Medicinrådet

Bilag til Medicinrådets vurdering af 177-Lu-vipivotide tetraxetan til behandling af PSMA-positiv metastatisk kastrationsresistent prostatakræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. 177-Lu-vipivotide tetraxetan
2. Forhandlingsnotat fra Amgros vedr. 177-Lu-vipivotide tetraxetan
3. Ansøgers endelige ansøgning vedr. 177-Lu-vipivotide tetraxetan

NOVARTIS | Reimagining Medicine

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19. november 2025

Notat vedr. Medicinrådets udkast til vurderingsrapport for Pluvicto® (177Lu vipivotide tetraxetan) til behandling af PSMA-positiv metastatisk kastrationsresistent prostatakræft

Vi takker for modtagelsen af udkastet til vurderingsrapporten for Pluvicto®, som vi generelt synes har en meget høj teknisk kvalitet.

Indledningsvis gør vi opmærksom på, det ikke er korrekt at benævne Pluvicto® "Lutetium-177". Vi foreslår i stedet "177Lu vipivotide tetraxetan" som benævnt i vores ansøgning, for ikke at skabe uklarhed - også relateret til et andet af vore radioaktive lægemidler, Lutathera® - 177Lu dotatate.

En indirekte sammenligning (efter Buchers metode) tilføjer yderligere usikkerhed pga væsentlige forskelle i studiedesign og patientpopulationer

I udkastet til vurderingsrapporten præsenteres og ligestilles to scenarier for sammenligningen af Pluvicto® og cabazitaxel. Disse scenarier bygger på to analyser (en uforankret MAIC-analyse og en ujusteret forankret indirekte sammenligning med Buchers metode). Disse to metoder er udvalgt blandt flere som de mest metodisk korrekte og troværdige. Vi anerkender, at begge metoder har deres styrker og begrænsninger. Dog mener vi, at anvendelsen af Buchers metode i denne kontekst er uhensigtsmæssig, da der med metoden, som der også står i udkastet til vurderingsrapporten, "*ikke tages højde for forskelle i studiedesign og patientpopulationer.*" Bucher metoden justerer desuden ikke for Treatment Effect Modifiers (TEMs), hvilket kan gøre resultaterne biased, hvis TEMs er ulige fordelt mellem de to forsøg.

Buchers metode forudsætter sammenlignelige populationer og studiedesigns[1]. Det må derudover forventes, at post 1-taxan populationen i VISION studiet har en dårligere almentilstand end den tilsvarende population i CARD studiet grundet forskelle i in- og eksklusionskriterier mellem de to studier. Især fremhæves inklusionskriterium #10[2]. At studiepopulationerne ikke kan sammenlignes konkluderes også i udkastet for vurderingsrapporten (side 69): "*Studiepopulationer og studiedesigns i de to studier er ikke sammenlignelige".*

Vi mener derfor, at scenariet, hvor Buchers metode bruges, giver et fejlagtigt grundlag for at vurdere effekten af Pluvicto® sammenlignet med cabazitaxel. Inddragelse af scenariet, og selv om det andet scenarie giver et modsat resultat, leder til den konklusion, at Pluvicto® ikke har effekt i forhold til cabazitaxel for post 1-taxan populationen. Selvom vi også anerkender de metodiske usikkerheder ved

[1] Tingle et al. (2025). Simple tool implementing Bucher's method for indirect treatment comparisons in meta-analyses. BMJ Evid Based Med. 21;30(2):130-133. EUnetHTA Guideline (2015): Direct_comparators_comparisons.
[2] Inclusion criterion #10, section 4.1: 10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if: a. The patient is not willing to receive a second taxane regimen or, b. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation or intolerance). VISION PROTOCOL NO. PSMA-617-01: nejmoa2107322_protocol.pdf.

MAIC-analysen, vurderer vi, at denne, ud af de to inkluderede scenarier, udgør det mest metodisk korrekte og troværdige grundlag for vurderingen af Pluvicto® i post 1-taxan populationen, og at resultaterne derfor bør tillægges størst vægt.

Relateret hertil finder vi det problematisk, at Medicinrådet vælger at inkludere analysen baseret på Buchers metode, når de samtidig argumenterer for at anvende stratificerede ekstrapoleringer (separate arm-fits for Pluvicto® og SoC) i overlevelseskurverne, netop fordi der er usikkerhed om proportional hazards mellem Pluvicto® og SoC. Buchers metode forudsætter, at proportional hazards gælder mellem Pluvicto® og SoC. I en situation, hvor denne antagelse er tvivlsom, vil en populationsjusteret tilgang (fx uforankret MAIC) være mere konsistent med den valgte strategi om separate arm-fits og ønsket om at udligne populationsforskelle.

OS ekstrapolering

Vedrørende valget af OS ekstrapolering i post 1-taxan populationen har Medicinrådet valgt den stratificerede Weibull-funktion. Hvis man fastholder en stratificeret ekstrapoleringsmetode, mener vi, at det mest retvisende valg ville være den funktion med det bedste statistiske fit, hvilket er den stratificerede gammafordeling.

Intet krav om hospitalsindlæggelse relateret til behandling med Pluvicto®

Medicinrådet har inkluderet omkostninger relateret til indlæggelse i 1 døgn efter administration af Pluvicto®. Vi gør opmærksom på, at dette ikke er et krav, jf. det af Lægemiddelstyrelsen godkendte produktresumé, men vi anerkender, at det ikke har den store indflydelse på ICER-resultatet.

Opfølgning af patienterne real-world kan reducere Medicinrådets usikkerhed om effekten af Pluvicto®

Novartis anerkender, at der kan være forskel på usikkerheden om effekten af Pluvicto®, afhængigt af hvilken analysemetode, som anvendes (NMA, MAIC eller Bucher ITC). En måde at håndtere denne usikkerhed på kan være opfølgning af patienterne real-world. Dette kan ske enten i post 1-taxan populationen, hvor usikkerheden omkring effekten af Medicinrådet vurderes at være størst, eller i begge patientpopulationer. Novartis hilser en sådan real-world opfølgning velkommen og indgår gerne i en dialog om denne.

Vi gør opmærksom på, at flere europæiske lande – deriblandt Frankrig, Belgien og Tyskland – har truffet positiv tilskudsbeslutning for Pluvicto® i hele VISION populationen, og således ikke har samme betænkeligheder omkring effekten af Pluvicto®.

Budgetkonsekvensen ved ibrugtagning af Pluvicto®

Ved vurdering af budgetkonsekvens ved ibrugtagning af Pluvicto® bør tidligere væsentlige budget-konsekvenser relateret til det ikke godkendte lægemiddel fra Curium tages med i betragtning.

Som lægemiddelvirksomhed i Danmark har vi en generel bekymring om, at man mod betaling eller i studieregi i udbredt grad anvender et ikke godkendt præparat, når der findes et EMA godkendt alternativ.

Vi ser frem til Medicinrådets endelige afgørelse vedr. Pluvicto® den 17. dec. 2025, og håber at en hårdt ramt patientgruppe også i Danmark får mulighed for at modtage en effektiv og godkendt behandling.

Med venlig hilsen,
Novartis Healthcare A/S

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21.11.2025

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	17.12.2025
Leverandør	Novartis
Lægemiddel	Pluvicto (lutetium-177)
Ansøgt indikation	Patienter med PSMA-positiv mCRPC som har modtaget behandling med en androgen receptor pathway inhibitor (ARPI) og henholdsvis 1 eller 2 taxaner.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel (radioaktivt lægemiddel)

Prisinformation

Amgros har forhandlet følgende pris på Pluvicto (lutetium-177):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Pluvicto	1.000 MBq/ml, (7,4 ml hætteglas)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Pluvicto, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Pluvicto er sammenlignet med cabazitaxel og standard of care (SOC) efter behandling med hhv. 1 og 2 taxaner. Der er ingen nuværende standard behandling efter behandling med 2 taxaner, men et eksperimentelt lægemiddel, Lu-177-PSMA-I&T, har tidligere været anvendt til patientpopulationen via udleveringstilladelse til den enkelte afdeling.

Pluvicto har tidligere været anvendt til behandling i Danmark i forbindelse med det kliniske studie, VISION, der danner grundlag for markedsføringstilladelsen af Pluvicto.

Tabel 2 viser lægemiddeludgiften for hhv. Pluvicto, cabazitaxel og Lu-177-PSMA-I&T for et behandlingsforløb. Pluvicto gives gennemsnitlig i hhv. 4,48 (efter 1 taxaner) og 4,36 doser (efter 2 taxaner), der er derfor opgjort en lægemiddeludgift for hhv. 4 og 5 doser, jf. Medicinrådets vurdering af lutetium-177 til behandling af PSMA-positiv metastatisk kastrationsresistent prostatakræft. Lu-177-PSMA-I&T antages at blive givet i samme antal doser som Pluvicto, og en pakning svarer til én dosering. Medicinrådet antager, at cabazitaxel gives gennemsnitlig i 7 doser, jf. Medicinrådets vurdering af lutetium-177 til behandling af PSMA-positiv metastatisk kastrationsresistent prostatakræft.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient pr. behandlingsforløb

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Pluvicto	1.000 MBq/ml, 7,4 ml hætteglas	7.400 MBq hver 6. uge i 4 serier, i.v. 7.400 MBq hver 6. uge i 5 serier, i.v.	[redacted]	[redacted]
Lu-177-PSMA-I&T	7.400 MBq, 1 hætteglas	7.400 MBq i 4 serier, i.v. 7.400 MBq i 5 serier, i.v.	[redacted]	[redacted]

Cabazitaxel "Sandoz"	10 mg/ml, 5 x 6 ml hætteglas	20 mg/m^2* hver 3. uge i 7 serier, i.v.	[redacted]	[redacted]

*BSA 1,9 m^2, jf. Medicinrådets vurdering af lutetium-177 til behandling af PSMA-positiv metastatisk kastrationsresistent prostatakræft

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til vurdering
England	Ikke anbefalet	Link til vurdering
Sverige	Ikke anbefalet	Link til vurdering

Opsummering

[redacted]

Application for the assessment of Pluvicto® (177Lu vipivotide tetraxetan) for PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

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

Contact information

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Tables and Figures

Abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ARPI	Androgen receptor pathway inhibition
BIC	Bayesian information criterion
BPI	Brief Pain Inventory
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
CRPC	Castration-resistant prostate cancer
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Danish Medicines Council

DSA	Deterministic sensitivity analysis
EMA	European Medicines Agency
EOT	End of treatment
EQ	EuroQoL
EQ-5D-5L	EuroQol 5-dimensions 5-level
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FE	Fixed effetcs
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
IPCW	Inverse probability of censoring weights
IV	Intravenously
KM	Kaplan Meier
LDH	Lactate dehydrogenase
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgren axis drugs
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NPH	Non-proportional hazard
NPR	National Patient Register
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PC	Prostate cancer
PFS	Progression-free survival
PH	Proportional hazards
PPP	Pharmacy purchasing price
PR	Partial response
PRO	Patient-reported outcome
PSA	Prostate-specific antigen (PSA) OR Probabilistic sensitivity analysis
PSMA	Prostate-specific membrane antigen
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RE	Random effects
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SC	Subcutaneously
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SRE	Skeletal-related event
SSE	Symptomatic skeletal event
TEAE	Treatment emergent adverse event
TTP	Time to progression
TTPP	Time to PSA progression

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Pluvicto®
Generic name	177Lu vipivotide tetraxetan
Therapeutic indication as defined by EMA	Pluvicto® in combination with androgen deprivation therapy (ADT), with or without androgen receptor pathway inhibition (ARPI), is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with ARPI and taxane-based chemotherapy.
Marketing authorization holder in Denmark	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
ATC code	V10XX05
Combination therapy and/or co-medication	Pluvicto® is used in combination with ADT (with or without ARPI).
(Expected) Date of EC approval	09-12-2022
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the Danish Medicines Council (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No.

Overview of the medicine	
	Is the product suitable for a joint Nordic assessment? No. If no, why not? Due to different treatment practices.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Administration: Intravenous Form: Solution for injection/infusion Strength: 7,400 MBq Pack: 1 dose/package

2. Summary table

Summary	
Indication relevant for the assessment	Pluvicto® in combination with ADT (with or without ARPI) is indicated for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy. In this application, the analyses will be made for two patient populations. 1) Post 1 taxane population: PSMA-positive mCRPC patients who have progressed after treatment with ARPI and docetaxel. 2) Post 2 taxanes population: PSMA-positive mCRPC patients who have progressed after treatment with ARPI, docetaxel, and cabazitaxel.
Dosage regiment and administration	The recommended dosage is 7,400 MBq intravenously (IV) every 6 weeks (±1 week) for up to a total of 6 doses, unless there is disease progression or unacceptable toxicity.
Choice of comparator	Cabazitaxel (Post 1 taxane population) and best supportive care (BSC)/standard of care (SoC) (Post 2 taxanes population). The comparators are in alignment with Danish clinical practice.
Prognosis with current treatment (comparator)	mCRPC is the terminal stage of prostate cancer that has spread to different parts of the body. The median overall survival (OS) has been reported as 13.6 months in patients receiving cabazitaxel (CARD) and 11.3 months in patients receiving BSC/SoC (VISION). Median OS has been reported as 15.3 months in patients receiving Pluvicto® (VISION).
Type of evidence for the clinical evaluation	Post 1 taxane population: Network meta-analysis (NMA). Post 2 taxanes population: Head-to-head comparison (sub-group).
Most important efficacy endpoints (Difference/gain compared to comparator)	In VISION, the median OS was 15.3 months (Pluvicto®) vs 11.3 months (BSC/SoC) (HR: 0.62, 95% CI 0.52–0.74; p<0.001), the median rPFS was 8.7 months vs 3.4 months (HR: 0.40, 99.2% CI 0.29–0.57; p<0.001), and the median time to the first symptomatic skeletal event (SSE) or death was 11.5 months vs 6.8 months (HR: 0.50, 95% CI 0.40–0.62; p<0.001). Post 1 taxane population: Based on the NMA, the OS HR was [redacted] (95% CI [redacted]), and the HR for rPFS was [redacted] (95% CI

Summary	
	[redacted]) when comparing Pluvicto® with cabazitaxel. This resulted in a modelled median OS of 18.4 months for Pluvicto® and 12.9 months for cabazitaxel. The modelled median rPFS was 6.9 months for Pluvicto® and 3.4 months for cabazitaxel. Post 2 taxanes population: In a post-hoc analysis of VISION patients who received at least two taxanes, the median OS was 13.6 months vs 10.6 months (HR: 0.73, 95% CI 0.53–0.99). Additionally, the median rPFS was 8.3 months vs 3.5 months (HR: 0.44, 95% CI 0.30–0.66), and the median time to first SSE was 10.2 months vs 5.6 months (HR: 0.43, 95% CI 0.30–0.61).
Most important serious adverse events for the intervention and comparator	No serious adverse events (SAEs) occurred with a frequency of at least 5% in either treatment arm (applies for both the Post 1 taxane population and the Post 2 taxanes population).
Impact on health-related quality of life (HRQoL)	Clinical documentation: EQ-5D and FACT-P (VISION) Health economic model: Similar impact for Pluvicto® and cabazitaxel. Better impact of Pluvicto® compared with BSC/SoC.
Type of economic analysis that is submitted	Type of analysis: Cost-utility analysis. Type of model: Partitioned survival model.
Data sources used to model the clinical effects	Post 1 taxane population: NMA (as previously described). Post 2 taxanes population: VISION study.
Data sources used to model the health-related quality of life	VISION study
Life years gained	Post 1 taxane population: 0.54 LY Post 2 taxanes population: 0.33 LY
QALYs gained	Post 1 taxane population: 0.42 QALY Post 2 taxanes population: 0.27 QALY
Incremental costs	Post 1 taxane population: DKK [redacted] Post 2 taxanes population: DKK [redacted]
ICER (DKK/QALY)	Post 1 taxane population: 1,301,927 DKK/QALY Post 2 taxanes population: 2,726,482 DKK/QALY
Uncertainty associated with the ICER estimate	Post 1 taxane population: OS HR between Pluvicto® vs cabazitaxel had the greatest uncertainty. Post 2 taxanes population: Parametric distribution for OS and number of Pluvicto® treatment cycles had greatest uncertainty.

Summary	
Number of eligible patients in Denmark	Incidence: 163 (Post 1 taxane population) and 151 new patients per year (Post 2 taxanes population). Prevalence: Not relevant due to the short life expectancy.
Budget impact (in year 5)	Post 1 taxane population: DKK 61,958,446 in year 5. Post 2 taxanes population: DKK 39,797,752 in year 5. (both based on PPP).

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

3.1 The medical condition

3.1.1 Pathophysiology of metastatic castration-resistant prostate cancer (mCRPC)

Metastatic castration-resistant prostate cancer (mCRPC) is the final, incurable form of prostate cancer (PC). PC originates in the gland cells of the prostate, where excessive and aberrant growth leads to the formation of tumours. These tumours can extend beyond prostate tissue and eventually metastasise to other parts of the body (1,2). The exact pathogenesis of mCRPC is not well characterised; however, as with most solid tumours, PC appears to develop through multistep carcinogenesis that involves the accumulation of damage to a cell's DNA, the transformation of the cell from normal to malignant, and subsequent hyperproliferation (3).

At diagnosis, 5–20% of patients present with metastatic disease (synchronous metastatic disease) (4,5). However, the majority of metastatic disease develops by progressing after radical local treatment of the primary tumour (metachronous metastatic disease). Typical sites of metastases are lymph nodes, bones, liver and lungs. Initially, disease progression tends to be androgen-dependent, meaning that the tumour will regress when androgen levels are reduced. At this stage, patients can be treated with androgen deprivation therapy (ADT) (6).

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is expressed in prostate tissue at modest levels. With PC progression, neoplastic and malignant prostate tissue have markedly elevated PSMA expression (7–9).

3.1.2 Clinical presentation and symptoms of mCRPC

Early PC has few or no noticeable symptoms (6,10). As the disease progresses, however, tumour tissue may interfere with local structures including the urethra, often resulting in urinary obstruction presenting as hesitation, weak urine stream, incomplete bladder emptying, and increased urgency and frequency of urination (10). With further disease progression, the symptoms become more severe, including urinary retention and loss of control and rectal obstruction (10,11).

If the condition has metastasised, patients may present with pain in other sites; bone pain is especially frequent. Additionally, patients often report fractures and spinal cord compression, and may also exhibit bone marrow failure and hypercalcaemia (10,12–14). In addition to experiencing urinary symptoms and pain, men with mCRPC might experience hormonal symptoms (e.g. hot flushing/night sweats, hair loss, and weight gain), fatigue, and sexual dysfunction (15).

3.1.3 Patient prognosis and prognosis with the current treatment options

Men with mCRPC face not only a decreased life expectancy compared to men without mCRPC but also many interfering symptoms (16). In a Danish population of patients newly diagnosed with metastatic PC (including mCRPC) between 2005 and 2009, the 5-year overall mortality was 73.2% (95% CI 71.4% to 75%), while the 5-year metastatic PC-specific mortality was 56.8% (95% CI 54.8% to 58.8%) (4). Additionally, the high rate of symptomatic skeletal events (SSEs), in clinical trials defined by spinal cord compression, pathological fracture, radiation to bone, and surgery to bone among men with mCRPC, leads to further health-related quality of life (HRQoL) decrements and increased occurrence of pain as well as higher pain intensity (16). Finally, elevated levels of PSMA expression are associated with even poorer clinical outcomes, including lower survival rates (17,18).

In contrast to early localized PC where patients can stay progression-free for years with available treatment options, progression is generally faster and the HRQoL worse with the current therapeutics available to treat mCRPC (6,19). For the two comparators included in this application (described in Section 3.5), the median overall survival (OS) is reported as 13.6 months for men with mCRPC treated with cabazitaxel, and 11.3 months when treated with best supportive care (BSC)/standard of care (SoC) (20,21).

3.1.4 Influence on patient functioning and health-related quality of life

The symptoms associated with mCRPC (as described above) can impact a patient's physical, emotional, and social well-being and can interfere with daily life (15). Additionally, the patient may suffer from the effect of emotional distress, depression, and anxiety (15). Patients with mCRPC in general are impacted by several factors, including watery eyes, decreased appetite, shortness of breath, swelling, cough, and numbness (22). Among Danish patients treated for mCRPC, however, fatigue and pain have especially been shown to interfere with daily activities (22). The findings in the Danish population are in line with findings from other European countries showing that

men with mCRPC are heavily impacted in their daily life by experiencing pain, discomfort, anxiety, and depression (23,24).

3.2 Patient population

The relevant Danish patient population for this application comprises adults with PSMA-positive mCRPC. To estimate more precisely the annual incidence and prevalence of patients over the past 5 years, data from the Danish registries were applied. Specifically, patients with mCRPC were identified in the National Patient Register (NPR) as individuals with minimum one registration of the ICD-10 diagnosis code for CRPC (DC619Z). In addition, mCRPC was conditioned on at least one registration of a diagnosis code (in NPR), a supplementary code (in NPR) or a SNOMED/Pathology code (in the Pathology Registry) indicating metastatic disease. For the incident population, a wash out period was applied, implying that individuals with a registration of PC in the NPR before 2020 were excluded from the incident population.

Since PSMA data were not available in the registries, the population could not be restricted to include PSMA-positive patients only. In the phase III clinical trial of Pluvicto®, 86.6% of the population were PSMA-positive (20). Hence, this proportion was used to estimate the relevant patient population in the table below.

Table 1 Incidence and prevalence of PSMA-positive mCRPC patients in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	580	543	695	455	365
Prevalence in Denmark	1,266	1,350	1,554	1,494	1,366
Global prevalence*	N/A	N/A	N/A	N/A	N/A

In accordance with the therapeutic indication as defined by the European Medicines Agency (EMA), the patient population eligible for Pluvicto® includes patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition (ARPI) and taxane-based chemotherapy (25). In Danish clinical practice, both of these therapies are recommended in the treatment of mCRPC (described in Section 3.3) (26).

In this application, two patient populations eligible for treatment with Pluvicto® are included (Figure 1). The first population consists of patients who experience disease progression following treatment with ARPI (abiraterone or enzalutamide) and *one taxane-based chemotherapy* (docetaxel). For these patients, Pluvicto® offers an alternative treatment to cabazitaxel, which is not taxane-based. Throughout the application, this patient population will be referred to as the Post 1 taxane population. In addition, this application includes a population of patients who experience disease progression following treatment with ARPI and *two taxane-based chemotherapies* (docetaxel and cabazitaxel). This patient population will be referred to as the Post 2

taxanes population. The inclusion of two patient populations is aligned with previous feedback from the Danish Medicines Council (DMC).

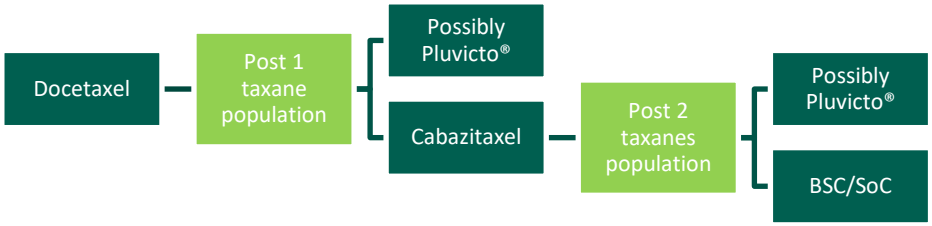

Figure 1 Illustration of patient populations included in the application

To estimate the size of these two patient populations in Denmark, data from the registries were used (i.e., the NPR and the Hospital Medicines Registry). The Post 1 taxane population was defined as the number of individuals who initiated treatment with cabazitaxel. The Post 2 taxanes population was defined as the number of individuals who stopped treatment with cabazitaxel (defined as more than 6 weeks with no registered cabazitaxel-treatment) and initiated SoC afterwards. Registration of treatment with cabazitaxel was defined by treatment code BWHA263 (in the NPR) or ATC-code L01CD04 (in the Hospital Medicines Registry). The expected number of patients per year who are eligible for treatment with Pluvicto® in the coming years was assumed to be the average number of patients per year in the prior 5 years.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years					
Post 1 taxane population	163	163	163	163	163
Post 2 taxanes population	151	151	151	151	151

3.3 Current treatment options

As mCRPC is incurable, the treatment of patients aims to be life-prolonging and palliative (26). The selection of treatment for mCRPC is multifactorial and generally depends on several factors, including the response to and pace of progression on any previous treatments (6,26).

In Denmark, patients with mCRPC are treated with ADT, including either pharmacologic or surgical castration to decrease testosterone levels and thereby inhibit tumour growth (26). In addition to ADT, mCRPC patients may be treated with ARPIs (abiraterone, enzalutamide), taxanes (docetaxel, cabazitaxel) radium-233, and/or olaparib (26). Most Danish patients follow one of three scenarios for first-line treatment:

- If not previously treated with ARPIs: Treatment with ARPI or/and docetaxel.
- If previously treated with ARPIs: Treatment with docetaxel.
- If previously treated with ARPIs and docetaxel: Treatment with cabazitaxel (27).

In general, it is recommended that patients with no or few symptoms and a performance status of 0-1 (i.e. patients who are most well-functioning) are treated with ARPI, whereas patients eligible for chemotherapy (often symptomatic patients with a performance status of 0-2, or patients who have experienced aggressive progression during ADT <12 months and/or visceral metastases) should be treated with docetaxel. If the patient progresses during treatment with docetaxel, cabazitaxel can be used as an alternative treatment (26).

Radium-223 can be used if the patient has symptomatic bone metastases, a limited number of visceral metastases, and if a minimum of two other treatments for mCRPC have been tried. For patients with BRCA1/2 mutations, olaparib can be used if chemotherapy is not indicated (26).

After these treatment options are exhausted, subsequent treatments in Danish clinical practice include radiation therapy and palliative care – for example, using morphine, prednisolone, dexamethasone, and denosumab (confirmed by the clinical expert).

3.4 The intervention

The VISION trial investigated the use of Pluvicto® + BSC/SoC compared with BSC/SoC alone (20). For simplicity, any reference to the Pluvicto® arm in the application implicitly includes the concurrent treatment with BSC/SoC. The active moiety of Pluvicto® is the radionuclide lutetium-177, which is linked to a small-molecule ligand that targets and binds with high affinity to PSMA. Upon binding to PSMA-expressing cancer cells, the beta-minus emission from lutetium-177 delivers therapeutic radiation to the targeted cell as well as to surrounding cells, and induces DNA damage which can lead to cell death (25).

Overview of intervention	Pluvicto®
Indication relevant for the assessment	Pluvicto® in combination with ADT (with or without ARPI) is indicated for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy (25).
ATMP	N/A
Method of administration	Pluvicto® is a ready-to-use solution for injection/infusion, for single use only (25).
Dosing	The recommended treatment regimen of Pluvicto® is 7400 MBq IV every 6 weeks (±1 week) (25).

Overview of intervention	Pluvicto®
Dosing in the health economic model (including relative dose intensity)	Based on the VISION trial, the data applied in the health economic model include administration of 7400 MBq IV every 6 weeks for [redacted] cycles.
Should the medicine be administered with other medicines?	Pluvicto® can be administered in combination with ADT (with or without ARPI), but no co-medication is necessary (25).
Treatment duration / criteria for end of treatment	May be administered for up to 6 cycles, unless there is disease progression or unacceptable toxicity (25).
Necessary monitoring, both during administration and during the treatment period	According to the Summary of Product Characteristics (SmPC), laboratory tests (haematology, kidney function, liver function) should be performed before and during treatment (25).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Patients eligible for Pluvicto® should be identified for treatment by PSMA imaging (25).
Package size(s)	Pluvicto® is available in a package with one vial of 1000 MBq/ml solution for injection (25).

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

In Danish clinical practice, Pluvicto® is anticipated for treatment of PSMA-positive mCRPC patients who either progress while treated with the first taxane-based chemotherapy (docetaxel) or progress while treated with the second taxane-based chemotherapy (docetaxel and cabazitaxel). In that respect, Pluvicto® will be an additional treatment option in the treatment algorithm and will hence extend the physicians' choice of medication towards PSMA-positive mCRPC taking the patient's characteristics and comorbidities into account. Especially for patients in the Post 1 taxane population, Pluvicto® will extend the number of treatment options available for the individual patient since the treatment will be available earlier in treatment algorithm as compared to the Post 2 taxanes population. Additionally, Pluvicto® results in a higher gain in life years and QALY if used for patients in the Post 1 taxane population compared to the Post 2 taxanes population (results described in section 12).

3.5 Choice of comparator(s)

In this application, the comparator will depend on the investigated patient population. However, comparators for each of the two patient populations are aligned with Danish clinical practice and with previous feedback from the DMC.

For the Post 1 taxane population, i.e. patients who have progressed after ARPI and docetaxel, the comparator is cabazitaxel (see Figure 1 and the table below). Since no head-to-head studies have compared Pluvicto® with cabazitaxel, a network meta-analysis (NMA) has been conducted for this population (described in Section 7).

Overview of comparator	Cabazitaxel
Generic name	Cabazitaxel
ATC code	L01CD04
Mechanism of action	Cabazitaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells. Cabazitaxel binds to tubulin and promotes the assembly of tubulin into microtubules while simultaneously inhibiting their disassembly. This leads to the stabilisation of microtubules, which results in the inhibition of mitotic and interphase cellular functions (28).
Method of administration	1-hour intravenous infusion (28).
Dosing	The recommended dose is 25 mg/m^2 every 3 weeks (28). In Danish clinical practice (confirmed by a clinical expert), the applied dosing is 20 mg/m^2 every 3 weeks.
Dosing in the health economic model (including relative dose intensity)	The dosing used in Danish clinical practice is applied, i.e. 20 mg/m^2 every 3 weeks (confirmed by a clinical expert).
Should the medicine be administered with other medicines?	Cabazitaxel should be administered in combination with oral prednisone or prednisolone 10 mg administered daily throughout treatment (28).
Treatment duration/ criteria for end of treatment	Cabazitaxel should be administered for 6-10 cycles (29). In Danish clinical practice, the average number of cycles is 6 (confirmed by a clinical expert).
Need for diagnostics or other tests (i.e. companion diagnostics)	None.
Package size(s)	Cabazitaxel is available in the following packages: - 20 mg/ml in 1 x 3 ml vial - 10 mg/ml in 1 x 6 ml vial - 10 mg/ml in 5 x 6 ml vials

For the Post 2 taxanes population, i.e. patients who have progressed after ARPI, docetaxel, and cabazitaxel, the comparator is BSC/SoC. In the VISION trial, Pluvicto® was compared directly with BSC/SoC, defined in this case as available care for the eligible

patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs (NAADs) (i.e. ARPIs such as enzalutamide or abiraterone) were allowed. Cytotoxic therapy, systemic radioisotopes (e.g. radium-223), immunotherapy, or drugs that were investigational when the trial was designed (e.g. olaparib) were not included as BSC/SoC (20). In the health economic analysis of this application, BSC/SoC is defined as dexamethasone (1 mg orally once per day), morphine (10 mg orally once per day) or denosumab (120 mg subcutaneously once every fourth week) (validated by clinical expert. Details are listed in section 11).

3.6 Cost-effectiveness of the comparator(s)

The DMC has not evaluated the cost-effectiveness of the included comparators (cabazitaxel and BSC/SoC) in treating patients with mCRPC.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The following efficacy outcomes are considered relevant and necessary to evaluate the effect of Pluvicto® versus cabazitaxel and BSC/SoC (also presented in the table below):

- Overall survival (OS)
- Radiographic progression-free survival (rPFS)
- Symptomatic skeletal events (SSEs)
- Health-related quality of life (HRQoL)

For the Post 1 taxane population, the efficacy of Pluvicto® versus cabazitaxel, including OS and rPFS, was evaluated in an NMA with six studies: VISION (20), CARD (21), TROPIC (30), AFFIRM (31), Sun et al. 2016 (32), and COU-AA-301 (33). Additionally, a sensitivity analysis in which a seventh study (TheraP (34,35)) was included was conducted (further described in Section 7). For the Post 2 taxanes population, the efficacy of Pluvicto® versus BSC/SoC, including OS, rPFS, SSE, and HRQoL, was evaluated in the VISION study.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS)			
VISION (20)	Data cutoff: 27 January 2021 Median follow-up: 20.9 months	The time (in months) from the date of randomisation to the date of death due to any cause.	If the patient is not known to have died, then OS will be censored. The censoring date is the date of the last study visit or last contact, or the date the patient was last

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			known to be alive, whichever is latest.
CARD (21)	Data cutoff: 27 March 2019 Median follow-up: 9.2 months	The time (in months) from the date of randomisation to the date of death due to any cause.	In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive or at the cutoff date, whichever came first.
TROPIC (30)	Data cutoff: 25 September 2009 Median follow-up: 12.8 months	The time from the date of randomisation to the date of death due to any cause.	In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive or at the cutoff date, whichever came first.
AFFIRM (31)	Data cutoff: 25 September 2011 Median follow-up: 14.4 months	The time from the date of randomisation to the date of death due to any cause.	The duration of OS was right-censored for participants who were lost to follow-up because of randomisation or who were not known to have died at the data analysis cutoff date (this includes participants who were known to have died after the analysis cutoff date).
Sun et al. 2016 (32)	Clinical cutoff: 30 April 2014 Follow-up: 12.9 months	The time from the date of randomisation to the date of death from any cause.	NR
COU-AA-301 (33)	Data cutoff: 20 September 2010 Median follow-up: 20.2 months	The time from the date of randomisation to the date of death from any cause.	Patients who were not deceased at the time of analysis were censored on the last date the patient was known to be alive or was lost to follow-up.
TheraP (34)	Data cutoff: 31 December 2021 Median follow-up: 35.7 months	Time from registration to death from any cause or last known follow-up alive.	NR
Radiographic progression-free survival (rPFS)			

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
VISION (20)	Data cutoff: 27 January 2021 Median follow-up: 20.9 months	The time (in months) from the date of randomisation to the date of radiographic disease progression, based on the central review assessment per the PCWG3 criteria or death due to any cause.	Patients without disease progression were censored at the date of their last evaluable scan. Patients with no evaluable scans were censored at the date of randomisation. Patients with two or more consecutive missed scans immediately before disease progression or death were censored at the date of their last evaluable scan before the two missed scans.
CARD (21)	Data cutoff: 27 March 2019 Median follow-up: 9.2 months	The time (in months) from the date of randomisation to the occurrence of either objective tumour progression, progression of bone lesions, or death due to any cause.	Assessed using RECIST 1.1 and PCWG2 criteria. If an imaging-based progression event or death did not occur during the trial, then the data were censored at the last tumour assessment or at the cutoff date, whichever occurred first.
AFFIRM (31)	Data cutoff: 25 September 2011 Median follow-up: 14.4 months	The time from the date of randomisation to the earliest evidence of radiographic progression or death due to any cause.	Assessment for objective disease progression at scheduled visits using PCWG2 guidelines. rPFS was defined by RECIST 1.1. Participants who did not reach the endpoint were right-censored at their last assessment.
COU-AA-301 (33)	Data cutoff: 20 September 2010 Median follow-up: 20.2 months	The time from the date of randomisation to the date of radiographically documented disease progression or death.	rPFS was defined by modified RECIST criteria as soft-tissue disease progression.
TheraP (35)	Data cutoff: 20 July 2020 Median follow-up: 18.4 months	The time from randomisation to the date of first evidence of radiographic progression or the date of last known follow-up without radiographic progression	rPFS was assessed using PCWG3 criteria for bone lesions and RECIST 1.1 for soft tissue lesions.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Symptomatic skeletal event (SSE)			
VISION (20)	Data cutoff: 27 January 2021 Median follow-up: 20.9 months	The time from the date of randomisation to the date of the first new SSE or death from any cause, whichever occurs first.	SSEs include symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention, and requirement for radiation therapy to relieve bone pain. Data were collected up through the end of treatment (EOT) visit. The censoring date was the date of the last study visit.
Health-related quality of life (HRQoL)			
VISION (20,36)	Data cutoff: 27 January 2021 Median follow-up: 20.9 months	Reported using the EuroQol 5-dimensions 5-level (EQ-5D-5L) questionnaire and the Functional Assessment of Cancer Therapy – Prostate (FACT-P).	Patients without an event were censored at the date of the last patient-reported outcome (PRO) assessment; patients without evaluable data were censored at randomisation. Participants need to complete all items for EQ-5D-5L and more than 80% of items for FACT-P to be considered evaluable. No methods for imputation of missing data were prespecified.

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

Validity of outcomes

The DMC has previously assessed OS, rPFS, and HRQoL as relevant outcomes among patients with mCRPC (37). OS is considered the gold standard endpoint in phase III trials. OS is clearly defined and simple to measure, and it translates into clinical benefit to patients (38). Additionally, rPFS is an endpoint commonly used in prostate cancer trials, and PCWG3 guidelines recommend rPFS as an appropriate measure to consider progression of mCRPC (39).

Regarding SSEs, PCWG3 advises reporting those that include only symptomatic events of clear significance, in contrast to skeletal-related events (SREs), which also include asymptomatic fractures (39). Finally, the importance of HRQoL measured through validated instruments has been recognized by PCWG3 (39).

4. Health economic analysis

The health economic analysis was a cost-utility analysis assessing the cost per quality-adjusted life year (QALY) of treating PSMA-positive mCRPC patients. The analysis included two comparisons informed by VISION and an NMA, as described in section 3.5. A Danish clinical expert was consulted to obtain and validate clinical inputs for the model, to ensure that the health economic analysis accurately reflects Danish clinical practice. In alignment with VISION, the model estimates the costs and health benefits for patients treated with Pluvicto® and cabazitaxel, both administered alongside BSC/SoC. Therefore, any reference to Pluvicto® and cabazitaxel in the application implicitly includes the concurrent treatment of BSC/SoC.

4.1 Model structure

The model was a partitioned survival model with three health states: progression-free, progressed, and dead. A partitioned survival model structure, which is commonly used in oncology modelling, was applied. This approach was also applied in previous NICE appraisals in mCRPC (40–42). The model structure assumes patients' health will not improve, reflecting their progressive condition. Using the partitioned survival approach enables modelling of OS and rPFS based on observed events, accurately replicating trial data and reflecting disease progression and survival profiles for patients treated with Pluvicto® versus comparator therapy.

The model estimated the proportion of patients in each health state at each time point. The probability of patients residing in each health state for any given time point was calculated by the methods explained below:

- rPFS: Probability a patient has not yet progressed and is still alive, calculated from the rPFS curve.
- Progressed state: (Probability a patient is alive, as calculated from the OS curve) – (probability a patient has not yet progressed and is still alive, as calculated from the PFS curve).
- Death: 1 – Probability a patient is alive, as calculated from the OS curve.

4.1.1 Patient flow in the model

Patients entered the model upon starting one of the included treatments. Each week, they might either remain progression free, experience disease progression, or die. In the progression-free state, patients received Pluvicto®, cabazitaxel, or BSC/SoC alone. Once patients progressed, they could receive subsequent lines of anticancer therapy and supportive care (see section 3.3). The distribution of patients in each health state over the model time horizon was based on the rPFS and OS curves.

SSEs are a significant cause of morbidity in mCRPC patients and can present in various ways, such as radiation to bone, a pathological fracture, surgery needed to bone, and spinal cord compression (43). The impact of SSEs was included in the model via the cost of managing each type of event.

4.2 Model features

Table 4 presents a summary of the model features. A limited societal perspective was applied in accordance with DMC guidelines, and costs and effects were discounted by 3.5% in years 0–35 (44). The cycle length used in the model was 1 week, and the time horizon in the base case was 10 years. Based on extrapolations of the survival curve of OS from VISION, all patients in the model are expected to die within 10 years (Appendix D). This was confirmed by the clinical expert during a validation session. The 1-week cycle length was chosen to ensure precise tracking of the number of patients in each health state over time in the early years of the model. The cycle length is relatively short compared to the 10-year time horizon. Therefore, no half-cycle correction is applied (45).

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Patients with PSMA-positive mCRPC. Two populations were included as defined in section 3.2.	The patient populations were specified based on initial dialogues with the expert committee and the DMC.
Perspective	Limited societal perspective.	According to DMC guidelines.
Time horizon	10 years in the base case.	To capture all health benefits and costs in line with DMC guidelines. Validated by Danish clinical expert.
Cycle length	One week.	Ensures precise tracking of the number of patients in each health state over time in the early years of the model.
Half-cycle correction	Not in the base case.	N/A due to short cycle length.
Discount rate	3.5%	The DMC applies a discount rate of 3.5% for years 0–35.
Intervention	Pluvicto® with BSC/SoC. Patients receive 7,400 MBq Pluvicto® IV every 6 weeks, for up to a total of 6 doses, unless there is disease progression or unacceptable toxicity.	In accordance with Pluvicto® SmPC.
Comparator(s)	Cabazitaxel (Post 1 taxane population) and BSC/SoC (Post 2 taxanes population).	In accordance with current SoC in Denmark, as described in section 3.3.
Outcomes	OS, rPFS, SSEs, and HRQoL and adverse events (AEs).	OS and rPFS were applied to account for increased mortality and the progressive nature of mCRPC. SSEs and

Model features	Description	Justification
		AEs were included to assess the costs associated with managing these events. HRQoL was included to account for in quality of life associated with treatment.

5. Overview of literature

5.1 Literature used for the clinical assessment

As described in Section 3.5, no head-to-head studies exist for Pluvicto® compared with cabazitaxel. Therefore, a systematic literature review (SLR) was conducted to assess efficacy in the Post 1 taxane population (described in Appendix H). Based on the SLR, six studies were included in an NMA (20,21,30–33). Additionally, a sensitivity analysis in which a seventh study was included in the NMA was conducted (34,35).

Since head-to-head data for Pluvicto® compared with BSC/SoC are available from VISION, these data are the most relevant for the assessment of the efficacy and safety of Pluvicto® in the Post 2 taxanes population. Thus, no SLR was conducted to assess efficacy in the Post 2 taxanes population.

All relevant literature included in this application to evaluate the efficacy and safety of Pluvicto® compared to cabazitaxel and BSC/SoC, respectively, is presented in Table 5.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Sartor O, de Bono J, Kim N, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021;385(12):1091-1103 (20). Data on file. Unpublished data, 2024: Post hoc subgroup analysis report (46). Data on file. Unpublished data, 2002: Clinical Study Report (47). Fizazi K, Herrmann K, Krause BJ, Rahbar K, Chi KN, Morris MJ, et al. Health-related quality of life and pain outcomes with [177Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(6):597-610 (36).	VISION	NCT03511664	Start: 29 May 2018 Completion (actual): 14 December 2023 Data cutoff for final analysis: 27 January 2021	Pluvicto® compared to cabazitaxel (Post 1 taxane population) Pluvicto® compared to BSC/SoC (Post 2 taxanes population)
de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med. 2019;381(26):2506-2518 (21).	CARD	NCT02485691	Start: 9 November 2015 Completion: 27 March 2019 (final data collection date for primary measure) Data cutoff: 27 March 2019	Pluvicto® compared to cabazitaxel (Post 1 taxane population)
de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-1154 (30).	TROPIC	NCT00417079	Start: 2 January 2007 Completion: 25 September 2009 (final data collection date for final analysis) Data cutoff: 25 September 2009	Pluvicto® compared to cabazitaxel (Post 1 taxane population)

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983-992 (33).	COU-AA-301	NCT00638690	Start: 8 May 2008 Primary completion: August 2010 Study completion: October 2010 Data cutoff: 10 September 2010	Pluvicto® compared to cabazitaxel (Post 1 taxane population)
Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97 (31).	AFFIRM	NCT00974311	Start: 30 September 2009 Completion: 2 November 2017 Data cutoff: 25 September 2011	Pluvicto® compared to cabazitaxel (Post 1 taxane population)
Sun Y, Zou Q, Sun Z, Changlin L, Du C, Chen Z, et al. Abiraterone acetate for metastatic castration-resistant prostate cancer after docetaxel failure: A randomized, double-blind, placebo-controlled phase 3 bridging study. Int J Urol. 2016;23(5):404-411 (32).	Sun et al.	NCT01695135	Start: 9 August 2012 Primary completion: 20 June 2014 Study completion: 8 May 2018 Data cutoff: 30 April 2014 (clinical cutoff date for final analysis)	Pluvicto® compared to cabazitaxel (Post 1 taxane population)
Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet. 2021;397(10276):797-804 (35). Hofman MS, Emmett L, Sandhu S, Iravani A, Buteau JP, Joshua AM, et al. Overall survival with [177Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-	TheraP	NCT03392428	Start: 29 January 2018 Primary completion: 31 December 2019 Study completion: 31 December 2021 Data cutoff (primary analysis): 20 July 2020	Several factors make the TheraP study insufficient to provide robust evidence to support a direct head-to-head comparison between 177Lu-PSMA-617 and cabazitaxel for the indication of relevance to this submission, e.g. that the compound investigated was not

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial. Lancet Oncology. 2024;25(1):99-107 (34).			Data cutoff (additional analyses): 31 December 2021	Pluvicto®. Hence, TheraP was included as a sensitivity analysis of Pluvicto® compared to cabazitaxel (Post 1 taxane population) (see details in section 6.1.11)

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

The HRQoL data were obtained solely from the VISION study. Thus, a literature search was not conducted.

Table 6 Relevant literature included for (documentation of) health-related quality of life (see Section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economic model

The health economic analysis was informed by VISION, the conducted NMA, input from clinical experts, DMC documents and DRG tariffs. Thus, no literature search was conducted.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of Pluvicto® compared to cabazitaxel for PSMA-positive mCRPC patients (Post 1 taxane population)

6.1.1 Description of the VISION population used for the demonstration of efficacy in the Post 1 taxane population

As previously described, an NMA was conducted to evaluate the efficacy of Pluvicto® compared to cabazitaxel in PSMA-positive mCRPC patients. This comparison is relevant for the Post 1 taxane population. The full VISION population was included in the NMA although the population in a post hoc analysis was stratified by the number of prior taxane regimens (maximum 1 taxane versus minimum 2 taxanes). There are several reasons for this choice.

First, the comparator arm was restricted to patients who received ARPI only in the NMA. This was done to facilitate the network in the analysis. When restricting the comparator arm, 146 patients were included in the analysis of OS and 107 patients were included in the analysis of rPFS. A reduced population would compromise the randomization and lead to interpretation issues. Additionally, stratification by the number of previous taxane regimens would limit the population even more and increase the uncertainty in the NMA. Table 8 presents an overview of the patient numbers in the full VISION population, the NMA population and the VISION post hoc population.

Second, when comparing the available baseline characteristics of the population used in the NMA and the subgroup population from the VISION post hoc analysis, they appear similar. Differences may be caused by the smaller patient number, especially in the ARPI arm in the NMA population.

Finally, when comparing the OS and rPFS results for the population included in the NMA and the subgroup population from the VISION post hoc analysis, the results are similar and with overlapping confidence intervals. This especially applies for the OS results. For the rPFS results, the HR for the NMA population is higher compared to the post hoc population, which might have led to an underestimation of the efficacy of Pluvicto® in the NMA. Results for the post hoc subgroup population are presented in Table 73 and results for the population included in the NMA are presented in Table 74.

Based on the above reasons and following thorough discussion with involved statisticians, the full VISION population was included in the NMA with a restriction on the comparator arm (ARPI only).

Table 8 Overview of VISION populations relevant for the comparison of Pluvicto® versus cabazitaxel

Population	Number of patients: OS			Number of patients: rPFS		
	Total	Intervention	Comparator	Total	Intervention	Comparator
Full VISION population	831	551	280	581	385	196
NMA population (full population with restriction on comparator arm)	697	551	146	492	385	107
VISION post hoc population (maximum of one prior taxane)	507	342	165	334	224	110

6.1.2 Relevant studies

The following trials were included in the NMA to demonstrate efficacy of Pluvicto® compared to cabazitaxel: VISION, CARD, TROPIC, AFFIRM, Sun et al. (2016), and COU-AA-301 (20,21,30–33). Additionally, the study TheraP was included in a sensitivity analysis of the NMA.

Table 9 presents an overview of the included studies. The main characteristics of the studies are described in detail in Appendix A.

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
VISION, NCT03511664 Sartor et al. 2021 (20) Fizazi et al. 2023 (36)	International, prospective, open-label, multicentre, randomised, phase III trial	The study consisted of, for each participant, a screening period (up to 28 days before starting randomised treatment), a treatment period (6–10 months), and a follow-up period (up to 24 months). Total duration of study was approximately 38 months.	Adults with mCRPC and at least one metastatic lesion on baseline CT, MRI, or bone-scan imaging.	177Lu-PSMA-617 (Pluvicto®) (7.4 GBq [+/- 10%]) administered IV once every 6 weeks (+/- 1 week) for a maximum of 6 cycles and BSC/SoC as defined by the local investigator.	BSC/SoC alone as defined by the local investigator.	Up to 32 months: rPFS, overall response rate, disease control rate, time to first SSE, PFS, time to worsening in Brief Pain Inventory (BPI)-SF Pain Intensity Scale, time to improvement after worsening in BPI-SF Pain Intensity Scale, time to worsening in BPI-SF Pain Interference Scale, time to improvement after worsening in BPI-SF Pain Interference Scale, time to worsening in BPI-SF Worst Pain Intensity Scale, time to worsening in FACT-P total score, time to worsening in EQ-5D-5L utility score. Up to 32 months and up to 66 months: OS. Until 30-day safety follow-up, assessed up to 66 months: treatment emergent AEs (TEAEs). Until 30-day safety follow-up, assessed up to 32 months: percentage of participants achieving PSA response, PSA80 response, best percentage change from baseline in alkaline phosphatase (ALP) level, best percentage change from baseline in lactate dehydrogenase (LDH) level, number of participants hospitalized as in-patient, duration of time in hospital following 177Lu-PSMA-617 administration, concomitant drug use, therapeutic interventions, best percentage change from baseline in PSA level. From first evidence of complete response (CR) or partial response (PR) until progression or death, assessed up to 32 months: duration of response. From first PSA response until 30-day safety follow-up, assessed up to 32 months: duration of PSA response. Baseline, cycle 2 to cycle 13, EOT: change from baseline in BPI-SF Pain Intensity Scale, change from baseline in BPI-SF Pain Interference Scale, change from baseline in FACT-P total score, change from baseline in EQ-5D-5L utility score, change from baseline in EQ-5D-5L EQ-VAS.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
CARD, NCT02485691 de Wit et al. 2019 (21)	Multicentre, randomised, open-label, phase IV trial	Patients were screened 4 weeks before randomisation for eligibility and baseline measurements. The duration of the study per participant was approximately 2 years.	Patients with mCRPC who were previously treated with docetaxel and who had disease progression while receiving androgen receptor (AR)-targeted therapy within 12 months of AR treatment initiation.	Cabazitaxel (25 mg/m^2 IV every 3 weeks) and prednisone (10 mg orally daily) and granulocyte colony-simulation factor.	Enzalutamide (160 mg orally once daily) or abiraterone (1000 mg orally once daily) and prednisone (5 mg orally twice daily).	Until progression, death, or data cutoff: rPFS, PFS, percentage of participants with overall objective tumour response, rPFS in participants with presence and absence of biomarker. To death or data cutoff: OS. To PSA response, death, or data cutoff: percentage of participants with PSA response. Until PSA progression, death, or data cutoff: time to PSA progression (TTPP). From first response to first documented tumour progression, death, or data cutoff: duration of tumour response. Until pain progression, first further anticancer therapy, or data cutoff percentage of participants achieving pain response assessed using BPI-SD. Until pain progression or data cutoff: time to pain progression. Until occurrence of first SSE or data cutoff: number of SSEs, time to SSE. Baseline, at day 1 of each of the following cycles: 2, 3, 4, 5, 6, 7, and 8, and at EOT: change in FACT-P, change in EQ-5D-5L Utility Single Index and VAS.
TROPIC de Bono et al. 2010 (30)	Randomised, open-label multicentre, multinational phase III trial	Patients were treated until disease progression, death, or unacceptable toxicity, or for a maximum of 10 cycles. Patients had long-term follow-up for a maximum of up to 2 years.	Patients with mCRPC who received hormone therapy, but whose disease progressed during or after treatment with a docetaxel-containing regimen.	Cabazitaxel (25 mg/m^2 IV every 3 weeks) and prednisone (10 mg orally daily).	Mitoxantrone (12 mg/m^2 IV every 3 weeks) and prednisone (10 mg orally daily).	Up to 104 weeks: OS, time to PFS, time to tumour progression, PSA response, time to pain progression, pain response . At screening at day 1 of every treatment cycle, up to 104 weeks: time to PSA.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
AFFIRM, NCT00974311 Scher et al. 2012 (31)	Multinational, randomised, double-blind (DB), placebo-controlled phase III trial	Maximum duration: Up to 101 months.	Patients with mCRPC after chemotherapy, of which at least one contained docetaxel.	Enzalutamide (160 mg orally daily as four 40 mg capsules).	Placebo (orally daily as four capsules).	Up to 101 months: OS. Up to 24 months: rPFS, time to first SSE, percentage of participants who were responders for FACT-P, percentage of participants with pain palliation, percentage of participants with PSA response, percentage of participants with soft-tissue objective response, percentage of participants with circulating tumour cell (CTC) conversion. Baseline and at every study visit from week 12 up to 24 months: time to PSA progression. Week 13: EQ-5D Scale. Baseline, up to safety follow-up visit or unscheduled visit or initiation of another antineoplastic therapy, up to 101 months: number of participants with TEAEs and serious AEs (SAEs), number of participants with clinically significant changes in vital signs, number of participants with grade 3/4 post-baseline laboratory toxicity. Baseline up to the end of DB phase or unscheduled visit, up to 24 months: number of participants with newly clinically significant abnormal finding in ECG.
Sun et al. (2016), NCT01695135 (32)	Double-blind, phase III trial	A double-blind treatment phase (28-day cycles until disease progression/unacceptable toxicity) was followed by a follow-up phase up to month 60, depending on survival status.	Patients with histologically/cytologically confirmed mCRPC who had failed previous docetaxel-containing chemotherapy; documented disease progression in soft tissue or bone despite castrate levels of serum	Abiraterone (1000 mg [4 x 250 mg tablets] taken orally once daily) and prednisone (5 mg tablet taken orally twice daily).	Placebo (4 tablets taken orally once daily) and prednisone (5 mg tablet taken orally twice daily).	Up to 1.8 years: TTPP. Up to approximately 3.8 years: OS, percentage of patients who achieved PSA response, objective response rate (ORR), change in FACT-P score, time to pain progression, percentage of participants experiencing pain palliation, change in BFI score.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
			testosterone (<50 ng/dL); and ≤2 ECOG PS score.			
COU-AA-301, NCT00638690 Fizazi et al. 2012 (33)	Phase III, multinational, double-blind, randomised placebo-controlled trial	Maximum duration: Up to 60 months.	Patients with mCRPC who were previously treated with docetaxel and a maximum of two previous chemotherapies.	Abiraterone (four 250 mg tablets once daily) and prednisone/ prednisolone (5 mg twice daily).	Placebo (four tablets once daily) and prednisone/pre dnisolone (5 mg twice daily).	Up to 60 months: OS. Up to 11 months: rPFS. Up to 12 months: number of patients achieving a PSA decline >=50%, time to PSA progression according to PSAWG group criteria.
TheraP, NCT03392428 Hofman et al. 2021 (35) Hofman et al. 2024 (34)	Open-label, randomised, 2-arm, multicentre phase II trial	The time frame of the trial was on average 4 years.	Participants were men with mCRPC progressing after docetaxel treatment.	6-8.5GBq of 177Lu-PSMA617 by IV injection once every 6 weeks until progressive disease, prohibitive toxicity or a maximum of 6 cycles.	20mg/m^2 Cabazitaxel by IV infusion once every 3 weeks until progressive disease, prohibitive toxicity or a maximum of 10 cycles + prednisolone 10mg orally per day for the duration of their	Measured through study completion (on average 4 years): Pain response rate, objective tumour response rate, PFS, PSA PFS, pain PFS, rPFS, HRQoL, OS. From first study dose to 12 weeks after completing study treatment: Frequency and severity of AEs.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
					cabazitaxel treatment.	

6.1.3 Comparability of studies

Of the seven included studies, five were phase III trials, one was a phase IV trial, and one was a phase II trial. Regarding the blinding status, four studies were open-label, while three were double-blinded (see Table 9). The primary outcomes varied across studies: four studies assessed OS as the primary outcome, rPFS was the primary outcome in two studies, Time to Progression (TTP) was assessed as the primary outcome in one study, and PSA Response Rate (PSA RR) was the primary outcome in one study.

6.1.3.1 Comparability of patients across studies

Various baseline parameters were evaluated to assess the clinical heterogeneity between the studies included in the NMA. These parameters included age, Gleason score, PSA values, prior treatment status, and ECOG performance status scores (Table 10 and Table 11). Baseline characteristics were relatively similar between trials for median age and ECOG PS 0–1. However, reported median PSA levels in trials of comparators were lower in the CARD trial when compared to the VISION trial. The information about the race of included patients was reported in four studies, with most patients being white, ranging from 83% (TROPIC) to 86% (VISION). The proportion of patients with Gleason score ≥8 varied from 50.7% to 67.4% across the studies. Notably, the VISION trial reported Gleason scores ≥8 for 58.8% of patients in the Pluvicto® + SoC arm and 67.4% in the ARPI arm. This is quite similar to some other studies, such as the CARD trial, where over 56% of patients had Gleason scores ≥8. Studies also differed in median baseline LDH (IU/ml) levels.

Table 10 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	VISION (FAS population)		VISION (post 1 taxane population from post hoc analysis)		VISION (population used in the NMA)		CARD		TROPIC	
	Pluvicto® + SoC	BSC/SoC	Pluvicto® + SoC	BSC/SoC	Pluvicto® + SoC*	ARPI**	Cabazitaxel	Enzalutamide or abiraterone + prednisone	Cabazitaxel + prednisone	Mitoxantrone + prednisone
N	551	280	342	165	551	146	129	126	378	377
Age, median	70.0	71.5	-	-	70	71	70	71	68	67
ECOG 0–1	92.6%	92.1%	-	-	92.6%	93.8%	95.3%	94.4%	93%	91%
Gleason score ≤7, median	≥8: 58.8%	≥8: 60.7%	≥8: 58.5%	≥8: 58.8%	≥8: 58.8%	≥8: 67.4%***	≥8: 56.6%	≥8: 64.3%	-	-
Race – White (%)	88.2%	83.9%	-	-	88.2%	85.62%	-	-	84%	83%
Prior surgery/ procedures	-	-	-	-	-	-	-	-	52%	54%
Baseline PSA levels; median (range) ng/ml	77.5 (0-6,988)	74.6 (0-8,995)	60.4 (0-6,360)	62.0 (0-8,995)	77.5 (0-6,988)	53.4 (0.19-5000)	62.0 (1.1-15000.0)	60.5 (1.5-2868.0)	143.9 (51.1-416)	127.5 (44-419)

Note: mcg/l, which is equivalent to ng/ml. *In the NMA, 385 patients were included in the rPFS analysis corresponding to the VISION PFS-FAS population presented in Table 14. **In the NMA, only patients treated with ARPI in the BSC/SoC arm of VISION were included. This was done to facilitate the connection in the NMA network. Data was extracted from the VISION individual patient data, and in the rPFS analysis, 107 patients were included. ***14 unknown out of 146.

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	AFFIRM		Sun et al. (2016)		COU-AA-301		TheraP	
	Enzalutamide	Placebo	Abiraterone + prednisone	Placebo + prednisone	Abiraterone + prednisone/ prednisolone	Placebo + prednisone/ prednisolone	177Lu-PSMA-617	Cabazitaxel
N	800	399	143	71	797	398	99	101
Age, median	69	69	68.2*	67.7*	69	69	72	72
ECOG 0–1	91%	92%	92%	93%	90%	89%	96%	95%
Gleason score ≤7, median	45%	44%	28%	23%	43%	41%	≥8: 54%	≥8: 50%
Race – White (%)	-	-	-	-	-	-	-	-
Prior surgery/ procedures	66%	61%	27%	28%	54%	49%	-	-
Baseline PSA levels; median (range) ng/ml	108 (0.4-11794)	128 (0.6-19000)	-	-	129 (0.4-9253)	138 (0.6-10110)	94 (44-219)	110 (64-245)

Note: mcg/l, which is equivalent to ng/ml. *=mean value.

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

In 2022, the median age at diagnosis of PC in Denmark was 72 years (48). Limited data on the characteristics of the Danish population of men with mCRPC have been identified, and a clinical expert was therefore consulted. The expert confirmed that it is valid to assume that the Danish population is similar to the population included in the VISION study.

Table 12 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age at diagnosis, median	72 years (48)	70.5 (20)
Gender, men	100%	100%
Patient weight	N/A	N/A
Gleason score 8 -10 at diagnosis	31.8% (48)	N/A

6.1.5 Efficacy – results per VISION trial

In the following, we present the results from the VISION study included in the comparative analysis of Pluvicto® and cabazitaxel, i.e. OS and rPFS. All the efficacy outcomes were analysed in intention to treat (ITT) populations. The analysis of OS included all patients who had undergone randomisation from study start 29 May 2018 (FAS), whereas rPFS was analysed in a subgroup of patients who had undergone randomisation on or after 5 March 2019 (PFS-FAS) (20). See Appendix A for an explanation and overview of the analysis setup.

In addition to results from FAS and PFS-FAS (section 6.1.5.2), to demonstrate the efficacy of Pluvicto®, we will present results from a post hoc analysis with a subgroup of patients who have received a maximum of one prior taxane regimen (section 6.1.5.3).

6.1.5.1 Treatment discontinuation in VISION

Of the 831 randomised patients in FAS, 529 out of 551 (96.0%) received Pluvicto® and 201 out of 280 (71.8%) randomised patients received BSC/SoC alone. In PFS-FAS (581 randomised patients), 366 out of the 385 (95.1%) randomised patients received Pluvicto® and 164 out of 196 (83.7%) randomised patients received BSC/SoC alone, respectively. Those who discontinued Pluvicto® numbered 279 (52.7%) from FAS and 191 (52.2%) from PFS-FAS compared to 196 (97.5%) and 160 (97.6%) in the BSC/SoC alone group.

The reasons for discontinuing Pluvicto® included progressive disease (127 (45.5% of discontinued) and 91 (47.6% of discontinued) patients), AEs (54 (19.4%) and 35 (18.3%)

patients), lack of clinical benefit (36 (12.9%) and 27 (14.1%) patients), withdrawal of consent to treatment (23 (8.2%) and 8 (4.2%) patients), withdrawn by the investigator (16 (5.7%) and 12 (6.3%) patients), died (14 (5.0%) and 11 (5.8%) patients), received prohibited therapy (6 (2.2%) and 4 (2.1%) patients), had other reasons (2 (0.7%) and 2 (1.0%) patients), and were lost to follow-up (1 (0.4%) and 1 (0.5%) patient).

The reasons for discontinuing BSC/SoC alone were progressive disease (73 (37.2% of discontinued) and 67 (41.0% of discontinued) patients), lack of clinical benefit (50 (25.5%) and 40 (25.0%) patients), withdrawal of consent (36 (18.4%) and 27 (16.9%) patients), received prohibited therapy (11 (5.6%) and 7 (4.4%) patients), withdrawn by the investigator (9 (4.6%) and 5 (3.1%) patients), died (8 (4.1%) and 7 (4.4%) patients), AEs (4 (2.0%) and 3 (1.9%) patients), did not adhere to regimen (3 (1.5%) and 3 (1.9%) patients), had protocol deviation (1 (0.5%) and 1 (0.6%) patients), and had other reasons (1 (0.5%) and 0 patients) (20).

6.1.5.2 OS and rPFS results from VISION

Below we present the results first for the full VISION study (consisting of both the Post 1 and Post 2 taxanes group) and subsequently for the Post 1 taxane group. In section 6.2.4.3 we present the results for the post 2 taxanes group.

