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HEALTH TECHNOLOGY ASSESSMENT:

^{177}Lu-PSMA-617 for treatment of metastatic castration resistant prostate cancer

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Table of content

Key messages

^{177}Lu-PSMA-617 is a new radioligand therapy that is being used in treating metastatic castration resistant prostate cancer. It consists of the radionuclide lutetium-177 labelled with the ligand PSMA-617 for specific binding to prostate-specific membrane antigen (PSMA) typically expressed by prostate cancer cells.

In this health technology assessment, we included three randomised controlled trials that compared the effect of ^{177}Lu-PSMA-617, either alone or in combination with standard of care therapy (SoC), to docetaxel, cabazitaxel, or SoC alone. The main efficacy outcome was survival, i.e., overall survival (OS), as well as progression-free survival (PFS). Safety outcome was severe adverse events ≥grade 3 (SAE). The results are presented as hazard ratio (HR) and risk ratio (RR), with an assessment of our conficence in the results (GRADE).

^{177}Lu-PSMA-617 + SoC versus SoC alone (total n=831)
- OS: HR 0.62 (0.52 to 0.74) (GRADE: high)
- PFS: HR 0.40 (0.31 to 0.51) (GRADE: high)
- SAE: RR 1.39 (1.14 to 1.69) (GRADE: moderate)

^{177}Lu-PSMA-617 versus cabazitaxel (total n=200)
- PFS: HR 0.63 (0.46 to 0.86) (GRADE: low)
- SAE: RR 0.73 (0.18 to 1.04) (GRADE: very low)

^{177}Lu-PSMA-617 versus docetaxel (total n=40)
- PFS: HR 0.90 (0.46 to 1.77) (GRADE: very low)
- SAE: RR 0.60 (0.27 to 1.34) (GRADE: very low)

Treatment with ^{177}Lu-PSMA-617 plus SoC therapy prolonged overall and progression-free survival with median four and five months, respectively, compared with SoC alone, but increased the risk of severe adverse events ≥grade 3 in patients previously treated with hormone therapy and taxane-based chemotherapy. We have high and moderate confidence in these results. ^{177}Lu-PSMA-617 prolonged progression-free survival and reduced the risk of severe adverse events ≥3 more than cabazitaxel in patients previously treated with docetaxel. However, we have low and very low confidence in these results. There is seemingly no difference in progression-free survival when comparing ^{177}Lu-PSMA-617

Title:
^{177}Lu-PSMA-617 for the treatment of metastatic castration resistant prostate cancer

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Type of publication:
Health technology assessment (HTA)

Doesn't answer everything:
We do not address ethical or legal aspects related to ^{177}Lu-PSMA-617 treatment of mCRPC

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with docetaxel in patients who were treatment-naïve, but ^{177}Lu-PSMA-617 reduced the risk of severe adverse events ≥3 more than docetaxel. However, we have very low confidence in these results. The most common adverse events associated with ^{177}Lu-PSMA-617 were fatigue, dry eyes and mouth, and pain. The incidence of more serious adverse events such as nephrotoxicity, was low.

Patients' expectation towards ^{177}Lu-PSMA-617 is first and foremost as a new option for life prolonging treatment for mCRPC. An implementation of ^{177}Lu-PSMA-617 in Norway will likely affect the current organisation and allocation of resources. Furthermore, implementation must ensure that the treatment is managed in line with the Norwegian radiation protection legislation.

Our cost-effectiveness analysis shows that treatment with ^{177}Lu-PSMA-617 together with SoC is more effective, but also more costly than SoC alone in mCRPC patients who previously have been treated with anti-androgen therapy and taxane-based chemotherapy. The incremental cost-effectiveness ratio (ICER) was NOK [redacted] per quality adjusted life year (QALY). The absolute shortfall for patients with mCRPC is equal to 11.67 QALYs.

Executive summary (English)

Introduction

Prostate cancer is the most common cancer type among Norwegian men. In 10-20% of these patients, the cancer will advance to metastatic, castration resistant prostate cancer (mCRPC). As mCRPC is incurable, the treatment options are limited to palliative therapy, using radiation and chemotherapy to manage symptoms and prolong life. Radioligand therapy (RLT) is increasingly being used for treating various malignancies. RLT for mCRPC uses the radionuclide lutetium-177 labelled with a binding ligand for prostate-specific membrane antigen (PSMA). ^{177}Lu-PSMA-617 was approved in both USA and Europe in 2022. The product is called Pluvicto™ (Novartis), and the drug name is formally called "lutetium (177Lu) vipivotide tetraxetan". Pluvicto™ is indicated for use in patients with progressive PSMA-positive mCRPC who previously have been treated with hormone therapy and taxane-based chemotherapy and is meant to be a supplement to life prolonging treatment.

Objective

To assess the clinical efficacy, safety, and cost-effectiveness of ^{177}Lu-PSMA-617 treatment of mCRPC with of implementing this treatment in Norway, in a health technology assessment (HTA). Important aspects linked to radiation safety, organisational implications and patient perspectives on ^{177}Lu-PSMA-617 is also included in this work.

Efficacy and safety

Method

We identified relevant publications from randomised controlled trials (RCTs) through a systematic search. Our selection criteria included men over 18 years diagnosed with mCRPC, and treatment with the radionuclide lutetium-177 labelled with the specific ligand PSMA-617. We had no limitations as to the possible comparators. The main efficacy outcome was survival, i.e., overall survival and progression free survival, and safety outcome was severe adverse events ≥grade 3. The included studies were critically appraised using the Cochrane Risk of Bias tool. We assessed the certainty of evidence for all outcomes using the GRADE approach (Grading of Recommendations Assessment,

Development and Evaluation), expressing the certainty as high, moderate, low, or very low, depending on the level of confidence we have in the effect estimates. The results are mainly presented as hazard ratios (HR) and risk ratios (RR) with 95% confidence intervals (CI).

Results

We included three RCTs that compared the effect of ^{177}Lu-PSMA-617, either alone or in combination with standard of care therapy[1], to different comparators, i.e., docetaxel (Satapathy 2021), cabazitaxel (TheraP: Hofman 2021), or standard of care therapy[1] (VISION: Sartor 2021). The study populations included 40 (Satapathy 2021), 200 (TheraP: Hofman 2021), and 831 (VISION: Sartor 2021) participants, respectively. The studies also varied with respect to the participants' previous treatments, from chemotherapy-naïve patients (Satapathy 2021), previous treatment with docetaxel and cabazitaxel being the next possible treatment (TheraP: Hofman 2021), to previous treatment with one approved anti-androgen therapy and 1-2 taxane-based chemotherapy regimens (VISION: Sartor 2021). Due to the limited number of studies, as well as the above-mentioned variation between the studies, we did not perform a meta-analysis, and their results are therefore not directly comparable.

