)		BRCAm		Non-BRCA HRRm	
	Olaparib + Abi (N = 111)	Placebo + Abi (N = 115)	Olaparib + Abi (N = 47)	Placebo + Abi (N = 38)	Olaparib + Abi (N = 64)	Placebo + Abi (N = 77)
Age (years)						
Median (range)	68 (43, 89)	70 (46, 86)	67 (43, 83)	70 (46, 85)	NR	NR
< 65, n (%)	40 (36.0%)	29 (25.2%)	17 (36.2%)	11 (28.9%)	23 (35.9%)	18 (23.4%)
≥ 65, n (%)	71 (64.0%)	86 (74.8%)	30 (63.8%)	27 (71.1%)	41 (64.1%)	59 (76.6%)
ECOG PS						
0	79 (71.2%)	74 (64.3%)	36 (76.6%)	20 (52.6%)	43 (67.2%)	54 (70.1%)
1	32 (28.8%)	41 (35.7%)	11 (23.4%)	18 (47.4%)	21 (32.8%)	23 (29.9%)
Baseline PSA (µg/L), median	27.2	21.8	29.0	22.5	NR	NR
Prior docetaxel at mHSPC	26 (23.4%)	25 (21.7%)	8 (17.0%)	10 (26.3%)	18 (28.1%)	15 (19.5%)
Site of metastases						
Bone only	55 (49.5%)	64 (55.7%)	25 (53.2%)	20 (52.6%)	30 (46.9%)	44 (57.1%)
Visceral	15 (13.5%)	18 (15.7%)	5 (10.6%)	8 (21.1%)	10 (15.6%)	10 (13.0%)
Other	41 (36.9%)	33 (28.7%)	17 (36.2%)	10 (26.3%)	24 (37.5%)	23 (29.9%)
Baseline pain score*						
None to mild	72 (64.9%)	89 (77.4%)	31 (66.0%)	26 (68.4%)	41 (64.1%)	63 (81.8%)
Moderate to severe	35 (31.5%)	20 (17.4%)	15 (31.9%)	10 (26.3%)	20 (31.3%)	10 (13.0%)

* BPI–SF, item 3 score

As analyses are based on post hoc subgroups, some imbalance in baseline characteristics can be expected. Due to the small size of the subgroups, sophisticated statistical methods to adjust results were not plausible. In their assessment of the BRCAm subgroup, the FDA used a prognostic model to assess overall balance among baseline prognostic risk factors for patients in subgroups by BRCA mutation status. The model used eight identified prognostic factors (opioid use, disease site, ECOG performance status, LDH, albumin, hemoglobin, alkaline phosphatase, and PSA) to calculate a composite risk score for each patient that predicts OS in the first-line chemotherapy setting for patients with mCRPC. After adjusting the OS and rPFS results for risk score, the FDA comment that "there were no overall changes in the conclusions for rPFS and OS subgroup analyses".[1]

As an exploratory post hoc analysis, the stratification of results for HRRm patients by BRCAm vs. non-BRCA is only conducted for rPFS and OS. As can be seen from Table 2, the additional of olaparib to abiraterone was associated with substantial improvements in both rPFS and OS in patients with BRCA mutations. In patients with other (non-BRCA) HRR mutations, this effect is more attenuated with a 20% reduction in the risk of disease progression or death compared to placebo + abiraterone, and similar overall survival.

Table 2. rPFS and OS results by mutation status

	rPFS INV (DCO1)		rPFS INV (DCO3)		OS (DCO3)	
	Olaparib + Abi	Placebo + Abi	Olaparib + Abi	Placebo + Abi	Olaparib + Abi	Placebo + Abi
HRRm (Overall)						
Events, n (%)	43 (38.7%)	73 (63.5%)	** (****%)	** (****%)	48 (43.2%)	69 (60.0%)
Median, months	NC	13.9	***	***	NC	28.5
HR (95% CI)	0.50 (0.34, 0.73)		*** (***, ***)		0.66 (0.45, 0.95)	
BRCAm						
Events, n (%)	14 (29.8%)	28 (73.7%)	** (****%)	** (****%)	13 (27.7%)	25 (65.8%)
Median, months	NC	8.4	***	***	NC	23.0
HR (95% CI)	0.23 (0.12, 0.43)		*** (***, ***)		0.29 (0.14, 0.56)	
Non-BRCA HRRm						
Events, n (%)	29 (45.3%)	45 (58.4%)	** (****%)	** (****%)	** (**.*%)	* (***%)
Median, months	NC	19.2	***	***	*	*
HR (95% CI)	0.80 (0.50, 1.27)		*** (***, ***)		*	

As shown in Figure 2 and Figure 3 below, by DCO3 olaparib + abiraterone was associated with a gain of 30.1 months in median rPFS in patients with BRCA mutations and 7.0 months in patients with non-BRCA HRR mutations. This compares to a median gain of 5.7 months in patients without HRR mutations, as presented in the initial application. Therefore, a benefit of olaparib can be seen across all biomarker subgroups, though this is most substantial in patients with BRCA mutations.

Figure 2. rPFS in the BCRAm subgroup (DCO3; 12 October 2022)

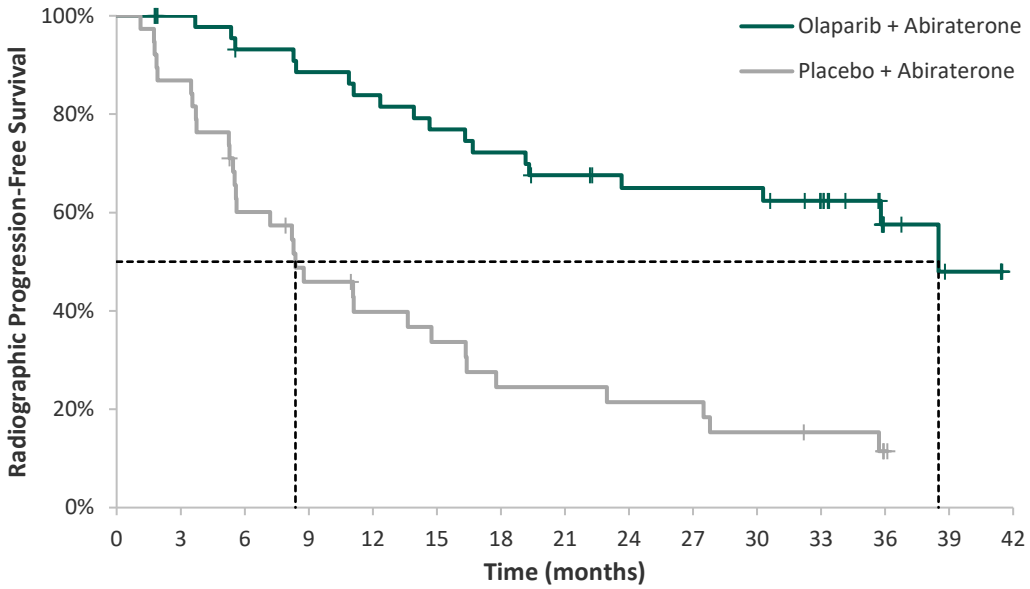


Figure 3. rPFS in the non-BRCA HRRm subgroup (DCO3; 12 October 2022)

[redacted]

At DCO3, olaparib + abiraterone was associated with a 71% reduction in the risk of death compared to abiraterone alone in BRCAm patients (Figure 4). As presented in the initial application, in patients without any HRR mutation there was a trend for improved survival with a gain in median OS of 3.2 months in the non-HRR subgroup (OS HR 0.89; 95% CI 0.70, 1.14). In patients with non-BRCA HRR mutations the survival curves cross between the arms resulting in comparable hazards of death during the trial follow-up period (Figure 5). Given the additional 7 months gain pre-progression, this indicates that survival after disease progression on first line is reduced for patients treated with olaparib + abiraterone. Whilst in the non-HRRm population the rPFS gain is greater than the OS gain, there does not appear to be a clear rationale why no survival gain would be observed in the

non-BRCA HRRm subgroup. Given the post hoc nature of the analysis, and the potential for imbalances in subsequent therapy as well as patient characteristics, it is possible with longer follow-up a survival benefit may be observed in this subgroup. Extended follow-up of overall survival the PROpel trial is ongoing, with planned analyses expected 12-24 months after DCO3. In the PAOLA-1 trial of olaparib in combination with bevacizumab for maintenance treatment in advanced ovarian cancer for patients with genomic instability in the homologous recombination pathway (HRD positive), at the final OS analysis a 29% reduction in the hazard of death was observed for HRD-positive tumors excluding those with a tumor BRCA mutation (55% vs. 44% 5-year survival),[2] [redacted]

Figure 4. OS in the BCRAm subgroup (DCO3; 12 October 2022)

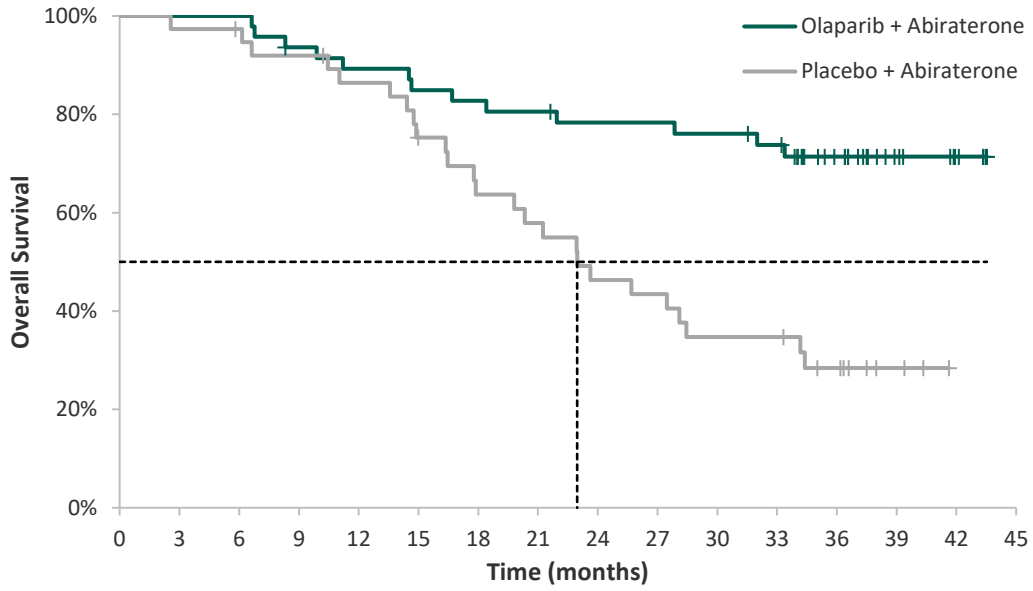


Figure 5. OS in the non-BRCA HRRm subgroup (DCO3; 12 October 2022)

In addition to rPFS and OS, selected additional data is also reported for the subgroup of patients with BRCA mutations (Table 3). To supplement the rPFS results by investigator assessed, at DCO1 olaparib + abiraterone was also superior to placebo + abiraterone with respect to rPFS as assessed by a blinded independent central review committee (BICR). Olaparib was also associated with a 22.6-month delay in time to first subsequent therapy or death by DCO3 as well as a 35.0-month delay in PSA progression.

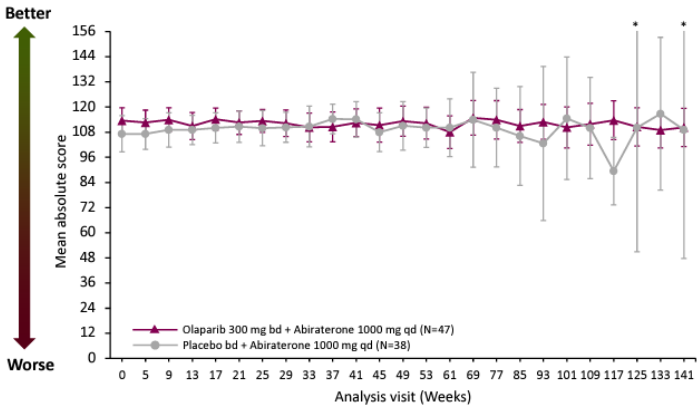
Table 3. Supplementary efficacy data for patients with BRCA mutations

	Olaparib + Abiraterone (N = 47)	Placebo + Abiraterone (N = 38)
rPFS BICR (DCO1; 30 July 2021)		
Events, n (%)	12 (25.5%)	31 (81.6%)
Median, months	NC	8.4
HR (95% CI)	0.18 (0.09, 0.34)	
Time to first subsequent therapy or death (DCO3; 12 October 2022)		
Events, n (%)	24 (51.1%)	30 (78.9%)
Median, months	37.4	14.8
HR (95% CI)	0.35 (0.21, 0.61)	
Time to PSA progression (DCO3; 12 October 2022)		

	Olaparib + Abiraterone (N = 47)	Placebo + Abiraterone (N = 38)
Events, n (%)	19 (40.4%)	30 (78.9%)
Median, months	40.6	5.6
HR (95% CI)	0.14 (0.08, 0.25)	

In addition to the efficacy data, subgroup analysis on the change in FACT-P total score from baseline showed no difference between olaparib + abiraterone and placebo + abiraterone in the BRCAm subgroup (Figure 6). Given that abiraterone treated patients generally report good quality of life, considering they have metastatic disease, olaparib is considered to offer life-prolonging benefits with no detriment to quality of life. Absolute scores in the BRCAm subgroup were similar to the overall population (data not shown), indicating that the presence of BRCA mutations is not a predictor of health-related quality of life.

Figure 6. Mean FACT-P total score for BRCAm subgroup



	BRCAm (Aggregate)	
Overall	Olaparib + Abiraterone N=36	Placebo + Abiraterone N=28
LS means (SE)	2.43 (2.95)	-1.21 (3.09)
Difference (95% CI)	3.64 (-4.05, 11.33)	

* Top end of the confidence limits is beyond the range of the score scale

[1]FACT-P, Functional Assessment of Cancer Therapy – Prostate

Note: FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156. A clinically meaningful change in FACT-P total score is 10.

In the safety analyses of the BRCAm subgroup, the incidences of adverse events (AEs) of grade ≥3, serious AEs (SAEs), AEs leading to an outcome of death, and AEs leading to treatment discontinuation in the olaparib + abiraterone arm of the BRCAm subgroup were lower compared with those observed in the full safety analysis set (SAS) of the trial. The lower incidence of grade ≥ 3 AEs in the BRCAm subgroup is largely driven by a lower incidence of anaemia compared to in the SAS (10.6% vs 16.1%, respectively). This difference is likely due to the small size of the BRCAm subgroup, where a 6% incidence of an AE reflects an absolute difference of only 2 to 3 patients. Therefore, it is concluded that the safety of olaparib + abiraterone in BRCAm patients is likely to be similar to the overall population.

Table 4. PROpel safety data in the safety analysis set and the BRCAm subgroup (DCO3; 12 October 2022)

	Full Safety Analysis Set		BRCAm Subgroup	
	Olaparib + Abi (N = 398)	Placebo + Abi (N = 398)	Olaparib + Abi (N = 47)	Placebo + Abi (N = 38)
Median total duration of exposure (days)				
Olaparib/Placebo	564.0	476.5	957.0	300.0
Abiraterone	612.0	477.0	960.0	300.0
Adverse events, n (%)				
Any AE	389 (97.7%)	380 (96.0%)	47 (100%)	34 (89.5%)
Any AE of CTCAE Grade ≥ 3	222 (55.8%)	171 (43.2%)	23 (48.9%)	15 (39.5%)
Any SAE	161 (40.5%)	126 (31.8%)	14 (29.8%)	12 (31.6%)
Any AE with outcome of death	26 (6.5%)	20 (5.1%)	1 (2.1%)	2 (5.3%)
Any AE leading to discontinuation of olaparib/placebo	69 (17.3%)	34 (8.6%)	6 (12.8%)	4 (10.5%)
Any AE leading to discontinuation of abiraterone	45 (11.3%)	37 (9.3%)	3 (6.4%)	4 (10.5%)

Given that the efficacy of olaparib + abiraterone appears to differ between patients with BRCAm and those with non-BRCA HRRm, AstraZeneca has fulfilled Medicinrådet's request by providing a health economic analysis of the olaparib + abiraterone in BRCAm patients. However, we would like to comment that there does appear to be some clinic benefit of olaparib + abiraterone both in patients with non-BRCA HRR mutations as well as in patients without HRR mutations, as presented in the initial submission.

4. Modelling of efficacy in the health economic analysis

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

4.1.1 Extrapolation of efficacy data

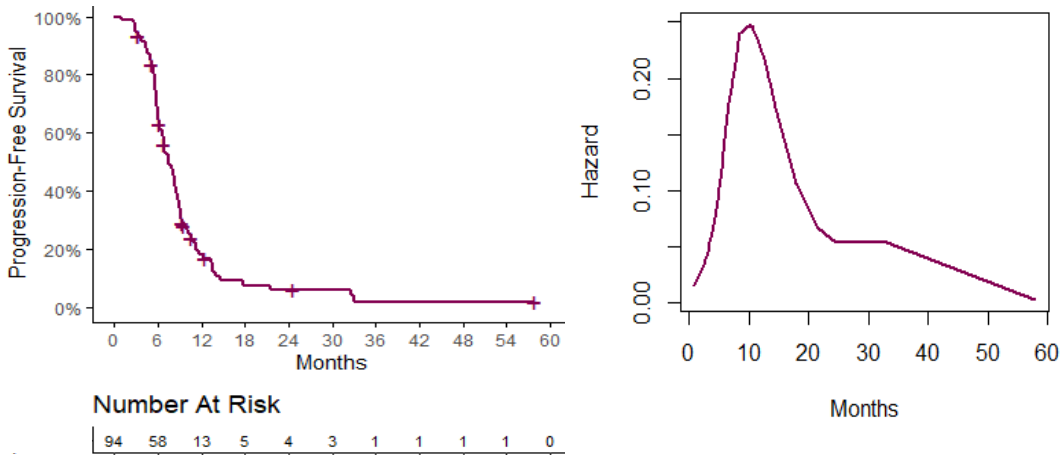
As per the initial submission, the extrapolated outcomes in the model are rPFS, OS, time to discontinuation of abiraterone, and time to discontinuation of olaparib. Given the differing durations of olaparib and abiraterone in the olaparib arm, this separation is deemed suitable. All time to event outcomes for use in the model were extrapolated from the patient-level data from the PROpel trial following the guidance from the NICE Decision Support Unit's Technical Support Document 14 and updated guidance on selecting survival models from Palmer et al.[3,4] as well as Medicinrådet's guidance on survival extrapolations. All extrapolations are based on the third data cut-off (DCO3) of the PROpel trial, dated 12 October 2022, for the BRCAm subgroup.

4.1.1.1 Extrapolation of rPFS

The summary statistics and Kaplan-Meier curve of investigator-assessed rPFS in the BRCAm population are shown in Table 2 and Figure 2 above. Data maturity did not significantly increase across data cuts, with most patients progressing rapidly in the placebo + abiraterone arm compared to sustained progression-free survival in the olaparib + abiraterone arm. Consequently, the hazard ratios were consistent across data cuts. The Schoenfeld residuals, quantile-quantile plots, and log-log and other diagnostic plots do not indicate any significant deviations from the proportional hazards or accelerated failure time assumptions (see Appendix A - Extrapolation). Therefore, both joint and independent modelling of treatment arms were considered plausible.

In terms of plausible long-term functional forms, the smoothed hazards from the trial in the placebo arm are not especially informative as the low number of patients in the BRCAm subgroup means these can only be evaluated for approximately the first year of follow-up. However, results from a recently presented analysis synthesizing survival outcomes for first line mCRPC patients treated with standard therapies (NHAs [65%] or taxanes [35%]) across five studies of patients with known BRCA mutations provides nearly 5 years of follow-up.[5] In this analysis, with 84% data maturity (79/94) for rPFS it was observed that most patients progress rapidly, but for a very limited number of patients longer-term rPFS is possible, resulting in a non-monotonic hazard (**Error! Reference s ource not found.**). Whilst this data includes some patients treated with chemotherapy (and therefore would not be eligible for olaparib + abiraterone), it is still assumed to be relevant for drawing inferences as the analysis also showed that rPFS outcomes were similar between taxanes and NHAs (HR 1.03; 95% CI 0.61, 1.73).[5]

Figure 7. Kaplan-Meier plot and smoothed hazards of rPFS for BRCAm patients in the CAPTURE study



Figures developed from pseudo-patient level data recreated from Olmos (2023)[5]

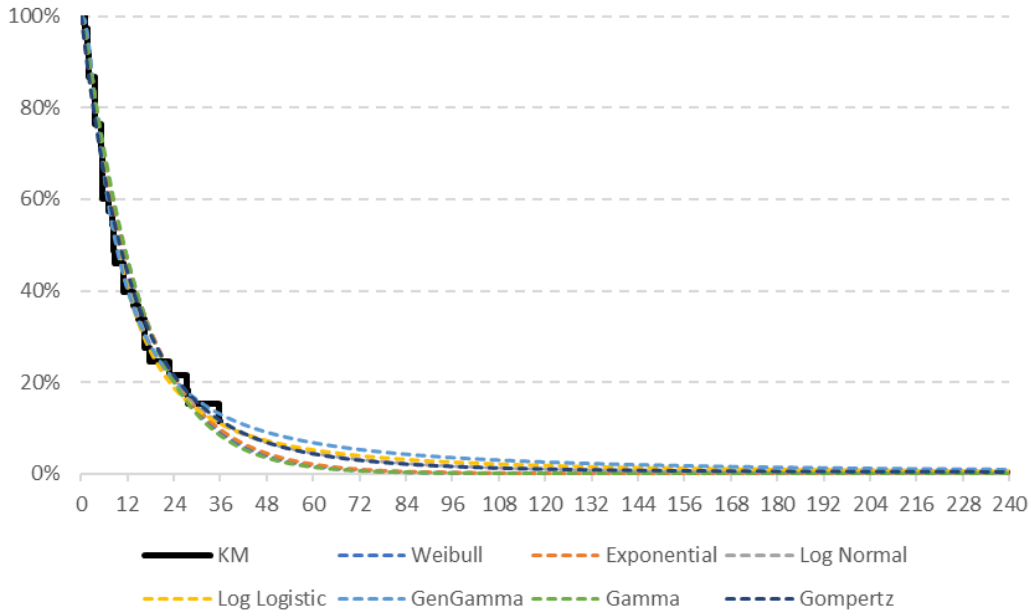
In the olaparib arm, the hazard was observed to be somewhat constant during trial follow-up, but at 3 years 58% of patients were still progression-free and therefore the shape of the long-term hazard is uncertain. However, as olaparib is given as an add-on to abiraterone and no drug-drug interactions have been observed, it is assumed that any long-term benefit of abiraterone would also apply to the olaparib + abiraterone arm, on top of the added benefit observed during trial follow-up. Therefore, non-monotonic functional forms are considered plausible.

The preference for these forms is supported by the AIC and BIC criteria, where the lognormal distribution provides the best fit in both arms and in joint models, though other parametric forms provide statistically good fits.

With regards to visual fit to the trial data, the lognormal, loglogistic, and generalised gamma distributions provide the best fit to both arms. However, in joint modelling the visual fit to the abiraterone arm is good but variable for the olaparib + abiraterone arm.

In comparison to external data, rPFS in the abiraterone arm was longer (median 8.4 months vs. 7.4 months; 3-year 11% vs. 2%). This is considered reasonable given the better performance status in PROpel (patients eligible for add-on therapy with olaparib are likely to be fitter). However, long-term outcomes may not differ substantially. Given the plausibility of a non-monotonic functional form, the lognormal distribution is preferred for the abiraterone arm given that it provides the lowest 5-year rPFS (4.5%) compared to the loglogistic (5.3%) or generalised gamma (6.7%).

Figure 8. rPFS extrapolations for the placebo + abiraterone arm in BRCAm patients



For the treatment effect in the olaparib arm, the flexibility of the generalised gamma distribution may produce overly optimistic results (Figure 9). Using joint modelling would assume that the observed effect of olaparib is sustained across the time horizon with no loss of relative effect, though in the non-monotonic models the hazards do begin to converge after ~5 years. On the basis that similar functional forms should be used for both the intervention and comparator, and its good statistical and visual fit, the lognormal distribution is selected for the base case for the olaparib arm. Independent modelling is preferred to joint modelling as this results in a better visual fit to the trial data for both arms.

Figure 9. rPFS extrapolations for the olaparib + abiraterone arm in BRCAm patients

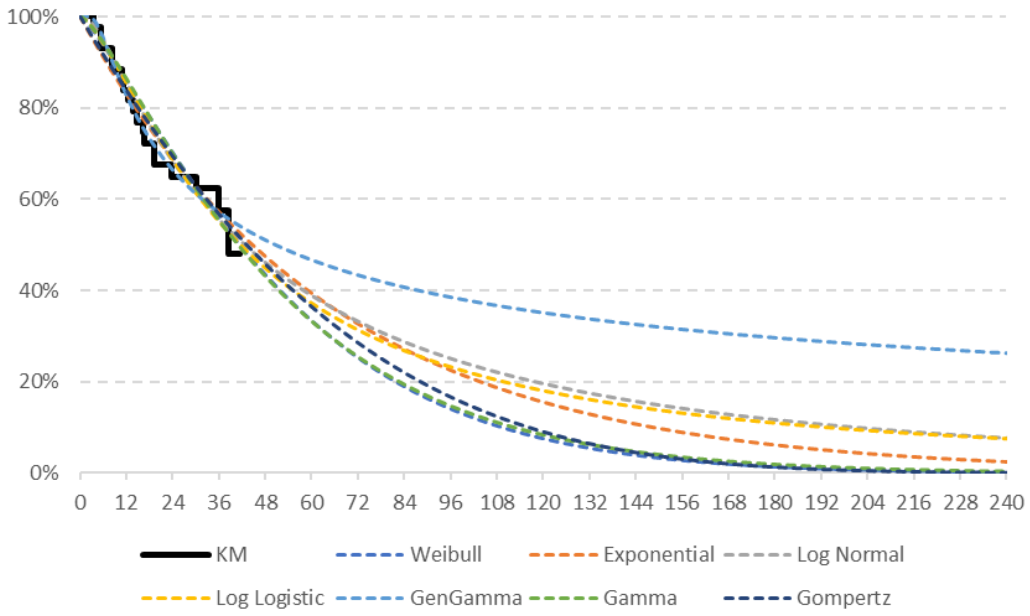


Table 5. Summary of assumptions associated with extrapolation of rPFS

Method/approach	Description/assumption
Data input	PROpel (BRCAm subgroup)
Model	Parametric models using exponential, Weibull, Gompertz, gamma, generalized gamma, lognormal, and loglogistic distributions.
Assumption of proportional hazards between intervention and comparator	Not applied in base case – no significant deviation from the proportional hazard assumption were observed in the data but joint models provided a poor visual fit to Kaplan-Meiers
Function with best AIC fit	Olaparib + Abiraterone: Lognormal Placebo + Abiraterone: Lognormal
Function with best BIC fit	Olaparib + Abiraterone: Exponential Placebo + Abiraterone: Lognormal
Function with best visual fit	Olaparib + Abiraterone: Generalised gamma Placebo + Abiraterone: Lognormal or generalized gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib + Abiraterone: Lognormal or loglogistic Placebo + Abiraterone: Unclear due to low number at risk after ~15 months
Validation of selected extrapolated curves (external evidence)	Comparison of hazard functions/survival with CAPTURE study of BRCAm/HRRm patients treated for first line mCRPC with standard therapies[5]

Method/approach	Description/assumption
Function with the best fit according to external evidence	Olaparib + Abiraterone: N/A Placebo + Abiraterone: Lognormal, loglogistic, or generalized gamma
Selected parametric function in base case analysis	Olaparib + Abiraterone: Lognormal Placebo + Abiraterone: Lognormal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable

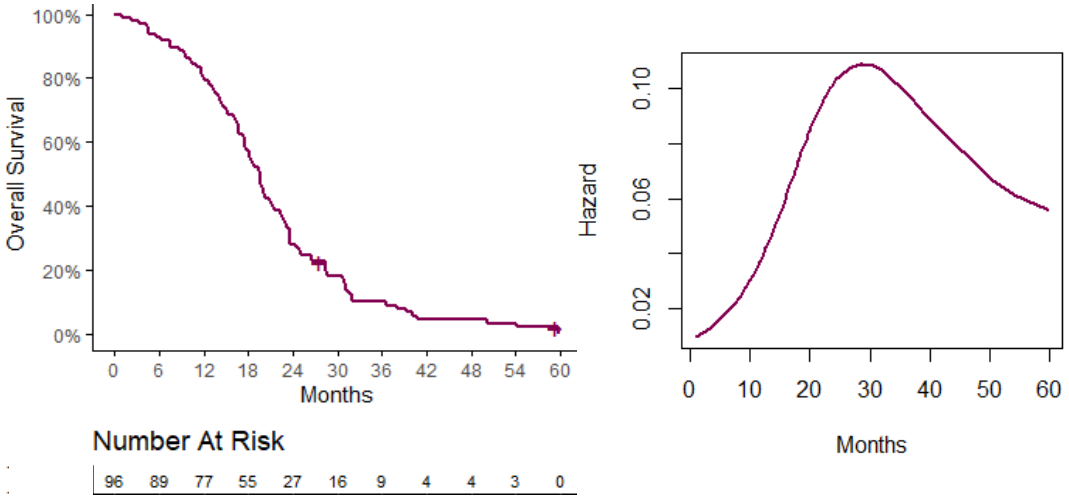
4.1.1.2 Extrapolation of OS

The summary statistics and Kaplan-Meier curve of OS in the BRCAm population are shown in Table 2 and Figure 4. The treatment benefit of olaparib appears to be grow over time, with a difference in OS of 3% after 1 year, 32% after 2 years, and 43% after 3 years.

The Schoenfeld residuals and quantile-quantile plots indicate that the proportional hazards assumption has been violated, supported by the diagnostic plots which show some touching or crossing of the curves up to around 10 months (see Appendix A - Extrapolation). Therefore, independent extrapolation of each arm was performed.