In FAS, 343 (62.3%) patients in the Pluvicto® arm died compared to 187 (66.8%) in the BSC/SoC arm (20). The median OS in FAS was 15.3 months in the Pluvicto® group compared with 11.3 months in the BSC/SoC group (HR: 0.62, 95% CI 0.52–0.74; p<0.001) (20). In other words, relative to BSC/SoC, Pluvicto® prolonged the median OS by 4.0 months and decreased the risk of death by 38%. The 12-month OS rate was 61.7%, with the same rate measuring 49.5% in the Pluvicto® and BSC/SoC groups, respectively; the 18-month OS rate was 42.8% and 30.5% in the two groups, respectively (47). Due to the low patient numbers (36 and 6 patients in each treatment group), we do not report the 24-month OS rate here. The median follow-up was 20.3 months (95% CI 19.8–21.0) in the Pluvicto® group and 19.8 months (95% CI 18.3–20.8) in the BSC/SoC group (20). OS results were similar in PFS-FAS (HR for death: 0.63, 95% CI 0.51–0.79) (20).

In PFS-FAS, 171 (44.4%) experienced imaging-based progression in the Pluvicto® arm compared to 59 (30.1%) in the BSC/SoC arm. Additionally, 83 (21.6%) died in the Pluvicto® arm compared with 34 (17.3%) in the BSC/SoC arm. Please note that these percentages include the full populations including the patients leaving the study population during the study period. The median rPFS among the 581 patients in PFS-FAS was 8.7 months in the Pluvicto® group compared with 3.4 months in the BSC/SoC group (HR for progression or death: 0.40, 99.2% CI 0.29–0.57; P<0.001) (20). In other words, Pluvicto® delayed disease progression by 5.3 months and decreased the risk of disease progression by 60%. Please note that as per protocol, the 99.2% CI has been presented instead of 95% CI, implying that the 95% CI would be even narrower and even more significant.

The Kaplan-Meier (KM) curves for OS and rPFS are presented in Figure 2.

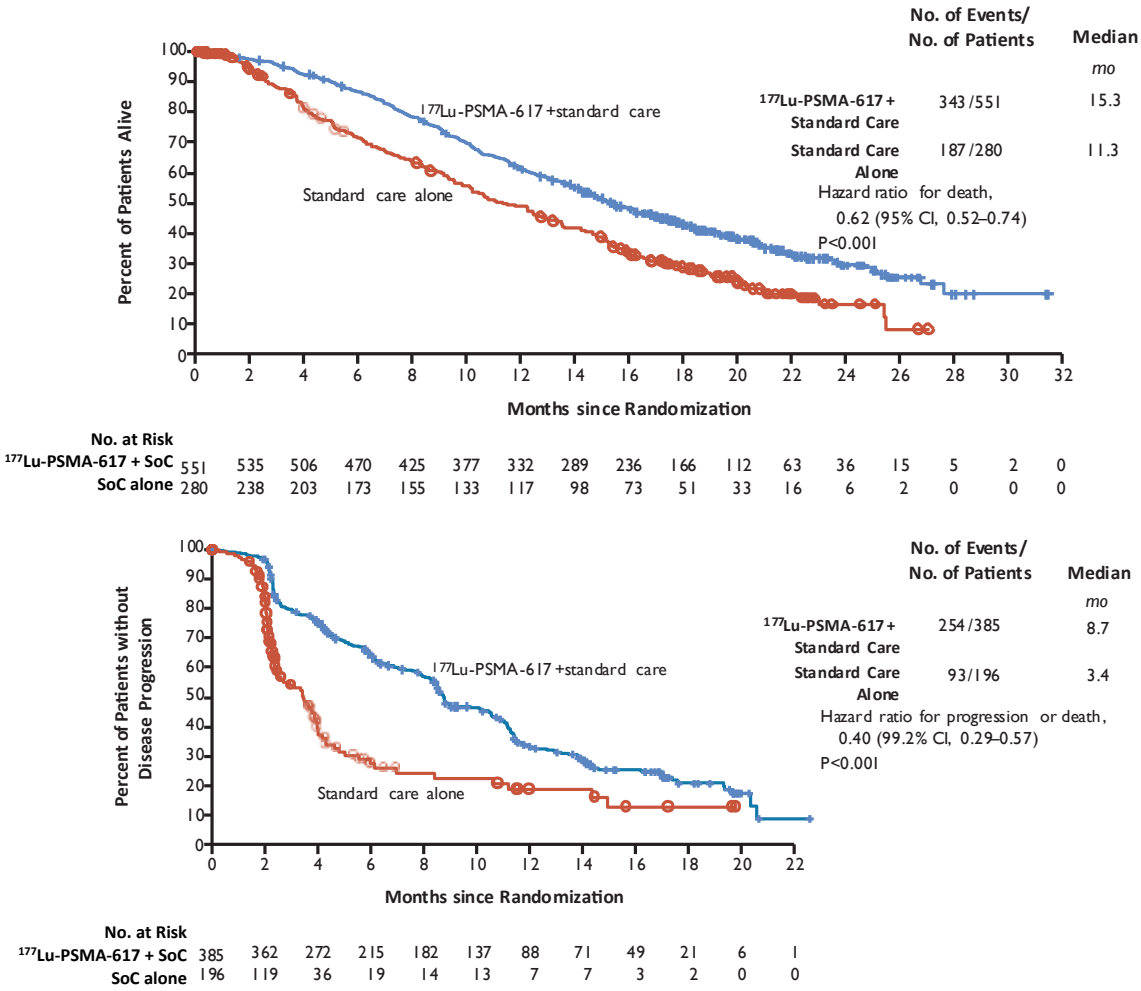

Figure 2 FAS OS and PFS-FAS rPFS Kaplan-Meier curves from Sartor et al. 2021 (VISION) (20)

6.1.5.3 Post hoc analysis of patients who received a maximum of one prior taxane

The subgroup of patients who received a maximum of one prior taxane comprised 507 patients in total: 342 in the Pluvicto® arm and 165 in the BSC/SoC arm. Pluvicto® demonstrated similar results in terms of OS and rPFS in this subgroup as in the FAS and PFS-FAS populations (46).

In this subgroup, the median OS in the Pluvicto® arm was 16.2 months (95% CI 14.7–18.1) compared to 11.8 months (95% CI 9.8–14.4) in the BSC/SoC arm (HR: 0.59, 95% CI 0.46–0.75). Thus, Pluvicto® demonstrated a 41% reduction in risk of death compared to BSC/SoC alone. In the Pluvicto® arm, the 12- and 18-month OS rates were 65.1% and 45.3%, respectively. In the BSC/SoC arm, these were 49.9% and 31.4%, respectively. The median follow-up time was 21.4 months in the Pluvicto® arm and 20.3 months in the BSC/SoC arm.

Additionally, the subgroup analysis showed that the median rPFS in the Pluvicto® arm was 8.9 months (95% CI 8.5–11.0) compared to 3.4 months (95% CI 2.4–4.0) in the BSC/SoC arm (HR: 0.39, 95% CI 0.27–0.54), so Pluvicto® delayed disease progression by

5.5 months, corresponding to a 61% reduction in risk of progression or death compared to BSC/SoC alone. The 12-month rPFS rate was 36.4% in the Pluvicto® arm and 25.7% in the BSC/SoC arm. Finally, the median follow-up time was 14.3 months in the Pluvicto® arm and 3.7 months in the BSC/SoC arm.

The KM plots on OS and rPFS among patients with a maximum of one prior taxane are presented in Figure 3 and Figure 4.

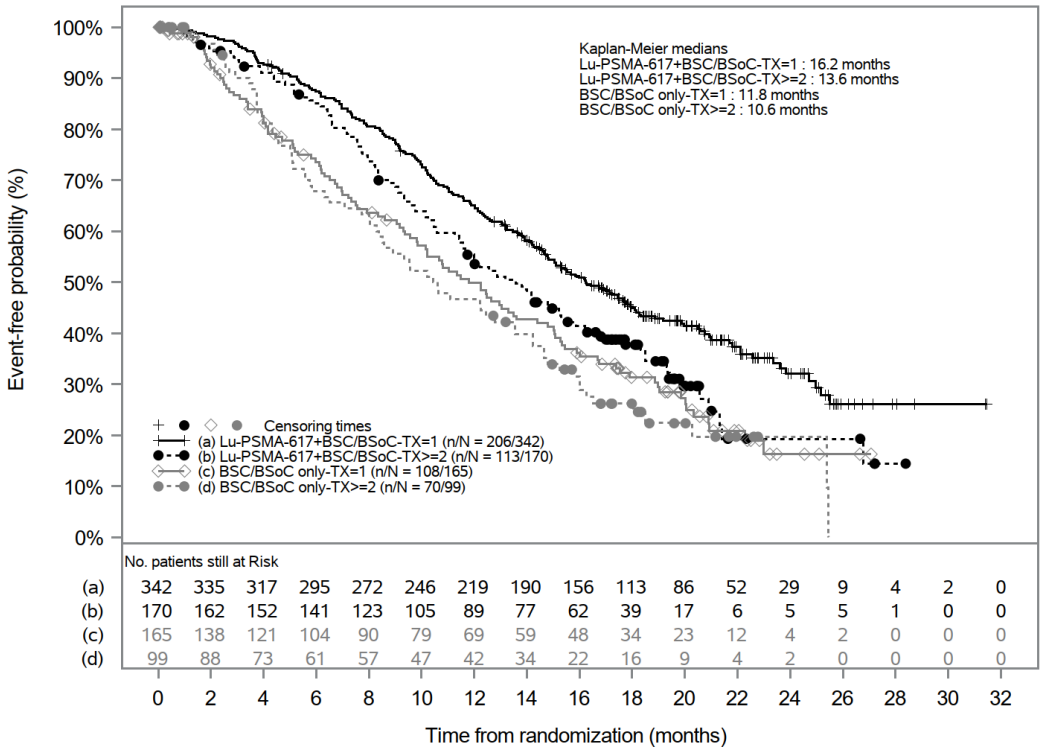

Figure 3 Kaplan-Meier curves on OS, by number of prior taxane-containing regimens (data on file) (46)

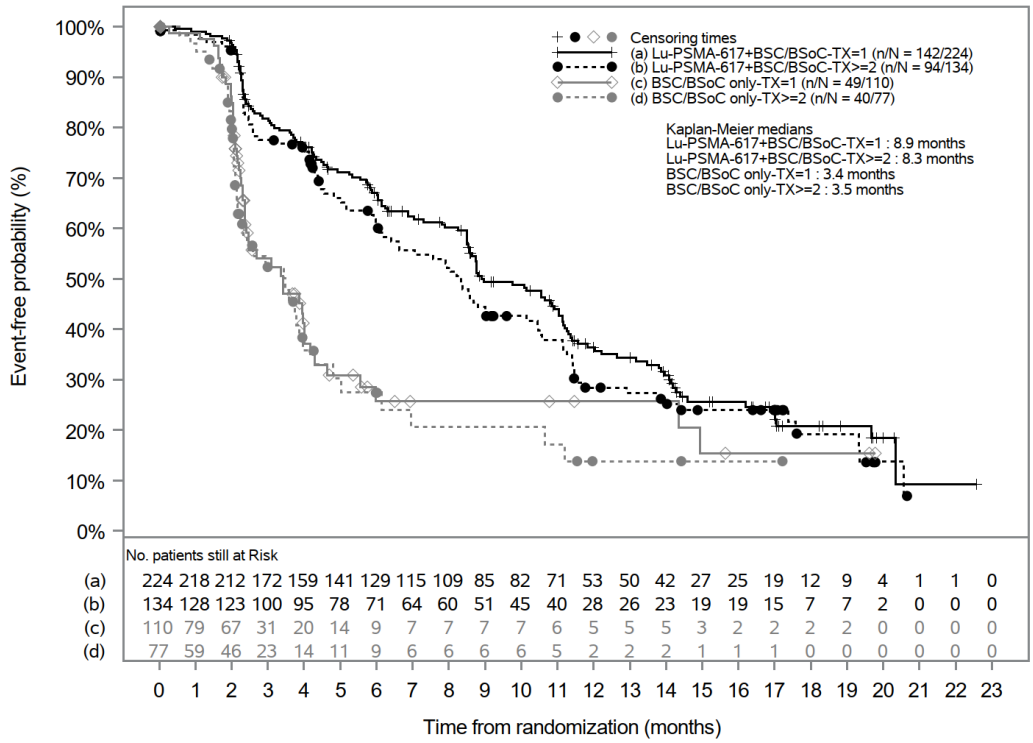

Figure 4 Kaplan-Meier curves on rPFS, by number of prior taxane-containing regimens (data on file) (46)

6.1.5.4 Efficacy summary for the VISION study

The efficacy of Pluvicto® compared to BSC/SoC alone was demonstrated in the large confirmatory phase III randomized trial, VISION, which included patients with PSMA-positive mCRPC who had received prior treatment with ARPI and taxane-based chemotherapy. Patients in the Pluvicto® group of the trial showed significantly extended median OS and median rPFS, supporting Pluvicto® as a treatment option that offers survival benefits compared to BSC/SoC alone in heavily pre-treated patients with PSMA-positive mCRPC. In addition, the post-hoc analysis of VISION data comprising patients who had received a maximum of one taxane showed results in line with the total population and demonstrated that Pluvicto® also provides clinical benefits in this specific subpopulation.

6.1.6 Efficacy – results per the CARD study

In CARD, a total of 255 patients were randomly assigned to receive cabazitaxel (129 patients) or ARPI (126 patients), which represented the ITT population. Of these patients, 250 were treated (126 with cabazitaxel and 124 with ARPI). Of the 124 patients who received ARPI, 58 received abiraterone and 66 received enzalutamide. Two patients in the cabazitaxel group were lost to follow-up. The principal reason for the discontinuation of treatment with cabazitaxel or ARPI was disease progression (in 43.7% and 71.0% of the patients, respectively) or an AE (in 19.8% and 8.9% of the patients, respectively). The median follow-up was 9.2 months (21).

At the cutoff date (27 March 2019), 153 deaths were noted, with 70 deaths (54.3% of the patients) occurring in the cabazitaxel group and 83 (65.9%) in the ARPI group. The median OS was 13.6 months in the cabazitaxel group, as compared with 11.0 months in the ARPI group (HR: 0.64, 95% CI 0.46–0.89; P = 0.008) (21).

At the cutoff date (27 March 2019), rPFS was reported in 196 patients, of whom 95 (73.6%) had been assigned to receive cabazitaxel and 101 (80.2%) had been assigned to receive ARPI. The median rPFS was 8.0 months in the cabazitaxel group compared to 3.7 months in the ARPI group (HR: 0.54, 95% CI 0.40–0.73; P<0.001) (21).

6.1.7 Efficacy – results per the TROPIC study

In the TROPIC study, a total of 755 men were randomised into the study, with 378 patients assigned to receive cabazitaxel plus prednisone and 377 patients assigned to receive mitoxantrone plus prednisone. This represented the ITT population. Patients in both groups received their respective treatments IV every three weeks, along with daily oral prednisone. The median follow-up time for the study was 12.7 months. During the study period, 356 patients (94%) in the mitoxantrone group discontinued treatment compared to 266 (70%) in the cabazitaxel group. The primary reason for discontinuation in the mitoxantrone group was disease progression (71%). In the cabazitaxel group, disease progression was also the leading cause of discontinuation (48%) (30).

At the cutoff date (25 September 2009), 234 patients in the cabazitaxel group and 279 patients in the mitoxantrone group had died. The median OS was 15.1 months for the cabazitaxel group compared to 12.7 months for the mitoxantrone group (HR: 0.70, 95% CI 0.59–0.83; p<0.001) (30). In the TROPIC study, rPFS was not investigated. Since the study provides results for cabazitaxel, which is the comparator for the Post 1 taxane population, results for PFS were included instead. For PFS, events were recorded for 377 patients in the mitoxantrone group and 378 patients in the cabazitaxel group at the cutoff date (25 September 2009). The median PFS was 2.8 months in the cabazitaxel group versus 1.4 months in the mitoxantrone group (HR: 0.74, 95% CI 0.64–0.86; p<0.001) (30).

6.1.8 Efficacy – results per the AFFIRM study

In the AFFIRM study, a total of 1,199 participants were enrolled and randomly assigned in a 2:1 ratio to receive enzalutamide (800 patients) or placebo (399 patients), representing the ITT population. Both enzalutamide and placebo were received orally as capsules delivering 160 mg per day; 159 patients completed the double-blind phase of 24 months (109 from the enzalutamide group and 50 from the placebo group) (31).

The median OS was 18.4 months among patients receiving enzalutamide and 13.6 months among patients receiving placebo. Patients receiving enzalutamide had a 37% reduced risk of death from any cause, compared to the placebo group (HR: 0.63, 95% CI 0.53–0.75, p<.001) (31). In the study, the median rPFS was 8.3 months among patients receiving enzalutamide, compared to 2.9 months among patients receiving placebo (HR: 0.4, 95% CI 0.35–0.47, p<.001) (31).

6.1.9 Efficacy – results per the Sun et al. (2016) study

In this study, a total of 214 participants were enrolled: 143 patients received abiraterone and prednisone, and 71 patients received placebo and prednisone. In both groups, treatment was administered orally. As of 30 April 2014 (the clinical cutoff date for the final analysis), treatment was ongoing for 45 patients (31.5%) in the abiraterone-prednisone group and 11 patients (15.5%) in the prednisone-alone group. The main reason for discontinuation from both groups was disease progression. The follow-up period was 12.9 months at the time of the final analysis. The ITT analysis set included all participants randomised into the study and classified according to their assigned treatment group, regardless of the actual treatment received (32).

A total of 56 deaths (32 in the abiraterone-prednisone group [22.4%] and 24 in the placebo-prednisone group [33.8%]) occurred (HR: 0.60; 95% CI 0.36–1.03; P = 0.0597). Due to the short follow-up time, median survival was not reached in either of the treatment groups (32). rPFS was not reported in Sun et al. (2016).

6.1.10 Efficacy – results per the COU-AA-301 study

Patients were enrolled between 8 May 2008 and 28 July 2009. The clinical cutoff date was 20 September 2010. Of the 1,195 eligible patients, 797 were randomly assigned to receive abiraterone acetate plus prednisone and 398 to receive placebo plus prednisone.

The presented analysis was done at a median follow-up of 20.2 months. At this time, 775 death events had occurred. The median OS for the abiraterone group was 15.8 months compared to 11.2 months in the placebo group (HR: 0.74, 95% CI 0.64–0.86; p<0.0001). rPFS was 5.6 months in the abiraterone group compared to 3.6 months in the placebo group (HR: 0.66, 95% CI 0.58–0.76, p<0.0001) (33).

6.1.11 Efficacy – results per the TheraP study

Several factors make the TheraP study insufficient to provide robust evidence to support a direct head-to-head comparison between 177Lu-PSMA-617 and cabazitaxel for the indication of relevance to this submission. These factors include discrepancies in methodology when comparing to the VISION study; the diagnostic process in TheraP; intervention production and dose (patients in the 177Lu-PSMA-617 arm of TheraP received a starting dose of 8.5 GBq, which reduced by 0.5 GBq per cycle. This differs from the recommended dose, which was used in VISION, of 7.4 GBq per cycle every 6 weeks); and the lack of stratification of people to assess OS (more details are included in Appendix A). Although not suitable for direct comparison, evidence from TheraP is included in the NMA as a sensitivity analysis.

The TheraP study was a phase II, multicentre, open-label, randomised trial in Australia which compared 177Lu-PSMA-617 with cabazitaxel in men with mCRPC who had received docetaxel and ARPI. Between 6 February 2018 and 3 September 2019, 291 participants were assessed for eligibility. Of these, 200 were randomly assigned to either cabazitaxel (101 patients) or 177Lu-PSMA-617 (99 patients) and constituted the ITT population. During the study period, 72 and 64 patients discontinued treatment in the

cabazitaxel arm and the 177Lu-PSMA-617 arm, respectively. The main reason for discontinuation in the cabazitaxel arm was a decision by either the patient (21 patients) or the clinician (17 patients). In the 177Lu-PSMA-617 arm, the main reason was radiological progression (18 patients). rPFS and OS were reported as secondary endpoints in the TheraP study.

In TheraP, rPFS was reported in the primary analysis with a cutoff date of 20 July 2020 and a median follow-up of 18.4 months. In the study, rPFS was significantly increased with 177Lu-PSMA-617 therapy compared with cabazitaxel (HR: 0.64, 95% CI 0.46–0.88, p=0.007) (35). Results on OS were reported in an updated analysis with a cutoff date of 31 December 2021. Following a median follow-up of 35.7 months, OS was similar in the two arms. The median OS in the cabazitaxel arm was 19.4 months compared with 16.4 months in the 177Lu-PSMA-617 arm (HR: 0.97, but insignificant; 95% CI 0.70–1.35 (34).

6.2 Efficacy of Pluvicto® compared to BSC/SoC for PSMA-positive mCRPC patients (Post 2 taxanes group)

6.2.1 Relevant studies

The efficacy of Pluvicto® compared to BSC/SoC in PSMA-positive mCRPC patients (Post 2 taxanes population) was assessed in a direct comparison in the VISION study (20).

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

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
VISION, NCT03511664 Sartor et al. 2021 (20) Fizazi et al. 2023 (36)	International, prospective, open-label, multicentre, randomised, phase III trial	The study for each participant consisted of a screening period (up to 28 days before starting randomised treatment), a treatment period (6–10 months), and a follow-up period (up to 24 months). Total duration of study was approximately 38 months.	Adults with mCRPC and at least one metastatic lesion on baseline CT, MRI, or bone-scan imaging.	177Lu-PSMA-617 (Pluvicto®) (7.4 GBq [+/- 10%]) administered IV once every 6 weeks (+/- 1 week) for a maximum of 6 cycles and BSC/SoC as defined by the local investigator.	BSC/SoC alone as defined by the local investigator.	Up to 32 months: rPFS, overall response rate, disease control rate, time to first SSE, PFS, time to worsening in Brief Pain Inventory (BPI)-SF Pain Intensity Scale, time to improvement after worsening in BPI-SF Pain Intensity Scale, time to worsening in BPI-SF Pain Interference Scale, time to improvement after worsening in BPI-SF Pain Interference Scale, time to worsening in BPI-SF Worst Pain Intensity Scale, time to worsening in FACT-P total score, time to worsening in EQ-5D-5L utility score. Up to 32 months and up to 66 months: OS. Until 30-day safety follow-up, assessed up to 66 months: TEAEs. Until 30-day safety follow-up, assessed up to 32 months: percentage of participants achieving PSA response, PSA80 response, best percentage change from baseline in alkaline phosphatase (ALP) level, best percentage change from baseline in lactate dehydrogenase (LDH) level, number of participants hospitalized as in-patient, duration of time in hospital following 177Lu-PSMA-617 administration, concomitant drug use, therapeutic interventions, best percentage change from baseline in PSA level. From first evidence of complete response (CR) or partial response (PR) until progression or death, assessed up to 32 months: duration of response. From first PSA response until 30-day safety follow-up, assessed up to 32 months: duration of PSA response. Baseline, cycle 2 to cycle 13, EOT: change from baseline in BPI-SF Pain Intensity Scale, change from baseline in BPI-SF Pain Interference Scale, change from baseline in FACT-P total score, change from baseline in EQ-5D-5L utility score, change from baseline in EQ-5D-5L EQ-VAS.

6.2.2 Comparability of studies

N/A

6.2.2.1 Comparability of patients across studies

The demographic and disease characteristics of the patients at baseline and at their previous treatments were balanced between the trial groups and between the randomisation periods in the VISION study.

In general, more patients in the Pluvicto® groups (for both FAS and PFS-FAS) were white (FAS: 88.2% versus 83.9%; PFS-FAS: 87.3% versus 84.7%); however, these differences were not significant. More patients in the Pluvicto® groups also had higher PSA and alkaline phosphate levels. Additionally, more patients in the Pluvicto® groups had one regimen of prior ARPI and one regimen of prior taxane therapy compared to the BSC/SoC groups; however, these differences were not significant.

Table 14 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	VISION (FAS)		VISION (PFS-FAS)		VISION (post 2 taxanes population from post hoc analysis)	
	Pluvicto®	**BSC/SoC**	**Pluvicto®**	**BSC/SoC**	**Pluvicto®**	**BSC/SoC**
N	551	280	385	196	170	99
Age, median	70.0	71.5	71.0	72.0	-	-
Race – White, n (%)	486 (88.2)	235 (83.9)	336 (87.3)	166 (84.7)	-	-
ECOG 0-1, n (%)	510 (92.6)	258 (92.1)	352 (91.4)	179 (91.3)	-	-
Site of disease, n (%)						
Lung	49 (8.9)	28 (10.0)	35 (9.1)	20 (10.2)	16 (9.4)	11 (11.1)
Liver	63 (11.4)	38 (13.6)	47 (12.2)	26 (13.3)	27 (15.9)	18 (18.2)
Lymph node	274 (49.7)	141 (50.4)	193 (50.1)	99 (50.5)	92 (54.1)	53 (53.5)
Bone	504 (91.5)	256 (91.4)	351 (91.2)	179 (91.3)	154 (90.6)	93 (93.9)
PSA level, median ng/ml	77.5	74.6	93.2	90.7	105.0	120.0
Alkaline phosphate level, median IU/litre	105.0	94.5	108.0	96.0	115.5	99.5
LDH, median IU/litre	221.0	224.0	230.5	232.0	229.5	233.0

	VISION (FAS)		VISION (PFS-FAS)		VISION (post 2 taxanes population from post hoc analysis)	
	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC
Gleason score at diagnosis						
8-10	324 (58.8)	170 (60.7)	226 (58.7)	118 (60.2)	100 (58.8)	64 (64.6)
Unknown	42 (7.6)	24 (8.6)	28 (7.3)	19 (9.7)	13 (7.6)	8 (8.1)
Previous ARPI, n (%)						
One regimen	298 (54.1)	128 (45.7)	213 (55.3)	98 (50.0)	-	-
Two regimens	213 (38.7)	128 (45.7)	150 (39.0)	86 (43.9)	-	-
More than two regimens	40 (7.3)	24 (8.6)	22 (5.7)	12 (6.1)	-	-
Previous taxane therapy, n (%)						
One regimen	325 (59)	156 (55.7)	207 (53.8)	102 (52.0)	-	-
Two regimens	220 (39.9)	122 (43.6)	173 (44.9)	92 (46.9)	-	-
Docetaxel	534 (96.9)	273 (97.5)	377 (97.0)	191 (97.4)	-	-
Cabazitaxel	209 (37.9)	107 (38.2)	161 (41.8)	84 (42.9)	-	-

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

As described in 6.1.4, the median age at diagnosis of PC was 72 years among the Danish population of men in 2022 (48). Because limited data on the characteristics of the Danish population of men with mCRPC have been identified, a clinical expert was consulted. The clinical expert confirmed that it is valid to assume that the Danish population is similar to the population included in the VISION study.

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age at diagnosis, median	72 years (48)	70.5 (20)
Gender, male	100%	100%
Patient weight	N/A	N/A
Gleason score 8 -10 at diagnosis	31.8% (48)	N/A

6.2.4 Efficacy – results per VISION trial

In the following, we present results from the VISION study included in the comparative analysis of Pluvicto® and BSC/SoC, i.e. OS, rPFS, and time to first SSE. All the efficacy outcomes were analysed in ITT populations. As described in Section 6.1.5, the analysis of OS included all the patients who had undergone randomisation (FAS), whereas rPFS was analysed in a subgroup of patients who had undergone randomisation on or after 5 March 2019 (PFS-FAS). Secondary endpoints, including time to SSE, were also investigated in PFS-FAS (20). See Appendix A for an overview of the analysis set.

In addition to results from FAS and PFS-FAS (defined in Section 6.1.5), we present results from a post hoc analysis with a subgroup of patients who received a minimum of two prior taxane regimens, to demonstrate the efficacy of Pluvicto® after two taxanes. Details on treatment discontinuation are presented in Section 6.1.5.

6.2.4.1 OS and rPFS results from VISION

The relevant results for OS and rPFS when comparing Pluvicto® to BSC/SoC are presented in Section 6.1.5.2 and KM plots are presented in Figure 2.

6.2.4.2 Time to first SSE

The median time to the first SSE or death among the 581 patients in PFS-FAS was 11.5 months in the Pluvicto® group compared to 6.8 months in the SoC group (HR: 0.50, 95% CI 0.40–0.62; P<0.001). This indicates that relative to SoC alone, Pluvicto® decreased the time to SSE or death by 4.7 months and decreased the risk by 50% (20). The KM plot for time to SSE is presented in Figure 5.

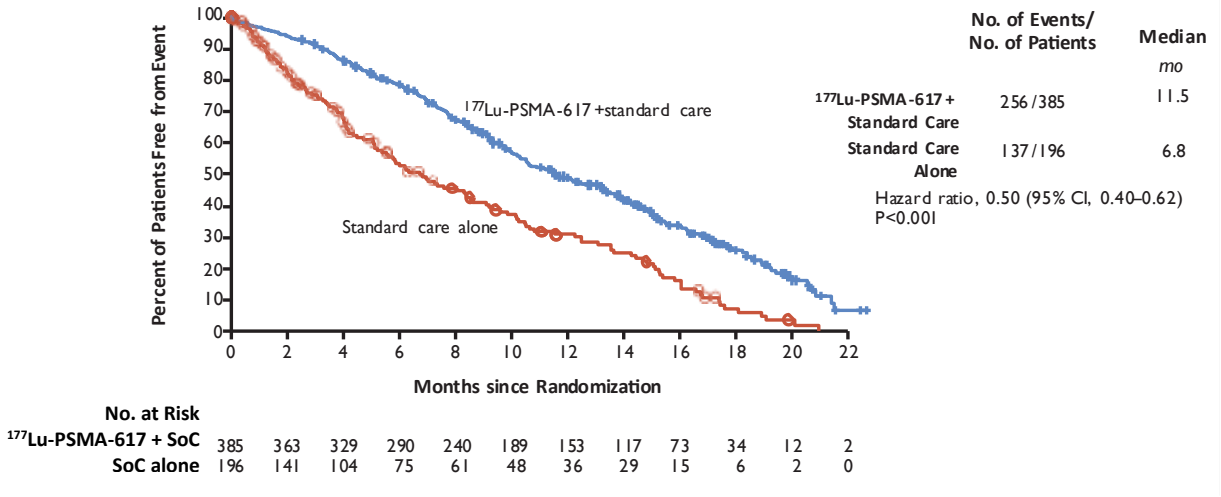

Figure 5 PFS-FAS SSE Kaplan-Meier curves from Sartor et al. 2021 (20)

6.2.4.3 Post hoc analysis of patients who received at least two taxanes

In the subgroup of patients who had received at least two taxanes, comprising 269 patients from the FAS population (170 in the Pluvicto® arm and 99 in the BSC/SoC arm) and 211 patients from the PFS-FAS population (134 in the Pluvicto® arm and 77 in the BSC/SoC arm), Pluvicto® demonstrated similar results for OS, rPFS, and time to SSE (46).

In this subgroup, the median OS in the Pluvicto® group was 13.6 months (95% CI 11.5–15.4) compared to 10.6 months (95% CI 8.3–13.5) in the BSC/SoC group (HR: 0.73, 95% CI 0.53–0.99), meaning that Pluvicto® demonstrated a 27% reduction in risk of death compared to BSC/SoC alone. In the Pluvicto® group, the 12- and 18-month OS rates were 54.8% and 37.8%, respectively. In the BSC/SoC group, these were 46.7% and 26.2%, respectively. The median follow-up time was 19.4 months in the Pluvicto® arm and 18.3 months in the BSC/SoC arm.

Additionally, the subgroup analysis showed that the median rPFS in the Pluvicto® group was 8.3 months (95% CI 6.2–10.4) compared to 3.5 months (95% CI 2.2–4.0) in the BSC/SoC group (HR: 0.44, 95% CI 0.30–0.66). That is, Pluvicto® demonstrated a 56% reduction in risk of progression or death compared to BSC/SoC alone. The 12-month rPFS rate was 28.4% in the Pluvicto® group and 13.8% in the BSC/SoC group. The median follow-up time was 17.0 months in the Pluvicto® group and 4.3 months in the BSC/SoC group.

Finally, the median time to first SSE in the subgroup of patients treated with at least two prior taxanes was 10.2 months (95% CI 8.3–13.8) in the Pluvicto® group compared to 5.6 months (95% CI 3.8–8.3) in the BSC/SoC group (HR: 0.43, 95% CI 0.30–0.61). Therefore, Pluvicto® demonstrated a 57% reduction in risk of SSE compared to BSC/SoC alone.

The OS and rPFS KM plots for patients after two taxanes are presented in Figure 3 and Figure 4. The SSE KM plot is presented in Figure 6.

Figure 6 Kaplan-Meier curves on SSE, by number of prior taxane-containing regimens (data on file) (46)

6.2.4.4 Efficacy summary for the VISION study

As described in section 6.1.5.4, treatment with Pluvicto© resulted in a reduced risk of radiographic disease progression and death in heavily pre-treated adults with PSMA-positive mCRPC when compared to BSC/SoC alone. Additionally, Pluvicto© maintained quality of life for longer, measured by extended time to SSE. Furthermore, the post-hoc analysis of VISION data comprising patients who had received at least two prior taxanes showed results in line with the total population, the results being more favorable in the Pluvicto® arm compared to the BSC/SoC alone also in this patient subgroup.

7. Comparative analyses of efficacy

7.1 Comparative analysis of Pluvicto® compared to cabazitaxel for PSMA-positive mCRPC patients (Post 1 taxane population)

For the Post 1 taxane population, Pluvicto® was indirectly compared to cabazitaxel through a Bayesian NMA consisting of six studies (seven studies in a sensitivity analysis).

7.1.1 Differences in definitions of outcomes between studies

In the NMA, results on OS and rPFS were included. Across all the included studies reporting the definition of OS, i.e. time from randomisation to death from any cause, no variability was observed. Also, no differences were reported amongst the studies

reporting the rPFS definition. It was commonly defined as the time from randomisation to the time of disease progression or death (definitions presented in Table 3). Sun et al. (2016) did not report rPFS data and was hence only included in the OS analysis.

The TROPIC study included PFS and not rPFS data. Both measures express disease progression, i.e. time to progression or death, but they are measured using different methods. In TROPIC, progression was defined as PSA progression, tumour progression, pain progression or death. Since TROPIC provides results for cabazitaxel, which is the comparator for the Post 1 taxane population, it was important to include the PFS data from TROPIC in the analysis. In the landscape of relevant clinical trials, we face a paucity of data, and the base case analysis for rPFS already includes only five studies with TROPIC. Removing TROPIC would further reduce this number, potentially compromising the robustness and validity of the findings. While TROPIC reports PFS rather than rPFS, this difference is outweighed by the value of including its data. The inclusion of PFS data from TROPIC allows for a more comprehensive synthesis of available evidence for cabazitaxel.

7.1.2 Method of synthesis

In the NMA, only patients treated with ARPI in the BSC/SoC arm of VISION were included. This was done to facilitate the connection in the NMA network. Both for OS and rPFS, an NMA was deemed viable due to the availability of a connected network. Data was extracted from the VISION individual patient data.

Clinical heterogeneity between studies was assessed using various baseline parameters, including age, Gleason score, PSA values, prior treatment status, and ECOG performance status scores (presented in section 6.1.3). While median age and ECOG PS 0–1 were relatively similar across trials, differences were observed in median PSA levels, Gleason scores, and baseline LDH levels. Due to a limited number of studies (<10), a meta-regression accounting for the differences in baseline characteristics such as median PSA (ng/ml) at baseline and median baseline LDH (IU/ml) levels could not be performed. The NMA conducted consisted of summary results reported in study publications and included the synthesis of the HR of OS and rPFS.

A network of the six interlinked studies for OS outcomes is presented in Figure 7. Additionally, a network of interlinked studies for rPFS outcomes is presented in

Figure 8. Network of the seven and six studies included in the sensitivity analyses of OS and rPFS, respectively, are illustrated in Figure 30 and Figure 31. Appendix C describes the methodology of the NMA in detail.

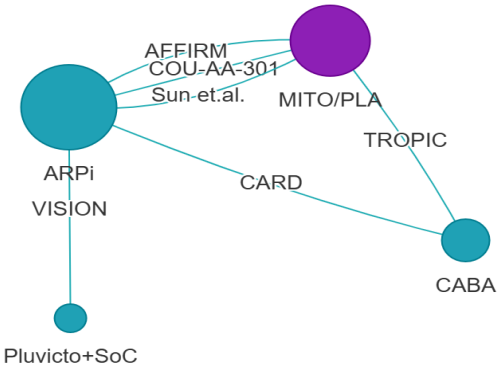

Figure 7 Network of evidence for OS (n=6 RCTs)

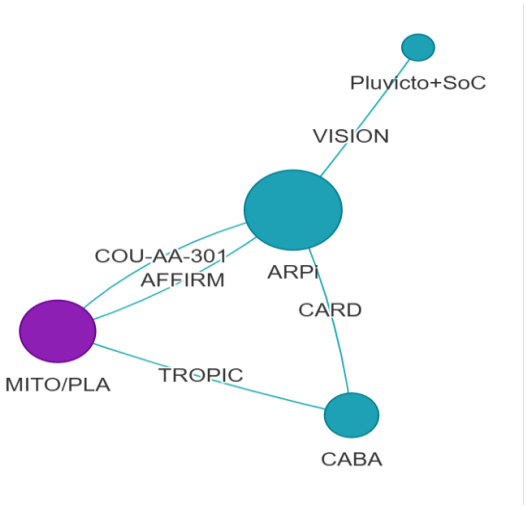

Figure 8 Network of evidence for rPFS (n=5 RCTs)

7.1.3 Results from the comparative analysis

Based on the NMA results, Pluvicto® demonstrated superior efficacy on both OS and rPFS compared to cabazitaxel (Table 16). The remaining results of the NMA are presented in Appendix C.

Table 16 Results from the comparative analysis of Pluvicto ® vs. cabazitaxel for PSMA-positive mCRPC patients (Post 1 taxane population)

Outcome measure	Result (base case)	Results (sensitivity analysis)
OS	HR: [redacted] (95% CI [redacted])	HR: [redacted] (95% CI [redacted])
rPFS	HR: [redacted] (95% CI [redacted])	HR: [redacted] (95% CI [redacted])

7.1.4 Efficacy – results per OS

Pluvicto® showed a statistically significant effect on OS compared with cabazitaxel (HR: [redacted], 95% CI [redacted]). In other words, relative to cabazitaxel, Pluvicto® decreases the risk of death by 38% among patients with mCRPC.

7.1.5 Efficacy – results per rPFS

Pluvicto® showed a statistically significant effect on rPFS compared with cabazitaxel (HR: [redacted], 95% CI [redacted]). In other words, relative to cabazitaxel, Pluvicto® decreases the risk of disease progression by 54% among patients with mCRPC.

7.2 Comparative analysis of Pluvicto® compared to BSC/SoC for PSMA-positive mCRPC patients (Post 2 taxanes population)

Pluvicto® was directly compared to BSC/SoC in the VISION head-to-head study.

7.2.1 Differences in definitions of outcomes between studies

N/A

7.2.2 Method of synthesis

N/A

7.2.3 Results from the comparative analysis

The results of the direct comparison between Pluvicto® and BSC/SoC in the Post 2 taxanes population have been presented in Section 6.2.4. The data cutoff date for the final analyses was 27 January 2021, and all efficacy outcomes were analysed in ITT populations (20). The relevant results are presented below (in the table below).

Table 17 Results from the comparative analysis of Pluvicto® vs. BSC/SoC for PSMA-positive mCRPC patients (Post 2 taxanes population)

Outcome measure	VISION study (20)			VISION study (post hoc analysis of patients with a minimum of two prior taxane regimens) (46)		
	Pluvicto® (FAS: N=551) (PFS-FAS: N=385)	BSC/SoC (FAS: N=280) (PFS-FAS: N=196)	Result	Pluvicto® (FAS: N=170) (PFS-FAS: N=134)	BSC/SoC (FAS: N=99) (PFS-FAS: N=77)	Result
OS, median (95% CI)	15.3 months (95% CI 14.2; 16.9)	11.3 months (95% CI 9.8; 13.5)	4 months HR: 0.62 (95% CI 0.52; 0.74)	13.6 months (95% CI 11.5; 15.4)	10.6 months (95% CI 8.3; 13.5)	3 months HR: 0.73 (95% CI 0.53; 0.99)
rPFS	Median: 8.7 months (99.2% CI 7.9; 10.8)	Median: 3.4 months (99.2% CI 2.4; 4.0)	5.3 months HR: 0.40 (99.2% CI 0.29; 0.57)	8.3 months (95% CI 6.2; 10.4)	3.5 months (95% CI 2.2; 4.0)	4.8 months HR: 0.44 (95% CI 0.30; 0.66)
Time to first SSE	Median: 11.5 months (95% CI 10.3; 13.2)	Median: 6.8 months (95% CI 5.2; 8.5)	4.7 months HR: 0.50 (95% CI 0.40; 0.62)	10.2 months (95% CI 8.3; 13.8)	5.6 months (95% CI 3.8; 8.3)	4.6 months HR: 0.43 (95% CI 0.30; 0.61)

7.2.4 Efficacy – results per outcome measure

Results per outcome measure for the head-to-head comparison of Pluvicto® versus BSC/SoC have already been described in sections 6.2.4.2 and 7.2.3.

8. Modelling of efficacy in the health economic analysis

Pluvicto® was compared to both cabazitaxel and BSC/SoC. The clinical effects of this comparison were modelled using extrapolations of OS and rPFS. The following sections describe these clinical effects and extrapolations for OS and rPFS used in the health economic analysis.

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

The health economic analysis compared the long-term effects of Pluvicto® to 1) cabazitaxel and 2) BSC/SoC. In Danish clinical practice, cabazitaxel is used earlier in the course of treatment than BSC/SoC alone (as described in section 3.3), meaning that patients receiving BSC/SoC have already discontinued treatment with cabazitaxel. To accommodate this and hence keep the analyses as close as possible to Danish clinical practice, OS and rPFS were derived from different VISION trial subpopulations who received 1 or 2 taxanes. Pluvicto® was compared to cabazitaxel based on patients from VISION who had received one taxane-based chemotherapy (Post 1 taxane population), while the comparison to BSC/SoC was based on patients from VISION who received two taxane-based chemotherapies (Post 2 taxanes population).

As a result, two sets of extrapolations were made for both OS and rPFS: one for the Post 1 taxane population and another for the Post 2 taxanes population. In both, the OS and rPFS extrapolations were made for Pluvicto® and BSC/SoC. For the Post 1 taxane population with cabazitaxel as comparator, the HRs from section 7 were applied to the hazards of OS and rPFS extrapolations for Pluvicto®. For the Post 2 taxanes population with BSC/SoC as comparator, the extrapolations were used directly. In the base case analysis, the instant hazards for BSC/SoC were constrained to always be equal to or greater than the instant hazards for Pluvicto®. This is based on the assumption that, since Pluvicto® is an add-on treatment to BSC/SoC, patients receiving Pluvicto® cannot be worse off than those receiving only BSC/SoC.

8.1.1 Extrapolation of efficacy data

Standard parametric fits (i.e. Exponential, Weibull, Stratified Weibull, Gompertz, Stratified Gompertz, Log-normal, Stratified log-normal, Log-logistic, Stratified log-logistic, Gamma, Stratified gamma, generalised gamma, and Stratified generalised gamma) were used on the KM curves based on trial data from the VISION study. The best parametric fits were selected based on visual checks, clinical plausibility, and Akaike information criterion (AIC)/Bayesian information criterion (BIC) statistics.

In addition to standard parametric models, flexible spline parametric models were applied to the KM data. Applying flexible spline parametric models to survival data for various types of cancer has demonstrated more accurate predictions and has outperformed standard parametric models (49).

8.1.1.1 Extrapolation of OS

The OS analysis was performed for the entire patient group of the VISION study that has been included since the start of the trial on 29 May 2018 (FAS). Unlike rPFS, OS data for patients who dropped out were available through mCRPC registries. As a result, OS was associated with a reduced risk of bias compared to rPFS.

The inverse probability of censoring weights (IPCW) method was chosen for extrapolating OS data. This decision was made in consultation with statisticians to correct for the potential bias introduced by informative censoring. Informative censoring occurs when the probability of censoring is related to the outcome of interest, which can distort the survival estimates. The extrapolations were conducted using the R package ipw as described by van der Wal and Geskus, 2011 (50).

By applying IPCW, the analysis adjusts for this bias, providing a more conservative and reliable estimate of OS. This method ensures that the extrapolated OS data reflect a more accurate long-term survival prediction, accounting for the censored observations.

Table 18 Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	VISION
Model	Parametric survival model.
Assumption of proportional hazards between intervention and comparator	Post 1 taxane population: N/A. Post 2 taxanes population: Proportional hazard assumption not met.
Function with best AIC fit	Post 1 taxane population: Log-logistic. Post 2 taxanes population: Stratified flexible Weibull (2 knots).
Function with best BIC fit	Post 1 taxane population: Log-logistic. Post 2 taxanes population: Weibull.
Function with best visual fit	Post 1 taxane population: Weibull, Stratified Weibull, Gamma, Stratified gamma, Flexible Weibull (1 knot), Flexible Weibull (2 knots), Stratified flexible Weibull (1 knot), Stratified flexible Weibull (2 knots). Post 2 taxanes population: Weibull, Stratified Weibull, Stratified gamma, Generalised gamma, Stratified generalised gamma, Flexible Weibull (1 knot), Flexible Weibull (2 knots), Flexible Weibull (3 knots), Stratified flexible Weibull (1 knot), Stratified flexible Weibull (3 knots).

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	Post 1 taxane population: N/A Post 2 taxanes population: N/A
Validation of selected extrapolated curves (external evidence)	Post 1 taxane population: Despite having the best AIC/BIC, the Log-logistic function provided a flat tail that never approached zero and thus was deemed unrealistic. The gamma function also provided good AIC/BIC while converging toward zero after 6–7 years, thus appearing to be the most realistic. The gamma function was considered clinically plausible by the clinical expert. Post 2 taxanes population: The Weibull and Stratified flexible Weibull (2 knots) functions provided the best AIC/BIC. On visual inspection, however, the stratified flexible Weibull (2 knots) function appeared more appealing. The flexible Weibull (2 knots) function was considered clinically plausible by the clinical expert.
Function with the best fit according to external evidence	Not assessed due to missing evidence.
Selected parametric function in base case analysis	Post 1 taxane population: Gamma. Post 2 taxanes population: Stratified flexible Weibull (2 knots).
Adjustment of background mortality with data from Statistics Denmark	In the model, OS is constrained to be equal to or higher than the general mortality rate observed in the Danish population. However, since the OS extrapolations in the base case already fulfil this criterion, it has no impact on the results.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

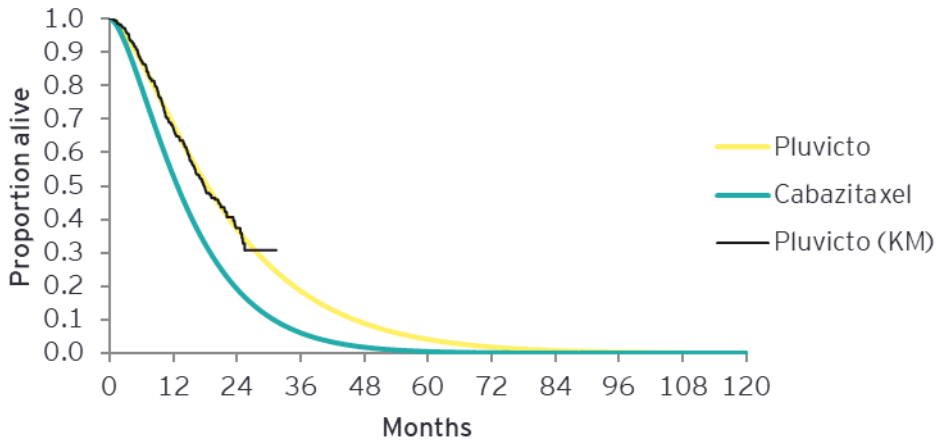

Figure 9 Post 1 taxane population: OS parametric fits and KM data (data on file)

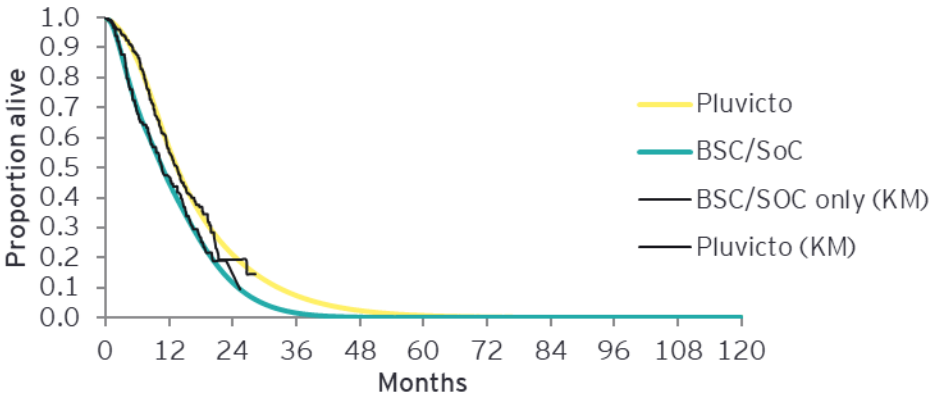

Figure 10 Post 2 taxanes population: OS parametric fits and KM data (data on file)

8.1.1.2 Extrapolation of rPFS

As described in section 6.1.5, the VISION study was affected by a high dropout rate observed before 5 March 2019 in the control arm. The number of patients withdrawing in the control arm could potentially influence the interpretation of rPFS. Therefore, the extrapolations for rPFS were based on the PFS-FAS data set from after 5 March 2019.

For rPFS, the analysis faced challenges due to poor model fit, as the KM data were influenced by informative censoring. Patients treated with BSC/SoC frequently dropped out of the study before progression occurred. This means that if a patient had not experienced progression by their last full check-up, they were marked as censored at that point even though the event happened later. To address this, interval imputation was used to estimate the event times for patients who were censored but known to have progressed or died during follow-up. This method corrects for the potential bias by imputing the missing event times, resulting in a more accurate representation of rPFS.

Parametric interval imputation was conducted following the method described by Anderson-Bergman (51) using the R package icenReg. This method fits a parametric model to the data and uses multiple imputation to impute the timestamp of progression for patients with interval data. For the imputation, it was assumed that progression could occur only at 2-month intervals after the date of the last adequate visit. If the imputed timestamp exceeded the date of progression/death, then the actual date of report of progression/death was used. This approach may be conservative because it does not allow for patients who died before progression was reported, so some imputed times may be greater than would actually have occurred. There was a higher proportion of patients with interval data in the control arm. In total, 50 imputed data sets were created, and a log-rank test was performed for each data set. The imputed data set with a chi-square test statistic that came closest to the statistic from the ensemble results using the multiple-imputed data was selected for the parametric extrapolation.

Table 19 Summary of assumptions associated with extrapolation of rPFS

Method/approach	Description/assumption
Data input	VISION
Model	Parametric survival model.
Assumption of proportional hazards between intervention and comparator	Post 1 taxane population: N/A. Post 2 taxanes population: Uncertainty exists around whether the proportional hazards assumption is met.
Function with best AIC fit	Post 1 taxane population: Flexible Weibull (2 knots). Post 2 taxanes population: Stratified flexible Weibull (3 knots).
Function with best BIC fit	Post 1 taxane population: Flexible Weibull (2 knots). Post 2 taxanes population: Gamma.
Function with best visual fit	Post 1 taxane population: Gamma, Flexible Weibull (2 knots), Stratified gamma, Stratified flexible Weibull (2 knots), Stratified flexible Weibull (3 knots). Post 2 taxanes population: Gamma, Stratified gamma, Generalised gamma, Flexible Weibull (2 knots), Flexible Weibull (3 knots), Stratified flexible Weibull (2 knots), Stratified flexible Weibull (3 knots).
Function with best fit according to evaluation of smoothed hazard assumptions	Post 1 taxane population: N/A Post 2 taxanes population: N/A
Validation of selected extrapolated curves (external evidence)	Post 1 taxane population: The flexible Weibull (2 knots) had the best AIC/BIC while also converging to zero and thus appeared to be the most appealing function. The

Method/approach	Description/assumption
	flexible Weibull (2 knots) was considered clinically plausible by the clinical expert. Post 2 taxanes population: Stratified flexible Weibull (3 knots) and gamma functions had the best AIC/BIC while also converging to zero. On visual inspection, the stratified flexible Weibull (3 knots) function appeared to be more appealing in the first 6 months of extrapolation compared to the gamma function. The stratified flexible Weibull (3 knots) was considered clinically plausible by the clinical expert.
Function with the best fit according to external evidence	Not assessed due to missing evidence.
Selected parametric function in base case analysis	Post 1 taxane population: Flexible Weibull (2 knots). Post 2 taxanes population: Stratified flexible Weibull (3 knots).
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

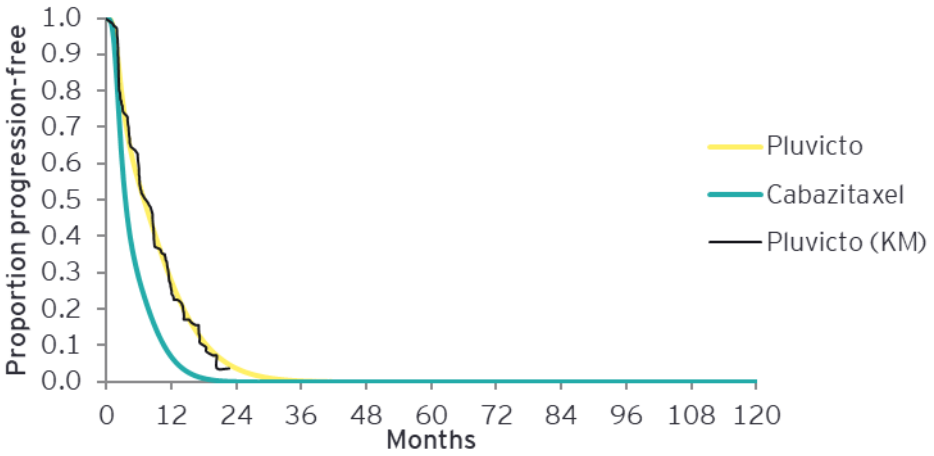

Figure 11 Post 1 taxane population: rPFS parametric fits and KM data (data on file)

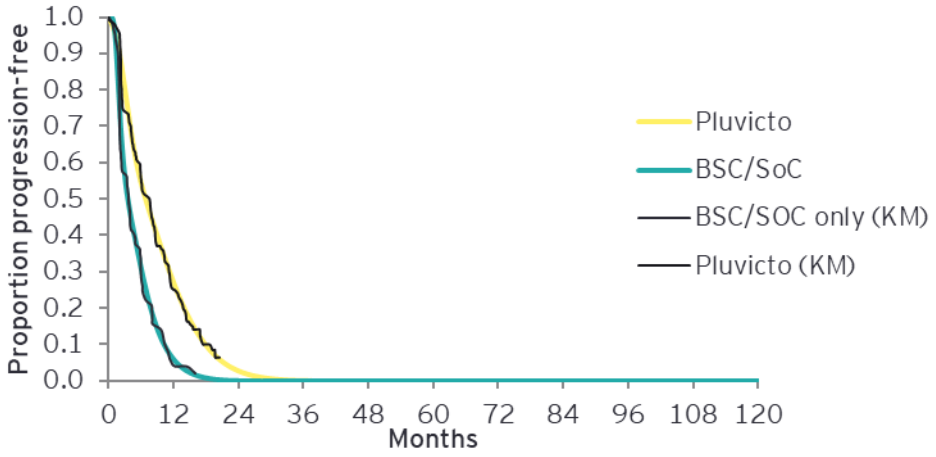

Figure 12 Post 2 taxanes population: rPFS parametric fits and KM data (data on file)

8.1.2 Calculation of transition probabilities

N/A

Table 20 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.1.2.1 Discontinuation

In the model, the treatment of Pluvicto® included an average of [redacted] doses (47) and the treatment of cabazitaxel included 6 doses (see more about Pluvicto® treatment and cabazitaxel in sections 3.4 and 3.5). The model does not account for the discontinuation of treatment, because both Pluvicto® and cabazitaxel are administered a specific number of times rather than continuously. All patients will receive BSC/SoC throughout the model's time horizon or until death.

8.2 Presentation of efficacy data from additional documentation

No other data were used to model efficacy.

8.3 Modelling effects of subsequent treatments

Subsequent treatment was included in the model only as a one-off cost associated with disease progression. Thus, subsequent treatment was not used to model efficacy.

8.4 Other assumptions regarding efficacy in the model

N/A

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

Table 21, Table 22 and Table 23 present estimates for the modelled averages and medians of OS and rPFS, as predicted by the extrapolation models (undiscounted estimates with no half-cycle correction). Additionally, medians from the trials are presented.

Table 21 OS estimates in the model

	Modelled average OS (reference in Excel: "Survival_Curves")	Modelled median OS (reference in Excel: "Survival_Curves")	Observed median from relevant study (VISION) (reference in Excel: "OS_rPFS")
Pluvicto®			
Post 1 taxane pop.	22.6 months	18.4 months	17.9 months
Post 2 taxanes pop.	16.4 months	13.3 months	13.5 months
Cabazitaxel	15.7 months	12.9 months	N/A
BSC/SoC	12.4 months	10.6 months	10.6 months

Table 22 rPFS estimates in the model

	Modelled average rPFS (reference in Excel: "Survival_Curves")	Modelled median rPFS (reference in Excel: "Survival_Curves")	Observed median from relevant study (VISION) (reference in Excel: "KM_rPFS")
Pluvicto®			
Post 1 taxane pop.	8.8 months	6.9 months	7.3 months
Post 2 taxanes pop.	8.6 months	6.9 months	7.6 months
Cabazitaxel	4.8 months	3.4 months	N/A
BSC/SoC	4.8 months	3.4 months	3.7 months

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half-cycle correction

Treatment	Duration of intervention	Duration of BSC/SoC *	Progression-free	Progressed	Dead
Intervention: Pluvicto®					

Post 1 taxane popn	6.1 months	22.6 months	8.8 months	13.8 months	97.4 months
Post 2 taxanes popn	6.1 months	16.4 months	8.6 months	7.8 months	103.6 months
Comparator:					
Cabazitaxel	4.1 months	15.7 months	4.8 months	11.0months	104.3 months
BSC/SoC	-	12.4 months	4.8 months	7.5 months	107.7 months

*BSC/SoC treatment is lifelong.

9. Safety

9.1 Safety of Pluvicto® compared to cabazitaxel for PSMA-positive mCRPC patients (Post 1 taxane population)

Safety data for Pluvicto® and cabazitaxel are presented below.

9.1.1 Safety data from the clinical documentation

The safety data for Pluvicto® is based on the FAS safety population from the VISION study (20). The FAS safety population consisted of all patients who received at least one dose of their allocated treatment. Of the 734 patients included in FAS safety, 529 were treated with Pluvicto®, and the remaining patients were treated with BSC/SoC. In addition to data on the FAS safety population, we present data from a post hoc analysis of the VISION study, investigating a subgroup of the study population who received a maximum of one prior taxane (46). AEs during the treatment period were those that occurred on or after the start of the randomised treatment, and up to 30 days after the last administration of the randomised treatment or before subsequent anticancer treatment. AEs were coded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

The safety data for cabazitaxel is based on the safety population from CARD (21), consisting entirely of patients who had undergone randomisation and had received at least one dose of trial treatment. Of the 250 patients included in the safety population, 126 were treated with cabazitaxel, and the remaining patients were treated with ARPI (abiraterone or enzalutamide). AEs were coded according to CTCAE, version 4.0.

Table 24 Overview of safety events at 38 months (VISION study) and 24 months (CARD study)

	VISION study		VISION post hoc		CARD study		Difference, % (95% CI)
	FAS safety (N=734) (20)		Maximum one prior taxane (N=453) (46)		Safety population (N=250) (21)		
	Pluvicto® (N=529)	BSC/SoC (N=205)	Pluvicto® (N=331)	BSC/SoC (N=122)	Cabazitaxel (N=126)	Abiraterone/ enzalutamide (N=124)	
Number of adverse events, n	NR	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse events, n (%)	519 (98.1)	170 (82.9)	328 (99.1)	101 (82.8)	124 (98.4)	117 (94.4)	NR
Number of serious adverse events, n	NR	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	192 (36.3)	57 (27.8)	117 (35.3)	35 (28.7)	49 (38.9)	48 (38.7)	NR
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	279 (52.7)	78 (38.0)	182 (55.0)	45 (36.9)	71 (56.3)	65 (52.4)	NR
Number of adverse reactions, n	NR	NR	NR	NR	NR	NR	NR
Number and proportion of patients who had ≥ 1 adverse reactions, n (%)	451 (85.3)	59 (28.8)	282 (85.2)	30 (24.6)	NR	NR	NR

	VISION study		VISION post hoc		CARD study		Difference, % (95% CI)
	FAS safety (N=734) (20)		Maximum one prior taxane (N=453) (46)		Safety population (N=250) (21)		
	Pluvicto® (N=529)	BSC/SoC (N=205)	Pluvicto® (N=331)	BSC/SoC (N=122)	Cabazitaxel (N=126)	Abiraterone/ enzalutamide (N=124)	
Number and proportion of patients who had a dose reduction, n (%)	30 (5.7)	7 (3.4)	19 (5.7)	6 (4.9)	27 (21.4)	47 (37.9)	NR
Number and proportion of patients who discontinued treatment regardless of reason, n (%)[a]	279 (45.4)[a]	196 (97.5)[b]	NR	NR	120 (95.2)	117 (94.4)	NR
Number and proportion of patients who discontinued treatment due to adverse events, n (%)	63 (11.9)	16 (7.8)	38 (11.5)	7 (5.7)	25 (19.8)	11 (8.9)	NR

[a] Patients who had been randomly assigned to receive Pluvicto® and who did not receive Pluvicto® but did receive SoC were included in the control group of the safety population; 1 patient (0.5%) had AEs during cycle 1 of Pluvicto® therapy that led to discontinuation. [b] N=201.

No SAEs occurred with a frequency of at least 5% in either treatment arm at the 27 January 2010 cutoff; therefore, Table 25 has not been filled out (52,53). A list of all SAEs observed in the FAS safety population from the VISION study is presented in Appendix E.

Table 25 Serious adverse events (time point)

Adverse events	Pluvicto® (N=529)		Cabazitaxel (N=126)	
	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs
AEs, n (%)	N/A	N/A	N/A	N/A

In the health economic model, safety data were included for all AEs of at least grade 3 if reported in more than 5% of patients for either Pluvicto® or cabazitaxel.

Table 26 Adverse events used in the health economic model

Adverse events	Pluvicto®	Cabazitaxel		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Anaemia, n (%)	68 (12.9)	10 (7.9)	(20,21)	More than 5% experienced grade 3 in either arm
Fatigue, n (%)	31 (5.9)	0 (0)	(20,21)	More than 5% experienced grade 3 in either arm
Neutropenia, n (%)	18 (3.4)	55 (43.7)	(20,21)	More than 5% experienced grade 3 in either arm
Thrombocytopenia, n (%)	42 (7.9)	4 (3.2)	(20,21)	More than 5% experienced grade 3 in either arm
Lymphopenia/ lymphocytopenia, n (%)	41 (7.8)	0 (0)	(20,21)	More than 5% experienced grade 3 in either arm
Leukopenia, n (%)	13 (2.5)	40 (31.7)	(20,21)	More than 5% experienced grade 3 in either arm
Infections, n (%)	58 (11)	10 (7.9)	(21,47)	More than 5% experienced grade 3 in either arm

9.1.2 Safety data from external literature applied in the health economic model

N/A. All safety data applied in the health economic model have been presented in Table 26.

Table 27 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with AEs	Number of AEs	Frequency used in economic model for intervention	Number of patients with AEs	Number of AEs	Frequency used in economic model for comparator	Number of patients with AEs	Number of AEs
AE, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

9.2 Safety of Pluvicto® compared to BSC/SoC for PSMA-positive mCRPC patients (Post 2 taxanes population)

Safety data for Pluvicto® and BSC/SoC for the Post 2 taxanes population are presented below.