Data on overall survival was only presented in the VISION study, which showed that treatment with ^{177}Lu-PSMA-617 plus standard of care therapy[1] prolonged survival with four months when compared with standard of care therapy[1] alone (median 15.3 months versus median 11.3 months), and this result was statistically significant; HR 0.62 (0.52 to 0.74) (GRADE: high). For progression-free survival, treatment with ^{177}Lu-PSMA-617 plus standard of care therapy[1] prolonged survival with 5.5 months when compared with standard of care therapy[1] alone (median 8.7 months versus median 3.4 months), and this result was statistically significant; HR 0.40 (0.31 to 0.51) (GRADE: high). When compared with cabazitaxel, treatment with ^{177}Lu-PSMA-617 overall prolonged progression-free survival, and this result was also statistically significant; HR 0.63 (0.46 to 0.86) (GRADE: low). However, this difference was not evident in the median progression-free survival time of 5.1 months in the ^{177}Lu-PSMA-617 group versus 5.1 months in the cabazitaxel group.[2] When compared with docetaxel, treatment with ^{177}Lu-PSMA-617 had little or no effect on progression-free survival; HR 0.90 (0.46 to 1.77) (GRADE: very low).

In terms of safety, treatment with ^{177}Lu-PSMA-617 plus standard of care therapy[1] increased the risk of severe adverse events ≥grade 3 when compared with standard of care therapy[1] alone, and this result was statistically significant; RR 1.39 (1.14 to 1.69) (GRADE: moderate). When compared with cabazitaxel, treatment with ^{177}Lu-PSMA-617 reduced the risk of severe adverse events ≥grade 3, but this result was not statistically significant; RR 0.73 (0.18 to 1.04) (GRADE: very low). When compared with docetaxel, treatment with ^{177}Lu-PSMA-617 reduced the risk of severe adverse events ≥grade 3, but

[1] The standard of care therapy in the VISION study was not permitted to include the use of any cytotoxic chemotherapeutic agent (e.g., taxanes), systemic radioisotopes (e.g., radium-223), immunotherapy, or drugs that were considered investigational at the start of the study (e.g., olaparib).

[2] The progression-free survival at 12 months however, was 12% in the ^{177}Lu-PSMA-617 group and 3% in the cabazitaxel group (TheraP: Hofman 2021)

this result was not statistically significant; RR 0.60 (0.27 to 1.34) (GRADE: very low). The most common adverse events associated with ^{177}Lu-PSMA-617 treatment were fatigue, dry eyes and mouth, and pain. The overall incidence of more serious adverse events such as nephrotoxicity, was low.

Health economics

Methods

In the health economic evaluation, we performed a cost-utility analysis (CUA) comparing ^{177}Lu-PSMA-617 plus standard of care therapy with standard of care therapy alone as treatment options in mCRPC. A partitioned survival analysis was developed and analysed in TreeAge Pro Healthcare® 2023. The efficacy input in the model was based on the survival and safety data from the VISION trial (Sartor 2021). Incremental cost-effectiveness rate (ICER) was estimated from a modified Norwegian health care perspective, incorporating all pertinent costs and health outcomes expressed in 2023 Norwegian kroner (NOK) and quality-adjusted life-years (QALYs). Both costs and effects were discounted at an annual rate of 4%. Probabilistic sensitivity analyses (ProbPSA), as well as a series of one-way sensitivity analyses were conducted to handle uncertainties in the model parameters. In line with the Government White Paper on priority setting (Meld. St. 34 2015-2016), we estimated the absolute shortfall for patients with mCRPC to quantify the severity criterion. Additionally, the budget impact of introducing ^{177}Lu-PSMA-617 in combination with standard of care as a treatment option for mCRPC patients in Norway, was estimated.

Results

The results of the cost-utility analysis in the base case scenario show that treatment with ^{177}Lu-PSMA-617 plus standard of care therapy patients with mCRPC is associated with higher QALY-gain (incremental QALYs: 0.44) and higher costs (incremental costs: NOK [redacted]) when compared to standard of care therapy alone. The resulting incremental cost-effectiveness ratio (ICER) is equal to NOK [redacted] per QALY. These results are most sensitive to changes in the parameters of survival functions as well as the price of ^{177}Lu-PSMA-617.

The calculated absolute shortfall for patients with mCRPC is equal to 11.67 quality-adjusted life-years, which implies that these patients loose on average 11.67 good years of life (defined as QALYs) compared to men of their age in the general population.

Results of the budget impact analysis show that the incremental annual total cost of introducing ^{177}Lu-PSMA-617 plus standard of care therapy for patients with mCRPC will reach NOK [redacted] over five years.

Radiation safety and legislation

Implementation of ^{177}Lu-PSMA-617 as a treatment option in Norway is associated with radiation safety aspects. The requirements in Norwegian radiation protection legislation must be implemented to reduce the risk of unintended exposure of staff, public and environment. Aspects about radiation protection will also have organisational or health

economic consequences. Implementation of ^{177}Lu-PSMA-617 is associated with an increase in patients treated with radiopharmaceuticals. This will therefore challenge amongst others waste management, capacity of patient room, dosimetry and personnel resources. ^{177}Lu-PSMA-617 treatment may be associated with some radiation toxicity to the organs at risk. However, the risk for long-term radiation effects, like radiation-induced malignancy, is neglectable for this patient group, due to the short life expectancy.

Organisational aspects

^{177}Lu-PSMA-617 will be a much-anticipated supplement to the existing treatment of mCRPC in Norway. With an estimated 400-500 new mCRPC patients per year, an average of 4.46 treatments with ^{177}Lu-PSMA-617 per patient per year, will lead to about 2 200 treatments in total per year. As such, the health-services need capacity for this patient load in terms of the treatment itself, but also treatment-related measures, including imaging, haematology, and radiation hygiene. Furthermore, necessary resources will also include staffing, equipment, and facilities in line with radiation safety requirements. Resource requirements are likely to depend on whether the ^{177}Lu-PSMA-617 treatment is provided in a centralised model (only university hospitals) or a decentralised model (university hospitals as well as local hospitals). Expert representatives have advocated for the treatment to be given in an outpatient setting. If the ^{177}Lu-PSMA-617 treatment is to be implemented for mCRPC in Norway, experts should be consulted to consider the organisational matters more in depth.

Patient perspectives

The patient group eligible for ^{177}Lu-PSMA-617 treatment are men with a relatively large spread in age, in different life situations, with diverse backgrounds, and with various preferences for how they want their life to be. Expectations related to the ^{177}Lu-PSMA-617 treatment may vary among patients. Overall, there is a high expectation of ^{177}Lu-PSMA-617, as a new option for life prolonging treatment for mCRPC when other treatments have not worked. Patients also expect that the proposed treatment will reduce the metastatic disease, thereby relieving pain and lessen the use of pain medications. By reducing the symptom burden and symptom treating medication, the treatment may have a positive impact on the patients' quality of life and result in better function and less use of municipal services.

Discussion

The work in this HTA have been executed in a systematic manner and in accordance with our project plan. However, our report is limited in having included only three RCTs; VISION (Sartor 2021), TheraP (Hofman 2021), and Satapathy 2021. The VISION study was the only study to report results on overall survival. We are aware that the TheraP study also have reported data on overall survival, but as these results were published in a conference abstract, we chose to exclude it from our HTA.