With regards to functional forms of the data, the smoothed hazards for both arms indicate non-monotonic forms. The non-monotonic functional forms also had the best statistical fit to the trial data in terms of AIC. As presented in the initial submission to Medicinrådet, previous studies of olaparib in BRCAm metastatic cancer have also shown longer tails and non-monotonic functional forms. For the placebo arm, insights were again drawn from the CAPTURE study. Figure 10 shows the overall survival for 96 BRCAm patients treated with NHAs or taxanes with 97% data maturity, where the hazards of death decline after approximately 30 months for some limited number of longer-term survivors. Outcomes in this study were poorer than observed for abiraterone treated patients in PROpel (median OS 19.6 months vs. 23.0 months), though in addition to the poor performance status the study also showed a trend for worse survival outcomes for taxane treated patients compared to NHA (HR 1.21; 95% CI 0.81, 1.82) and therefore it is plausible that a pure NHA treated cohort would have better survival. It is also unclear what subsequent therapies these patients received.

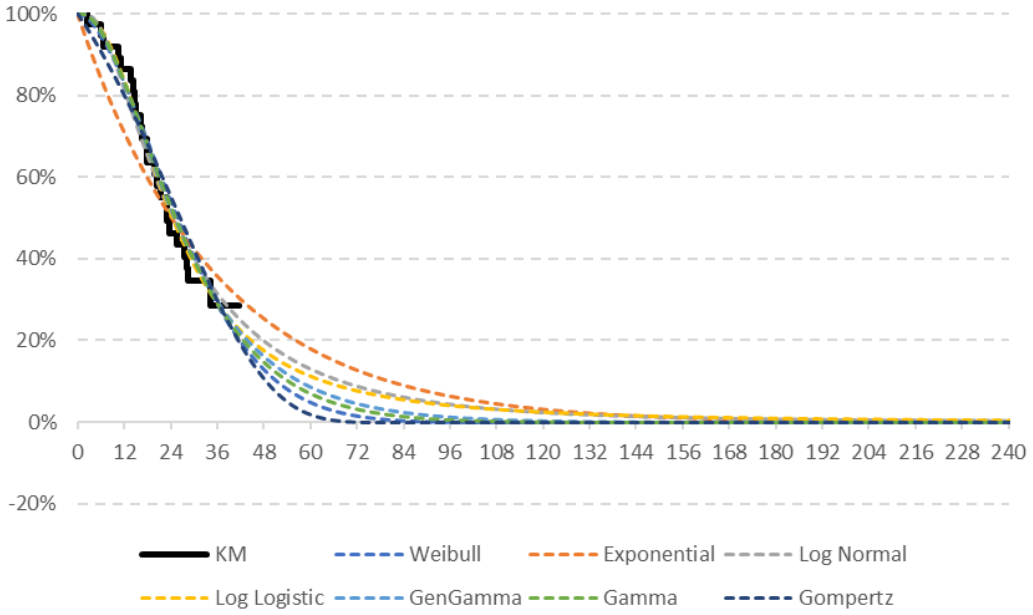
Figure 10. Kaplan-Meier plot and smoothed hazards of OS for BRCAm patients in the CAPTURE study



Figures developed from pseudo-patient level data recreated from Olmos (2023)[5]

With regards to visual fit, the exponential, Weibull, and Gompertz distributions have a poor fit to the placebo + abiraterone arm, with the loglogistic having the most appealing fit. The generalised gamma, lognormal, and gamma are also plausible alternatives, though the hazard functions for the gamma and generalised gamma are not as well aligned to the trial or external data. However, the loglogistic and lognormal distributions produce 5-year survival estimates of 11-13%, compared to 7-9% for the gamma and generalised gamma, and 2% for external evidence.

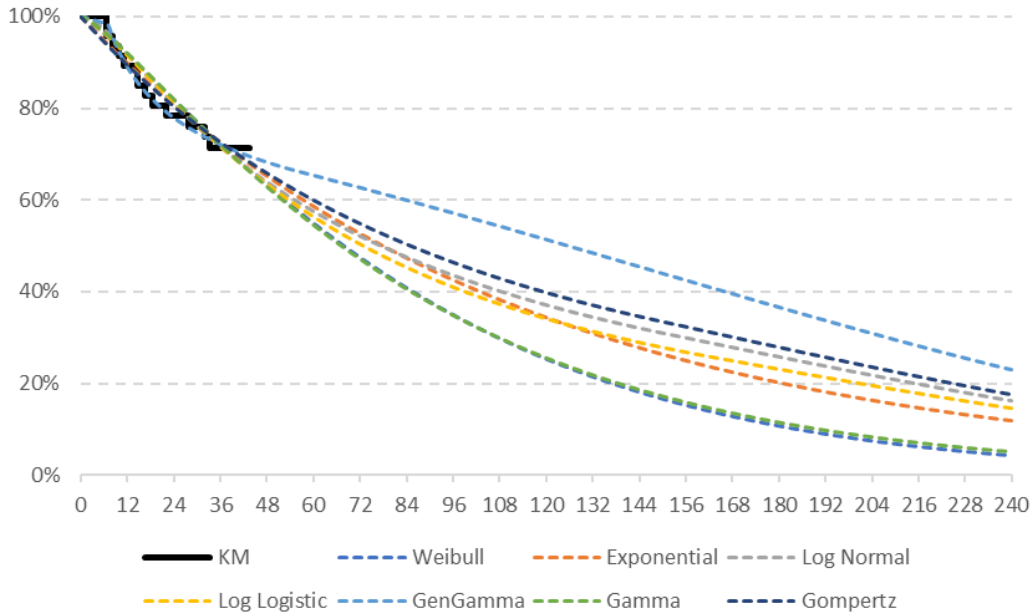
Figure 11. OS extrapolations for the placebo + abiraterone arm in BRCAm patients



Given the low number of events in the olaparib arm, all parametric curves provide a similarly good visual fit to the trial data, but with relatively modest variation in the tail (except for the generalised gamma; see Figure 12) as the long-term hazard functions are relatively similar between forms, suggesting a somewhat constant hazard after approximately 12 months. Of the remaining fits, the

gamma and Weibull distributions provide the most pessimistic survival outcomes with 20-year survival of 4-5%, compared to the lognormal and Gompertz giving estimates of 16-18%.

Figure 12. OS extrapolations for the olaparib + abiraterone arm in BRCAm patients



If one believes that longer tails and non-monotonic hazards are plausible, as the data would indicate, the loglogistic distribution provides the most conservative survival estimates for both arms, which may be the most plausible given that this is a metastatic cancer with a relatively poor prognosis with current treatment options. However, given the that all models for olaparib converge to a relatively constant hazard, the exponential distribution may also be a plausible option.

In the absence of conclusive long-term evidence on survival for mCRPC patients with BRCA mutations treated with NHA-based therapies, for the base case the loglogistic distribution is selected for the placebo + abiraterone arm. This is due to the good statistical fit, the alignment of the smoothed hazards with both trial and external data, and also reflects that for patients who may go on to receive olaparib monotherapy as a subsequent therapy in clinical settings there is the potential for some long-term benefit. For the olaparib + abiraterone arm, the exponential distribution is selected for the base case. This constant hazard for OS may also partially reflect the low hazard of death pre-progression for the long-term responders to olaparib, but also an increase hazard of death post-progression as limited effective treatment options exists for BRCAm patients.

Table 6. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	PROpel (BRCAm subgroup)
Model	Parametric models using exponential, Weibull, Gompertz, gamma, generalized gamma, lognormal, and loglogistic distributions.

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	No – proportional hazards assumption violated
Function with best AIC fit	Olaparib + Abiraterone: Generalised gamma Placebo + Abiraterone: Loglogistic
Function with best BIC fit	Olaparib + Abiraterone: Generalised gamma Placebo + Abiraterone: Loglogistic
Function with best visual fit	Olaparib + Abiraterone: Generalised gamma or lognormal Placebo + Abiraterone: Loglogistic, generalized gamma, or gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib + Abiraterone: Lognormal Placebo + Abiraterone: Lognormal or loglogistic
Validation of selected extrapolated curves (external evidence)	Comparison of hazard functions/survival with CAPTURE study of BRCAm/HRRm patients treated for first line mCRPC with standard therapies[5]
Function with the best fit according to external evidence	Olaparib + Abiraterone: N/A Placebo + Abiraterone: Lognormal, loglogistic, or generalized gamma
Selected parametric function in base case analysis	Olaparib + Abiraterone: Exponential Placebo + Abiraterone: Loglogistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No

4.1.1.3 Extrapolation of time to discontinuation of abiraterone

The summary statistics and Kaplan-Meier curve of time to discontinuation of abiraterone (TDA) in the BRCAm population are shown in Appendix A - Extrapolation. Of note, in this subgroup the median time on treatment is longer than the median rPFS for the placebo + abiraterone, but time on treatment is still shorter than rPFS for the olaparib + abiraterone arm. The curves are separated across the horizon, and the Schoenfeld residuals and quantile-quantile plots indicate that proportional hazards or accelerated failure time models may be plausible. The diagnostic plots also show that the curves do not cross and follow mostly straight lines, though the gradients of the linear fits diverge slightly. This is further supported by the smoothed hazards plot, which show that for the olaparib arm the hazards of discontinuation are somewhat constant, but for the placebo arm there is a sharp increase in the hazard up to 15 months after which time there is insufficient information on which to draw inferences, though given the maturity of the data this was not

considered to be a significant concern. Therefore, both independent models and joint fitting of the curves seems plausible based on the initial review of the data.

With regards to visual and statistical fit, the loglogistic, lognormal, and generalised gamma are preferred for the placebo + abiraterone arm (Figure 13). For the olaparib + abiraterone arm, the slight change in the hazard after around 15 months indicates a preference for more flexible forms (Figure 12), with the generalised gamma giving the best visual fit, though following a similar form to the lognormal which has the lowest AIC. In joint models, the lognormal, loglogistic, and generalised gamma distributions again offer the best statistical fit, but no parametric model provided a good visual fit to Kaplan-Meier in either arm. This implies that whilst similar functional forms between arms are plausible, there is a requirement for flexibility of both the shape and the scale parameters and so independent modelling is preferred.

Figure 13. TDA extrapolations for the placebo + abiraterone arm in BRCAm patients

Given the maturity of the data, the good visual and statistical fit, and alignment the with preferred long-term hazard for rPFS, the loglogistic distribution is favoured for the placebo + abiraterone arm in the base case. As the loglogistic distribution also provides a good fit to the olaparib + abiraterone arm in terms of visual and statistical fit and is well aligned with the smoothed hazards from the trial, it is also applied in the base case.

Figure 14. TDA extrapolations for the olaparib + abiraterone arm in BRCAm patients

Table 7. Summary of assumptions associated with extrapolation of TDA

Method/approach	Description/assumption
Data input	PROpel (BRCAm subgroup)
Model	Parametric models using exponential, Weibull, Gompertz, gamma, generalized gamma, lognormal, and loglogistic distributions.
Assumption of proportional hazards between intervention and comparator	Not applied in base case – no significant deviation from the proportional hazard assumption were observed in the data but joint models provided a poor visual fit to Kaplan-Meiers
Function with best AIC fit	Olaparib + Abiraterone: Lognormal Placebo + Abiraterone: Loglogistic
Function with best BIC fit	Olaparib + Abiraterone: Lognormal or exponential Placebo + Abiraterone: Loglogistic
Function with best visual fit	Olaparib + Abiraterone: Generalized gamma, lognormal, or loglogistic Placebo + Abiraterone: Loglogistic, lognormal, or generalized gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib + Abiraterone: Lognormal or loglogistic Placebo + Abiraterone: Unclear due to low number at risk after ~15 months
Validation of selected extrapolated curves (external evidence)	No evidence of treatment duration in BRCAm patients, but trial data is relatively mature and aligned with rPFS in the abiraterone arm and consistently shorter than rPFS in the olaparib arm

Method/approach	Description/assumption
Function with the best fit according to external evidence	Olaparib + Abiraterone: Lognormal or loglogistic Placebo + Abiraterone: Lognormal, loglogistic, or generalized gamma
Selected parametric function in base case analysis	Olaparib + Abiraterone: Loglogistic Placebo + Abiraterone: Loglogistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable

4.1.1.4 Extrapolation of time to discontinuation of olaparib

The summary statistics and Kaplan-Meier curve of time to discontinuation of investigational treatment (TDT) are shown in Appendix A - Extrapolation. Time to discontinuation of olaparib was highly aligned with time to discontinuation of abiraterone in this subgroup, though slightly shorter (Figure 15), therefore it was a priori considered that a similar functional form should be applied. The goodness-of-fit statistics are aligned with those on time to discontinuation of abiraterone, suggesting that the lognormal, generalised gamma, or loglogistic distributions have the best fit.

Figure 15. Comparison of time to treatment discontinuation and rPFS for patients with BRCA mutations in the olaparib + abiraterone arm

With regards to visual fit of the extrapolated curves to the Kaplan-Meier, all explored fits were comparable, with the generalised gamma providing the best fit. However, as with time to discontinuation of abiraterone, this may be overfitting and producing an implausibly long tail. Despite some potential for differences in discontinuation rates due to the different adverse event profiles of olaparib and abiraterone, it is largely expected that the curves would follow a similar functional form in the long-term due to disease progression and mortality. Therefore, if the

loglogistic distribution is preferred for time to abiraterone discontinuation in olaparib treated patients, the loglogistic distribution would also be plausible here and is thus selected for the base case.

Figure 16. TDT extrapolations for the olaparib + abiraterone arm in BRCAm patients

Table 8. Summary of assumptions associated with extrapolation of TDT

Method/approach	Description/assumption
Data input	PROpel (BRCAm subgroup)
Model	Parametric models using exponential, Weibull, Gompertz, gamma, generalized gamma, lognormal, and loglogistic distributions.
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Olaparib + Abiraterone: Lognormal
Function with best BIC fit	Olaparib + Abiraterone: Lognormal
Function with best visual fit	Olaparib + Abiraterone: Loglogistic or generalized gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Olaparib + Abiraterone: Loglogistic or lognormal
Validation of selected extrapolated curves (external evidence)	Internally validated against time to discontinuation of abiraterone

Method/approach	Description/assumption
Function with the best fit according to external evidence	Olaparib + Abiraterone: Lognormal or loglogistic, based on comparison to preferred fit for time to discontinuation of abiraterone and rPFS
Selected parametric function in base case analysis	Olaparib + Abiraterone: Loglogistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable

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

Table 9 shows the modelled average and modelled median of the effect measures predicted by the extrapolation model. The estimates are undiscounted and without half-cycle correction but have been adjusted for background mortality of the Danish population.

Table 9. Treatment duration estimates in the model

	Modelled mean	Modelled median	Observed median from PROpel
Olaparib + Abiraterone			
rPFS	75.4 months	42.6 months	38.5 months
OS	107.5 months	77.8 months	NR
Time on olaparib	52.1 months	26.7 months	31.4 months
Time on abiraterone	58.2 months	29.5 months	33.4 months
Abiraterone			
rPFS	17.6 months	9.5 months	8.4 months
OS	34.1 months	24.6 months	23.0 months
Time on abiraterone	15.8 months	9.8 months	9.9 months

NR, not reached

The comparison between endpoints is also shown graphically in Figure 17 for olaparib + abiraterone and Figure 18 for placebo + abiraterone.

Figure 17. Modelled time to event outcomes for the olaparib + abiraterone arm

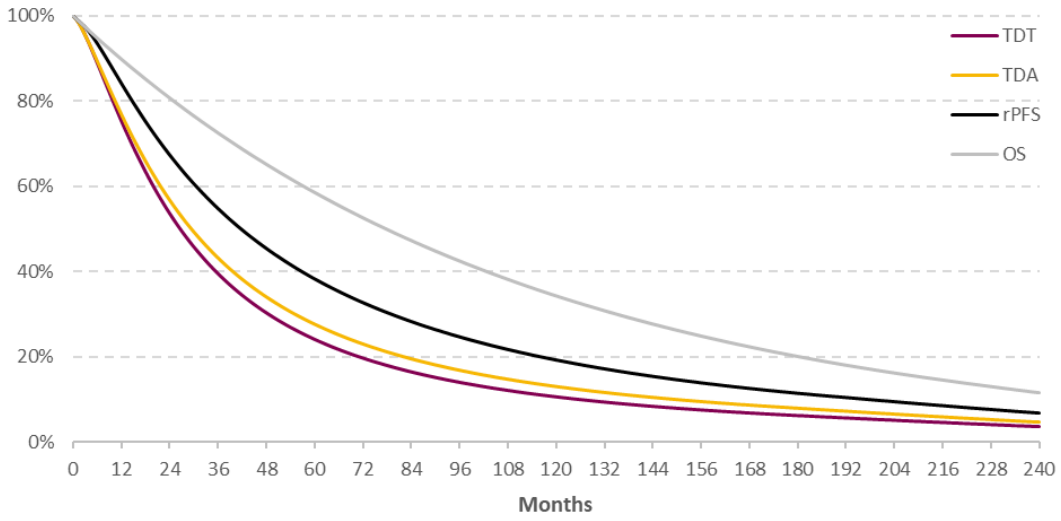
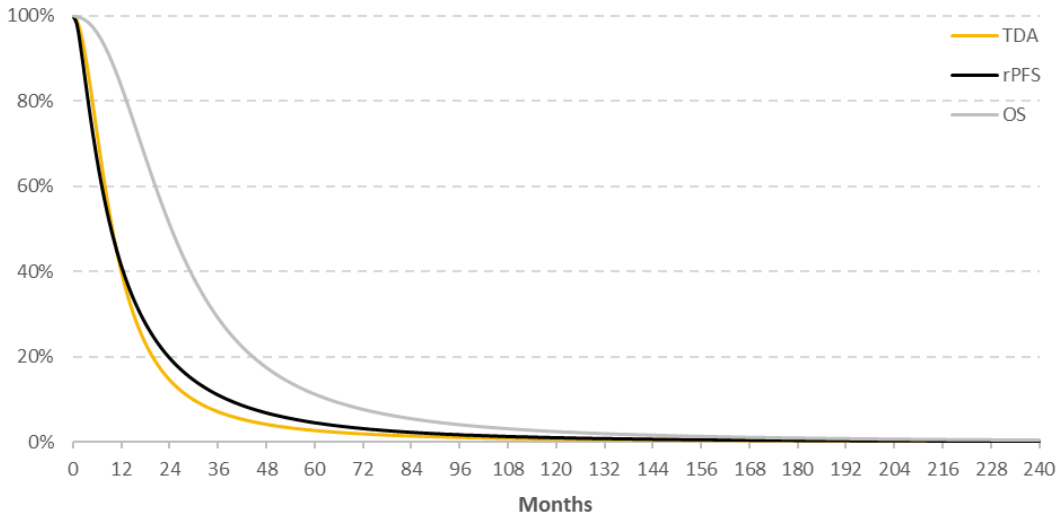


Figure 18. Modelled time to event outcomes for the placebo + abiraterone arm



5. Resource use and associated costs

The majority of cost parameters remain unchanged from the initial submission as there was no identified rationale for different drug costs, routine healthcare, patient costs, or adverse event costs. However, two cost categories were considered to have relevant changes for the BRCAm subgroup:

- **Costs of genetic testing**: to identify patients with BRCA mutations at first line in future, as opposed to second or later lines today when patients may be eligible for olaparib monotherapy
- **Subsequent therapies**: as a subgroup of BRCAm patients is being modelled, all patients in the overall mCRPC population who may receive olaparib monotherapy as a subsequent therapy today would fall within the BRCAm population, and therefore subsequent treatment distributions have been modified to reflect this.

5.1 BRCAm testing

The approach for applying costs of genetic testing in patients who would be treated with olaparib + abiraterone remains unchanged from the initial submission, based on the estimated prevalence of mutations and the number needed to treat.

The unit cost of mutation testing was estimated to be 11 000 DKK (based on the cost reported in Medicinrådet's assessment of olaparib monotherapy for BRCAm mCRPC). Based on a known BRCAm prevalence of 10.7% in PROpel, the number needed to test to identify one patient eligible for olaparib + abiraterone at first line is 9.4.

For patients starting olaparib monotherapy at second line (after abiraterone at first line), these patients are also required to have a known BRCA mutation. As BRCA testing is not routinely conducted at first line, despite the modelled population being BRCAm patients it is not known in current clinical practice that these patients have a BRCA mutation until starting olaparib. Therefore, the number needed to test is equivalent to in a biomarker unselected population (i.e., 9.4 per olaparib-treated patient). Consequently, for each patient modelled to receive olaparib monotherapy at second line, 9.4 patients are assumed to have been tested for BRCA mutations.

5.2 Subsequent treatment costs

The distribution of subsequent treatments has been updated to reflect a patient population with BRCA mutations, though the proportion of patients progressing to subsequent therapy after disease progression remains unchanged from the previous submissions, as the number of BRCAm patients receiving subsequent treatment as a proportion of patients surviving beyond disease progression (93.0%) is similar to that in the overall PROpel population (93.6%).

The initial distributions of subsequent therapies were based on feedback from four Nordic clinical experts (including one with clinical experience in Denmark) on how treatments are sequenced in clinical practice. On average, the clinicians estimated that [redacted] of patients treated with abiraterone at first line would receive olaparib monotherapy as a second line therapy. As olaparib monotherapy is only indicated and reimbursed for patients with BRCA mutations, this estimate was deemed plausible based on the estimated prevalence of BRCA mutations in mCRPC (10.7% of patients randomised in PROpel had a known BRCA mutation, and 11.0% of patients with successful test results in the PROfound screening had a BRCA mutation). For the subgroup of patients with BRCA mutations, the initial distributions must be adjusted. As a proportion of an all-comers population, the number of patients treated with olaparib is relatively small, but as a proportion of patients with BRCA mutations the proportion treated with olaparib is relatively large (Figure 19). Assuming a BRCAm prevalence of 10.7% in the overall mCRPC population, and [redacted] of all abiraterone-treated mCRPC patients would receive olaparib as a subsequent therapy, it is assumed that [redacted] of BRCAm patients receiving abiraterone as their first line therapy would get olaparib as their second line treatment. As no other currently approved treatment in Denmark for mCRPC (e.g., docetaxel, cabazitaxel, radium-223, or NHA rechallenge) is contingent on a biomarker, it was assumed that all other treatments could be weighted down proportionally to account for this increase. Table 10 shows the distribution of subsequent therapies applied in the base case.

Figure 19. Adjustment of subsequent treatment distributions

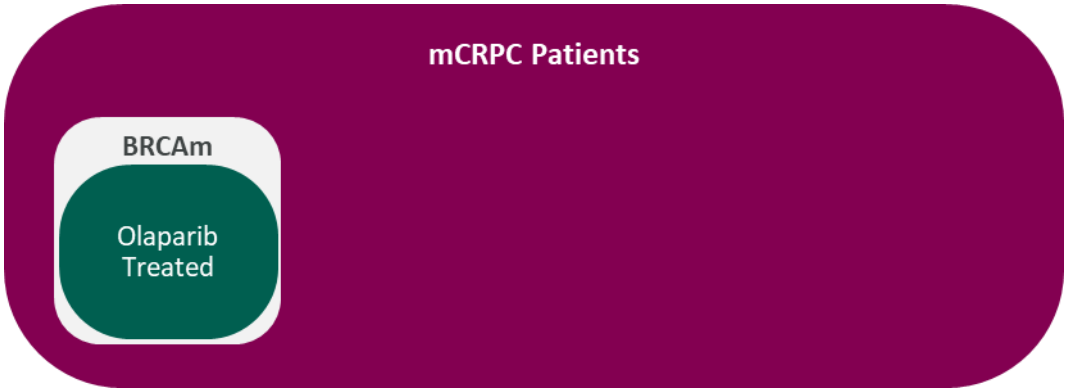


Table 10. Modelled distribution of subsequent treatments in the BRCAm subgroup

	Olaparib + Abiraterone	Abiraterone	Enzalutamide
Abiraterone	***	***	***
Cabazitaxel	***	***	***
Docetaxel	***	***	***
Enzalutamide	***	***	***
Olaparib (mono)	***	***	***
Radium-223	***	***	***

All other factors relating to subsequent treatments (e.g., costs of drugs, duration of treatments) remain unchanged from the ITT population.

6. Results

As the primary comparator, only the results vs. abiraterone are presented here. Cost-effectiveness results compared to enzalutamide can be found in the Excel model. The main results from the base case analysis are summarised in Table 11. Over the lifetime horizon, treatment with olaparib + abiraterone was associated with higher costs than with abiraterone alone, but with some cost savings related to subsequent therapy given the shift of olaparib treatment from second line to first line. Olaparib + abiraterone was also associated with longer survival, resulting in palliative care cost savings, and a greater number of QALYs gained. The resulting incremental cost per QALY for olaparib + abiraterone versus abiraterone alone at the pharmacy purchase price (AIP) was 382 563 DKK. The costs of diagnostic testing are expected to increase as, despite high use of olaparib as a second line therapy, only a certain proportion of patients survive beyond disease progression in order to receive second line treatment.

Table 11. Base case results, discounted estimates

	Olaparib + Abiraterone	Abiraterone	Difference
Pharmaceutical costs	[redacted]	[redacted]	1 435 739
Administration	0	0	0
Diagnostic testing	103 012	54 942	48 069
Disease management costs	323 849	119 164	204 685
Costs associated with management of adverse events & SSREs	13 606	10 886	2 721
Subsequent treatment costs	[redacted]	[redacted]	- 228 235
Patient costs	34 697	12 767	21 930
Palliative care costs	35 994	58 317	- 22 323
Total costs	[redacted]	[redacted]	**1 462 586**
Life years gained (pre-progression)	5.11	1.35	3.76
Life years gained (post-progression)	1.96	1.25	0.71
Total life years	**7.07**	**2.60**	**4.47**
QALYs (pre-progression)	4.44	1.19	3.26
QALYs (post-progression)	1.62	1.05	0.57
QALYs (adverse reactions & SSREs)	-0.00	-0.00	-0.00
Total QALYs	**6.05**	**2.23**	**3.82**
Incremental costs per life year gained		**327 408**	
Incremental cost per QALY gained (ICER)		**382 563**	

7. References

1. Food and Drug and Administration. FDA Briefing Document: NDA 208558/Supplement 25. Silver Spring, MD: Food and Drug Administration, 2023.
2. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann Oncol* 2023; **34**(8): 681-92.
3. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Sheffield, UK: ScHARR, University of Sheffield, 2011.
4. Palmer S, Borget I, Friede T, et al. A Guide to Selecting Flexible Survival Models to Inform Economic Evaluations of Cancer Immunotherapies. *Value Health* 2023; **26**(2): 185-92.
5. Olmos D, Lorente D, Alameda D, et al. Presence of somatic/germline homologous recombination repair (HRR) mutations and outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving first-line (1L) treatment stratified by BRCA status. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2023; **41**: 5003.

Appendix A. Extrapolation

A.1 Extrapolation of radiographic progression-free survival

A.1.1 Descriptive statistics

The number of subjects and events per treatment arm:

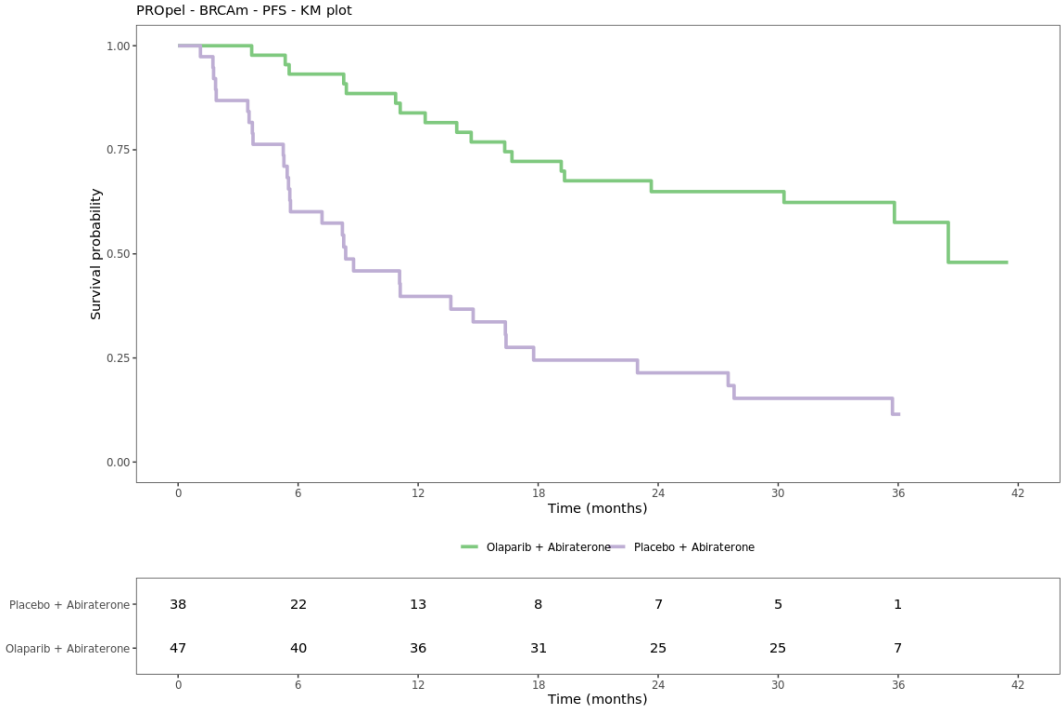
Arm	N	Events	Maturity
Placebo + Abiraterone	38	31	81.6%
Olaparib + Abiraterone	47	18	38.3%

Mean and median survival estimates:

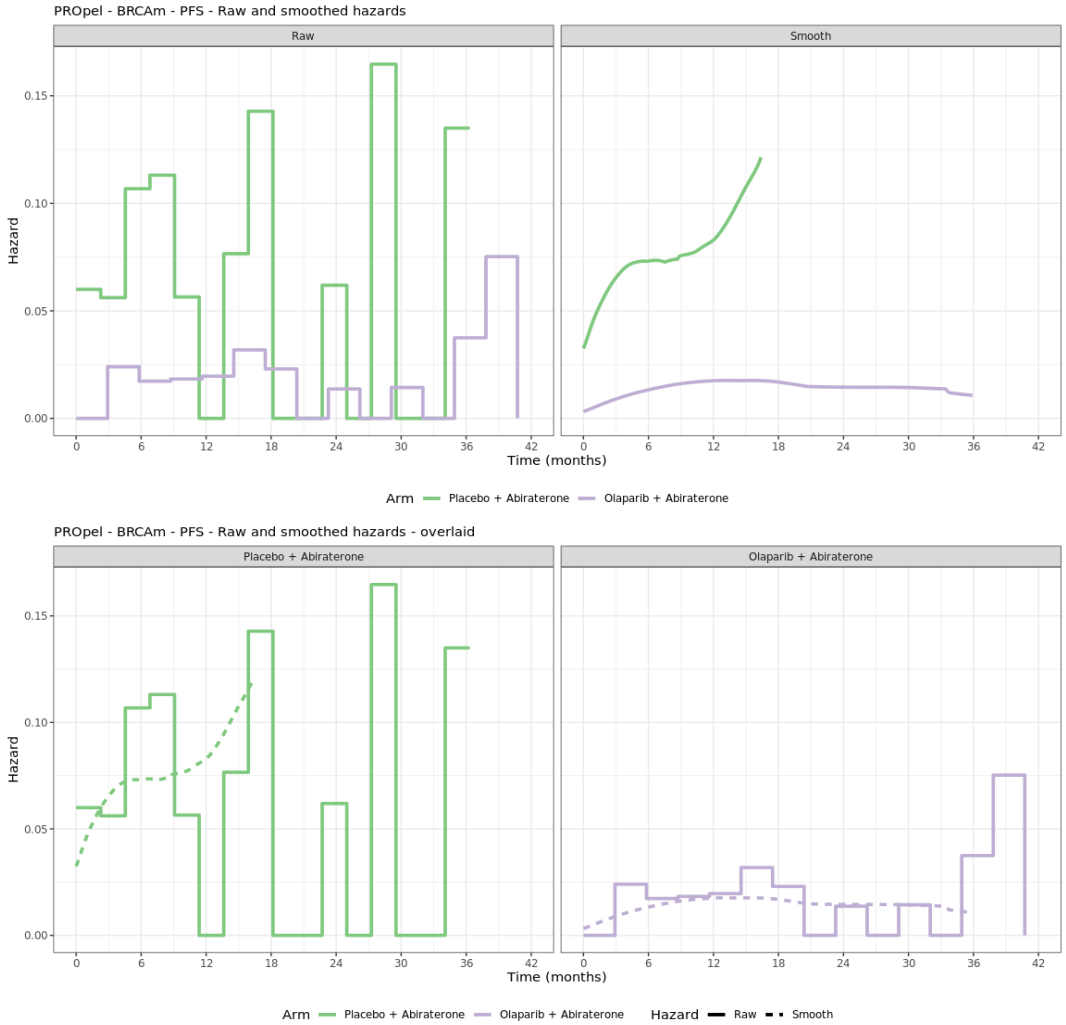
Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	13.6 (9.8, 17.5)	8.4 (5.5, 14.8)
Olaparib + Abiraterone	27.8 (24.3, 31.2)	38.5 (23.7, NR)

The RMST calculation uses a cut-off value of 36.1 months. This is the smallest value among the largest observed times across the treatment groups.