9.2.1 Safety data from the clinical documentation

The safety data of Pluvicto® compared to BSC/SoC (Post 2 taxanes population) are based on the FAS safety population from the VISION study, consisting of all patients who received at least one dose of their allocated treatment (20). Of the 734 patients included in FAS safety, 529 were treated with Pluvicto® and 205 were treated with BSC/SoC. In addition to data on the FAS safety population, we present data from a post hoc analysis of the VISION study, investigating a subgroup of the study population who received at least two prior taxanes (46). AEs during the treatment period were those that occurred on or after the start of the randomised treatment, and up to 30 days after the last administration of the randomised treatment or before subsequent anticancer treatment. AEs were coded according to CTCAE, version 5.0.

Table 28 Overview of safety events at 38 months

	VISION study (20) FAS safety (N=734)		VISION study (post hoc) (46) Minimum two prior taxanes (N=234)		Difference, % (95% CI)
	Pluvicto® (N=529)	BSC/SoC (N=205)	Pluvicto® (N=160)	BSC/SoC (N=74)	
Number of adverse events, n	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse events, n (%)	519 (98.1)	170 (82.9)	154 (96.3)	60 (81.1)	NR
Number of serious adverse events*, n	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	192 (36.3)	57 (27.8)	64 (40.0)	20 (27.0)	NR
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events,§ n (%)	279 (52.7)	78 (38.0)	83 (51.9)	32 (43.2)	NR
Number of adverse reactions, n	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	451 (85.3)	59 (28.8)	136 (85.0)	22 (29.7)	NR
Number and proportion of patients who had a dose reduction, n (%)	30 (5.7)	7 (3.4)	9 (5.6)	1 (1.4)	NR
Number and proportion of patients who discontinued treatment regardless of reason, n (%)	279 (45.4)[a]	196 (97.5)[b]	NR	NR	NR

	VISION study (20) FAS safety (N=734)		VISION study (post hoc) (46) Minimum two prior taxanes (N=234)		Difference, % (95% CI)
	Pluvicto® (N=529)	BSC/SoC (N=205)	Pluvicto® (N=160)	BSC/SoC (N=74)	
Number and proportion of patients who discontinued treatment due to adverse events, n (%)	63 (11.9)	16 (7.8)	17 (10.6)	8 (10.8)	NR

[a] Patients who had been randomly assigned to receive Pluvicto® and who did not receive Pluvicto® but did receive SoC were included in the control group of the safety population; 1 patient (0.5%) had adverse events during cycle 1 of Pluvicto® therapy that led to discontinuation. [b] N=201.

No SAEs occurred with a frequency of at least 5% in either treatment arm at the 27 January 2010 cutoff, and therefore Table 29 has not been filled out. A list of all SAEs observed in the FAS safety population from the VISION study is presented in Appendix E.

Table 29 Serious adverse events

Adverse events	Pluvicto® (N=529)		BSC/SoC (N=205)	
	Number of patients with AEs	Number of AEs	Number of patients with AEs	Number of AEs
Adverse event, n (%)	N/A	N/A	N/A	N/A

In the health economic model, safety data was included for all AEs of at least grade 3 if reported in more than 5% of patients for either Pluvicto® or BSC/SoC. All safety data applied in the health economic model is presented in Table 30.

Table 30 Adverse events used in the health economic model

Adverse events	Pluvicto®	BSC/SoC		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Anaemia, n (%)	68 (12.9)	10 (4.9)	(20)	More than 5% experienced grade 3 in either arm.
Fatigue, n (%)	31 (5.9)	3 (1.5)	(20)	More than 5% experienced grade 3 in either arm.
Thrombocytopenia, n (%)	42 (7.9)	2 (1)	(20)	More than 5% experienced grade 3 in either arm.
Lymphopenia/lymphocytopenia, n (%)	41 (7.8)	1 (0.5)	(20)	More than 5% experienced grade 3 in either arm.
Infections, n (%)	58 (11)	9 (4.4)	(47)	More than 5% experienced grade 3 in either arm.

9.2.2 Safety data from external literature applied in the health economic model

N/A. No external literature on safety data were applied in the health economic model. All safety data applied in the health economic model is presented in Table 30.

Table 31 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with AEs	Number of AEs	Frequency used in economic model for intervention	Number of patients with AEs	Number of AEs	Frequency used in economic model for comparator	Number of patients with AEs	Number of AEs
AE, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

In this section, we present HRQoL results from both the EuroQol instrument and the FACT-P questionnaire from the VISION trial. Additionally, we present HRQoL results from the EuroQoL instrument from the CARD trial.

The EuroQoL (EQ) instrument consists of the EQ-5D-5L and the EQ-VAS (EuroQol-Visual Analogue Scale) score. The EQ-5D-5L, a well-validated instrument, comprises questions, asking subjects to indicate their health state at the time of survey by ticking the box next to the most appropriate statement in each of the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, unable. In addition, a health state assessment is made using a visual analogue scale (VAS). The assessment records the respondent's self-rated health on a 100 mm (or 100-point) vertical VAS, where 100 is labelled "Best imaginable health state" and 0 is labelled "Worst imaginable health state" (36,54).

The FACT-P questionnaire, a relevant and validated, worldwide tool used for assessing the HRQoL in men with prostate cancer, consists of the Functional Assessment of Cancer Therapy-General (27 items) and the Prostate Cancer Subscale (12 items), which is designed specifically to measure PC-specific quality of life. The FACT-P score (range 0–156) is the sum of these two scores (39 items), with higher scores indicating greater HRQoL. FACT-P subscales include physical well-being, social or family well-being, emotional well-being, functional well-being, prostate cancer subscale, and pain-related subscale. For the VISION trial, the trial outcome index is a composite of physical well-being, functional well-being, and prostate cancer subscales (36,55).

Table 32 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	VISION	Used to demonstrate the clinical effectiveness of Pluvicto® in terms of HRQoL and to generate utilities for the health economic model.
FACT-P	VISION	Used to demonstrate the clinical effectiveness of Pluvicto® in terms of HRQoL.
EQ-5D-5L	CARD*	Used to demonstrate the clinical effectiveness of cabazitaxel in terms of HRQoL.

*In CARD, HRQoL was also measured by FACT-P.

10.1 Presentation of the health-related quality of life measured with EQ-5D-5L data from VISION

10.1.1 Study design and measuring instrument

As previously described, mCRPC is an incurable and fatal disease. Patients with progressive mCRPC who have previously received ARPI and taxanes have few treatment options and are at high risk of impaired HRQoL, morbidity, and mortality (36). Receiving treatment for this type of cancer is associated with pronounced physical, emotional, and functional well-being impairment, and HRQoL is an important outcome to consider when making treatment decisions for patients with mCRPC. The application of EQ-5D-5L is in accordance with DMC guidelines.

10.1.2 Data collection

EQ-5D-5L and EQ-VAS data were collected in VISION at baseline, on the first day of every treatment cycle thereafter, and at the EOT visit. Patients in the intervention arm received Pluvicto® for up to 6 cycles and could then continue SoC for Cycles 7 and beyond. Data on QoL was collected until treatment discontinuation of the Pluvicto® or SoC, whichever came later. For the BSC/SoC arm, QoL data was collected until treatment discontinuation of the treatment. Data were also collected for each patient on the final visit (defined as the last assessment on or after the date of disease progression). The number of patients who provided EQ-5D-5L scores at each treatment cycle is presented in Table 33. HRQoL in the VISION study was self-reported by patients (or via interview format) using the EQ-5D-5L. Completion was defined as having at least one response captured at a scheduled visit. Information on the characteristics of patients with missing values is not available. No methods for imputation of missing data were prespecified.

Table 33 Pattern of missing data and completion for EQ-5D-5L, PFS-FAS

Time point	HRQoL population, N		Missing, N (%)		Expected to complete, N		Completion, N (%)	
	Number of patients at randomisation (PFS-FAS)		Number of patients for whom data is missing (% of patients at randomisation)*		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC
Baseline	385	196	18 (4.7)	10 (5.1)	385	196	367 (95)	186 (95)
Cycle 1	385	196	36 (9.4)	49 (25.0)	369	164	349 (95)	147 (90)
Cycle 2	385	196	50 (13.0)	94 (48.0)	349	115	335 (96)	102 (89)

Time point	HRQoL population, N		Missing, N (%)		Expected to complete, N		Completion, N (%)	
Cycle 3	385	196	89 (23.1)	141 (71.9)	308	61	296 (96)	55 (90)
Cycle 4	385	196	143 (37.1)	164 (83.7)	252	36	242 (96)	32 (89)
Cycle 5	385	196	188 (48.8)	175 (89.3)	208	24	197 (95)	21 (88)
Cycle 6	385	196	215 (55.8)	183 (93.4)	182	14	170 (93)	13 (93)
Cycle 7	385	196	258 (67.0)	185 (94.4)	-	-	127	11
Cycle 8	385	196	298 (77.4)	191 (97.4)	-	-	87	5
Cycle 9	385	196	329 (85.5)	190 (96.9)	-	-	56	6
Cycle 10	385	196	352 (91.4)	194 (99.0)	-	-	33	2
Cycle 11	385	196	373 (96.9)	194 (99.0)	-	-	12	2
Cycle 12	385	196	381 (98.9)	196 (100.0)	-	-	4	0
Cycle 13	385	196	384 (99.7)	196 (100.0)	-	-	1	0
EOT	385	196	208 (54.0)	109 (55.6)	354	192	177 (50)	87 (45)

*Difference between patients at randomisation and patients who completed the questionnaire. Source: Fizazi et al. 2023 supplementary appendix (36).

10.1.3 HRQoL results

The EQ-5D-5L values by treatment cycle are presented in Table 34. The EQ-VAS scores by treatment cycle are presented in Table 35 and the EQ-VAS scores displayed as mean change from baseline are presented in Figure 13. For treatment cycles 1 through 6, the EQ-VAS scores increased for the Pluvicto® treatment arm, whereas the mean change from baseline in the scores for the BSC/SoC treatment arm is negative, with wide confidence intervals especially for treatment cycles 5 and 6 due to low number of patients.

Table 34 HRQoL EQ-5D-5L summary statistics by treatment cycle

	Pluvicto®		BSC/SoC		Intervention vs. comparator
	N	Mean (SE*)	N	Mean (SE*)	Difference (95% CI) p-value
Baseline	351	0.711 (0.197)	186	0.721 (0.203)	N/A
Cycle 2	334	0.742 (0.209)	102	0.648 (0.256)	N/A
Cycle 3	296	0.749 (0.197)	55	0.715 (0.201)	N/A
Cycle 4	242	0.748 (0.207)	32	0.660 (0.276)	N/A
Cycle 5	197	0.758 (0.198)	21	0.673 (0.263)	N/A
Cycle 6	170	0.749 (0.203)	13	0.777 (0.173)	N/A
EOT	177	0.644 (0.244)	86	0.646 (0.258)	N/A

* SD is reported instead of SE. Note: N for each visit is the number of patients with non-missing score at that visit. “Intervention vs. comparator” not available. “Intervention vs. comparator” is not available. Source: Fizazi et al. 2023 supplementary appendix (36).

Table 35 HRQoL EQ-VAS scores summary statistics by treatment cycle

	Pluvicto®		BSC/SoC		Intervention vs. comparator
	N	Mean (SE*)	N	Mean (SE*)	Difference (95% CI) p-value*
Baseline	385	NR	196	NR	N/A
Cycle 1	351	68.3 (0.99)	185	68.5 (1.47)	0.20 (-3.28, 3.68), 0.910
Cycle 2	335	71.4 (1.07)	102	65.1 (2.21)	-6.30 (-11.11, -1.49), 0.011
Cycle 3	295	71.3 (1.16)	55	69.6 (3.13)	-1.70 (-8.24, 4.84), 0.611
Cycle 4	242	73.2 (1.22)	32	71.0 (3.47)	-2.20 (-9.41, 5.01), 0.550
Cycle 5	197	74.1 (1.27)	21	64.6 (5.59)	-9.50 (-20.73, 1.73), 0.099

	Pluvicto®		BSC/SoC		Intervention vs. comparator
Cycle 6	170	72.2 (1.62)	13	76.2 (4.44)	4.00 (-5.27, 13.27), 0.399
EOT	177	62.6 (1.78)	87	60.0 (2.58)	-2.60 (-8.75, 3.55), 0.408

*Calculated. Note: N for each visit is the number of patients with non-missing score at that visit. Source: Fizazi et al. 2023 supplementary appendix (36).

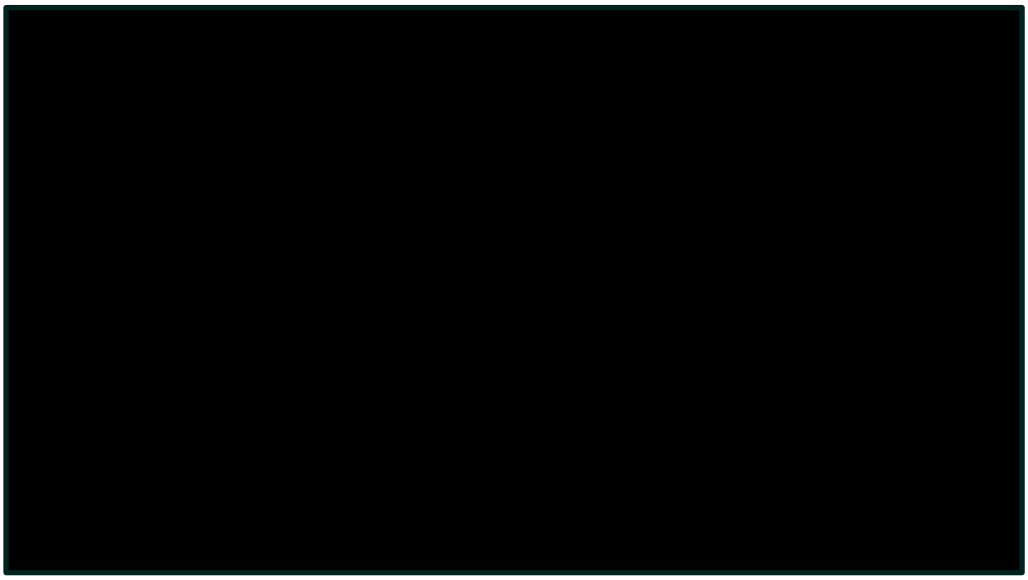

Figure 13 EQ-VAS scores, mean change from baseline

10.2 Presentation of the health-related quality of life measured with FACT-P data from VISION

10.2.1 Study design and measuring instrument

In VISION, the change from baseline in FACT-P total score was analysed using general linear models for repeated measures.

10.2.2 Data collection

As for EQ-5D-5L data, FACT-P data were collected at baseline, on the first day of every succeeding treatment cycle, and at the EOT visit. Data were also collected on the final visit of each patient, defined as the last assessment on or after the date of disease progression. The number of patients who provided FACT-P scores at each treatment cycle is presented in Table 36. Responses to the FACT-P questionnaire were elicited by self-administration or by interview. Questionnaire completion is defined as having at least one response captured at the scheduled visit. Further information on the

characteristics of patients with missing values is not available. No methods for imputation of missing data were prespecified.

Table 36 Pattern of missing data and completion for FACT-P, PFS-FAS

Time point	HRQoL population, N		Missing, N (%)		Expected to complete, N		Completion, N (%)	
	Number of patients at randomisation (PFS-FAS)		Number of patients for whom data is missing (% of patients at randomisation)*		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC	Pluvicto®	BSC/SoC
Baseline	385	196	18 (4.7)	10 (5.1)	385	196	367 (95)	186 (95)
Cycle 1	385	196	36 (9.4)	50 (25.5)	369	164	349 (95)	146 (89)
Cycle 2	385	196	50 (13.0)	94 (48.0)	349	115	335 (96)	102 (89)
Cycle 3	385	196	93 (24.2)	141 (71.9)	308	61	292 (95)	55 (90)
Cycle 4	385	196	142 (36.9)	164 (83.7)	252	36	243 (96)	32 (89)
Cycle 5	385	196	187 (48.6)	175 (89.3)	208	24	198 (95)	21 (88)
Cycle 6	385	196	215 (55.8)	183 (93.4)	182	14	170 (93)	13 (93)
EOT	385	196	210 (54.5)	109 (55.6)	354	192	175 (49)	87 (45)

*Difference between patients at randomisation and patients who completed the questionnaire. Source: Fizazi et al. 2023 supplementary appendix (36).

10.2.3 HRQoL results

Change from baseline in FACT-P total score by treatment cycle is presented in Table 37 and Figure 14. For treatment cycles 1 through 6, the FACT-P total scores increased for the Pluvicto® treatment arm, whereas the mean change from baseline in the scores for the BSC/SoC treatment arm is negative. As with the mean change from baseline for the EQ-VAS scores, low patient numbers, especially in cycles 5 and 6, led to wide confidence intervals for the BSC/SoC arm.

Table 37 HRQoL FACT-P total scores summary statistics by treatment cycle

	Pluvicto® (N=385)		BSC/SoC (N=196)		Intervention vs. comparator
	N	Mean (SE*)	N	Mean (SE*)	Difference (95% CI) p-value*
Baseline	352	108.4 (1.08)	186	110.1 (1.46)	1.70 (-1.87, 5.27), 0.351
Cycle 2	334	112.7 (1.13)	102	105.6 (2.22)	-7.10 (-11.99, -2.21), 0.005
Change from baseline	304	3.6 (0.95)	100	-7.2 (1.79)	-10.80 (-14.77, -6.83), <0.001
Cycle 3	292	113.2 (1.20)	54	110.2 (2.87)	-3.00 (-9.10, 3.10), 0.336
Change from baseline	269	3.8 (1.07)	52	-2.6 (1.94)	-6.40 (-10.74, -2.06), 0.004
Cycle 4	243	114.3 (1.39)	32	110.5 (3.77)	-3.80 (-11.67, 4.07), 0.345
Change from baseline	222	5.4 (1.07)	32	-1.3 (3.25)	-6.70 (-13.41, 0.01), 0.051
Cycle 5	198	114.1 (1.52)	21	106.3 (5.73)	-7.80 (-19.41, 3.81), 0.189
Change from baseline	181	4.0 (1.21)	21	-5.9 (6.07)	-9.90 (-22.04, 2.24), 0.111
Cycle 6	169	114.3 (1.71)	13	114.5 (6.65)	0.20 (-13.26, 13.66), 0.977
Change from baseline	158	4.1 (1.21)	13	-5.0 (7.45)	-9.10 (23.90, 5.70), 0.230
EOT	175	101.7 (1.82)	87	101.8 (2.71)	0.10 (-6.31,6.51), 0.976
Change from baseline	161	-9.4 (1.71)	86	-10.4 (2.00)	-1.00 (-6.16, 4.16), 0.704

*Calculated. Note: N for each visit is the number of patients with non-missing score at that visit. Source: Fizazi et al. 2023 supplementary appendix (36).

Figure 14 Mean change from baseline in FACT-P total score

10.3 Presentation of the health-related quality of life measured with EQ-5D-5L data from CARD

10.3.1 Study design and measuring instrument

Please see details in section 10.1.1.

10.3.2 Data collection

In CARD, HRQoL assessments were carried out at baseline, every 3 weeks at each visit, and then every 12 weeks until disease progression, start of subsequent cancer therapy, or data cutoff date, whichever came first. The number of patients who provided EQ-5D-5L scores at each treatment cycle is presented in Table 38. Each assessment was done by means of paper and pencil versions and no assistance was given to patients while they were completing the forms. No formal imputation for missing data was done, and reasons for missing data were not centrally recorded.

Table 38 Pattern of missing data and completion for EQ-5D-5L

Time point	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)*

Time point	HRQoL population, N		Missing, N (%)		Expected to complete, N		Completion, N (%)	
	Cabazitaxel	Abiraterone/enzalutamide	Cabazitaxel	Abiraterone/enzalutamide	Cabazitaxel	Abiraterone/enzalutamide	Cabazitaxel	Abiraterone/enzalutamide
Baseline	129	126	6 (4.7)	5 (4.0)	129	126	123 (95)	121 (96)
Cycle 2	129	126	13 (10.1)	8 (6.3)	122	123	116 (95)	118 (96)
Cycle 3	129	126	18 (14.0)	20 (15.9)	118	116	111 (94)	106 (91)
Cycle 4	129	126	21 (16.3)	34 (27.0)	114	98	108 (95)	92 (94)
Cycle 5	129	126	40 (31.0)	61 (48.4)	97	69	89 (92)	65 (94)
Cycle 6	129	126	53 (41.1)	79 (62.7)	84	50	76 (91)	47 (94)
Cycle 7	129	126	61 (47.3)	86 (68.3)	70	42	68 (97)	40 (95)
Cycle 8	129	126	70 (54.3)	98 (77.8)	62	34	59 (95)	28 (82)
EOT	129	126	-	-	NR	NR	NR	NR

*≥50% items complete.

10.3.3 HRQoL results

The mean baseline values for EQ-5D-5L utility index were 0.70 (SD 0.26) for the cabazitaxel group and 0.70 (SD 0.22) for the abiraterone/enzalutamide group). Additionally, the mean baseline EQ-VAS scores were 65.8 (SD 20.4) in the cabazitaxel group and 66.3 (SD 18.5) in the abiraterone/enzalutamide group. Results per cycle are not presented in the CARD study. Figure 15 presents the mean change from baseline the HRQoL scores

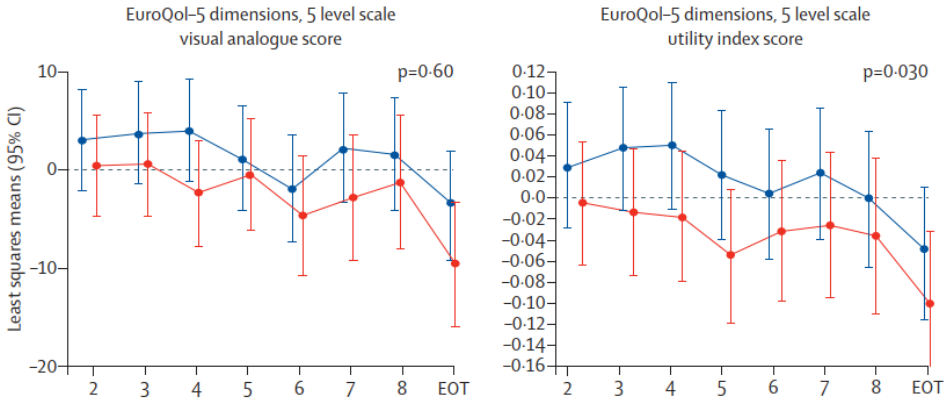

Figure 15 Mean change from baseline in EQ-5D-5L utility index score (left) and VAS score (right)

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

10.4.1 HSUV calculation

VISION utility data weighted by the Danish preference value set were used to inform the health economic model (56). State-specific utilities were defined for the following health states in the health economic model:

- Post 1 taxane population
  - Pre-progressed state
  - Progressed state
- Post 2 taxanes population
  - Pre-progressed state
  - Progressed state

Death = 0.

Furthermore, using the VISION patient-level data, treatment specific HSUVs were derived and included in a sensitivity analysis. Since, patient-level data for patients with mCRPC treated with cabazitaxel were not available, an assumption was made that patients treated with cabazitaxel have the same HSUVs as patients treated with Pluvicto® in both the pre-progressed and progressed health states. All relevant HSUVs are presented in Table 39.

10.4.1.1 Mapping

N/A

10.4.2 Disutility calculation and age adjustment

Treatment with Pluvicto®, cabazitaxel, and BSC/SoC is associated with AEs. Generally, disutility values for AEs (experienced by at least 5% of patients) are included in the health economic analysis. However, since the applied HSUVs are based on self-reported

patient-level data from the VISION trial, patients will have included the possible discomfort of an experienced AE when completing the EQ-5D-5L questionnaire. Thus, to avoid double counting, disutilities associated with AEs are not included in the health economic model.

Likewise, no age adjustment of the HSUVs was done. As described earlier, it is valid to assume that the Danish population is similar to the population included in the VISION study. The applied HSUVs are based on a population with a median age of 72 years (as in VISION trial participants: 71 years for the Pluvicto® arm, 72 years for the BSC/SoC arm, and 72 years for the Danish PC population). Based on the DMC guidelines regarding age adjustment, a population aged 70-79 can be considered to have the same baseline utility (57). Therefore, age adjustment should not be performed until the model population reaches 80 years of age. Given the model's 10-year time horizon and the fact that very few patients are expected to survive to the age of 80 (see Section 6.1.5), age adjustment of utility values was deemed irrelevant for the analysis.

10.4.3 HSUV results

As described in section 10.4.1, both health state specific HSUVs and treatment specific HSUVs were derived from VISION. Health state specific HSUVs were included in the base case analysis, whereas treatment specific HSUVs were included in a sensitivity analysis to reflect differences between Pluvicto® and comparators. All relevant HSUVs are presented in Table 39.

Table 39 Overview of health state utility values (EQ-5D health state utilities) derived from VISION patient-level data (Danish weight set)

	Results [95% CI]	Instrument	Patient number	Number of observations	Tariff (value set) used	Comments
Health state specific HSUVs (Post 1 taxane population)						
Pre-progressed	0.814 [0.805-0.823]	EQ-5D-5L	478	1946	DK	Used in base case analysis
Progressed	0.756 [0.725-0.786]	EQ-5D-5L	209	272	DK	Used in base case analysis
Health state specific HSUVs (Post 2 taxanes population)						
Pre-progressed	0.818 [0.806-0.830	EQ-5D-5L	345	1232	DK	Used in base case analysis
Progressed	0.786 [0.745-0.824]	EQ-5D-5L	126	171	DK	Used in base case analysis
Treatment specific HSUVs (Post 1 taxane population)						
Pre-progressed: Pluvicto®	0.824 [0.814-0.834]	EQ-5D-5L	323	1633	DK	Used in sensitivity analysis
Progressed: Pluvicto®	0.751 [0.717-0.783]	EQ-5D-5L	170	230	DK	Used in sensitivity analysis
Pre-progressed: Cabazitaxel	Assumed to be equal to BSC®					Used in sensitivity analysis
Progressed: Cabazitaxel	Assumed to be equal to BSC®					Used in sensitivity analysis
Treatment specific HSUVs (Post 2 taxanes population)						

	Results [95% CI]	Instrument	Patient number	Number of observations	Tariff (value set) used	Comments
Pre-progressed: Pluvicto®	0.829 [0.817-0.841]	EQ-5D-5L	226	1016	DK	Used in sensitivity analysis
Progressed: Pluvicto®	0.811 [0.777-0.843]	EQ-5D-5L	99	141	DK	Used in sensitivity analysis
Pre-progressed: BSC/Soc	0.766 [0.732-0.798]	EQ-5D-5L	119	216	DK	Used in sensitivity analysis
Progressed: BSC/SoC	0.668 [0.593-0.739]	EQ-5D-5L	27	30	DK	Used in sensitivity analysis

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

N/A

10.5.1 Study design

N/A

10.5.2 Data collection

N/A

10.5.3 HRQoL Results

N/A

10.5.4 HSUV and disutility results

N/A

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 41 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

All costs (including medicines, administration, disease management, AE management, subsequent treatment, patient and other costs) related to treating PSMA-positive mCRPC patients with Pluvicto®, cabazitaxel, and BSC/SoC were included in the model. Estimates on resource use and unit costs were based on inputs from the clinical expert, the VISION study, the SmPC's of Pluvicto®, cabazitaxel and other pharmacological treatments included in BSC/SoC as well as selected assumptions. Descriptions of each cost element and how the element was valued in the health economic analysis are presented below.

11.1 Medicines - intervention and comparator

The intervention and comparator medicines included in the model were Pluvicto®, cabazitaxel, and BSC/SoC treatments (see Table 42). BSC/SoC treatments were sourced from the DMC evaluation of olaparib for mCRPC and validated by the clinical expert. The treatments comprised denosumab 120 mg subcutaneously (SC) every fourth week, morphine 10 mg orally once daily, and dexamethasone 1 mg orally once daily.

All patients in the model received BSC/SoC throughout the model's time horizon or until death. Treatments with Pluvicto® and cabazitaxel were used as a supplement to BSC/SoC. According to the clinical expert, some BSC/SoC patients do not require morphine and dexamethasone. However, due to the low cost of these drugs, adding them to the model for all patients was considered acceptable.

According to the clinical expert, the syringes for cabazitaxel treatment are prepared by the hospital pharmacy. Consequently, no waste due to half-empty vials being discarded was anticipated. However, the clinical expert informed us that due to acute illness, some patients treated with cabazitaxel miss planned treatments, resulting in an estimated 10% drug waste as the syringes prepared by the hospital pharmacy cannot not be reused. The clinical expert explained that patients treated with cabazitaxel receive 20 mg/m^2 and has an average body surface area of 1.9m^2, resulting in a dose of 38 mg per administration.

No waste was assumed for Pluvicto®, as treatment dosages are the same for all patients. Unlike cabazitaxel, which requires patient-specific dose preparation, making reuse impractical, Pluvicto® doses can be reassigned to another patient in the event of an acute illness that prevents the originally scheduled treatment.

All medicine costs were based on the pharmacy purchasing price (PPP) obtained in April 2025. The PPPs of the packages included are presented below (see Table 43).

Table 42 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Pluvicto®	7,400 MBq	Not included	Every 6 weeks (±1 week), up to a total of 6 doses	N/A
Cabazitaxel	38 mg	Not included	Every 3 weeks	Yes
Dexamethasone	1 mg	Not included	Once per day	N/A
Morphine	10 mg	Not included	Once per day	N/A
Denosumab	120 mg	Not included	Once every fourth week	N/A

Table 43 Package information on Pluvicto®, cabazitaxel, and BSC/SoC (source: Medicinpriser.dk, April 2025)

Pharmaceutical	Strength	Package size	PPP, DKK
Pluvicto®	1,000 MBq/ml	1 vial	150,000*
Cabazitaxel	10 mg/ml	5 x 6 ml	105,000
Dexamethasone	1 mg	100 tablets	518
Morphine	10 mg	100 tablets	64**
Denosumab	120 mg	1 vial	1,858

*Provided by Novartis and reported to the Danish Medicines Agency on 6 January 2025. **The cost of the 30 mg tablets was used as substitute for the 10 mg tablets (Contalgin), as this dose is currently withdrawn from the Danish market. Due to the low cost of morphine, this is assumed to be acceptable.

11.2 Medicines– co-administration

No co-administrations are necessary for Pluvicto® or cabazitaxel. According to a reference from Rigshospitalet on treatment with Pluvicto® (58), 25 mg prednisolone and 8 mg ondansetron should be taken 30 minutes prior to infusion with Pluvicto® to avoid nausea. According to a reference from Herlev Hospital on treatment with cabazitaxel (29), patients should receive 10 mg prednisolone daily during treatment as well as 50 mg prednisolone both the night before and 2 hours before cabazitaxel infusion. Given the relatively low costs of prednisolone and ondansetron, these products were not included in the model.

11.3 Administration costs

11.3.1 Pluvicto administration

Pluvicto® is administered IV at the hospital every 6 weeks, up to a total of 6 doses (59). In the model, a median of [redacted] doses was applied (47).

Pluvicto® infusions can be administered at outpatient visits. The unit cost for the outpatient visits for IV administrations of Pluvicto® was based on the DRG 2025 tariff 11MA98 (DKK 1,543) obtained by combining the diagnosis code DC619Z with the procedure code BWGG6C in interactive DRG.

11.3.2 Cabazitaxel administration

Cabazitaxel is administered IV at the hospital every 3 weeks (29). According to the clinical expert, patients receive an average of 6 administrations of cabazitaxel. The treatment can be administered at an outpatient visit (29). According to the clinical experts, blood

tests are done the day before the cabazitaxel administration. As such, two outpatient visits were included for each administration with cabazitaxel.

The unit cost for the outpatient visits was based on the DRG 2025 tariff 11MA98 (DKK 1,543), obtained by combining the diagnosis code DC619Z with the procedure codes BWAA6 and DR798 in interactive DRG.

11.3.3 BSC/SoC administration

As mentioned in section 11.1, the BSC/SoC arm of the model comprises denosumab, morphine, and dexamethasone. Denosumab is administered SC, while morphine and dexamethasone are administered orally. It was assumed that patients would administer denosumab at home after having received training in the administration technique. Thus, no administration costs for BSC/SoC were included in the model.

Table 44 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient IV infusion of Pluvicto®	Every 6 weeks	1,543	11MA98	DRG 2025
Outpatient IV infusion of cabazitaxel	Every 3 weeks	1,543 (2 visits)	11MA98	DRG 2025

11.4 Disease management costs

Disease management costs were included in the analysis because patients with PSMA-positive mCRPC are regularly monitored at the hospital. These follow-up visits are conducted in addition to the visits described in section 11.3. The resource use was based on input from the clinical expert. The frequencies and costs are presented below (see Table 45). Additionally, several pre-examinations relevant for patients treated with Pluvicto® are described in section 11.4.1.

11.4.1 Pluvicto management costs

Before the first administration with Pluvicto®, patients have to undergo a thorough check-up which includes blood tests, an ECG, a bone scan, and either a CT scan or an MR scan to assess whether the patient is eligible for Pluvicto® treatment (58). If the patient is eligible, an additional PET-CT scan will be done to assess whether PSMA is present on the surface of the cancer cells.

The costs of the blood tests and the ECG were based on one outpatient visit, DRG 2025 tariff 11MA98 (DKK 1,543); the bone scan was based on DRG 2025 tariff 30PR19 (DKK 1,811); the CT or MR scan was based on DRG 2025 tariff 30PR06 (DKK 2,701); and the PET-CT scan was based on DRG 2025 tariff 36PR02 (DKK 8,492) (see Table 45).

Table 45 Pluvicto® pre-examinations prior to treatment initiation

Activity	Frequency	Unit cost (DKK)	DRG code	Reference	Applied codes
Blood test and ECG	Once	1,543	11MA98	DRG 2025	Diagnosis code: DC619Z Procedure codes: ZZ4299, ZZ3925
Bone scan	Once	1,811	30PR19	DRG 2025	Diagnosis code: DC619Z Procedure codes: UXRH00
CT scan	Once	2,701	30PR06	DRG 2025	Diagnosis code: DC619Z Procedure codes: UXCD61
PET/CT scan	Once	8,492	36PR02	DRG 2025	Diagnosis code: DC619Z Procedure codes: WMFCSXYXX, WDTPSXYXX

According to the clinical expert, for a general assessment of disease progression, patients treated with Pluvicto® were expected to have a follow-up outpatient visit every 6 weeks, and a CT scan and a bone scan every 3 months, during the active treatment. In the pre-progressed health state after the active treatment has stopped, the clinical expert expected that patients would have a follow-up outpatient visit, a CT scan, and a bone scan every 3 months.

11.4.2 Cabazitaxel management costs

According to the clinical expert, patients treated with cabazitaxel should have an outpatient visit every 3 weeks and should undergo a CT scan and a bone scan every 3 months during the active treatment phase. Once the active treatment is completed and patients remain in the pre-progressed state, they are monitored less intensively, with significant variation in the frequency of follow-ups and scans. The expert estimated that most patients would have one outpatient visit every 3 months, while CT and bone scans would be performed very rarely. Consequently, in the analysis, we did not include any CT or bone scans in the pre-progressed health state.

11.4.3 BSC/SoC management costs

According to the clinical expert, patients receiving BSC/SoC alone would have one outpatient visit every 6 months and would not receive any CT or bone scans.

Table 46 Disease management costs used in the model

Activity	Frequency					Unit cost (DKK)	DRG code (DRG 2025)
	Pluvicto®		Cabazitaxel		BSC/SoC		
	Active treatment	Pre-progressed	Active treatment	Pre-progressed	Active treatment/ post-progressed		
Outpatient visit	Every 6 weeks	Every 13 weeks	Every 3 week	Every 13 weeks	Every 26 weeks	1,543	11MA98
CT scan	Every 13 weeks	Every 13 weeks	Every 13 weeks	None	None	2,701	30PR06
Bone scan	Every 13 weeks	Every 13 weeks	Every 13 weeks	None	None	1,811	30PR19

11.5 Costs associated with management of adverse events

This section describes the costs associated with AEs and SSEs.

11.5.1 Adverse events

The cost of AEs has been applied in the model as a one-time cost based on section 9. Only AEs with an incidence of 5% or higher in one of the treatment arms have been included. Based on inputs from the clinical expert, there are only two AEs with an incidence of 5% or higher requiring treatment: infection and neutropenia. According to the clinical expert, patients experiencing these AEs would typically be treated with antibiotics. In the analysis, we assumed one outpatient visit for each of these AEs where patients would receive the antibiotic treatment. The cost of this was based on the DRG 2025 tariff 11MA98 (DKK 1,543) (see Table 47).

Table 47 Cost associated with management of adverse events

	DRG code	Unit cost (DKK)/DRG tariff
Neutropenia	11MA98	1,543
Infection	11MA98	1,543

11.5.2 Symptomatic skeletal events

SSEs were also included in the analysis. SSEs were recorded in VISION as a secondary endpoint. The costs of SSEs were based on the total risk of experiencing an SSE reported in the VISION study (Pluvicto® and BSC/SoC) (36) and the CARD study (cabazitaxel) (21).

The costs of SSEs were included as a cost at time of progression. There were 256 events (66.5%; 60 SSE events and 196 deaths) in the Pluvicto® arm, and 137 events (69.9%; 34 SSE events and 103 deaths) in the BSC/SoC arm (36). This implies that 60 out of 385 patients (15.6%) in the Pluvicto® arm and 34 out of 196 patients (17.3%) in the BSC/SoC arm had an SSE event during follow-up. This risk of SSEs for patients treated with cabazitaxel was 18.6% during follow-up (21).

As mentioned in section 4.1.1, there are four main types of SSEs: radiation to bone, pathological fracture, surgery to bone, and spinal cord compression. The risk of SSEs and the unit cost for each SSE by event type are presented in Table 48. The clinical expert expected that the distribution of SSEs by type of event among Danish patients would be the same as in VISION. Thus, the SSE distribution in the model was based on the PFS-FAS overall population from VISION.

Table 48 Distribution and costs associated with management of SSEs (SSE distribution: data on file)

Event	Pluvicto®	BSC/SoC	Cabazitaxel	Unit cost (DKK)	Note
Patients with at least one SSE	15.6%	17.3%	18.6%	-	(21,36)
SSE distribution					
Radiation to bone		59.3%		11,505	DRG 2025: 27MP14 Diagnosis code: DC619Z Procedure codes: BWGA10, BWGC1
Pathological fracture		13.6%		46,114	DRG 2025: 08MA02 Diagnosis code: DM844, DC619Z Procedure codes: N/A
Surgery to bone		11.9%		29,552	DRG 2025: 08MP59 Diagnosis code: DM844A, DC619Z

Event	Pluvicto®	BSC/SoC	Cabazitaxel	Unit cost (DKK)	Note
					Procedure codes: KNAK12
Spinal cord compression		15.3%		54,790	DRG 2025: 08MP06 Diagnosis code: DM844A, DC619Z Procedure codes: KABC99
Total for all SSEs		100%			

Note: The SSE distribution presented in the table consists of rounded numbers.

11.6 Subsequent treatment costs

The cost of subsequent treatments was applied in the model as a one-off cost at the time of disease progression. The subsequent treatments included in the model were based on consultations with the clinical expert and are presented in Table 49. The proportion of patients receiving each subsequent therapy was based on inputs from the clinical expert to ensure this reflected Danish clinical practice. The medicine costs and administration costs associated with subsequent treatments are presented in Table 50.

According to the clinical expert, three subsequent treatments were relevant in the analysis. Cabazitaxel was relevant only for the patients in the Post 1 taxane population, as these were the only patients who had not received this treatment already. The clinical expert expected that about [redacted]% of patients would be treated with cabazitaxel.

Radium-223 dichloride was considered a relevant subsequent treatment for the population previously treated with cabazitaxel in the Post 1 taxane population, but not for those treated with Pluvicto® or BSC/SoC. According to the clinical expert, about 50% of the relevant patients would receive an average of 4 treatments of radium-223.

Radiotherapy was also considered relevant as a subsequent treatment after Pluvicto® and cabazitaxel, but not for patients receiving BSC/SoC as they would not benefit from additional treatment. According to the clinical expert, patients would receive 1–5 fractions of radiotherapy. In the analysis, we assumed that patients would receive 2 fractions on average. The expert estimated that 5% of patients previously treated with Pluvicto® and cabazitaxel would receive radiotherapy as subsequent treatment.

Table 49 Medicines of subsequent treatments

Medicine	Dose	Strength	Pack size	Relative dose intensity	Number of dosages/treatments	PPP (DKK)	Vial sharing	Source
Cabazitaxel	38 mg	10 mg/ml	5 x 6 ml	N/A	6	100,500	Yes	Medicinpriser.dk
Radium-223 dichloride	6,000 KBq	6,000 KBq	1 vial	N/A	4	31,648*	N/A	(60)
Radiotherapy	N/A	N/A	N/A	N/A	2	11,505	N/A	DRG 2025: 27MP14

*No price available in Denmark. We used the TLV Health economic evaluation of Xofigo (assumes 1 syringe per 28 days, valid up to 132 kg body weight) to estimate the cost of radium-223. PPP was calculated using pharmacy markup in Sweden in 2014 (SEK 38,600) and converted to DKK using the average exchange rate (DKK:SEK) in 2014.

Table 50 Proportion of patients receiving subsequent therapy (source: clinical expert)

Therapy	% after Pluvicto® (Post 1 taxane population)	% after Pluvicto® (Post 2 taxanes population)	% after BSC/SoC	% after cabazitaxel	Number of treatment cycles	Administration cost (DKK)
Cabazitaxel	[redacted]%	0%	0%	0%	6	3,086 (DRG 2025: 11MA98)
Radium-223 dichloride	0%	0%	0%	50%	4	1,543 (DRG 2025: 11MA98)
Radiotherapy	5%	5%	0%	5%	2	N/A

11.7 Patient costs

In accordance with DMC guidelines, patient-related time use, and transportation costs were included in the model. The patient time associated with Pluvicto®, cabazitaxel, and BSC/SoC treatments was based on the time spent on both treatment-related activities and travelling to and from the hospital. Based on the DMC guidelines, a cost of DKK 188 per patient hour was applied. Neither caregiver time or costs nor patient costs related to AEs or subsequent treatments were included in the model.

In terms of transportation, 20 km to and from the hospital (40 km in total per visit) was assumed. In accordance with DMC guidelines, a transportation cost of DKK 140 was applied for each hospital visit. It was assumed that patients spend 30 minutes on transportation to and from the hospital, i.e. 60 minutes per visit. The activities to which patient time use and transportation were ascribed — and the time spent by the patient on each activity, including 60 minutes of transportation — are presented in Table 51.

11.7.1 Pluvicto® patient costs

As described previously, prior to initiating Pluvicto® treatment, the patient needs to undergo a thorough check-up. It was assumed that the ECG and the blood test were performed at an outpatient visit lasting 20 minutes, while the bone scan, the CT/MR scan, and the PET-CT scan took 30 minutes each. It was further assumed that the blood test, ECG, bone scan, and CT/MR scan would be conducted during the same hospital visit, while the PET/CT would be conducted at a separate visit. Thus, these pre-examinations resulted in a total of 3.83 hours per patient, including 2 hours of transportation.

Each Pluvicto® infusion takes approximately 30 minutes, but the patient must remain at the hospital for 6 hours. Thus, it was assumed that the outpatient administrations of Pluvicto® were associated with 6.5 hours of patient time at the hospital plus 1 hour of transportation, i.e. 7.5 hours in total per outpatient administration.

11.7.2 Cabazitaxel patient time

Cabazitaxel is administered at outpatient visits, and the infusion takes approximately 1 hour (61). An additional 1.5 hours were included in the model to account for waiting time and preparation of the infusion. Blood tests are performed the day prior to each treatment in order to assess PSA levels and do other blood work (61). The blood tests were assumed to take 15 minutes. As such, with two visits to the hospital (i.e. 2 hours of transportation) included in the model for each administration with cabazitaxel, 3.75 hours of patient time were included per administration.

Pre-medication with prednisolone the night before treatment with cabazitaxel (29) was assumed to take place in the patient's own home. Thus, no patient time was included for the pre-medication.

11.7.3 BSC/SoC patient time

No patient time was included for treatment with BSC/SoC.

11.7.4 Patient costs associated with monitoring

According to the clinical expert, an outpatient visit typically takes about 20 minutes, and as described both CT and bone scans each take approximately 30 minutes. In the analysis we included 1 hour of transportation for each monitoring visit. The frequency of monitoring visits is presented in section 11.4.

Table 51 Patient costs used in the model

Activity	Time spent (minutes, hours)	Visits to hospital
Diagnostic tests prior to first administration with Pluvicto®	3.83 hours	2
Pluvicto® infusions (outpatient)	7.5 hours	1
Cabazitaxel administration + blood tests (per infusion)	3.75 hours	2
Outpatient visit (monitoring)	1.33 hours	1
CT scan (monitoring)	1.5 hours	1
Bone scan (monitoring)	1.5 hours	1

Note: Time estimates include transportation time (1 hour per visit).

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

Costs associated with palliative care were included in the model based on the DRG 2025 tariff 26MP47 of DKK 89,879. This cost was applied to all persons in the model who died.

12. Results

12.1 Base case overview

Table 52 provides an overview of the settings applied in the base case of the cost-effectiveness analysis for the Post 1 taxane population and the Post 2 taxanes population.

Table 52 Base case overview

Feature	Description
Comparator	Post 1 taxane population: Cabazitaxel Post 2 taxanes population: BSC/SoC
Type of model	Partitioned survival model
Time horizon	10 years (lifetime)
Treatment line	Post 1 taxane population: After ARPI and docetaxel Post 2 taxanes population: After ARPI, docetaxel, and cabazitaxel
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L as reported in VISION; Danish population weights were used to estimate HSUVs
Costs included	Medicine costs Administration costs Disease management costs Costs of AEs Patient and transportation costs
Dosage of medicine	Pluvicto®: 7,400 MBq Cabazitaxel: Based on body surface area (20 mg/m^2) BSC/SoC: Dexamethasone 1 mg, morphine 10 mg, denosumab 120 mg
Average time on treatment	Pluvicto®: 6.1 months ([redacted] treatment cycles) Cabazitaxel: 4.1 months (6 treatment cycles) BSC/SoC: Lifelong
Parametric function for rPFS	Post 1 taxane population: Flexible Weibull (2 knots) Post 2 taxanes population: Stratified flexible Weibull (3 knots)
Parametric function for OS	Post 1 taxane population: Gamma Post 2 taxanes population: Stratified flexible Weibull (2 knots)
Inclusion of waste	10% for cabazitaxel 0% for Pluvicto®

Feature	Description			
Average time in model health state (months)	Post 1 taxane population		Post 2 taxanes population	
Treatment	Pluvicto®	Cabazitaxel	Pluvicto®	BSC/SoC
Progression-free	8.8	4.8	8.6	4.8
Progressed	13.8	11.0	7.8	7.5
Death	97.4	104.3	103.6	107.7

12.1.1 Base case results (Post 1 taxane population)

Table 53 shows the incremental cost and the incremental QALY per patient for Pluvicto® compared to cabazitaxel (Post 1 taxane population) with a 10-year time horizon.

Please note that numbers have been rounded and therefore they may not add up.

Table 53 Base case results of Pluvicto® compared to cabazitaxel (Post 1 taxane population), discounted estimates (DKK)

	Pluvicto®	Cabazitaxel	Difference
Medicine costs	[redacted]	121,650	[redacted]
Medicine costs – co-administration	0	0	0
Administration	6,875	18,516	-11,641
Disease management costs	35,095	14,895	20,199
Costs associated with management of adverse events	4,066	5,426	-1,360
Subsequent treatment costs	[redacted]	66,812	[redacted]
Patient costs	12,657	9,381	3,276
Palliative care costs	85,673	87,363	-1,690
Total Cost	[redacted]	**324,044**	[redacted]
Life years gained (pre-progressed)	0.73	0.40	0.33
Life years gained (progressed)	1.09	0.89	0.20
Total life years	**1.82**	**1.28**	**0.54**
QALYs gained (pre-progressed)	0.59	0.32	0.27

	Pluvicto®	Cabazitaxel	Difference
QALYs gained (progressed)	0.83	0.67	0.15
Total QALYS	**1.42**	**0.99**	**0.42**
Incremental costs per life year gained		**1,030,949**	
Incremental cost per QALY gained (ICER)		**1,301,927**	

12.1.2 Base case results (Post 2 taxanes population)

Table 54 presents the incremental cost and the incremental QALY per patient for Pluvicto® compared to BSC/SoC (Post 2 taxanes population) with a 10-year time horizon.

Again, please note that numbers have been rounded and therefore they may not add up.

Table 54 Base case results of Pluvicto® compared to BSC/SoC (Post 2 taxanes population), discounted estimates (DKK)

	Pluvicto®	BSC/SoC	Difference
Medicine costs	[redacted]	26,792	[redacted]
Medicine costs – co-administration	0	0	0
Administration	6,875	0	6,875
Disease management costs	33,350	3,147	30,203
Costs associated with management of adverse events	4,016	4,385	-369
Subsequent treatment costs	[redacted]	0	[redacted]
Patient costs	12,415	797	11,618
Palliative care costs	87,242	88,121	-879
Total Cost	[redacted]	**123,242**	[redacted]
Life years gained (pre-progressed)	0.71	0.40	0.31
Life years gained (progressed)	0.63	0.62	0.01
Total life years	**1.34**	**1.02**	**0.33**
QALYs gained (pre-progressed)	0.58	0.33	0.26

	Pluvicto®	BSC/SoC	Difference
QALYs gained (progressed)	0.49	0.48	0.01
Total QALYS	**1.08**	**0.81**	**0.27**
Incremental costs per life year gained		**2,227,235**	
Incremental cost per QALY gained (ICER)		**2,726,482**	

When comparing the ICER for the two populations included in this application, the ICER for the Post 1 taxane group is half the size of the ICER for the Post 2 taxanes group. This result is driven by more life years/QALYs gained and lower cost difference for the Post 1 taxane group.

12.2 Sensitivity analyses

Uncertainty about the input parameters in the model has been explored through deterministic sensitivity analyses (DSA), a probabilistic sensitivity analysis (PSA), and scenario analyses. These are presented below.

12.2.1 Deterministic sensitivity analyses (Post 1 taxane population)

The DSAs included in the present application are presented in Table 55 for the Post 1 taxane population. A tornado diagram with the 10 most influential parameters is presented in Figure 16. While the DSA demonstrates a widespread in the ICER when varying the HR for OS, it is important to recognize that this variation reflects the full span of the 95% CI, not the relative likelihood of each value within that interval.

The base case HR represents the most statistically plausible value, as it corresponds to the point estimate derived from the underlying NMA. In contrast, the outer bounds of the 95% CI are by definition less likely to reflect the true HR. The probability density of the HR distribution is highest near the point estimate and decreases toward the tails of the CI. Therefore, ICERs associated with extreme HR values in the DSA should be interpreted with caution, as they are based on less probable scenarios.

Table 55 Deterministic sensitivity analysis results (Post 1 taxane population)

	Low value	High value	Reason/ rationale/ source	ICER lower bound case (DKK/QALY)	ICER upper bound case (DKK/QALY)
Base case				[redacted]	
HR (Pluvicto vs Cabazitaxel). OS	0.45	0.84	95% CI	[redacted]	[redacted]

	Low value	High value	Reason/ rationale/ source	ICER lower bound case (DKK/QALY)	ICER upper bound case (DKK/QALY)
Pluvicto. Number of cycles	4.31	4.60	95% CI	[redacted]	[redacted]
Utility (state specific). Post-progression	0.725	0.786	95% CI	[redacted]	[redacted]
HR (Pluvicto vs Cabazitaxel). rPFS	0.32	0.68	95% CI	[redacted]	[redacted]
Subsequent treatment cost. Cabazitaxel	60,261	73,653	± 10%	[redacted]	[redacted]
Utility (state specific). Pre-progression	0.805	0.823	95% CI	[redacted]	[redacted]
Discount rate. Outcomes	3.2%	3.9%	± 10%	[redacted]	[redacted]
Subsequent treatment cost. Pluvicto	14,868	18,172	± 10%	[redacted]	[redacted]
Pluvicto. Monitoring cost (active treatment)	544	665	± 10%	[redacted]	[redacted]
Cabazitaxel. Monitoring cost (active treatment)	775	948	± 10%	[redacted]	[redacted]

Figure 16 Tornado diagram (Post 1 taxane population)

Scenario analyses (see Table 56) were performed to assess the impact of alternative model choices on the result of the base case.

Table 56 Scenario analysis (Post 1 taxane population)

Scenario	ICER (DKK/QALY)
HRs based on NMA that include TheraP	[redacted]
Treatment specific utilities (BSC/SoC assumed for Cabazitaxel)	[redacted]
Discounting excluded	[redacted]
rPFS gamma extrapolation	[redacted]
OS Weibull extrapolation	[redacted]
5-year time horizon	[redacted]

12.2.2 Deterministic sensitivity analysis (Post 2 taxanes population)

The DSAs included in the present application for the Post 2 taxanes population are presented in Table 57. A tornado diagram with the 10 most influential parameters is presented in Figure 17.

Table 57 Deterministic sensitivity analysis results (Post 2 taxanes population)

	Low value	High value	Reason/ rationale/ source	Lower bound case (DKK/QALY)	Upper bound case (DKK/QALY)
Base case				[redacted]	
Pluvicto. Number of cycles	[redacted]	[redacted]	95% CI	[redacted]	[redacted]
Utility (state specific). Pre-progression	0.806	0.830	95% CI	[redacted]	[redacted]
Discount rate. Outcomes	3.2%	3.9%	± 10%	[redacted]	[redacted]
Pluvicto. Monitoring cost (active treatment)	544	665	± 10%	[redacted]	[redacted]
Utility (state specific). Post-progression	0.745	0.824	95% CI	[redacted]	[redacted]
Pluvicto. Monitoring cost (Pre-progression)	419	512	± 10%	[redacted]	[redacted]
SSE rate. BSC/SoC	15.4%	19.4%	95% CI	[redacted]	[redacted]
SSE cost per patient. BSC/SoC	22,448	27,436	± 10%	[redacted]	[redacted]
SSE cost per patient. Pluvicto	22,448	27,436	± 10%	[redacted]	[redacted]
SSE rate. Pluvicto	14.3%	16.9%	95% CI	[redacted]	[redacted]

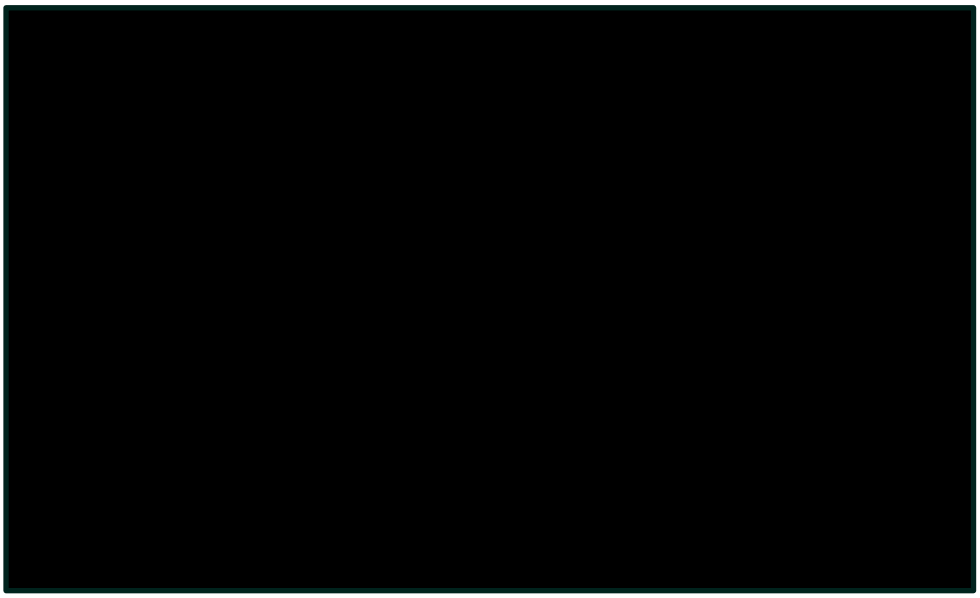

Figure 17 Tornado diagram (Post 2 taxanes population)

Scenario analyses (see Table 58) were performed to assess the impact of alternative model choices on the result of the base case.

Table 58 Scenario analysis (Post 2 taxanes population)

Scenario	ICER (DKK/QALY)
Instant hazard rate not constrained	[redacted]
Treatment specific utilities	[redacted]
Discounting excluded	[redacted]
rPFS gamma extrapolation	[redacted]
OS Weibull extrapolation	[redacted]
5-year time horizon	[redacted]

12.2.3 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the model, a PSA was performed using 1,000 iterations. The PSA evaluated the result of the health economic analysis when several parameters of the models were varied simultaneously.

12.2.3.1 PSA results (Post 1 taxane population)

Figure 18 presents a cost-effectiveness acceptability curve (CEAC) that illustrates the cost-effectiveness probability at different willingness-to-pay thresholds. Figure 19

presents the scatter plot from the PSA. As is evident, all the simulated ICERs from the PSA are in the northeast quadrant, meaning that Pluvicto® is associated with both increased health benefits and increased costs. As illustrated in Figure 19, the ICER cloud extends horizontally, reflecting greater uncertainty in the QALY gain relative to the associated costs. Figure 20 presents convergence plots of the estimated ICER mean as a function of the number of PSA simulations.

Figure 18 Cost-effectiveness acceptability curve (Post 1 taxane population)

Figure 19 PSA scatter (Post 1 taxane population)

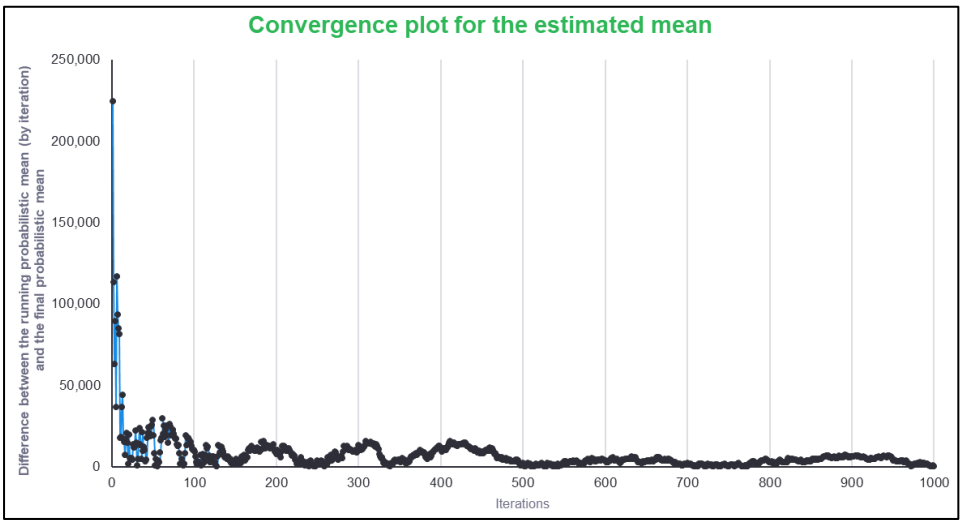

Figure 20 Convergence plot of the estimated ICER (Post 1 taxane population)

12.2.3.2 PSA results (Post 2 taxanes population)

Figure 21 showcases the CEAC, which demonstrates the probability of cost-effectiveness at various willingness-to-pay thresholds. In Figure 22, the scatter plot from the PSA is displayed. Also here, all the simulated ICERs from the PSA are located in the northeast quadrant, indicating that Pluvicto® is linked with both higher health benefits and increased costs. As illustrated in Figure 22, the ICER cloud extends horizontally, reflecting greater uncertainty in the QALY gain relative to the associated costs. Lastly, Figure 23 presents the convergence plots of the estimated ICER mean as a function of the number of PSA simulations.

Figure 21 Cost-effectiveness acceptability curve (Post 2 taxanes population)

Figure 22 PSA scatter (Post 2 taxanes population)

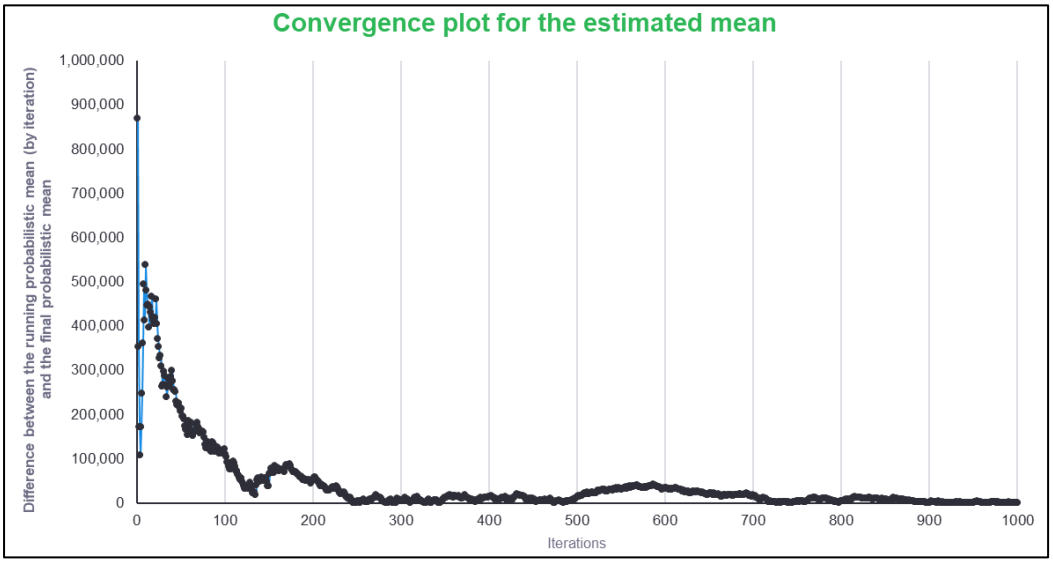

Figure 23 Convergence plot of the estimated ICER (Post 2 taxanes population)

13. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending Pluvicto® as a standard treatment for patients with mCRPC, either after one taxane or after two taxanes. The budget impact was estimated per year in the first 5 years after the recommendation of Pluvicto®. The budget impact analysis compares the expenditures in the scenario where Pluvicto® is recommended as a possible standard treatment with the scenario where Pluvicto® is not recommended as a possible standard

treatment. The total budget impact per year is the difference between these two scenarios.

The budget impact analysis is based on the undiscounted cost per patient calculations in the first 5 years from the cost-utility analysis. Only health sector costs were included in the budget impact analysis; the costs related to patient time and transportation were not included.

13.1 Budget impact of Pluvicto® (Post 1 taxane population)

Number of patients (including assumptions of market share)
To accurately estimate the expected number of patients eligible for Pluvicto® in each year of the analysis, the number of incident cases each year was extracted from Danish registry data (see section 3.2). The market share with a recommendation is estimated by Novartis as the proportion of eligible patients receiving Pluvicto®. The estimates are based on Novartis' experience with Pluvicto® in other countries. A zero percent market share was assumed in the non-recommendation scenario.