The three included studies differed in terms of study populations. First, the inclusion criteria varied between the included studies, causing the study participants to be in different stages of their mCRPC treatment plan. Second, the studies were conducted in various countries, causing the study populations to differ in terms of race and ethnicities, which may (in part) influence morbidity and mortality of prostate cancer. As such, the results from the studies with predominantly Caucasian patient population, i.e., VISION and TheraP, will likely be most relevant to a Norwegian setting. Third, the three studies were also powered differently according to their main outcomes, with the VISION study being the only study with sufficient power for assessing overall survival. Although treatment with ^{177}Lu-PSMA-617 in combination with standard of care therapy showed greater risk of severe adverse events ≥3 compared with standard of care therapy alone, the most common adverse events related to ^{177}Lu-PSMA-617 are mostly mild. Furthermore, long-term effects such as radiation-induced malignancies probably have little relevance as the patient population has a short life expectancy.

While cabazitaxel is considered the most relevant treatment alternative for patients with mCRPC in the Norwegian clinical practice, due to unavailability of good quality complete data that directly compare ^{177}Lu-PSMA-617 with cabazitaxel, we chose to base efficacy input in our cost-effectiveness analysis on the VISION trial. This was the only study we regarded as high certainty evidence for main outcomes that shaped our model, with data available for both the overall and progression-free survival. We assumed an outpatient setting for treatment with ^{177}Lu-PSMA-617 in our analyses. Willingness to pay for additional quality-adjusted life-year is not officially defined in Norway, we therefore abstained from concluding about cost-effectiveness, as well as from performing a net benefits analysis.

In the decision-making process, the sections on clinical effect and health economics should be considered together in order to evaluate the treatment under consideration in terms of the three criteria (benefits, resource use and severity) applicable in priority setting in the Norwegian health care system. The clinical efficacy and safety section of this report provides the necessary information for establishing the clinical benefit of treatments in terms of gains in overall and progression-free survival, and safety considerations. The health economic evaluation section combines that information in the health economic model with resource use in treatments, to determine incremental costs in relation to health gains measured in terms of QALYs, as well as severity, measured as absolute shortfall.

Conclusion

Treatment with ^{177}Lu-PSMA-617 plus standard of care therapy[1] prolongs overall and progression-free survival more than standard of care therapy[1] alone but has a higher risk of severe adverse events ≥grade 3. However, ^{177}Lu-PSMA-617 treatment has shown mostly mild adverse events, and long-term radiation-induced malignancies can be disregarded due to short life expectancy for this population. For patients, the main expectation regarding ^{177}Lu-PSMA-617 treatment is first and foremost as a new option for life prolonging treatment for mCRPC. In terms of health economics, we assumed that the ^{177}Lu-PSMA-617 would take place in an outpatient setting. The cost-utility analysis indicates that treatment with ^{177}Lu-PSMA-617 is more effective, but also more costly

than standard of care therapy alone. Implementation of ^{177}Lu-PSMA-617 treatment in Norway will likely affect the current organisation and allocation of resources that needs to be further explored.

Hovedbudskap

^{177}Lu-PSMA-617 er en ny radioligandterapi som brukes for behandling av metastatisk kastrasjonsresistent prostatakreft (mCRPC). Legemidlet består av radionukliden lutetium-177 koblet til liganden PSMA-617 for spesifikk binding til prostata-spesifikt membranantigen (PSMA), som uttrykkes i prostatakreftceller.

I denne metodevurderingen inkluderte vi tre randomiserte kontrollerte studier som sammenliknet effekten av ^{177}Lu-PSMA-617, enten alene eller i kombinasjon med standard behandling, med docetaksel, kabazitaksel, eller standard behandling alene. Hovedutfallsmålet var overlevelse, det vil si totaloverlevelse (OS), i tillegg til progresjonsfri overlevelse (PFS). Utfallsmål på sikkerhet var alvorlige uønskede hendelser (SAE) ≥grad 3. Resultatene er presentert som hasard ratio (HR) og relativ risiko (RR), sammen med en vurdering av vår tillit til resultatene (GRADE).

^{177}Lu-PSMA-617 + standard behandling versus standard behandling alene

- OS: HR 0,62 (0,52 til 0,74) (GRADE: høy)
- PFS: HR 0,40 (0.31 til 0,51) (GRADE: høy)
- SAE ≥grad 3: RR 1,39 (1,14 til 1,69) (GRADE: moderat)

^{177}Lu-PSMA-617 versus kabazitaksel

- PFS: HR 0,63 (0,46 til 0.86) (GRADE: lav)
- SAE ≥grad 3: RR 0,73 (0,18 to 1,04) (GRADE: veldig lav)

^{177}Lu-PSMA-617 versus docetaksel

- PFS: HR 0,90 (0,46 to 1,77) (GRADE: veldig lav)
- SAE ≥grade 3: RR 0,60 (0,27 to 1,34) (GRADE: veldig lav)

Behandling med ^{177}Lu-PSMA-617 i tillegg til standard behandling forlenget totaloverlevelse og progresjonsfri overlevelse med fire og fem måneder, sammenliknet med standard behandling alene, men gav høyere risiko for alvorlige uønskede hendelser ≥grade 3 blant pasienter tidligere behandlet med hormonterapi og taksan-basert kjemoterapi. Vi har høy og moderat tiltro til disse resultatene. ^{177}Lu-PSMA-617 forlenget progresjonsfri overlevelse og reduserte risikoen for alvorlige uønskede hendelser ≥grad 3 mer enn kabazitaksel,

Tittel:
^{177}Lu-PSMA-617 til behandling av metastatisk kastrasjonsresistent prostatakreft

Publikasjonstype:
Fullstendig metodevurdering

Svarer ikke på alt:
Vi har ikke sett på etiske eller juridiske aspekter knyttet til behandling med ^{177}Lu-PSMA-617 ved mCRPC

Hvem står bak denne publikasjonen?
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum for nye metoder

Når ble litteratursøket utført?
Søk etter studier ble avsluttet August 2022.

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blant pasienter tidligere behandlet med docetaksel. Vi har imidlertid lav og veldig lav tiltro til disse resultatene. Det virker ikke å være noen forskjell i progresjonsfri overlevelse ved sammenlikning av ^{177}Lu-PSMA-617 og docetaksel i pasienter som ikke tidligere hadde vært behandlet med kjemoterapi. Vi har imidlertid veldig lav tiltro til disse resultatene. De vanligste uønskede hendelsene assosiert med ^{177}Lu-PSMA-617 behandling var fatigue, tørr munn og tørre øyne, og smerte. Insidensen av mer alvorlige uønskede hendelser, som nefrotoksisitet, var lav.

Pasienters forventning til ^{177}Lu-PSMA-617 er først og fremst som en ny livsforlengende behandling ved mCRPC. Implementering av ^{177}Lu-PSMA-617 i Norge vil sannsynligvis påvirke den nåværende organiseringen og allokeringen av ressurser. Videre må implementering sikre at behandlingen foregår i tråd med norske lover og forskrifter om strålevern.