The KM curve is shown below.

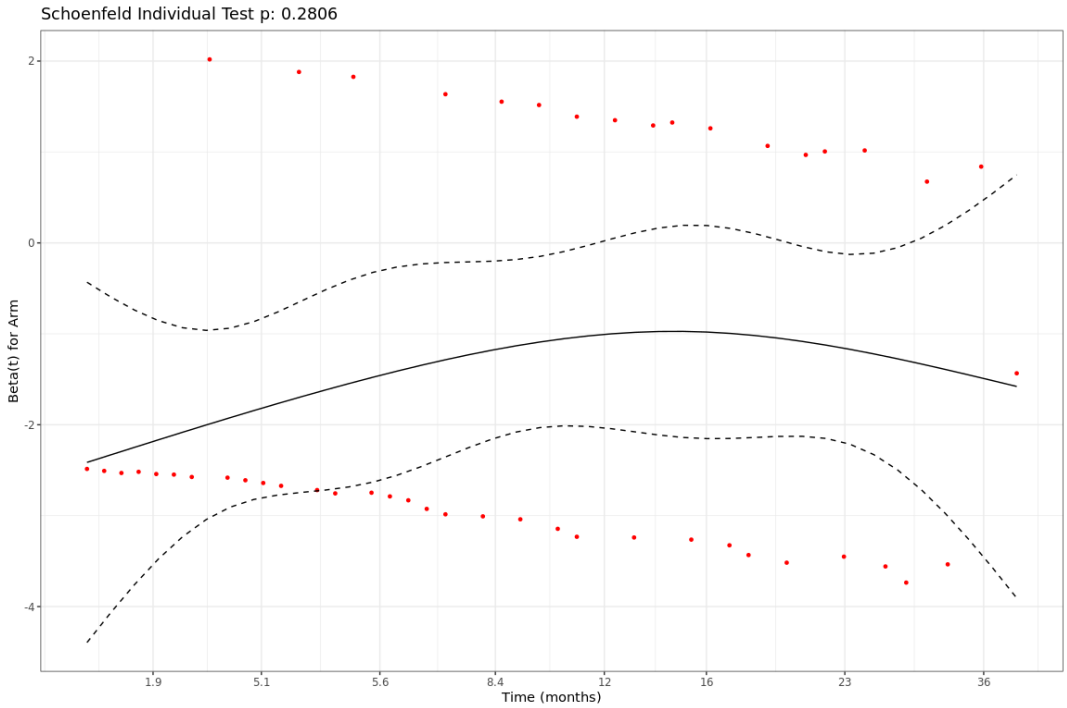


The smooth and unsmoothed hazard plots by arm is shown below.



A.1.2 Diagnostic plots

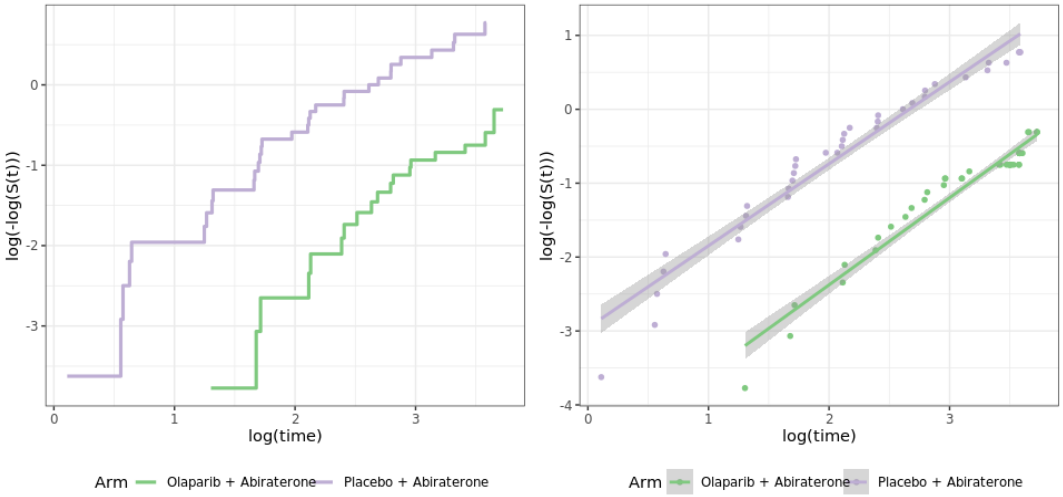
The Schoenfeld residual plot is shown below.



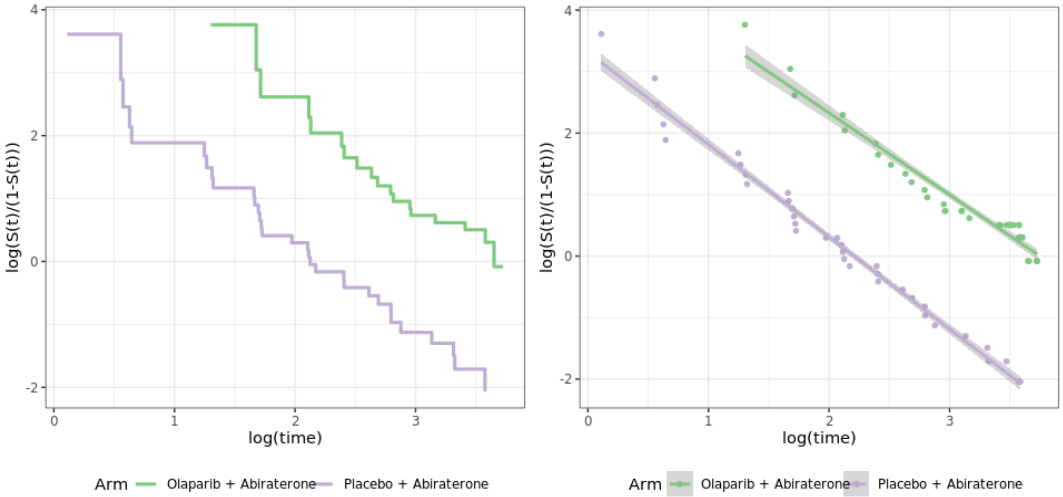
The log cumulative hazards, log odds and log normal versus log time plots are shown below.

Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log cumulative hazards plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds diagnostic plot, parallel lines indicate proportional odds and in the log normal diagnostic plot, parallel lines indicate constant acceleration.

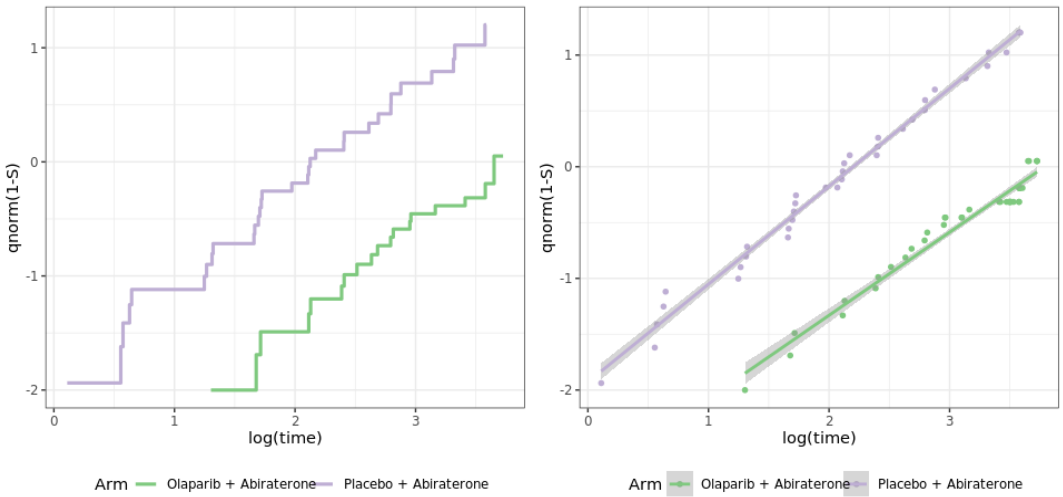
Log cumulative hazards vs. log time



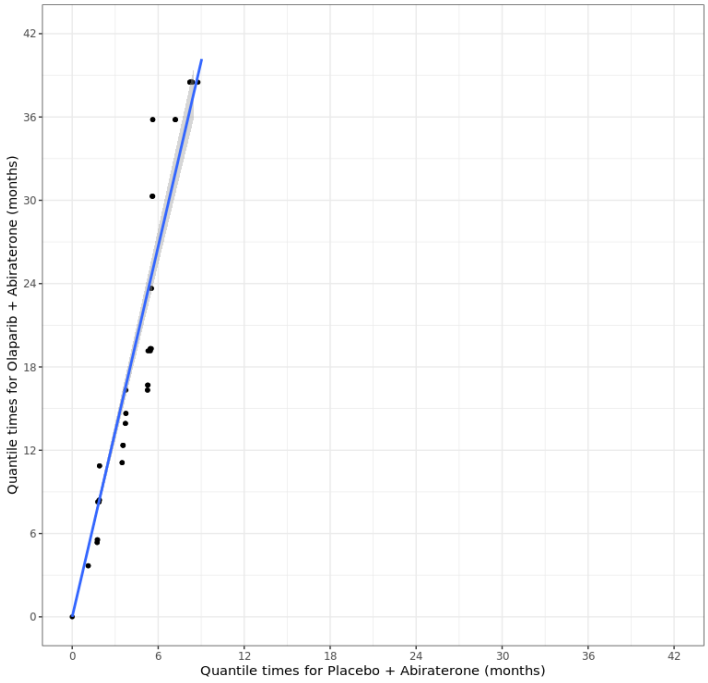
Log odds vs. log time



Log normal vs. log time



The QQ-plot is shown below.



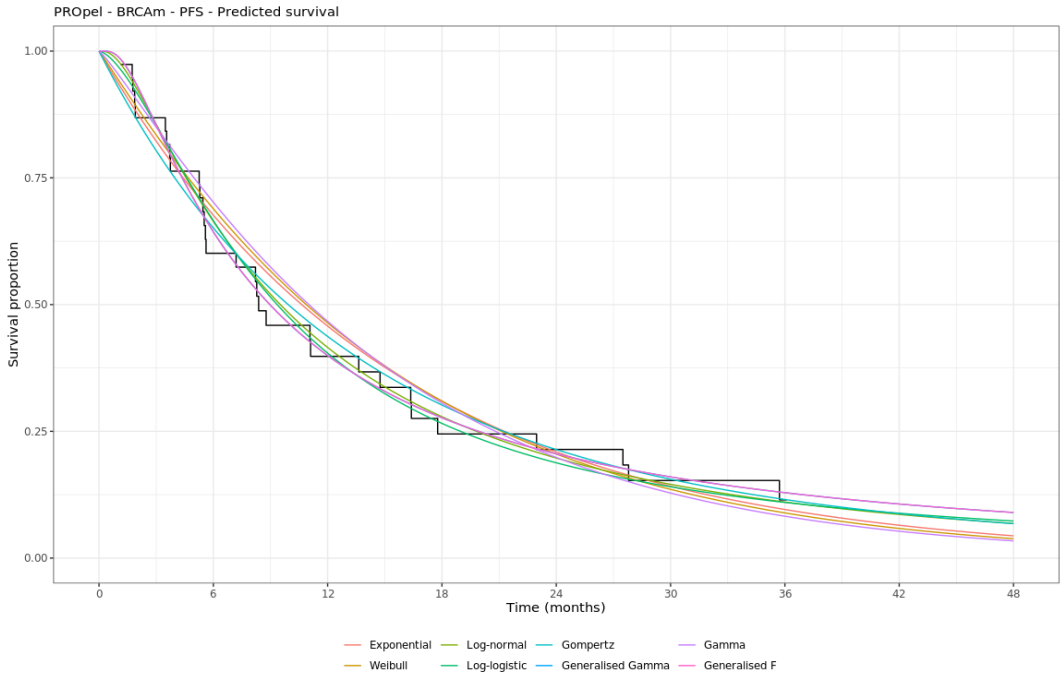
A.1.3 Independent models

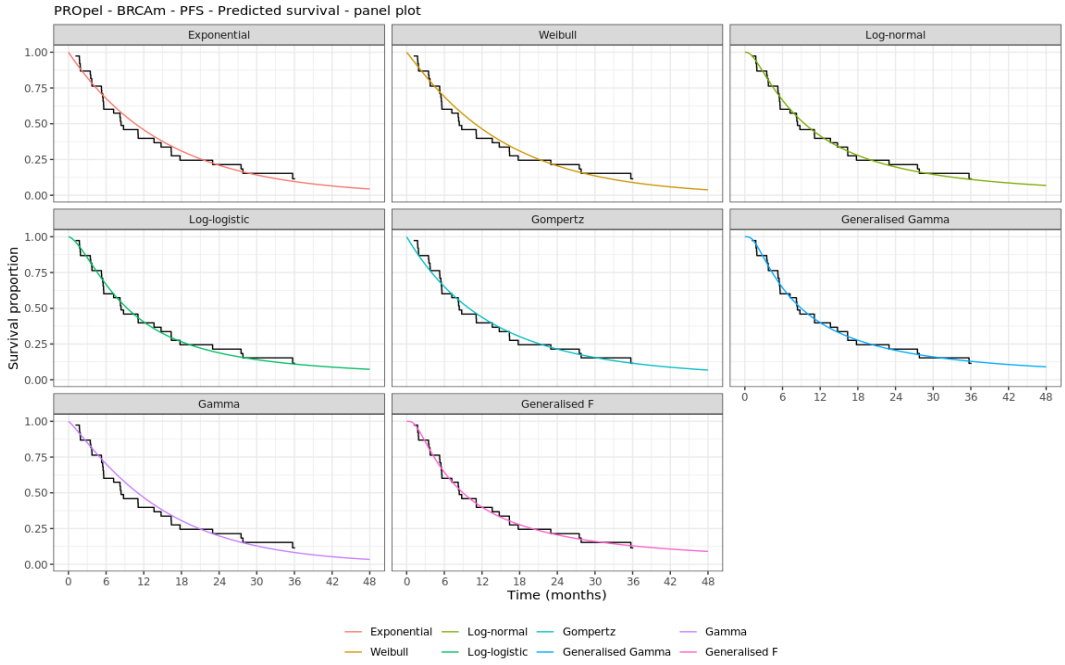
Separate distributions have been fitted per arm. The model goodness of fit statistics are shown below; the best (lowest) AIC value is shown in bold.

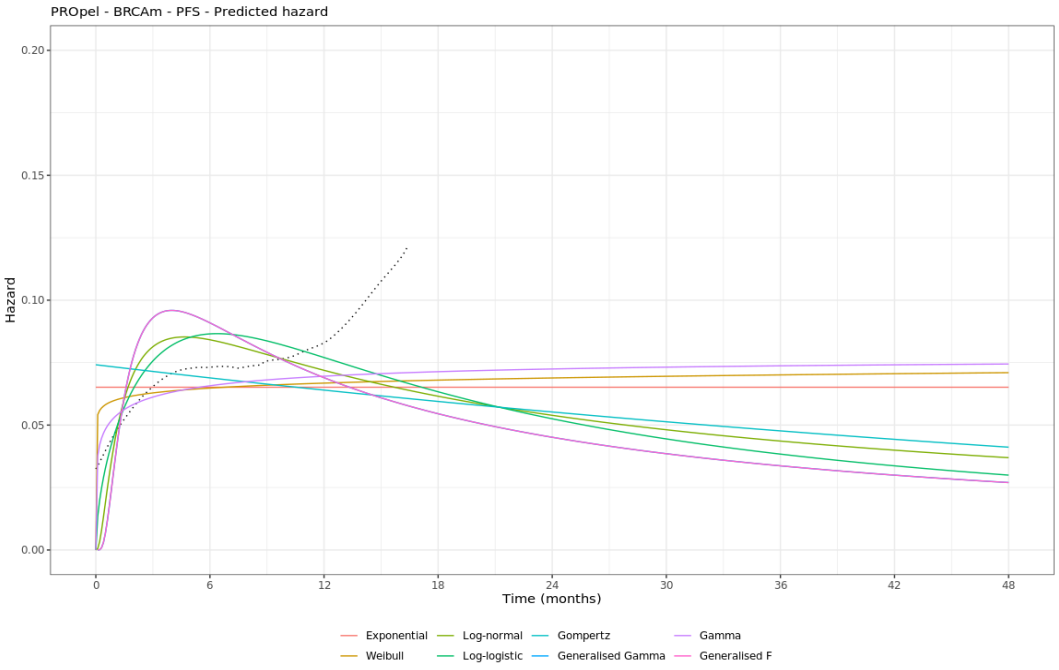
Goodness of fit statistics by model:

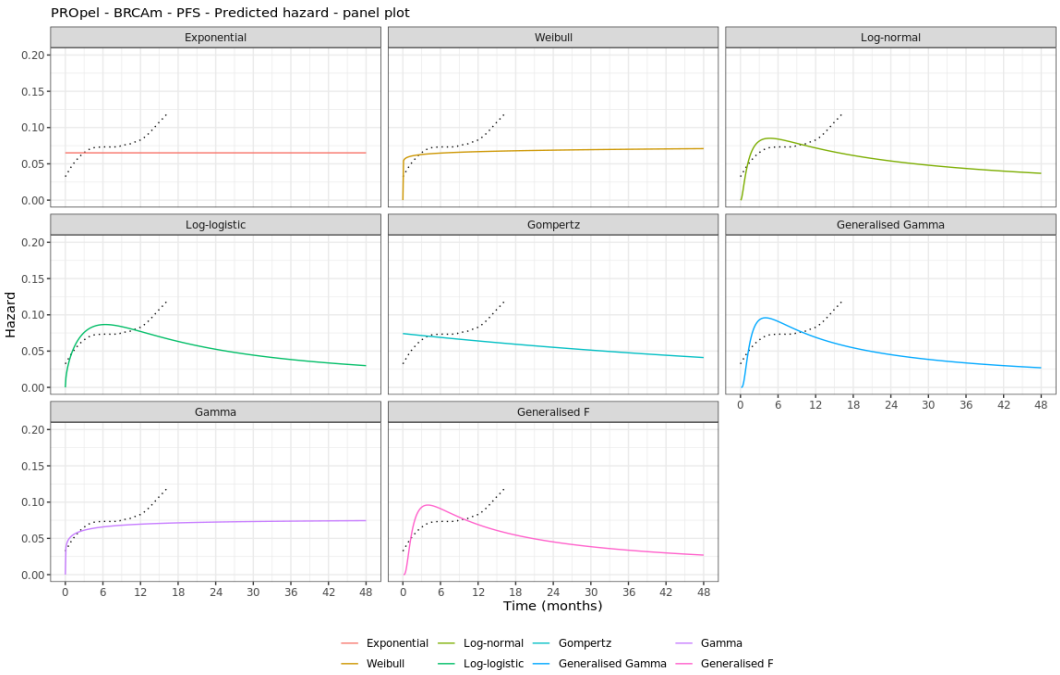
Arm	Distribution	Converged	AIC	BIC	Arm	Distribution	Converged	AIC	BIC
Placebo + Abiraterone	Exponential	True	233.3	235.0	Olaparib + Abiraterone	Exponential	True	187.9	189.7
	Weibull	True	235.2	238.5		Weibull	True	189.0	192.7
	Log-normal	True	**230.6**	233.9		Log-normal	True	**186.7**	190.4
	Log-logistic	True	231.6	234.9		Log-logistic	True	188.1	191.8
	Gompertz	True	234.9	238.2		Gompertz	True	189.8	193.5
	Generalised Gamma	True	232.1	237.0		Generalised Gamma	True	187.2	192.7
	Gamma	True	234.9	238.2		Gamma	True	188.6	192.3
	Generalised F	True	234.1	240.6		Generalised F	True	189.2	196.6

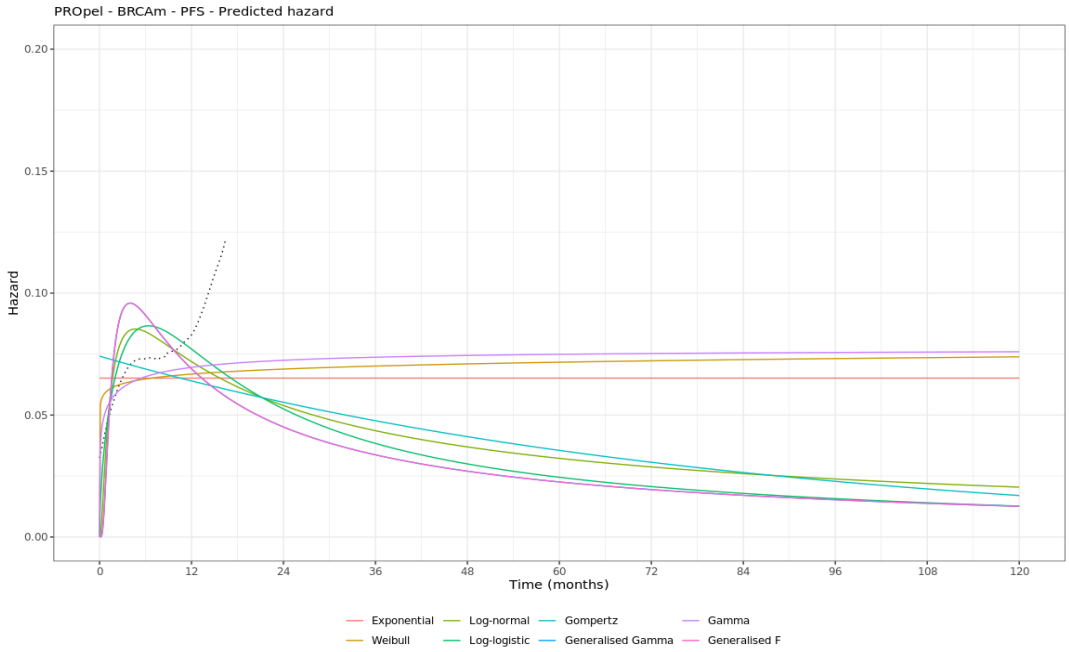
A.1.3.1 Placebo + Abiraterone

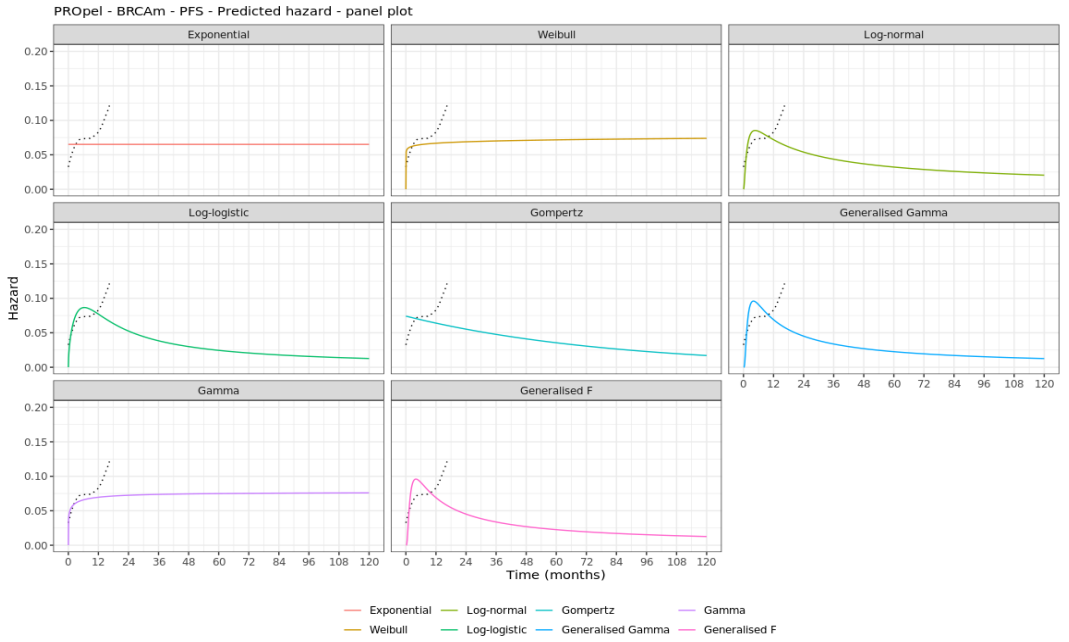

PROpel - BRCAm - PFS - Predicted survival
Survival proportion
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F


PROpel - BRCAm - PFS - Predicted survival - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Survival proportion
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F

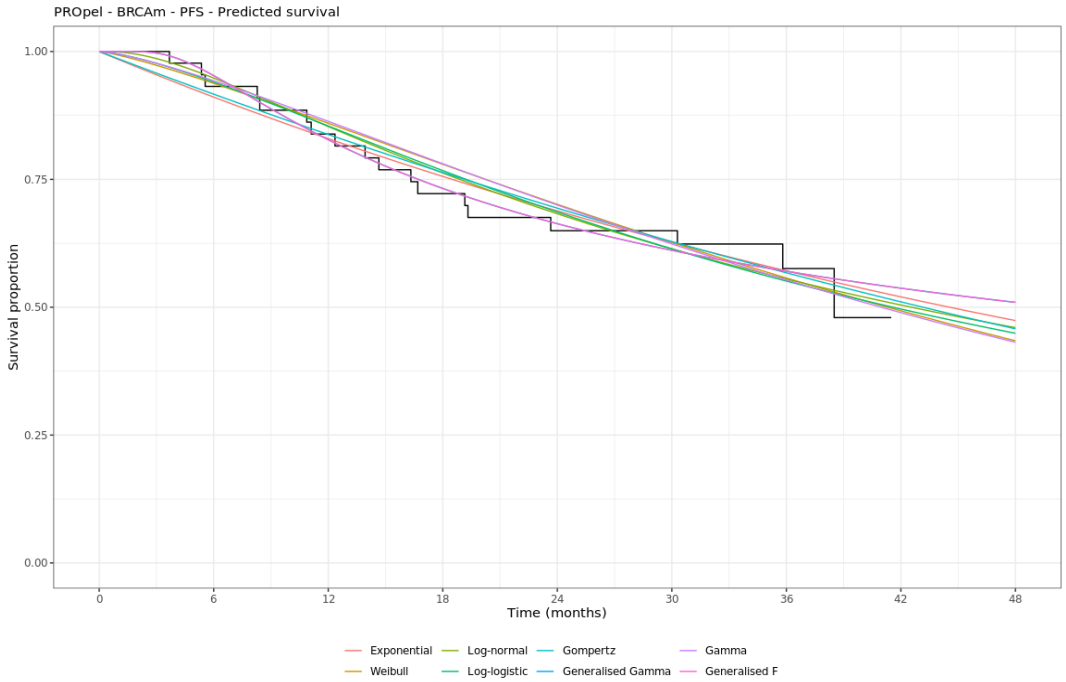

PROpel - BRCAm - PFS - Predicted hazard
Hazard
0.20
0.15
0.10
0.05
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F