Table 59 Number of incident patients per year eligible for Pluvicto® and expected market share for Pluvicto® (Post 1 taxane population)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patients	163	163	163	163	163
Market share (with recommendation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 60 Number of new patients expected to be treated over the next 5 years if Pluvicto® is introduced, adjusted for market share (Post 1 taxane population)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Pluvicto®	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Pluvicto®	0	0	0	0	0
Cabazitaxel	163	163	163	163	163

Budget impact

Table 61 Expected budget impact of recommending Pluvicto® (Post 1 taxane population) (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Pluvicto® is recommended	83,369,250	95,340,508	102,937,621	108,703,616	113,695,182
Pluvicto® is NOT recommended	40,650,418	47,997,872	50,592,195	51,464,067	51,736,736
Budget impact of the recommendation	42,718,832	47,342,635	52,345,426	57,239,549	61,958,446

13.2 Budget impact of Pluvicto® (Post 2 taxanes population)

Number of patients (including assumptions of market share)

To accurately estimate the expected number of patients eligible for Pluvicto® in each year of the analysis (see section 3.2), the number of incident cases each year was extracted from Danish registry data. The market share with a recommendation is estimated by Novartis as the proportion of eligible patients receiving Pluvicto®. The estimates are based on Novartis' experience with Pluvicto® in other countries. A zero percent market share was assumed in the non-recommendation scenario.

Table 62 Number of incident patients per year eligible for Pluvicto® and expected market share for Pluvicto® (Post 2 taxanes population)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patients	151	151	151	151	151
Market share (with positive recommendation)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 63 Number of new patients expected to be treated over the next 5 years if Pluvicto® is introduced, adjusted for market share (Post 2 taxanes population)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Pluvicto®	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC/SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Pluvicto®	0	0	0	0	0

	Year 1	Year 2	Year 3	Year 4	Year 5
BSC/SoC	151	151	151	151	151

Budget impact

Table 64 Expected budget impact of recommending Pluvicto® (Post 2 taxanes population) (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Pluvicto® is recommended	37,627,624	46,423,220	51,750,348	54,976,059	58,609,940
Pluvicto® is NOT recommended	11,256,218	16,970,184	18,574,473	18,794,349	18,812,188
Budget impact of the recommendation	26,371,407	29,453,036	33,175,874	36,181,709	39,797,752

14. List of experts

Peter Meidahl Petersen, medical doctor, PhD, professor and senior consultant at the Department of Oncology, Rigshospitalet, has been consulted to validate the assumptions and input used in the health economic parts of this application and the health economic model. The input is based on his extensive clinical and research experience within prostate cancer.

15. References

1. Huang Y, Jiang X, Liang X, Jiang G. Molecular and cellular mechanisms of castration resistant prostate cancer (Review). Oncol Lett [Internet]. 2018 Feb 27 [cited 2025 Apr 15]; Available from: http://www.spandidos-publications.com/10.3892/ol.2018.8123

2. Cancer Research UK. What is prostate cancer? [Internet]. 2022 [cited 2025 Apr 15]. Available from: https://about-cancer.cancerresearchuk.org/about-cancer/prostate-cancer/about

3. Packer JR, Maitland NJ. The molecular and cellular origin of human prostate cancer. Biochim Biophys Acta BBA - Mol Cell Res. 2016 Jun;1863(6):1238–60.

4. Helgstrand JT, Røder MA, Klemann N, Toft BG, Lichtensztajn DY, Brooks JD, et al. Trends in incidence and 5-year mortality in men with newly diagnosed, metastatic prostate cancer—A population-based analysis of 2 national cohorts. Cancer. 2018 Jul 15;124(14):2931–8.

5. DaProCa: Dansk Prostata Cancer Database Årsrapport 2022 [Internet]. [cited 2025 Jun 13]. Available from: https://ducg.dk/fileadmin/ingen_mappe_valgt/Prostata_rapport_2022_version_til_offentliggoerelse_12062023_final.pdf

6. EAU. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer [Internet]. 2025 Mar [cited 2025 Apr 16]. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2025_2025-03-24-120144_rinw.pdf

7. Pomykala KL, Czernin J, Grogan TR, Armstrong WR, Williams J, Calais J. Total-Body^{68} Ga-PSMA-11 PET/CT for Bone Metastasis Detection in Prostate Cancer Patients: Potential Impact on Bone Scan Guidelines. J Nucl Med. 2020 Mar;61(3):405–11.

8. Donin NM, Reiter RE. Why Targeting PSMA Is a Game Changer in the Management of Prostate Cancer. J Nucl Med. 2018 Feb;59(2):177–82.

9. Hupe MC, Philippi C, Roth D, Kümpers C, Ribbat-Idel J, Becker F, et al. Expression of Prostate-Specific Membrane Antigen (PSMA) on Biopsies Is an Independent Risk Stratifier of Prostate Cancer Patients at Time of Initial Diagnosis. Front Oncol. 2018 Dec 20;8:623.

10. Lægehåndbogen. Prostatakræft [Internet]. 2022 [cited 2025 Apr 15]. Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/mandlige-koensorganer/tilstande-og-sygdomme/prostata/prostatakraeft/

11. Leonel Almeida P, Jorge Pereira B. Local Treatment of Metastatic Prostate Cancer: What is the Evidence So Far? Prostate Cancer. 2018;2018:1–7.

12. Berruti A, Tucci M, Mosca A, Tarabuzzi R, Gorzegno G, Terrone C, et al. Predictive factors for skeletal complications in hormone-refractory prostate cancer patients with metastatic bone disease. Br J Cancer. 2005 Sep;93(6):633–8.

13. Frieling JS, Basanta D, Lynch CC. Current and Emerging Therapies for Bone Metastatic Castration-Resistant Prostate Cancer. Cancer Control. 2015 Jan;22(1):109–20.

14. Nguyen-Nielsen M, Liede A, Maegbaek ML, Borre M, Harving N, Hernandez RK, et al. Survival and PSA-markers for mortality and metastasis in nonmetastatic prostate cancer treated with androgen deprivation therapy. Cancer Epidemiol. 2015 Aug;39(4):623–32.

15. Holmstrom S, Naidoo S, Turnbull J, Hawryluk E, Paty J, Morlock R. Symptoms and Impacts in Metastatic Castration-Resistant Prostate Cancer: Qualitative Findings from Patient and Physician Interviews. Patient - Patient-Centered Outcomes Res. 2019 Feb;12(1):57–67.

16. Nørgaard M, Jensen AØ, Jacobsen JB, Cetin K, Fryzek JP, Sørensen HT. Skeletal Related Events, Bone Metastasis and Survival of Prostate Cancer: A Population Based Cohort Study in Denmark (1999 to 2007). J Urol. 2010 Jul;184(1):162–7.

17. Paschalis A, Sheehan B, Riisnaes R, Rodrigues DN, Gurel B, Bertan C, et al. Prostate-specific Membrane Antigen Heterogeneity and DNA Repair Defects in Prostate Cancer. Eur Urol. 2019 Oct;76(4):469–78.

18. Vlachostergios PJ, Niaz MJ, Sun M, Mosallaie SA, Thomas C, Christos PJ, et al. Prostate-Specific Membrane Antigen Uptake and Survival in Metastatic Castration-Resistant Prostate Cancer. Front Oncol. 2021 Feb 18;11:630589.

19. Turco F, Gillessen S, Cathomas R, Buttigliero C, Vogl UM. Treatment Landscape for Patients with Castration-Resistant Prostate Cancer: Patient Selection and Unmet Clinical Needs. Res Rep Urol. 2022 Sep;Volume 14:339–50.

20. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021 Sep 16;385(12):1091–103.

21. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019 Dec 26;381(26):2506–18.

22. Stormoen DR, Baeksted C, Taarnhøj GA, Johansen C, Pappot H. Patient reported outcomes interfering with daily activities in prostate cancer patients receiving antineoplastic treatment. Acta Oncol. 2021 Apr 3;60(4):419–25.

23. Wolff JM, Donatz V, Klier J, Erhardt W, Dass RN, Geiges G. PCN120 Quality of Life Among German Patients With Metastatic Castration-Resistant Prostate Cancer. Value Health. 2012 Nov;15(7):A431.

24. Dearden L, Shalet N, Artenie C, Mills A, Jackson C, Grant L, et al. Fatigue, treatment satisfaction and health-related quality of life among patients receiving novel drugs suppressing androgen signalling for the treatment of metastatic castrate-resistant prostate cancer. Eur J Cancer Care (Engl). 2019 Jan;28(1):e12949.

25. EMA. Pluvicto: EPAR. 2025.

26. DaProCa. Behandling af kastraktionsresistent prostatacancer (CRPC). 2024.

27. Medicinrådet. Medicinrådets behandlingsvejledning vedrørende lægemidler til metastatisk kastrationssensitiv prostatakræft. 2024 Aug.

28. EMA. Cabazitaxel: EPAR. 2024.

29. Regionshospitalet Gødstrup. Cabazitaxel (i.v.) [Internet]. Available from: https://www.regionshospitalet-goedstrup.dk/patientvejledninger/kraftafdelingen/prostatakraft/cabazitaxel-iv/#:~:text=Cabazitaxel%20er%20oprindeligt%20udvundet%20fra,eller%20stofskifte%20p%C3%A5%20forskellig%20m%C3%A5de.

30. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate

cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet. 2010 Oct;376(9747):1147–54.

31. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187–97.

32. Sun Y, Zou Q, Sun Z, Li C, Du C, Chen Z, et al. Abiraterone acetate for metastatic castration-resistant prostate cancer after docetaxel failure: A randomized, double-blind, placebo-controlled phase 3 bridging study. Int J Urol. 2016 May;23(5):404–11.

33. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012 Oct 1;13(10):983–92.

34. Hofman MS, Emmett L, Sandhu S, Iravani A, Buteau JP, Joshua AM, et al. Overall survival with [177Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial. Lancet Oncol. 2024 Jan;25(1):99–107.

35. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. The Lancet. 2021 Feb;397(10276):797–804.

36. Fizazi K, Herrmann K, Krause BJ, Rahbar K, Chi KN, Morris MJ, et al. Health-related quality of life and pain outcomes with [177Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023 Jun;24(6):597–610.

37. Medicinrådet. Medicinrådets anbefaling vedr. olaparib i kombination med abirateron of prednisolon til behandling af metastatisk kastrationsresistent kræft i blærehalskirtlen. 2024 Sep.

38. Halabi S, Roy A, Rydzewska L, Guo S, Godolphin P, Hussain M, et al. Radiographic Progression-Free Survival and Clinical Progression-Free Survival as Potential Surrogates for Overall Survival in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2024 Mar 20;42(9):1044–54.

39. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016 Apr 20;34(12):1402–18.

40. Evidence | Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen | Guidance | NICE [Internet].

NICE; 2012 [cited 2025 Apr 23]. Available from: https://www.nice.org.uk/guidance/ta259/evidence

41. Evidence | Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel | Guidance | NICE [Internet]. NICE; 2016 [cited 2025 Apr 23]. Available from: https://www.nice.org.uk/guidance/ta391/evidence

42. Evidence | Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen | Guidance | NICE [Internet]. NICE; 2014 [cited 2025 Apr 23]. Available from: https://www.nice.org.uk/guidance/ta316/evidence

43. Saad F, Fleshner NE, So A, Le Lorier J, Perrault L, Poulin-Costello M, et al. The burden of symptomatic skeletal events in castrate-resistant prostate cancer patients with bone metastases at three Canadian uro-oncology centres. Can Urol Assoc J [Internet]. 2018 Jun 19 [cited 2025 Apr 15];12(12). Available from: https://cuaj.ca/index.php/journal/article/view/5053

44. Finansministeriet. Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente [Internet]. 2021 Jan [cited 2023 Jun 21]. Available from: https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf

45. Nemeth B, Vincziczki Á. The Role of Half-Cycle Correction in the Models Used for Health Technology Assessment. Value Health. 2013 Nov 1;16(7):A592–3.

46. Novartis. Post-hoc subgroup analysis report (data on file). 2024 Feb.

47. Novartis. Clinical Study Report (data on file). 2022 Nov.

48. RKKP. DaProCa: Dansk Prostata Caner Database. 2023 Jun.

49. Gray J, Sullivan T, Latimer NR, Salter A, Sorich MJ, Ward RL, et al. Extrapolation of Survival Curves Using Standard Parametric Models and Flexible Parametric Spline Models: Comparisons in Large Registry Cohorts with Advanced Cancer. Med Decis Mak Int J Soc Med Decis Mak. 2021 Feb;41(2):179–93.

50. Wal WM van der, Geskus RB. ipw: An R Package for Inverse Probability Weighting. J Stat Softw. 2011 Sep 14;43:1–23.

51. Anderson-Bergman C. **icenReg** : Regression Models for Interval Censored Data in *R*. J Stat Softw [Internet]. 2017 [cited 2025 Apr 15];81(12). Available from: http://www.jstatsoft.org/v81/i12/

52. ClinicalTrials.gov [Internet]. 2022. Cabazitaxel Versus the Switch to Alternative AR-targeted Agent (Enzalutamide or Abiraterone) in Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients Previously Treated With Docetaxel and Who Rapidly Failed a Prior AR-targeted Agent (CARD). Available from: https://clinicaltrials.gov/study/NCT02485691?term=NCT02485691&rank=1

53. Clinicaltrials.gov [Internet]. 2025. Study of 177Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer (VISION). Available from: https://clinicaltrials.gov/study/NCT03511664?term=NCT03511664&rank=1

54. EuroQoL Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199–208.

55. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy-prostate instrument. Urology. 1997 Dec;50(6):920–8.

56. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy. 2021 Jul;19(4):579–91.

57. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet, Medicinrådet [Internet]. [cited 2025 May 8]. Available from: https://medicinraadet.dk/media/mbtgpjjl/efter-1-januar-2021-appendiks-til-medicinr%C3%A5dets-metodevejledning-aldersjustering-adlegacy.pdf

58. Rigshospitalet. Lu-177 PSMA-behandling [Internet]. [cited 2025 Mar 21]. Available from: https://www.rigshospitalet.dk/undersoegelse-og-behandling/find-undersoegelse-og-behandling/Sider/Lu-177-PSMA-behandling-2542803.aspx

59. European Medicines Agency. Summary of product characteristics: PLUVICTO [Internet]. [cited 2025 Mar 20]. Available from: https://www.ema.europa.eu/en/documents/product-information/pluvicto-epar-product-information_en.pdf

60. Xofigo (radium-223) Hälsoekonomiskt kunskapsunderlag - TLV [Internet]. [cited 2025 May 6]. Available from: https://www.tlv.se/download/18.467926b615d084471ac33aaf/1510316360981/Kunskapsunderlag_xofigo.pdf

61. Cabazitaxel, behandling af patienter med prostatakræft [Internet]. [cited 2025 May 5]. Available from: https://www.herlevhospital.dk/undersoegelse-og-behandling/find-undersoegelse-og-behandling/Sider/Cabazitaxel-behandling-med-23512.aspx

62. Sanofi ICDS. A Randomized, Open Label Multi-Center Study of XRP6258 at 25 mg/m^2 in Combination With Prednisone Every 3 Weeks Compared to Mitoxantrone in Combination With Prednisone For The Treatment of Hormone Refractory Metastatic Prostate Cancer Previously Treated With A Taxotere®-Containing Regimen [Internet]. clinicaltrials.gov; 2011 Mar [cited 2025 May 5]. Report No.: NCT00417079. Available from: https://clinicaltrials.gov/study/NCT00417079

63. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence Synthesis for Decision Making 2: A Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized Controlled Trials. Med Decis Making. 2013 Jul;33(5):607–17.

64. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012 Dec;12(1):9.

65. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515–26.

66. Michael H, Thornton S, Xie M, Tian L. Exact Inference on the Random-Effects Model for Meta-Analyses With Few Studies. Biometrics. 2019 Jun 1;75(2):485–93.

67. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557–60.

68. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010 Mar 30;29(7–8):932–44.

69. Gelman A. Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). Bayesian Anal [Internet]. 2006 Sep 1 [cited 2025 Jun 20];1(3). Available from: https://projecteuclid.org/journals/bayesian-analysis/volume-1/issue-3/Prior-distributions-for-variance-parameters-in-hierarchical-models-comment-on/10.1214/06-BA117A.full

70. Latimer NR. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Mak Int J Soc Med Decis Mak. 2013 Aug;33(6):743–54.

71. NICE health technology evaluations: the manual.

72. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;n71.

73. Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in healthcare. 3. ed. York: York Publ. Services; 2009. 281 p. (Systematic reviews).

74. Instructions for companies | Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template | Guidance | NICE [Internet]. NICE; 2015 [cited 2025 May 27]. Available from: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies

75. Basch EM, Scholz M, De Bono JS, Vogelzang N, De Souza P, Marx G, et al. Cabozantinib Versus Mitoxantrone-prednisone in Symptomatic Metastatic Castration-resistant Prostate Cancer: A Randomized Phase 3 Trial with a Primary Pain Endpoint. Eur Urol. 2019 Jun;75(6):929–37.

76. Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016 Sep 1;34(25):3005–13.

77. Antonarakis ES, Park SH, Goh JC, Shin SJ, Lee JL, Mehra N, et al. Pembrolizumab Plus Olaparib for Patients With Previously Treated and Biomarker-Unselected Metastatic Castration-Resistant Prostate Cancer: The Randomized, Open-Label, Phase III KEYLYNK-010 Trial. J Clin Oncol. 2023 Aug 1;41(22):3839–50.

78. Chi KN, Fleming MT, Sunderland K, Albany C, Gingerich J, Saad F, et al. PACIFIC trial: A randomized phase II study of apatorsen and abiraterone in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) who have had PSA progression while receiving abiraterone (ABI). J Clin Oncol. 2017 Feb 20;35(6_suppl):146–146.

79. Macaulay VM, Lord S, Hussain S, Maroto JP, Jones RH, Climent MÁ, et al. A Phase Ib/II study of IGF-neutralising antibody xentuzumab with enzalutamide in metastatic castration-resistant prostate cancer. Br J Cancer. 2023 Oct 5;129(6):965–73.

80. Kim JW, McKay RR, Radke MR, Zhao S, Taplin ME, Davis NB, et al. Randomized Trial of Olaparib With or Without Cediranib for Metastatic Castration-Resistant Prostate Cancer: The Results From National Cancer Institute 9984. J Clin Oncol. 2023 Feb 1;41(4):871–80.

81. Rescigno P, Porta N, Finneran L, Riisnaes R, Figueiredo I, Carreira S, et al. Capivasertib in combination with enzalutamide for metastatic castration resistant prostate cancer after docetaxel and abiraterone: Results from the randomized phase II RE-AKT trial. Eur J Cancer. 2024 Jul;205:114103.

82. De Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020 May 28;382(22):2091–102.

83. Powles T, Yuen KC, Gillessen S, Kadel EE, Rathkopf D, Matsubara N, et al. Atezolizumab with enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer: a randomized phase 3 trial. Nat Med. 2022 Jan;28(1):144–53.

84. Clarke N, Wiechno P, Alekseev B, Sala N, Jones R, Kocak I, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2018 Jul;19(7):975–86.

85. De Bono JS, De Giorgi U, Rodrigues DN, Massard C, Bracarda S, Font A, et al. Randomized Phase II Study Evaluating Akt Blockade with Ipatasertib, in Combination with Abiraterone, in Patients with Metastatic Prostate Cancer with and without PTEN Loss. Clin Cancer Res. 2019 Feb 1;25(3):928–36.

86. Blumenstein B, Saad F, Hotte S, Chi KN, Eigl B, Gleave M, et al. Reduction in serum clusterin is a potential therapeutic biomarker in patients with castration-resistant prostate cancer treated with custirsen. Cancer Med. 2013 Aug;2(4):468–77.

87. Nieuweboer AJM, De Graan AJM, Hamberg P, Bins S, Van Soest RJ, Van Alphen RJ, et al. Effects of Budesonide on Cabazitaxel Pharmacokinetics and Cabazitaxel-Induced

Diarrhea: A Randomized, Open-Label Multicenter Phase II Study. Clin Cancer Res. 2017 Apr 1;23(7):1679–83.

88. Hotte SJ, Winquist E, Chi KN, Ellard SL, Sridhar S, Emmenegger U, et al. CCTG IND 232: A phase II study of durvalumab with or without tremelimumab in patients with metastatic castration resistant prostate cancer (mCRPC). Ann Oncol. 2019 Oct;30:v885.

89. Rosenberg JE, Weinberg VK, Kelly WK, Michaelson D, Hussain MH, Wilding G, et al. Activity of second-line chemotherapy in docetaxel-refractory hormone-refractory prostate cancer patients: Randomized phase 2 study of ixabepilone or mitoxantrone and prednisone. Cancer. 2007 Aug;110(3):556–63.

90. Beer TM, Hotte SJ, Saad F, Alekseev B, Matveev V, Fléchon A, et al. Custirsen (OGX-011) combined with cabazitaxel and prednisone versus cabazitaxel and prednisone alone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (AFFINITY): a randomised, open-label, international, phase 3 trial. Lancet Oncol. 2017 Nov;18(11):1532–42.

91. Fizazi K, Jones R, Oudard S, Efstathiou E, Saad F, De Wit R, et al. Phase III, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or After Docetaxel-Based Therapy: ELM-PC 5. J Clin Oncol. 2015 Mar 1;33(7):723–31.

92. Joly F, Delva R, Mourey L, Sevin E, Bompas E, Vedrine L, et al. Clinical benefits of non-taxane chemotherapies in unselected patients with symptomatic metastatic castration-resistant prostate cancer after docetaxel: the GETUG-P02 study: Non-taxane chemotherapy after docetaxel in metastatic CRPC. BJU Int. 2015 Jan;115(1):65–73.

93. Michaelson MD, Oudard S, Ou YC, Sengeløv L, Saad F, Houede N, et al. Randomized, Placebo-Controlled, Phase III Trial of Sunitinib Plus Prednisone Versus Prednisone Alone in Progressive, Metastatic, Castration-Resistant Prostate Cancer. J Clin Oncol. 2014 Jan 10;32(2):76–82.

94. Fizazi K, Ulys A, Sengeløv L, Moe M, Ladoire S, Thiery- Vuillemin A, et al. A randomized, double-blind, placebo-controlled phase II study of maintenance therapy with tasquinimod (TASQ) in patients (pts) with mCRPC responsive to or stabilized during first-line docetaxel chemotherapy. J Clin Oncol. 2016 Jan 10;34(2_suppl):201–201.

95. Annala M, Fu S, Bacon JVW, Sipola J, Iqbal N, Ferrario C, et al. Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase II trial. Ann Oncol. 2021 Jul;32(7):896–905.

96. Hoskin P, Sartor O, O'Sullivan JM, Johannessen DC, Helle SI, Logue J, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol. 2014 Nov;15(12):1397–406.

97. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, Van Den Eertwegh AJM, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014 Jun;15(7):700–12.

98. Van Der Zande K, Van Der Noort V, Busard M, Hamberg P, Ras - Van Spijk S, De Feijter J, et al. 1818P Final results from a randomized phase II study of cabazitaxel (CBZ) versus an androgen receptor targeted agent (ARTA) in patients with poor-prognosis castration-resistant prostate cancer (mCRPC). Ann Oncol. 2023 Oct;34:S985.

99. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. N Engl J Med. 2010 Jul 29;363(5):411–22.

100. Noguchi M, Fujimoto K, Arai G, Uemura H, Hashine K, Matsumoto H, et al. Personalized peptide vaccination for castration-resistant prostate cancer progressing after docetaxel chemotherapy: A randomized, double-blind, placebo-controlled, phase III trial. J Clin Oncol. 2019 May 20;37(15_suppl):5033–5033.

101. Fizazi K, De Bono JS, Flechon A, Heidenreich A, Voog E, Davis NB, et al. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. Eur J Cancer. 2012 Jan;48(1):85–93.

102. Fleming MT, Sonpavde G, Kolodziej M, Awasthi S, Hutson TE, Martincic D, et al. Association of Rash With Outcomes in a Randomized Phase II Trial Evaluating Cetuximab in Combination With Mitoxantrone Plus Prednisone After Docetaxel for Metastatic Castration-resistant Prostate Cancer. Clin Genitourin Cancer. 2012 Mar;10(1):6–14.

103. Beer TM, Hotte SJ, De Bono JS, Beuzeboc P, Gabrail NY, Cain D, et al. Pain palliation as an oncology label indication: Lessons learned in custirsen phase III development. J Clin Oncol. 2014 Feb;32(4_suppl):222–222.

104. Hakenberg OW, Perez-Gracia JL, Castellano D, Demkow T, Ali T, Caffo O, et al. Randomised phase II study of second-line olaratumab with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. Eur J Cancer. 2019 Jan;107:186–95.

105. Ryan CJ, Rosenthal M, Ng S, Alumkal J, Picus J, Gravis G, et al. Targeted MET Inhibition in Castration-Resistant Prostate Cancer: A Randomized Phase II Study and Biomarker Analysis with Rilotumumab plus Mitoxantrone and Prednisone. Clin Cancer Res. 2013 Jan 1;19(1):215–24.

106. Bouman-Wammes EW, Van Den Berg HP, De Munck L, Beeker A, Smorenburg CH, Vervenne WL, et al. A randomised phase II trial of docetaxel versus docetaxel plus carboplatin in patients with castration-resistant prostate cancer who have progressed after response to prior docetaxel chemotherapy: The RECARDO trial. Eur J Cancer. 2018 Feb;90:1–9.

Appendix A. Main characteristics of studies included

Main characteristics of VISION

Table 65 Main characteristics of VISION. Source: clinical study report, clinicaltrials.gov, and Sartor et al. 2021.

Trial name: VISION	NCT number: NCT03511664
Objective	The primary objective of VISION was to compare the two alternate endpoints of rPFS and OS in patients with progressive PSMA-positive mCRPC who received 177Lu-PSMA-617 (Pluvicto®) in addition to BSC/SoC versus patients treated with BSC/SoC alone.
Publications – title, author, journal, year	Sartor O, de Bono J, Kim N, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021;385(12):1091-1103. Iravani A, Violet J, Azad A, Hofman MS. Lutetium-177 prostate-specific membrane antigen (PSMA) theranostics: practical nuances and intricacies. Prostate Cancer Prostatic Dis. 2020;23(1):38-52. Chi KN, Yip SM, Bauman G, Probst S, Emmenegger U, Kollmannsberger CK, et al. 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer: a review of the evidence and implications for canadian clinical practice. Curr Oncol. 2024;31(3):1400-1415. Fizazi K, Herrmann K, Krause BJ, Rahbar K, Chi KN, Morris MJ, et al. Health-related quality of life and pain outcomes with [177Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(6):597-610. Herrmann K, Rahbar K, Eiber M, Sparks R, Baca N, Krause BJ, et al. Renal and Multiorgan Safety of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer in the VISION Dosimetry substudy. J Nucl Med. 2024;65(1):71-78. Kuo PH, Yoo DC, Avery R, Seltzer M, Calais J, Nagarajah J, et al. A VISION substudy of reader agreement on ^{68}Ga-PSMA-11 PET/CT scan interpretation to determine patient eligibility for ^{177}Lu-PSMA-617 radioligand therapy. J Nucl Med. 2023;64(8):1259-1265. Armstrong AJ, Sartor O, de Bono J, Chi K, Fizazi K, Krause BJ, et al. Association of declining prostate-specific antigen levels with clinical outcomes in patients with metastatic castration-resistant prostate cancer receiving [^{177}Lu]Lu-PSMA-617 in the phase 3 VISION trial. Eur Urol. 2024;86(6):552-562.

Trial name: VISION	NCT number: NCT03511664
	Chi KN, Armstrong AJ, Krause BJ, Herrmann K, Rahbar K, de Bono J, et al. Safety analyses of the phase 3 VISION trial of [^{177}Lu]Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. Eur Urol. 2024;85(4):382-391. Herrmann K, Gafita A, de Bono J, Sartor O, Chi KN, Krause BJ, et al. Multivariable models of outcomes with [^{177}Lu]Lu-PSMA-617: analysis of the phase 3 VISION trial. eClinicalMedicine. 2024;77:102862. Kuo PH, Morris MJ, Hesterman J, Kendi AT, Rahbar K, Wei XX, et al. Quantitative ^{68}Ga-PSMA-11 PET and clinical outcomes in metastatic castration-resistant prostate cancer following ^{177}Lu-PSMA-617 (VISION trial). Radiology. 2024;312(2):e233460. Morris MJ, de Bono J, Nagarajah J, Sartor O, Wei XX, Nordquist LT, et al. Correlation analyses of radiographic progression-free survival with clinical and health-related quality of life outcomes in metastatic castration-resistant prostate cancer: Analysis of the phase 3 VISION trial. Cancer. 2024;130(20):3426-3435.
Study type and design	This was a phase III, open-label, international, randomized study. At screening, potential patients underwent a gallium (68Ga) gozetotide PET/CT scan to evaluate PSMA positivity. Patients with PSMA positive scans were randomized in a 2:1 ratio to receive either Pluvicto® + BSC/SoC or BSC/SoC only. BSC/SoC was determined prior to randomization by the treating physician/investigator but excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs (NAADs) such as abiraterone or enzalutamide, also known as ARPI, were allowed. Randomized patients were stratified by the following factors: LDH level (≤ or > 260 UI/L), presence of liver metastases (Yes or No), eastern cooperative oncology group (ECOG) score (0-1 or 2) and inclusion of NAAD in BSC/SOC (at time of randomization, Yes or No).
Sample size (n)	1,179 patients were assessed for eligibility and 1,003 underwent 68Ga-PSMA-11 PET–CT. A total of 831 patients were randomized to either the Pluvicto® + BSC/SoC arm (N=551) or the BSC/SoC only arm (N=280), while 581 underwent randomization on or after March 5, 2019. 529 patients (96.7%) randomized to the Pluvicto® + BSC/SoC arm received at least one dose of randomized treatment (Pluvicto® and/or BSC/SoC) and 4 patients (0.7%) in this arm received only BSC/SoC and 18 (3.3%) did not receive any treatment. 201 patients (71.8%) randomized to the BSC/SoC only arm received at least one dose of treatment. The majority of patients who were randomized to this arm were never treated and had withdrawn their consent (46 patients, 16.4%). At the time of final data cut-off, 28 patients (5.1%) in the Pluvicto® + BSC/SoC arm and 6 patients (2.1%) in the BSC/SoC only arm had completed the study. All other patients had discontinued from the study. The main reasons for

Trial name: VISION	NCT number: NCT03511664

study discontinuation were death (82.9% vs. 71.8%) and withdrawal of consent (7.3% vs. 22.5%).

Analysis sets

All the efficacy outcomes were analysed in ITT populations.

Full Analysis Set (FAS): All randomized patients. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This is an intent to treat analysis set. This analysis set was used for the analysis of OS.

PFS Full Analysis Set (PFS-FAS): All patients randomized on or after 05-Mar-2019. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This analysis set is used for the primary analyses of rPFS and all secondary endpoints except ORR and DCR.

FAS Safety Analysis Set: The subset of patients in the FAS who received at least one dose of randomized treatment. Patients were included in the treatment arm corresponding to the actual treatment received.

	Total	Pluvicto®	BSC/SoC
FAS	831 patients	551 patients	280 patients
PFS-FAS	581 patients	385 patients	196 patients
FAS safety	734 patients	529 patients	205 patients

Main inclusion criteria

Adult male patients had to meet the following key criteria at screening to qualify for enrollment:

- Had a histological, pathological, and/or cytological confirmation of PC.
- Had progressive mCRPC. Documented progressive mCRPC was based on any one of the following as defined by the PCWG3 criteria for clinical trial entry: serum PSA progression, soft-tissue progression, or progression of bone disease.
- Had received at least one NAAD.
- Were previously treated with at least 1, but no more than 2 prior taxane regimens.

Trial name: VISION	NCT number: NCT03511664
	- Had a positive gallium (68Ga) gozetotide PET/CT scan, as determined by the Sponsor's central reader - Had an ECOG performance status of 0 to 2. - Had ≥1 metastatic lesion that was present on baseline CT, MRI, or bone scan imaging. - Had adequate bone marrow reserve, hepatic and renal function.
Main exclusion criteria	Patients who met any of the following key criteria at screening were excluded from the study: - Previous treatment with any of the following within 6 months of randomization: strontium-89, samarium-153, rhenium-186, rhenium-188, radium-223, or hemi-body irradiation. Previously treated with PSMA-targeted RLT. - Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy) within 28 days prior to day of randomization. - Any investigational agents within 28 days prior to day of randomization. - Known hypersensitivity to the components of the study therapy or its analogues. - Patients with a history of CNS metastases who did not receive therapy (surgery, radiotherapy, gamma knife) and were neurologically unstable, symptomatic, and were receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease, and prior cord involvement and were untreated, unstable, and neurologically impaired. - Concurrent serious (as determined by the PI) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the Investigator would impair study participation or co-operation.
Intervention	Pluvicto® was administered as a slow IV injection at a dose of 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles. After the cycle 4 treatment and prior to cycle 5 treatment, the Investigator had to determine if: - The patient showed evidence of response (i.e. radiological, PSA, clinical benefit) - The patient had signs of residual disease on CT with contrast/MRI or bone scan

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	- The patient had shown good tolerance to the Pluvicto® treatment If the patient met all of the criteria above and agreed to continue with additional treatment of Pluvicto®, the investigator could administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy was allowed. If the patient did not meet any of the criteria or did not agree to additional Pluvicto® treatment, then no additional doses of Pluvicto® were administered after cycle 4. After the last cycle of Pluvicto®, patients continued BSC/SoC alone, as long as the investigator felt they were clinically benefiting or until they required a treatment regimen not allowed in this study. For both treatment arms, the cycle duration for cycle 1-6 was 6 weeks and for cycle 7 and beyond, 12 weeks. From Cycle 7 onwards, all patients from both treatment arms only received BSC/SoC.
Comparator(s)	The treatment options included in the BSC/SoC arm in VISION were predefined by protocol. BSC/SoC treatments were administered as per physician's orders and protocol at the institution, and whenever feasible, BSC/SoC were optimized for all patients prior to randomization. Patients were treated with BSC/SoC as long as the Investigator felt they were clinically benefiting (regardless of radiographic progressive disease based on Investigator's assessment per PCWG3 criteria) or until they required a treatment regimen not allowed on the study. Treatments for PC not specifically excluded as part of the study could include, but were not limited to, any of the interventions mentioned below: - Supportive measures (pain medications, hydration, transfusions, etc.) - Ketoconazole - Hormonal agents (single or combination, including diethylstilbestrol and estradiol, as well as luteinizing hormone-releasing hormone analogue for testosterone suppression) - Androgen reducing agents (including any corticosteroid and 5-alpha reductases) - Abiraterone, enzalutamide, apalutamide or any other NAAD - Radiation in any external beam or seeded form, as well as Y90 beads; systemic radioisotopes such as radium-223 or hemi-body radiotherapy treatment were not permitted on study - Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates.

Trial name: VISION	NCT number: NCT03511664
	Combinations of any, and all, of the above were allowed on the study and could be modified over time as needed
Follow-up time	The median follow-up was 20.9 months. For OS, the median follow-up was 20.3 months (95% CI 19.8 to 21.0) in the Pluvicto® + BSC/SoC arm and 19.8 months (95% CI, 18.3 to 20.8) in the BSC/SoC alone arm (20).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary outcome measures (from clinicaltrials.gov)** - rPFS (From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 32 months) - OS (From date of randomization until date of death from any cause, assessed up to 32 months (cut-off date = 27 January 2021) and up to 66 months (14 December 2023) **Secondary outcome measures (from clinicaltrials.gov)** - Number of Participants With Randomized/Study Treatment-emergent Adverse Events (TEAE) - Overall Response Rate (ORR) - Disease Control Rate (DCR) - Duration of Response (DOR) - Time to First Symptomatic Skeletal Event (SSE) - Progression-free Survival (PFS) - Best Percentage Change From Baseline in Prostate-specific Antigen (PSA) Level - Percentage of Participants Achieving Prostate-specific Antigen (PSA) Response - Prostate-specific Antigen 80 (PSA80) Response - Duration of PSA Response - Best Percentage Change From Baseline in ALP Level - Best Percentage Change From Baseline in LDH Level - Time to Worsening in BPI-SF Pain Intensity Scale - Time to Improvement After Worsening in BPI-SF Pain Intensity Scale - Time to Worsening in BPI-SF Pain Interference Scale - Time to Improvement After Worsening in BPI-SF Pain Interference Scale

Trial name: VISION	NCT number: NCT03511664
	- Time to Worsening in BPI-SF Worst Pain Intensity Scale (Time to Disease Related Pain) - Change From Baseline in BPI-SF (Brief-Pain Inventory - Short Form) Pain Intensity Scale - Change From Baseline in BPI-SF (Brief-Pain Inventory - Short Form) Pain Interference Scale - Time to Worsening in FACT-P Total Score - Change From Baseline in FACT-P (Functional Assessment of Cancer Therapy - Prostate) Total Score - Time to Worsening in EQ-5D-5L Utility Score - Change From Baseline in the European Quality of Life (EuroQol) - 5 Domain 5 Level Scale (EQ-5D-5L) Utility Score - Change From Baseline in the European Quality of Life (EuroQol) - 5 Domain 5 Level Scale (EQ-5D-5L) EQ-VAS - Number of Participants Hospitalized as In-patient - Duration of Time in Hospital Following 177Lu-PSMA-617 Administration **Endpoints included in this application:** - rPFS - OS - Time to First SSE - Change From Baseline in the EuroQol - 5 Domain 5 Level Scale (EQ-5D-5L) EQ-VAS - Change From Baseline in FACT-P (Functional Assessment of Cancer Therapy - Prostate) Total Score - Safety outcomes according to DMC template
Method of analysis	The principal method of statistical comparison for the primary and key secondary time-to-event end points was the log-rank test, with stratification according to the randomization factors. The method for all other time-to-event end points was the Wald chi-square test from the stratified Cox proportional-hazards model. The stratified Cox model was used to estimate hazard ratios and associated confidence intervals. Medians, percentiles, and associated confidence intervals were estimated with the use of the Kaplan–Meier method. All the confidence intervals were two-sided, and one-sided P values from the analyses of the primary efficacy outcomes were converted to two-sided P values for this article. The Hochberg procedure was used to adjust for multiple testing of the key secondary efficacy end points, with the use of the two-sided alpha from the final overall survival analysis, if it was positive (20).

Trial name: VISION	NCT number: NCT03511664
Subgroup analyses	The VISION trial included the following prespecified subgroup analyses: - ARPI as part of planned standard care (Yes/No) - LDH (≤260 IU/L, >260 IU/L) - Liver metastases (Yes/No) - ECOG score (0 or 1, or 2) - Age (<65 years, ≥65 years) - Race (white, African American or Black, Asian) In addition to the prespecified subgroup analyses mentioned above, a post-hoc subgroup analysis of patients who had received two taxanes were conducted and results from this post hoc analysis is presented in the comparison of Pluvicto® + BSC/SoC compared to BSC/SoC alone for patients who have received two taxanes (docetaxel and cabazitaxel).
Other relevant information	After the trial started, a high incidence of withdrawal from the trial was noted in the control group at certain sites and was attributed principally to patient disappointment. After discussion with regulatory authorities, enhanced trial-site education measures were implemented on March 5, 2019 to reduce the incidence of withdrawal. The high incidence of withdrawal could have affected the interpretability of radiographic end points. Therefore, the primary analysis of imaging-based progression-free survival and the analyses of key secondary end points were amended to include only the patients who had undergone randomization on or after March 5, 2019. To maintain statistical power for the analysis of imaging-based progression-free survival, a planned sample of 557 patients who had been enrolled on or after March 5, 2019, was required. To ensure that this number was reached, the planned total sample size was increased from 750 to 814 in the protocol amendment on July 8, 2019. Key secondary efficacy outcomes were analyzed in patients who had disease that could be evaluated according to RECIST, version 1.1, at baseline and who had undergone randomization on or after March 5, 2019. The safety of the randomized trial treatments was assessed according to treatment received in all the patients who received at least one dose (20).

Main characteristics of CARD

Table 66 Main characteristics of CARD. Source: de Wit et al. 2019.

Trial name: The CARD study	NCT number: NCT02485691
Objective	The primary objective was to compare the rPFS (using RECIST 1.1 for tumor lesions and PCWG2 criteria for bone scan lesions

Trial name: The CARD study	NCT number: NCT02485691
	or death due to any cause) with cabazitaxel plus prednisone versus enzalutamide or abiraterone acetate plus prednisone in mCRPC participants who have been treated with docetaxel and who had disease progression while receiving AR-targeted therapy within 12 months of AR treatment initiation
Publications – title, author, journal, year	de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med. 2019;381(26):2506-2518. de Wit R, Wulfing C, Castellano D, Kramer G, Eymard JC, Sternberg CN, et al. Baseline neutrophil-to-lymphocyte ratio as a predictive and prognostic biomarker in patients with metastatic castration-resistant prostate cancer treated with cabazitaxel versus abiraterone or enzalutamide in the CARD study. ESMO Open. 2021;6(5):100241. Sternberg CN, Castellano D, de Bono J, Fizazi K, Tombal B, Wülfing C, et al. Efficacy and safety of cabazitaxel versus abiraterone or enzalutamide in older patients with metastatic castration-resistant prostate cancer in the CARD Study. Eur Urol. 2021;80(4):497-506. Fizazi K, Kramer G, Eymard JC, Sternberg CN, de Bono J, Castellano D, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. Lancet Oncol. 2020;21(11):1513-1525.
Study type and design	Multicenter, randomized, open-label, phase IV clinical trial. Patients were randomly assigned in a 1:1 ratio and stratification criteria were the ECOG performance-status score (0 or 1 vs. 2; scores are on a 5-point scale, with higher numbers indicating greater disability), time to disease progression (≤6 months vs. >6 to 12 months), and timing of the previous alternative androgen-signaling–targeted inhibitor (before vs. after docetaxel).
Sample size (n)	A total of 255 patients were randomly assigned to receive cabazitaxel (129 patients) or an androgen-signaling-targeted inhibitor (abiraterone or enzalutamide; 126 patients), which represented the intention-to-treat population. Of these patients, 250 were treated (126 with cabazitaxel and 124 with an androgen-signaling-targeted inhibitor). Of the 124 patients who received an androgen-signaling–targeted inhibitor, 58 received abiraterone and 66 received enzalutamide. Two patients in the cabazitaxel group were lost to follow-up.
Main inclusion criteria	Main inclusion criteria from the protocol: - Histologically or cytologically confirmed prostate adenocarcinoma

Trial name: The CARD study	NCT number: NCT02485691

- Metastatic disease
- Effective castration with serum testosterone levels <0.5 ng/mL (1.7 nmol/L)
- Progressive disease by at least one of the following:
    - Progression in measurable disease (RECIST 1.1 criteria). Patient with measurable disease must have at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be at least 10 mm when measured by computed tomography (CT) [CT scan thickness no greater than 5 mm] or magnetic resonance imaging (MRI). Lymph nodes should be ≥ 15 mm in short axis. As defined by PCWG2, if lymph node metastasis is the only evidence of metastasis, it must be ≥ 20 mm in diameter when measured by spiral CT or MRI. Previously irradiated lesions, primary prostate lesion and bone lesions will be considered non-measurable disease, and/or
    - Appearance of 2 or more new bone lesions (PCWG2). They must be confirmed by other imaging modalities (CT; MRI) if ambiguous results, and/or
    - Rising PSA defined (PCWG2) as at least two consecutive rises in PSA to be documented over a reference value (measure 1) taken at least one week apart. The first rising PSA (measure 2) should be taken at least 7 days after the reference value. A third confirmatory PSA measure is required (2nd beyond the reference level) to be greater than the second measure and it must be obtained at least 7 days after the 2nd measure. If this is not the case, a fourth PSA measure is required to be taken and be greater than the 2nd measure. The third (or the fourth) confirmatory PSA should be taken within 4 weeks prior to randomization.
- Having received prior docetaxel (before or after an AR targeted therapy)
- Having progressive disease while receiving AR targeted therapy with abiraterone acetate or enzalutamide within 6 months of AR treatment initiation (≤ 6 months)
- A PSA value of at least 2 ng/mL is required at study entry
- Prior AR targeted therapy (abiraterone acetate or enzalutamide) must be stopped at least 2 weeks before study treatment

Trial name: The CARD study	NCT number: NCT02485691
	- Signed informed consent
Main exclusion criteria	Main exclusion criteria from protocol: Related to methodology: - Prior chemotherapy other than docetaxel for prostate cancer, except estramustine and except adjuvant/neoadjuvant treatment completed >3 years ago - Less than 28 days elapsed from prior treatment with chemotherapy, radiotherapy or surgery to the time of randomization - AEs (excluding alopecia and those listed in the specific exclusion criteria) from any prior anticancer therapy of Grade >1 (National Cancer Institute Common Terminology Criteria [NCI CTCAE] v4.0) at the time of randomization - Less than 18 years (or country's legal age of majority if the legal age is >18 years) - ECOG PS >2 (ECOG 2 must be related to prostate cancer, not to other comorbidities) - Prior malignancy. Adequately treated basal cell or squamous cell skin or superficial (pTis, pTa, and pT1) bladder cancer are allowed, as well as any other cancer for which treatment has been completed ≥5 years ago and from which the patient has been disease-free for ≥5 years - Participation in another clinical trial and any concurrent treatment with any investigational drug within 30 days prior to randomization. - Acquired immunodeficiency syndrome (AIDS related illnesses) or known HIV disease requiring antiretroviral treatment. - Patients with reproductive potential who do not agree to use accepted and effective method of contraception during the study treatment period and up to 6 months after the last administered dose. The definition of "effective method of contraception" will be based on the investigator's judgment. Related to study treatment: - Known allergies, hypersensitivity or intolerance to prednisone or excipients of abiraterone acetate or enzalutamide or docetaxel or polysorbate 80. - Known history of mineralocorticoid excess or deficiency. - History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain arteriovenous

Trial name: The CARD study	NCT number: NCT02485691

	malformation, brain metastases or the use of concomitant medications that may lower the seizure threshold.
	- Unable to swallow a whole tablet or capsule.
	- Inadequate organ and bone marrow function as evidenced by:
	  o Hemoglobin <10.0 g/dL
	  o Absolute neutrophil count <1.5x 10^9/L
	  o Platelet count <100 x 10^9/L
	  o AST/SGOT and/or ALT/SGPT >1.5 x ULN
	  o Total bilirubin >1.0 x ULN
	  o Potassium <3.5 mmol/L
	  o Child-Pugh Class C
	  o Creatinine clearance (CrCl) <50 mL/min
	- Contraindications to the use of corticosteroid treatment.
	- Symptomatic peripheral neuropathy Grade >2 (NCI CTCAE v.4.0).
	- Uncontrolled severe illness or medical condition including uncontrolled diabetes mellitus, history of cardiovascular disease (uncontrolled hypertension, arterial thrombotic events in the past 6 months, congestive heart failure, severe or unstable angina pectoris, recent myocardial infraction within last 6 months or uncontrolled cardiac arrhythmia).

Intervention	Cabazitaxel at a dose of 25 mg per square meter of body-surface area, according to the European label, was administered intravenously over a period of 1 hour every 3 weeks. Patients in the cabazitaxel group also received oral prednisone at a dose of 10 mg daily. Premedication included an antihistamine, glucocorticoid (dexamethasone at a dose of 8 mg or equivalent), and histamine2-receptor antagonist. Antiemetic prophylaxis was administered at the physician's discretion. Primary prophylactic granulocyte-colony stimulating factor was a requirement of this trial during each cycle of cabazitaxel.
Comparator(s)	Patients who had been assigned to receive an androgen-signaling-targeted inhibitor received either abiraterone (1000 mg orally once daily and oral prednisone 5 mg twice daily) or enzalutamide (160 mg orally once daily) continuously. Abiraterone was given to patients who had previously received enzalutamide before trial entry, and enzalutamide was given to patients who had previously received abiraterone.

Trial name: The CARD study	NCT number: NCT02485691
Follow-up time	The median follow-up (from randomization to the end of the trial) was 9.2 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoints (from clinicaltrials.gov)** - rPFS **Secondary endpoints (from clinicaltrials.gov)** - OS - PFS - Percentage of Participants With Prostate Specific Antigen (PSA) Response - Percentage of Participants With Overall Objective Tumor Response - Time to PSA Progression (TTPP) - Duration of Tumor Response - Percentage of Participants Achieving Pain Response Assessed Using Brief Pain Inventory-Short Form (BPI-SF) Pain Intensity Score - Time to Pain Progression - Number of Symptomatic Skeletal Events (SSE) - Time to Symptomatic Skeletal Event - Health-Related Quality of Life (HRQOL): Change From Baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment - Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Utility Single Index and Visual Analogue Scale (VAS) Scores at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment - rPFS in Participants With Presence and Absence of Biomarke **Endpoints included in this application:** - OS - rPFS

Trial name: The CARD study	NCT number: NCT02485691
Method of analysis	All the efficacy analyses used data that were obtained at the cutoff date of 27 March 2019, as specified in the protocol. If an imaging-based progression event or death did not occur during the trial, then the data on imaging-based PFS were censored at the last tumor assessment or at the cutoff date, whichever occurred first. If no valid tumor assessment was available, data were censored at the date of randomization. No interim analysis was performed. The efficacy analysis included all the patients who had undergone randomization. Stratified log-rank tests were used to analyze time-to-event data. The primary analysis compared imaging-based PFS between the two treatment groups with the use of a stratified log-rank test. Survival curves were generated with the use of Kaplan–Meier estimates. Hazard ratios and associated 95% CIs were estimated with the use of a stratified Cox proportional-hazards model. Stratified Cochran–Mantel–Haenszel chi-square tests were used to analyze categorical data. Descriptive statistics were used to summarize the characteristics of the patients. The safety population, which included all the patients who had undergone randomization and had received at least one dose of trial treatment, was used for all safety analyses. To control for type I error due to multiple comparisons, a hierarchical testing procedure was applied for the primary and key secondary end points. Only if imaging-based PFS differed significantly between two treatment groups would key secondary end points be tested in the following order: OS, PFS, PSA response, and tumor response. Further tests were stopped once a comparison was found not to be significant at a two-sided alpha level of 0.05.
Subgroup analyses	The following subgroup analyses were conducted in CARD: - ECOG performance-status score (0 or 1, or 2) - Time from initiation of androgen-signaling–targeted inhibitor to progression (≤6 months/>6–12 months) - Timing of androgen-signaling–targeted inhibitor (Before docetaxel/after docetaxel) - Duration of first androgen-deprivation therapy (<12 months/ ≥12 months) - Age (<70 yr/ ≥70 yr) - Visceral metastases (yes/no) - Gleason score 8–10 at diagnosis (Yes/no) - M1 disease at diagnosis /yes/no) - Previous therapy with curative intent for localized disease (yes/no)

Trial name: The CARD study	NCT number: NCT02485691
	- Type of progression (PSA only, Imaging-based, without pain, pain)
Other relevant information	None

Main characteristics of TROPIC

Table 67 Main characteristics of TROPIC. Source: de Bono et al. 2010.

Trial name: TROPIC	NCT number: NCT00417079
Objective	The aim of the TROPIC trial was to assess whether cabazitaxel plus prednisone improves overall survival compared with mitoxantrone plus prednisone in men with metastatic castration-resistant prostate cancer who had progressed after docetaxel-based chemotherapy. The primary objective was overall survival. Secondary objectives included progression free survival, overall response rate, PSA response/progression, pain response/progression, overall safety, and pharmacokinetics. Patients was treated until disease progression, death, unacceptable toxicity, or for a maximum of 10 cycles. Patients had long-term follow-up for a maximum of up to 2 years.
Publications – title, author, journal, year	Oudard, S. TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. Future Oncology. 2011;7(4):497–506. Bahl A, Oudard S, Tombal B, Ozgüroglu M, Hansen S, Kocak I, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol. 2013;24(9):2402-2408. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-1154.
Study type and design	Phase III, randomized, open-label, multi-center study.
Sample size (n)	755 men were allocated to treatment groups (377 mitoxantrone, 378 cabazitaxel) and were included in the intention-to-treat analysis.
Main inclusion criteria	- Histologically or cytologically confirmed adenocarcinoma of the prostate that is refractory to hormone therapy and previously treated with a Taxotere®-containing regimen. - Documented progression of disease (demonstrating at least one visceral or soft tissue metastatic lesion, including a new

Trial name: TROPIC	NCT number: NCT00417079
	lesion). Patients with non-measurable disease must have documented rising prostate-specific antigen (PSA) levels or appearance of new lesion. - Surgical or hormone-induced castration - Life expectancy > 2 months - ECOG performance status 0 - 2
Main exclusion criteria	- Previous treatment with mitoxantrone - Previous treatment with <225 mg/m^2 cumulative dose of Taxotere (or docetaxel) - Prior radiotherapy to ≥ 40% of bone marrow - Surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrollment in the study - Other prior malignancy, except for adequately treated superficial basal cell skin cancer, or any other cancer from which the patient has been disease-free for less than 5 years - Known brain or leptomeningeal involvement - Other concurrent serious illness or medical conditions - Inadequate organ function evidenced by unacceptable laboratory results
Intervention	25 mg/m^2 cabazitaxel intravenously over 1 h every 3 weeks.
Comparator(s)	12 mg/m^2 mitoxantrone intravenously over 15–30 min.
Follow-up time	The median follow-up for both treatment groups combined was 12.8 months (IQR 7.8–16.9).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint:** - OS **Secondary endpoints:** - PFS - Overall Tumor Response - Time to Tumor Progression - Time to Prostatic Specific Antigen (PSA) Progression - PSA (Prostate-Specific Antigen) Response

Trial name: TROPIC	NCT number: NCT00417079
	- Time to Pain Progression - Pain Response **Endpoints included in this application:** - OS - PFS
Method of analysis	SAS (version 9.1.3) was used for all analyses. The study required an estimated sample size of 720 patients (360 per group) to detect a 25% reduct ion in the hazard ratio (HR) for death in the cabazitaxel group relative to the mitoxantrone group with 90% power, with a two-sided log-rank test at a significance level of 0.05 and on the assumption of 8 months median overall survival in the mitoxantrone group. The final analysis was planned to take place when 511 deaths had occurred. Analysis of the primary endpoint was for the intention-to-treat population (all patients randomly assigned to treatment groups). Safety analyses included patients who received at least part of one dose of study drug. Overall survival was analyzed using the Kaplan-Meier method, with log-rank comparisons stratified according to disease measurability (measurable versus non-measureable) and ECOG performance status (0–1 versus 2). HRs and 95% CIs were calculated with a Cox proportional hazards model (for both primary and secondary analyses). Overall survival data were censored at the last date the patient was known to be alive or at the analysis cutoff date, whichever was earliest. Progression-free survival and progression of tumour, PSA, and pain were compared between treatments by log-rank testing. A planned futility analysis of progression-free survival was done after 225 patients had a progression event. Additionally, an interim analysis of the primary efficacy endpoint of overall survival was planned after 307 events but was actually done after 365 events with an adjusted significance level of 0.016, on the basis of the O'Brien-Fleming type 1 error spending function. A two-sided significance level of 0.0452 was used for the final analysis. Although the study team was masked to treatment allocation and patient outcomes throughout the trial, an independent contract statistician provided unmasked results to an independent data monitoring committee with the appropriate analyses for assessment.
Subgroup analyses	Subgroup analyses on overall survival and incidence of neutropenia and diarrhea were performed defined by baseline characteristics. Subgroup analyses performed on OS: - Age (<65 yr/≥65 yr)

Trial name: TROPIC	NCT number: NCT00417079
	- ECOG status (0, 1 / 2) - Measurable disease (yes/no) - Number of previous chemotherapies (1/≥2) - Pain at baseline (yes/no) - Rising PSA at baseline (yes/no) - Total docetaxel dose (<225 mg/m^2 / ≥225–450 mg/m^2 / ≥450–675 mg/m^2 / ≥675–900 mg/m^2 / ≥900 mg/m^2) - Progression during/after docetaxel treatment (During docetaxel treatment / <3 months after docetaxel treatment / ≥3 months after docetaxel treatment) Subgroup analyses performed on incidence of neutropenia and diarrhea in patients treated with cabazitaxel: - Age (diarrhea: <75 yr/≥75 yr, neutropenia: <65 yr/≥65 yr) - Prior radiotherapy (yes/no) - Region (North America/Europe/Other) - Race - Baseline liver function - Baseline renal function - ECOG performance status - Prior chemotherapy
Other relevant information	None

Main characteristics of AFFIRM

Table 68 Main characteristics of AFFIRM. Source: Scher et al. (2012)

Trial name: AFFIRM	NCT number: NCT00974311
Objective	The primary objective of the AFFIRM study was to compare the clinical benefit of enzalutamide versus placebo in patients with castration-resistant prostate cancer who have been previously treated with docetaxel-based chemotherapy.
Publications – title, author, journal, year	Cella D, Ganguli A, Turnbull J, Rohay J, Morlock R. US Population reference values for health-related quality of life questionnaires based on demographics of patients with prostate cancer. Adv Ther. 2022;39(8):3696-3710. Joshua AM, Armstrong A, Crumbaker M, Scher HI, de Bono J, Tombal B, et al. Statin and metformin use and outcomes in patients with castration-resistant prostate cancer treated with

Trial name: AFFIRM	NCT number: NCT00974311

enzalutamide: A meta-analysis of AFFIRM, PREVAIL and PROSPER. Eur J Cancer. 2022;170:285-295.

Zhao JL, Fizazi K, Saad F, Chi KN, Taplin ME, Sternberg CN, et al. The effect of corticosteroids on prostate cancer outcome following treatment with enzalutamide: A multivariate analysis of the phase III AFFIRM trial. Clin Cancer Res. 2022;28(5):860-869.

Tombal BF, Freedland SJ, Armstrong AJ, Beer TM, Stenzl A, Sternberg CN, et al. Impact of enzalutamide on patient-reported fatigue in patients with prostate cancer: data from the pivotal clinical trials. Prostate Cancer Prostatic Dis. 2022;25(2):288-295.

Armstrong AJ, Al-Adhami M, Lin P, Parli T, Sugg J, Steinberg J, et al. Association between new unconfirmed bone lesions and outcomes in men with metastatic castration-resistant prostate cancer treated with enzalutamide: Secondary analysis of the PREVAIL and AFFIRM randomized clinical trials. JAMA Oncol. 2020;6(2):217-225.

Poon DMC, Wong KCW, Chan TW, Law K, Chan K, Lee EKC et al. Survival outcomes, prostate-specific antigen response, and tolerance in first and later lines of enzalutamide treatment for metastatic castration-resistant prostate cancer: a real-world experience in Hong Kong. Clin Genitourin Cancer. 2018;16(5):402-412.e1.

Heller G, McCormack R, Kheoh T, Molina A, Smith MR, Dreicer R, et al. Circulating tumor cell number as a response measure of prolonged survival for metastatic castration-resistant prostate cancer: A comparison with prostate-specific antigen across five randomized phase iii clinical trials. J Clin Oncol. 2018;36(6):572-580.

Antoun S, Bayar A, Ileana E, Laplanche A, Fizazi K, di Palma M, et al. High subcutaneous adipose tissue predicts the prognosis in metastatic castration-resistant prostate cancer patients in post chemotherapy setting. Eur J Cancer. 2015;51(17):2570-2577.

Gibbons JA, Ouatas T, Krauwinkel W, Ohtsu Y, van der Walt JS, Beddo V, et al. Clinical pharmacokinetic studies of enzalutamide. Clin Pharmacokinet. 2015;54(10):1043-1055.

Cella D, Ivanescu C, Holmstrom S, Bui CN, Spalding J, Fizazi K. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial. Ann Oncol. 2015;26(1):179-185.

Saad F, de Bono J, Shore N, Fizazi K, Loriot Y, Hirmand M, et al. Efficacy outcomes by baseline prostate-specific antigen quartile in the AFFIRM trial. Eur Urol. 2015;67(2):223-230.

Trial name: AFFIRM	NCT number: NCT00974311
	Merseburger AS, Scher HI, Bellmunt J, Miller K, Mulders PF, Stenzl A, et al. Enzalutamide in European and North American men participating in the AFFIRM trial. BJU Int. 2015;115(1):41-49. Fizazi K, Scher HI, Miller K, Basch E, Sternberg CN, Cella D, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol. 2014;15(10):1147-1156. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-97.
Study type and design	International, randomized, double-blinded, placebo-controlled phase 3 trial. Enrolled patients were randomly assigned to the study treatment centrally by the means of an interactive voice-response system after stratification according to the baseline ECOG performance status and the Brief Pain Inventory-Short Form (BPI-SF) question 3 score addressing the average pain over the 7 days before randomization. Patients were randomly assigned in a 2:1 ratio. Permuted-block randomization was used. The trial was triple-masked (participant, investigator, and outcomes assessor).
Sample size (n)	A total of 1,199 men with castration-resistant prostate cancer were allocated to receive either oral enzalutamide (n = 800) or placebo (n = 399).
Main inclusion criteria	- Progressive prostate cancer - Medical or surgical castration with testosterone less than 50 ng/dl - One or two prior chemotherapy regimens. At least one chemotherapy regimen must have contained docetaxel - ECOG performance status 0-2 - Adequate bone marrow, hepatic, and renal function - Able to swallow the study drug and comply with study requirements - Informed consent
Main exclusion criteria	- Metastases in the brain or active epidural disease - Another malignancy within the previous 5 years - Clinically significant cardiovascular disease - Gastrointestinal disorder affecting absorption

Trial name: AFFIRM	NCT number: NCT00974311
Intervention	160 mg Enzalutamide orally once per day.
Comparator(s)	Matched placebo capsules.
Follow-up time	Median follow-up of 14.4 months.
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Primary endpoints:** - OS **Secondary endpoints:** - rPFS - Time to first skeletal-related event - Percentage of participants who were responders for Functional Assessment of Cancer Therapy Prostate (FACT-P) - Time to Prostate-specific Antigen (PSA) Progression - Percentage of participants with pain palliation - Percentage of participants with PSA response - Percentage of participants with soft-tissue objective response - European Quality of Life Five-Domain (EQ-5D) Scale - Percentage of participants wit Circulating Tumor Cell (CTC) **Endpoints included in this application:** - OS - rPFS
Method of analysis	All analyses were performed by the sponsor using data obtained as of the cutoff date of September 25, 2011. The primary efficacy end point was a between-group comparison of the time from randomization to death from any cause (OS) in the intention-to-treat population (all randomly assigned patients). OS was presented as Kaplan-Meier curves, and a log-rank test was used to evaluate OS, with stratification according to the ECOG performance-status score and the baseline pain score (as measured by the BPI-SF score). Supportive analyses of overall survival were performed with the use of the unstratified log-rank test and Cox proportional-hazards models. Only if the OS analysis showed statistical superiority of enzalutamide over placebo was the testing of the key secondary end points to be undertaken, in the rank-prioritized order — the

Trial name: AFFIRM	NCT number: NCT00974311
	time to PSA progression, rPFS, and the time to the first skeletal-related event — with the significance of the previous end point gating further testing. These end points were tested by means of the stratified log-rank test in a protected hierarchical manner, each at the two-sided significance level of 0.05.
Subgroup analyses	Subgroup analyses for OS were conducted to determine whether treatment effects were consistent across patient subgroups. A multivariate analysis was also performed. The following subgroups were assessed: - Age (<65 yr vs. ≥65 yr) - Baseline ECOG performance status score (0-1 vs. 2) - Baseline pain score on BPI-SF (<4 vs. ≥4) - Geographic region (North America vs. Other) - No. of previous hormonal treatment (≤2 vs. >2) - No. of previous chemotherapy regiments (1 vs. ≥2) - Type of disease progression at study entry (PSA progression only vs. Radiographic progression with or without PSA progression) - No. of bone lesions (≤20 vs. >20) - Visceral (liver or lung) disease at baseline (No vs. Yes) - Baseline PSA level (≤Median vs. >Median) - Baseline LDH level (≤Median vs. >Median)
Other relevant information	The trial included two phases. In the double-blind phase 1,199 participants were enrolled and randomized to receive either enzalutamide or placebo. Out of these, 159 participants entered the optional open-label extension (OLE) phase. All participants who continued in the OLE phase, received enzalutamide. The DB phase lasted for 24 months, and the OLE phase lasted for 77 months, resulting in a total study period of 101 months.

Main characteristics of Sun et al. 2016

Table 69 Main characteristics of Sun et al. 2016. Source: Clinicaltrials.gov + Sun et al. (2016).

Trial name:	NCT number: NCT01695135
Objective	To evaluate the efficacy and safety of abiraterone acetate-prednisone versus placebo-prednisone in Asian metastatic castration-resistant prostate cancer patients who have failed docetaxel-based chemotherapy.