Vår helseøkonomisk vurdering viser at behandling med ^{177}Lu-PSMA-617 er både mer effektiv og mer kostbar enn standard behandling alene, med en inkrementell kostnad-nyttebrøk (ICER) på NOK [redacted] per kvalitetsjusterteleveår (QALY). Absolutt prognosetap for aktuelle pasienter er beregnet til 11,67 QALYs.

Sammendrag

Innledning

Prostatakreft er den mest vanlige formen for kreft blant norske menn. I 10-20% av tilfellene vil kreften utvikle seg til metastatisk kastrasjonsresistent prostatakreft (mCRPC). Ettersom mCRPC er uhelbredelig, er behandlingsmulighetene begrenset til palliasjon: stråling og kjemoterapi benyttes for symptomlindring og livsforlengende behandling. Radioligandterapi (RLT) er i økende grad brukt i behandling av ulike krefttyper. RLT-behandling av mCRPC bruker radionukliden lutetium-177 bundet til en ligand for prostataspesifikt, membranantigen (PSMA). ^{177}Lu-PSMA-617 fikk markedsføringstillatelse i USA og Europa i 2022. Produktet heter Pluvicto™ (Novartis), og virkestoffnavnet er formelt lutetium (177Lu) vipivotide tetraxetan. Pluvicto™ er indisert for pasienter med progressiv PSMA-positiv mCRPC som tidligere har vært behandlet med hormonterapi og taksanbasert kjemoterapi, og er ment som et tillegg til livsforlengende behandling.

Hensikt

Å utrede effekt og sikkerhet ved bruk av ^{177}Lu-PSMA-617 til behandling av mCRPC, samt helseøkonomiske konsekvenser av å innføre behandlingen i Norge, i en fullstendig metodevurdering. Viktige aspekter knyttet til strålevernshensyn, organisatoriske implikasjoner og pasientperspektiver ved ^{177}Lu-PSMA-617 behandling er også inkludert i arbeidet.

Effekt og sikkerhet

Metode

Vi identifiserte relevante publikasjoner fra randomiserte, kontrollerte studier (RCTer) gjennom et systematisk søk. Inklusjonskriteriene var menn over 18 år diagnostisert med mCRPC, som fikk behandling med radionukliden lutetium-177 koblet til den spesifikke liganden PSMA-617. Vi hadde ingen begrensninger med hensyn på mulige komparatorer (behandling i kontroll-arm). Det viktigste utfallsmålet for effekt var overlevelse, det vil si totaloverlevelse og progresjonsfri overlevelse, og utfallsmålet for sikkerhet var forekomst av alvorlige uønskede hendelser ≥grad 3. Vi vurderte risiko for systematiske skjevheter i alle inkluderte studier ved hjelp av *Cochrane Risk of Bias tool*. Vi vurderte også tillit til resultatene ved hjelp av GRADE-tilnærmingen (*Grading of Recommendations Assessment, Development and Evaluation*), som uttrykkes som høy, middels, lav, og svært

lav, avhengig av hvor stor tillit vi har til effektestimatene. Resultatene presenteres hovedsakelig som hasard ratio (HR) og relativ risiko (RR) med 95 % konfidensintervall (KI).

Resultater

Vi inkluderte tre RCTer som sammenliknet effekten av ^{177}Lu-PSMA-617, enten alene eller i kombinasjon med standard behandling[3], med ulike komparatorer; docetaksel (Satapathy 2021), kabazitaksel (TheraP: Hofman 2021), eller standard behandling[3] (VISION: Sartor 2021). Populasjonsstørrelsen i studiene var henholdsvis 40 (Satapathy 2021), 200 (TheraP: Hofman 2021) og 831 deltakere (VISION: Sartor 2021). Studiene varierte også med hensyn på studiedeltakernes tidligere behandlinger, fra pasienter ubehandlet med kjemoterapi (Satapathy 2021), til tidligere behandling med docetaksel hvor kabazitaksel var neste mulige behandling (TheraP: Hofman 2021), til tidligere behandling med én godkjent antiandrogen behandling, og 1-2 taksan-baserte kjemoterapeutiske regimer (VISION: Sartor 2021). På grunn av det begrensede antallet studier, i tillegg til de overnevnte variasjonene mellom studiene, valgte vi ikke å gjennomføre en metaanalyse, og resultatene fra dem bør ikke sammenliknes direkte.

Behandling med ^{177}Lu-PSMA-617 i kombinasjon med standard behandling[3] forlenget totaloverlevelsen med fire måneder sammenliknet med standard behandling[3] alene (median 15,3 måneder versus median 11,3 måneder), og resultatet var statistisk signifikant; HR 0,62 (0,52 til 0,74) (GRADE: høy tiltro). Behandling med ^{177}Lu-PSMA-617 i kombinasjon med standard behandling[3] forlenget progresjonsfri overlevelse med 5,5 måneder sammenliknet med standard behandling[3] alene (median 8,7 måneder versus median 3,4 måneder), og resultatet var statistisk signifikant; HR 0,40 (0,31 til 0,51) (GRADE: høy). Sammenliknet med kabazitaksel, forlenget behandling med ^{177}Lu-PSMA-617 totalt sett den progresjonsfrie overlevelsen, og resultatet var også statistisk signifikant; HR 0,63 (0,46 til 0,86) (GRADE lav tiltro). Denne forskjellen var imidlertid ikke synlig ved median progresjonsfri overlevelse på 5,1 måned i ^{177}Lu-PSMA-617-gruppen versus 5,1 måned i kabazitaxel-gruppen.[4] Sammenliknet med docetaksel hadde behandling med ^{177}Lu-PSMA-617 liten eller ingen effekt på progresjonsfri overlevelse,; HR 0,90 (0,46 til 1,77) (GRADE: veldig lav tiltro).

Behandling med ^{177}Lu-PSMA-617 i kombinasjon med standard behandling økte risikoen for alvorlige uønskede hendelser ≥grad 3 sammenliknet med standard behandling alene, og resultatet var statistisk signifikant; RR 1,39 (1,14 til 1,69) (GRADE: moderat tiltro). Sammenliknet med kabazitaksel, reduserte behandling med ^{177}Lu-PSMA-617 risiko for alvorlige uønskede hendelser ≥grad 3, men resultatet var ikke statistisk signifikant; RR 0,73 (0,18 to 1,04) (GRADE: veldig lav tiltro). Sammenliknet med docetaksel, reduserte

[3] I standard behandling i VISION studien var det ikke tillatt brukt cytotoksisk kjemoterapeutikum (f.eks. taksaner), systemiske radioisotoper (f.eks. radium-223), immunterapi, eller legemidler som var under utredning ved starten av studien (f.eks. olaparib).

[4] Progresjonsfri overlevelse ved 12 måneder var 12% i 177Lu-PSMA-617-gruppen og 3% i kabazitaxel-gruppen (TheraP: Hofman 2021).

behandling med ^{177}Lu-PSMA-617 risiko for alvorlige uønskede hendelser ≥grad 3, men resultatet var ikke statistisk signifikant; RR 0,60 (0,27 to 1,34) (GRADE: veldig lav tiltro).