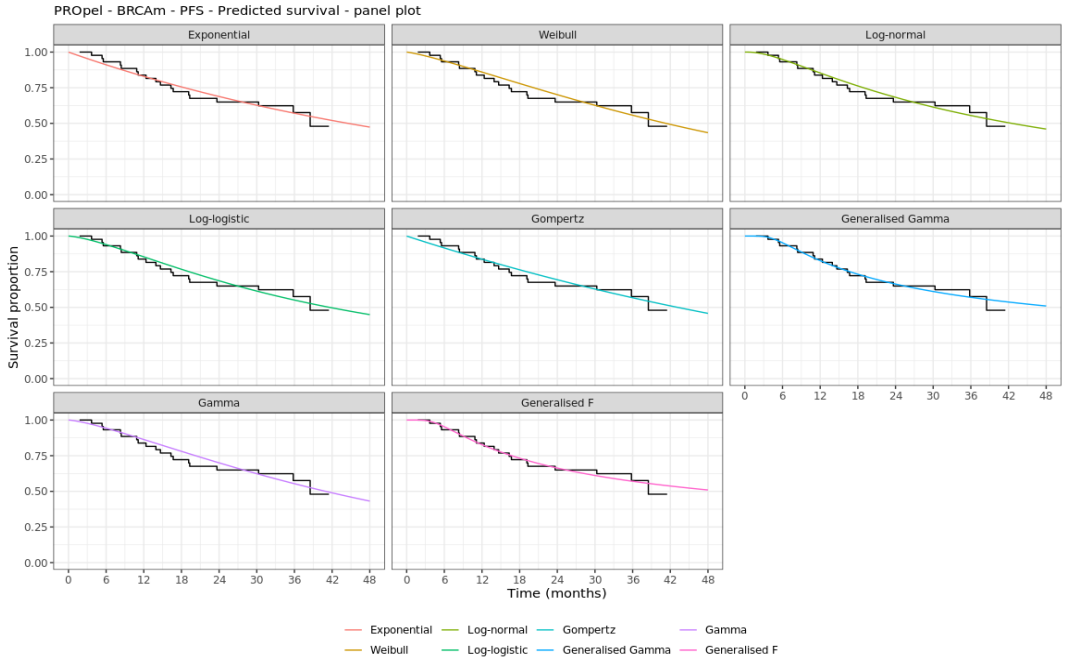

PROpel - BRCAm - PFS - Predicted hazard - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Hazard
0.20
0.15
0.10
0.05
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F

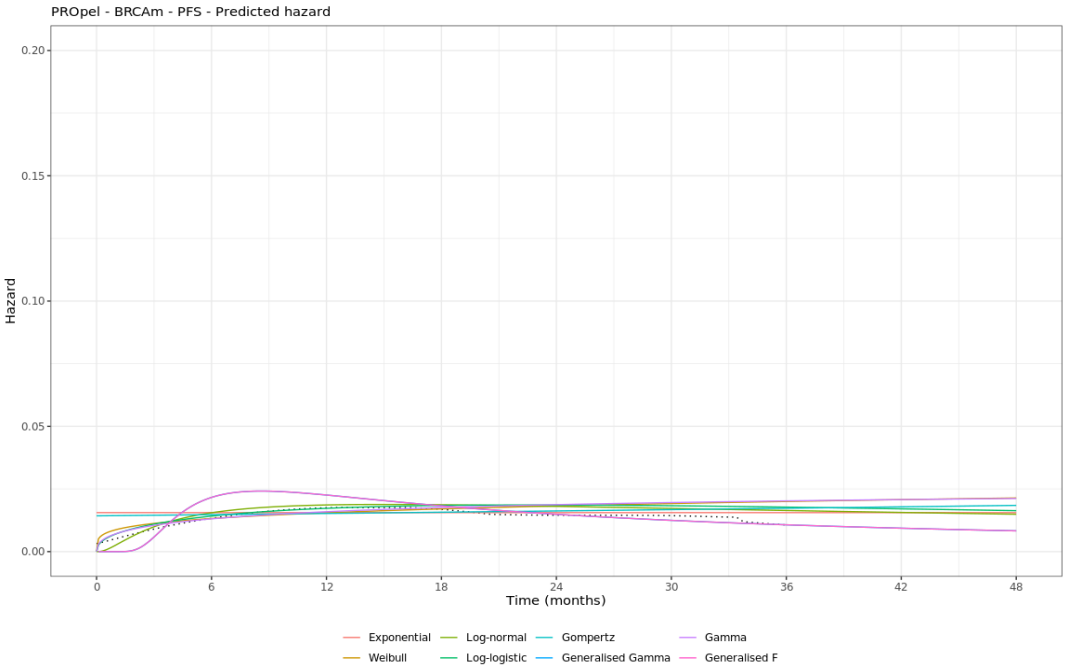


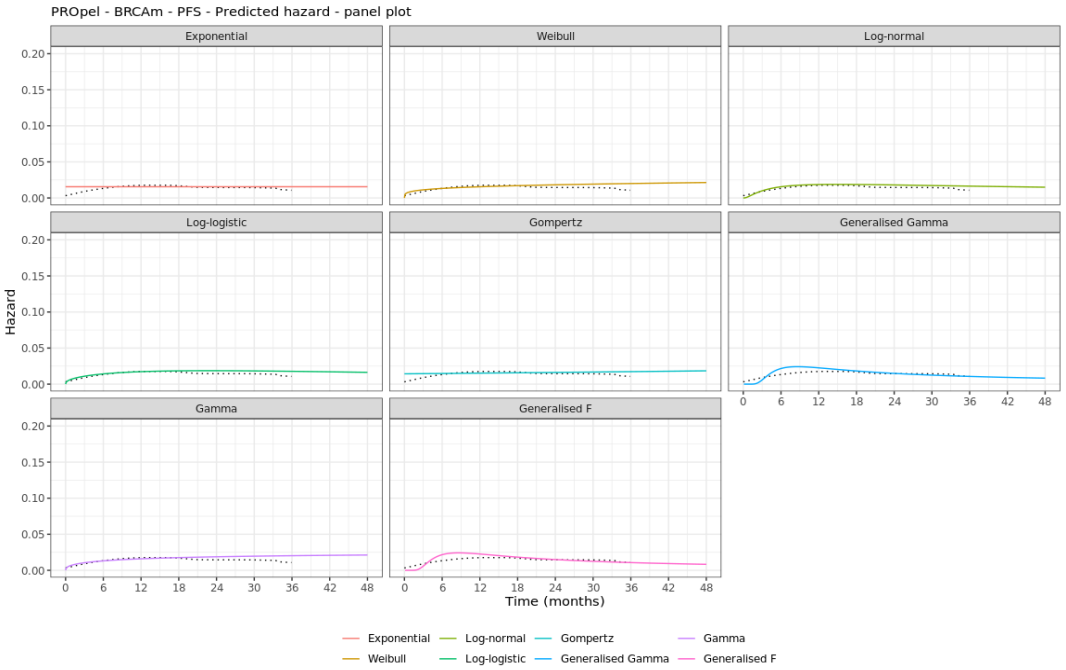


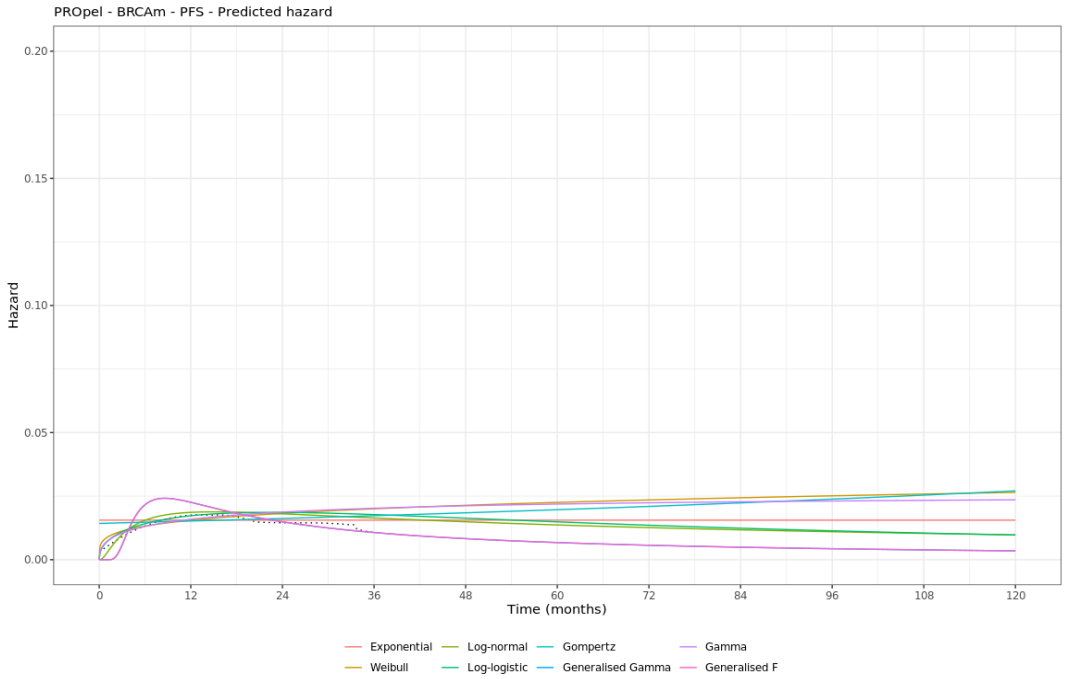
A.1.3.2 Olaparib + Abiraterone

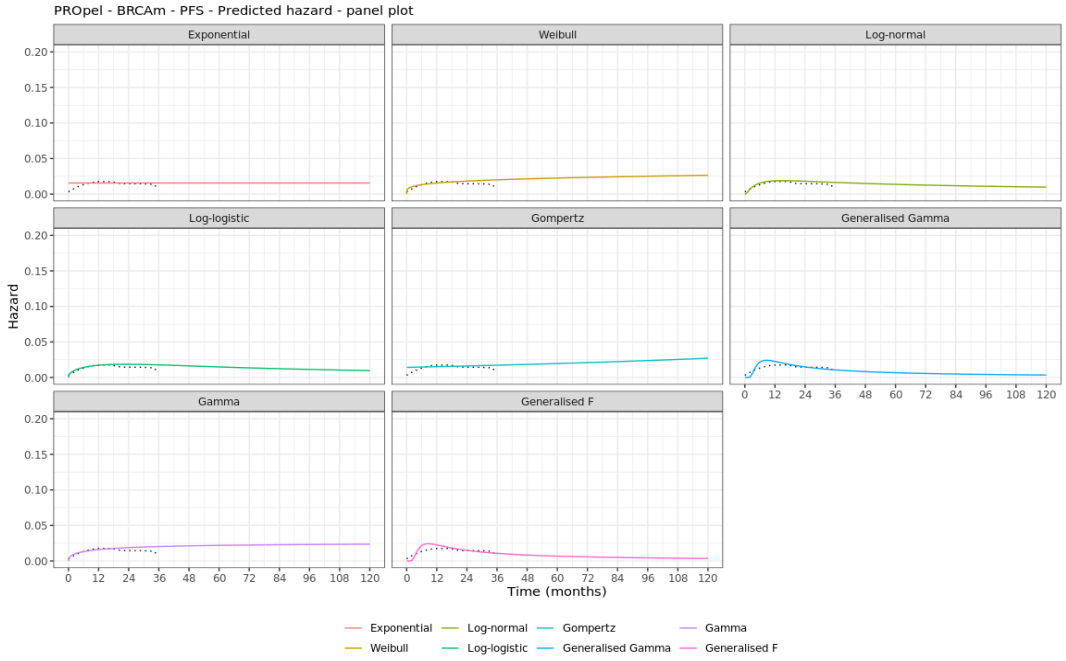

PROpel - BRCAm - PFS - Predicted survival
Survival proportion
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F


PROpel - BRCAm - PFS - Predicted survival - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Survival proportion
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F


PROpel - BRCAm - PFS - Predicted hazard
Hazard
0.20
0.15
0.10
0.05
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F


PROpel - BRCAm - PFS - Predicted hazard - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Hazard
0.20
0.15
0.10
0.05
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F



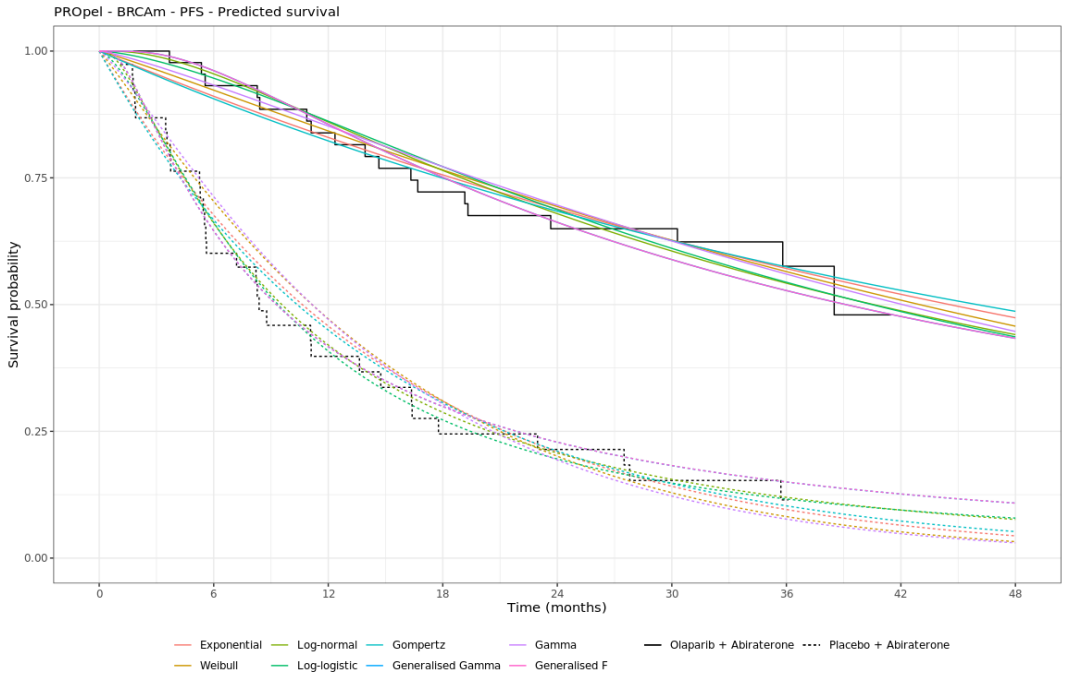


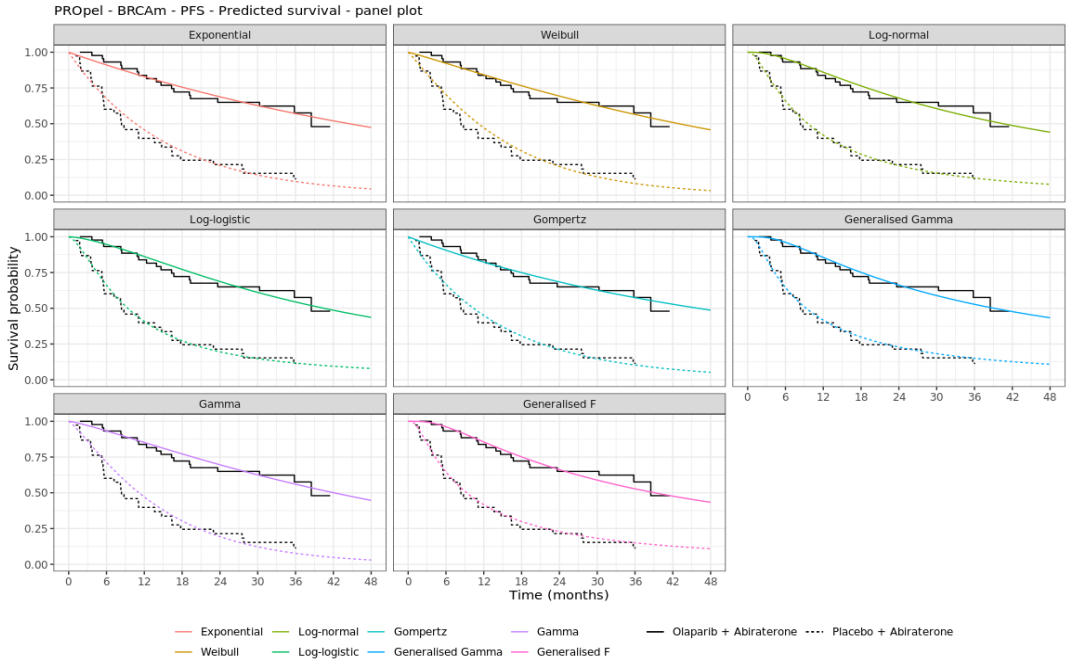
A.1.4 Joint models

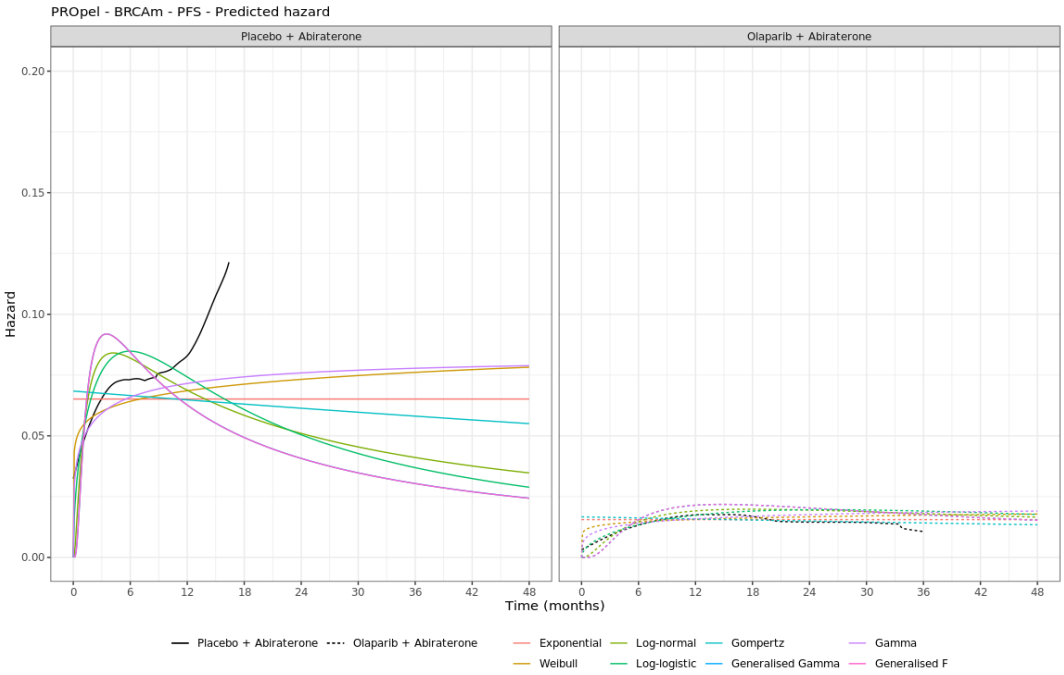
Models have been fitted with treatment as the only predictor. The model goodness of fit statistics are shown below; the best (lowest) AIC value is shown in bold.

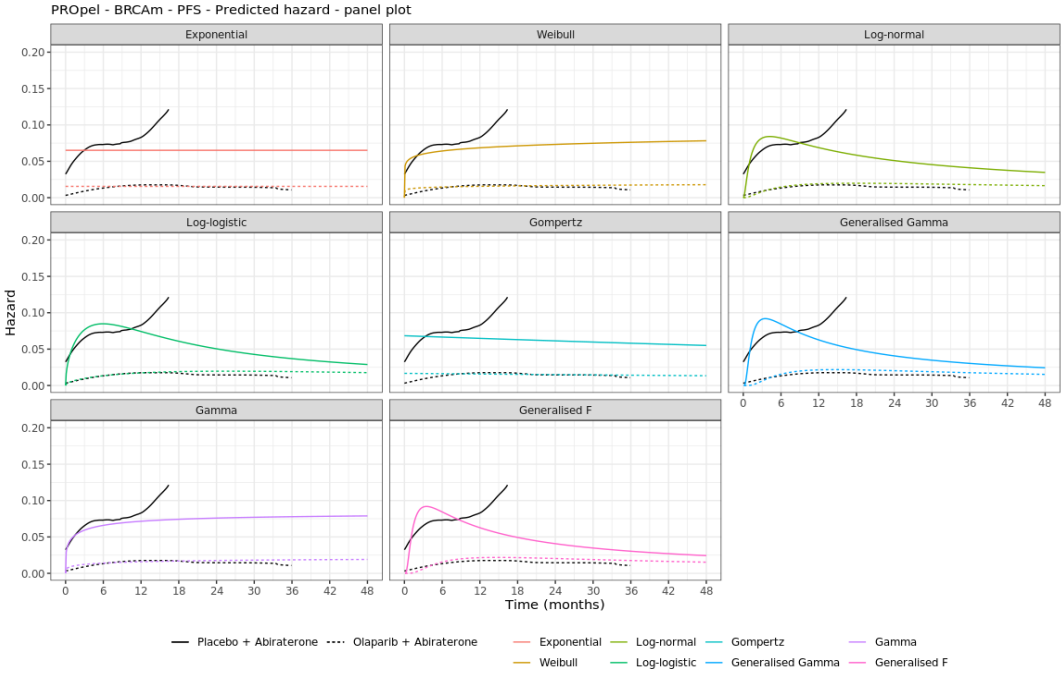
GoF by model:

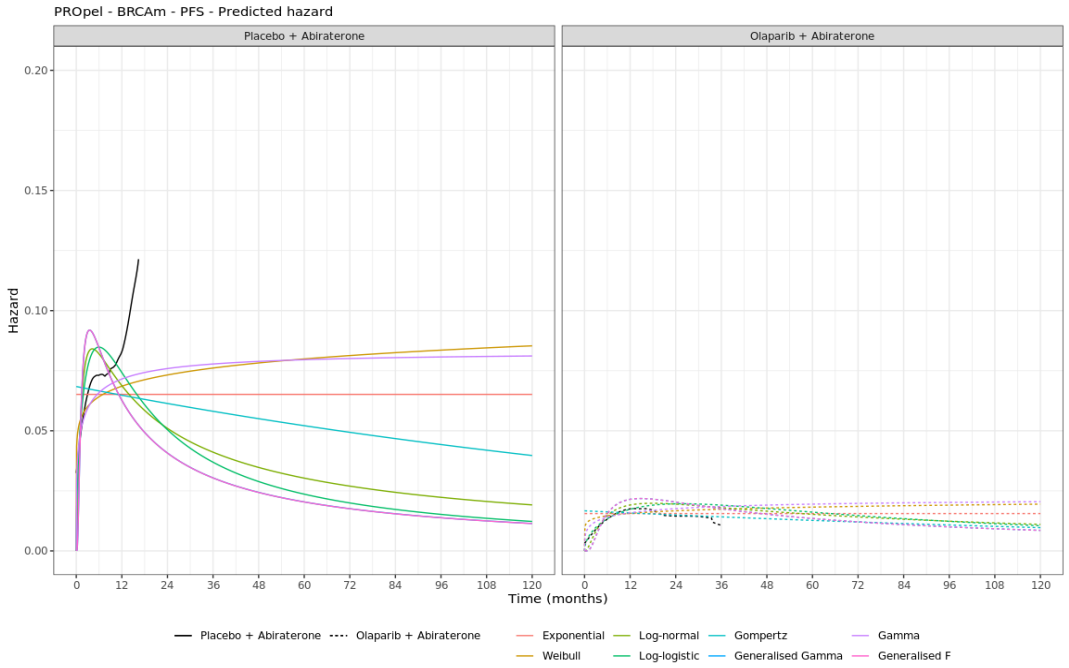
Distribution	Converged	AIC	BIC
Exponential	True	421.2	426.1
Weibull	True	422.6	430.0
Log-normal	True	**415.5**	422.8
Log-logistic	True	417.8	425.2
Gompertz	True	423.1	430.4
Generalised Gamma	True	416.8	426.5
Gamma	True	421.8	429.1
Generalised F	True	418.8	431.0

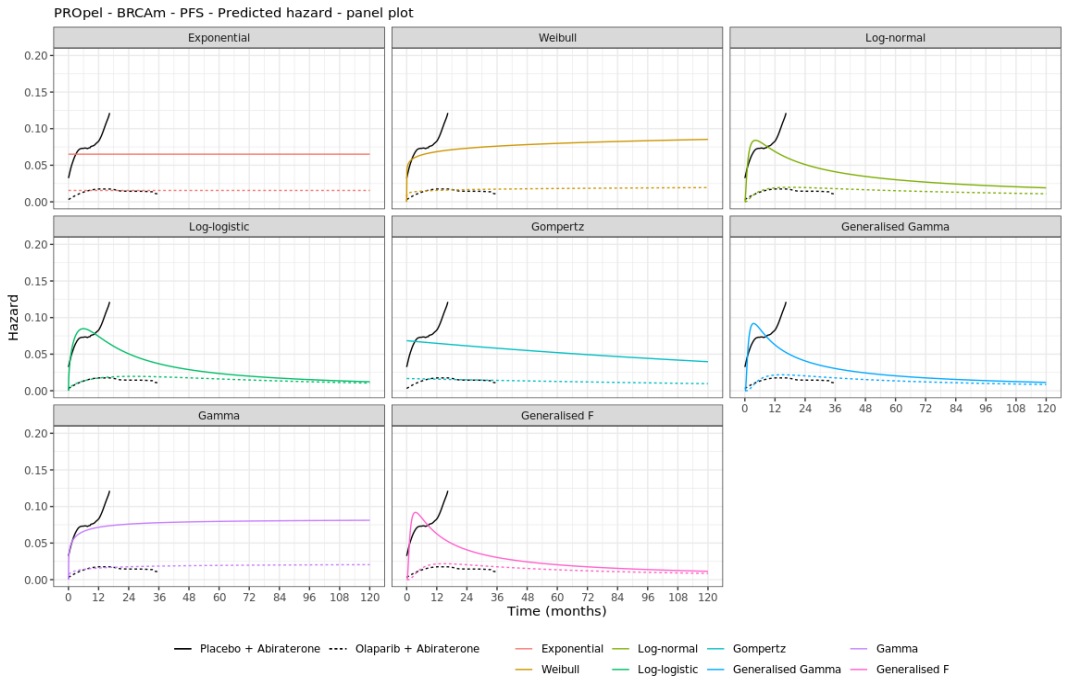

PROpel - BRCAm - PFS - Predicted survival
Survival probability
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Olaparib + Abiraterone
Placebo + Abiraterone


PROpel - BRCAm - PFS - Predicted survival - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Survival probability
Time (months)
Olaparib + Abiraterone
Placebo + Abiraterone


PROpel - BRCAm - PFS - Predicted hazard
Placebo + Abiraterone
Olaparib + Abiraterone
Hazard
0.20
0.15
0.10
0.05
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Placebo + Abiraterone
Olaparib + Abiraterone
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F


PROpel - BRCAm - PFS - Predicted hazard - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Hazard
0.20
0.15
0.10
0.05
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Placebo + Abiraterone
Olaparib + Abiraterone





A.2 Extrapolation of overall survival

A.2.1 Descriptive statistics

The number of subjects and events per treatment arm:

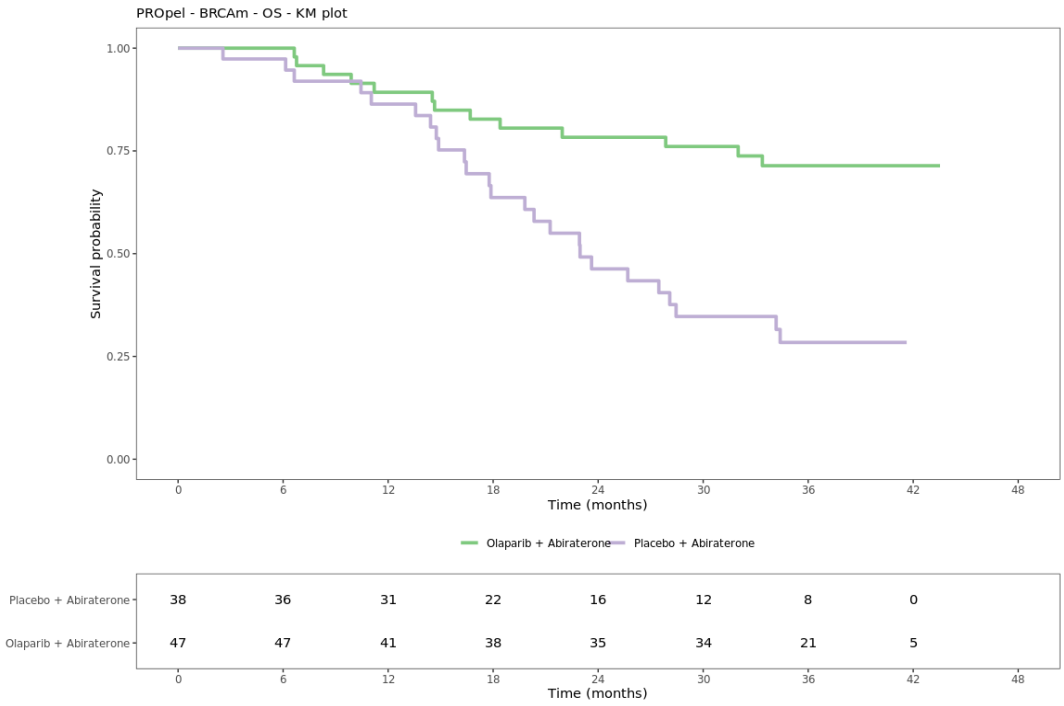
Arm	N	Events	Maturity
Placebo + Abiraterone	38	25	65.8%
Olaparib + Abiraterone	47	13	27.7%

Mean and median survival estimates:

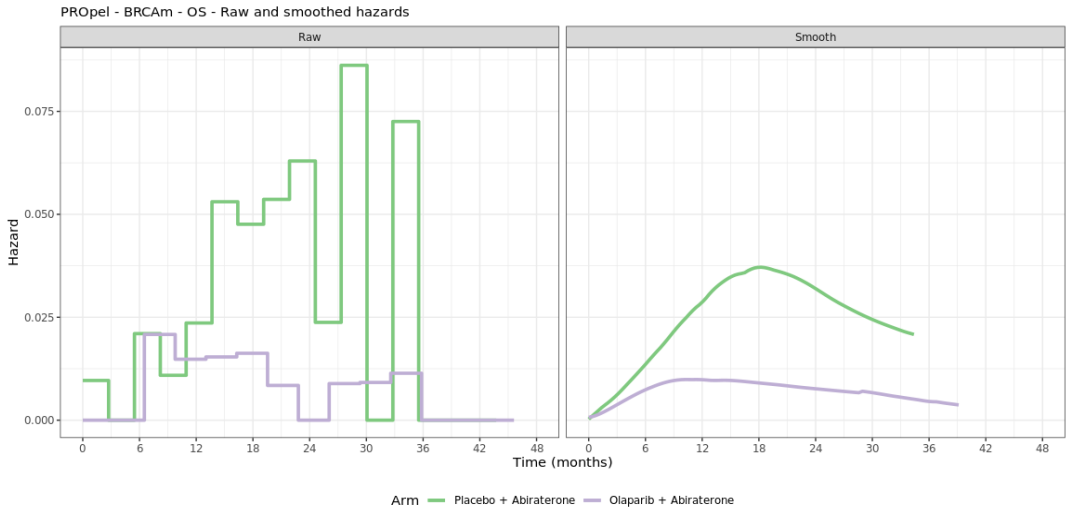
Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	25.6 (21.5, 29.6)	23.0 (17.8, 34.2)
Olaparib + Abiraterone	34.7 (31.2, 38.1)	NR (NR, NR)

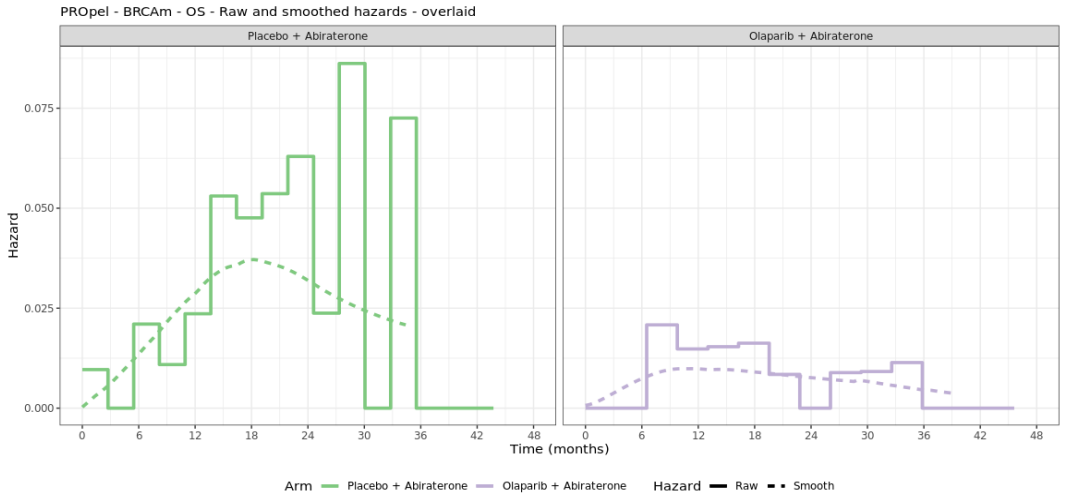
The RMST calculation uses a cut-off value of 41.6 months. This is the smallest value among the largest observed times across the treatment groups.