Trial name:	NCT number: NCT01695135
Publications – title, author, journal, year	Sun Y, Zou Q, Sun Z, Changlin L, Du C, Chen Z, et al. Abiraterone acetate for metastatic castration-resistant prostate cancer after docetaxel failure: A randomized, double-blind, placebo-controlled phase 3 bridging study. Int J Urol. 2016;23(5):404-411.
Study type and design	Multicenter, double-blind, placebo-controlled, phase 3 study with a randomization allocation ratio of 2:1 between the treatment group and the placebo group. The study consisted of three phases: 1) screening (within 28 days before randomization on cycle 1 day 1), 2) double-blind treatment phase (28-day cycles until disease progression/unacceptable toxicity), and 3) follow-up phase (every 3 months up to month 60, depending on survival status). During the double-blind phase, eligible patients were randomized to receive either abiraterone acetate (1000 mg once daily) plus prednisone (5 mg twice daily) or placebo plus prednisone orally on an empty stomach. No cross-over was allowed. Randomization was carried out using an interactive response system.
Sample size (n)	214 men with mCRPC progressing after docetaxel chemotherapy were enrolled across 22 sites in China between 9 August 2012 and 7 November 2013. As of 30 April 2014 (clinical cut-off date for the final analysis), treatment was ongoing for 45 patients (31.5%) in the abiraterone–prednisone group and 11 patients (15.5%) in the prednisone-alone group. The main reason for discontinuation from both groups was disease progression (abiraterone–prednisone [55.2%]; placebo–prednisone [69%]).
Main inclusion criteria	Men aged ≥18 years with histologically/cytologically confirmed mCRPC were eligible if they had failed previous docetaxel-containing chemotherapy; documented disease progression according to PSAWG criteria or radiographic progression in soft tissue or bone despite castrate levels of serum testosterone (<50 ng/dL); and ≤2 ECOG PS score.
Main exclusion criteria	- Active infection or any medical condition either contraindicating prednisone use or requiring higher doses (>5 mg, twice daily) - Neuroendocrine carcinoma of the prostate including small cell carcinoma - Uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic ≥95 mmHg) - Active or symptomatic viral hepatitis or chronic liver disease - Pituitary or adrenal dysfunction - Clinically significant heart disease - Known brain metastasis

Trial name:	NCT number: NCT01695135
	- Prior therapy with abiraterone acetate, ketoconazole or other CYP17 inhibitors, or any other agent targeting the androgen receptor (taken within 4 weeks [flutamide] and 6 weeks [bicalutamide/nilutamide] before day 1 of cycle 1) for metastatic prostate cancer.
Intervention	Abiraterone acetate (1000 mg once daily [4 x 250 mg tablets] taken orally) plus prednisone (5 mg twice daily, taken orally), n = 143
Comparator(s)	Placebo (4 tablets taken orally) plus prednisone (5 mg twice daily, taken orally), n = 71
Follow-up time	12.9 months
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Primary endpoints:** - Median TTPP **Secondary endpoints:** - OS - PSA response rate - ORR - Time to pain progression and pain palliation rate - Scores for quality of life and fatigue assessment Safety evaluations included adverse events reporting, clinical laboratory tests, vital signs measurements, physical examinations, 12-lead electrocardiogram, multiple gated acquisition scan or cardiac echocardiogram. **Endpoints included in this application:** OS
Method of analysis	For TTPP and OS, the distribution, median time and 95% CI were estimated using the Kaplan-Meier method. The non-stratified log-rank test was used for treatment comparison. Supportive analysis was carried out using a non-stratified Cox proportional hazards model. Response endpoints and safety data were summarized using descriptive statistics. The relative risk between both groups was reported along with the associated two-tailed 95% CI, and significance was inferred

Trial name:	NCT number: NCT01695135
	using X^2-test or Fischer's exact test, and the overall significance level was $P = 0.05$.
Subgroup analyses	Subgroup analysis for TTPP was carried out for the factors of age (<65 years, ≥65 years) and baseline ECOG PS score (0 or 1, 2).
Other relevant information	During the follow-up phase, patients with disease progression will be provided open-label (identity of assigned study drug will be known) extension treatment with abiraterone acetate. In the event of a positive study result at the time of the final analysis, participants in the placebo group who have not shown progressive disease in the double-blind treatment Phase of the study will be enrolled in an open-label extension treatment with abiraterone acetate treatment based on the participant's choice and treating physician's endorsement if they meet the criteria for subsequent abiraterone acetate.

Main characteristics of COU-AA-301

Table 70 Main characteristics of COU-AA-301. Source: Clinicaltrials.gov + Fizazi et al.

Trial name: COU-AA-301	NCT number: NCT00638690
Objective	To compare the clinical benefit of abiraterone acetate plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed one or two chemotherapy regimens.
Publications – title, author, journal, year	Heller G, McCormack R, Kheoh T, Molina A, Smith MR, Dreicer R, et al. Circulating tumor cell number as a response measure of prolonged survival for metastatic castration-resistant prostate cancer: a comparison with prostate-specific antigen across five randomized phase III clinical trials. J Clin Oncol. 2018;36(6):572-580. Chi KN, Kheoh T, Ryan CJ, Molina A, Bellmunt J, Vogelzang NJ, et al. A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. Ann Oncol. 2016;27(3):454-460. Fizazi K, Flaig TW, Stockle M, Scher HI, de Bono JS, Rathkopf DE, et al. Does Gleason score at initial diagnosis predict efficacy of abiraterone acetate therapy in patients with metastatic castration-resistant prostate cancer? An analysis of abiraterone acetate phase III trials. Ann Oncol. 2016;27(4):699-705. Antoun S, Bayar A, Ileana E, Laplanche A, Fizazi K, di Palma M, et al. High subcutaneous adipose tissue predicts the prognosis in metastatic castration-resistant prostate cancer patients in post chemotherapy setting. Eur J Cancer. 2015;51(17):2570-2577.

Trial name: COU-AA-301	NCT number: NCT00638690
	Xu XS, Ryan CJ, Stuyckens K, Smith MR, Saad F, Griffin TW, et al. Correlation between prostate-specific antigen kinetics and overall survival in abiraterone acetate-treated castration-resistant prostate cancer patients. Clin Cancer Res. 2015;21(14):3170-3177. Scher HI, Heller G, Molina A, Attard G, Danila DC, Jia X, Peng W, Sandhu SK, Olmos D, Riisnaes R, McCormack R, Burzykowski T, Kheoh T, Fleisher M, Buyse M, de Bono JS. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. J Clin Oncol. 2015;33(12):1348-1355. Mulders PF, Molina A, Marberger M, Saad F, Higano CS, Chi KN, et al. Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy. Eur Urol. 2014;65(5):875-883. Harland S, Staffurth J, Molina A, Hao Y, Gagnon DD, Sternberg CN, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. Eur J Cancer. 2013;49(17):3648-3657. Ryan CJ, Molina A, Li J, Kheoh T, Small EJ, Haqq CM, et al. Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: results from an analysis of a randomized phase III trial. J Clin Oncol. 2013;31(22):2791-2798. Logothetis CJ, Basch E, Molina A, Fizazi K, North SA, Chi KN, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol. 2012;13(12):1210-1217. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983-992. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005.
Study type and design	Phase III, randomized, double-blind, placebo-controlled, multinational study
Sample size (n)	1195 patients were randomly assigned to receive either abiraterone acetate plus prednisone or placebo plus prednisone.
Main inclusion criteria	**Inclusion criteria:**

Trial name: COU-AA-301	NCT number: NCT00638690
	Adult men with: • Metastatic Castration-Resistant Prostate Cancer Progression after one or two prior cytotoxic chemotherapies • At least one chemotherapy must have contained docetaxel • Eastern Cooperative Oncology Group (ECOG) Performance Status <= 2 • Medical or surgical castration with testosterone < 50 ng/dL • Adequate bone marrow, hepatic and renal function • Potassium >= 3.5 mmol/L • Able to swallow the study drug whole as a tablet • Informed Consent
Main exclusion criteria	**Exclusion criteria:** • More than two prior cytotoxic chemotherapy regimens • Prior Ketoconazole for prostate cancer • Prior abiraterone acetate or other CYP17 inhibitor or investigational agents targeting the androgen receptor for prostate cancer • Uncontrolled hypertension • Active or symptomatic viral hepatitis or chronic liver disease • History of pituitary or adrenal dysfunction • Clinically significant heart disease • Other malignancy • Known brain metastasis • GI disorder affecting absorption • Not willing to use contraception
Intervention	Abiraterone acetate (1000 mg, once daily and orally) plus prednisone (5 mg, twice daily and orally), n = 797
Comparator(s)	Placebo (once daily, and orally) plus prednisone (5 mg, twice daily and orally), n = 398
Follow-up time	Median follow-up of 20.2 months (IQR 18.4–22.1)

Trial name: COU-AA-301	NCT number: NCT00638690
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary:** OS (up to 60 months) **Secondary:** rPFS (up to 11 months) **Other endpoints:** • Time to Prostate-Specific Antigen Progression According to Prostate Specific Antigen Working Group Criteria (up to 12 months) • Number of Patients Achieving a Prostate-Specific Antigen Decline >=50% (up to 12 months) **Endpoints included in this application:** • **Primary:** OS (up to 60 months) • **Secondary:** rPFS (up to 11 months)
Method of analysis	OS was analysed in the ITT population. Post-hoc exploratory analyses of the OS benefit of abiraterone acetate plus prednisone was done on the basis of previous timing of docetaxel administration, duration of docetaxel treatment, and reason for discontinuation of docetaxel. The planned sample size of about 1158 patients was needed to provide 85% power with a two-sided significance level of 0.05 to detect an HR of 0.80. The assumed median survival for abiraterone acetate was 15 months, and 12 months for placebo. The study required a total of 797 death events. A group sequential trial design incorporating the Lan-DeMets α-spending method with the O'Brien-Fleming boundary was used. One interim analysis was planned after the reporting of 534 death events (67% of 797 total events), and a final analysis was to be done after 797 events were observed. The stratified log-rank test was used to compare the treatment differences, whereas the Cox proportional hazards model was used to obtain the estimated HR and its associated 95% CIs for both the primary overall survival analyses and by stratification factors. Homogeneity at a 0.1 significance level was tested. A multivariate analysis using the Cox model and sensitivity analyses for overall survival with the non-stratified log-rank test were also done. The relative risk (treatment:control) along with the associated 95% CIs for dichotomous outcomes were reported; The statistical inference using the χ^2 statistic and used the Fisher's exact test if the expected counts in some cells were small were assessed.

Trial name: COU-AA-301	NCT number: NCT00638690
Subgroup analyses	Prespecified subgroup analyses were done to examine known adverse prognostic factors for men with metastatic castration-resistant prostate cancer. Group baseline stratification factor was used to assess whether or not treatment effects were consistent across the subgroups analysed. Patients were stratified according to baseline ECOG performance status (0–1 vs 2); worst pain over the past 24 h on the BPI-SF (0–3 for absent vs 4–10 for present); number of previous chemotherapy regimens (one vs two); and type of progression (PSA progression only vs radiographic progression with or without PSA progression).
Other relevant information	None.

Main characteristics of TheraP

Table 71 Main characteristics of TheraP. Source: Hofman et al. (2021), Hofman et al. (2024), and clinicaltrials.gov.

Trial name: TheraP	NCT number: NCT03392428
Objective	To determine the activity and safety of Lu-PSMA radionuclide therapy in men with progressive metastatic castration resistant prostate cancer.
Publications – title, author, journal, year	Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet. 2021;397(10276):797-804. Hofman MS, Emmett L, Sandhu S, Iravani A, Buteau JP, Joshua AM, et al. Overall survival with [177Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): secondary outcomes of a randomised, open-label, phase 2 trial. Lancet Oncology. 2024;25(1):99-107. Viljoen B, Hofman MS, Chambers SK, Dunn J, Dhillon HM, Davis ID, et al. Experiences of participants in a clinical trial of a novel radioactive treatment for advanced prostate cancer: A nested, qualitative longitudinal study. PLoS One. 2022;17(11):e0276063. Buteau JP, Martin AJ, Emmett L, Iravani A, Sandhu S, Joshua AM, et al. PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial. Lancet Oncol. 2022;23(11):1389-1397. Viljoen B, Hofman MS, Chambers SK, Dunn J, Dhillon H, Davis ID, et al. Advanced prostate cancer experimental radioactive

Trial name: TheraP	NCT number: NCT03392428
	treatment-clinical trial decision making: patient experiences. BMJ Support Palliat Care. 2021:bmjspcare-2021-002994. Iravani A, Violet J, Azad A, Hofman MS. Lutetium-177 prostate-specific membrane antigen (PSMA) theranostics: practical nuances and intricacies. Prostate Cancer Prostatic Dis. 2020;23(1):38-52.
Study type and design	TheraP was a multicentre, unblinded, randomised phase 2 trial done at 11 centres in Australia. Participants were randomly assigned to cabazitaxel or [^{177}Lu]Lu-PSMA-617. Participants were randomly assigned (1:1) via a centralised web-based system that stratified by disease burden (>20 sites *vs* ≤20 sites by PSMA PET-CT), previous treatment with enzalutamide or abiraterone, and study site using minimisation with a random component. Neither participants nor investigators were masked to group assignment.
Sample size (n)	291 men were screened, of whom 200 were eligible on PET imaging. Study treatment was received by 98 (99%) of 99 men randomly assigned to [177Lu]Lu-PSMA-617 versus 85 (84%) of 101 randomly assigned to cabazitaxel.
Main inclusion criteria	Eligible participants were men with metastatic castration-resistant prostate cancer for whom cabazitaxel was considered the next appropriate standard treatment. Participants were required to have adequate renal, haematological, and liver function, and an Eastern Cooperative Oncology Group performance status of 0–2 (appendix p 14). Previous treatment with androgen receptor-directed therapy was allowed. Men underwent gallium-68 [68Ga]Ga-PSMA-11 and 2-flourine-18 [18F]fluoro-2-deoxy-D-gluycose (FDG) PET-CT scans. PET eligibility criteria for the trial were PSMA-positive disease with a maximum standardised uptake value (SUVmax) of at least 20 at a site of disease and greater than 10 at all other measurable sites of metastatic disease, and no sites of metastatic disease with discordant 2-[18F]FDG-positive and PSMA-negative findings.
Main exclusion criteria	Exclusion Criteria: - Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components - Site(s) of disease that are FDG positive with minimal PSMA expression defined as FDG intensity > 68Ga-PSMA activity OR 68Ga-PSMA SUVmax < 10 - Sjogren's syndrome - Prior treatment with cabazitaxel or Lu-PSMA - Contraindications to the use of corticosteroid treatment

Trial name: TheraP	NCT number: NCT03392428
	- Active malignancy other than prostate cancer - Concurrent illness, including severe infection that may jeopardise the ability of the participant to undergo the procedures outlined in this protocol with reasonable safety - Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse - Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception
Intervention	The experimental group was treated with [177Lu]Lu-PSMA-617 intravenously, every 6 weeks for a maximum of six cycles. The administered starting dose of radioactivity was 8·5 GBq and was decreased by 0·5 GBq per cycle down to 6·0 GBq for the sixth cycle.
Comparator(s)	Participants in the control group were treated with cabazitaxel 20 mg/m2 intravenously, every 3 weeks for a maximum of ten cycles + prednisolone 10mg orally per day for the duration of their cabazitaxel treatment.
Follow-up time	During study treatment, participants were reviewed every 3 weeks, which included routine haematology, biochemistry, and serum PSA. CT of the chest, abdomen and pelvis, and technetium-99m bone scans were done every 12 weeks until radiological progression. Follow-up continued every 12 weeks thereafter.
Is the study used in the health economic model?	Used in a sensitivity analysis.
Primary, secondary and exploratory endpoints	**Primary:** • PSA response rate (follow-up: through study completion, on average 4 years) **Secondary:** • Pain response rate (follow-up: through study completion, on average 4 years) • Objective tumour response rate (follow-up: through study completion, on average 4 years) • Progression free survival (follow-up: through study completion, on average 4 years) • PSA progression free survival (follow-up: through study completion, on average 4 years)

Trial name: TheraP	NCT number: NCT03392428
	• Pain progression free survival (follow-up: through study completion, on average 4 years) • rPFS (follow-up: through study completion, on average 4 years) • Health-related quality of life (follow-up: through study completion, on average 4 years) • OS (follow-up: through study completion, on average 4 years) • Frequency and severity of adverse events (follow-up: from first study dose to 12 weeks after completing treatment) **Endpoints included in this application:** • Secondary endpoint: OS • Secondary endpoint: rPFS
Method of analysis	The primary analysis was by intention-to-treat, and participants who withdrew after randomisation were not replaced. Sensitivity analyses according to treatment received (per protocol) were also done. The per-protocol population comprised all randomly assigned participants who received at least one dose of assigned treatment. Additionally, time-to-event outcomes were analysed with Kaplan-Meier curves and stratified log-rank tests with the stratification factors at randomisation. Cox proportional hazards regression was used to estimate HRs and 95% CIs, adjusted for stratification factors.
Subgroup analyses	N/A
Other relevant information	Despite representing the only direct head-to-head study comparing 177Lu-PSMA-617 to cabazitaxel, a number of factors make the TheraP unsuitable to inform efficacy of Pluvicto®, e.g. that the compound investigated in TheraP was not Pluvicto®. These include: 1. The TheraP study was a phase II trial (does not meet the study design eligibility criteria for inclusion in the NMA. 2. The version of 177Lu-PSMA-617 used in the TheraP study was 'hospital compounded' (i.e., not company-manufactured) and thus, the molecule is potentially subject to variability from company-specific production. The bioequivalence of Pluvicto® with 177Lu-PSMA-617 is not established. 3. Patients in the 177Lu-PSMA-617 arm of TheraP received a starting dose of 8.5 GBq, which reduced by 0.5 GBq per cycle. This differs from the recommended dose of

Trial name: TheraP	NCT number: NCT03392428
	Pluvicto©, which was used in VISION, of 7.4 GBq per cycle every 6 weeks. 4. Randomisation in TheraP was stratified by disease burden (>20 sites versus ≤20 sites), previous ARPI treatment, and study site. All these differ from the stratification factors applied to randomisation in the VISION study. 5. Patients in the TheraP study received 18F-FDG PET/CT imaging at baseline (in addition to 68Ga PET/CT) in order to exclude patients with FDG-positive disease sites with minimal PSMA expression. 6. The TheraP study was primarily designed to evaluate PSA response (defined as a reduction of PSA ≥50% from baseline) and was not powered sufficiently to evaluate secondary endpoints. As a result of the above listed challenges, the TheraP study was included in the NMA in a sensitivity analysis.

Appendix B. Efficacy results per study

Results per study (VISION)

Table 72 Results of VISION (key endpoints)

Results of VISION (NCT03511664)											
				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	Pluvicto®	385	8.7 (7.9-10.8) months	5.3 months	NR	NR	HR: 0.40	0.29-0.57*	<0.001	Log-rank test with stratification according to the randomization factors. Stratified Cox model was used to estimate HRs and associated CIs. Medians, percentiles, and associated confidence intervals were estimated with the use of the KM method.	(20)
	BSC/SoC	196	3.4 (2.4-4.0) months								
OS	Pluvicto®	551	15.3 (14.2-16.9) months	4.0 months	NR	NR	HR: 0.62	0.52-0.74	<0.001	Log-rank test with stratification according to the randomization factors. Stratified Cox model was used to estimate HRs and associated CIs. Medians, percentiles, and associated CIs were estimated	(20)
	BSC/SoC	280	11.3 (9.9-13.5) months								

Results of VISION (NCT03511664)											
				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		
										with the use of the KM method.	
Time to first SSE	Pluvicto®	385	11.5 (10.3-13.2) months	4.7 months	NR	NR	HR: 0.50	0.40-0.62	<0.001	Log-rank test with stratification according to the randomization factors. Stratified Cox model was used to estimate HRs and associated CIs. Medians, percentiles, and associated confidence intervals were estimated with the use of the KM method.	(20)
	BSC/SoC	196	6.8 (5.2-8.5) months								

*: 99.2% CI.

Table 73 Results of VISION study (post hoc analysis of Post 1 taxane population in VISION – data on file)

Results of VISION (post hoc analysis of patients who had received maximum one taxane – data on file)											
				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	Pluvicto®	224	8.9 (8.5-11.0) months	5.5 months	NR	NR	HR: 0.39	0.27-0.54	NR	HR was based on stratified Cox Proportional Hazard model. Distributions were estimated using the KM method.	(46)
	BSC/SoC	110	3.4 (2.4-4.0) months								
OS	Pluvicto®	342	16.2 (14.7-18.1) months	4.4 months	NR	NR	HR: 0.59	0.46-0.75	NR	HR was based on stratified Cox Proportional Hazard model. Distributions were estimated using the KM method.	(46)
	BSC/SoC	165	11.8 (9.8-14.4) months								

Table 74 Results of VISION study (population included in NMA: full VISION population with a restriction on the comparator arm (ARPI only) – data on file)

Results of VISION (population included in NMA: full VISION population with a restriction on the comparator arm (ARPI only) – data on file)											
				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	Pluvicto®	385	8.7 (8.5-10.5) months	4.8 months	NR	NR	HR: 0.51	0.36-0.73	NR	HR was based on stratified Cox Proportional Hazard model.	NMA
	ARPI	107	3.9 (3.4-10.6) months								
OS	Pluvicto®	551	15.3 (14.2-17.0) months	1.8 months	NR	NR	HR: 0.57	0.44-0.74	NR	HR was based on stratified Cox Proportional Hazard model.	NMA
	ARPI	146	13.5 (12.2-16.0) months								

Table 75 Results of VISION study (post hoc analysis of Post 2 taxanes population in VISION – data on file)

Results of VISION (post hoc analysis of patients who had received at least two taxanes – data on file)											
				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	Pluvicto®	134	8.3 (6.2-10.4) months	4.8 months	NR	NR	HR: 0.44	0.30-0.66	NR	HR was based on stratified Cox Proportional Hazard model. Distributions were estimated using the KM method.	(46)
	BSC/SoC	77	3.5 (2.2-4.0) months								
OS	Pluvicto®	170	13.6 (11.5-15.4) months	3.0 months	NR	NR	HR: 0.73	0.53-0.99	NR	HR was based on stratified Cox Proportional Hazard model. Distributions were estimated using the KM method.	(46)
	BSC/SoC	99	10.6 (8.3-13.5) months								
Time to first SSE	Pluvicto®	134	10.2 (8.3-13.8) months	4.6 months	NR	NR	HR: 0.43	0.30-0.61	NR	HR was based on stratified Cox Proportional Hazard model. Distributions were estimated using the KM method.	(46)
	BSC/SoC	77	5.6 (3.8-8.3) months								

Results per study (CARD)

Table 76 Results of CARD

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (from date of randomization up to 141 weeks)	Cabazitaxel	129	13.6 (11.5–17.5) months	2.6 months	NR	NR	HR: 0.64	0.46–0.89	0.008	Analysis was performed on the ITT population. Stratified log-rank tests were used. HRs and 95% CIs were estimated with the use of a stratified Cox proportional-hazards model.	(21)
	Androgen-signaling-targeted inhibitor	126	11.0 (9.2–12.9) months								
rPFS (from date of randomization up to 141 weeks)	Cabazitaxel	129	8.0 (5.7–9.2) months	4.3 months	NR	NR	HR: 0.54	0.40–0.73	<0.001	Analysis was performed on the ITT population. Stratified log-rank tests were used. HRs and 95% CIs were estimated with the use of a stratified Cox proportional-hazards model.	(21)
	Androgen-signaling-targeted inhibitor	126	3.7 (2.8–5.1) months								

Results per study (TROPIC)

Table 77 Results of TROPIC

Results of TROPIC (NCT00417079)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (from date of randomization up to 104 weeks)	Mitoxantrone + Prednisone	377	12.7 (11.6-13.7)	-2.4 months	NR	NR	HR: 0.70	0.59-0.83	<0.0001	Analysis was performed on the ITT population. HRs and 95% CIs were calculated with a Cox proportional hazards model.	(62)
	Cabazitaxel + Prednisone	378	15.1 (14.1-16.3)								
PFS (from date of randomization up to 104 weeks)	Mitoxantrone + Prednisone	377	1.4 (1.4-1.7)	-1.4 months	NR	NR	HR: 0.74	0.64-0.86	<0.0001	Analysis was performed on the ITT population. HRs and 95% CIs were calculated with a Cox proportional hazards model.	(62)
	Cabazitaxel + Prednisone	378	2.8 (2.4-3.0)								

Results per study (AFFIRM)

Table 78 Results of AFFIRM

Results of AFFIRM (NCT00974311)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (from date of randomization up to 101 months)	Enzalutamide	800	18.4 (17.3–NA*) months	4.8 months	NR	NR	HR: 0.63	0.53–0.75	<.001	Analysis was performed on the ITT population. The median OS is based on the KM estimator. The HR for death and 95% CI is based on a Cox proportional hazards model.	(31)
	Placebo	399	13.6 (11.3–15.8) months								
rPFS (from date of randomization up to 24 months)	Enzalutamide	800	8.3 (8.2–9.4) months	5.4 months	NR	NR	HR: 0.40	0.35–0.47	<.001	Analysis was performed on the ITT population. The median rPFS is based on the KM estimator. The HR for death and 95% CI is based on a Cox proportional hazards model.	(31)
	Placebo	399	2.9 (2.8–3.4) months								

* The upper limit of the 95% CI was not calculable because an insufficient number of participants reached the event at the final time point for assessment.

Results per study (Sun et al. 2016)

Table 79 Results of Sun et al. (2016)

Results of Sun et al. (2016) (NCT01695135)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (defined as the time interval from the date of randomization to the date of death from any cause)	Abiraterone + prednisone	143	NR	NR	NR	NR	HR: 0.604	0.356-1.026	0.0597	The distribution, median time, and 95% CI were estimated using the KM method. The non-stratified log-rank test was used for comparison. Supportive analysis was carried out using a non-stratified Cox proportional hazards model.	(32)
	Placebo + prednisone	71	NR								

Results per study (COU-AA-301)

Table 80 Results of COU-AA-301

Results of COU-AA-301 (NCT00638690)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS (the time interval from the date of randomization to the date of death from any cause up to 60 months)	Acetate plus prednisone	797	15.8 (14.8–17.0) months	4.6 months	NR	NR	HR: 0.74	0.64–0.86	<0.0001	OS was analysed in the ITT population. The stratified log-rank test was used to compare the treatment differences, whereas the Cox proportional hazards model was used to obtain the estimated HR and its associated 95% CIs for both the primary OS analyses and by stratification factors.	(33)
	Placebo plus prednisone	398	11.2 (10.4–13.1) months								
rPFS (from date of randomisation to date of radiographically	Acetate plus prednisone	797	5.6 (5.6–6.5) months	2.0 months	NR	NR	HR: 0.66	0.58–0.76	<0.0001	rPFS was based on imaging studies according to modified RECIST. The stratified log-rank test was used to compare the treatment differences, whereas the Cox proportional hazards model was used to	(33)
	Placebo plus prednisone	398	3.6 (2.9–5.5) months								

Results of COU-AA-301 (NCT00638690)											
				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**		
documented disease progression up to 11 months)										obtain the estimated HR and its associated 95% CIs for both the primary analyses and by stratification factors.	

* The upper limit of the 95% CI was not calculable because an insufficient number of participants reached the event at the final time point for assessment.

Results per study (TheraP)

Table 81 Results of TheraP

Results of TheraP (NCT03392428 and)											
				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	177Lu-PSMA-617	99	NR	NR	NR	NR	HR: 0.64	0.46-0.88	p=0.007	rPFS was quantified using the KM method and compared using a stratified log-rank test accounting for relevant stratification factors. Multivariable Cox PH regression was used to estimate HR (with 95% CIs) for relevant stratification factors and assigned treatment.	(35)
	Cabazitaxel	101	NR								
OS	Lu-PSMA-617	99	16.4 (13.7-19.4) months	-3.0 months	NR	NR	HR: 0.97	0.70-1.35	p=0.99	OS was quantified using the KM method and compared using a stratified log-rank test accounting for relevant stratification factors. Multivariable Cox PH regression was used to estimate HRs (with 95% CIs) for relevant stratification factors and assigned treatment.	(34)
	Cabazitaxel	101	19.4 (14.0-21.7) months								

Appendix C. Comparative analysis of efficacy

C.1 Post 1 taxane population

Since no head-to-head studies have compared Pluvicto® with cabazitaxel for the Post 1 taxane population, an NMA was conducted. The methodology and results of the NMA are described below.

C.1.1 NMA methodology

In scenarios where more than two studies report on different treatments with a shared comparator, Bayesian NMA is often used to synthesise indirect evidence. The prerequisites to conduct a Bayesian PH NMA are:

A. Studies should have an overlapping distribution of baseline characteristics
B. Common comparators (e.g., control groups) are sufficiently similar to make the combination of relative effects viable.
C. The properties of randomisation hold within the individual studies.

The NMA was conducted utilising summary results from the study publications identified via the SLR. These analyses synthesised HRs for OS and rPFS. The implementation of this Bayesian NMA was carried out using WinBUGS version 1.4.3 (developed by MRC Biostatistics Unit, Cambridge, UK), employing the coding methodology described by Dias et al. (63). This approach ensures a robust and comprehensive analysis of the available data, allowing for meaningful comparisons across different treatment regimens in mCRPC.

The results of the Bayesian proportional hazards (PH) NMA were based on 200,000 iterations on three chains, with a burn-in of 50,000 iterations. Convergence was assessed by visual inspection of trace plots. The accuracy of the posterior estimates was assessed using the Monte Carlo error for each parameter (Monte Carlo error <1% of the posterior standard deviation, or Monte Carlo error divided by posterior standard deviation should be less than 0.05). The results of the NMA were presented in terms of 'point estimates' (median of posterior) for the comparative treatment effects, along with the 95% credible intervals (95% CI).

C.1.2 NMA feasibility assessment results

C.1.2.1 Studies contributing to the evidence network

The base case NMA includes six studies identified via an SLR (see 5.1 and Appendix H). A seventh study (TheraP) was included in a sensitivity analysis of the NMA.

C.1.2.2 Comparison of study and patient characteristics

As per the best practice in evidence synthesis and NMA, studies included in the evidence network were assessed for differences in study and patient characteristics. The comparability of studies and patients across studies is presented in section 6.1.3. Additionally, the definition of outcomes and the similarity of outcome definitions across studies is presented in section 3.7.1 and section 7.1.1.

C.1.2.3 Proportional hazards assumption testing

The most reported measure of the effectiveness of new treatment as compared to SoC in randomised controlled trials (RCTs) with time-to-event outcome is HR. The estimate of drug effect using the HR requires that the PH assumption is valid over the duration of the study. Where this assumption is violated, the HR effect may not provide an adequate estimate of drug effect because the result is dependent on follow-up time (e.g. with longer or shorter follow-up, the HR will change).

For any endpoint to follow the PH assumption, the ratio of cumulative hazards for OS/rPFS must be approximately constant and hence proportional over time. The crossing of hazard curves or the increasing or decreasing separation of curves over time is evidence that this assumption has been violated. We tested the PH assumption by regenerating individual patient data from published KM curves as per Guyot et al. (64). Additionally, statistical testing was performed using Harrell and Grambsch and Therneau's tests (65).

The details related to the PH assumption tests for OS and rPFS Kaplan-Meier curves are provided in Table 82. Additionally, Schoenfeld residual plots and log-log plots are presented in Figure 24 and Figure 25.

As per the global test, the output is non-significant for all the studies except one (COU-AA-301) reporting OS; the data uphold the PH assumption, with no contradictory evidence found. Similarly, for studies reporting rPFS, the output is non-significant for three studies, showing a lack of evidence to contradict the proportionality assumption, and significant for two studies showing a violation of the proportionality assumption. In conclusion, since PH assumption was valid for most of the studies, conventional/PH NMA was performed.

Table 82 Proportional hazards assumption testing for studies reporting OS and rPFS curves

Trial name	Outcome	Global test (Chi-sq., p values)	PH assumption true (yes/no) by log-log plot
VISION	OS	2.21, p=0.1367	Yes
TROPIC	OS	0.87, p=0.3500	Yes
CARD	OS	0.05, p=0.8164	Yes
AFFIRM	OS	0.83, p=0.3612	Yes

Trial name	Outcome	Global test (Chi-sq., p values)	PH assumption true (yes/no) by log-log plot
COU-AA-301	OS	8.03, p=0.0046	No
Sun et.al, 2016	OS	1.13, p=0.2884	Yes
VISION	rPFS	9.49, p=0.0021	No
TROPIC	PFS*	9.49, p=0.0021	No
CARD	rPFS	3.20, p=0.0735	Yes
AFFIRM	rPFS	3.27, p=0.0706	Yes
COU-AA-301	rPFS	0.05, p=0.8232	Yes

* PFS data from TROPIC was included in the rPFS analysis (as described in section 7.1.1).

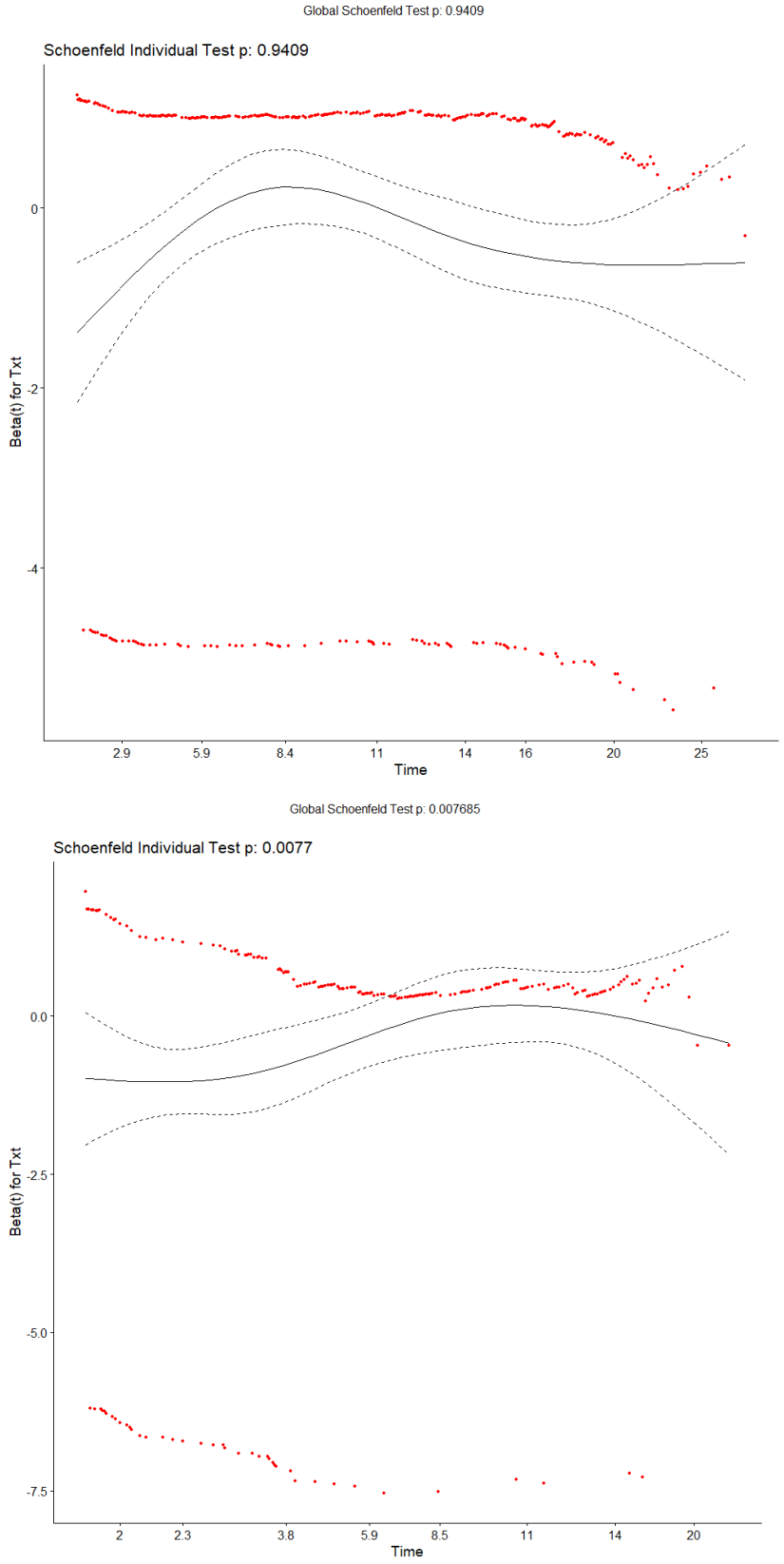


Figure 24 Schoenfeld residuals for OS (top) and rPFS (bottom)

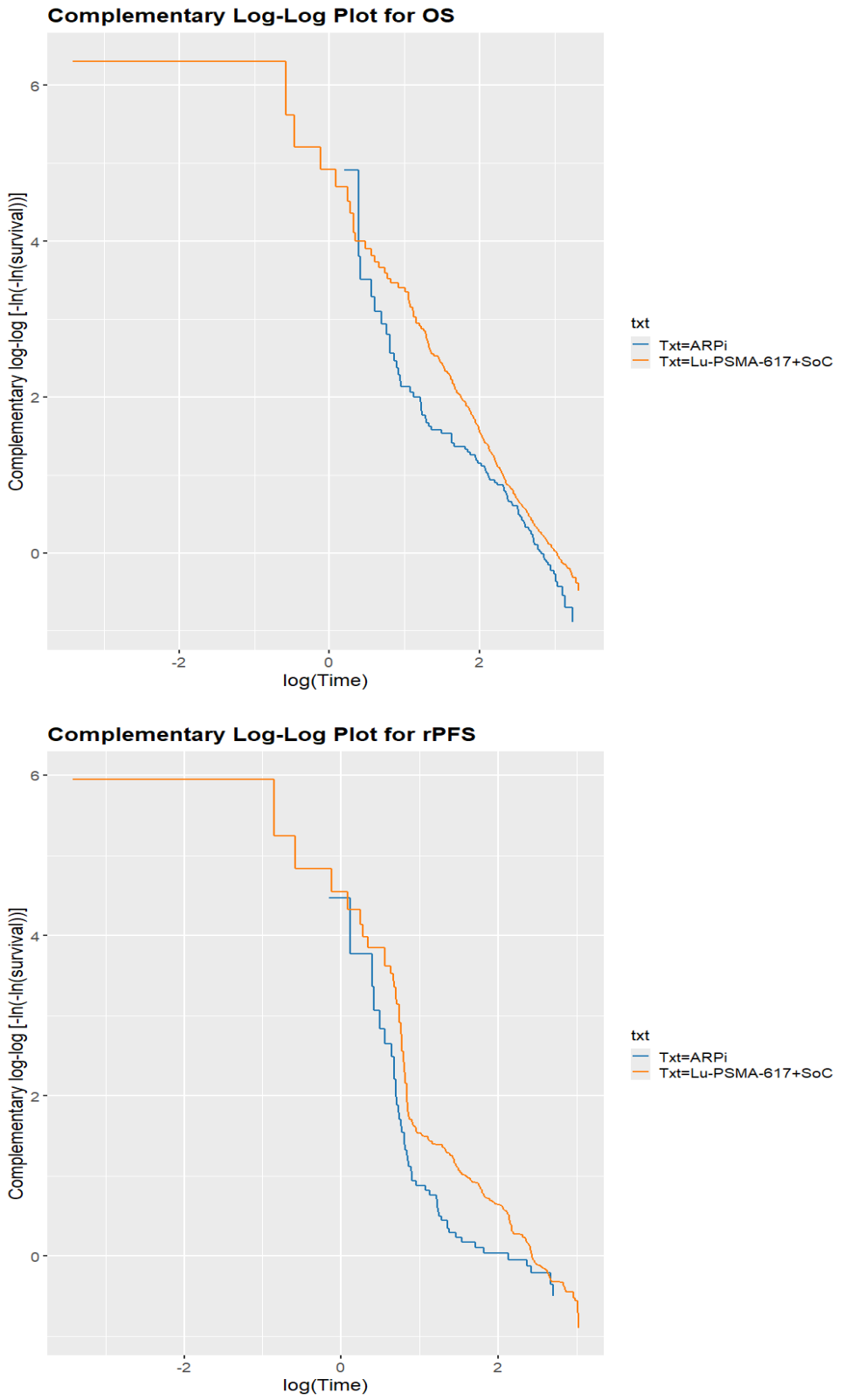


Figure 25 Log-log plots for OS (top) and rPFS (bottom)

C.1.2.4 Heterogeneity assessment between reference arms

As a part of heterogeneity assessment, statistical heterogeneity has been tested for each outcome using I^2 statistics (a standard assessment of heterogeneity) between the reference arms across trials. I^2 is a transformation that describes the proportion of total variation in study estimates that is due to heterogeneity (66). It is interpreted as (67):

- I^2 = 25%: low heterogeneity
- I^2 = 50%: moderate heterogeneity
- I^2 = 75%: substantial heterogeneity

The selected reference should either be a placebo or the most common comparator therapy. Among the included studies, mitoxantrone/placebo was identified as the most common comparator and subsequently chosen as the reference treatment for this analysis.

Table 83 Statistical heterogeneity assessment results

Outcome	Main analysis			Sensitivity analysis (including TheraP		
	N*	I² [95% CI]	Statistical heterogeneity	N*	I² [95% CI]	Statistical heterogeneity
OS	6	64.7% [0.0%-88.0%]	Moderate	7	66.7% [13.4%-87.2%]	Moderate
rPFS	5	96.2% [92%-98.2%]	Substantial	6	94.4% [88.9%-97.2%]	Substantial

* Number of studies

C.1.2.5 Inconsistency assessment in NMA

Inconsistency in NMA arises when direct and indirect evidence for a particular comparison conflict, often due to variations in study characteristics or effect modifiers across comparisons. To evaluate the coherence of evidence in the NMA, inconsistency checks were conducted using fixed effects (FE) models.

The node-splitting method, a robust approach that systematically compares direct and indirect evidence for each treatment comparison within the network, was employed (68). Typically, a p-value greater than 0.05 for all comparisons would suggest no significant inconsistency, indicating alignment between direct and indirect evidence. The presence or absence of inconsistency can impact the reliability of NMA results and the validity of derived treatment effect estimates.

Figure 26 and Figure 27 illustrate the inconsistency plot for OS and rPFS, respectively (base case). In both figures, p-values for all the indirect estimates are significant ($p<0.05$), indicating inconsistency in the Bayesian NMA. Further inconsistency analyses for the sensitivity analysis (including TheraP) are depicted in Figure 28 (OS) and Figure 29 (rPFS).

For OS, p-values for indirect estimate are significant (p<0.05), indicating inconsistency in the Bayesian NMA. Results based on VISION and TheraP show borderline NMA consistency. For rPFS, p-values for indirect estimate are significant (p<0.05), indicating inconsistency in the Bayesian NMA except for Pluvicto® + SoC vs ARPI and Pluvicto® SoC vs CABA pairs.

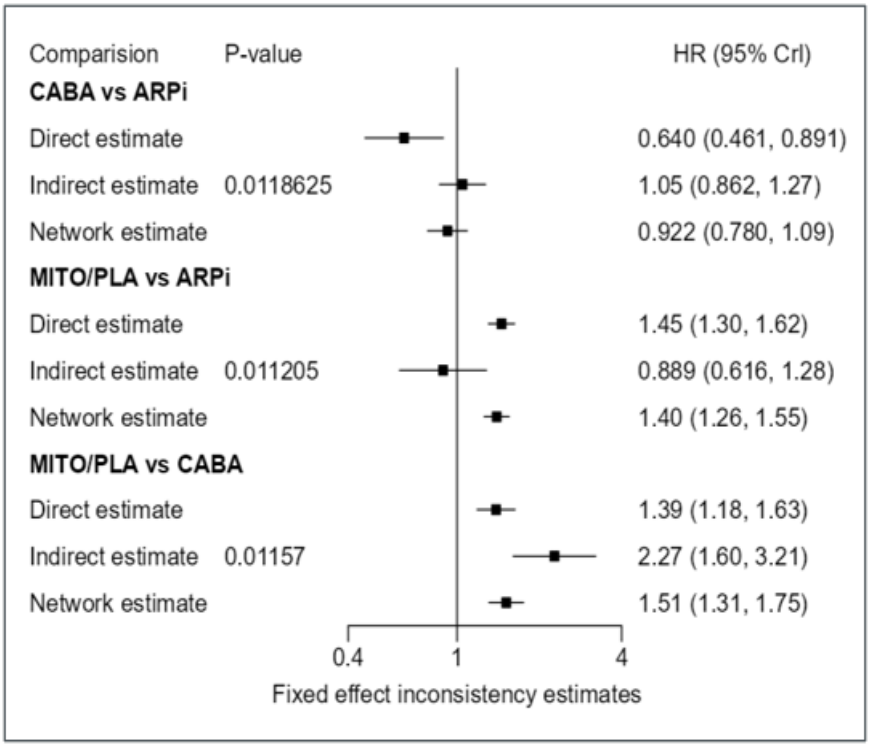


Figure 26 Inconsistency check for OS FE model (base case)

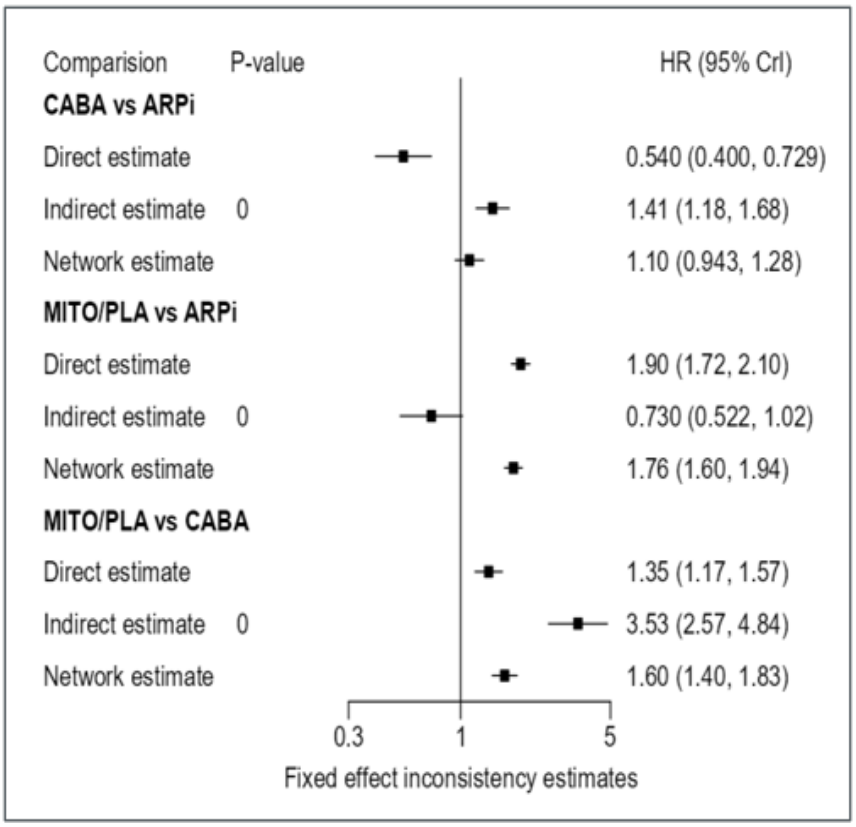


Figure 27 Inconsistency check for rPFS FE model (base case)

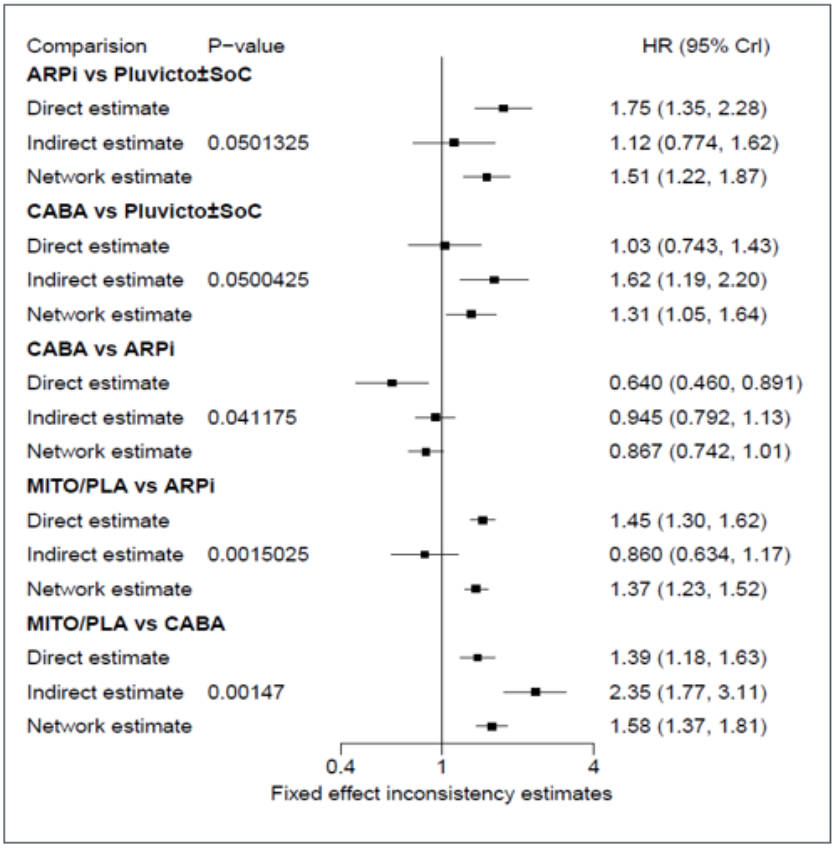


Figure 28 Inconsistency check for OS FE model (sensitivity analysis)

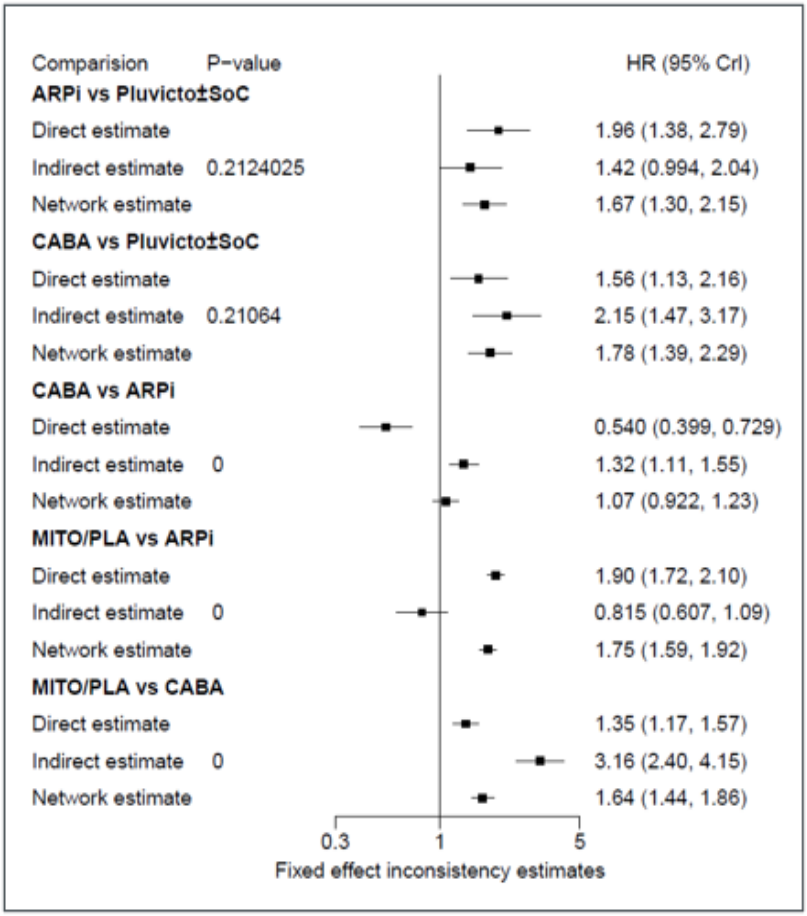


Figure 29 Inconsistency check for rPFS FE model (sensitivity analysis)

C.1.2.6 Summary of feasibility assessment

This application presents two distinct analyses:

1. Base case: Bayesian PH NMA for OS and rPFS
2. Sensitivity Analysis: Bayesian PH NMA including TheraP trial

Both for OS and rPFS, an NMA was deemed viable due to the availability of a connected network. The base case for OS included six trials, and the sensitivity analysis included seven. For rPFS, the base case included five trials, and the sensitivity analysis included six. Due to a limited number of studies (<10), a meta-regression accounting for the differences in baseline characteristics such as median PSA (ng/ml) at baseline and median baseline LDH (IU/ml) levels could not be performed.

The scarcity of data is a critical consideration in our methodological approach. Random-effects models rely heavily on vague prior distributions for between-study heterogeneity parameters. Accurate estimation of these parameters demands a substantial number of trials per comparison - optimally 4-5, with a minimum of 3 (Gelman et al.) (69). Our dataset falls short of this threshold. With insufficient data, the posterior distribution of the between-study standard deviation (σ) in a random-effects model can be poorly

defined. This imprecision can lead to the inclusion of implausibly high or low values, potentially skewing the results and compromising the integrity of our conclusions. Among the included studies, despite some variations in prior treatments across the included studies, clinical heterogeneity was observed to be low. This homogeneity further supports the appropriateness of a fixed-effect model. The fixed-effect model hence offers a more reliable and interpretable result given our data constraints.

C.1.3 NMA results (base case)

Table 84 presents results of the comparative analysis of Pluvicto® versus cabazitaxel. Table 85 and Table 86 present the remaining results for the NMA.

Table 84 Comparative analysis of studies comparing Pluvicto® to cabazitaxel for PSMA-positive mCRPC patients (Post 1 taxane population)

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Overall survival	ViSION, CARD, TROPIC, Sun et al., AFFIRM, COU-AA-301	N/A	N/A	N/A	HR: [redacted]	[redacted]	N/A	The HRs for the studies included were synthesized using fixed effects Bayesian NMA.	Yes
Radiographic progression free survival	ViSION, CARD, TROPIC, AFFIRM, COU-AA-301	N/A	N/A	N/A	HR: [redacted]	[redacted]	N/A	The HRs for the studies included were synthesized using fixed effects Bayesian NMA.	Yes

Table 85 All OS results of the conducted NMA (base case)

	Pluvicto® + SoC	Cabazitaxel	ARPI	Mitoxantrone /Placebo
Pluvicto® + SoC	-	1.62 (1.19 – 2.21)*	1.75 (1.35 – 2.27)*	2.45 (1.85 – 3.24)*
Cabazitaxel	[redacted]*	-	1.08 (0.92 – 1.28)	1.51 (1.31 – 1.75)*
ARPI	0.57 (0.44 – 0.74)*	0.92 (0.78 – 1.09)	-	1.40 (1.26 – 1.55)*
Mitoxantrone /Placebo	0.41 (0.31 – 0.54)*	0.66 (0.57 – 0.76)*	0.72 (0.64 – 0.80)*	-

* Statistical significance. Note: Moving from top to bottom in the 1st column with HR<1 and moving from left to right in the 1st row with HR>1 suggests Pluvicto® + SoC is significantly better than other treatments.

Table 86 All rPFS results of the conducted NMA (base case)

	Pluvicto® + SoC	ARPI	Cabazitaxel	Mitoxantrone /Placebo
Pluvicto® + SoC	-	1.96 (1.38 – 2.79)*	2.15 (1.46 – 3.17)*	3.45 (2.39 – 4.99)*
ARPI	0.51 (0.36 – 0.73)*	-	1.10 (0.94 – 1,28)	1.76 (1.60 – 1.94)*
Cabazitaxel	[redacted]*	0.91 (0.78 – 1.06)	-	1.60 (1.40 – 1.83)*
Mitoxantrone /Placebo	0.29 (0.20 – 0.42)*	0.57 (0.52 – 0.61)*	0.62 (0.55 – 0.71)*	-

* Statistical significance. Note: Moving from top to bottom in the 1st column with HR<1 and moving from left to right in the 1st row with HR>1 suggests Pluvicto® + SoC is significantly better than other treatments.

C.1.3.1 Overall survival

A network of interlinked studies for OS outcomes is presented in Figure 7. Based on the NMA, Pluvicto® showed a statistically significant effect on OS compared with cabazitaxel (HR: [redacted], 95% CI [redacted]).

C.1.3.2 Radiographic progression-free survival

A network of interlinked studies for rPFS outcomes is presented in

Figure 8. Based on the NMA, Pluvicto® showed a statistically significant effect on rPFS compared with cabazitaxel (HR: [redacted], 95% CI [redacted]).

C.1.4 NMA results (sensitivity analysis)

Table 87 presents results of the comparative analysis of Pluvicto® versus cabazitaxel. Table 88 and Table 89 present the remaining results for the NMA sensitivity analysis.

Table 87 Comparative analysis (sensitivity analysis) of studies comparing Pluvicto® to cabazitaxel for PSMA-positive mCRPC patients (Post 1 taxane population)

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Overall survival	ViSION, CARD, TROPIC, Sun et al., AFFIRM, COU-AA-301, TeraP	N/A	N/A	N/A	HR: [redacted]	[redacted]	N/A	The HRs for the studies included were synthesized using fixed effects Bayesian NMA.	Yes, in sensitivity analysis
Radiographic progression free survival	ViSION, CARD, TROPIC, AFFIRM, COU-AA-301, TheraP	N/A	N/A	N/A	HR: [redacted]	[redacted]	N/A	The HRs for the studies included were synthesized using fixed effects Bayesian NMA.	Yes, in sensitivity analysis

Table 88 All OS results of the conducted NMA (sensitivity analysis)

	Pluvicto® + SoC	Cabazitaxel	ARPI	Mitoxantrone /Placebo
Pluvicto® + SoC	-	1.31 (1.04 – 1.64)*	1.51 (1.22 – 1.87)*	2.07 (1.65 – 2.58)*
Cabazitaxel	[redacted]*	-	1.15 (0.99 – 1.35)	1.58 (1.37 – 1.81)*

	Pluvicto® + SoC	Cabazitaxel	ARPI	Mitoxantrone /Placebo
ARPI	0.66 (0.54 – 0.82)*	0.87 (0.74 – 1.01)	-	1.37 (1.23 – 1.52)*
Mitoxantrone /Placebo	0.48 (0.39 – 0.60)*	0.63 (0.55 – 0.73)*	0.73 (0.66 - 0.81)*	-

* Statistical significance. Note: Moving from top to bottom in the 1st column with HR<1 and moving from left to right in the 1st row with HR>1 suggests Pluvicto® + SoC is significantly better than other treatments.

Table 89 All rPFS results of the conducted NMA (sensitivity analysis)

	Pluvicto® + SoC	ARPI	Cabazitaxel	Mitoxantrone /Placebo
Pluvicto® + SoC	-	1.67 (1.30 – 2.15)*	1.79 (1.39 – 2.29)*	2.92 (2.26 – 3.77)*
ARPI	0.60 (0.46 – 0.77)*	-	1.07 (0.92 – 1.23)	1.75 (1.59 – 1.92)*
Cabazitaxel	[redacted]*	0.94 (0.81 – 1.09)	-	1.64 (1.44 – 1.86)*
Mitoxantrone /Placebo	0.34 (0.27 – 0.44)*	0.57 (0.52 – 0.63)*	0.61 (0.54 – 0.70)*	-

* Statistical significance. Note: Moving from top to bottom in the 1st column with HR<1 and moving from left to right in the 1st row with HR>1 suggests Pluvicto® + SoC is significantly better than other treatments.

C.1.4.1 Overall survival

A network of interlinked studies for OS outcomes is presented in Figure 30. Based on the NMA, Pluvicto® showed a statistically significant effect on OS compared with cabazitaxel (HR: [redacted], 95% CI [redacted]). In other words, relative to cabazitaxel, Pluvicto® decreases the risk of death by 24%.

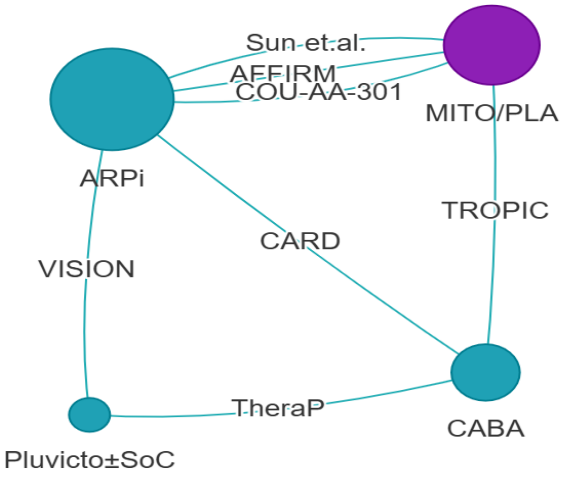


Figure 30 Network of evidence for OS (n=7 RCTs)

C.1.4.2 Radiographic progression-free survival

A network of interlinked studies for rPFS outcomes is presented in Figure 31. Based on the NMA, Pluvicto® showed a statistically significant effect on rPFS compared with cabazitaxel (HR: [redacted], 95% CI [redacted]). In other words, relative to cabazitaxel, Pluvicto® decreased the risk of disease progression by 44%.

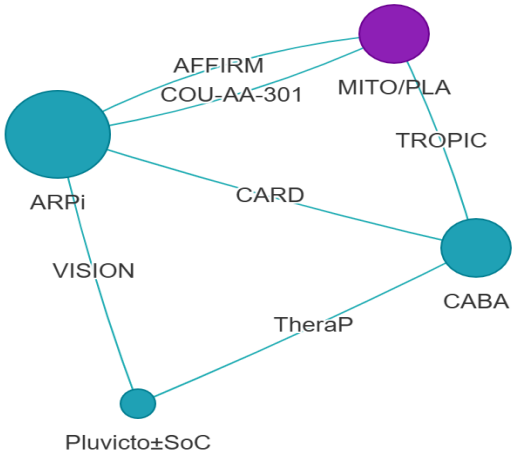


Figure 31 Network of evidence for rPFS (n=6 RCTs)

C.1.5 Summary

The objective of this NMA was to assess the comparative efficacy of 177Lu-PSMA-617 versus cabazitaxel in patients with mCRPC previously treated with at least one ARPI and one or two taxane regimens. A Bayesian NMA was performed.

To facilitate the connection in the NMA network, the ARPI component of BSC/SoC was extracted from VISION patient-level data. Two sets of analyses were performed, including a base case NMA and a sensitivity analysis NMA. Six studies were included in the base case NMA for OS, and five studies were included in the base case NMA for rPFS. In the sensitivity analysis, one additional study (TheraP) was included in both the OS and the rPFS analysis.

The decision of excluding TheraP from the base case analysis was based on several factors that limit the generalizability and interpretation of the TheraP findings. Strict eligibility criteria, particularly high PSMA levels, restrict applicability to the broader mCRPC population. Crossover from cabazitaxel to 177Lu-PSMA-617 potentially confounded OS results. Additionally, differences in 177Lu-PSMA-617 formulation, dosing regimens, and combination therapies between TheraP and VISION trials, as well as TheraP's protocol of suspending treatment for exceptional responders, further complicate comparisons. These limitations led to TheraP's exclusion from the main analysis and are only a part of the sensitivity analysis.

In conclusion, the NMA demonstrated statistically significant superiority of Pluvicto® + SoC over cabazitaxel in both base case and sensitivity analyses for OS and rPFS. In general, it should be emphasised that the analysis is limited by the small number of studies, and the results should therefore be interpreted with this in mind. However, the effects are of a significant magnitude, i.e. mortality and progression are reduced by 38% and 54%, respectively.

C.2 Post 2 taxanes population

Pluvicto® was directly compared to BSC/SoC in the VISION head-to-head study. Results of the comparison are presented in Table 17.