Helseøkonomi

Metode

I den helseøkonomiske evalueringen utførte vi en kostnad-nytteanalyse (CUA) for ^{177}Lu-PSMA-617 i kombinasjon med standard behandling, sammenliknet med standard behandling alene som behandlingsalternativer for pasienter med mCRPC. Vi utviklet og brukte en overlevelsesanalyse (partitioned survival analysis) i TreeAge Pro Healthcare® 2023. Input-data for effekt i modellen var basert på overlevelsesdata fra VISION studien (Sartor 2021). Kostnad-effekt-brøker (incremental-cost-effectiveness-ratios, ICERs) ble estimert ut fra et modifisert norsk helsetjenesteperspektiv, hvor alle inkluderte relevante kostnader uttrykkes i 2023 norske kroner (NOK) og helseutfall i kvalitetsjusterte leveår (QALYs). Vi brukte en diskonteringsfaktor på 4% for både kostnader og helsegevinster. Både probabilistisk sensitivitetsanalyse (PSA) og en rekke enveis sensitivitets- og scenarioanalyser ble gjennomført for å håndtere usikkerheten i modellparametere. Vi estimerte absolutt prognosetap for pasienter med mCRPC i tråd med stortingsmelding om prioriteringskriterier (Meld. St. 34 2015-2016). I tillegg beregnet vi budsjettkonsekvens for implementering av ^{177}Lu-PSMA-617 i kombinasjon med standard behandling som behandlingsalternativ for pasienter med mCRPC i Norge.

Resultater

Resultatene fra kostnad-nytteanalysen i hovedanalysen viser at behandling av pasienter med mCRPC med ^{177}Lu-PSMA-617 i kombinasjon med standard behandling er forbundet med høyere QALY-gevinst (inkrementelle QALYs: 0,44), og høyere kostnader (inkrementell kostnad: NOK [redacted]) sammenliknet med standard behandling alene. Som et resultat blir den inkrementelle kostnadseffektivitetsratioen (ICER) lik [redacted] NOK/QALY. Disse resultatene er mest sensitive for endringer i estimater for overlevelsesfunksjoner og pris på behandling med ^{177}Lu-PSMA-617. Kalkulert absolutt prognosetap for pasienter med mCRPC er lik 11,67 QALYs.

Resultatene av budsjettkonsekvensanalysen viser at de inkrementelle årlige totale kostnadene knyttet til introduksjon av ^{177}Lu-PSMA-617 i kombinasjon med standard behandling for pasienter med mCRPC kan nå NOK [redacted] i løpet av fem år.

Strålevern og strålingsrelatert lovverk

Implementering av ^{177}Lu-PSMA-617 som standard behandling i Norge er forbundet med aspekter relatert til strålevern. Kravene i strålevernregelverket må implementeres for å redusere risikoen for uønsket eksponering av ansatte, allmenheten og miljø. Strålevernsaspekter vil også føre med seg organisatoriske og helseøkonomiske konsekvenser. Implementering av ^{177}Lu-PSMA-617 er forbundet med en økning i antall pasienter som blir behandlet med radiofarmaka. Dette vil blant annet skape utfordringer knyttet til avfallshåndtering, romkapasitet, dosimetri og personalressurser. Behandling med ^{177}Lu-PSMA-617 kan føre til noe stråletoksisitet for risikoorganer. Risikoen for

seneffekter, som stråleindusert kreft, er derimot neglisjerbar for denne pasientgruppen, på grunn av kort forventet levetid.

Organisatoriske aspekter

^{177}Lu-PSMA er et etterlengtet tillegg til eksisterende behandling for mCRPC i Norge. Med en estimert populasjon på 400-500 nye mCRPC pasienter per år, vil gjennomsnittlig 4,46 behandlinger med ^{177}Lu-PSMA-617per pasient per år, føre til cirka 2200 behandlinger totalt per år. Helsetjenesten må dermed ha tilstrekkelig kapasitet for denne pasientbelastningen med tanke på selve behandlingen, men også behandlingsrelaterte målinger, inkludert billedtagning, hematologi og strålevern. Nødvendige ressurser vil også inkludere personell, utstyr og fasiliteter i tråd med krav til strålevern. Ressursbehovet vil avhenge av om ^{177}Lu-PSMA-617 behandlingen skal tilbys sentralisert (ved universitetssykehus) eller desentralisert (ved universitetssykehus i tillegg til lokalsykehus). Ekspertrepresentanter har tatt til orde for at behandlingen skal gis poliklinisk. Dersom ^{177}Lu-PSMA-617 behandlingen skal implementeres i Norge, bør eksperter konsulteres for videre å vurdere organisatoriske aspekter ved innføring.

Pasient perspektiver

Pasientgruppen som er aktuell for ^{177}Lu-PSMA-617 behandling er menn med relativt stor spredning i alder, i ulike livssituasjoner, med mangfoldig bakgrunn, og med ulike preferanser for hvordan de ønsker at livet skal være. Deres forventninger knyttet til ^{177}Lu-PSMA-617 behandlingen kan være ulike. Samlet sett er det høye forventninger til ^{177}Lu-PSMA-617 som et nytt tilbud om livsforlengende behandling for mCRPC når annen behandling ikke har virket. Pasientene forventer også at den foreslåtte behandlingen vil redusere metastaser, og dermed lindre smerte og redusere bruken av smertestillende medisiner. Ved å redusere symptombyrden og behovet for smertestillende medikamenter, kan den foreslåtte behandlingen ha en positiv innvirkning på pasientenes livskvalitet og funksjon og også bidra til mindre bruk av kommunale tjenester.

Diskusjon

Arbeidet i denne metodevurderingen er gjennomført på systematisk vis og i henhold til prosjektplanen. Det begrenses likevel av vi kun har inkludert tre RCTer: VISION (Sartor 2021), TheraP (Hofman 2021) og Satapathy 2021, og VISION studien var den eneste som rapporterte data på totaloverlevelse. Vi er klar over at det finnes data på totaloverlevelse fra TheraP studien, men ettersom disse ble publisert i et konferansesammendrag valgte vi å ekskludere det fra denne metodevurderingen. Studiepopulasjonene i hver av de inkluderte studiene varierer på flere ulike måter. For det første, ulike inklusjonskriterier gjør at studiene har inkludert populasjoner som er i ulike stadium i behandlingen. For det andre, ble studiene gjennomført i ulike land, og studiepopulasjonene varierer dermed i etnisitet og rase, som igjen er vist å kunne være en bidragende faktor med hensyn på morbiditet og mortalitet ved prostatakreft. På grunn av dette vil resultatene fra studier med hovedsakelig kaukasisk studiepopulasjon (VISION og TheraP) være mest

relevante i en norsk setting. For det tredje, varierte styrkeberegningen for de tre inkluderte studiene i henhold til deres hovedutfallsmål, hvor VISION studien var den eneste med tilstrekkelig statistisk styrke for å kunne rapportere på totaloverlevelse. Selv om behandling med ^{177}Lu-PSMA-617 har vist å gi økt risiko for alvorlige uønskede hendelser grad ≥ 3, er de vanligste uønskede hendelsene stort sett av mild karakter. Langtidseffekter som strålingsindusert malignitet har sannsynligvis liten relevans ettersom pasientpopulasjonen har lav forventet levetid.