The KM curve is shown below.



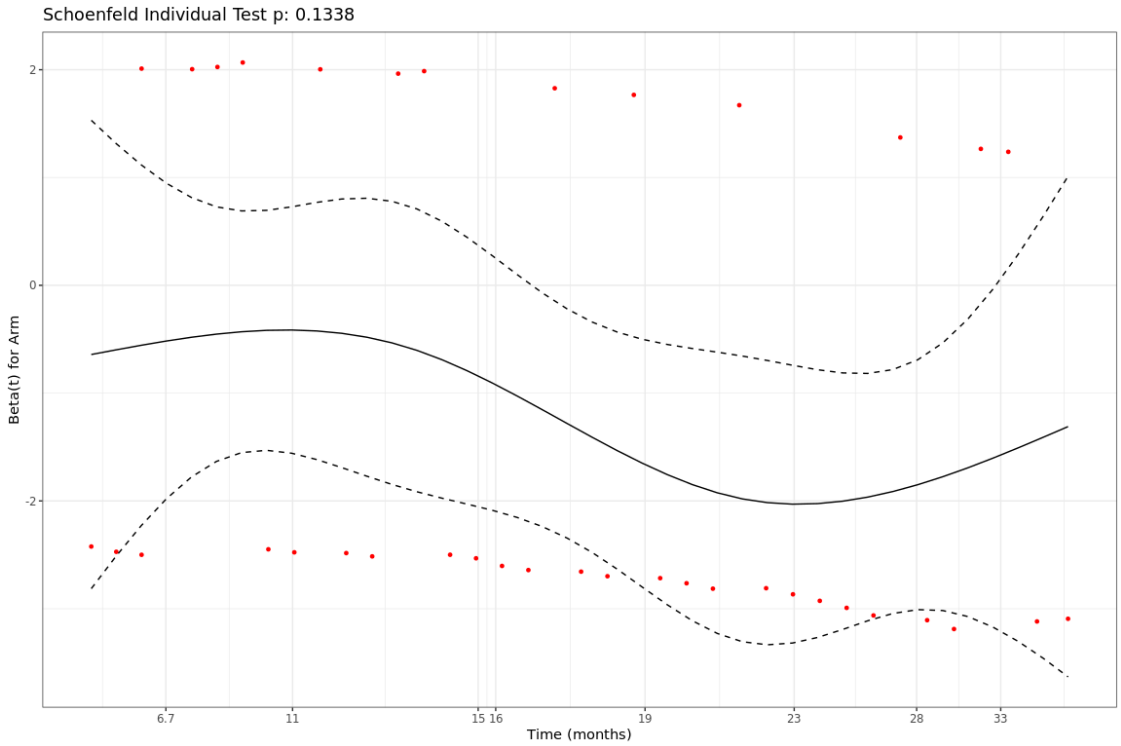
The smooth and unsmoothed hazard plots by arm is shown below.





A.2.2 Diagnostic plots

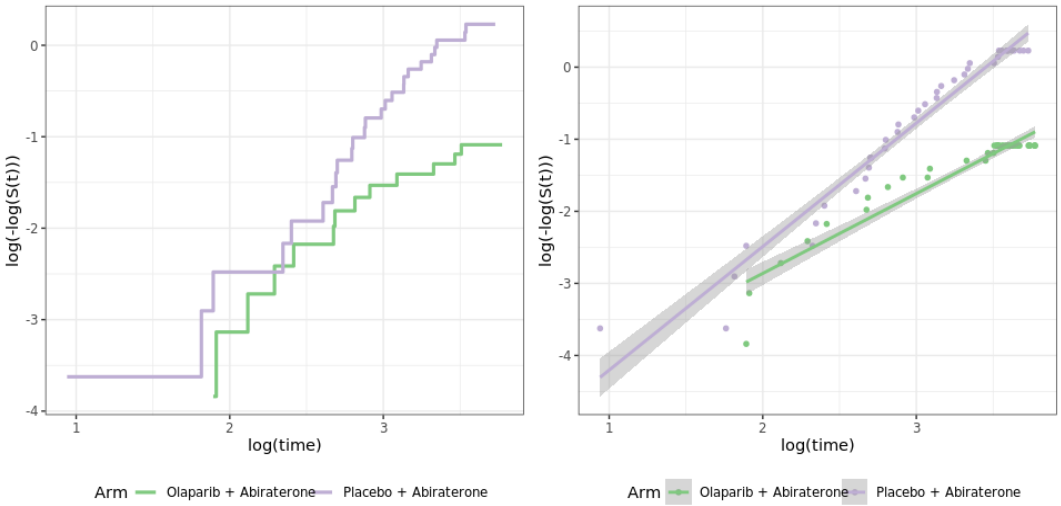
The Schoenfeld residual plot is shown below.



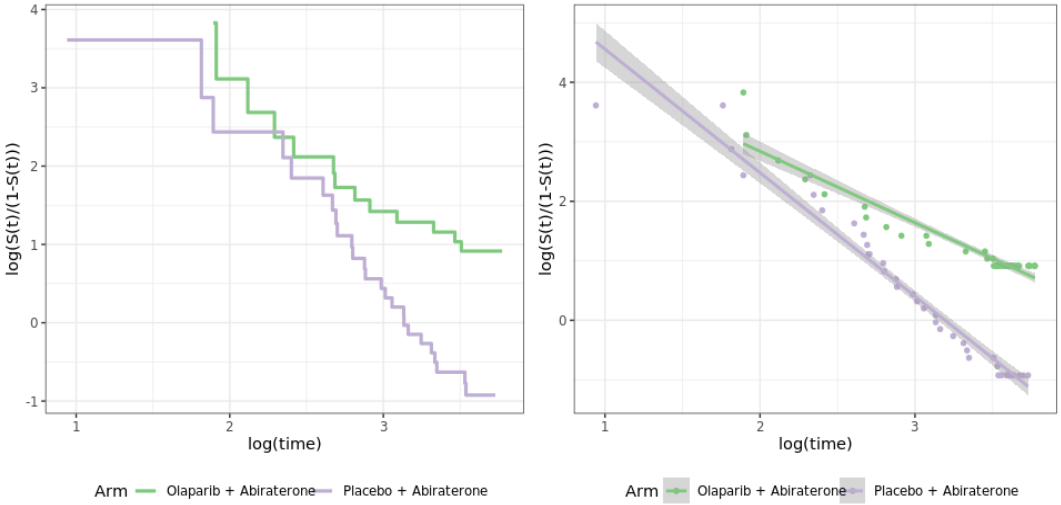
The log cumulative hazards, log odds and log normal versus log time plots are shown below.

Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log cumulative hazards plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds diagnostic plot, parallel lines indicate proportional odds and in the log normal diagnostic plot, parallel lines indicate constant acceleration.

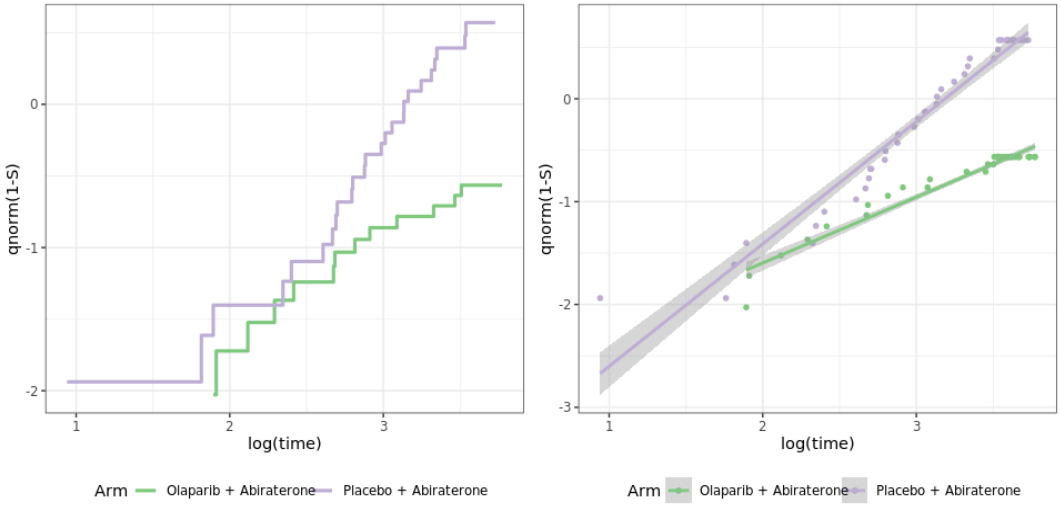
Log cumulative hazards vs. log time



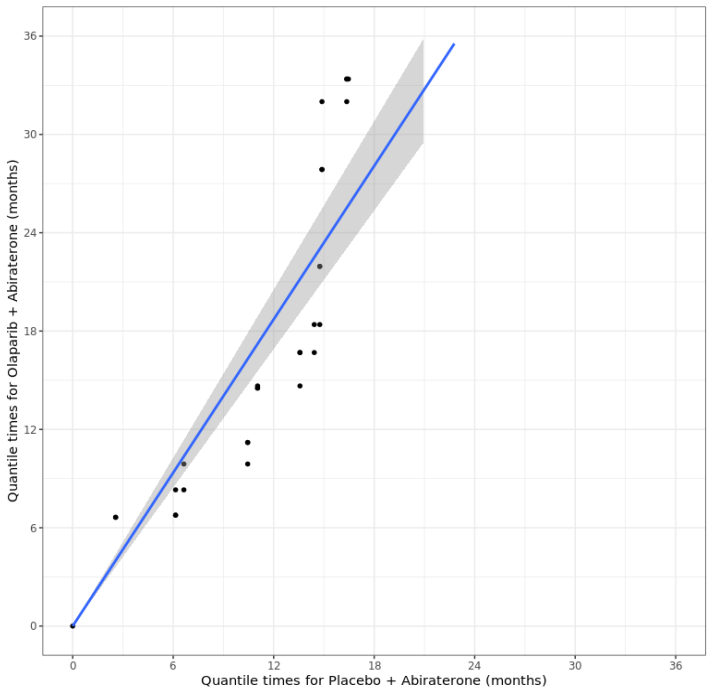
Log odds vs. log time



Log normal vs. log time



The QQ-plot is shown below.



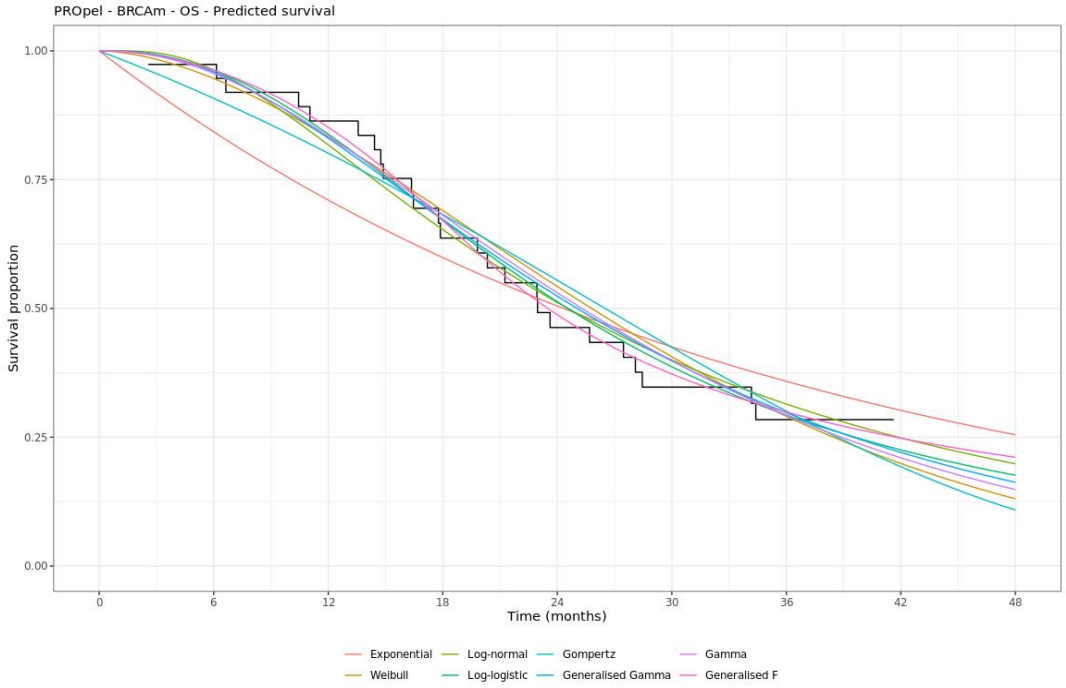
A.2.3 Independent models

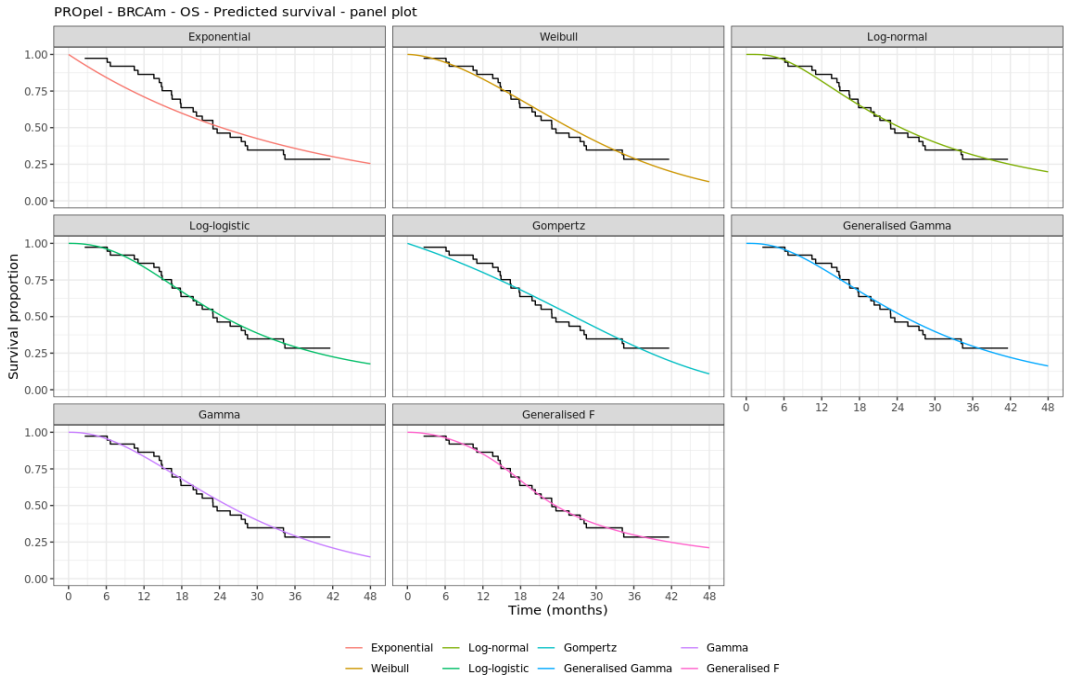
Separate distributions have been fitted per arm. The model goodness of fit statistics are shown below; the best (lowest) AIC value is shown in bold.

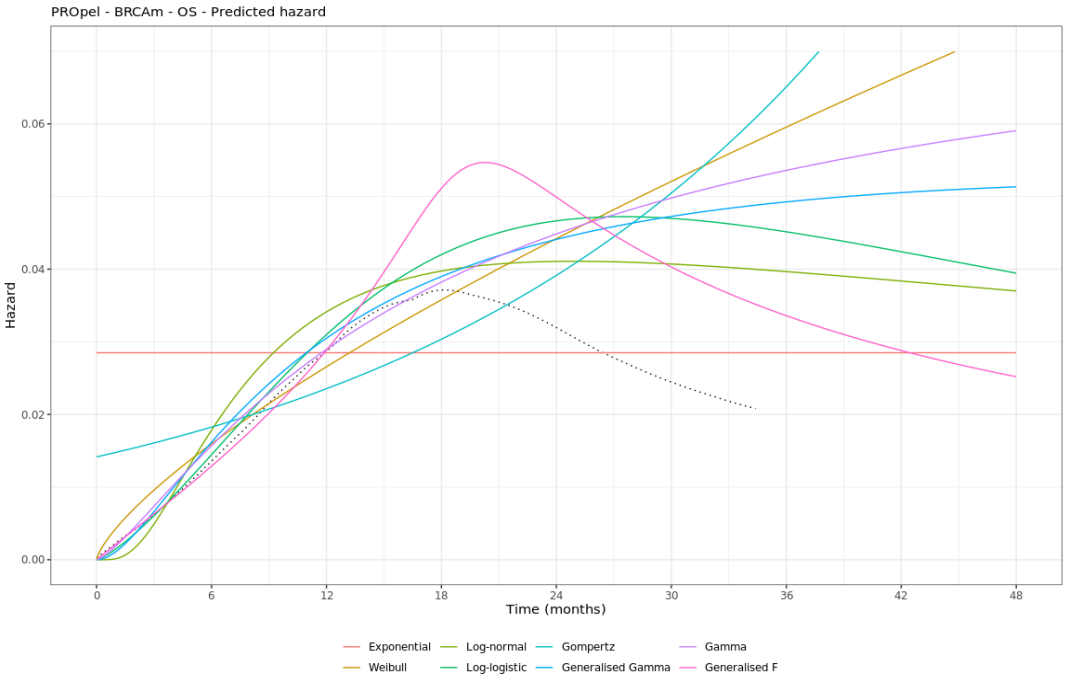
Goodness of fit statistics by model:

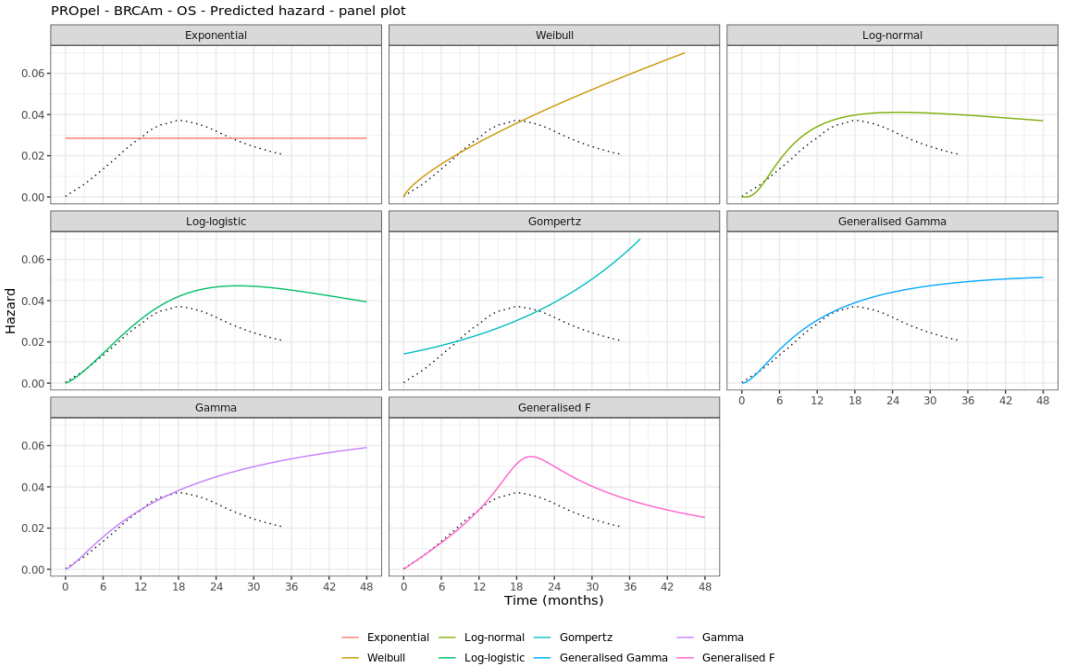
Arm	Distribution	Converged	AIC	BIC	Arm	Distribution	Converged	AIC	BIC
Placebo + Abiraterone	Exponential	True	229.9	231.5	Olaparib + Abiraterone	Exponential	True	150.7	152.6
	Weibull	True	223.5	226.8		Weibull	True	152.3	156.0
	Log-normal	True	223.4	226.6		Log-normal	True	150.3	154.0
	Log-logistic	True	**222.0**	225.3		Log-logistic	True	151.7	155.4
	Gompertz	True	226.9	230.1		Gompertz	True	152.7	156.4
	Generalised Gamma	True	224.7	229.6		Generalised Gamma	True	**145.3**	150.8
	Gamma	True	222.8	226.1		Gamma	True	152.1	155.8
	Generalised F	True	224.8	231.4		Generalised F	False	-	-

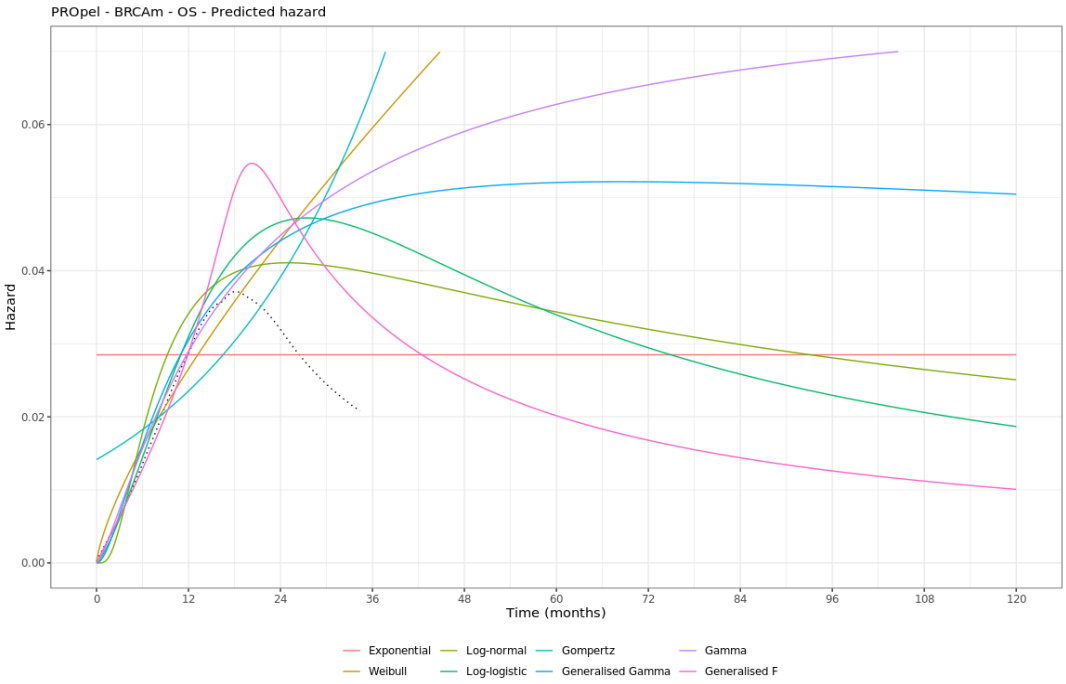
A.2.3.1 Placebo + Abiraterone

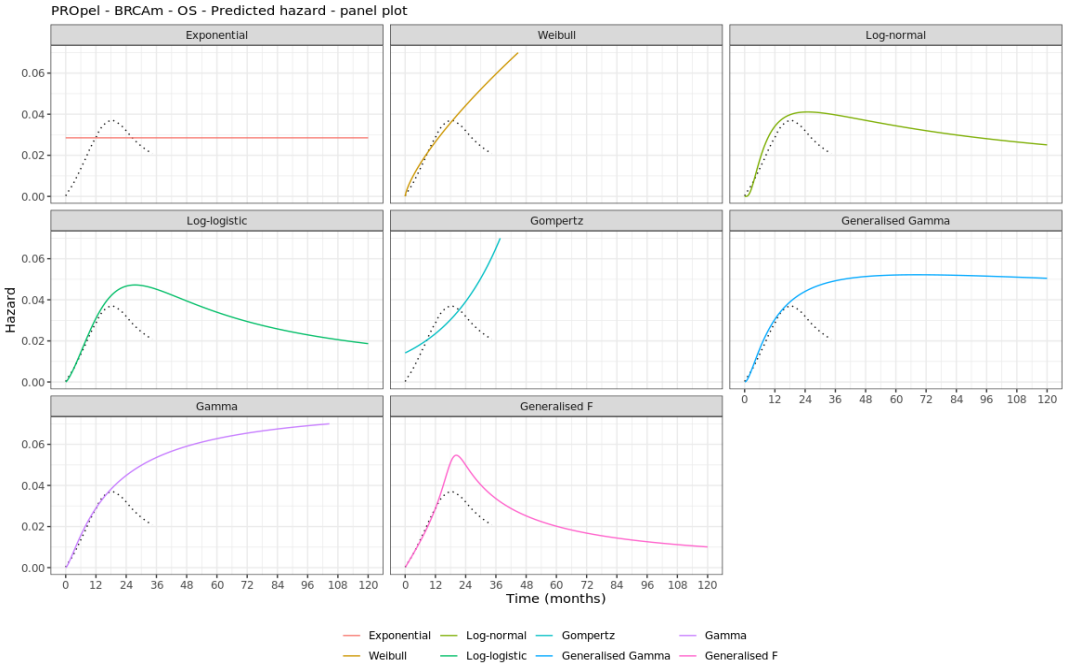




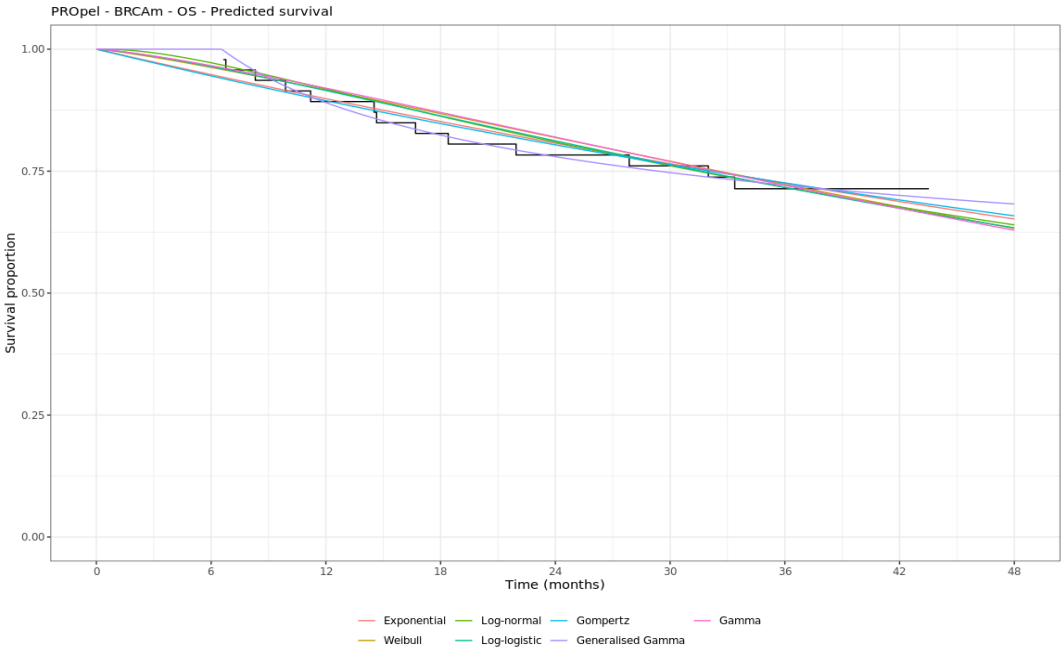

PROpel - BRCAm - OS - Predicted hazard
Hazard
0.00
0.02
0.04
0.06
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F