Table 90 Comparative analysis of studies comparing Pluvicto® to BSC/SoC for PSMA-positive mCRPC patients (Post 2 taxanes population)

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix D. Extrapolation

D.1 Extrapolation of rPFS (Post 1 taxane population)

D.1.1 Data input

Extrapolation of rPFS for the Post 1 taxane population was based on the VISION population that had received a maximum of one prior taxane.

D.1.2 Model

Parametric survival model

D.1.3 Proportional hazards

Not applicable, as the Pluvicto® is compared to cabazitaxel through an NMA.

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

Table 91 presents the AIC and the BIC for rPFS in the Post 1 taxane population. The flexible Weibull (2 knots) function had the best statistical fit based on AIC and BIC.

Table 91 Statistical fit of parametric models for rPFS, Post 1 taxane population (data on file)

Model	AIC	BIC
Exponential	1,566.8	1,574.3
Weibull	1,530.8	1,542.0
Stratified Weibull	1,532.7	1,547.6
Gompertz	1,555.0	1,566.2
Stratified Gompertz	1,556.1	1,571.0
Log-normal	1,504.0	1,515.2
Stratified log-normal	1,503.3	1,518.2
Log-logistic	1,510.2	1,521.4
Stratified log-logistic	1,508.1	1,523.0
Gamma	1,519.1	1,530.3
Stratified gamma	1,520.7	1,535.6
Generalised gamma	1,506.0	1,520.9
Stratified generalised gamma	1,506.7	1,529.1
Flexible Weibull (1 knot)	1,505.3	1,520.2
Flexible Weibull (2 knots)	1,485.6	1,504.3
Flexible Weibull (3 knots)	1,486.0	1,508.4
Stratified flexible Weibull (1 knot)	1,501.8	1,524.2
Stratified flexible Weibull (2 knots)	1,487.0	1,516.9
Stratified flexible Weibull (3 knots)	1,487.4	1,524.7

D.1.5 Evaluation of visual fit

The rPFS extrapolations for Pluvicto® are presented in Figure 32. The rPFS curves for cabazitaxel are presented in Figure 33. There is no KM for cabazitaxel, as the extrapolations are based on an NMA.

Generally, all extrapolations are meaningful as they converge toward zero. Based on the visual fit to the KM curve, the Gamma, Stratified gamma, Stratified flexible Weibull (2 knots), and Stratified flexible Weibull (3 knots) functions seem to be most appealing because they are closer to the KM curve toward the end of follow-up.

Due to lack of a KM curve for cabazitaxel, an evaluation of visual fit of curves cannot be done.

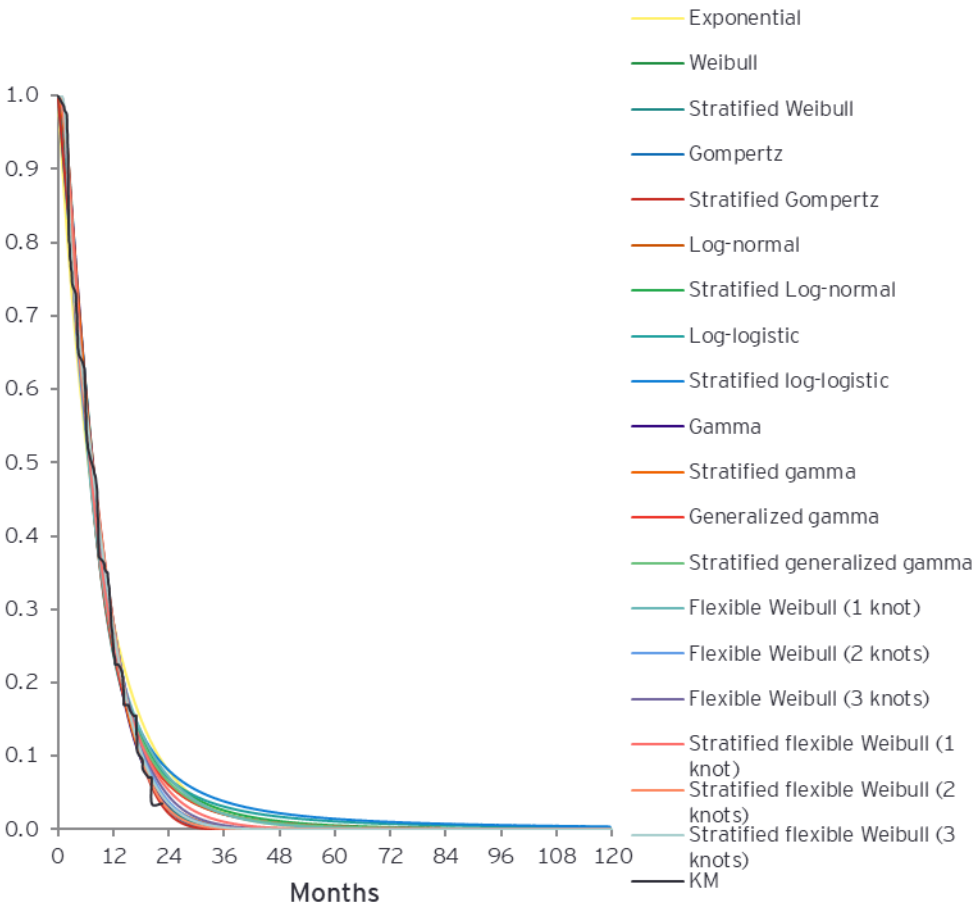


Figure 32 rPFS survival functions for Pluvicto®, Post 1 taxane population (data on file)

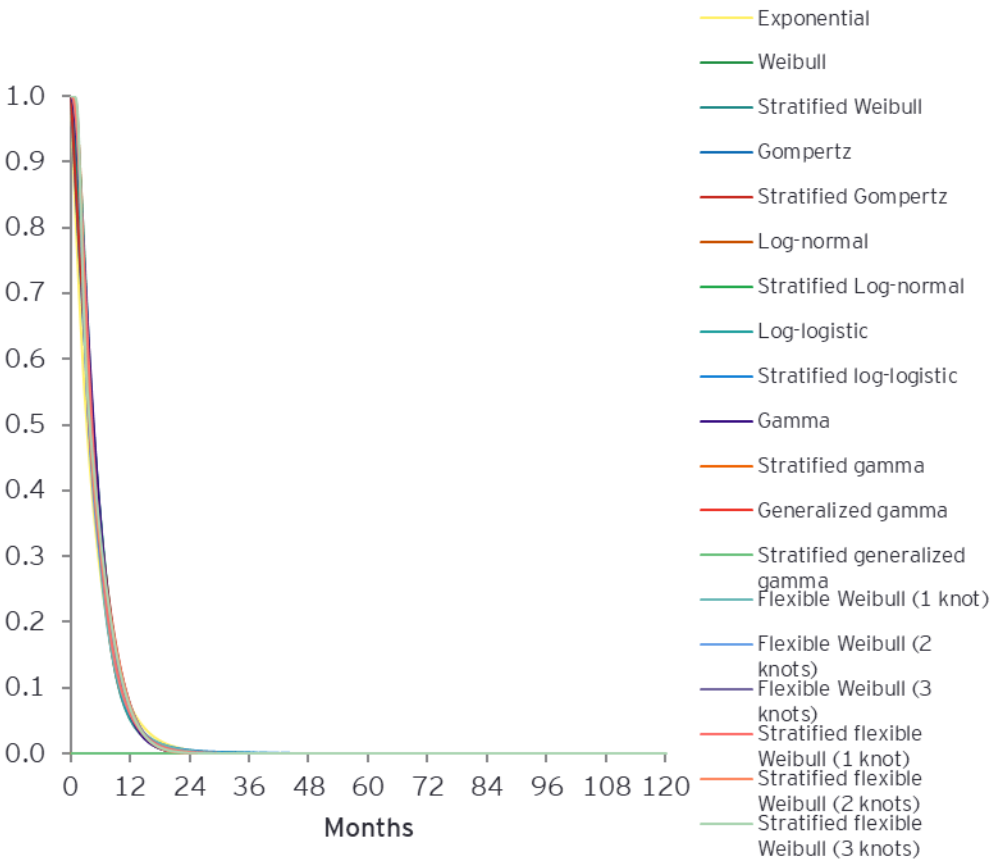


Figure 33 rPFS survival functions for cabazitaxel, Post 1 taxane population (data on file)

D.1.6 Evaluation of hazard functions

Figure 34 presents the rPFS hazard function for Pluvicto® (Post 1 taxane population) for the observed data. Figure 35 presents the rPFS hazard function for Pluvicto® (Post 1 taxane population) for the extrapolations.

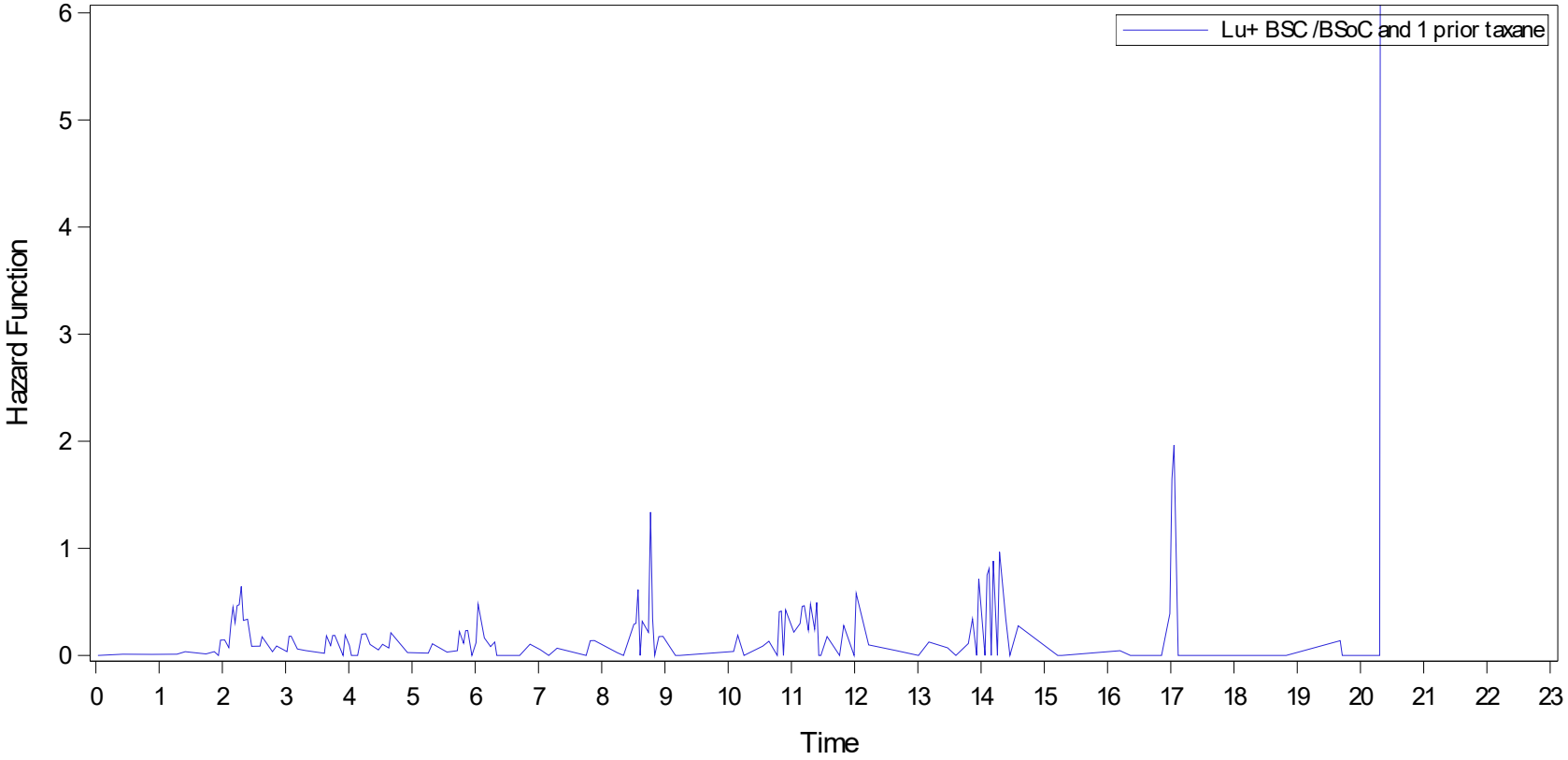
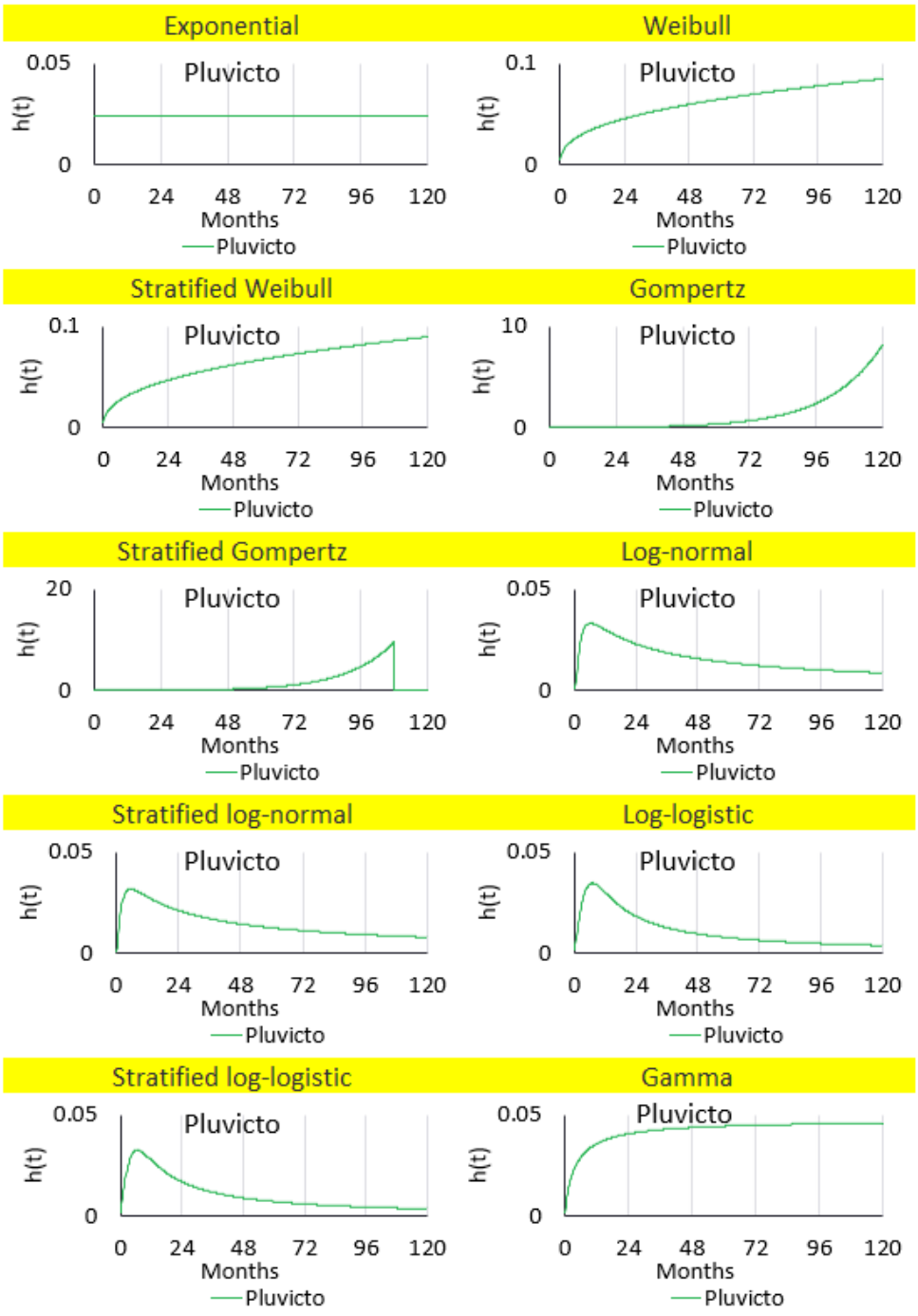


Figure 34 Pluvicto® rPFS hazard function based on Kaplan-Meier estimate, Post 1 taxane population



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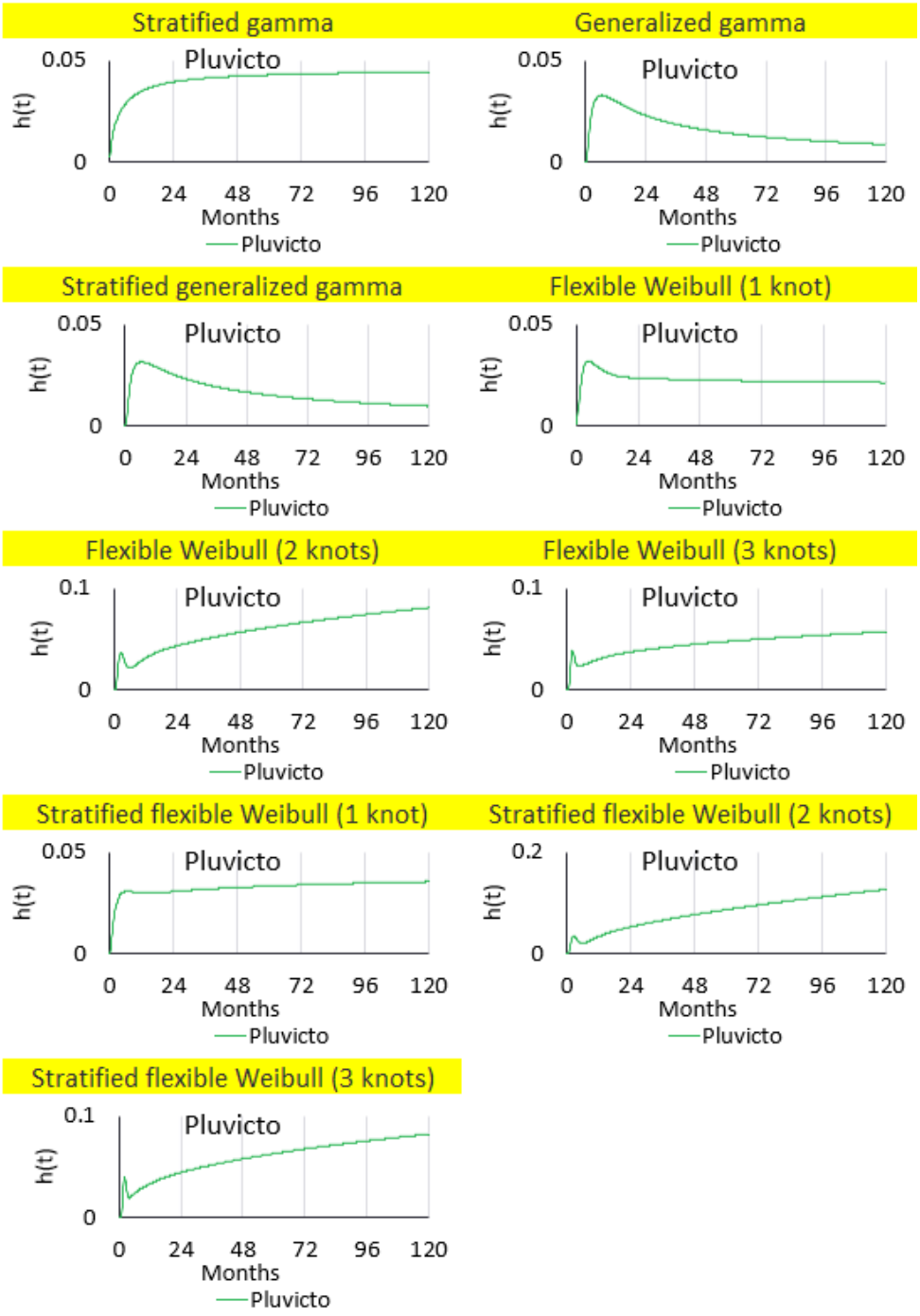


Figure 35 Pluvicto® rPFS hazard function for extrapolations, Post 1 taxane population (data on file)

D.1.7 Validation and discussion of extrapolated curves

The flexible Weibull (2 knots) had the best statistical fit based on AIC and BIC. This curve also converged toward zero, thus appearing to be plausible in nature. The clinical expert interviewed in connection with the application assessed that the curve for the flexible

Weibull (2 knots) function was clinically relevant and meaningful, and that it reflected the expectation for rPFS in Denmark. For these reasons, the flexible Weibull (2 knots) function was used to estimate rPFS in the Post 1 taxane population.

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of rPFS (Post 2 taxanes population)

D.2.1 Data input

Extrapolation of rPFS for the Post 2 taxanes population was based on the VISION population that had received a minimum of two prior taxanes.

D.2.2 Model

Parametric survival model.

D.2.3 Proportional hazards

Figure 36 shows the trend in the Schoenfeld residuals over time, which is not significant (chi-square = 0.76; degrees of freedom = 1; p = 0.38).

Figure 37 shows the log-(Log) survival, indicating that the lines are reasonably parallel and do not intersect. Based on the figures and the significance test, uncertainty exists regarding the proportional hazard assumption. Fitting different parametric models of the same type to each of the treatment arms separately (i.e. stratified) is expected to provide the best fit (70). Due to the uncertain proportional hazard, both stratified and non-stratified models are applied. In addition to standard parametric models, flexible spline parametric models were applied to the KM data.

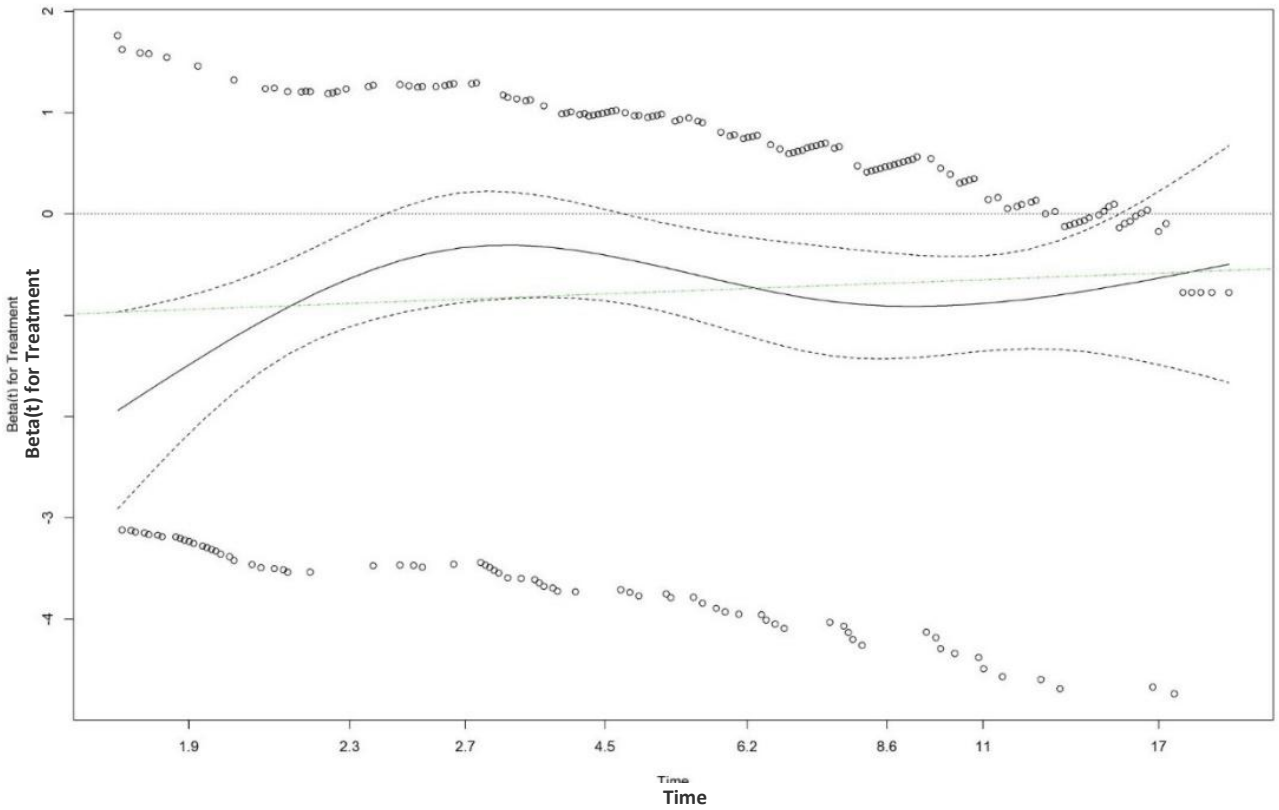


Figure 36 Schoenfeld residuals for rPFS from VISION trial data, Post 2 taxanes population (data on file)

Figure 37 Log-(log) survival plot for rPFS from VISION trial data, Post 2 taxanes population (data on file)

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

Table 92 presents the AIC and the BIC for rPFS in the Post 2 taxanes population. The stratified flexible Weibull (3 knots) had the best fit based on AIC, and the gamma function had the best statistical fit based on BIC.

Table 92 Statistical fit of parametric models for rPFS, Post 2 taxanes population (data on file)

Model	AIC	BIC
Exponential	1,419.0	1,426.2
Weibull	1,387.6	1,398.4
Stratified Weibull	1,389.3	1,403.8
Gompertz	1,404.2	1,415.0
Stratified Gompertz	1,405.9	1,420.3
Log-normal	1,394.4	1,405.3
Stratified log-normal	1,390.6	1,405.0
Log-logistic	1,386.0	1,396.8
Stratified log-logistic	1,385.4	1,399.8
Gamma	1,382.4	1,393.2
Stratified gamma	1,383.2	1,397.6
Generalised gamma	1,382.3	1,396.8
Stratified generalised gamma	1,380.7	1,402.3
Flexible Weibull (1 knot)	1,380.5	1,394.9
Flexible Weibull (2 knots)	1,377.1	1,395.2
Flexible Weibull (3 knots)	1,378.8	1,400.4
Stratified flexible Weibull (1 knot)	1,382.5	1,404.1
Stratified flexible Weibull (2 knots)	1,378.0	1,406.9
Stratified flexible Weibull (3 knots)	1,375.1	1,411.2

D.2.5 Evaluation of visual fit

The rPFS extrapolations for Pluvicto® are presented in Figure 38. The rPFS curves for BSC/SoC are presented in Figure 39.

Generally, all extrapolations are meaningful as they converge toward zero for both Pluvicto® and BSC/SoC. Based on the visual fit to the KM curve, the Gamma, Stratified gamma, Generalised gamma, Flexible Weibull (2 knots), Flexible Weibull (3 knots), Stratified flexible Weibull (2 knots), and Stratified flexible Weibull (3 knots) functions seem to be most appealing because they are closer to the KM curve in both the beginning and end of follow-up.

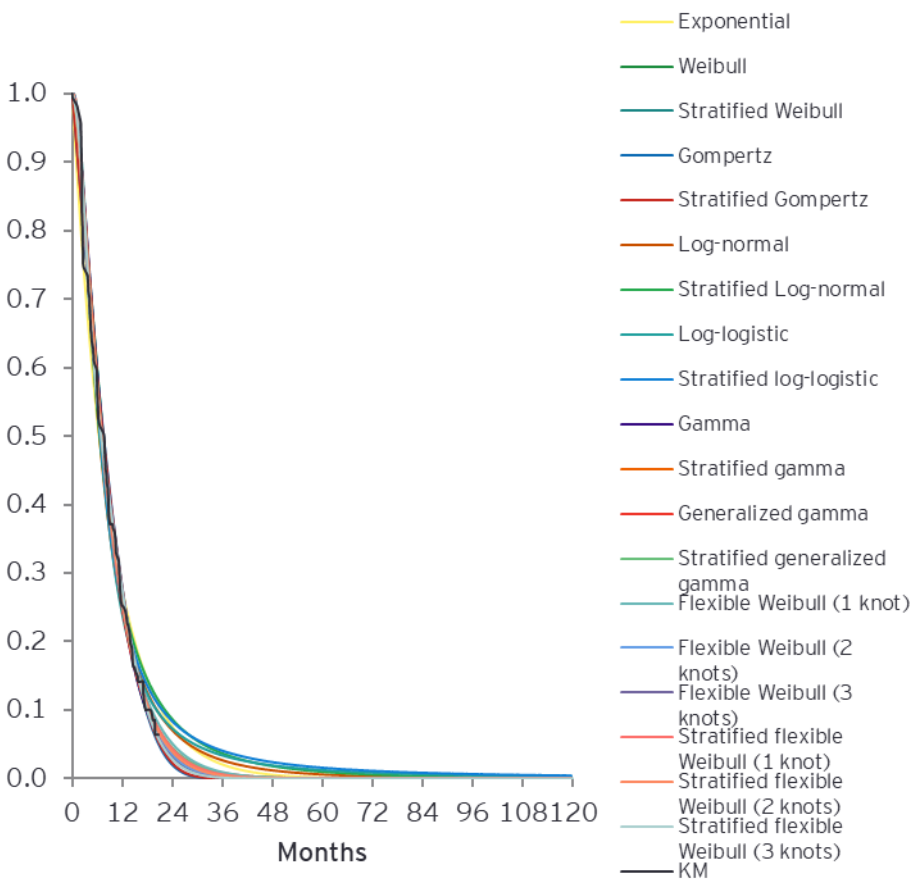


Figure 38 rPFS survival functions for Pluvicto®, Post 2 taxanes population (data on file)

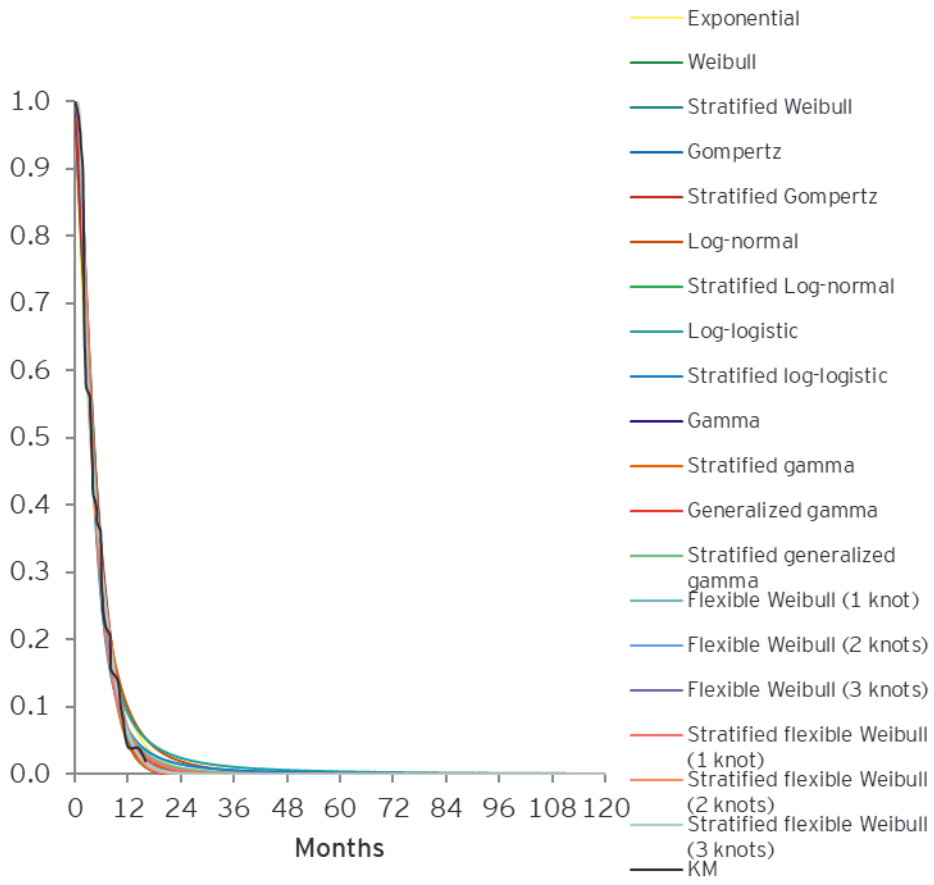


Figure 39 rPFS survival functions for BSC/SoC, Post 2 taxanes population (data on file)

D.2.6 Evaluation of hazard functions

Figure 40 and Figure 41 present the rPFS hazard functions for Pluvicto® and BSC/SoC, respectively, for the observed data. Figure 42 presents the rPFS hazard function for Pluvicto® (Post 2 taxanes population) for the extrapolations.

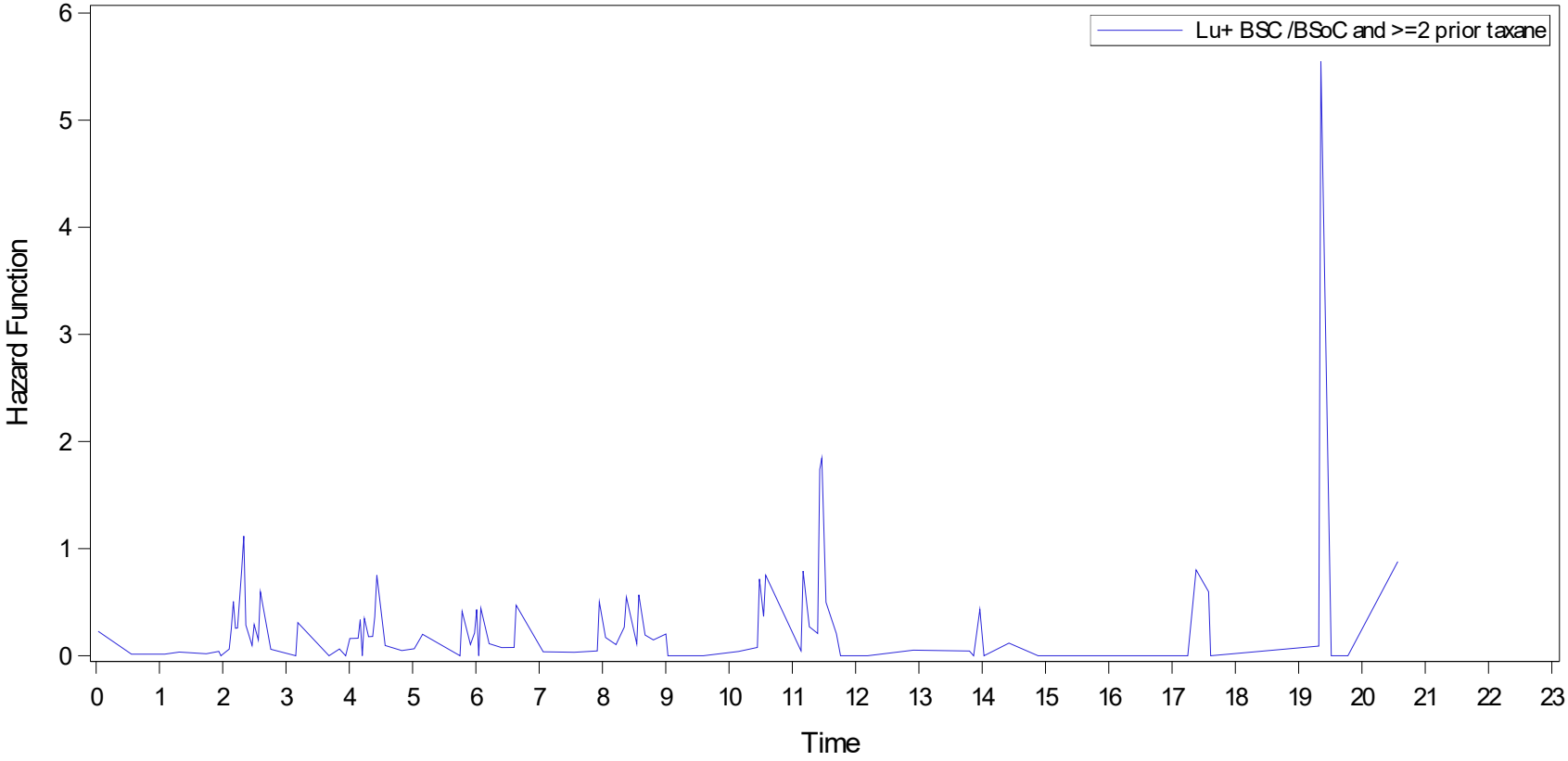


Figure 40 Pluvicto® rPFS hazard function based on Kaplan-Meier estimate, Post 2 taxanes population (data on file)

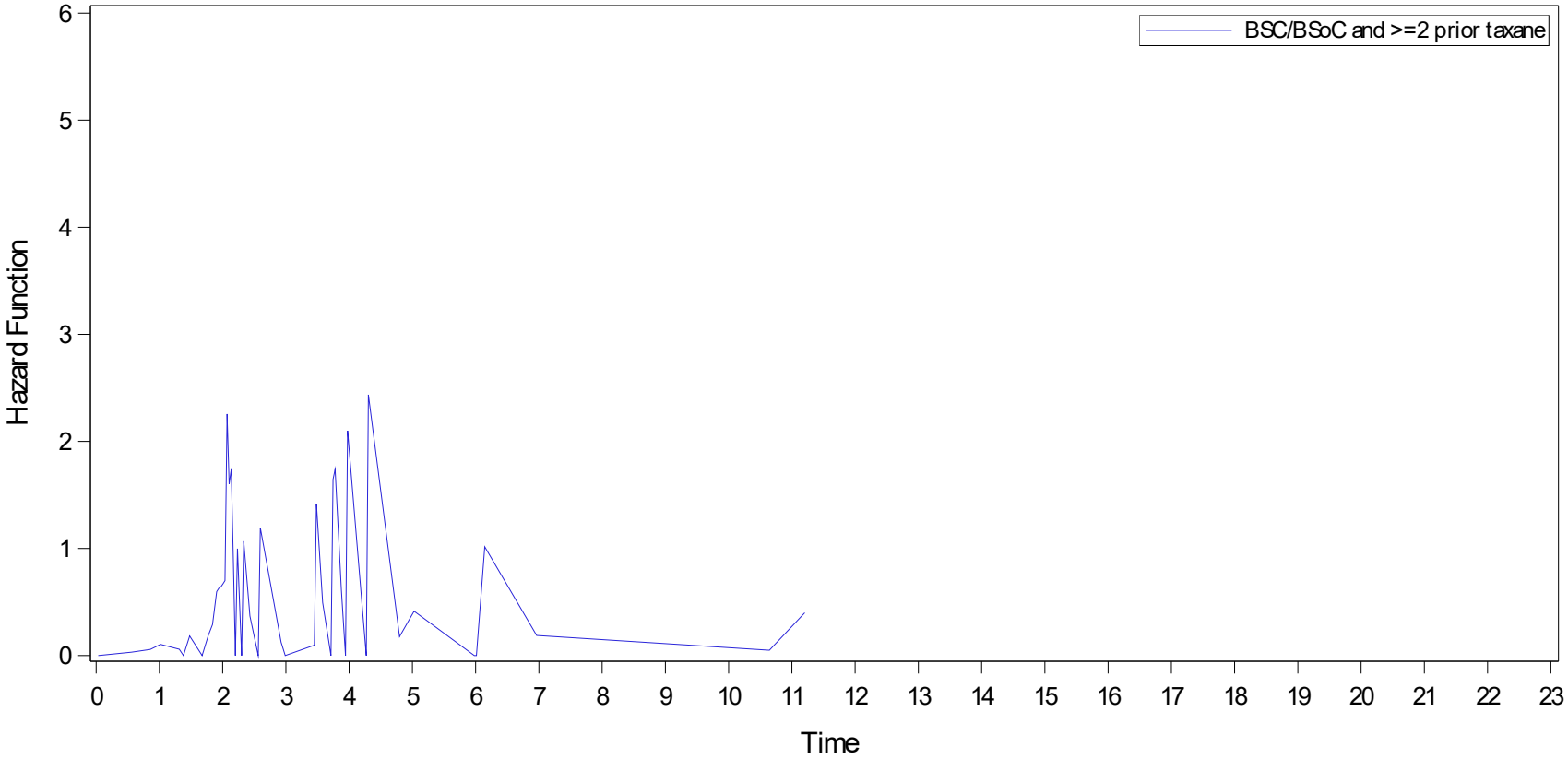
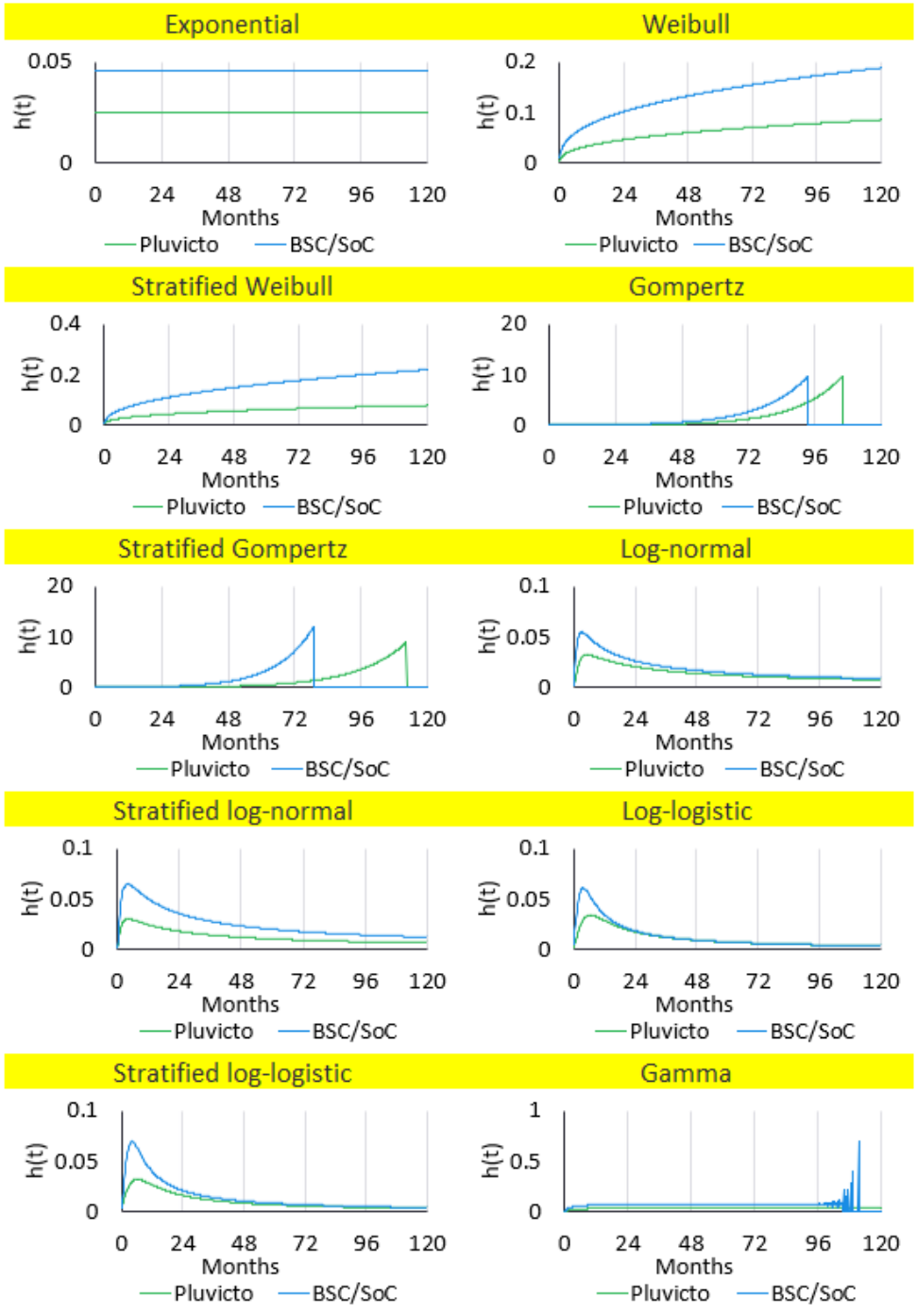


Figure 41 BSC/SoC rPFS hazard function based on Kaplan-Meier estimate, Post 2 taxanes population (data on file)



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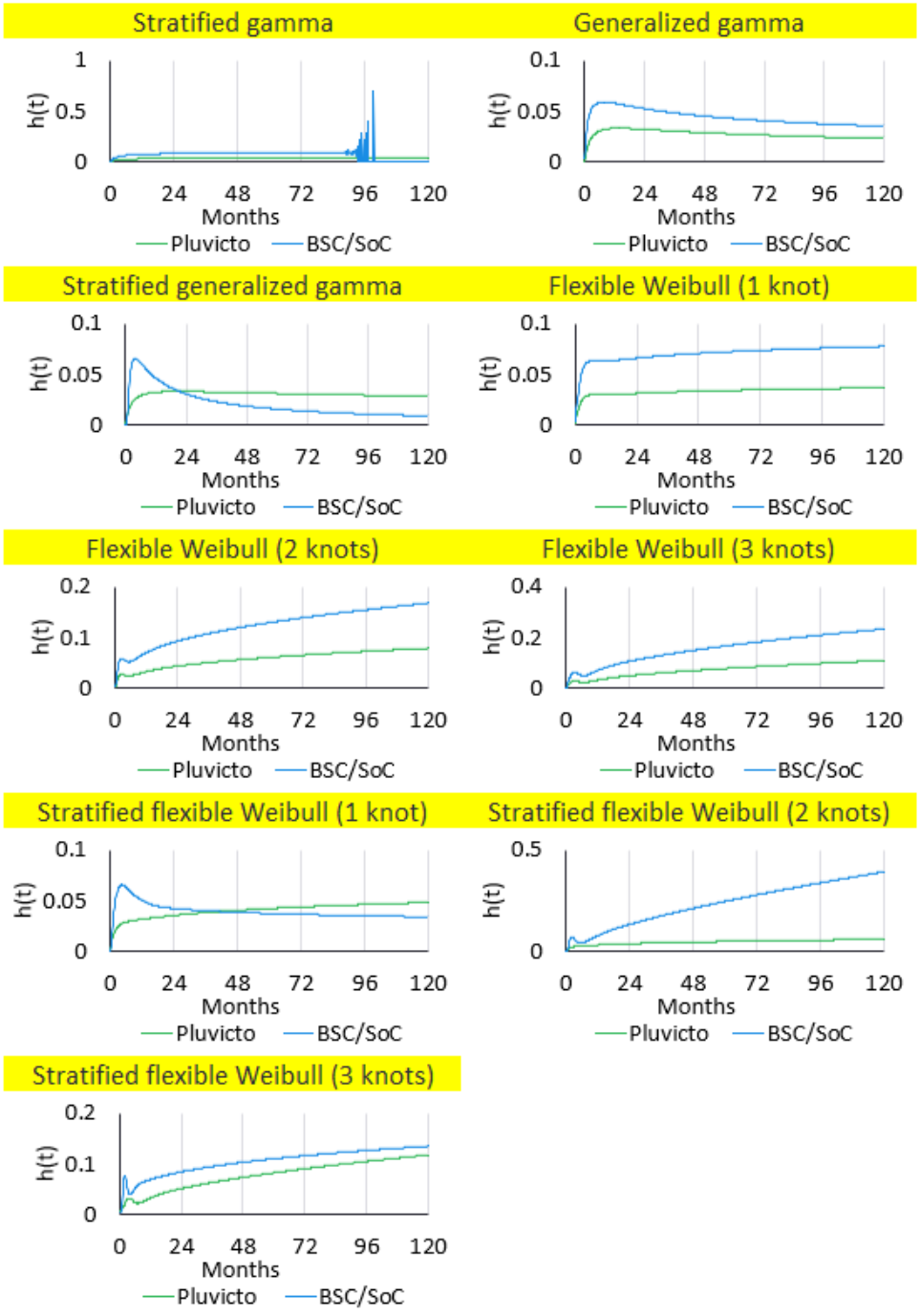

Figure 42 Pluvicto® rPFS hazard functions for extrapolations, Post 2 taxanes population

D.2.7 Validation and discussion of extrapolated curves

The stratified flexible Weibull (3 knots) had the best fit based on AIC, and the gamma function had the best statistical fit based on BIC. Both curves converged toward zero, thus appearing to be plausible in nature. On visual inspection, the stratified flexible Weibull (3 knots) function seems to be more appealing in the first 6 months of extrapolation compared to the gamma function. The clinical expert assessed that the

curve for the stratified flexible Weibull (3 knots) function was clinically relevant and meaningful, and that it reflected the expectation for rPFS in Denmark. For these reasons, the stratified flexible Weibull (3 knots) function was used to estimate rPFS in the Post 2 taxanes population.

D.2.8 Adjustment of background mortality

N/A

D.2.9 Adjustment for treatment switching/cross-over

N/A

D.2.10 Waning effect

N/A

D.2.11 Cure-point

N/A

D.3 Extrapolation of OS (Post 1 taxane population)

D.3.1 Data input

Extrapolation of OS for the Post 1 taxane population was based on the VISION population that had received a maximum of one prior taxane.

D.3.2 Model

Parametric survival model.

D.3.3 Proportional hazards

Not applicable, as Pluvicto® is compared to cabazitaxel through an NMA.

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

Table 93 presents both the AIC and the BIC for OS in the Post 1 taxane population. The Log-logistic function had the best fit based on AIC and BIC.

Table 93 Statistical fit of parametric models for OS, Post 1 taxane population (data on file)

Model	AIC	BIC
Exponential	2,214.2	2,228.0
Weibull	2,180.4	2,201.0
Stratified Weibull	2,180.8	2,208.3
Gompertz	2,195.5	2,216.1

Stratified Gompertz	2,196.8	2,224.4
Log-normal	2,180.8	2,201.5
Stratified log-normal	2,181.6	2,209.2
Log-logistic	2,175.8	2,196.5
Stratified log-logistic	2,176.8	2,204.3
Gamma	2,177.3	2,197.9
Stratified gamma	2,177.8	2,205.3
Generalised gamma	2,177.6	2,205.1
Stratified generalised gamma	2,180.2	2,221.5
Flexible Weibull (1 knot)	2,179.2	2,206.7
Flexible Weibull (2 knots)	2,181.1	2,215.5
Flexible Weibull (3 knots)	2,182.7	2,223.9
Stratified flexible Weibull (1 knot)	2,180.5	2,221.8
Stratified flexible Weibull (2 knots)	2,184.2	2,239.2
Stratified flexible Weibull (3 knots)	N/A	N/A

D.3.5 Evaluation of visual fit

The OS extrapolations for Pluvicto® are presented in Figure 43. The OS curves for cabazitaxel are presented in Figure 44.

Based on the visual fit, the Log-normal, Stratified log-normal, Log-logistic, and stratified log-logistic seem to plateau near the end of the time horizon without approaching zero, thus appearing unrealistic. Based on the visual fit to the KM curve, the Weibull, Stratified Weibull, Gamma, Stratified gamma, Flexible Weibull (1 knot), Flexible Weibull (2 knots), Stratified flexible Weibull (1 knot), and Stratified flexible Weibull (2 knots) functions seem to be most appealing because they are close to the KM curve.

The curves for cabazitaxel were not assessed on visual fit because there is no KM curve.

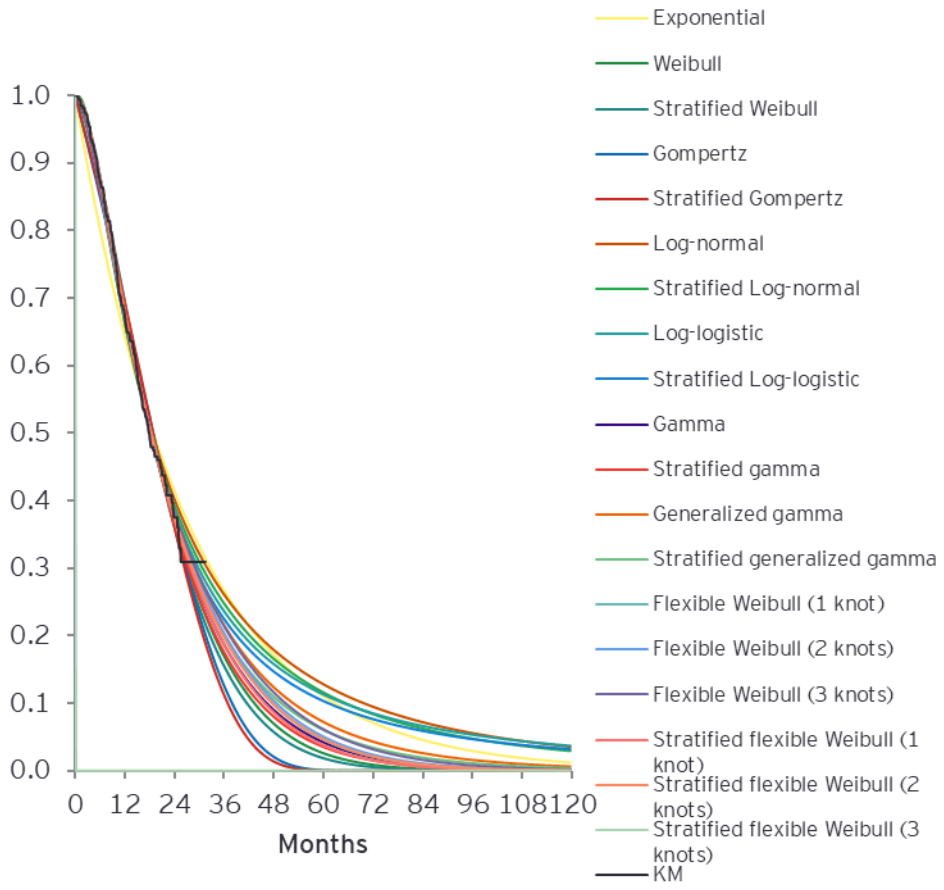

Figure 43 OS survival functions for Pluvicto®, Post 1 taxane population (data on file)

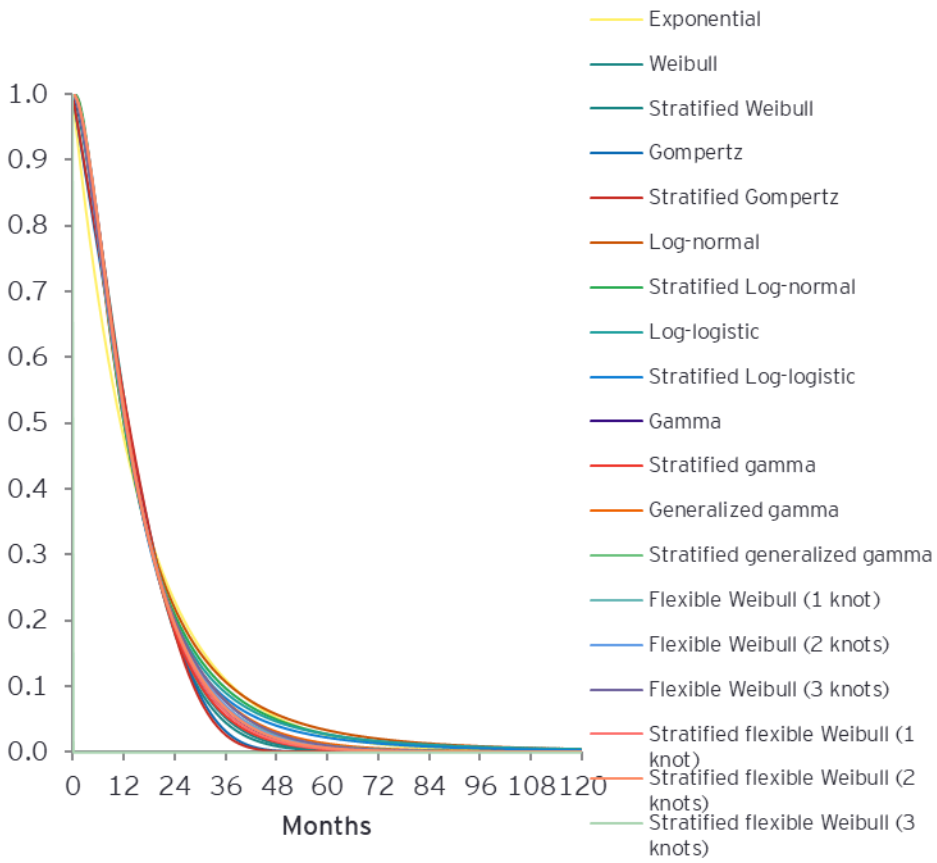

Figure 44 OS survival functions for cabazitaxel, Post 1 taxane population (data on file)

D.3.6 Evaluation of hazard functions

Figure 45 presents the OS hazard function for Pluvicto® (Post 1 taxane population) for the observed data. Figure 46 presents the OS hazard function for Pluvicto® (Post 1 taxane population) for the extrapolations.

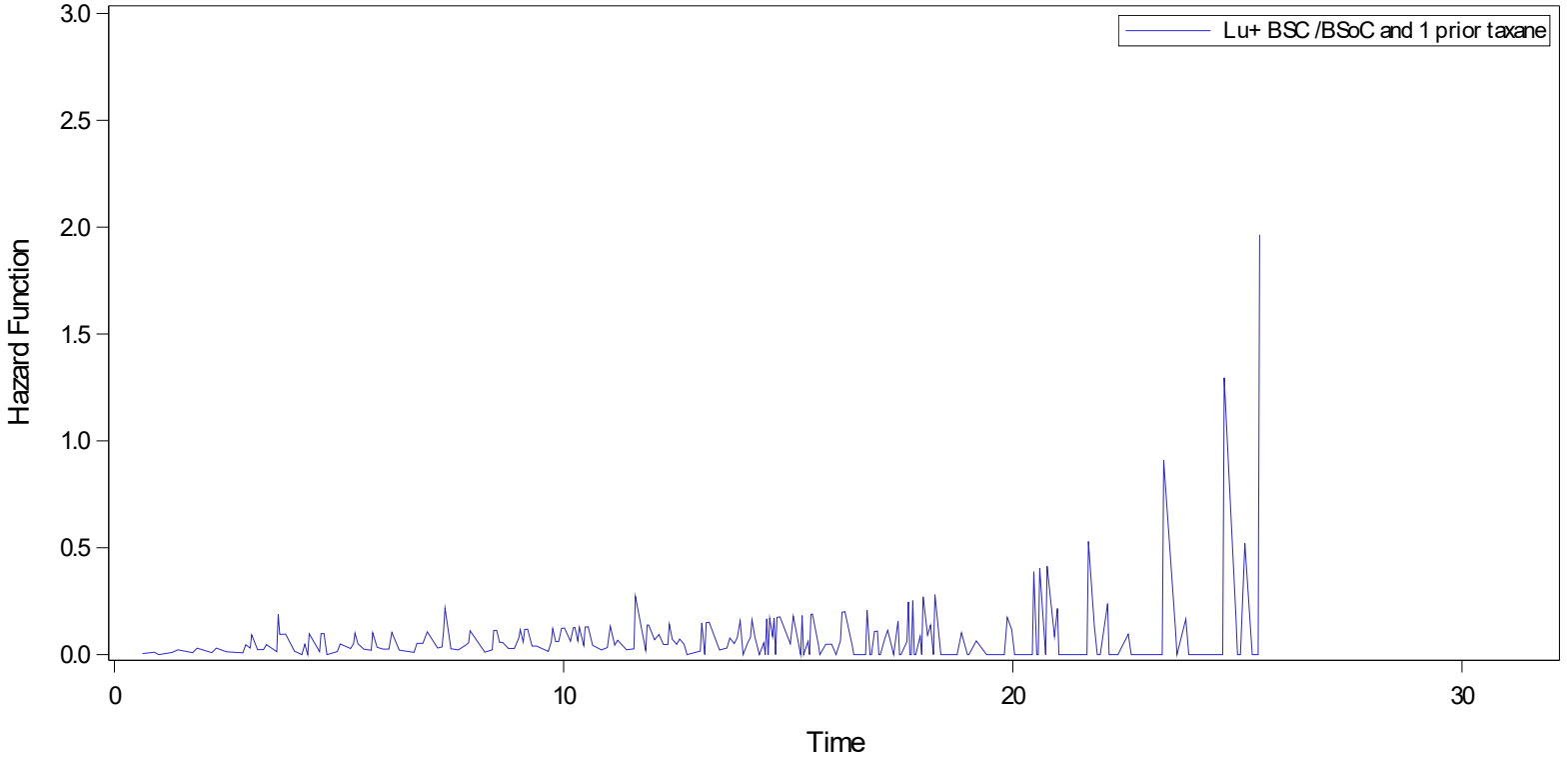

Figure 45 Pluvicto® OS hazard function based on Kaplan-Meier estimate, Post 1 taxane population (data on file)

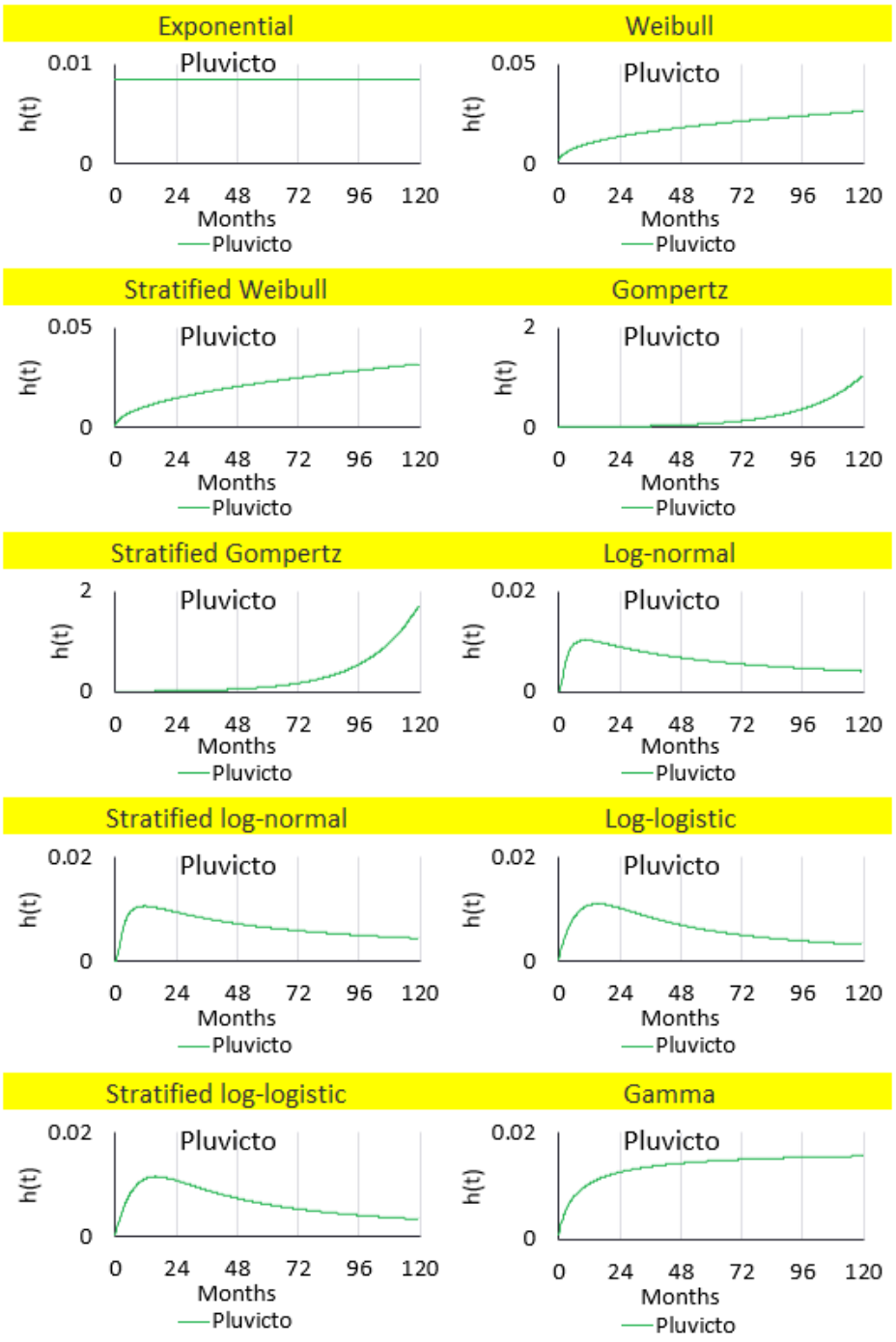

*Figure continued at the next page.