Til tross for at cabazitaxel anses som det mest relevante behandlingsalternativet for pasienter med mCRPC i norsk klinisk praksis, valgte vi å basere vår kostnadseffektivitetsanalyse på VISION studien på grunn av manglende tilgjengelighet av data av god kvalitet som direkte sammenligner ^{177}Lu-PSMA-617 med cabazitaxel. Dette var den eneste studien ansett som høy kvalitet for utfall som la grunn til modellen vår, med data tilgjengelig for både total- og progresjonsfri overlevelse. Betalingsviljen for QALYs er ikke offisielt definert i Norge, vi avsto derfor fra å konkludere om kostnadseffektivitet, samt fra å utføre en netto nytteanalyse.

I beslutningsprosessen bør avsnittene om klinisk effekt og helseøkonomi vurderes samlet for å vurdere behandlingen i forhold til de tre prioriteringskriteriene (nytte, ressursbruk og alvorlighetsgrad) som gjelder i det norske helsevesenet. Den kliniske effekten og sikkerheten gir den nødvendige informasjonen for å fastslå klinisk nytte av behandlingen i form av gevinster i total- og progresjonsfri overlevelse, og sikkerhetsprofil. Den helseøkonomiske evalueringen kombinerer denne informasjonen med ressursbruk i en modell, for å fastslå kostander i forhold til helsegevinster (målt som QALYs) samt alvorlighetsgrad, målt i absolutt prognosetap.

Konklusjon

Behandling med ^{177}Lu-PSMA-617 i kombinasjon med standard behandling[3] forlenger totaloverlevelse og progresjonsfri overlevelse mer enn standard behandling alene hos pasienter med mCRPC, men gir høyere risiko for alvorlige uønskede hendelser ≥grade 3. ^{177}Lu-PSMA-617 behandling er vist å ha stort sett milde uønskede hendelser, og selv om behandlingen kan føre til noe stråletoksisitet for risikoorganer, er risikoen for seneffekter som stråleindusert kreft neglisjerbar på grunn av kort forventet levetid for denne pasientgruppen. Pasienters forventning til ^{177}Lu-PSMA-617 behandling er først og fremst som en ny livsforlengende behandling ved mCRPC. I den helseøkonomiske analysen antok vi at ^{177}Lu-PSMA-617 vil utføres poliklinisk. Kostnad-nytteanalysen indikerer at ^{177}Lu-PSMA-617 er mer effektiv, men også dyrere enn standard behandling alene. Implementering av ^{177}Lu-PSMA-617 behandling i Norge vil trolig påvirke nåværende organisering og allokering av ressurser, og bør utforskes ytterligere i en egen prosess.

Preface

This Health Technology Assessment (HTA) was commissioned by the Regional Health Authorities: The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Bestillerforum for nye metoder).

In August 2018, the Regional Health Authorities (RHA) forum assessed a proposal for a new national assessment regarding the use of ^{177}Lu-PSMA for treating prostate cancer. The National Institute of Public Health (NIPH) was commissioned to perform a single technology assessment based on documentation package by the Finnish company MAP Medical Technologies Oy. The commission was later changed from a single technology assessment to a heath technology assessment (HTA) and was put on hold until survival data was published. The work on this HTA was officially initiated in June 2022 (see *Appendix 12* for progress log).

This HTA includes assessments of clinical efficacy and safety, health economy, organisational aspects, radiation hygiene aspects and patient perspectives with regards to using with ^{177}Lu-PSMA-617 in the treatment of metastatic castration resistant prostate cancer.

The internal working group consisted of:

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- Ingeborg Beate Lidal, *senior advisor*
- Beate Charlotte Fagerlund Kvist, *health economist*
- Anna Stoinska-Schneider, *health economist*
- Gunn Eva Næss, *information specialist*
- Martin Robert Lerner, *unit director*

In addition, the following persons have also contributed to the work:

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- Eva Godske Friberg, *Senior Medial Application Adviser, Norwegian Radiation and Nuclear Safety Authority*
- Daniel Ask, *patient representative*
- Nick Evans, *patient representative*

Reviewers – internal (at NIPH):

- Kjetil Gundro Brurberg, *unit director*
- Vida Hamidi, *health economist (reviewed the health economy section)*
- Elisabet Vivianne Hafstad, *information specialist (reviewed the search strategy)*

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Conflict of interest

All authors and external group members have declared no potential conflicts of interest. We will emphasise that although the clinical experts and external reviewers have contributed with valuable input and comments, NIPH is responsible for the content of this report. The Norwegian Radiation and Nuclear Safety Authority is responsible for the chapter on Radiation safety and legislative aspects.

Kåre Birger Hagen *Director of Reviews and Health Technology Assessment*	Martin Robert Lerner *Department director*	Ingrid Kristine Ohm *Project coordinator*

Introduction

Description of the disease

Prostate cancer

Prostate cancer is the most common type of cancer to affect Norwegian men (1). Every year, around 5,000 new cases are diagnosed and per December 2021, there were close to 60,000 men living with a prostate cancer diagnosis in Norway (1). The median age at the time of diagnosis is 70 years (2). Prostate cancer is also among the most frequent causes of cancer-related deaths among Norwegian men, with around 1000 deaths each year (1).

Metastatic castration resistant prostate cancer

In 10-20% of patients, the prostate cancer will progress to what is known as *metastatic castration resistant prostate cancer* (mCRPC) (3;4). Normally, prostate cancer cells are dependent on testosterone to grow and develop (5). This feature is targeted through hormone therapy (i.e., castration therapy) by reducing the levels of testosterone in the body, either by blocking the production (through orchiectomy or gonadotropin-releasing hormone-agonists), or by blocking the receptors (using antiandrogens) (5). However, castration resistant cancer will continue to grow regardless of low testosterone levels (5). At this stage of the disease, with the cancer being castration resistant and having metastasized beyond the prostate gland (e.g., to lymph nodes and bone), a curative outcome is no longer possible (6;7). For this patient group, the only available treatment options are palliative therapy i.e., to provide good quality of life for as long as possible (symptom relief, life prolonging) (6;7).

Treatment of mCRPC in Norway

The Norwegian national action program describes the current treatment options for mCRPC (7). In brief, the provided treatment includes the following life-prolonging drugs: anti-androgen therapy with abiraterone or enzalutamide, olaparib (for patients with BRCA1/2 mutations), chemotherapy with docetaxel and cabazitaxel, and systemic treatment with the radioisotope radium-223. The choice of treatment is mainly based on progression of the disease, previous treatment, and tolerability.