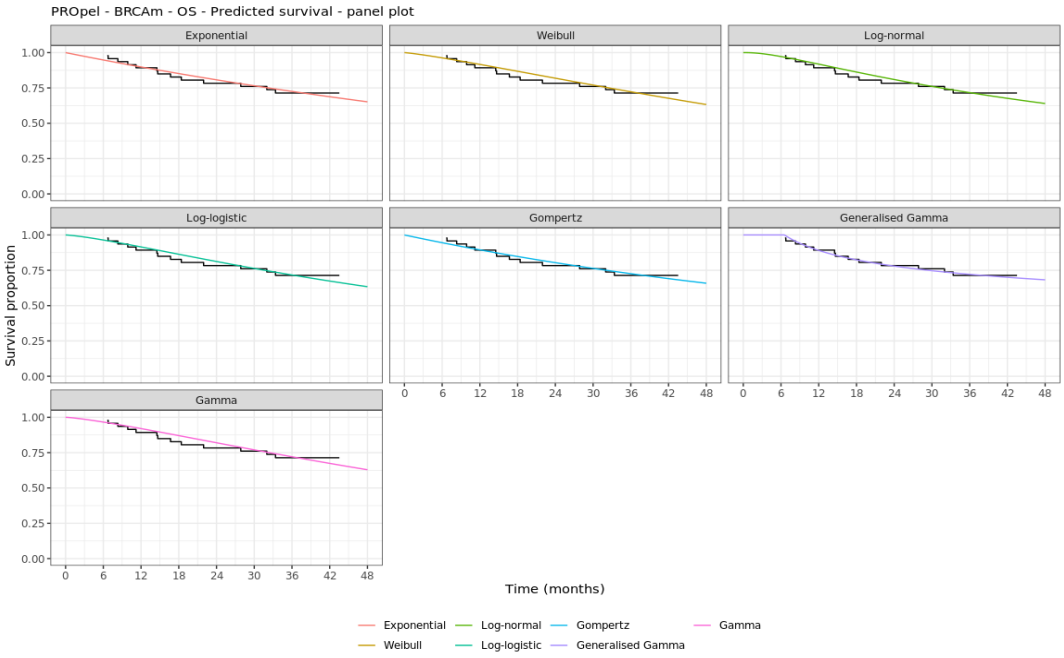

PROpel - BRCAm - OS - Predicted hazard - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F
Hazard
0.00
0.02
0.04
0.06
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Generalised F

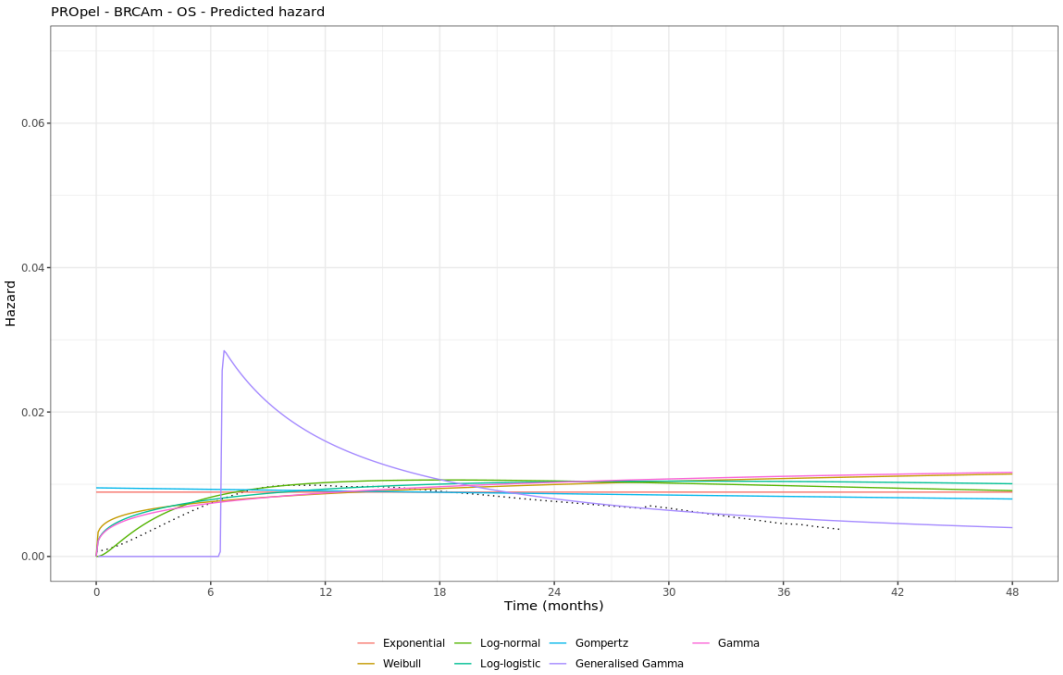


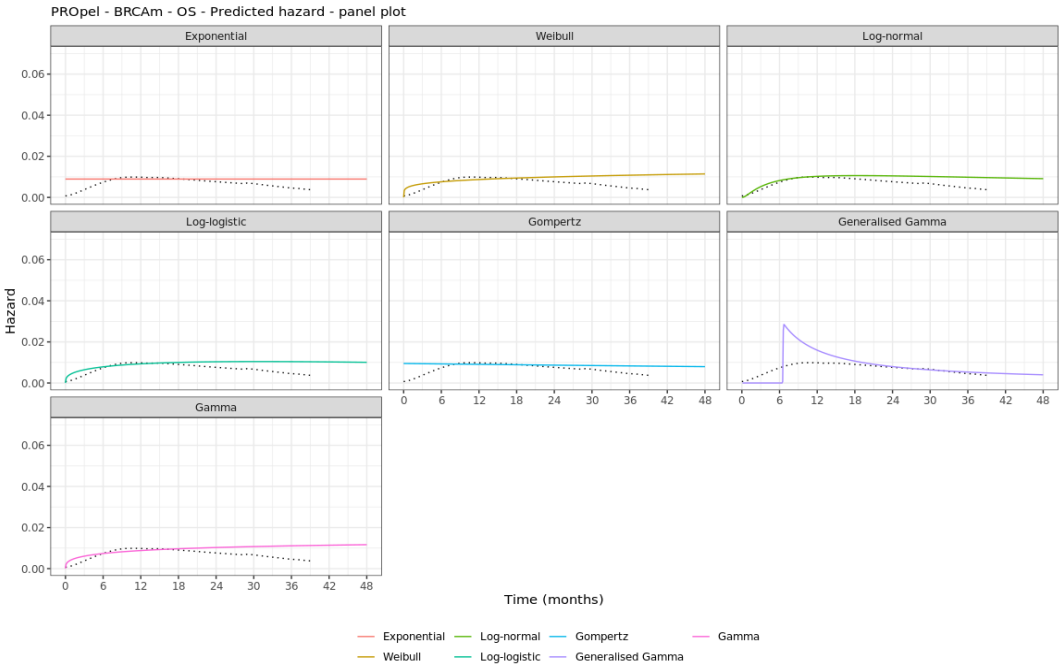


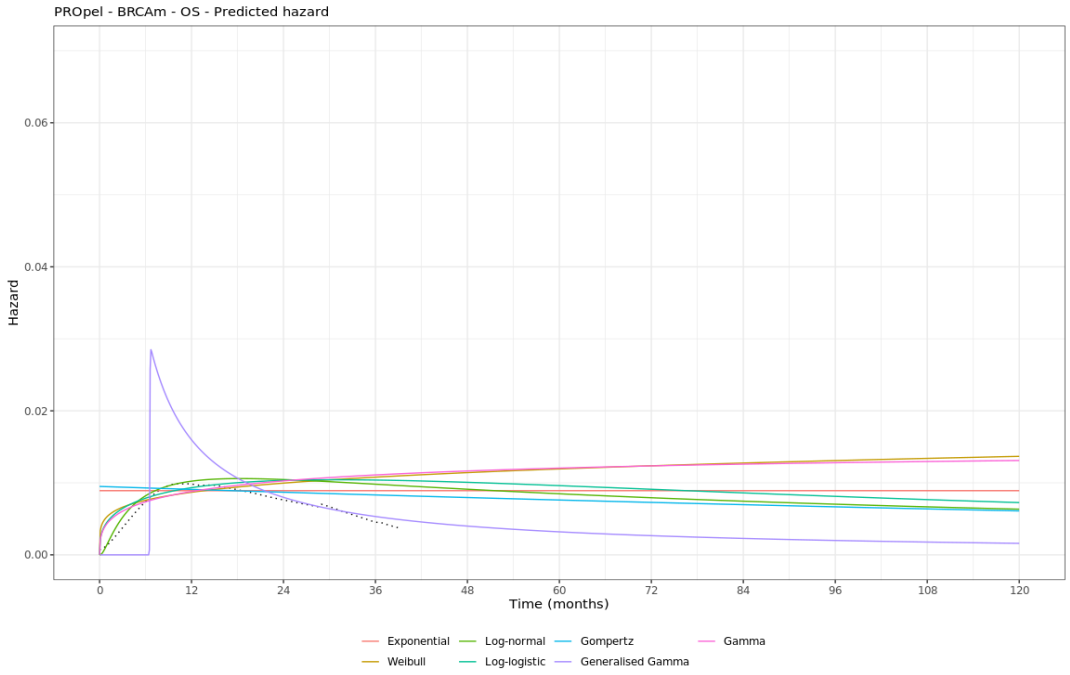
A.2.3.2 Olaparib + Abiraterone

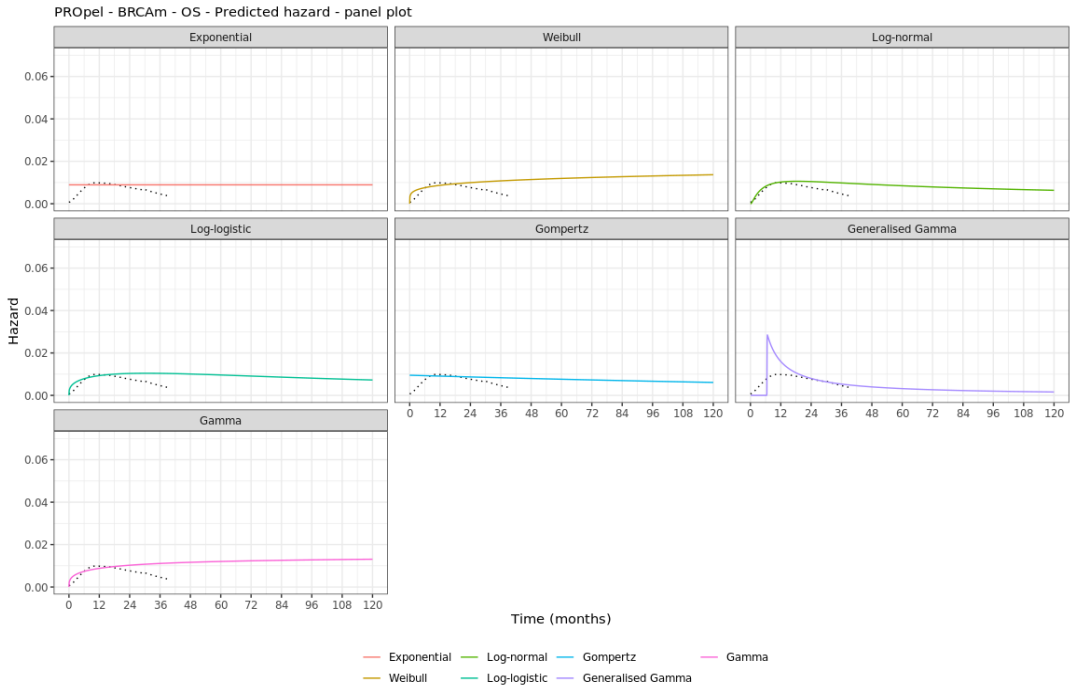

PROpel - BRCAm - OS - Predicted survival
Survival proportion
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Log-normal
Gompertz
Gamma
Weibull
Log-logistic
Generalised Gamma


PROpel - BRCAm - OS - Predicted survival - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Survival proportion
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Log-normal
Gompertz
Gamma
Weibull
Log-logistic
Generalised Gamma


PROpel - BRCAm - OS - Predicted hazard
Hazard
0.06
0.04
0.02
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma


PROpel - BRCAm - OS - Predicted hazard - panel plot
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma
Hazard
0.06
0.04
0.02
0.00
0
6
12
18
24
30
36
42
48
Time (months)
Exponential
Weibull
Log-normal
Log-logistic
Gompertz
Generalised Gamma
Gamma





A.3 Extrapolation of time to discontinuation of abiraterone

A.3.1 Descriptive statistics

The number of subjects and events per treatment arm:

Arm	N	Events	Maturity
Placebo + Abiraterone	38	[redacted]	[redacted]
Olaparib + Abiraterone	47	[redacted]	[redacted]

Mean and median survival estimates:

Arm	RMST (95% CI)	Median (95% CI)
Placebo + Abiraterone	[redacted]	[redacted]
Olaparib + Abiraterone	[redacted]	[redacted]

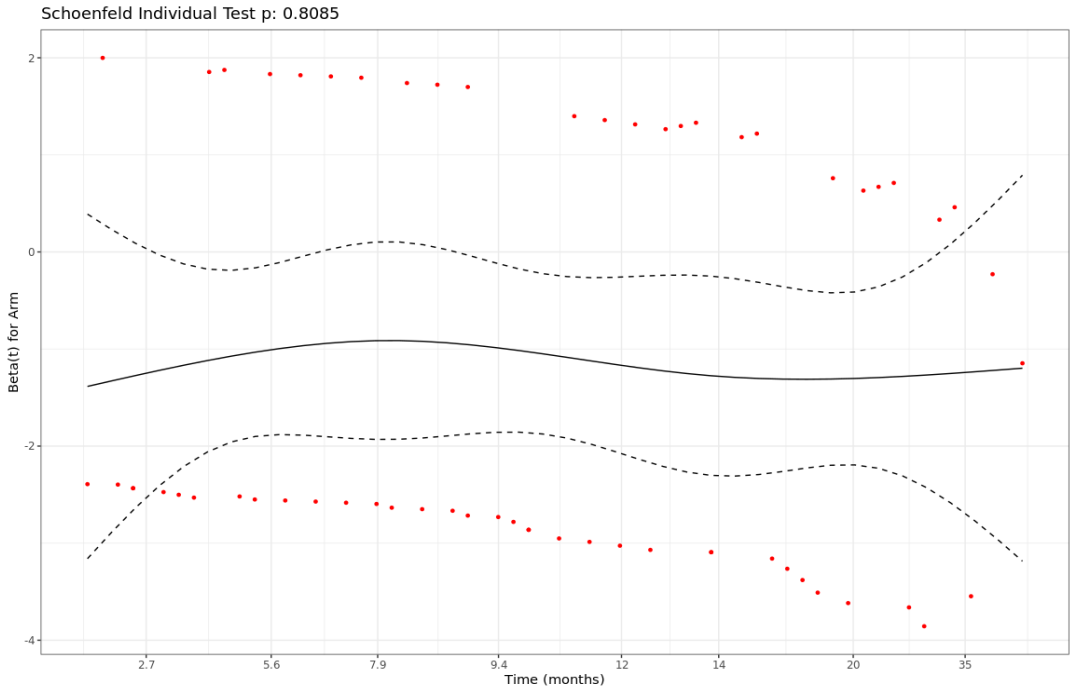
The RMST calculation uses a cut-off value of 38.0 months. This is the smallest value among the largest observed times across the treatment groups.

The KM curve is shown below.

The smooth and unsmoothed hazard plots by arm is shown below.

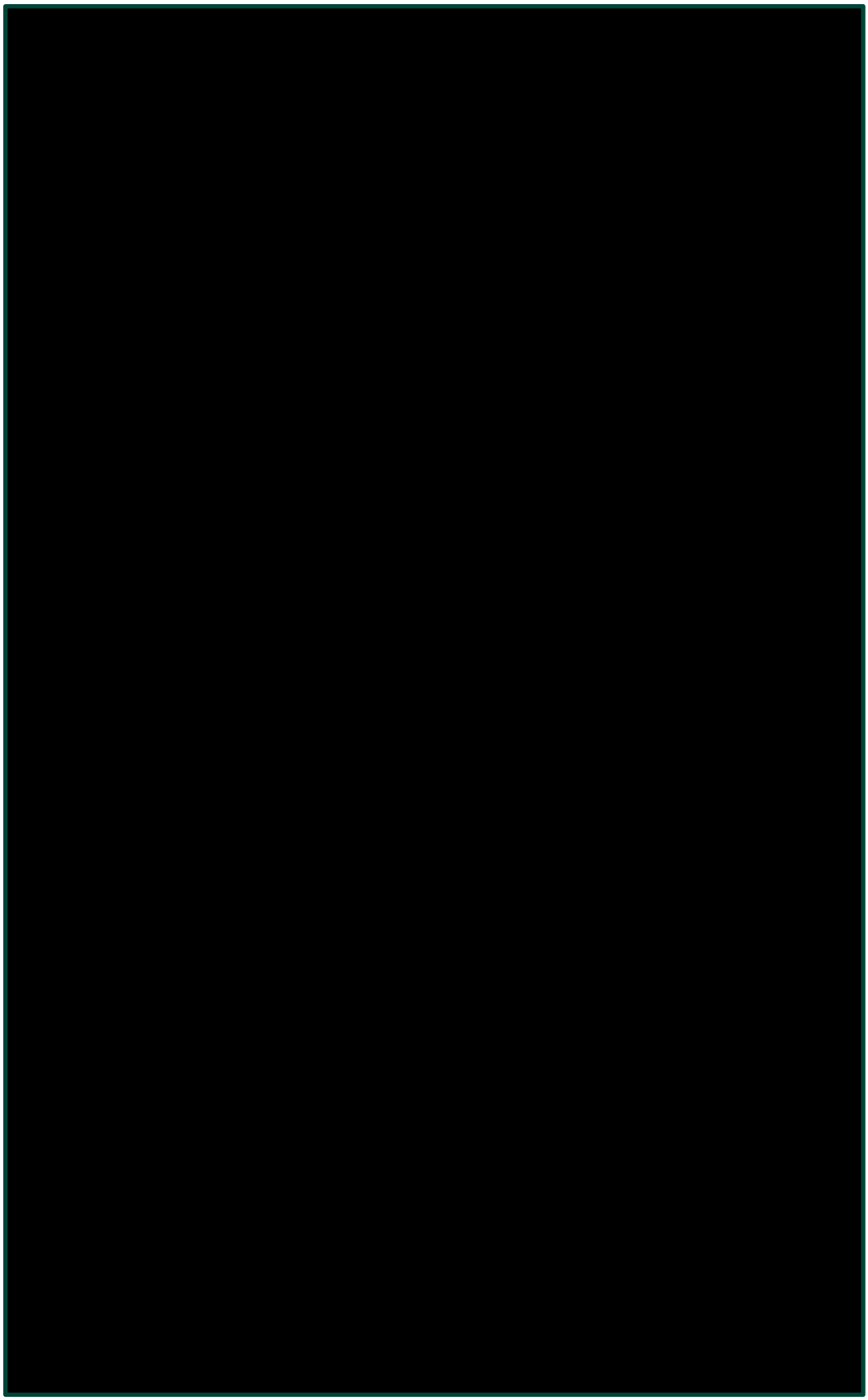
A.3.2 Diagnostic plots

The Schoenfeld residual plot is shown below.

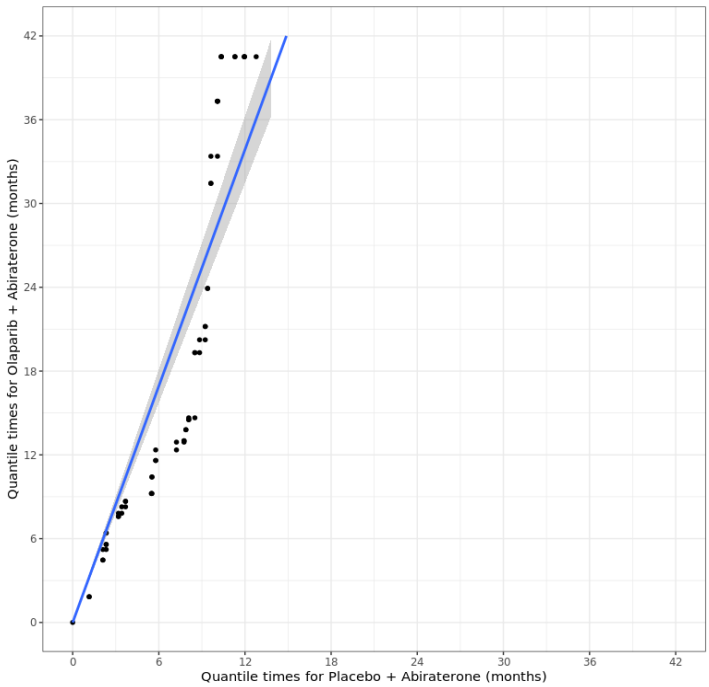


The log cumulative hazards, log odds and log normal versus log time plots are shown below.

Linear trends indicate that there are no clear violations to the model assumptions for the corresponding distribution. In the log cumulative hazards plot, parallel lines indicate proportional hazards and a gradient of 1 indicates exponential survival. In the log odds diagnostic plot, parallel lines indicate proportional odds and in the log normal diagnostic plot, parallel lines indicate constant acceleration.



The QQ-plot is shown below.



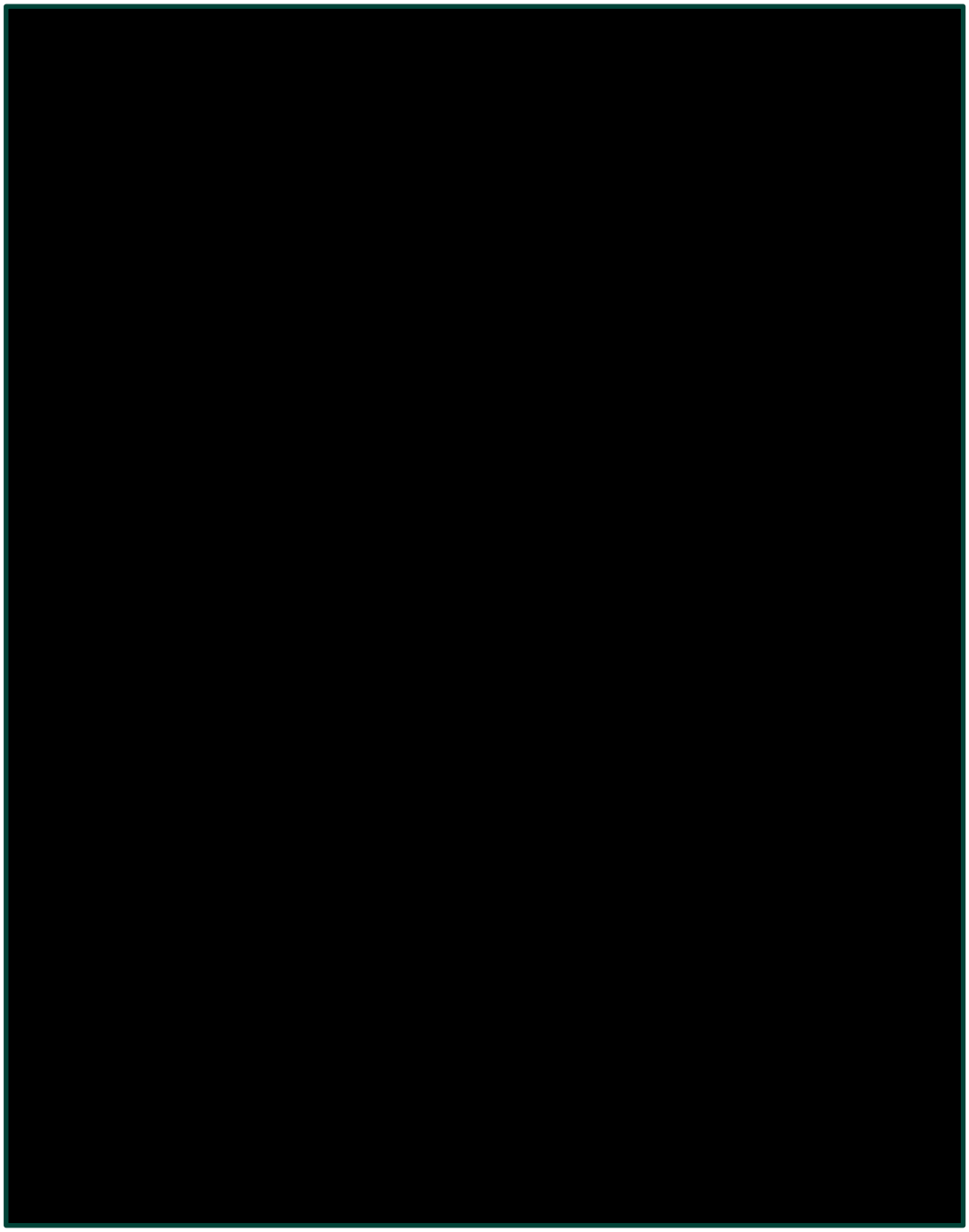
A.3.3 Independent models

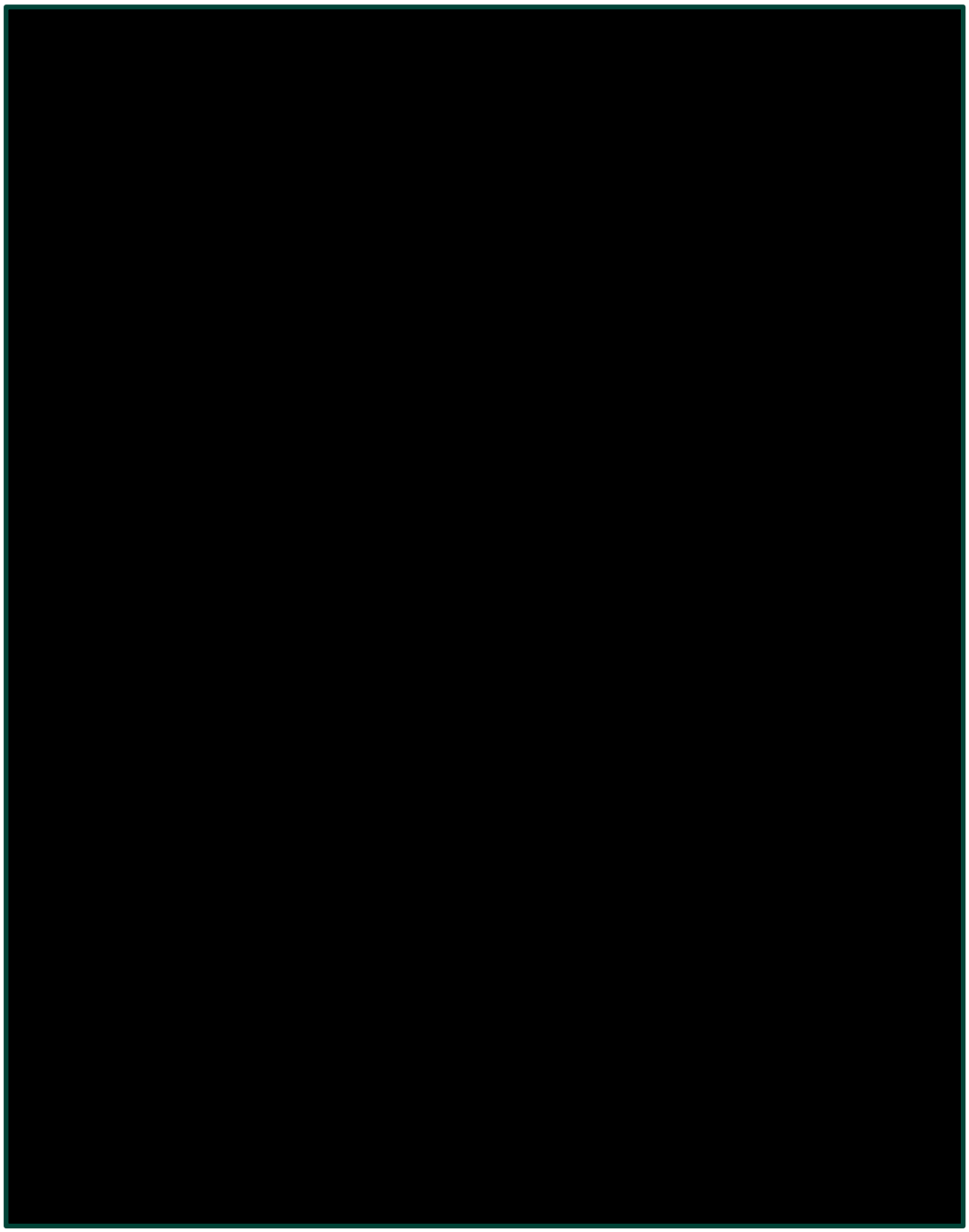
Separate distributions have been fitted per arm. The model goodness of fit statistics are shown below; the best (lowest) AIC value is shown in bold.