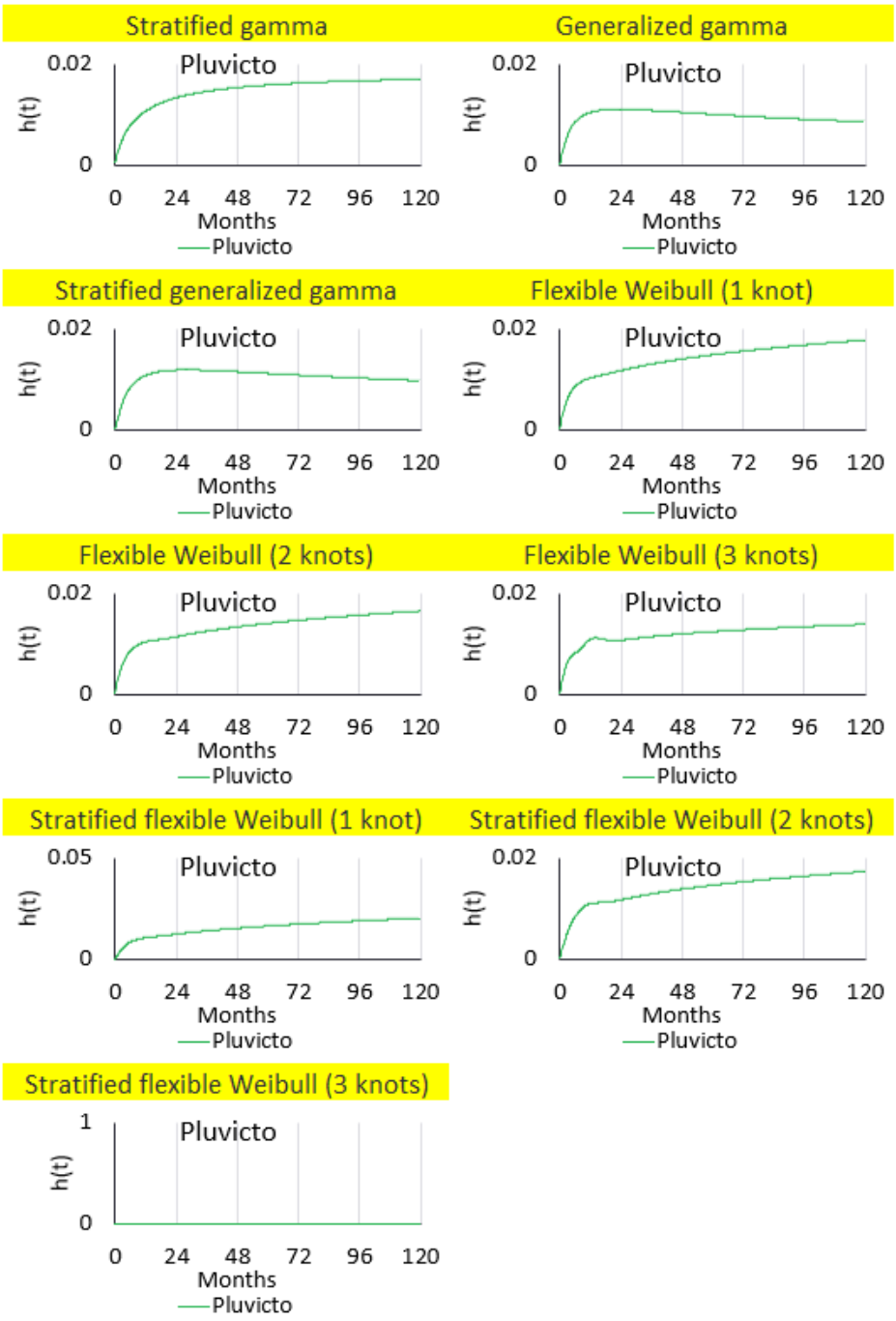

Figure 46 Pluvicto® OS hazard functions for extrapolations, Post 1 taxane population (data on file)

D.3.7 Validation and discussion of extrapolated curves

The log-logistic function had the best statistical fit based on AIC and BIC. However, this function provided a flat tail that never approached zero, and thus it was deemed unrealistic. The gamma function also provided good AIC/BIC while converging toward zero, thus appearing the most realistic. The clinical expert assessed that the curve for the

gamma function was clinically relevant and meaningful, and that it reflected the expectation for OS in Denmark. For these reasons, the gamma function was used to estimate OS in the Post 1 taxane population.

D.3.8 Adjustment of background mortality

Adjustment of background mortality was not included in the analysis as an add-on to the OS from VISION, since the OS data from VISION already reflect all-cause mortality. Adding background mortality on top of this would have resulted in an overestimation of deaths. In the model, OS is constrained to be equal to or higher than the general mortality observed in the Danish population. However, since the OS extrapolations in the base case already fulfil this criterion, this constraint is not triggered.

D.3.9 Adjustment for treatment switching/cross-over

N/A

D.3.10 Waning effect

N/A

D.3.11 Cure-point

N/A

D.4 Extrapolation of OS (Post 2 taxanes population)

D.4.1 Data input

Extrapolation of OS for the Post 2 taxanes population was based on the VISION population that had received a minimum of two prior taxanes.

D.4.2 Model

Parametric survival model.

D.4.3 Proportional hazards

Figure 47 shows the trend in the Schoenfeld residuals over time, which is not significant (chi-square = 3.1; degrees of freedom = 1; p = 0.078). Figure 48 shows the log-(Log) survival, indicating that the lines touch at the beginning but then run reasonably parallel. Based on the figures and the significance test, the proportional hazard assumption has not been met. Thus, fitting different parametric models of the same type to each of the treatment arms separately (i.e. stratified) is expected to provide the best fit (70). In addition to standard parametric models, flexible spline parametric models are also applied to the KM data to enhance the analysis.

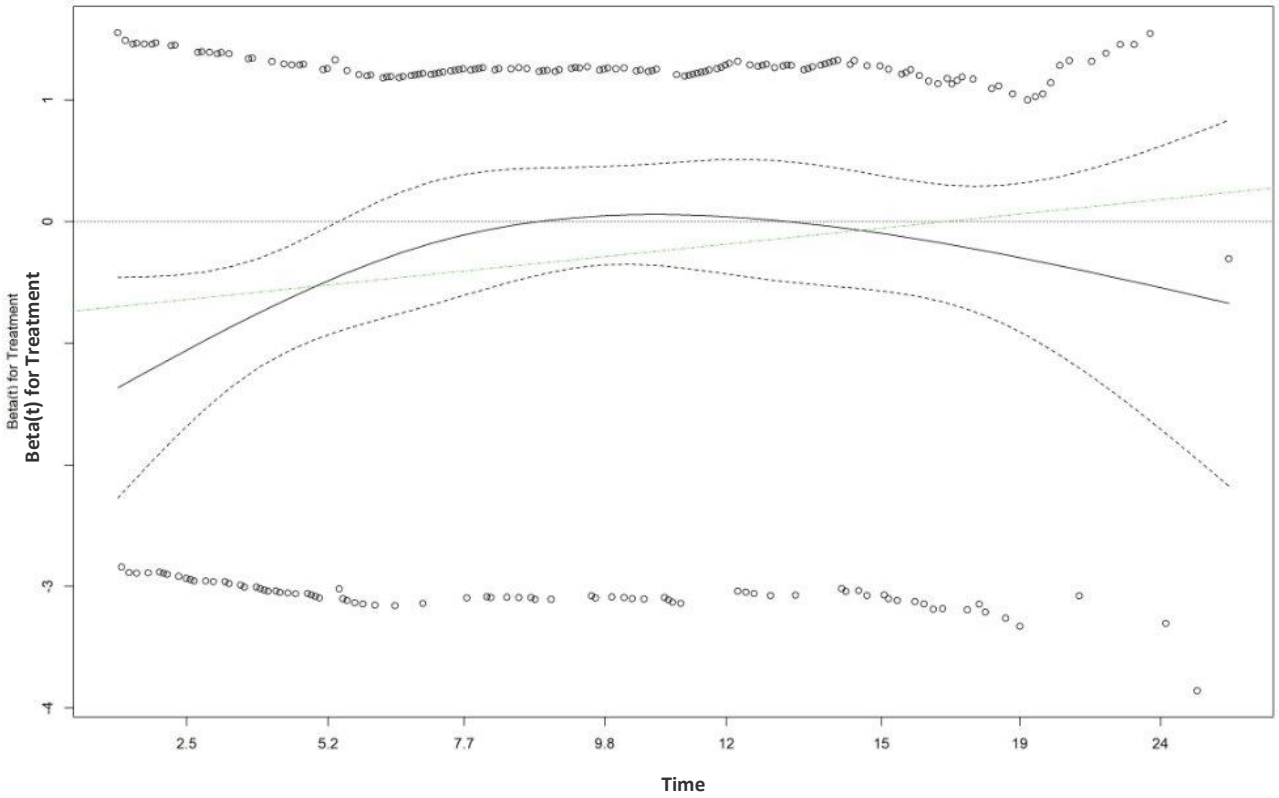

Figure 47 Schoenfeld residuals for OS from VISION trial data, Post 2 taxanes population (data on file)

Figure 48 Log-(log) survival plot for OS from VISION trial data, Post 2 taxanes population (data on file)

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

Table 94 presents the AIC and the BIC for OS in the Post 2 taxanes population. The Stratified flexible Weibull (2 knots) function had the best fit based on AIC, and the Weibull function had the best fit based on BIC.

Table 94 Statistical fit of parametric models for OS, Post 2 taxanes population (data on file)

Model	AIC	BIC
Exponential	1,799.3	1,812.2
Weibull	1,756.1	1,775.5
Stratified Weibull	1,755.7	1,781.5
Gompertz	1,765.5	1,784.9
Stratified Gompertz	1,766.2	1,792.0
Log-normal	1,789.0	1,808.3
Stratified log-normal	1,791.0	1,816.8
Log-logistic	1,760.9	1,780.3
Stratified log-logistic	1,760.9	1,786.7
Gamma	1,756.9	1,776.3
Stratified gamma	1,757.4	1,783.2
Generalised gamma	1,758.0	1,783.8
Stratified generalised gamma	1,758.7	1,797.4
Flexible Weibull (1 knot)	1,758.0	1,783.8
Flexible Weibull (2 knots)	1,759.1	1,791.4
Flexible Weibull (3 knots)	1,760.6	1,799.3
Stratified flexible Weibull (1 knot)	1,757.2	1,795.9
Stratified flexible Weibull (2 knots)	1,752.5	1,804.1
Stratified flexible Weibull (3 knots)	1,756.4	1,820.9

D.4.5 Evaluation of visual fit

The OS extrapolations for Pluvicto® are presented in Figure 49. The OS curves for BSC/SoC are presented in Figure 50.

Based on the visual fit for Pluvicto®, the Log-normal, Stratified log-normal, Log-logistic, and stratified log-logistic seem to plateau near the end of the time horizon without approaching zero, thus appearing to be unrealistic. Based on the visual fit to the KM curve, the Weibull, Stratified Weibull, Stratified gamma, Generalised gamma, Stratified generalised gamma, Flexible Weibull (1 knot), Flexible Weibull (2 knots), Flexible Weibull (3 knots), Stratified flexible Weibull (1 knot), and Stratified flexible Weibull (3 knots) functions seem to be most appealing because they are reasonably close to the KM curve for both Pluvicto® and BSC/SoC.

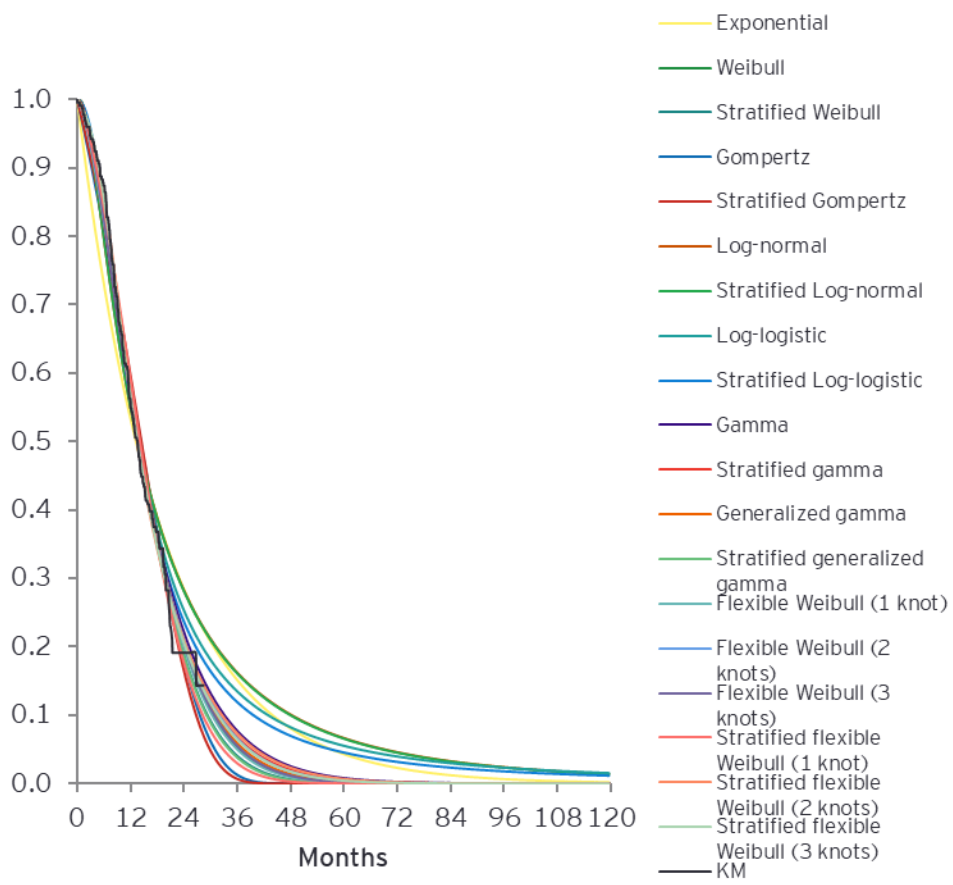

Figure 49 OS survival functions for Pluvicto®, Post 2 taxanes population (data on file)

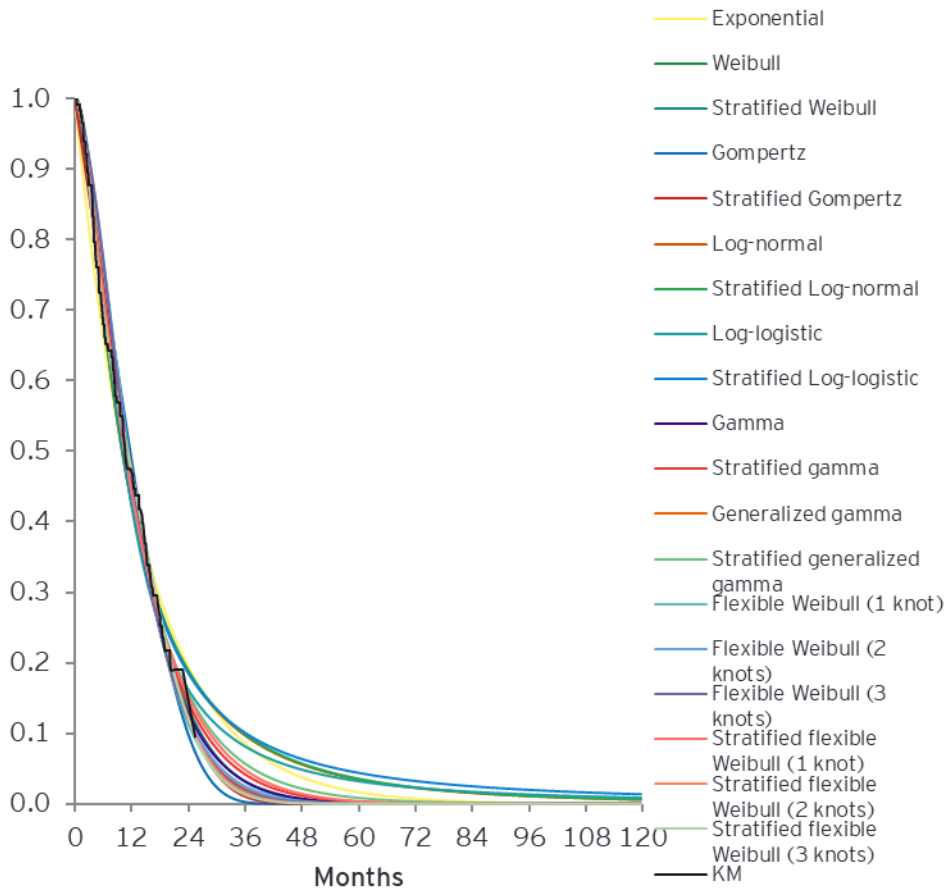

Figure 50 OS survival functions for BSC/SoC, Post 2 taxanes population (data on file)

D.4.6 Evaluation of hazard functions

Figure 51 and Figure 52 present the OS hazard function for Pluvicto® and BSC/SoC, respectively, for the observed data. Figure 53 presents the OS hazard function for Pluvicto® (Post 2 taxanes population) for the extrapolations.

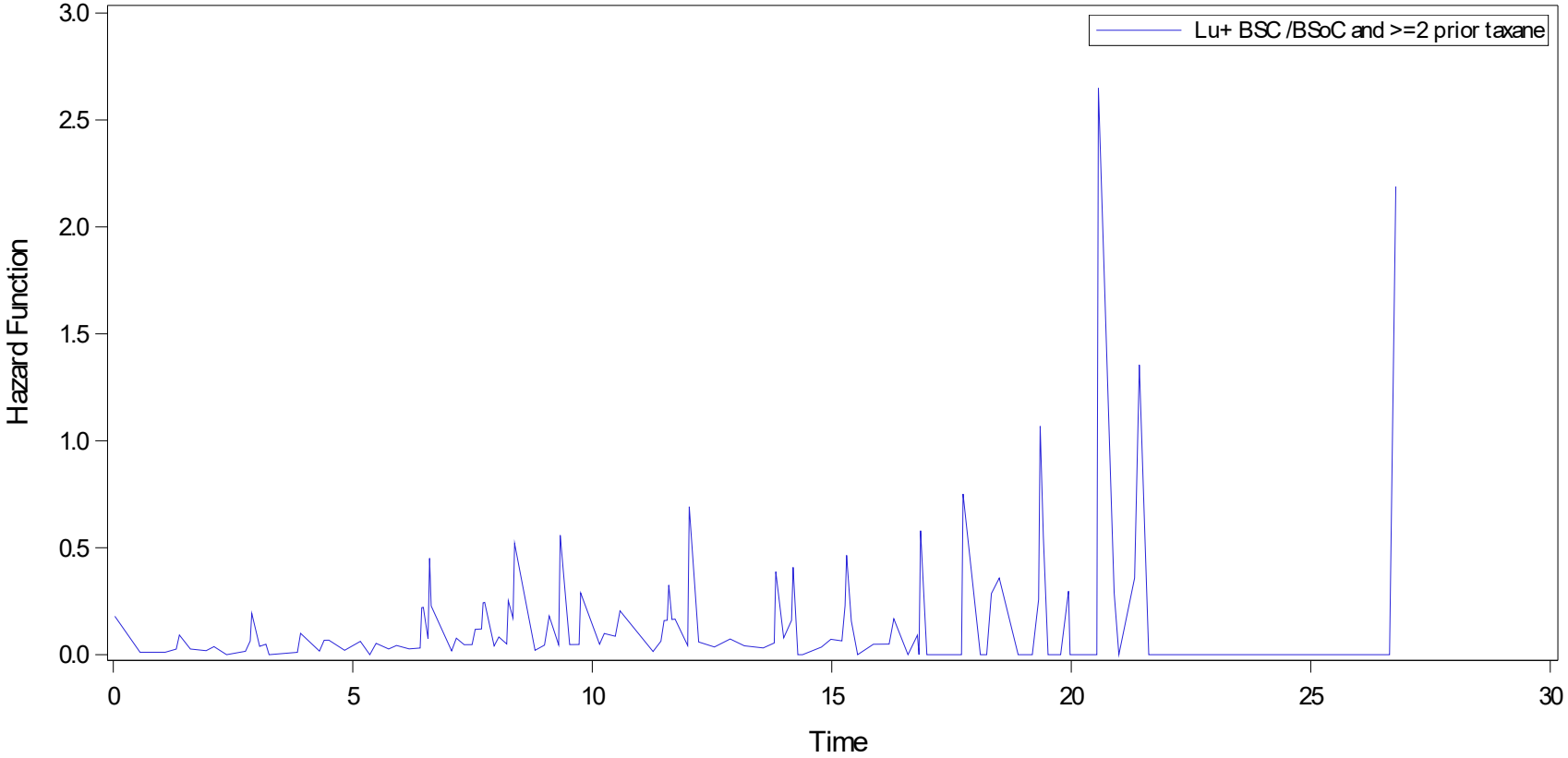

Figure 51 Pluvicto® OS hazard function based on Kaplan-Meier estimate, Post 2 taxanes population (data on file)

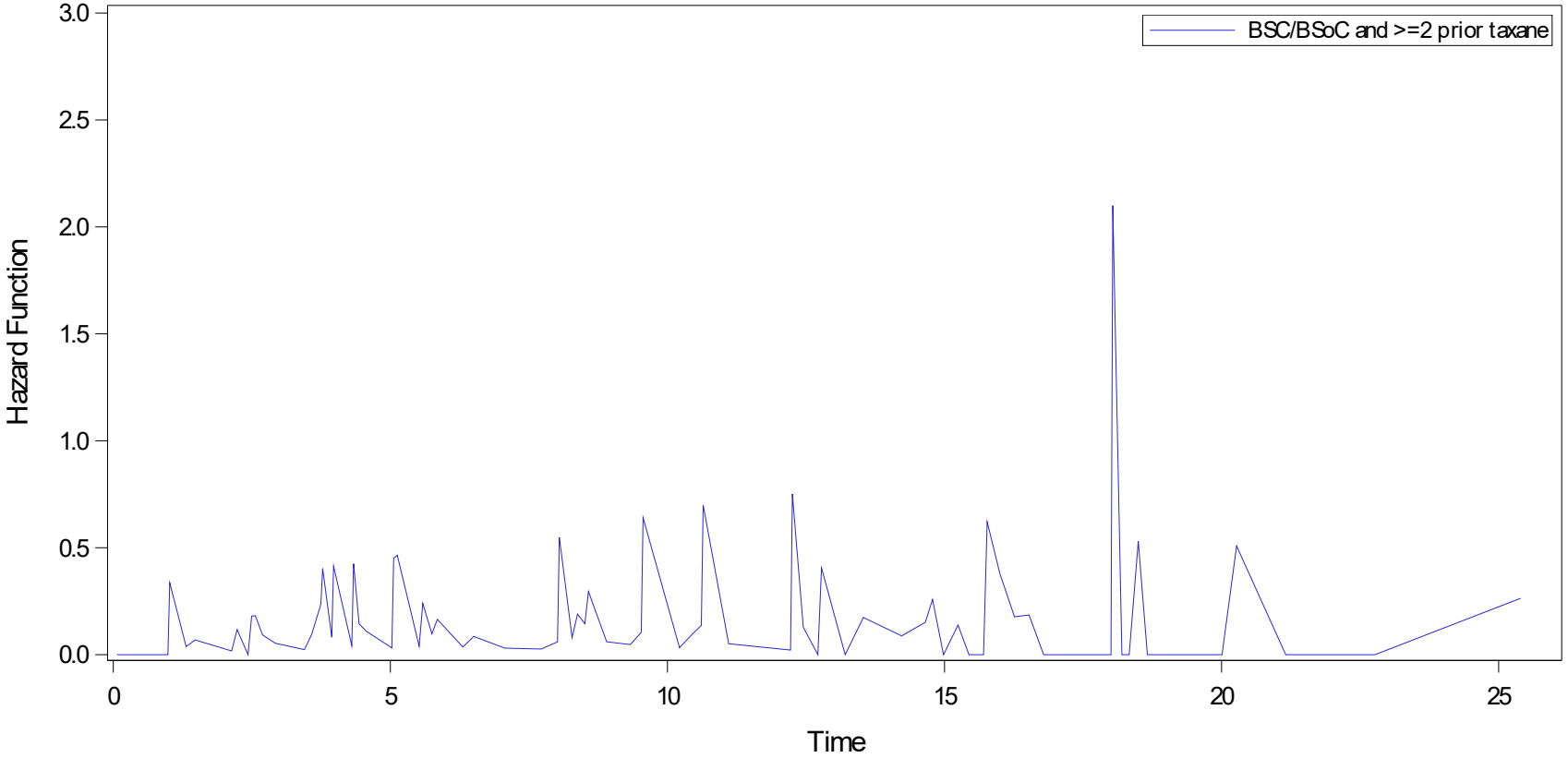

Figure 52 BSC/SoC OS hazard function based on Kaplan-Meier estimate, Post 2 taxanes population (data on file)

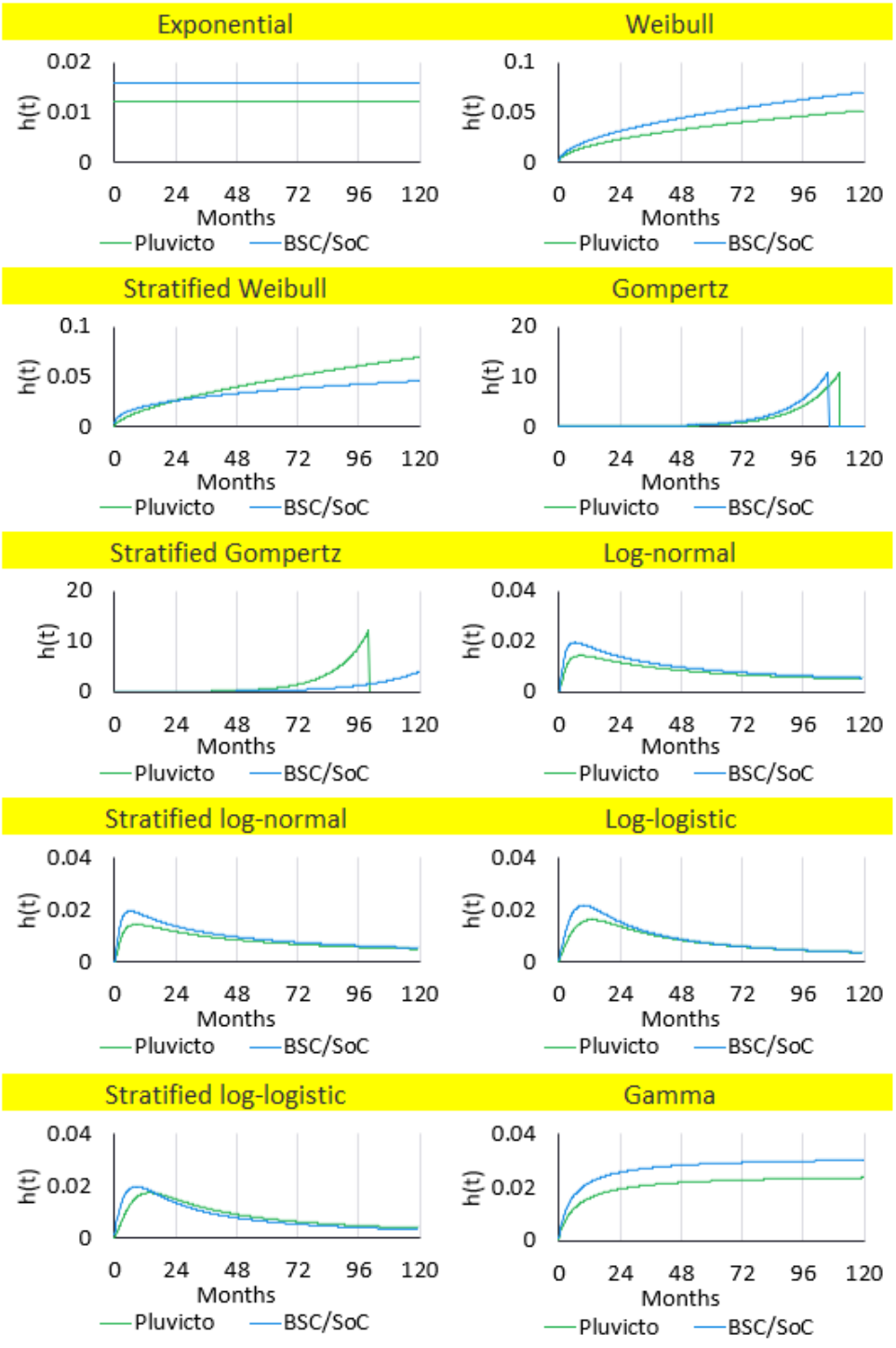

*Figure continued at the next page.

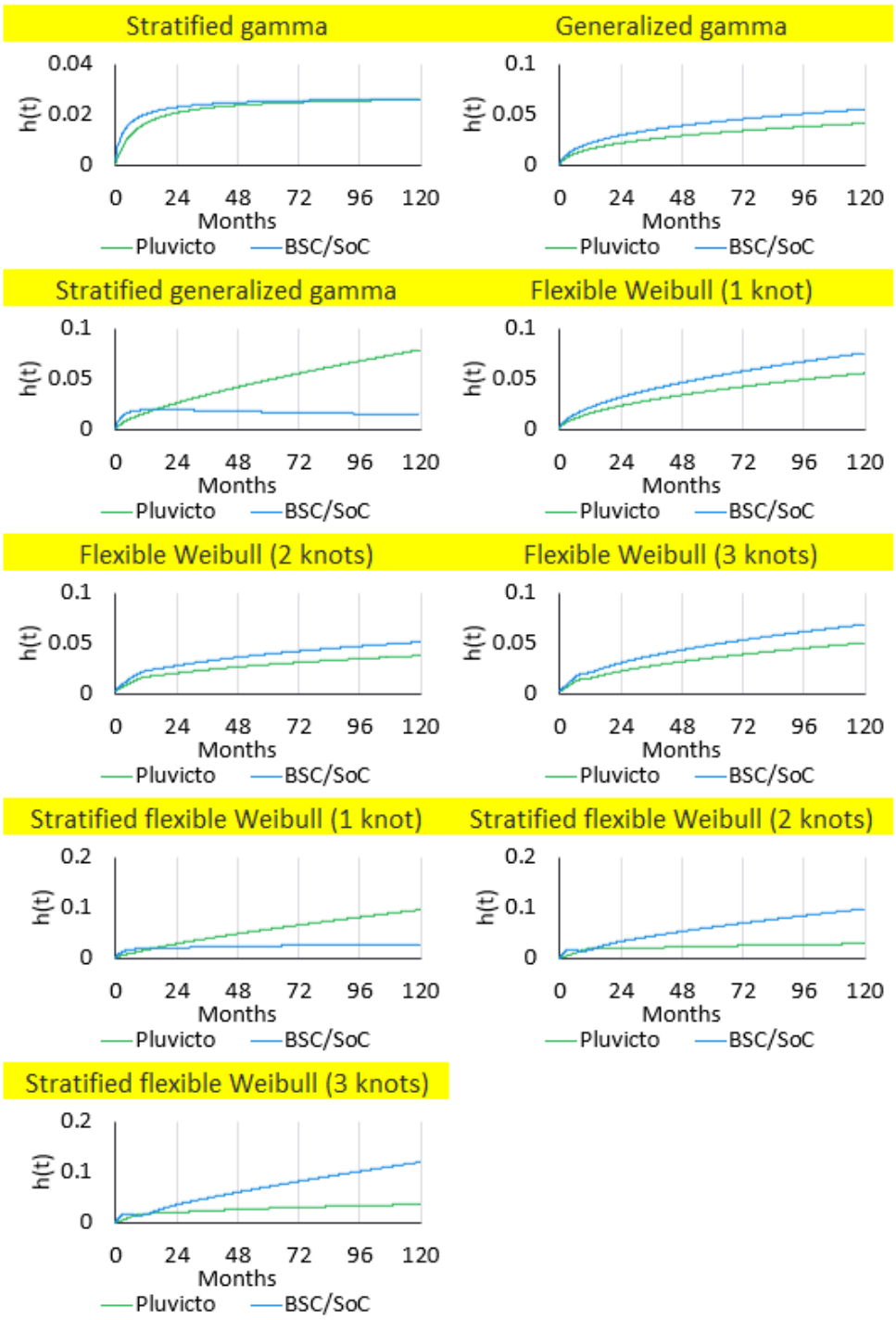

Figure 53 Pluvicto® OS hazard functions for extrapolations, Post 2 taxanes population

D.4.7 Validation and discussion of extrapolated curves

The Stratified flexible Weibull (2 knots) function had the best fit based on AIC, and the Weibull function had the best fit based on BIC. Both curves converged toward zero, thus appearing to be plausible in nature. On visual inspection, the stratified flexible Weibull (2

knots) function appeared more appealing because the extrapolation was closer to the KM curve during the first 12 months. The clinical expert assessed that the curve for the stratified flexible Weibull (2 knots) function was clinically relevant and meaningful, and that it reflected the expectation for OS in Denmark. For these reasons, the stratified flexible Weibull (2 knots) function was used to estimate OS in the Post 2 taxanes population.

D.4.8 Adjustment of background mortality

Adjustment of background mortality was not included in the analysis as an add-on to the OS from VISION, since the OS data from VISION already reflect all-cause mortality. Adding background mortality on top of this would have resulted in an overestimation of deaths. In the model, OS is constrained to be equal to or higher than the general mortality observed in the Danish population. However, since the OS extrapolations in the base case already fulfil this criterion, this constraint is not triggered.

D.4.9 Adjustment for treatment switching/cross-over

N/A

D.4.10 Waning effect

N/A

D.4.11 Cure-point

N/A

Appendix E. Serious adverse events

In the table below, we present the SAEs reported for the FAS safety population at January 27, 2021, from in the VISION study (53).

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Total	195 (36.86)	58 (28.29%)
Blood and lymphatic system disorders		
Anaemia	15 (2.84%)	1 (0.49%)
Bone marrow failure	1 (0.19%)	0 (0.00%)
Febrile neutropenia	2 (0.38%)	0 (0.00%)
Leukopenia	2 (0.38%)	0 (0.00%)
Neutropenia	1 (0.19%)	0 (0.00%)
Pancytopenia	6 (1.13%)	0 (0.00%)
Thrombocytopenia	3 (0.57%)	0 0.00%)
Cardiac disorders		
Arrhythmia	1 (0.19%)	0 (0.00%)
Atrial fibrillation	1 (0.19%)	0 (0.00%)
Cardiac failure	1 (0.19%)	0 (0.00%)
Cardiac failure congestive	2 (0.38%)	0 (0.00%)
Cardio-respiratory arrest	0 (0.00%)	1 (0.49%)
Cardiomyopathy	1 (0.19%)	0 (0.00%)
Myocardial infarction	1 (0.19%)	0 (0.00%)
Supraventricular tachycardia	0 (0.00%)	1 (0.49%)
Ventricular tachycardia	2 (0.38%)	0 (0.00%)
Congenital, familial, and genetic disorders		

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Vascular malformation	1 (0.19%)	0 (0.00%)
Ear and labyrinth disorders		
Vertigo	1 (0.19%)	0 (0.00%)
Endocrine disorders		
Adrenal insufficiency	1 (0.19%)	0 (0.00%)
Inappropriate antidiuretic hormone secretion	0 (0.00%)	1 (0.49%)
Eye disorders		
Vision blurred	1 (0.19%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal pain	4 (0.76%)	1 (0.49%)
Abdominal pain lower	1 (0.19%)	0 (0.00%)
Ascites	1 (0.19%)	0 (0.00%)
Constipation	5 (0.95%)	1 (0.49%)
Chron’s disease	0 (0.00%)	0 (0.00%)
Diarrhoea	0 (0.00%)	1 (0.49%)
Duodenal ulcer	1 (0.19%)	0 (0.00%)
Dysphagia	1 (0.19%)	1 (0.49%)
Gastric haemorrhage	1 (0.19%)	0 (0.00%)
Gastrointestinal haemorrhage	0 (0.00%)	1 (0.49%)
Gastroesophageal reflux disease	1 (0.19%)	0 (0.00%)
Haematemesis	1 (0.19%)	0 (0.00%)
Intestinal obstruction	0 (0.00%)	1 (0.49%)
Intestinal perforation	1 (0.19%)	0 (0.00%)
Intestinal pseudo-obstruction	1 (0.19%)	0 (0.00%)

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Large intestinal obstruction	1 (0.19%)	0 (0.00%)
Lower gastrointestinal haemorrhage	1 (0.19%)	1 (0.49%)
Nausea	3 (0.57%)	1 (0.49%)
Rectal haemorrhage	1 (0.19%)	0 (0.00%)
Small intestinal obstruction	1 (0.19%)	1 (0.49%)
Stomatitis	1 (0.19%)	0 (0.00%)
Upper gastrointestinal haemorrhage	1 (0.19%)	0 (0.00%)
Volvulus	0 (0.00%)	1 (0.49%)
Vomiting	5 (0.95%)	1 (0.49%)
General disorders		
Asthenia	0 (0.00%)	1 (0.49%)
Disease progression	2 (0.38%)	1 (0.49%)
Fatigue	2 (0.38%)	0 (0.00%)
General physical health deterioration	0 (0.00%)	1 (0.49%)
Generalised oedema	1 (0.19%)	0 (0.00%)
Influenza like illness	0 (0.00%)	1 (0.49%)
Malaise	1 (0.19%)	0 (0.00%)
Multiple organ dysfunction syndrome	1 (0.19%)	0 (0.00%)
Oedema	0 (0.00%)	1 (0.49%)
Oedema peripheral	1 (0.19%)	0 (0.00%)
Pain	5 (0.95%)	1 (0.49%)
Pyrexia	8 (1.51%)	0 (0.00%)
Systemic inflammatory response syndrome	1 (0.19%)	0 (0.00%)
Hepatobiliary disorders		

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Acute hepatic failure	1 (0.19%)	0 (0.00%)
Bile duct stenosis	1 (0.19%)	0 (0.00%)
Cholecystitis	1 (0.19%)	0 (0.00%)
Cholestasis	1 (0.19%)	0 (0.00%)
Hepatic cytolysis	0 (0.0%)	2 (0.98%)
Hepatic failure	1 (0.19%)	0 (0.00%)
Hepatic lesion	1 (0.19%)	0 (0.00%)
Infections and infestations		
Appendicitis	2 (0.38%)	0 (0.00%)
Bacterial sepsis	1 (0.19%)	0 (0.00%)
Bronchitis	1 (0.19%)	0 (0.00%)
COVID-19	1 (0.19%)	0 (0.00%)
Diverticulitis	1 (0.19%)	0 (0.00%)
Enterococcal bacteraemia	1 (0.19%)	0 (0.00%)
Enterocolitis infectious	1 (0.19%)	0 (0.00%)
Escherichia sepsis	1 (0.19%)	0 (0.00%)
Extradural abscess	1 (0.19%)	0 (0.00%)
Fungaemia	1 (0.19%)	0 (0.00%)
Herpes zoster	1 (0.19%)	0 (0.00%)
Infection	3 (0.57%)	2 (0.98%)
Kidney infection	1 (0.19%)	0 (0.00%)
Klebsiella sepsis	1 (0.19%)	0 (0.00%)
Lower respiratory tract infection	1 (0.19%)	0 (0.00%)
Osteomyelitis	1 (0.19%)	0 (0.00%)

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Pharyngitis	0 (0.00%)	1 (0.49%)
Pneumonia	7 (1.32%)	3 (1.46%)
Pneumonia aspiration	1 (0.19%)	0 (0.00%)
Pyelonephritis	1 (0.19%)	0 (0.00%)
Pyelonephritis acute	1 (0.19%)	0 (0.00%)
Sepsis	10 (1.89%)	2 (0.98%)
Septic shock	2 (0.38%)	0 (0.00%)
Staphylococcal bacteraemia	1 (0.19%)	0 (0.00%)
Streptococcal bacteraemia	1 (0.19%)	0 (0.00%)
Urinary tract infection	13 (2.46%)	1 (0.49%)
Urosepsis	3 (0.57%)	0 (0.00%)
Viral infection	1 (0.19%)	0 (0.00%)
Wound infection	1 (0.19%)	0 (0.00%)
Injury, poisoning and procedural complications		
Acetabulum fracture	1 (0.19%)	0 (0.00%)
Fall	1 (0.19%)	1 (0.49%)
Femoral neck fracture	1 (0.19%)	0 (0.00%)
Femur fracture	1 (0.19%)	0 (0.00%)
Hip fracture	1 (0.19%)	0 (0.00%)
Muscle strain	0 (0.00%)	1 (0.49%)
Overdose	1 (0.19%)	0 (0.00%)
Rib fracture	0 (0.00%)	1 (0.49%)
Spinal fracture	2 (0.38%)	0 (0.00%)
Subdural haematoma	4 (0.76%)	2 (0.98%)

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Wound complication	0 (0.00%)	1 (0.49%)
Investigations		
Blood creatinine increase	0 (0.00%)	1 (0.49%)
Metabolism and nutrition disorders		
Cachexia	1 (0.19%)	0 (0.00%)
Decreased appetite	1 (0.19%)	0 (0.00%)
Dehydration	5 (0.95%)	1 (0.49%)
Failure to thrive	2 (0.38%)	0 (0.00%)
Hypervolaemia	0 (0.00%)	1 (0.49%)
Hypocalcaemia	1 (0.19%)	0 (0.00%)
Hypoglycaemia	1 (0.19%)	1 (0.49%)
Hypokalaemia	2 (0.38%)	1 (0.49%)
Hyponatraemia	0 (0.00%)	1 (0.49%)
Hypophosphatemia	0 (0.00%)	1 (0.49%)
Tumour lysis syndrome	1 (0.19%)	0 (0.00%)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (0.38%)	0 (0.00%)
Back pain	10 (1.89%)	3 (1.46%)
Bone pain	6 (1.13%)	2 (0.98%)
Flank pain	1 (0.19%)	0 (0.00%)
Intervertebral disc compression	1 (0.19%)	0 (0.00%)
Intervertebral disc protrusion	1 (0.19%)	0 (0.00%)
Neck pain	2 (0.38%)	0 (0.00%)
Osteolysis	1 (0.19%)	0 (0.00%)

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Pain in extremity	1 (0.19%)	0 (0.00%)
Pathological fracture	1 (0.19%)	0 (0.00%)
Spinal pain	1 (0.19%)	0 (0.00%)
Spinal stenosis	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl.cysts and polyps)		
Cancer pain	0 (0.00%)	0 (0.00%)
Metastases to central nervous system	2 (0.38%)	0 (0.00%)
Metastases to meninges	1 (0.19%)	0 (0.00%)
Pancreatic carcinoma	1 (0.19%)	0 (0.00%)
Nervous system disorders		
Brain oedema	0 (0.00%	1 (0.49%)
Cauda equina syndrome	1 (0.19%)	1 (0.49%)
Cerebellar infraction	1 (0.19%)	0 (0.00%)
Cerebral haemorrhage	1 (0.19%)	0 (0.00%)
Cerebral infarction	1 (0.19%)	0 (0.00%)
Cognitive disorder	1 (0.19%)	0 (0.00%)
Diplegia	0 (0.00%)	1 (0.49%)
Dizziness	2 (0.38%)	0 (0.00%)
Dysarthria	1 (0.19%)	0 (0.00%)
Encephalopathy	0 (0.00%)	1 (0.49%)
Haemorrhage intracranial	2 (0.38%)	0 (0.00%)
Headache	2 (0.38%)	0 (0.00%)
Hypoglossal nerve paralysis	1 (0.19%)	0 (0.00%)
Ischaemic stroke	3 (0.57%)	0 (0.00%)

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Loss of consciousness	1 (0.19%)	0 (0.00%)
Metabolic encephalopathy	1 (0.19%)	1 (0.49%)
Myelopathy	0 (0.00%)	1 (0.49%)
Pachymeningitis	1 (0.19%)	0 (0.00%)
Paraesthesia	2 (0.38%)	0 (0.00%)
Paraplegia	0 (0.00%)	0 (0.00%)
Peripheral motor neuropathy	1 (0.19%)	0 (0.00%)
Radiculopathy	2 (0.38%)	0 (0.00%)
Seizure	1 (0.19%)	0 (0.00%)
Spinal cord compression	6 (1.13%)	11 (5.37%)
Spinal cord disorder	0 (0.00%)	1 (0.49%)
Syncope	4 (0.76%)	0 (0.00%)
Transient ischaemic attack	1 (0.19%)	0 (0.00%)
Tremor	1 (0.19%)	0 (0.00%)
Psychiatric disorders		
Confusional state	2 (0.38%)	1 (0.49%)
Delirium	1 (0.19%)	1 (0.49%)
Mental status changes	3 (0.57%)	0 (0.00%)
Mixed anxiety and depressive disorders	1 (0.19%)	0 (0.00%)
Renal and urinary disorders		
Acute kidney injury	10 (1.89%)	6 (2.93%)
Dysuria	1 (0.19%)	0 (0.00%)
End stage renal disease	0 (0.00%)	0 (0.00%)
Haematuria	11 (2.08%)	1 (0.49%)

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Hydronephrosis	1 (0.19%)	1 (0.49%)
Malignant urinary tract obstruction	1 (0.19%)	0 (0.00%)
Nephrolithiasis	1 (0.19%)	0 (0.00%)
Renal tubular acidosis	1 (0.19%)	0 (0.00%)
Urinary retention	5 (0.95%)	2 (0.98%)
Urinary tract obstruction	4 (0.76%)	0 (0.00%)
Reproductive system and breast disorders		
Benign prostatic hyperplasia	1 (0.19%)	0 (0.00%)
Penile pain	1 (0.19%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	1 (0.19%)	0 (0.00%)
Chronic obstructive pulmonary disease	1 (0.19%)	0 (0.00%)
Dyspnoea	5 (0.95%)	1 (0.49%)
Epistaxis	1 (0.19%)	0 (0.00%)
Haemoptysis	1 (0.19%)	0 (0.00%)
Hypoxia	1 (0.19%)	0 (0.00%)
Pleural effusion	2 (0.38%)	1 (0.49%)
Pulmonary embolism	6 (1.13%)	2 (0.98%)
Pulmonary hypertension	0 (0.00%)	1 (0.49%)
Surgical and medical procedures		
Euthanasia	1 (0.19%)	0 (0.00%)
Neck dissection	1 (0.19%)	0 (0.00%)
Pain management	1 (0.19%)	0 (0.00%)
Vascular disorders		

SAE	Pluvicto® (N=529)	BSC/SoC (N=205)
Aortic stenosis	1 (0.19%)	0 (0.00%)
Arteriosclerosis	0 (0.00%)	1 (0.49%)
Deep vein thrombosis	3 (0.57%)	0 (0.00%)
Embolism	2 (0.38%)	0 (0.00%)
Hypotension	4 (0.76%)	0 (0.00%)
Orthostatic hypotension	1 (0.19%)	0 (0.00%)

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

Table 95 and Table 96 show the point estimate, lower and upper bound, and probability distribution for the parameters used in the Post 1 taxane population and Post 2 taxanes population analyses, respectively.

Table 95 Overview of parameters in the PSA (Post 1 taxane population)

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Efficacy				
rPFS	Multivariate normal (sheet: RTC Survival_rPFS)			Flexible Weibull (2 knots)
OS	Multivariate normal (sheet: RTC Survival_OS)			Gamma
rPFS hazard rate	[redacted]	[redacted]	[redacted]	Normal
OS hazard rate	[redacted]	[redacted]	[redacted]	Normal
Total probability of SSE (Pluvicto®)	15.58%	14.29%	16.92%	Beta
Total probability of SSE (Cabazitaxel)	18.60%	16.06%	21.29%	Beta
SSE distribution: Radiation to bone	59.32%	Multivariate dirichlet (sheet: Default data)		
SSE distribution: Pathological fracture	13.56%	Multivariate dirichlet (sheet: Default data)		
SSE distribution: Surgery to bone	11.86%	Multivariate dirichlet (sheet: Default data)		
SSE distribution: Spinal cord compression	15.25%	Multivariate dirichlet (sheet: Default data)		
Adverse events				
Pluvicto®: Abdominal pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Anaemia	12.85%	11.91%	13.82%	Beta
Pluvicto®: Asthenia	0.00%	0.00%	0.00%	Beta
Pluvicto®: Back pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Bone pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Dyspnoea	0.00%	0.00%	0.00%	Beta
Pluvicto®: Fatigue	5.86%	5.40%	6.34%	Beta
Pluvicto®: Hypokalaemia	0.00%	0.00%	0.00%	Beta
Pluvicto®: Muscular weakness	0.00%	0.00%	0.00%	Beta
Pluvicto®: Musculoskeletal pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Neutropenia	3.40%	3.13%	3.69%	Beta
Pluvicto®: Thrombocytopenia	7.94%	7.33%	8.57%	Beta
Pluvicto®: Lymphopenia/lymphocytopenia	7.75%	7.15%	8.37%	Beta
Pluvicto®: Leukopenia	2.46%	2.26%	2.67%	Beta
Pluvicto®: Urinary tract infection	0.00%	0.00%	0.00%	Beta

Pluvicto®: Haematuria	0.00%	0.00%	0.00%	Beta
Pluvicto®: Acute kidney injury	0.00%	0.00%	0.00%	Beta
Pluvicto®: Spinal cord compression	0.00%	0.00%	0.00%	Beta
Pluvicto®: Hypertension	0.00%	0.00%	0.00%	Beta
Pluvicto®: Infections	10.96%	10.15%	11.81%	Beta
Cabazitaxel: Abdominal pain	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Anaemia	7.94%	6.71%	9.26%	Beta
Cabazitaxel: Asthenia	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Back pain	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Bone pain	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Dyspnoea	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Fatigue	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Hypokalaemia	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Muscular weakness	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Musculoskeletal pain	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Neutropenia	43.65%	39.38%	47.97%	Beta
Cabazitaxel: Thrombocytopenia	3.17%	2.66%	3.73%	Beta
Cabazitaxel: Lymphopenia/ lymphocytopenia	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Leukopenia	31.75%	28.02%	35.59%	Beta
Cabazitaxel: Urinary tract infection	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Haematuria	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Acute kidney injury	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Spinal cord compression	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Hypertension	0.00%	0.00%	0.00%	Beta
Cabazitaxel: Infections	7.94%	6.71%	9.26%	Beta
HRQoL				
Pre-progressed	0.814	0.805	0.823	Beta
Progressed	0.756	0.725	0.786	Beta
Costs				
Pluvicto® treatment exposure (cycles)	[redacted]	[redacted]	[redacted]	Gamma
Cabazitaxel treatment exposure (cycles) *	6.00	4.88	7.23	Gamma
Radium-223 dichloride treatment exposure (cycles) *	4.00	3.25	4.82	Gamma
Cabazitaxel drug waste *	10.00%	8.13%	12.04%	Beta
Pluvicto (1Tax) subsequent treatment - Cabazitaxel *	15.00%	12.18%	18.05%	Beta
Pluvicto (1Tax) subsequent treatment - Radium-223 dichloride *	0.00%	0.00%	0.00%	Beta

Pluvicto (1Tax) subsequent treatment - Radiotherapy *	5.00%	4.07%	6.02%	Beta
Cabazitaxel subsequent treatment - Cabazitaxel *	0.00%	0.00%	0.00%	Beta
Cabazitaxel subsequent treatment - Radium-223 dichloride *	50.00%	40.22%	59.78%	Beta
Cabazitaxel subsequent treatment - Radiotherapy *	5.00%	4.07%	6.02%	Beta
Pluvicto (active treatment) monitoring - Outpatient visit *	0.17	0.14	0.20	Gamma
Pluvicto (active treatment) monitoring - CT scan *	0.08	0.06	0.09	Gamma
Pluvicto (active treatment) monitoring - Bone scan *	0.08	0.06	0.09	Gamma
Pluvicto pre-progression monitoring - Outpatient visit *	0.08	0.06	0.09	Gamma
Pluvicto pre-progression monitoring - CT scan *	0.08	0.06	0.09	Gamma
Pluvicto pre-progression monitoring - Bone scan *	0.08	0.06	0.09	Gamma
Cabazitaxel (active treatment) monitoring - Outpatient visit *	0.33	0.27	0.40	Gamma
Cabazitaxel (active treatment) monitoring - CT scan *	0.08	0.06	0.09	Gamma
Cabazitaxel (active treatment) monitoring - Bone scan *	0.08	0.06	0.09	Gamma
Cabazitaxel pre-progression monitoring - Outpatient visit *	0.08	0.06	0.09	Gamma
Cabazitaxel pre-progression monitoring - CT scan *	0.00	0.00	0.00	Gamma
Cabazitaxel pre-progression monitoring - Bone scan *	0.00	0.00	0.00	Gamma
SOC monitoring - Outpatient visit *	0.04	0.03	0.05	Gamma
SOC monitoring - CT scan *	0.00	0.00	0.00	Gamma
SOC monitoring - Bone scan *	0.00	0.00	0.00	Gamma
Patient time (Pluvicto) per administration (hours) *	6.50	5.29	7.83	Gamma
Patient time (Cabazitaxel) per administration (hours) *	1.50	1.22	1.81	Gamma
Patient time - Transportation (per hospital visit) *	1.00	0.81	1.21	Gamma
Patient time - Outpatient visit *	0.33	0.27	0.40	Gamma
Patient time - CT scan *	0.50	0.41	0.60	Gamma
Patient time - Bone scan *	0.50	0.41	0.60	Gamma
Patient time - Blood tests (hospital) *	0.25	0.20	0.30	Gamma

Patient time - PET/CT-scan *	0.50	0.41	0.60	Gamma

Note: * The lower and upper bounds were derived by assuming a standard error equal to 10% of the point estimate.

Table 96 Overview of parameters in the PSA (Post 2 taxanes population)

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Efficacy				
rPFS	Multivariate normal (sheet: RTC Survival_rPFS)			Stratified flexible Weibull (3 knots)
OS	Multivariate normal (sheet: RTC Survival_OS)			Stratified flexible Weibull (2 knots)
Total probability of SSE: Pluvicto®	15.58%	14.29%	16.92%	Beta
Total probability of SSE: BSC/SoC	17.35%	15.39%	19.40%	Beta
SSE distribution: Radiation to bone	59.32%	Multivariate dirichlet (sheet: Default data)		
SSE distribution: Pathological fracture	13.56%	Multivariate dirichlet (sheet: Default data)		
SSE distribution: Surgery to bone	11.86%	Multivariate dirichlet (sheet: Default data)		
SSE distribution: Spinal cord compression	15.25%	Multivariate dirichlet (sheet: Default data)		
Adverse events				
Pluvicto®: Abdominal pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Anaemia	12.85%	11.91%	13.82%	Beta
Pluvicto®: Asthenia	0.00%	0.00%	0.00%	Beta
Pluvicto®: Back pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Bone pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Dyspnoea	0.00%	0.00%	0.00%	Beta
Pluvicto®: Fatigue	5.86%	5.40%	6.34%	Beta
Pluvicto®: Hypokalaemia	0.00%	0.00%	0.00%	Beta
Pluvicto®: Muscular weakness	0.00%	0.00%	0.00%	Beta
Pluvicto®: Musculoskeletal pain	0.00%	0.00%	0.00%	Beta
Pluvicto®: Neutropenia	0.00%	0.00%	0.00%	Beta
Pluvicto®: Thrombocytopenia	7.94%	7.33%	8.57%	Beta
Pluvicto®: Lymphopenia/lymphocytopenia	7.75%	7.15%	8.37%	Beta
Pluvicto®: Leukopenia	0.00%	0.00%	0.00%	Beta
Pluvicto®: Urinary tract infection	0.00%	0.00%	0.00%	Beta
Pluvicto®: Haematuria	0.00%	0.00%	0.00%	Beta
Pluvicto®: Acute kidney injury	0.00%	0.00%	0.00%	Beta
Pluvicto®: Spinal cord compression	0.00%	0.00%	0.00%	Beta
Pluvicto®: Hypertension	0.00%	0.00%	0.00%	Beta
Pluvicto®: Infections	10.96%	10.15%	11.81%	Beta

BSC/SoC: Abdominal pain	0.00%	0.00%	0.00%	Beta
BSC/SoC: Anaemia	4.88%	4.26%	5.53%	Beta
BSC/SoC: Asthenia	0.00%	0.00%	0.00%	Beta
BSC/SoC: Back pain	0.00%	0.00%	0.00%	Beta
BSC/SoC: Bone pain	0.00%	0.00%	0.00%	Beta
BSC/SoC: Dyspnoea	0.00%	0.00%	0.00%	Beta
BSC/SoC: Fatigue	1.46%	1.27%	1.67%	Beta
BSC/SoC: Hypokalaemia	0.00%	0.00%	0.00%	Beta
BSC/SoC: Muscular weakness	0.00%	0.00%	0.00%	Beta
BSC/SoC: Musculoskeletal pain	0.00%	0.00%	0.00%	Beta
BSC/SoC: Neutropenia	0.00%	0.00%	0.00%	Beta
BSC/SoC: Thrombocytopenia	0.98%	0.85%	1.11%	Beta
BSC/SoC: Lymphopenia/lymphocytopenia	0.49%	0.42%	0.56%	Beta
BSC/SoC: Leukopenia	0.00%	0.00%	0.00%	Beta
BSC/SoC: Urinary tract infection	0.00%	0.00%	0.00%	Beta
BSC/SoC: Haematuria	0.00%	0.00%	0.00%	Beta
BSC/SoC: Acute kidney injury	0.00%	0.00%	0.00%	Beta
BSC/SoC: Spinal cord compression	0.00%	0.00%	0.00%	Beta
BSC/SoC: Hypertension	0.00%	0.00%	0.00%	Beta
BSC/SoC: Infections	4.39%	3.83%	4.98%	Beta
HRQoL				
Pre-progressed	0.818	0.806	0.830	Beta
Progressed	0.786	0.745	0.824	Beta
Costs				
Pluvicto® treatment exposure (cycles)	[redacted]	[redacted]	[redacted]	Gamma
Radium-223 dichloride treatment exposure (cycles) *	4.00	3.25	4.82	Gamma
Cabazitaxel drug waste *	10%	8.13%	12.04%	Beta
Pluvicto (2Tax) subsequent treatment - Cabazitaxel *	0%	0.00%	0.00%	Beta
Pluvicto (2Tax) subsequent treatment - Radium-223 dichloride *	0%	0.00%	0.00%	Beta
Pluvicto (2Tax) subsequent treatment - Radiotherapy *	5%	4.07%	6.02%	Beta
SOC subsequent treatment - Cabazitaxel *	0%	0.00%	0.00%	Beta
SOC subsequent treatment - Radium-223 dichloride *	0%	0.00%	0.00%	Beta
SOC subsequent treatment - Radiotherapy *	0%	0.00%	0.00%	Beta

SOC monitoring - Outpatient visit *	0.04	0.03	0.05	Gamma
SOC monitoring - CT scan *	0.00	0.00	0.00	Gamma
SOC monitoring - Bone scan *	0.00	0.00	0.00	Gamma
Patient time (Pluvicto) per administration (hours) *	6.50	5.29	7.83	Gamma
Patient time (Cabazitaxel) per administration (hours) *	1.50	1.22	1.81	Gamma
Patient time - Transportation (per hospital visit) *	1.00	0.81	1.21	Gamma
Patient time - Outpatient visit *	0.33	0.27	0.40	Gamma
Patient time - CT scan *	0.50	0.41	0.60	Gamma
Patient time - Bone scan *	0.50	0.41	0.60	Gamma
Patient time - Blood tests (hospital) *	0.25	0.20	0.30	Gamma
Patient time - PET/CT-scan *	0.50	0.41	0.60	Gamma

Note: * The lower and upper bounds were derived by assuming a standard error equal to 10% of the point estimate.

Appendix H. Literature searches for the clinical assessment

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

An SLR was performed. The objective of the search was to assess the efficacy and safety of Pluvicto® and cabazitaxel in adult patients with progressive PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy.

The SLR was conducted in line with the requirements of NICE (71) and in accordance with methodology established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (72), as well as principles of conduct for systematic reviews as detailed in 'Guidance for Undertaking Reviews in Health Care' from the University of York's Centre for Reviews and Dissemination (73).

A search strategy was developed using combinations of Medical Subject Heading (MeSH) or Emtree terms and free-text search terms. All published records from database date of inception till October 10, 2024, were retrieved by conducting the searches on the various bibliographic databases as mentioned below using the Ovid platform (Table 97).

Additionally, conference abstracts were searched to retrieve the latest studies that had not yet been published in journals as full-text articles, or to supplement the results of previously published studies (Table 99). Disease terms were used to identify relevant conference abstracts. Websites of the following conferences were searched to identify abstract for the last three years (2022–November 2024) to capture publications that are not yet indexed within the database searches.

Table 97 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid platform	1974 to 2024 October 09	10.10.2024
Ovid MEDLINE(R) ALL	Ovid platform	1946 to October 09, 2024	10.10.2024
EBM Reviews - Cochrane Database of Systematic Reviews	Ovid platform	2005 to October 9, 2024	10.10.2024
EBM Reviews - Cochrane Central Register of Controlled Trials	Ovid platform	1991 to September 2024	10.10.2024

Database	Platform/source	Relevant period for the search	Date of search completion
EBM Reviews - Cochrane Clinical Answers	Ovid platform	2012 to September 2024	10.10.2024
EBM Reviews - Health Technology Assessment	Ovid platform	2012 to 4th Quarter 2016*	10.10.2024
EBM Reviews - Cochrane Methodology Register	Ovid platform	1995 to 3rd Quarter 2012*	10.10.2024
EBM Reviews - Database of Abstracts of Reviews of Effects	Ovid platform	1991 to 1st Quarter 2016*	10.10.2024

Note: The database is no longer being updated, which is why the search period does not extend to the present date.

Table 98 Other sources included in the literature search

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

Table 99 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
International Society For Pharmacoeconomics and Outcomes Research annual meeting (ISPOR)	https://www.ispor.org/	Manual search	Disease terms (Table 100)	10.10.2024
American Society of Clinical Oncology annual meeting (ASCO)	https://www.asco.org/	Manual search	Disease terms (Table 100)	18.11.2024
Academy of Managed Care Pharmacy annual meeting (AMCP)	https://amcpannual.org/	Manual search	Disease terms (Table 100)	18.11.2024
European Society for Medical Oncology annual meeting (ESMO)	https://www.esmo.org/	Manual search	Disease terms (Table 100)	19.11.2024
International Society For Pharmacoeconomics and Outcomes Research Europe (ISPOR EU)	https://www.ispor.org/	Manual search	Disease terms (Table 100)	21.11.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Academy of Managed Care Pharmacy Nexus (AMCP nexus)	https://amcpnexus.org/	Manual search	Disease terms (Table 100)	18.11.2024
American Association for Cancer Research (AACR)	https://www.aacr.org/	Manual search	Disease terms (Table 100)	10.10.2024
American Society of Clinical Oncology Quality Care Symposium (ASCO QCS)	https://www.asco.org/quality	Manual search	Disease terms (Table 100)	19.11.2024
ASCO Genitourinary Cancers Symposium (ASCO GU)	https://conferences.asco.org/gu/	Manual search	Disease terms (Table 100)	21.11.2024

H.1.1 Search strategies

The scope of the clinical SLR was defined in terms of criteria such as the Patient population, the Intervention, the Comparators, the Outcomes measures, and the Study design (PICOS Statement).