Description of the intervention

Targeted radioligand therapy

Targeted radioligand therapy (RLT) is used as a treatment strategy in various malignancies, such as neuroendocrine cancer, leukaemia, and lymphoma (8-10). The treatment principle is similar to that of external radiation therapy or brachytherapy: to use ionizing radiation to kill cancer cells through cytotoxic DNA-damage (11). However, RLT specifically targets cancer cells by linking the radionuclide with a ligand, e.g., a monoclonal antibody (targeted radioimmunotherapy), peptide or small molecule that has high binding affinity to a specific target on malignant cells (10;12;13). This allows for specifically directing the radiation to cancer cells, with minimal harmful effect on surrounding tissue.

^{177}Lu-PSMA

RLT treatment of prostate cancer involves the radionuclide lutetium-177 labelled with a ligand for prostate specific membrane antigen (PSMA). Lutetium-177 makes a good therapy agent for prostate cancer due to its physical properties: it is a medium energy β-emitter (maximum 490 keV), with a tissue range of around 2 mm (8;14). This allows the β-radiation to penetrate and affect the cancer cells, with minimal effect on surrounding tissue. Furthermore, as lutetium-177 is a reactor-made isotope, the relatively long half-life ($t_{1/2}$) of 6.7 days permits transportation from production facility to the clinic (14). In addition to being used for therapeutic purposes, lutetium-177 also emits low-energy γ-radiation that can be used in imaging for diagnostic and dosimetry purposes (8;15).

PSMA is a type II transmembrane glycoprotein which is overexpressed in prostate epithelium, with a large extracellular part that ligands can bind to (16). PSMA is an ideal binding target in RLT as expression levels are low in normal prostate tissue, but high in almost all prostate cancers (17). Cancer aggressiveness, androgen-independence and metastatic disease seem to be related to the level of PSMA expression, as higher levels are seen in more serious forms of prostate cancer than in less aggressive forms (17;18). PSMA is however, not exclusively expressed in prostate cells, as low levels are found in the kidneys, small intestine, and salivary glands (15;19-21). As ^{177}Lu-PSMA will bind specifically to all sites that express PSMA, some radiation will inevitably be delivered to non-malignant tissues that express PSMA (15). An additional factor that makes PSMA a good binding target is its ability to internalise molecules bound to the cell surface, into intracellular endosomes (22). For RLT-treatment, this allows the radionuclide lutetium-177 to be concentrated inside the cell, with resulting precise tumour irradiation (22).

There are several different types of PSMA-ligands, although the most studied are PSMA-I&T (Imaging & Therapy) and PSMA-617 (23). These two ligand types differ in molecular structure (i.e., type of chelator) and have been shown to have somewhat different biodistribution in preclinical trials, although differences in effect have not been shown in clinical studies (23;24).

The RLT drug ^{177}Lu-PSMA-617 is currently marketed as Pluvicto™ (active substance name: lutetium [^{177}Lu] vipivotide tetraxetan), with Novartis being the marketing-authorisation holder (25). Pluvicto™ was first approved in USA by Food and Drug Administration (FDA) in March 2022 (26), and subsequently in Europe by the European

Medicines Agency (EMA) in December 2022 (27). Expert representatives point out that the drug is in clinical use in USA and in several countries in Europe. Pluvicto™ is indicated for use in patients with progressive PSMA-positive mCRPC who previously have been treated with hormone therapy and taxane-based chemotherapy (28). Although formally the drug name is lutetium (^{177}Lu) vipivotide tetraxetan, we have chosen to use "^{177}Lu-PSMA-617" throughout this report to avoid any confusion with what is reported in the literature.

Use of ^{177}Lu-PSMA in Norway

^{177}Lu-PSMA is not in clinical use in Norway as per May 2023. However, the Norwegian Health Authorities have funded ^{177}Lu-PSMA treatment of about 30 Norwegian mCRPC patients abroad, either in Finland or in Germany. Furthermore, two patients have received treatment with ^{177}Lu-PSMA I&T in Norway: one at the University Hospital of North Norway in Tromsø, and one at Haukeland University Hospital in Bergen, either funded by the regional health authorities, or locally by hospital department. Additionally, some patients have received treatment with ^{177}Lu-PSMA abroad in Finland or Germany, at their own expense.

A glossary with abbreviations and explanations of important terms is presented in *Appendix 1*.

Aim

The aim of this HTA is to:

1) Systematically identify, assess and summarize available research regarding efficacy and safety of ^{177}Lu-PSMA-617 in the treatment of mCRPC
2) Assess the cost-effectiveness of introducing ^{177}Lu-PSMA-617 treatment for patients with mCRPC against the priority criteria in Norway
3) Assess organisational aspects, radiation safety aspects, and patient perspectives linked to establishing ^{177}Lu-PSMA-617 as a treatment option in Norway

Efficacy and safety

Methods – efficacy and safety

As prespecified in our protocol (*Appendix 11*), this health technology assessment (HTA) was conducted in accordance with the handbook "Slik oppsummerer vi forskning", by NIPH (29;30). In our protocol, we planned to use a documentation package by Novartis for the efficacy and safety assessment, as well as for the health economy analysis. However, this was conditional on receiving the documentation package in suitable time. When we received the documentation package in mid-December 2022, we were in the process of finishing our data analysis. As such, we chose not to include any studies or results from the documentation package in this HTA, and our work is based solely on studies identified through a systematic search.

Literature search

The systematic literature search was conducted in August 2022. An information specialist performed the search in accordance with the project plan (*Appendix 11*), and another information specialist peer reviewed the search strategy. The search used index terms (Medical Subject Headings and EMTREE terms where appropriate), and free text terms related to the population, generic drug names and study designs of interest (the "PICOS" described in *Table 1*). No restrictions with regards to publication year or language were applied to the search. The bibliographies of selected publications were screened for potentially relevant studies missed by the electronic searches. The search strategies are detailed in *Appendix 2*.

Inclusion criteria

The inclusion criteria are presented in *Table 1* with overall survival being our main outcome.

Table 1: Inclusion criteria

PICOS	Inclusion
Population	Men diagnosed with metastatic castration resistant prostate cancer
Intervention	Radionuclide: Lutetium-177, Ligand: PSMA-617
Comparator	All possible comparators: - Standard of care treatment* - Best supportive care - Placebo - No treatment

Outcome	Efficacy: - Overall survival - Progression-free survival - PSA-level - Time to first skeletal event - Quality of life Safety: Severe adverse events grade ≥3 Serious adverse events
Study design	Randomised controlled trials (RCTs)

**Standard of care treatment could contain, but were not limited to e.g., antiandrogens, chemotherapy, and/or radiation*

Article selection

The studies included in this HTA were selected in a two-step process. In both steps, two persons worked independently, assessing articles against the inclusion criteria (*Table 1*).

In the first step, two persons read all titles and abstracts of the references retrieved by the literature search. We used Rayyan for the title- and abstract screening (31). In the second step, all selected references were read in full text by the same two persons to decide which should be included in the HTA. Any disagreements throughout this work were resolved through discussion.

Risk of bias assessment of included studies

Two researchers independently assessed the methodological quality of the included studies by using the Cochrane Risk of Bias Tool RoB1 for RCTs (32). Each study was rated as being at low, unclear, or high risk of bias on seven domains: selection bias (random sequence generation and allocation bias), performance bias, detection bias, attrition bias, reporting bias, and other bias. Any disagreements were resolved through discussion.