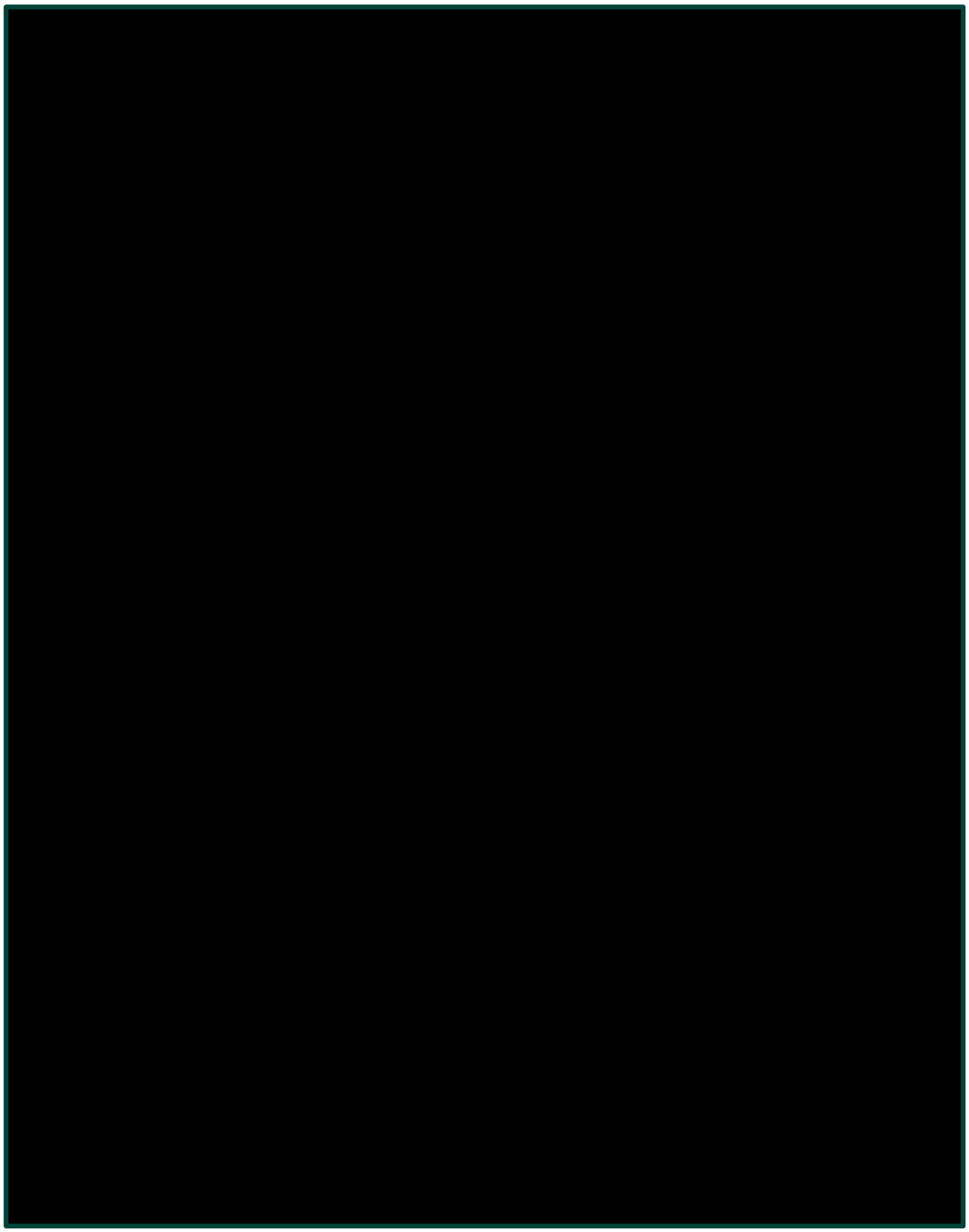
Goodness of fit statistics by model:

Arm	Distribution	Converged	AIC	BIC	Arm	Distribution	Converged	AIC	BIC
Placebo + Abiraterone	Exponential	True	257.1	258.7	Olaparib + Abiraterone	Exponential	True	252.3	254.1
	Weibull	True	256.9	260.1		Weibull	True	254.1	257.8
	Log-normal	True	252.5	255.7		Log-normal	True	**250.4**	254.1
	Log-logistic	True	**251.8**	255.1		Log-logistic	True	252.0	255.7
	Gompertz	True	259.0	262.3		Gompertz	True	254.1	257.8
	Generalised Gamma	True	254.5	259.4		Generalised Gamma	True	251.0	256.5
	Gamma	True	255.4	258.7		Gamma	True	253.8	257.5
	Generalised F	False	-	-		Generalised F	True	251.6	259.0

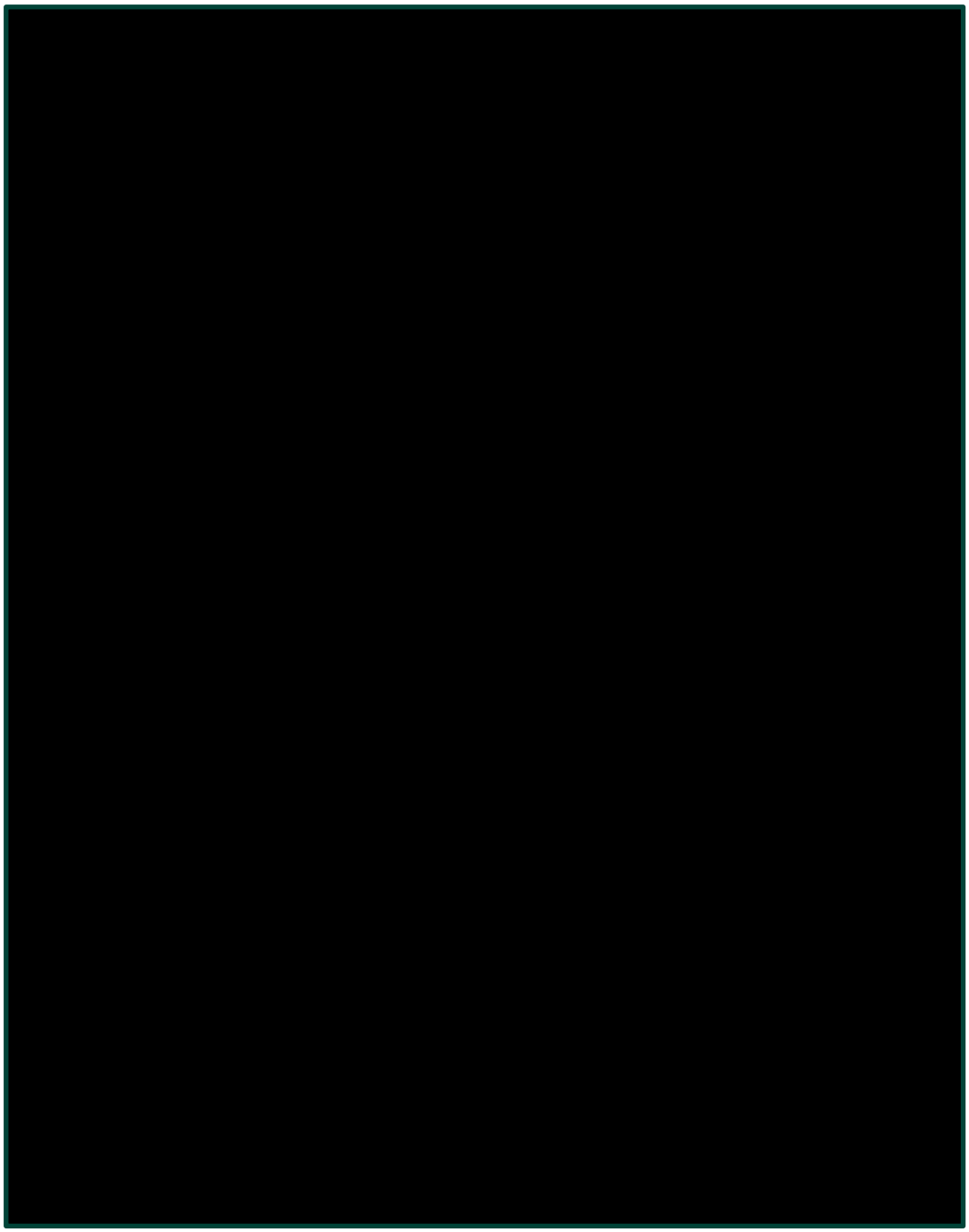
A.3.3.1 Placebo + Abiraterone

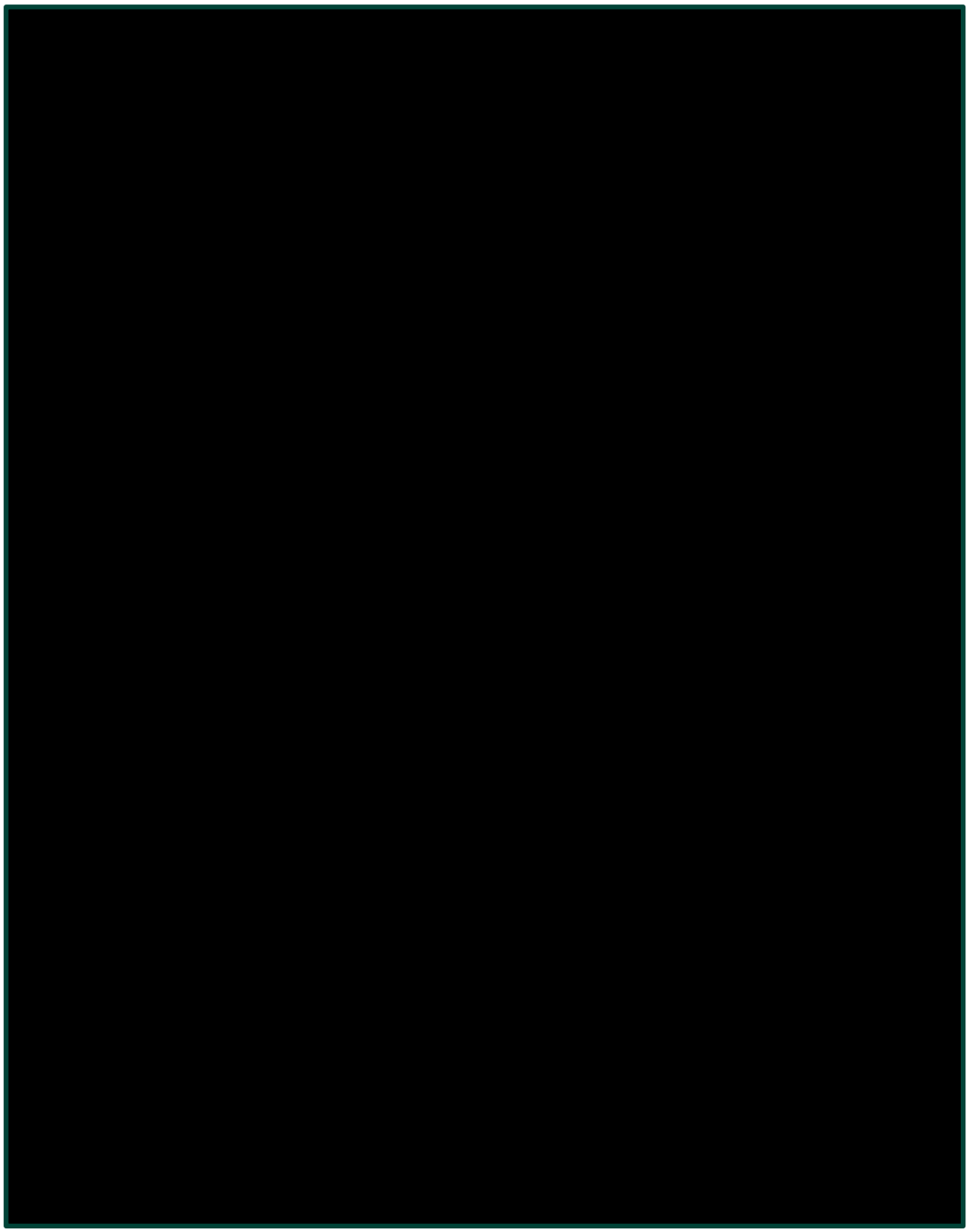


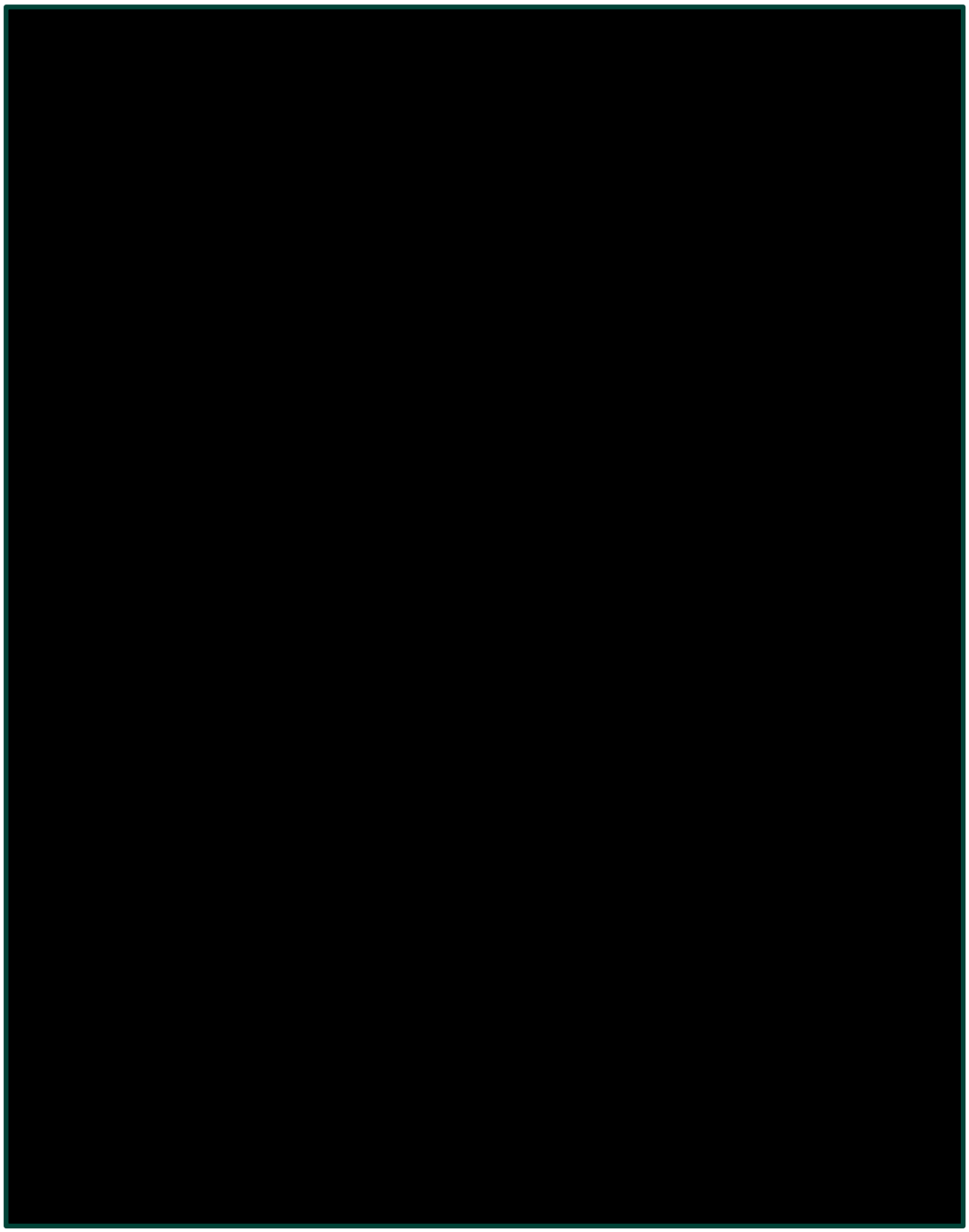




A.3.3.2 Olaparib + Abiraterone





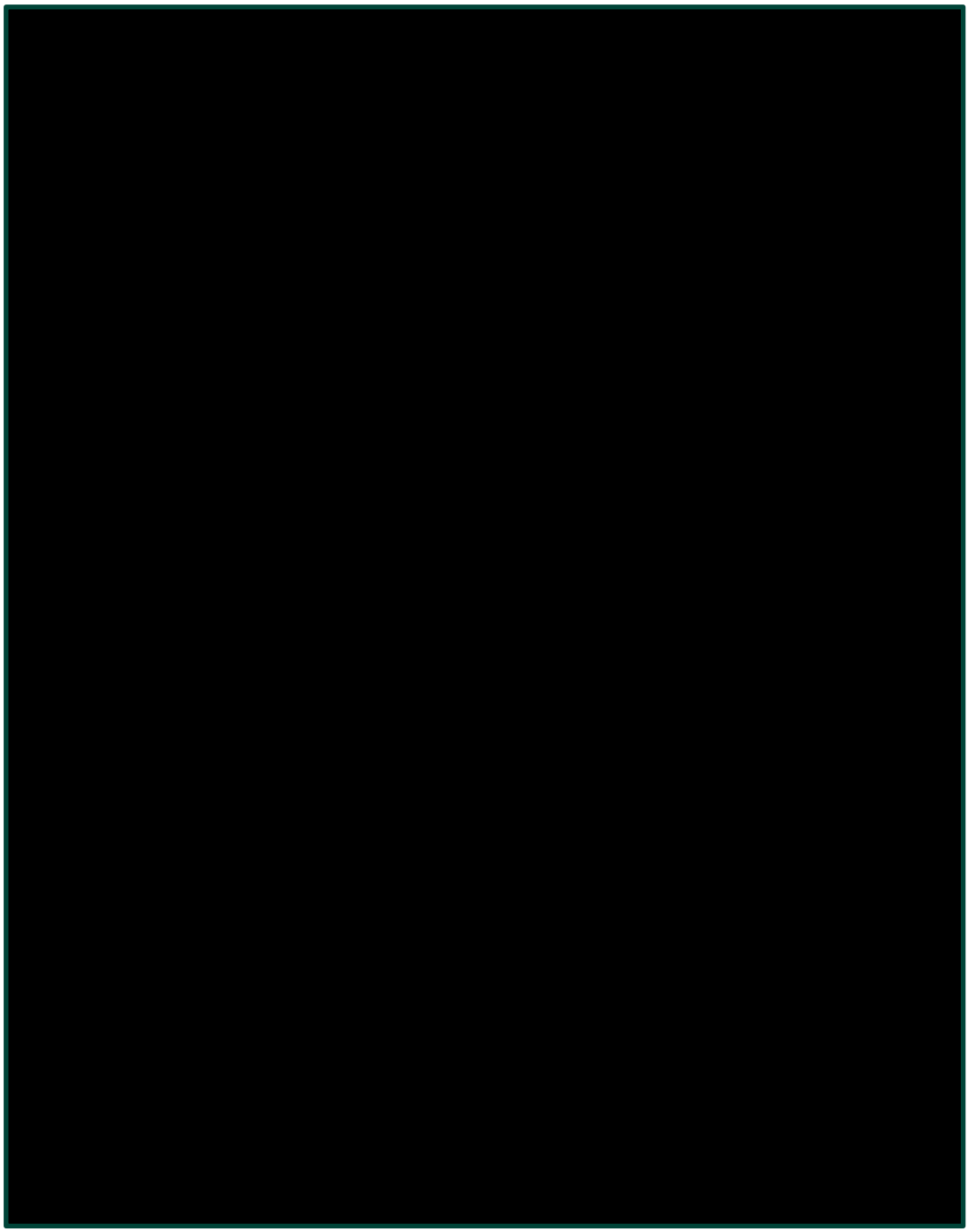


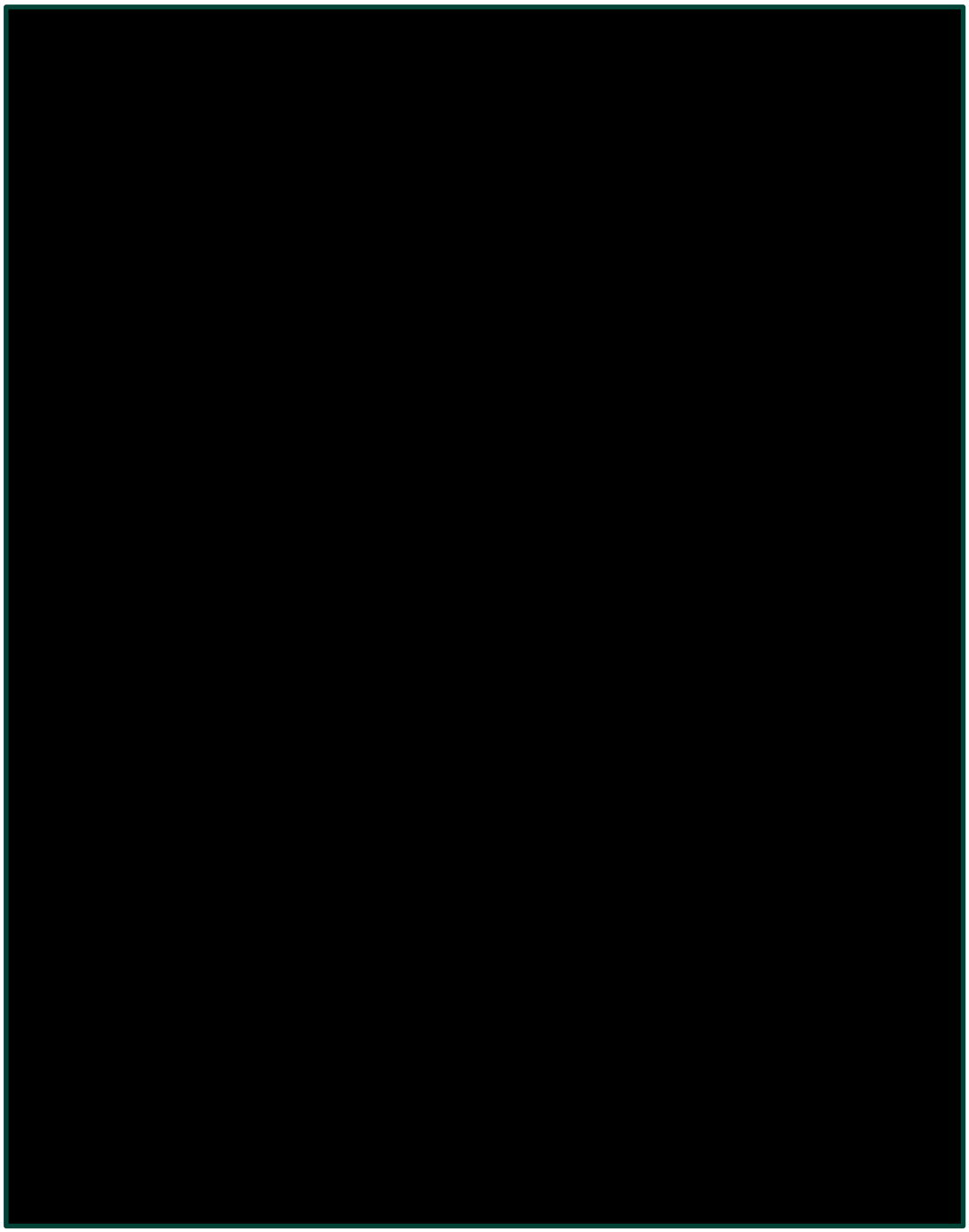
A.3.4 Joint models

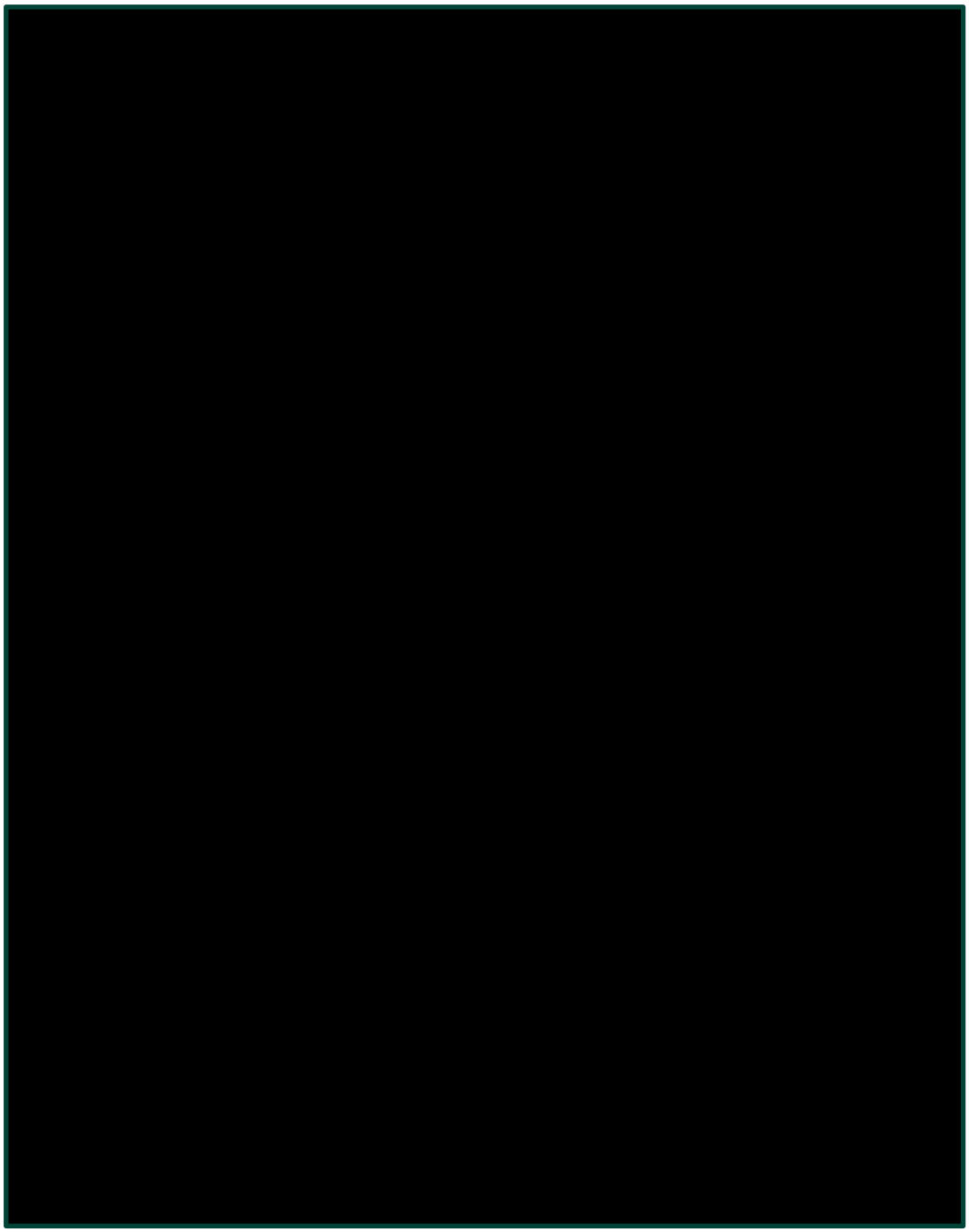
Models have been fitted with treatment as the only predictor. The model goodness of fit statistics are shown below; the best (lowest) AIC value is shown in bold.

GoF by model:

Distribution	Converged	AIC	BIC
Exponential	True	509.4	514.3
Weibull	True	509.2	516.6
Log-normal	True	**503.5**	510.8
Log-logistic	True	504.9	512.3
Gompertz	True	511.3	518.7
Generalised Gamma	True	505.5	515.3
Gamma	True	507.9	515.2
Generalised F	True	507.5	519.7







A.4 Extrapolation of time to discontinuation of olaparib

A.4.1 Descriptive statistics

The number of subjects and events per treatment arm:

Arm	N	Events	Maturity
Olaparib + Abiraterone	47	[redacted]	[redacted]

Mean and median survival estimates:

RMST (95% CI)	Median (95% CI)
[redacted]	[redacted]

The RMST calculation uses a cut-off value of 43.5 months. This is the largest observed time in the data.

The KM curve is shown below.

The smooth and unsmoothed hazard plots by arm is shown below.