The search terms used in the search string (Table 100) constituted the following facets:

1) Terms to capture the disease
2) Terms to capture the study design
3) Terms to combine 1) and 2)
4) Terms to exclude non-relevant citations
5) Terms to remove duplicates

Table 100 Search strategy for the SLR using Ovid platform

#	Query	Facet	Results
1	exp castration resistant prostate cancer/ or exp Prostatic Neoplasms, Castration-Resistant/	Disease	30,742
2	mcrpc.ab,ti.		13,513
3	exp prostate tumor/ or exp Prostatic Neoplasms/ or ((prostate or prostatic) adj2 (neoplasm or neoplasm$ or cancer or cancer$ or carcinoma or carcinoma$ or adenocarcinoma or adenocarcinoma$ or tumour or tumour$ or tumor or tumor$)).ab,ti.		565,521
4	(((castrate or castration) adj3 resistan$) or 'hormone-refractory' or 'hormone refractory' or 'androgen-independent' or 'androgen independent').ab,ti.		54,953
5	(advanced or metastat* or refract* or recurren* or salva* or (late adj2 stage) or resistan* or stage iii or (stage and iii*) or stage iv or stage 3 or stage 4).ab,ti.		7,711,417

6	metastasis/ or Neoplasm Metastasis/ or exp Recurrence/ or recurrent disease.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]		961,836
7	5 or 6		8,089,093
8	3 and 4 and 7		50,560
9	1 and 7		28,011
10	2 or 8 or 9		54,115
11	exp Randomized Controlled Trial/ or exp Random Allocation/ or exp randomization/	Study design	1,683,509
12	exp Placebos/		487,407
13	exp Double-Blind Method/ or exp Single-Blind Method/		698,371
14	exp clinical trial/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp clinical trial, phase iv/ or exp controlled clinical trial/		2,980,690
15	exp controlled clinical trials as topic/ or exp Randomized Controlled Trials as Topic/ or exp clinical trials as topic/		968,238
16	exp Multicenter Study/		771,470
17	exp Randomized Controlled Trial/ or exp Random Allocation/ or exp randomization/		1,683,509
18	exp placebo/		420,070
19	exp double blind procedure/ or exp single blind procedure/ or exp crossover procedure/		332,781
20	exp clinical trial/ or exp phase 2 clinical trial/ or exp phase 3 clinical trial/ or exp Phase 4 Clinical Trial/ or exp controlled clinical trial/		2,980,690
21	exp "controlled clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/		472,733
22	exp multicenter Study/		771,470
23	randomized controlled trial.pt.		630,405
24	controlled clinical trial.pt.		95,680
25	random$.ti,ab,kw.		5,161,096
26	blind$.ti,ab,kw.		1,359,488
27	(placebo$ or assign* or allocat* or volunteer*).ti,ab,kw.		3,114,604
28	(parallel$ or factorial$ or crossover* or cross over*).ti,ab,kw.		1,361,584
29	trial.ti.		1,247,440
30	('phase 3' or 'phase 2' or 'phase 4' or 'phase IV' or 'phase III' or 'phase II' or (phase adj2 ('2' or '3' or '4' or 'ii' or 'iii' or 'iv'))).af.		818,952
31	((single or double or triple) adj3 (blind* or mask* or dummy)).af.		1,172,471
32	('double-blind' or 'double-blinded').af.		972,412
33	(open label or open-label).af.		287,146
34	("single arm" or "single-arm" or "single group" or "single-group").ti,ab.		69,123
35	exp Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp "Systematic Review"/		1,090,412
36	exp meta analysis/ or exp "meta analysis (topic)"/ or exp "systematic review"/		1,064,894

37	(meta analy* or meta-analy* or metanaly* or metaanaly*).ti,ab.		782,193
38	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.		1,004,347
39	(reference list* or bibliograph* or hand search* or manual search* or relevant journal*).ab.		139,607
40	(search strategy or search criteria or systematic search or study selection or data extraction).ab.		222,583
41	(search* adj4 literature).ab.		262,274
42	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.		988,791
43	cochrane.jw.		58,656
44	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.		13,449
45	or/11-44		11,711,903
46	10 and 45	Combination	21,035
47	(addresses or bibliography or biography or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lectures or letter or monograph or news or "newspaper article" or practice guideline or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial or twin study).pt.	Exclusion of non-relevant citations	4,974,115
48	case report/ or case reports/		5,658,336
49	(animals/ not (humans/ and animals/)) or (animal/ not (human/ and animal/))		6,510,367
50	47 or 48 or 49		16,417,941
51	46 not 50		20,147
52	limit 51 to english language [Limit not valid in ACP Journal Club,CDSR,CCA,CLCMR,DARE; records were retained]		19,615
53	limit 52 to human [Limit not valid in ACP Journal Club,CDSR,CCTR,CCA,CLCMR,DARE; records were retained]		18,552
54	limit 53 to yr="1860 - 2013" [Limit not valid in DARE; records were retained]	Deduplication	5,717
55	limit 53 to yr="2014 - 2018" [Limit not valid in DARE; records were retained]		5,607
56	limit 53 to yr="2019 - 2022" [Limit not valid in DARE; records were retained]		4,838
57	limit 53 to yr="2023 -Current" [Limit not valid in DARE; records were retained]		2,393
58	54 or 55 or 56 or 57		18,552
59	remove duplicates from 54		4,018
60	remove duplicates from 55		4,110
61	remove duplicates from 56		3,553
62	remove duplicates from 57		1,725
63	59 or 60 or 61 or 62	**Final**	**13,403**

H.1.2 Systematic selection of studies

Publications identified through the systematic review were evaluated in a two-step process to assess whether they should be included for data extraction. This procedure complies with stringent HTA guidelines surrounding the methodology of systematic reviews.

H.1.2.1 Step 1: Abstract review

All the citations were reviewed against the inclusion/exclusion criteria (presented in Table 101) based on their title and abstract by two reviewers independently. The conflicts between the two reviewers were resolved by a third independent reviewer. All citations included by the reviewers at the end of this stage were retained for Step 2. Citations excluded from this abstract review stage were disregarded, and the exclusion reason was documented for use in the PRISMA flow diagram according to the CRD guidance to increase the transparency of the selection process (73).

H.1.2.2 Step 2: Full text review

Full-text publications for citations included after abstract review (from Step 1) were obtained for a full review of the text. Studies meeting the inclusion criteria were included for the next step, i.e., linking and data extraction (Table 101). A record was kept of papers excluded at this stage along with a clear justification for their exclusion – this is reported in the table format in the Clinical SLR Excel Report (separate file) as per the NICE guidance (74).

Two independent reviewers screened all the full-text articles and any discrepancies in their decisions were resolved by a third independent reviewer.

During this stage, included trials were categorized into ten groups based on the sub-population categorization criteria based on prior therapy received in mCRPC setting (Table 102) and were mapped to patient population relevant for ^{177}Lu-PSMA-617 studies (Table 103).

Table 101. Inclusion/exclusion criteria for the SLR

	Inclusion criteria	Exclusion criteria
Patient population	• Adult males (≥18 years old) with pre-treated or treatment-naive mCRPC • Subpopulations: Taxane and ARPI naïve, Taxane naïve-ARPI pretreated, Taxane pretreated-ARPI naïve, Taxane and ARPI pretreated, Taxane pre-treated-Prior ARPI mix, Prior Taxane mix-ARPI pretreated, Taxane naïve-Prior ARPI mix, Prior Taxane mix-ARPI naïve, Taxane and ARPI mix • Note: If prior treatment % is ≥ 80%, studies were considered as pretreated; If prior treatment % is ≤ 20%, studies were considered as naïve • Note: For mixed subpopulation, studies have been classified as Others and are included in the list of evidence • Note: ARPI includes ARPI, ARSI, ADT, new anti-androgen, second generation anti-androgen, or new hormonal therapy, such as abiraterone, enzalutamide, apalutamide, darolutamide; Old ADT (such as LHRH agonist or antagonist) was not included	• Children and adolescents
Intervention and comparators	• No restriction in terms of intervention or comparator	• None
Outcomes measures	• Efficacy: OS; PFS; Time to symptomatic skeletal events; Time to PSA progression; Time to tumor progression; Objective response rate; Complete response/remission; Duration of response; Partial response/remission; Resistant disease; PSA response; Disease control rate; Patients with symptomatic skeletal events; Patients with tumor or PSA progression; Time to first response; Time to remission; Progressive disease; Time to treatment failure; Stable disease; Time to pain progression • Safety/tolerability: Adverse events (Grade 3+, all grades); Hypertension; Diarrhea; Nausea/Vomiting; Fatigue; Anorexia; Peripheral edema; Constipation; Dehydration/hypotension; Infection; Arthralgia; Decreased weight; Urinary tract infection; Thrombocytopenia; Leukopenia; Febrile neutropenia; Abdominal pain; Anemia; Leukopenia; Neurotoxicity; Pain; Bleeding; Veno-occlusive disease; Death [30- and/or 60-	• Studies not reporting any of the efficacy or safety outcomes of interest

	day, induction death, treatment related, and overall]; Discontinuations due to AEs	
Study design	• Phase II,III, and IV RCTs • Systematic literature reviews: Reference lists were reviewed with a view of identifying any potential trial not identified through the database searches	• Narrative reviews, editorials, commentary, letters, notes, short survey, case series or reports, animal or in vitro studies, open-label extensions, phase I trials, cross-over studies without relevant data prior to cross-over, observational studies
Language restrictions	• English	• Non-English publications

Abbreviations: ADT: Androgen Deprivation Therapy; AE: Adverse Event; ARPI: Androgen Receptor Pathway Inhibitor; ARSI: Androgen Receptor Signaling Inhibitor; CRPC: Castration-Resistant Prostate Cancer; LHRH: Luteinizing Hormone-Releasing Hormone; mCRPC: Metastatic Castration-Resistant Prostate Cancer; OS: Overall Survival; PFS: Progression-Free Survival; PSA: Prostate-Specific Antigen; RCT: Randomized Controlled Trial.

Table 102. VISION criteria

VISION

• **Study inclusion criteria**
  • Patients must have received at least one androgen-receptor–pathway inhibitor (ARPI: such as enzalutamide and/or abiraterone)
  • Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens
• **SLR population classifications**
  • VISION-Exact: Taxane pretreated & ARPI pretreated
  • VISION-Like: Taxane pretreated & ARPI mix; Taxane mix & ARPI pretreated

Table 103 Population categorization criteria based on prior therapy received in mCRPC setting

Prior therapy	Categorization	Broad category	Priority for extraction
Taxane naïve-ARPI pretreated	PSMAfore Exact	PSMAfore relevant	Prioritized for data extraction
Taxane naïve-Prior ARPI mix*	PSMAfore Like		Prioritized for data extraction
Prior Taxane mix-ARPI pretreated	PSMAfore and VISION Like	PSMAfore and VISION relevant	Prioritized for data extraction
Taxane and ARPI pretreated	VISION Exact	VISION relevant	Prioritized for data extraction
Taxane pretreated-Prior ARPI mix*	VISION Like		Prioritized for data extraction
Taxane pretreated-ARPI naïve/unclear	VISION Like		Prioritized for data extraction
Taxane and ARPI mix* with subgroup	VISION Like		Prioritized for data extraction

* Mix includes pretreated population ranging from >20% to <80%. Studies categorised as PSMAfore-relevant were not included in the application.

H.1.2.3 Data extraction

Data from included studies (from Step 2) were extracted into a pre-defined Excel-based template, ensuring that data were extracted uniformly and were comparable across studies. Data were extracted by one researcher and independently checked by a second researcher. Only VISION relevant studies were prioritized for data extraction (defined in Table 103).

This search of the literature databases yielded 13,403 citations (Figure 54). Owing to the overlap of coverage among the databases, 878 citations were identified as duplicates and removed prior to screening. The remaining 12,525 citations were screened based on their titles and abstracts, resulting in 1,463 potentially relevant citations being included for full-text review. Full-text reports of these citations were downloaded for a more detailed evaluation. Of these, 32 were not retrieved, all being conference abstracts published prior to year 2003. Following the full-text review, 641 publications were included. Additionally, 19 publications were identified through conference searches and five publications from bibliography search. This process finally led to the inclusion of 665 publications. Among these, 63 unique studies from 220 publications were identified as relevant to VISION and were prioritized for data extraction. After excluding dose ranging studies, disconnected studies and maintenance therapy studies, a total of 40 studies were caried forward for a final review for potential inclusion in the NMA. A total of 7

studies were identified as relevant for the NMA (Table 104). A detailed list of the 33 publications excluded in this final review is provided in Table 105.

Figure 54 PRISMA diagram

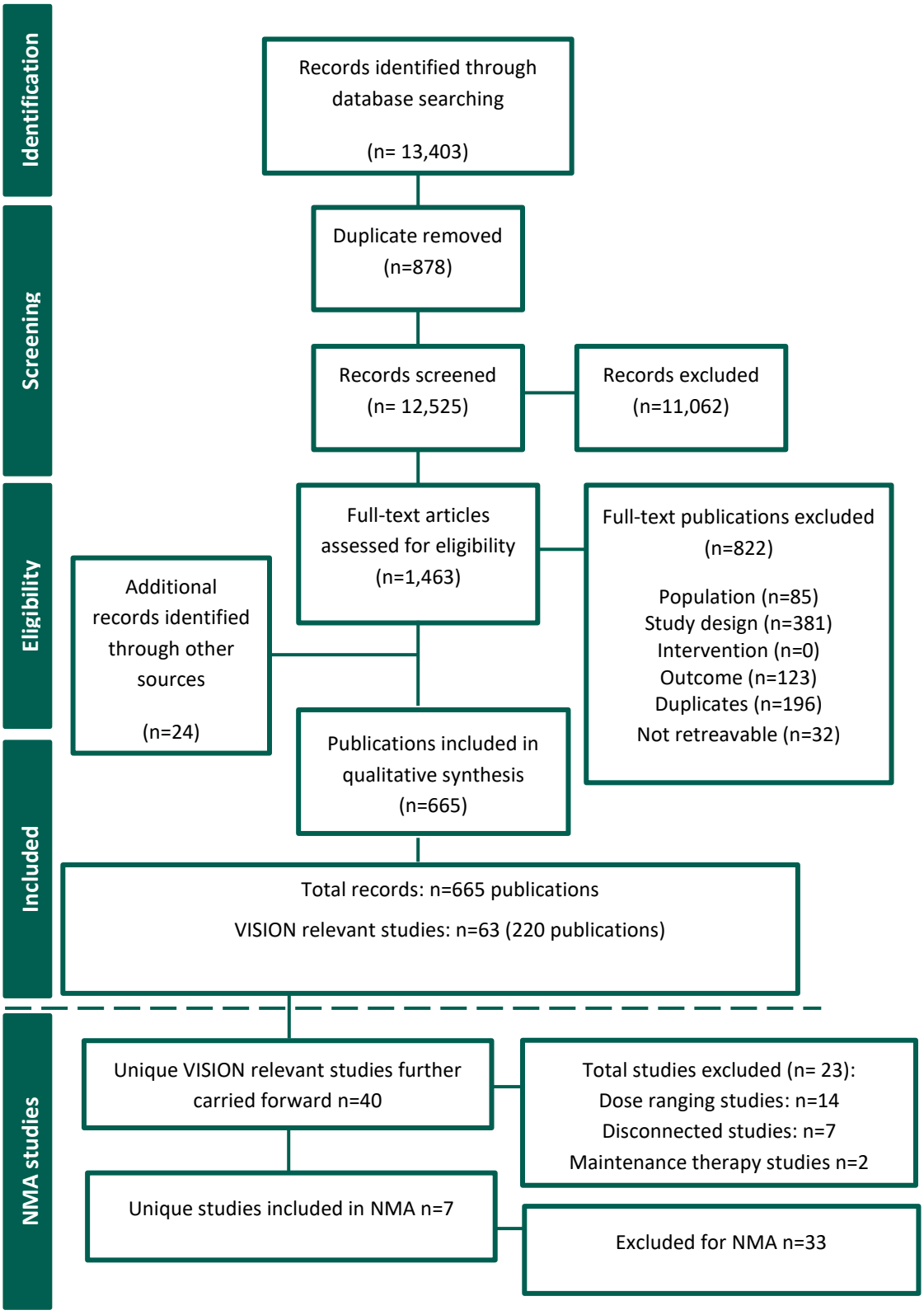

Table 104 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period (from clinicaltrials.org)	Secondary outcome and follow-up period (from clinicaltrials.org)
VISION, NCT03511664 Sartor et al. 2021 (20)	The primary objective of VISION was to compare the two alternate endpoints of rPFS and OS in patients with progressive PSMA-positive mCRPC who received 177Lu-PSMA-617 (Pluvicto®) in addition to BSC/SoC versus patients treated with BSC/SoC alone.	International, prospective, open-label, multicentre, randomised, phase III trial	Adults with mCRPC and at least one metastatic lesion on baseline CT, MRI, or bone-scan imaging.	Intervention (n=551): 177Lu-PSMA-617 (Pluvicto®) (7.4 GBq [+/- 10%]) administered IV once every 6 weeks (+/- 1 week) for a maximum of 6 cycles and BSC/SoC as defined by the local investigator. Comparator (n=280): BSC/SoC alone as defined by the local investigator.	- rPFS (From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 32 months) - OS (From date of randomization until date of death from any cause, assessed up to 32 months (cut-off date = 27 January 2021) and up to 66 months (14 December 2023)	- Number of Participants With Randomized/Study Treatment-emergent Adverse Events (TEAE) - Overall Response Rate (ORR) - Disease Control Rate (DCR) - Duration of Response (DOR) - Time to First Symptomatic Skeletal Event (SSE) - Progression-free Survival (PFS) - Best Percentage Change From Baseline in Prostate-specific Antigen (PSA) Level - Percentage of Participants Achieving Prostate-specific Antigen (PSA) Response - Prostate-specific Antigen 80 (PSA80) Response - Duration of PSA Response - Best Percentage Change From Baseline in ALP Level - Best Percentage Change From Baseline in LDH Level - Time to Worsening in BPI-SF Pain Intensity Scale - Time to Improvement After Worsening in BPI-SF Pain Intensity Scale - Time to Worsening in BPI-SF Pain Interference Scale - Time to Improvement After Worsening in BPI-SF Pain Interference Scale - Time to Worsening in BPI-SF Worst Pain Intensity Scale (Time to Disease Related Pain) - Change From Baseline in BPI-SF (Brief-Pain Inventory - Short Form) Pain Intensity Scale

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period (from clinicaltrials.org)	Secondary outcome and follow-up period (from clinicaltrials.org)
						- Change From Baseline in BPI-SF (Brief-Pain Inventory - Short Form) Pain Interference Scale - Time to Worsening in FACT-P Total Score - Change From Baseline in FACT-P (Functional Assessment of Cancer Therapy - Prostate) Total Score - Time to Worsening in EQ-5D-5L Utility Score - Change From Baseline in the European Quality of Life (EuroQol) - 5 Domain 5 Level Scale (EQ-5D-5L) Utility Score - Change From Baseline in the European Quality of Life (EuroQol) - 5 Domain 5 Level Scale (EQ-5D-5L) EQ-VAS - Number of Participants Hospitalized as In-patient Duration of Time in Hospital Following 177Lu-PSMA-617 Administration
CARD, NCT02485691 de Wit et al. 2019 (21)	The primary objective was to compare the rPFS (using RECIST 1.1 for tumor lesions and PCWG2 criteria for bone scan lesions or death due to any cause) with cabazitaxel plus prednisone versus enzalutamide or abiraterone acetate	Multicentre, randomised, open-label, phase IV trial	Patients with mCRPC who were previously treated with docetaxel and who had disease progression while receiving androgen receptor (AR)-targeted therapy within 12 months of AR treatment initiation.	Intervention (n=129): Cabazitaxel (25 mg/m^2 IV every 3 weeks) and prednisone (10 mg orally daily) and granulocyte colony-simulation factor. Comparator (n=126): Enzalutamide (160 mg orally once daily) or	- rPFS. The median follow-up (from randomization to the end of the trial) was 9.2 month (until progression, death, or data cutoff)	- OS - PFS - Percentage of Participants With Prostate Specific Antigen (PSA) Response - Percentage of Participants With Overall Objective Tumor Response - Time to PSA Progression (TTPP) - Duration of Tumor Response - Percentage of Participants Achieving Pain Response Assessed Using Brief Pain Inventory-Short Form (BPI-SF) Pain Intensity Score - Time to Pain Progression - Number of Symptomatic Skeletal Events (SSE) - Time to Symptomatic Skeletal Event

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period (from clinicaltrials.org)	Secondary outcome and follow-up period (from clinicaltrials.org)
	plus prednisone in mCRPC participants who have been treated with docetaxel and who had disease progression while receiving AR-targeted therapy within 12 months of AR treatment initiation			abiraterone (1000 mg orally once daily) and prednisone (5 mg orally twice daily).		- Health-Related Quality of Life (HRQOL): Change From Baseline in Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment - Change From Baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) Utility Single Index and Visual Analogue Scale (VAS) Scores at Cycle 2, 3, 4, 5, 6, 7, 8 and End of Treatment - rPFS in Participants With Presence and Absence of Biomarke
TROPIC de Bono et al. 2010 (30)	The aim of the TROPIC trial was to assess whether cabazitaxel plus prednisone improves overall survival compared with mitoxantrone plus prednisone in men with metastatic castration-resistant prostate cancer who had progressed after	Randomised, open-label multicentre, multinational phase III trial	Patients with mCRPC who received hormone therapy, but whose disease progressed during or after treatment with a docetaxel-containing regimen.	Intervention (n=378): Cabazitaxel (25 mg/m^2 IV every 3 weeks) and prednisone (10 mg orally daily). Comparator (n=377): Mitoxantrone (12 mg/m^2 IV every 3 weeks) and prednisone (10 mg orally daily).	OS (up to 104 weeks)	- PFS - Overall Tumor Response - Time to Tumor Progression - Time to Prostatic Specific Antigen (PSA) Progression - PSA (Prostate-Specific Antigen) Response - Time to Pain Progression - Pain Response

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period (from clinicaltrials.org)	Secondary outcome and follow-up period (from clinicaltrials.org)
	docetaxel-based chemotherapy.					
AFFIRM, NCT00974311 Scher et al. 2012 (31)	The primary objective of the AFFIRM study was to compare the clinical benefit of enzalutamide versus placebo in patients with castration-resistant prostate cancer who have been previously treated with docetaxel-based chemotherapy.	Multinational, randomised, double-blind (DB), placebo-controlled phase III trial	Patients with mCRPC after chemotherapy, of which at least one contained docetaxel.	Intervention (n=800): Enzalutamide (160 mg orally daily as four 40 mg capsules). Comparator (n=399): Placebo (orally daily as four capsules).	- OS (Up to 101 months)	- rPFS - Time to first skeletal-related event - Percentage of participants who were responders for Functional Assessment of Cancer Therapy Prostate (FACT-P) - Time to Prostate-specific Antigen (PSA) Progression - Percentage of participants with pain palliation - Percentage of participants with PSA response - Percentage of participants with soft-tissue objective response - European Quality of Life Five-Domain (EQ-5D) Scale - Percentage of participants wit Circulating Tumor Cell (CTC
Sun et al. (2016), NCT01695135 (32)	To evaluate the efficacy and safety of abiraterone acetate-prednisone versus placebo-prednisone in Asian metastatic castration-resistant prostate cancer	Double-blind, phase III trial	Patients with histologically/cytologically confirmed mCRPC who had failed previous docetaxel-containing chemotherapy;	Intervention (n=143): Abiraterone (1000 mg [4 x 250 mg tablets] taken orally once daily) and prednisone (5 mg tablet taken orally twice daily).	Median TTPP (Up to 1.8 years)	- OS (Up to approximately 3.8 years) - PSA response rate - ORR - Time to pain progression and pain palliation rate - Scores for quality of life and fatigue assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period (from clinicaltrials.org)	Secondary outcome and follow-up period (from clinicaltrials.org)
	patients who have failed docetaxel-based chemotherapy.		documented disease progression in soft tissue or bone despite castrate levels of serum	Comparator (n=71): Placebo (4 tablets taken orally once daily) and prednisone (5 mg tablet taken orally twice daily).		Safety evaluations included adverse events reporting, clinical laboratory tests, vital signs measurements, physical examinations, 12-lead electrocardiogram, multiple gated acquisition scan or cardiac echocardiogram.
COU-AA-301, NCT00638690 Fizazi et al. 2012 (33)	To compare the clinical benefit of abiraterone acetate plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer who have failed one or two chemotherapy regimens.	Phase III, multinational, double-blind, randomised placebo-controlled trial	Patients with mCRPC who were previously treated with docetaxel and a maximum of two previous chemotherapies.	Intervention (n=797): Abiraterone (four 250 mg tablets once daily) and prednisone/ prednisolone (5 mg twice daily). Comparator (n=398): Placebo (four tablets once daily) and prednisone/prednisolone (5 mg twice daily).	- OS (up to 60 months)	- rPFS (up to 11 months)
TheraP, NCT03392428	To determine the activity and safety of Lu-PSMA radionuclide therapy in men with	Open-label, randomised, 2-	Participants were men with mCRPC progressing after	Intervention (n=98): 6-8.5GBq of 177Lu-PSMA617 by IV injection once every 6	- PSA response rate (follow-up: through	- Pain response rate (follow-up: through study completion, on average 4 years) - Objective tumour response rate (follow-up: through study completion, on average 4 years)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period (from clinicaltrials.org)	Secondary outcome and follow-up period (from clinicaltrials.org)
Hofman et al. 2021 (35) Hofman et al. 2024 (34)	progressive metastatic castration resistant prostate cancer.	arm, multicentre phase II trial	docetaxel treatment.	weeks until progressive disease, prohibitive toxicity or a maximum of 6 cycles. Comparator (n=85): 20mg/m^2 Cabazitaxel by IV infusion once every 3 weeks until progressive disease, prohibitive toxicity or a maximum of 10 cycles + prednisolone 10mg orally per day for the duration of their	study completion, on average 4 years)	- Progression free survival (follow-up: through study completion, on average 4 years) - PSA progression free survival (follow-up: through study completion, on average 4 years) - Pain progression free survival (follow-up: through study completion, on average 4 years) - rPFS (follow-up: through study completion, on average 4 years) - Health-related quality of life (follow-up: through study completion, on average 4 years) - OS (follow-up: through study completion, on average 4 years) Frequency and severity of adverse events (follow-up: from first study dose to 12 weeks after completing treatment)

H.1.3 Excluded fulltext references

Of the 40 studies carried forward for a final review for potential inclusion in the NMA, a total of 7 studies were identified as relevant for the NMA. The remaining 33 studies are listed in the Table 105.

Table 105 Overview of studies excluded from NMA

Study identifier	Author Year	Trial name/NCT	Intervention	Comparator 1	Population category	NMA relevance	KM Curve Available	Line of treatment	Included in NMA
12	Basch 2019 (75)	COMET-2	Cabozantinib	Mitoxantrone/ prednisone (MP)	VISION-Exact	Prior docetaxel and 2nd gen ARPi agents pretreated	OS	3L	No. Not relevant to network
13	Smith 2016 (76)	COMET-1	Cabozantinib	Prednisone	VISION-Exact	Prior docetaxel and 2nd gen ARPi agents pretreated	Yes (OS and rPFS)	3L	No. Not relevant to network
35	Antonarakis 2023 (77)	KEYLYNK-010 NCT03834519	Pembrolizumab + Olaparib	Abiraterone Enzalutamide	VISION-Exact	Prior docetaxel and 2nd gen ARPi agents pretreated	Yes (OS and rPFS)	3L	No. Not relevant to network
60	Chi 2017 (78)	PACIFIC	Abiraterone + Prednisone	Abiraterone + Prednisone + Apatorsen	VISION-Exact	Excluded (no prior chemo, only prior ARPi, abstract (no KM curve)	No data	3L	No. Data N/A

Study identifier	Author Year	Trial name/NCT	Intervention	Comparator 1	Population category	NMA relevance	KM Curve Available	Line of treatment	Included in NMA
88	Macaulay 2023 (79)	EudraCT 2013-004011-41	Xentuzumab + Enzalutamide	Enzalutamide	VISION-Exact	Prior docetaxel and 2nd gen ARPi agents pretreated but distribution not reported	Yes (OS and rPFS/PFS)	3L	No. Not relevant to network
107	Kim 2022 (80)	NCT02893917	Olaparib + Cediranib	Olaparib	VISION-Exact	Prior docetaxel and 2nd gen ARPi agents pretreated	Yes (OS and rPFS) (ITT)	3L	No. Not relevant to network
135	Rescigno 2024 (81)	RE-AKT NCT02525068	Enzalutamide + Capivasertib	Enzalutamide+Placebo	VISION-Exact	Prior docetaxel and 2nd gen ARPi agents pretreated	Yes (OS and rPFS)	3L	No. Not relevant to network
92	de Bono 2020 (82)	PROfound	Olaparib	Physician choice (ABI/ENZA)	VISION-Like	~65% pretreated with docetaxel and 2nd Gen ARPi pretreated, Mateo et al report ~70% Docetaxel and 100% 2nd gen ARPi data	Yes (OS and rPFS)	2L+	No. Not relevant to network
93	Powles 2022 (83)	IMbassador250	Atezolizumab + Enzalutamide	Enzalutamide	VISION-Like	~50% pretreated with prior docetaxel and prior ARPi pretreated	Yes (OS and rPFS)	2L+	No. Not relevant to network

Study identifier	Author Year	Trial name/NCT	Intervention	Comparator 1	Population category	NMA relevance	KM Curve Available	Line of treatment	Included in NMA
76	Clarke 2018 (84)	NCT01972217	Olaparib + Abiraterone	Abiraterone + Placebo	VISION-Like	Prior docetaxel pretreated	OS, rPFS	2L	No. Not relevant to network
11	De Bono 2019 (85)	GO27983	Ipatasertib 400+ Abiraterone + Prednisone	Ipatasertib 200 + Abiraterone + Prednisone Placebo + Abiraterone + Prednisone	VISION-Like	Prior docetaxel and hormonal agents pretreated	Yes (OS and rPFS)	2L+	No. Not relevant to network
39	Blumenstein 2013 (86)	NCT00327340	Custirsen + Mitoxantrone + Prednisone	Custirsen + Docetaxel + Prednisone	VISION-Like	Exclude	None	2L+	No. Not relevant to network. Data N/A
80	Nieuweboer 2017 (87)	Dutch trial	Budesonide + Cabazitaxel + Prednisone	Cabazitaxel + Prednisone	VISION-Like	No outcome	None	2L+	No. Data N/A
91	Hotte 2019 (88)	NCT02788773	Durvalumab + Tremelimumab	Durvalumab	VISION-Like	No outcome, Disconnected	None	2L+	No. Data N/A

Study identifier	Author Year	Trial name/NCT	Intervention	Comparator 1	Population category	NMA relevance	KM Curve Available	Line of treatment	Included in NMA
223	Hart 2006	NR	ARM A: IROF + Prednisone ARM B: IROF + Cyclophosphamide + Prednisone	ARM C: Mitoxantrone + Prednisone	VISION-Like	Prior treatment with docetaxel	No	2L	No. Data N/A
226	Rosenberg 2007 (89)	NR	Ixabepilone	Mitoxantrone and prednisone	VISION-Like	Prior treatment with docetaxel	Yes	2L	No. Discontinued agent
59	Beer 2017 (90)	AFFINITY	Cabazitaxel + Prednisone + Custirsen	Cabazitaxel + Prednisone	VISION-Like	Prior docetaxel and 2nd gen ARPi agents pretreated (59%)	Yes (OS)	2L+	No. Custirsen discontinued agent
54	Fizazi 2015 (91)	ELM-PC 5	Orteronel + Prednisone	Placebo + Prednisone	VISION-Like	Prior docetaxel and ADT allowed	Yes (OS and rPFS/PFS)	2L	No. Ortonel discontinued agent
7	Joly 2015 (92)	GETUG-P02	Mitoxantrone + Prednisone	Etoposide + Prednisone and Vinorelbine + Prednisone	VISION-Like	Assuming all pretreated with DOC Irrelevant outcome	Irrelevant outcome	2L	No. Relevant outcome N/A

Study identifier	Author Year	Trial name/NCT	Intervention	Comparator 1	Population category	NMA relevance	KM Curve Available	Line of treatment	Included in NMA
9	Michaelson 2014 (93)	Sun-1120/ NCT00676650	Sunitinib + Prednisone	Placebo + Prednisone	VISION-Like	Prior docetaxel and hormone therapy pre-treated	Yes (OS and rPFS/PFS)	2L	No. Not relevant to network
41	Fizazi 2016 (94)	NCT01732549	Tasquinimod	Placebo	VISION-Like	1L Maintenance, Excluded		1L M	No. Population not relevant
44	Annala 2021 (95)	NCT02254785	Cabazitaxel + Prednisone	Enzalutamide + Abiraterone + Prednisone	VISION-Like	No pretreated ARPI, prior DOC treated is ~30%, Excluded	OS, PFS	1L+	No. Population not relevant.
49	Hoskin 2014 (96)	ALSYMPCA	Radium-223 + Best Supportive Care	Placebo + Best Supportive Care	VISION-Like	Prior docetaxel pretreated	Yes (OS)	1L+/2L	No. Not relevant to network
51	Kwon 2014 (97)	CA184-043	Ipilimumab + Radiotherapy	Placebo + Radiotherapy	VISION-Like	Prior docetaxel pretreated	Yes (OS)	2L	No. Not relevant to network
95	van der Zande 2023 (98)	OSTRICh	Cabazitaxel	ARTA (ABI/ENZA)	VISION-Like	No KM curve (Abstract),No data, Excluded	NR	2L	No. Data N/A

Study identifier	Author Year	Trial name/NCT	Intervention	Comparator 1	Population category	NMA relevance	KM Curve Available	Line of treatment	Included in NMA
138	Kantoff 2010 (99)	IMPACT	Sipuleucel-T	Placebo	VISION-Like	1L Population	Yes (OS)	1L	No. Population not relevant
275	Noguchi 2019 (100)	UMIN000011308	Personalized Peptide Vaccination (PPV)	Placebo	VISION-Like	Prior treatment with docetaxel	Yes (PFS)	2L	No. Not relevant to network
45	Fizazi 2012 (101)	NCT00385827	Mitoxantrone + Prednisone	Siltuximab + Mitoxantrone + Prednisone	VISION-Like	Assuming all pretreated with DOC	Yes (OS and PFS)	2L	No. Discontinued agent
47	Fleming 2012 (102)	NCT00661492	Cetuximab + Mitoxantrone + Prednisone	Mitoxantrone + Prednisone	VISION-Like	Prior docetaxel and hormonal agents pretreated	Yes (OS and PFS)	2L	No. Discontinued agent
53	Beer 2014 (103)	NCT01083615	Docetaxel + Cabazitaxel + Prednisone + Custirsen	Docetaxel + Cabazitaxel + Prednisone + Placebo	VISION-Like	Excluded (Abstract)	NR	2L	No. Discontinued agent

Study identifier	Author Year	Trial name/NCT	Intervention	Comparator 1	Population category	NMA relevance	KM Curve Available	Line of treatment	Included in NMA
55	Hakenberg 2019 (104)	NCT01204710	Olaratumab + Mitoxantrone + Prednisone	Mitoxantrone + Prednisone	VISION-Like	Only one line DOC allowed, % pretreated with DOC not reported	Yes (OS and PFS)	2L	No. Discontinued agent
84	Ryan 2013 (105)	NR	Rilotumumab 15 + Mitoxantrone + Prednisone	Rilotumumab 7.5+ Mitoxantrone + Prednisone and Mitoxantrone + Prednisone + Placebo	VISION-Like	Only one line of prior taxane allowed	Yes (OS and PFS)	2L	No. Discontinued agent
100	Bouman-Wammes 2018 (106)	RECARDO	Docetaxel + Carboplatin + Prednisone	Docetaxel + Prednisone	VISION-Like	Disconnected	Yes (OS and PFS)	2L	No. Not relevant to network

H.1.4 Quality assessment

The literature search that was performed has a number of strengths. The search was conducted in several databases to identify relevant literature to address the objective of the literature search. The PICO and the inclusion and exclusion criteria were defined prior to the literature search, and relevant search terms were applied. The screening of literature and selection of studies were conducted by two researchers independently and in parallel based on the pre-defined inclusion and exclusion criteria. Any disagreements were resolved by discussion or involvement of a third independent reviewer. Additionally, the search was restricted in terms of time frame to include all relevant literature. The search was restricted to the English language which raises the possibility that relevant trials published in other languages were missed, but this is unlikely given the search topic.

H.1.5 Unpublished data

Data from the VISION clinical study report and a VISION post hoc subgroup analysis report have been applied in the present application (presented in Table 5).

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

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

N/A since the HRQoL data came from the VISION trial.

Table 106 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	N/A	N/A
Medline	Ovid	N/A	N/A
Specific health economics databases[1]	N/A	N/A	N/A

Abbreviations:

Table 107 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk	N/A	N/A
CEA Registry	Tufts CEA - Tufts CEA	N/A	N/A

Table 108 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A
	N/A	N/A	N/A	N/A

I.1.1 Search strategies

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

N/A

Table 109 Search strategy for [name of database]

No.	Query	Results
#1	N/A	N/A
#2	N/A	N/A
#3	N/A	N/A
#4	N/A	N/A
#5	N/A	N/A
#6	N/A	N/A
#7	N/A	N/A
#8	N/A	N/A
#9	N/A	N/A
#10	N/A	N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

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

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

N/A since no external literature was used to inform the health economic model.

J.1.1 Example: Systematic search for […]

N/A

Table 110 Sources included in the search

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

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

N/A

Table 111 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk	N/A	N/A
	N/A	N/A	N/A

Abbreviations:

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
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Supplement for Novartis' Pluvicto® (lutetium Lu 177 vipivotide tetraxetan) application for PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

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1. Background

Following the Danish Medicines Council's (DMC) Expert Committee meeting regarding the Pluvicto® application for prostate-specific membrane antigen (PSMA) positive metastatic castration-resistant prostate cancer (mCRPC), questions have been raised concerning the results of the network meta-analysis (NMA) presented in the application to illustrate efficacy for the post 1 taxane population. These concerns stem primarily from the inclusion of studies that the Expert Committee may not find relevant for the comparison, most notably the TROPIC trial from 2010, which compares cabazitaxel with mitoxantrone in mCRPC patients previously treated with docetaxel. It is well known that the treatment landscape has changed since the TROPIC study was conducted, particularly with the introduction of Androgen Receptor Pathway Inhibitor (ARPI) therapies. This has raised uncertainty from the Expert Committee about whether the TROPIC study population and the comparator are representative of the patients eligible for Pluvicto®.

To address this uncertainty, the DMC Secretariat has conducted a simplified indirect treatment comparison (ITC) using data from both the VISION trial and the CARD trial. Here, a Bucher analysis was applied to compare Pluvicto® with cabazitaxel. Two versions of the analysis were performed for two different subgroups of the VISION patient population. The DMC Secretariat has informed Novartis that the analysis yielded results notably different from the NMA results for both overall survival (OS) and radiographic progression-free survival (rPFS).

Considering these findings, DMC has asked Novartis to submit a corresponding ITC of Pluvicto® versus cabazitaxel. This request was made to ensure the highest possible quality in the evidence base for the DMC's decision-making.

Although Novartis believes that the approach used in the original application is preferable for several reasons, ITCs of the described populations have been conducted for OS and rPFS, respectively, to accommodate the Secretariat's request. Furthermore, Novartis points to results from two additional ITCs of Pluvicto® versus cabazitaxel. These analyses consider the important differences between the VISION and CARD studies.

In this document, Novartis presents the results of both the requested analyses and the additional analyses.

2. Conclusion

This document presents four methods for estimating the effect measures (OS and rPFS) of Pluvicto® relative to cabazitaxel, alongside results from the previously submitted NMA, which Novartis still consider the most reliable approach.

In general, direct comparison using only data from the VISION and CARD trials may omit relevant evidence due to limited available research. The NMA (base case; described in the application) enables a broader inclusion of existing data, thus offering a more comprehensive comparison, though it does not account for methodological or population differences across studies.

Comparisons based solely on VISION and CARD should include adjustments to baseline characteristics, inclusion criteria and should acknowledge methodological differences between the studies. Therefore, a matching-adjusted indirect comparison (MAIC – weighted; section 3.1) offers the most robust comparison between the two trials. An ITC (Bucher method) that adjusts the VISION population to match CARD inclusion criteria yields less reliable results (section 3.2), while unadjusted Bucher ITCs (as performed by the DMC; section 3.3) provide the least reliable estimates and hence should be interpreted with caution.

Figure 1 and Figure 2 present the HRs for OS and rPFS for each of the explored analyses.

Figure 1. Alternative HRs explored for OS

Figure 2. Alternative HRs explored for rPFS

The following sections present the differences between the VISION and CARD studies, as well as the four different indirect comparison methodologies and their results.

3. Indirect treatment comparisons (ITCs) of Pluvicto® versus cabazitaxel

In the Pluvicto® application, the base case includes a comparison of Pluvicto® versus cabazitaxel based on an NMA. The NMA includes six studies identified in a comprehensive systematic literature review (SLR) of the existing evidence (1–6). This approach follows the DMC official guidelines and was selected to ensure that the comparison between Pluvicto® and cabazitaxel proceeded from the largest possible evidence base.

Considering the concerns raised by the DMC Secretariat and the Expert Committee, Novartis acknowledges the limitation of the TROPIC trial. However, Novartis maintains that the most accurate comparison of Pluvicto® versus cabazitaxel is based on the NMA presented in the application, due to several reasons.

Firstly, Novartis acknowledges that the submitted NMA is associated with uncertainty due to heterogeneity between trial populations, including differences between the VISION and CARD populations. For that reason, and due to the paucity of data on cabazitaxel, Novartis assesses that it is crucial to include as much evidence on cabazitaxel as possible to ensure that the comparison between Pluvicto® and cabazitaxel is based on the most relevant and accurate evidence. Additionally, including more evidence will prevent the comparison from being biased by results presented in a single trial – the CARD trial – which does not have the same inclusion criteria as the VISION trial.

Secondly, Novartis acknowledges that the CARD trial is the most recent trial for cabazitaxel. However, differences between the VISION and CARD populations make a simple comparison of the two studies (as suggested by the DMC Secretariat) inappropriate for estimating the relative efficacy of Pluvicto® versus cabazitaxel. These differences include:

- An eligibility criterion of the CARD trial was that patients had previously experienced disease progression during 12 months of treatment with an ARPI, indicating a possibility that the CARD patient population was more likely to be resistant to ARPI treatment compared to the VISION population. This ARPI resistance might have biased the relative treatment effect towards cabazitaxel in the CARD trial, since these patients would show poor outcomes with receipt of a second ARPI. In comparison, patients in VISION had received a prior ARPI, but no criteria existed relating to the duration of response prior to progression. In fact, only a small proportion of patients in VISION (~[redacted]) were reported to have progressed within 12 months of initiating a prior ARPI (post hoc, data on file).
- Since the timing of progression on a prior ARPI previously has been assessed as a likely treatment effect modifier, the direct comparison of treatment effects from VISION and CARD is challenged by the inclusion discrepancies. This treatment-modifying effect has been investigated in a Canadian observational study in mCRPC, which found that the treatment effect for patients treated with cabazitaxel was greater, when patients progressed more rapidly, within 12-months of an ARPI, compared to patients who progressed after 12 months of commencing an ARPI, as reflected in the greater relative OS increase (7).
- Additionally, the observational study reported that only 68% of the real-world mCRPC patient population had disease progression within 12 months of initiating their first ARPI treatment (7). Therefore, the CARD trial apparently fails to account for about one-third of the mCPRC patient population in a real-world setting.
- Finally, some patients in the VISION trial who received Pluvicto® had previously received cabazitaxel (37.9%). Since it is well known that prognosis is worse for pre-treated patients, these

patients would be expected to achieve poorer clinical outcomes than those patients in the CARD trial when receiving similar treatment. Therefore, this further limits the suitability of performing a direct comparison of the full VISION and CARD studies (1).

The high levels of heterogeneity between the VISION trial and the CARD trial patient populations thus increase the bias of a simple comparison of treatment effects. To reduce heterogeneity and the resulting bias in the ITC, two further ITCs were conducted in addition to the requested direct Bucher ITCs.

Firstly, an unanchored matching adjusted indirect comparison (MAIC) was explored. Secondly, a Bucher ITC adjusted for inclusion discrepancies was explored. All conducted ITCs are described in more detail in the following sections.

3.1. Unanchored matching adjusted indirect treatment comparison (MAIC)

This section presents the methodology and results of an unanchored MAIC comparing Pluvicto® with cabazitaxel based on the VISION trial and the CARD trial.

In order to maximise patient numbers available and adjust for differences in variables across the VISION and CARD trials, an unanchored MAIC was carried out between the intervention arms of the CARD trial (n=129) and the ARPI-subgroup population of the VISION trial (n=243). In the analysis, the VISION population was adjusted for differences in key prognostic variable and treatment effect modifiers. This approach permits a more comprehensive and accurate adjustment for differences in trial populations.

Methodology of MAIC

To determine which variables should be adjusted for in the unanchored MAIC, the status for each variable as a prognostic factor and effect modifier was examined. In relation to the Pluvicto® HTA application in the UK, an SLR was performed to identify prognostic factors in mCRPC, and clinical feedback was sought to confirm the importance of key baseline characteristics available from the VISION and CARD trials as prognostic factors or treatment effect modifiers. Based on the SLR and in line with the clinical feedback received in the UK, the following baseline characteristics were selected for inclusion in the MAIC:

- Proportion of patients with ECOG performance status of 0–1
- Presence of liver or lung metastases
- Presence of bone metastases
- Proportion of patients who received docetaxel before ARPI
- Median age
- Proportion of patients with Gleason score 8–10

An unanchored MAIC was conducted using both individual patient data from the Pluvicto® arm of the VISION trial and published data from the cabazitaxel arm of the CARD trial.

A propensity score weighting approach was taken where patients in the Pluvicto® arm of the VISION trial were assigned weights so that the weighted mean baseline characteristics were comparable to those reported for the cabazitaxel arm of the CARD trial. The analysis involved estimating a logistic propensity score model that was conditional on prognostic factors and effect modifiers identified in the previous step. This is equivalent to the following model on the dependent variable of log weight, i.e.

$$log(w_{it}) = \alpha_0 + \alpha_1^T X_{it}$$

where α is a vector of covariates that predict weight, and X_{it}^{EM} is the patient characteristic. Given the unanchored nature of the comparison, both effect modifiers and prognostic factors were matched/adjusted. Note, however, that the inclusion of too many variables will reduce the effective sample size (ESS) and may inflate the standard error due to overmatching.

Weights were estimated using the "method of moments" approach to match the variable distributions between the two studies. This is equivalent to minimising the function

$$\sum_{i,j} \exp\left(\alpha_1{}^{T} X_{ii}^{EM}\right)$$

when $E[X_{ii}^{EM}] = 0$. For this condition to be satisfied, the variables included in the model were "centred" by subtracting the $E[X_{ii}^{EM}]$ in the target population (e.g. cabazitaxel) from the X_{ii}^{EM} in the Pluvicto® population.

To estimate α_1, the *fminsearch* function was used to minimise the method of moments function using the Nelder–Mead simplex algorithm.

Weights were estimated for each patient in the study based on the fitted α_1 and each individual patient characteristic X_{ii}^{EM}. The weights were rescaled such that they were relative to the original unit weights of each individual, e.g. if weight >1, then the patient has more weight than prior to matching; if <1, then the patient has less weight than prior to matching; and if =1, then the individual has the same weight as prior to matching. The rescaled weights were plotted on a histogram to assess the spread of weights across the population. This approach assessed whether the matched population was dependent on a small number of patients with high weights, or the weights were more evenly spread across the population. Ideally, the matched population should be based on a broad sample and not too heavily dependent on a small number of patients. The maximum ESS is equal to the original trial size and occurs if the patient characteristics of VISION and CARD are identical.

After this matching process, the baseline characteristics selected for adjustment were exactly matched between the trials, and the ESS was [redacted]. This represents an approximately [redacted] reduction in sample size, suggesting there were no extreme weights used in the rebalancing. The rescaled weights range from [redacted] to [redacted]. The histogram of rescaled weights, presented in Figure 3, demonstrates a lack of extreme weights, and no patients in the VISION trial were assigned zero weight.

Figure 3. Distribution of weights – Pluvicto® (VISION) versus cabazitaxel (CARD)

Results of MAIC

Table 1 presents patient baseline characteristics before and after weighting in the unanchored MAIC of the VISION Pluvicto® arm versus the CARD cabazitaxel arm. Before weighting, baseline characteristics were generally well balanced across the treatment arms. After weighting, key baseline characteristics adjusted for in the analysis exactly matched across the VISION and CARD arms, with only small changes observed for unadjusted baseline characteristics.

Table 1. Baseline characteristics for Pluvicto® vs cabazitaxel before and after weighting in the unanchored MAIC

Baseline characteristic	Before weighting		After weighting	
	Cabazitaxel	Pluvicto®	Cabazitaxel	Pluvicto®
ECOG PS (0-1)[a]	95.3%	[redacted]	95.3%	[redacted]
Liver/lung metastases[a]	16.3%	[redacted]	16.3%	[redacted]
Bone metastases[a]	81.4%	[redacted]	81.4%	[redacted]
Docetaxel before ARPI[a]	38.8%	[redacted]	38.8%	[redacted]
Median age[a]	70	[redacted]	70	[redacted]
Gleason score 8–10[a]	56.6%	[redacted]	56.6%	[redacted]
Mean PSA, ng/ml	264.4	[redacted]	264.4	[redacted]
Mean alkaline phosphatase, IU/litre	226.6	[redacted]	226.6	[redacted]
Mean lactate dehydrogenase, IU/litre	331	[redacted]	331	[redacted]
Mean haemoglobin, g/litre	122	[redacted]	122	[redacted]
Mean neutrophil count per cu mm	5000	[redacted]	5000	[redacted]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, Prostate specific antigen.

Table 2 presents the results of the unanchored MAIC for OS and rPFS before and after weighting. The results show [redacted] survival benefits of Pluvicto® as compared to cabazitaxel, for both rPFS and OS.

Table 2. OS and rPFS for Pluvicto® (VISION) versus cabazitaxel (CARD) before and after weighting

Comparison	Measure	Before weighting			After weighting		
		HR	95% CI	p-value	HR	95% CI	p-value
Pluvicto® vs cabazitaxel	OS	[redacted]					
	rPFS	[redacted]					

The Kaplan–Meier survival plots for Pluvicto® (before and after weighting) versus cabazitaxel are shown for OS and rPFS in Figure 4 and Figure 5, respectively.

Figure 4. OS Kaplan–Meier plot for Pluvicto® (before and after weighting) versus cabazitaxel (based on the MAIC between CARD and VISION)

Figure 5. rPFS KM plot for Pluvicto® (before and after weighting) versus cabazitaxel (based on the MAIC between CARD and VISION)

Whilst this unanchored comparison of Pluvicto® and cabazitaxel remains susceptible to bias from unobserved confounding, the analysis presents various advantages. First, the analysis is based on larger patient numbers compared to the Bucher ITC with adjustment for inclusion discrepancies (presented in section 3.2).

Secondly, the analysis does not adjust for differences in time to progression on prior ARPI therapy. However, because the analysis is unanchored – meaning it does not maintain a direct link to the comparators in the VISION and CARD studies – the influence of this effect modifier no longer biases the estimate of the relative effect between cabazitaxel and ARPI. In this context, ARPI resistance is likely to have a greater negative impact on outcomes for sequential ARPI than for cabazitaxel, thereby affecting the observed relative difference in efficacy. Had an unanchored approach not been used to account for this, the relative efficacy of cabazitaxel versus ARPI would likely have overestimated efficacy of cabazitaxel when compared to Pluvicto®.

Accordingly, while differences in response to prior ARPI (poor response vs. strong response) may influence the relative efficacy of cabazitaxel, Watson et al. (2022) suggests that cabazitaxel's median OS is largely unaffected by prior ARPI response. Specifically, they found that patients who progressed within 12 months of initiating ARPI and those who progressed after 12 months had similar OS outcomes (16.9 months vs. 17.1 months, respectively) (7).

Finally, the analysis allows for more comprehensive adjustment for observed differences in prognostic variables and treatment effect modifiers, strengthening the robustness of the comparative findings.

3.2. Bucher ITC adjusted for inclusion discrepancies between VISION and CARD

This section presents the methodology and results of a Bucher ITC adjusted for inclusion discrepancies between the VISION and CARD trials.

In order to address the heterogeneity in eligibility criteria across the VISION and CARD trials, a subgroup analysis of the VISION trial was explored for the purpose of exploring a Bucher ITC. This subgroup is described in the following section.

Methodology of Bucher ITC adjusted for inclusion discrepancies

In this Bucher analysis, data from the CARD population was compared with data from a subgroup of the VISION population who met the eligibility criterion of the CARD trial, i.e. patients having progressed within 12 months of receipt of a prior ARPI, who are likely to have developed rapid ARPI resistance. This approach aims to directly address the heterogeneity between the VISION and CARD trials.

Table 3 presents the baseline characteristics of this specific VISION subgroup. Additionally, Table 4 and Table 5 present OS and rPFS data for the subgroup, and Figure 6 and Figure 7 illustrate Kaplan-Meier plots for OS and rPFS, respectively, in the subgroup.

Given the common comparator ARPI arm in the ARPI subgroup population of both the VISION trial and the CARD trial, a Bucher ITC was carried out to conduct a naïve comparison of Pluvicto® and ARPI to cabazitaxel.

Table 3. Baseline characteristics for VISION subgroup who progressed ≤12 months of receipt of a prior ARPI

Characteristic	PFS-FAS (N = [redacted])		FAS (N = [redacted])	
	Pluvicto® + ARPI (N = [redacted])	ARPI (N = [redacted])	Pluvicto® + ARPI (N = [redacted])	ARPI (N = [redacted])
Median age (range), years	[redacted]	[redacted]	[redacted]	[redacted]
ECOG ≤1, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Site of disease				
Lung	[redacted]	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]	[redacted]
Median PSA level (range), ng/ml	[redacted]	[redacted]	[redacted]	[redacted]
Median alkaline phosphatase level (range), IU/litre	[redacted]	[redacted]	[redacted]	[redacted]
Median LDH (range), IU/litre	[redacted]	[redacted]	[redacted]	[redacted]
Median time since diagnosis (range), years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PSA, Prostate specific antigen; LDH, Lactate dehydrogenase.

Table 4. OS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (FAS)

	Pluvicto® + ARPI (N = [redacted])	ARPI (N = [redacted])
Deaths	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Alive	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Median OS [99.2% CI]	[redacted]	[redacted]
OS rates (%)		
3 months (SE) [99.2% CI]	[redacted]	[redacted]
6 months (SE) [99.2% CI]	[redacted]	[redacted]
12 months (SE) [99.2% CI]	[redacted]	[redacted]
Log-rank test and Cox regression model		
HR (99.2% CI)[a,b]	[redacted]	
Follow-up time (months)[c]		
Median [95% CI]	[redacted]	[redacted]
Minimum, maximum	[redacted]	[redacted]

[a]Hazard ratio of Pluvicto® + standard of care (SoC) vs SoC from stratified Cox **proportional hazards (PH)** model. [b]Both Cox PH model and log-rank test are stratified for LDH (≤ 260 IU/L vs > 260 IU/L); presence of liver metastases (yes vs no); ECOG score (0 or 1 vs 2); and inclusion of ARPI in best supportive/standard of care at time of randomisation (yes vs no). [c]Follow-up time = (Date of event or censoring – randomisation date + 1)/30.4375 (months) censoring for deaths.

Table 5. rPFS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (PFS-FAS)

	Pluvicto® + ARPI (N = [redacted])	ARPI (N = [redacted])
Events	[redacted]	[redacted]
Radiographic progressions	[redacted]	[redacted]
Deaths	[redacted]	[redacted]
Censored	[redacted]	[redacted]
Ongoing without event	[redacted]	[redacted]
Event documented after 2 or more missed tumour assessments	[redacted]	[redacted]
Adequate assessment not available	[redacted]	[redacted]
Median rPFS [99.2% CI]	[redacted]	[redacted]
rPFS rates (%)		
3 months (SE) [99.2% CI]	[redacted]	[redacted]

6 months (SE) [99.2% CI]	[redacted]	[redacted]
12 months (SE) [99.2% CI]	[redacted]	[redacted]
Log-rank test and Cox regression model		
HR (99.2% CI)[a,b]	[redacted]	
Follow-up time (months)[d]		
Median [95% CI]	[redacted]	[redacted]
Minimum, Maximum	[redacted]	[redacted]

[a]Hazard ratio of Pluvicto® + SoC vs SoC only. [b]Both Cox PH model and log-rank test are stratified for LDH (≤ 260 IU/L vs > 260 IU/L); presence of liver metastases (yes vs no); ECOG score (0 or 1 vs 2); and inclusion of ARPI in SoC at time of randomisation (yes vs no). [c]Patients censored without adequate post-baseline evaluations or adequate baseline assessment. [d]Follow-up time = (Date of event or censoring - randomisation date + 1)/30.4375 (months) censoring for death or radiographic progression.

Figure 6. Kaplan–Meier plot of OS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (FAS)


[redacted]

Stratified log-rank test and stratified Cox model using strata defined by LDH level, presence of liver metastases, ECOG score, and inclusion of ARPI in SoC at time of randomisation. n/N: number of events/number of patients in treatment arm.

Figure 7. Kaplan–Meier plot of rPFS in VISION subgroup who progressed ≤12 months of receipt of a prior ARPI (PFS-FAS)

Stratified log-rank test and stratified Cox model using strata defined by LDH level, presence of liver metastases, ECOG score, and inclusion of ARPI in SoC at time of randomisation. n/N: number of events/number of patients in treatment arm.

Results of Bucher ITC adjusted for inclusion discrepancies

Table 6 presents the results of the Bucher ITC adjusted for inclusion discrepancies between VISION and CARD. The results indicate an OS and rPFS benefit for Pluvicto® compared to cabazitaxel.

Table 6. OS and rPFS estimates for Pluvicto® versus cabazitaxel (Bucher ITC adjusted for inclusion discrepancies)

Comparison	Measure	HR	95% CI
Pluvicto® vs cabazitaxel	OS	[redacted]	[redacted]
	rPFS	[redacted]	[redacted]

Although this analysis aims to directly address the heterogeneity between the VISION and CARD trials, some limitations might impact the results.

First, time to progression on an ARPI was not a stratification factor in the VISION trial. Therefore, the subgroup analysis of the VISION trial focusing on patients who progressed within 12 months of receipt of a prior ARPI breaks randomisation. Baseline characteristics were reasonably well matched across treatment arms, but given the lack of randomisation, observed or unobserved differences in patients' characteristics across treatment arms could contribute to differences in observed treatment outcomes and thereby confound the results of the analysis.

Second, the number of patients in the subgroup of the VISION trial who progressed within 12 months of initiating ARPI treatment was low, suggesting a poor overlap in patient populations between VISION and CARD, and resulting in wide confidence intervals. Given that the subgroup analysis breaks randomisation, adjusting for differences in patient characteristics across the VISION treatment arms was considered, but was not feasible given the already small patient numbers available for adjustment.

Finally, there is an important distinction between treatment with an ARPI as part of SoC in the VISION trial, and as part of the control arm of CARD. Patients in VISION were prescribed ARPI as part of SoC based on clinical judgement, likely where there may be an expectation of additional clinical benefit. In contrast, patients receiving a second ARPI were mandated in the control arm of CARD, regardless of any anticipated clinical benefit and disease progression within 12 months of treatment with an ARPI, typically associated with rapid ARPI resistance. This suggests that the control arms of the two trials are heterogeneous in their treatment intentions, and thus the treatment effects derived from each trial are not directly comparable.

3.3. Bucher ITCs without adjustment for inclusion discrepancies between VISION and CARD

This section presents the methodology and results of the Bucher analyses requested by the DMC Secretariat, i.e. no adjustment for inclusion discrepancies between VISION and CARD.

Novartis would like to emphasise that the NMA presented in the original application is the preferred approach to compare efficacy of Pluvicto® versus cabazitaxel due to the paucity of data on cabazitaxel as well as the heterogeneity between patient populations in the cabazitaxel trials (CARD and TROPIC) and the Pluvicto® trial (VISION).

Methodology of Bucher ITCs without adjustment for inclusion discrepancies

As previously described, the DMC Secretariat has conducted a simplified ITC using data from both the VISION trial and the CARD trial. Two versions of the analysis were performed for two different subgroups of the VISION patient population: one restricted to patients who had received one taxane (Post 1 taxane), and another aligned with the original NMA criteria, requiring ARPI treatment in the comparator arm.

As requested by the DMC Secretariat and the Expert Committee, Novartis has conducted similar analyses using the Bucher method (8). With this approach, the effect of intervention B relative to intervention A can be estimated indirectly as follows, using the direct estimators for the effects of intervention C relative to intervention A ($Effect_{AC}$) and of intervention C relative to intervention B ($Effect_{BC}$):

$$Effect_{AB} = Effect_{AC} - Effect_{BC}$$

The variance of the indirect estimator $Effect_{AB}$ is the sum of the variances of the direct estimators:

$$Variance_{AB} = Variance_{AC} + Variance_{BC}$$

The corresponding two-tailed 95% confidence interval can thus be calculated as follows:

$$Effect_{AB} \pm Z_{0.975} \times Variance_{AB}^{1/2}$$

Table 7 and Table 8 present the direct estimates of treatment effects (HR) for OS and rPFS, respectively, used as inputs for the ITC. Both VISION populations (post 1 taxane and full population with ARPI as comparator) have been compared indirectly to cabazitaxel via the CARD study.

Table 7. OS study results included in Bucher ITC without adjustment for inclusion discrepancies by population

Population	N	HR (95%CI)	Reference
VISION (post 1 taxane)	Pluvicto®: 342 BSC/SoC: 165	0.59 (0.46; 0.75)	VISION post hoc (9)
VISION (full population with ARPI as comparator)	Pluvicto®: 551 BSC/SoC: 146	0.57 (0.44; 0.74)	VISION post hoc (9)
CARD (full population	Cabazitaxel: 129 ARPI: 126	0.64 (0.46; 0.89)	CARD (2)

Table 8. rPFS study results included in Bucher ITC without adjustment for inclusion discrepancies by population

Population	N	HR (95%CI)	Reference
VISION (post 1 taxane)	Pluvicto®: 224 BSC/SoC: 110	0.39 (0.27; 0.54)	VISION post hoc (9)
VISION (full population with ARPI as comparator)	Pluvicto®: 385 BSC/SoC: 107	0.51 (0.36; 0.73)	VISION post hoc (9)
CARD (full population)	Cabazitaxel: 129 ARPI: 126	0.54 (0.40; 0.73)	CARD (2)

Results of Bucher ITCs without adjustment for inclusion discrepancies

Table 9 shows the ITC results for OS and rPFS, as HRs for Pluvicto® versus cabazitaxel.

Table 9. OS and rPFS estimates for Pluvicto® versus cabazitaxel (Bucher ITC without adjustment for inclusion discrepancies)

Population	Comparison	OS HR (95%CI)	rPFS HR (95%CI)
VISION (post 1 taxane) vs CARD (full population)	Pluvicto® vs cabazitaxel	0.92 (0.61; 1.39)	0.72 (0.46; 1.14)
VISION (full population with ARPI as comparator) vs CARD (full population)	Pluvicto® vs cabazitaxel	0.89 (0.59; 1.36)	0.94 (0.59; 1.50)

References

1. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021 Sep 16;385(12):1091–103.

2. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019 Dec 26;381(26):2506–18.

3. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet. 2010 Oct;376(9747):1147–54.

4. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187–97.

5. Sun Y, Zou Q, Sun Z, Li C, Du C, Chen Z, et al. Abiraterone acetate for metastatic castration-resistant prostate cancer after docetaxel failure: A randomized, double-blind, placebo-controlled phase 3 bridging study. Int J Urol. 2016 May;23(5):404–11.

6. Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012 Oct 1;13(10):983–92.

7. Watson AS, Gagnon R, Batuyong E, Alimohamed N, Lee-Ying R. Real-World Cabazitaxel Use and Outcomes in Metastatic Castrate-Resistant Prostate Cancer: The Impact of Response to First ARPI. Clin Genitourin Cancer. 2022 Oct;20(5):496.e1-496.e9.

8. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. 1997;

9. Novartis. Post-hoc subgroup analysis report (data on file). 2024 Feb.