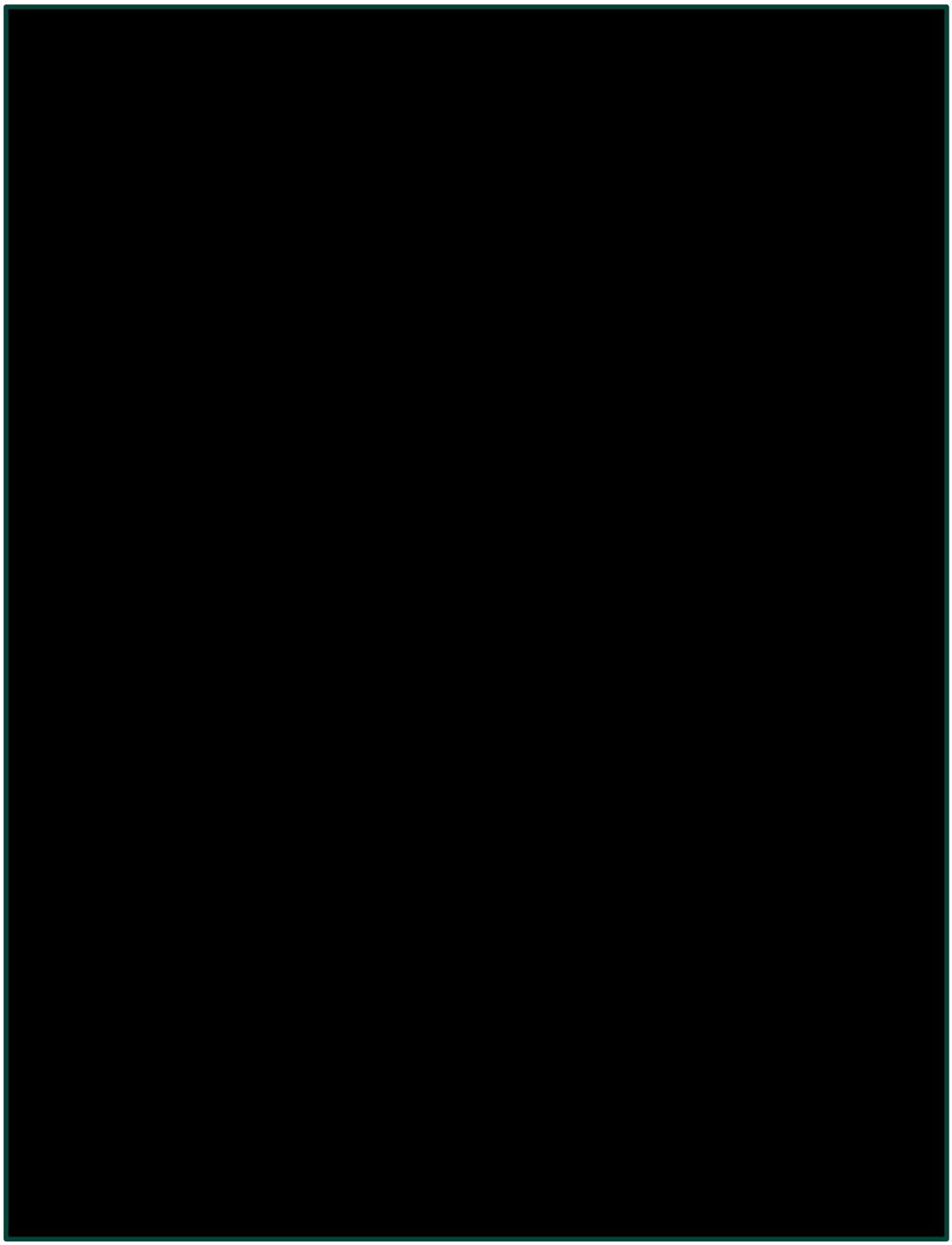
A.4.2 Independent models

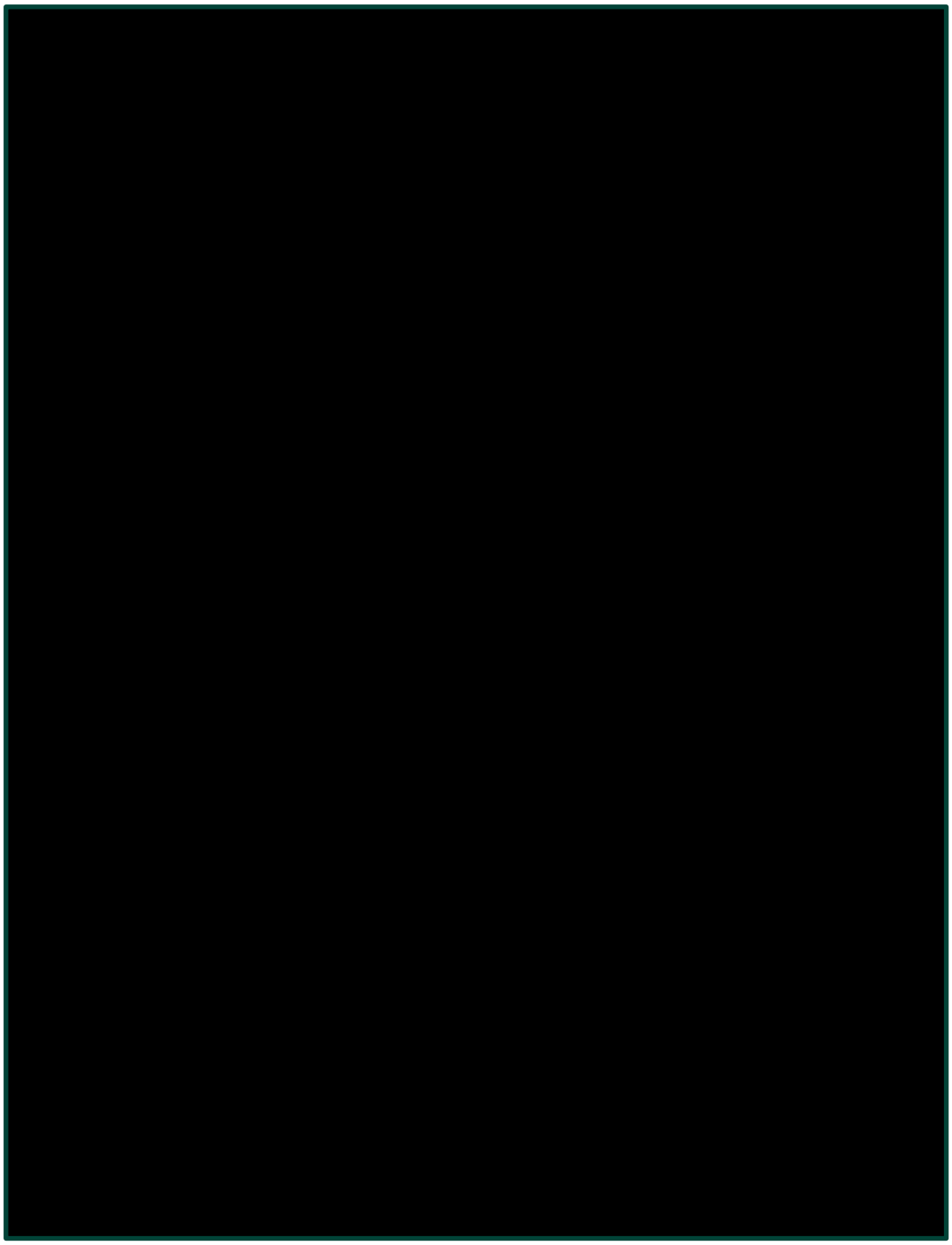
Separate distributions have been fitted per arm. The model goodness of fit statistics are shown below; the best (lowest) AIC value is shown in bold.

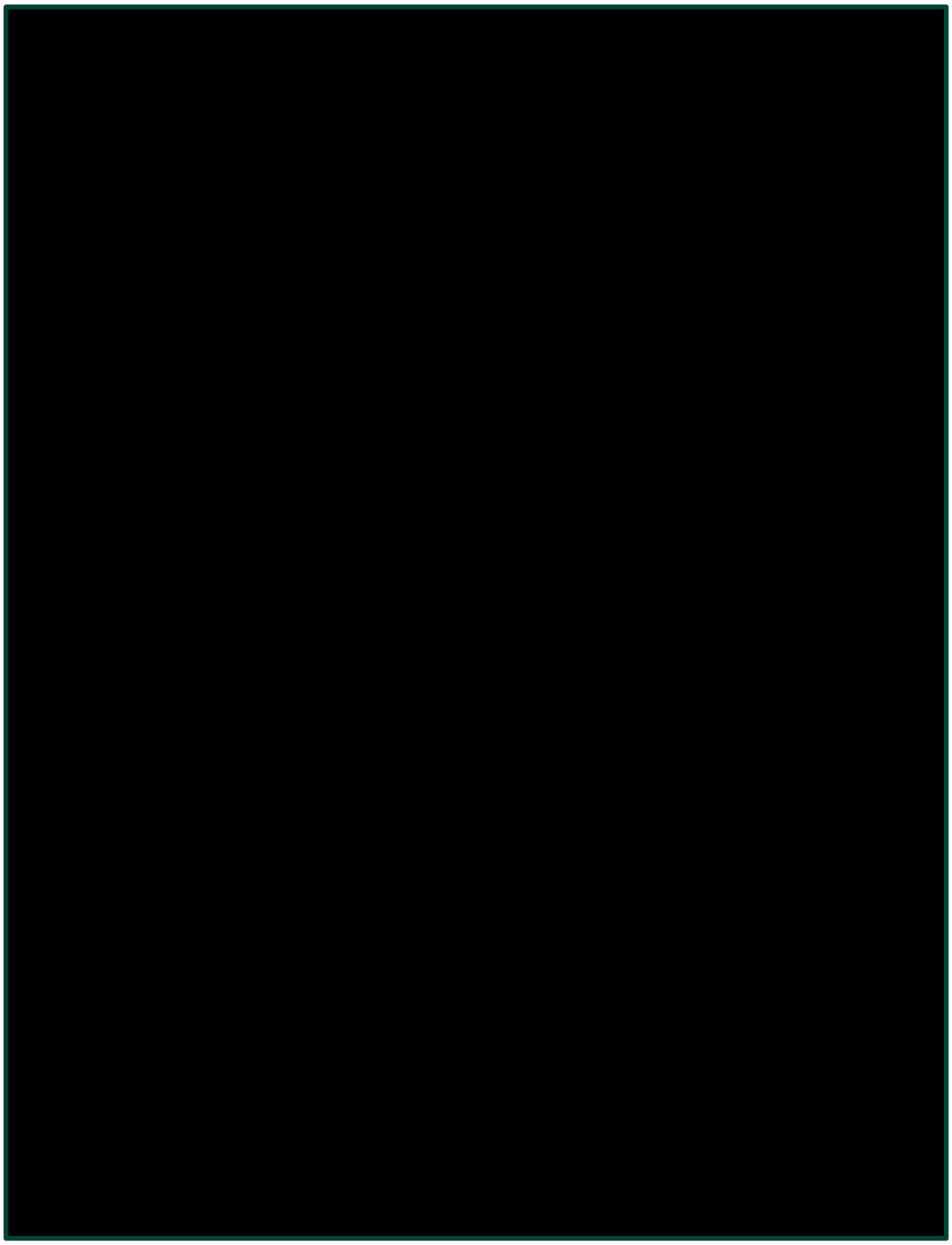
Goodness of fit statistics by model:

Arm	Distribution	Converged	AIC	BIC
Olaparib + Abiraterone	Exponential	True	265.9	267.8
	Weibull	True	267.4	271.1
	Log-normal	True	**264.0**	267.7
	Log-logistic	True	265.6	269.3
	Gompertz	True	267.9	271.6
	Generalised Gamma	True	265.1	270.6
	Gamma	True	267.1	270.8
	Generalised F	True	267.0	274.4

A.4.2.1 Olaparib + Abiraterone







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medicinraadet@medicinraadet.dk

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Supplementary documentation for the assessment of Lynparza in combination with abiraterone and prednisolone for metastatic castration-resistant prostate cancer

20th September 2023

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
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Abbreviations

BRCA[m]	Breast Cancer gene [mutation]
BSC	Best supportive care
CI	Confidence interval
DKK	Danish kroner
FACT-P	Functional Assessment of Cancer Therapy –Prostate
HRR[m]	Homologous recombination repair [mutation]
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
MAR	Missing at random
MCAR	Missing completely at random
mCRPC	Metastatic castration-resistant prostate cancer
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
PRO	Patient reported outcome
QALY	Quality-adjusted life year
SD	Standard deviation
VAS	Visual analogue scale

1. Background

On Friday 15 September, AstraZeneca received several questions from Medicinrådet relating to the health-related quality of life (HRQoL) data presented in the submission for olaparib (Lynparza) in combination with abiraterone and prednisolone for metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. The specific questions received were:

1. *Vi har brug for lidt yderligere information i afsnittet omkring helbredsrelateret livskvalitet herunder:*
    a. *Angiv antal besvarelser i interventions- og komparatorarmen for FACT-P*
    b. *Definer compliance rate*
    c. *Vi studsede over forskellige %-dele som besvarede for FACT-P og EQ-5D. Vil I knytte en kommentar til det?*
    d. *Inkluder en opgørelse (graf) af gennemsnitlig ændring fra baseline og frem for EQ-VAS*
2. *Hvor mange besvarelser samt patientantal er nytteværdien for det progressionsfrie stadie baseret på?*

In addition, one question was received about subsequent therapies used in the cost-effectiveness model:

3. *Best supportive care er listet som en behandlingsmulighed til efterfølgende behandling i tabel 41, 42 og 43. Hvor stor en andel af patienterne i hver arm antages at modtage BSC?*

2. Health-related quality of life

2.1 FACT-P response rates and compliance

Angiv antal besvarelser i interventions- og komparatorarmen for FACT-P

With respect to the FACT-P results presented in section 7.1.2.7 of the initial submission (pages 37-38), the overall difference in least squares mean score on the FACT-P reported (-0.54; 95% CI -3.00, 1.92; p = 0.6675) was estimated from 278 patients in the olaparib + abiraterone arm and 295 patients in the placebo + abiraterone arm. The number of responses by week are shown in Table 1.

Definer compliance rate

When reporting the overall compliance rate of 69.8% in the olaparib + abiraterone arm and 74.5% in the placebo + abiraterone arm in the initial submission, this is calculated as the number of patients with an evaluable baseline and at least one evaluable follow-up form, divided by the number of patients expected to have completed at least a baseline form. The compliance rate has also been calculated separately for each visit as the number of patients with an evaluable format that time point divided by number of patients still expected to complete forms at that visit. All patients who are progression-free or within 12 weeks of confirmed disease progression and have

not discontinued the study were expected to complete the FACT-P. The compliance rates were defined the same way for both the FACT-P and EQ-5D-5L in PROpel.

Table 1. Summary of FACT-P responses used in MMRM analysis for change in FACT-P score from baseline

Study Week	Olaparib + Abiraterone (N = 399)	Placebo + Abiraterone (N = 397)
Overall	278	295
Week 5	259	284
Week 9	252	277
Week 13	240	257
Week 17	232	249
Week 21	226	239
Week 25	215	235
Week 29	213	223
Week 33	202	212
Week 37	193	202
Week 41	188	196
Week 45	180	189
Week 49	180	179
Week 53	175	168
Week 61	161	151
Week 69	152	129
Week 77	144	116
Week 85	131	111
Week 93	121	96
Week 101	114	83
Week 109	103	81
Week 117	93	68
Week 125	88	63
Week 133	90	64
Week 141	76	52
Week 149	66	42
Week 157	49	35
Week 165	34	23

2.2 Missing data

Vi studsede over forskellige %-dele som besvarede for FACT-P og EQ-5D. Vil I knytte en kommentar til det?

With respect to the differing proportions of patients responding to the EQ-5D-5L and the FACT-P, no formal assessments on data missingness have been conducted and data were not explicitly imputed. However, if one wishes to assess whether the results from the EQ-5D and FACT-P can be considered valid, and that the conclusion of comparable HRQoL between olaparib + abiraterone and placebo + abiraterone is sustained, some basic assessments can be conducted.

Both health state utilities and change in FACT-P score were estimated using mixed models for repeated measures (MMRM) which handle missing data implicitly. This method does not explicitly impute the missing values, but rather assumes that the subject's missing data would have followed the trend of his or her own treatment group based on variables included in the model. MMRM models can handle missing data when the data are missing at random (MAR), conditional on one of the variables included in the MMRM analysis. The approach remains valid if data are missing completely at random (MCAR) but can induce bias if the data are missing not at random (MNAR). Therefore, one must comment on the likelihood that data missingness is due to unmeasured variables and the potential impact of that. In the assessment of utilities, variables explored were treatment arm and/or progression status. In the assessment of change in FACT-P these were treatment arm, visit, baseline score, site of metastases, and prior docetaxel, as well as treatment arm by visit and baseline score by visit interaction terms. Therefore, if we plausibly believe that the reason for missing data would be associated with any of these factors then missingness is unlikely to influence our conclusions on comparable HRQoL between olaparib and placebo.

As baseline characteristics and baseline HRQoL were balanced between arms, as well as the number of observations per HRQoL measure (Table 2), and there were no known extenuating circumstances (e.g., study site closures) which may influence completion of the HRQoL data, it is assumed that observed changes in HRQoL would be attributable to treatment and prognosis. However, compliance may be associated with health status in those who would otherwise be willing to complete the forms.

Table 2. Summary of HRQoL scores at baseline

	Olaparib + Abiraterone	Placebo + Abiraterone
EQ-5D-5L: Mobility	n = 270	n = 279
Mean (SD)	1.58 (0.90)	1.55 (0.81)
Median (Range)	1.00 (1, 5)	1.00 (1, 5)
EQ-5D-5L: Self Care	n = 270	n = 279
Mean (SD)	1.24 (0.61)	1.18 (0.47)
Median (Range)	1.00 (1, 5)	1.00 (1, 5)
EQ-5D-5L: Usual Activities	n = 270	n = 279
Mean (SD)	1.44 (0.76)	1.42 (0.68)
Median (Range)	1.00 (1, 4)	1.00 (1, 4)

	Olaparib + Abiraterone	Placebo + Abiraterone
EQ-5D-5L: Pain/Discomfort	n = 270	n = 279
Mean (SD)	1.71 (0.83)	1.65 (0.78)
Median (Range)	2.00 (1, 4)	1.00 (1, 5)
EQ-5D-5L: Anxiety/Depression	n = 270	n = 279
Mean (SD)	1.40 (0.66)	1.47 (0.71)
Median (Range)	1.00 (1, 5)	1.00 (1, 5)
EQ-5D-5L: VAS Score	n = 270	n = 279
Mean (SD)	75.91 (18.33)	76.93 (17.73)
Median (Range)	80.00 (18, 100)	80.00 (21, 100)
FACT-P: Total Score	n = 283	n = 300
Mean (SD)	113.55 (19.63)	113.24 (20.79)
Median (Range)	115.00 (59, 154)	116.25 (56, 152)

Figure 1 shows the compliance rate to the FACT-P over time. Compliance remains somewhat constant in the olaparib + abiraterone arm over time (70-80%), indicating that there may be a subset of consistently non-compliant patients. However, as the patient numbers on which change from baseline can be calculated (Table 1) are consistent with expectations, given that the questionnaire is only completed up until 12 weeks after disease progression, the statistical adjustment for baseline and the similar baseline values mean that the impact of these non-compliant patients is limited when measuring differences between arms.

In the placebo + abiraterone arm, there appears to be a gradual decline in compliance over time. The specified MMRM analysis model assumes that patients with missing data at a visit would have similar outcomes to patients with observed data for that treatment arm at that visit, with respect to site of metastases at randomisation and prior docetaxel use. If the reason for non-compliance is reduced willingness to complete the questionnaires over time and unrelated to other factors, then results would not be impacted. If prognosis is associated with compliance, then better performing patients are expecting to be more compliant which may overestimate HRQoL in the placebo + abiraterone arm. Therefore, whilst there may be some bias in estimates, this is in favour of the placebo + abiraterone arm and olaparib may be associated with improved rather than equal HRQoL compared to placebo.

Figure 1. FACT-P compliance rate

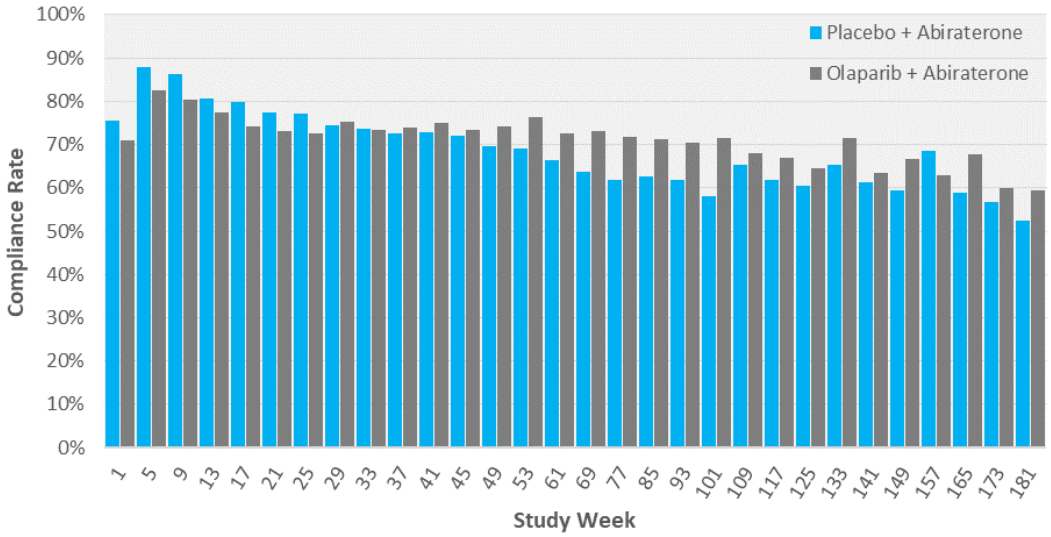
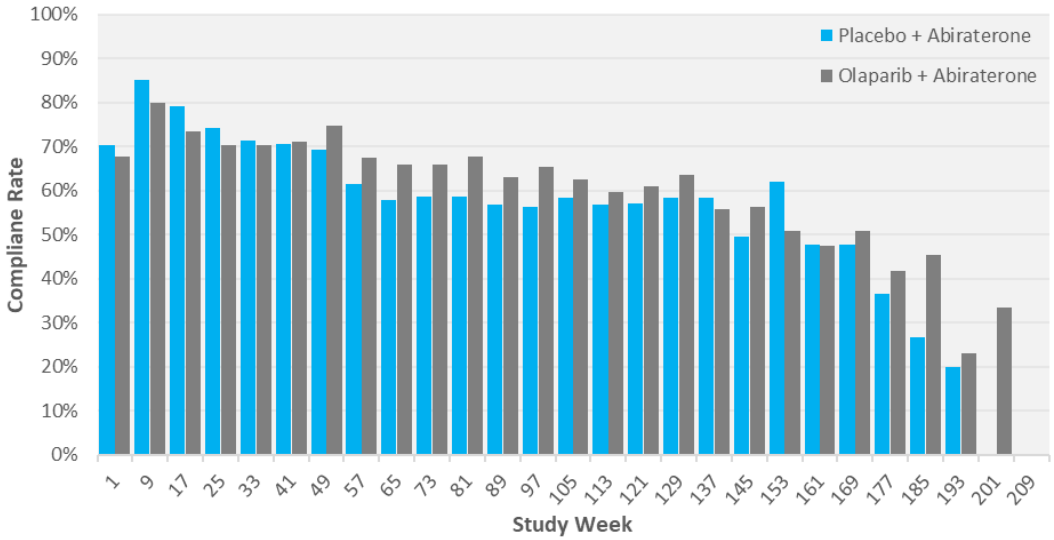


Figure 2 shows the EQ-5D-5L compliance rate over time. It is noticeable that the compliance rate in general is lower than compared to the FACT-P. This may be somewhat attributable to the protocol-specified order of administration of PROs, where the FACT-P should always be completed before the EQ-5D and that all PROs should be completed before any study procedures on that visit day.

Compliance to the EQ-5D in the placebo + abiraterone arm first begins to decline on a similar timeline to radiographic progression-free survival (rPFS). Median rPFS in the placebo + abiraterone arm is 16.5 months (95% CI 13.9, 19.2), approximately equivalent to week 73 (95% CI 62, 85), at which time there is ~10% drop in compliance. Therefore, it could be hypothesised that for some patients treated with abiraterone alone the burden of disease progression may result in not completing the EQ-5D. Conversely, the first meaningful decline in compliance for the olaparib arm begins around week 137 (~31 months). This timepoint is not clearly associated with the timing of any major clinical outcomes, but a small decline could be observed around the median rPFS in this around (approximately week 110). The impact of disease progression may not be a significant on health to impact compliance in patients treated with add-on olaparib.

Figure 2. EQ-5D-5L compliance rate



On the basis of this basic assessment, we believe that the utilities for the progression-free health state are probably not influenced by missing data as the MMRM analyses can account for missingness conditional on the treatment arm (for which no difference in effect was observed). For the progression state, it is possible that patients in the worse health (e.g., most heavily burdened by subsequent therapy or who have developed symptomatic disease) are not compliant and do not provide EQ-5D data. Therefore, the data are at risk of being MNAR. However, feedback provided to AstraZeneca from the Swedish clinical expert engaged by TLV in their assessment of PROpel is that HRQoL is largely determined by how symptomatic the disease is and partly by the side effects of any future treatments. In their clinical experience, even after first-line disease progression the disease is asymptomatic apart from fatigue, and that it is rather the treatment that affects QoL the most, and that patients also have a relatively good HRQoL during second- and third-line treatment. Based on this feedback, even if the data are MNAR the small decrement in utility observed upon disease progression in PROpel is probably reflective of clinical practice.

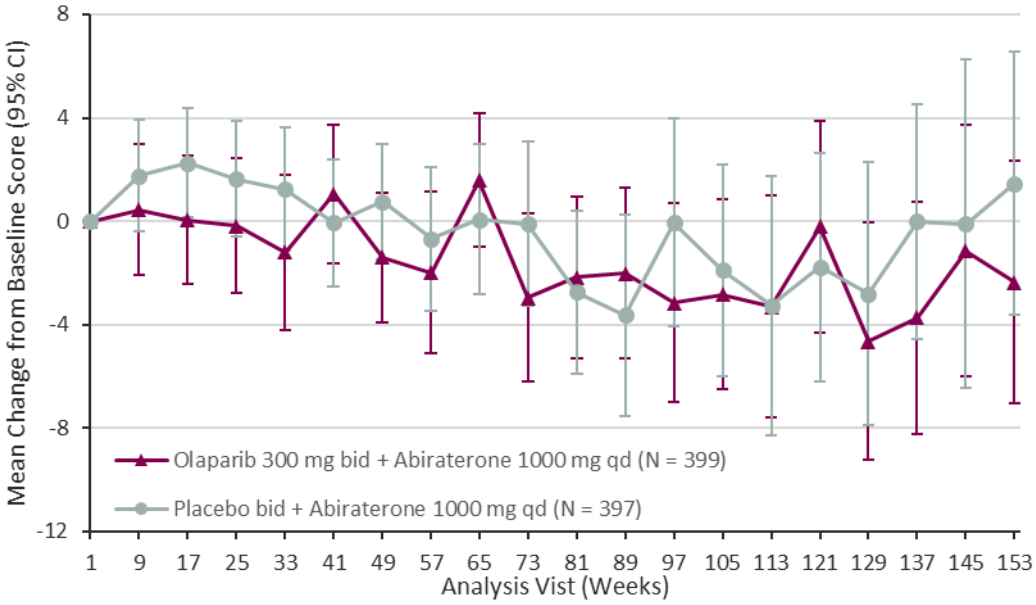
As the comparison between treatment arms is based on all available data and the patterns of missingness and the plausible reasons for missingness seem to be similar between arms, conclusions on comparable HRQoL between treatment arms in PROpel can be sustained.

2.3 EQ-5D VAS

Inkluder en opgørelse (graf) af gennemsnitlig ændring fra baseline og frem for EQ-VAS

In PROpel, the EQ-5D VAS was collected every 8 weeks until 12 weeks after confirmed progressive disease. The mean change from baseline in EQ-5D VAS scores over time are shown in Figure 3. Change from baseline was analysed until there are less than 10% of patients with evaluable data. The mean scores were similar at baseline (see Table 2 above) and remained similar during the course of follow-up. On the basis of the overall observed results, it is concluded that HRQoL is likely to be similar between treatment arms, as was observed on the pre-specified endpoint of the FACT-P.

Figure 3. Mean change from baseline in EQ-5D VAS score for ITT population of PROpel



2.4 Health state utilities

Hvor mange besvarelser samt patientantal er nytteværdien for det progressionsfrie stadie baseret på?

In total, 727 patients provided 6 717 observations on the EQ-5D-5L during follow-up. Table 3 shows the total observations by treatment arm and health state. As health state utilities in the cost-effectiveness model were not treatment specific as no different in HRQoL was observed between treatment arms, the health state utility for the "progression-free" health state is based on 6 175 observations from a total of 718 patients.

Table 3. EQ-5D-5L observations by health state in PROpel

Treatment	Progression Status	Subjects	Observations
Placebo + Abiraterone	Progression-Free	361	2 916
	Progressed Disease	136	281
	Total	368	3 197
Olaparib + Abiraterone	Progression-Free	357	3 259
	Progressed Disease	93	261
	Total	359	3 520
Combined	Progression-Free	718	6 175
	Progressed Disease	229	542
	Total	727	6 717

3. Subsequent therapies in the health economic model

Best supportive care er listet som en behandlingsmulighed til efterfølgende behandling i tabel 41, 42 og 43. Hvor stor en andel af patienterne i hver arm antages at modtage BSC?

On page 72 of the initial application it states that "all patients who survive beyond first line treatment discontinuation but who do not receive subsequent anticancer therapy are assumed to receive best supportive care". This is on the assumption that patients with mCRPC would always receive some care whilst they are alive, even if they were not considered candidates for life-prolonging anti-cancer therapy. Therefore, the distributions of treatments given in Tables 39 and 40 (and Table 10 of the supplementary information for the BRCAm subgroup) represent the distributions of treatments given to patients eligible for anti-cancer treatment, but do not include those receiving BSC alone.

To derive the number of patients receiving BSC, one must determine the proportion of patients surviving beyond discontinuation of first line therapy and then what proportion of patients surviving beyond first line therapy receive subsequent anticancer therapy, to determine those who are alive but do not receive anticancer therapy. However, we have noticed an error in the implementation of this in the model which results in an underestimation of the costs of BSC. This error has now been corrected in the attached model.

Table 4 shows the reported distribution of subsequent treatments for the ITT population in the initial submission, as a proportion of patients who are determine to receive active subsequent anticancer therapy. Table 5 shows the distribution of post-first line treatment outcomes, including BSC or death during first line treatment, to indicate what proportion of all first line mCRPC patients would be expected to receive each treatment.

Table 4. Distribution of subsequent treatments in ITT population as a proportion of patients receiving subsequent anticancer therapy

	Olaparib + Abiraterone	Abiraterone	Enzalutamide
Abiraterone	***	***	***
Cabazitaxel	***	***	***
Docetaxel	***	***	***
Enzalutamide	***	***	***
Olaparib (mono)	***	***	***
Radium-223	***	***	***

Table 5. Modelled distribution of post-first line treatment outcomes in ITT population as a proportion of all first line patients

	Olaparib + Abiraterone	Abiraterone	Enzalutamide
Death on first line treatment	***	***	***
No further anticancer therapy (BSC)	***	***	***
Subsequent anticancer therapy	***	***	***
Abiraterone	***	***	***
Cabazitaxel	***	***	***
Docetaxel	***	***	***
Enzalutamide	***	***	***
Olaparib (mono)	***	***	***
Radium-223	***	***	***

The technical correction for the costs of BSC in the model has very little impact on cost-effectiveness results. Table 6 compares results with the previous version of the model with the corrected version with applying the intended costs for BSC. Incremental cost-effectiveness ratios remain largely unchanged.

Table 6. Comparison of results with corrected implementation of BSC costs

Population	Total Incremental Costs (DKK)		ICER (DKK per QALY)	
	Previous	Corrected	Previous	Corrected
ITT	1 021 255	1 019 448	745 651	744 332
HRRm	1 232 606	1 217 030	566 630	559 470
BRCAm	1 462 586	1 462 901	382 563	382 646

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