Data extraction

One researcher extracted relevant data from the included full-text articles. A second researcher then verified the extracted data. Disagreements were resolved through discussion. The relevant data is described in *Table 2*.

Table 2: Relevant data extracted from included studies

About	Information extracted
The study	Authors, publication year, study design, country, clinical trial identification number, eligibility criteria, follow-up time, funding source (industry or non-industry).
The participants	For each trial arm and each outcome: numbers of participants randomized; numbers of participants included in analyses; median age; ethnicity; disease severity at baseline; PSA-level at baseline; median time since diagnosis; number of participants who had received previous treatment; number of participants with metastases according to site
The treatments*	For each trial arm: name of treatment (including combinations); posology (incl. dose level, frequency, duration, and route of administration).
The outcomes	For each pairwise comparison and each outcome: name of relative treatment effect estimate (e.g., HR, RR, OR); point estimate; name of measure of precision (e.g., 95% CI, SE, SD); precision (e.g., limits of the 95% CI).

** Interventions and comparators. CI: confidence interval, HR: hazard ratio, OR: odds ratio, RR: risk ratio, SD: standard deviation, SE: standard error*

For one study, we used WebPlotDigitizer to extract data points from figures showing changes over time in the reported quality-of-life index domains (33). We tried to follow the intention-to-treat (ITT) principle and included all patients recruited, and analysed patients in the groups to which they were randomised, where this was possible.

Analyses

We extracted the published data point estimates of hazard ratio and measures of precision (confidence interval; CI) for overall survival, progression-free survival, and first symptomatic skeletal event. For PSA-level and severe adverse events ≥grade 3, we calculated the risk ratios using the number of patients with the event, i.e., ≥50% reduction in PSA-level, and severe adverse events ≥grade 3, and the total number of patients for the two outcomes. For quality of life, we present the results individually, due to the included studies having used different quality of life questionnaires with different measurement properties.

Minimal important difference

A statistically significant result of an intervention in a clinical trial does not necessarily mean that it is a clinically important effect (34). Thus, setting a relevant threshold of what could be considered as an important effect for patients, i.e., a minimal clinically important difference, would help us assess the results of clinical trials (34;35). We did not specify the smallest important difference for the outcomes in our protocol. As such, to set a relevant threshold for our outcomes and population, we consulted with our clinical experts regarding what could be considered a clinically important effect for all our outcomes (overall survival, progression-free survival, PSA-level, first symptomatic skeletal event, severe adverse events ≥grade 3, and quality of life) in patients with mCRPC.

Minimal important difference for survival outcomes

Although any prolonged survival is likely to be meaningful for the individual patient, clinical experts pointed out that interventions that lead to improvements of 2-3 months survival in progression-free survival or overall survival could be defined as clinically important. Based on this, we used the lower survival time (2 months) as the threshold for important difference. We acknowledge that these are opinions, and that others may disagree.

Minimal important difference for non-survival outcomes

Clinical experts suggested that a 20% relative improvement, e.g., a hazard or risk ratio ≤0.8, could be considered as clinically important for our non-survival outcomes, i.e., PSA-level, first symptomatic skeletal event and severe adverse events ≥grade 3. Again, we acknowledge that these are opinions, and that others may disagree.

Minimal important difference for quality of life

For quality of life, we found two papers suggesting that an absolute change in the EORTC QLQ-C30 score of 5-10 could be considered important by patients with different types of cancers (35;36). Based on this, we used the lower absolute score change of 5 as the threshold for important difference.

GRADE: assessing the certainty of evidence

The certainty of evidence for our outcomes was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach in accordance with the GRADE handbook (37). In the GRADE approach, RCTs are as a starting point, considered to provide high quality evidence. The subsequent rating of the quality of evidence may be reduced after further assessment, thereby reducing the confidence of the effect estimate (37). As all the included studies in our HTA are RCTs, our outcomes were set to start out at high certainty of evidence for each treatment regimen. The quality was then further assessed with regards to the following factors: 1) study limitations (risk of bias), 2) inconsistency, 3) indirectness, 4) imprecision, and 5) publication bias (37). Certainty of evidence is classified as in *Table 3*. Two researchers assessed certainty of evidence, and any disagreement were resolved through discussion.

Table 3: GRADE definitions

Quality level (GRADE)	Definition	Symbols
High	We are very confident that the true effect lies close to that of the estimate of the effect	⊕⊕⊕⊕
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	⊕⊕⊕
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	⊕⊕
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	⊕

Standardised statements for the reporting of effect

We also present textual descriptions of effect estimates using standardised statements for the reporting of effects (38). A standardised statement in "plain language" was chosen and adapted to communicate the magnitude, direction, and the certainty of evidence of an effect estimate (*Table 4*). This was based on judgements about whether the effect estimate corresponded to be an important, less important, or no important benefit or harm; as seen in the columns of *Table 4*, and the GRADE assessment of the certainty of evidence; as seen in the rows of *Table 4*.

Table 4: Standardised sentences for reporting effect

GRADE	Important benefit/harm	Less important benefit/harm	No important benefit/harm
High	[Intervention] improves/reduces [outcome] (high certainty evidence)	[Intervention] slightly improves/reduces [outcome] (high certainty evidence)	[Intervention] makes little or no difference to [outcome] (high certainty evidence) Or [Intervention] does not have an important effect on [outcome] Or [Intervention] has little or no effect on [outcome]
Moderate	[Intervention] probably improves/reduces [outcome] (moderate certainty evidence)	[Intervention] probably slightly improves/reduces [outcome] (moderate certainty evidence) Or [Intervention] probably leads to slightly better/worse/less/more [outcome] (moderate certainty evidence)	Intervention] probably makes little or no difference to [outcome] (moderate certainty evidence)
Low	Intervention] may improve/reduce [outcome] (low certainty evidence)	[Intervention] may slightly improve/reduce [outcome] (low certainty evidence	[Intervention] may make little or no difference to [outcome] (low certainty evidence
Very low	We don't know if/It is uncertain whether [intervention] improves/reduces [outcome] because the certainty of this evidence is very low		

Ethical aspects

Ethics was not assessed for this HTA.

Legal aspects

Legal aspects and considerations were not assessed for this HTA. Norwegian legislation related to radiation safety is covered in chapter *Radiation safety and legislative aspects*. That said, this HTA has investigated the efficacy and safety, and cost-effectiveness and other health economic aspects related to the radionuclide lutetium-177 labelled with the PSMA-617 ligand and is therefore limited to this treatment agent. The ^{177}Lu-PSMA-617 drug (lutetium [^{177}Lu] vipivotide tetraxetan; Pluvicto) is currently patented by Novartis.

Results – efficacy and safety

Description of studies

Results of literature search

The search identified 1618 references, of which 1607 were excluded on the basis of titles and abstracts. Of the remaining eleven studies, eight were excluded after full text evaluation (see *Appendix 3* for reasons for exclusion) and three studies (RCTs) were ultimately included in our HTA (39-41). The selection process is presented in *Figure 1*.

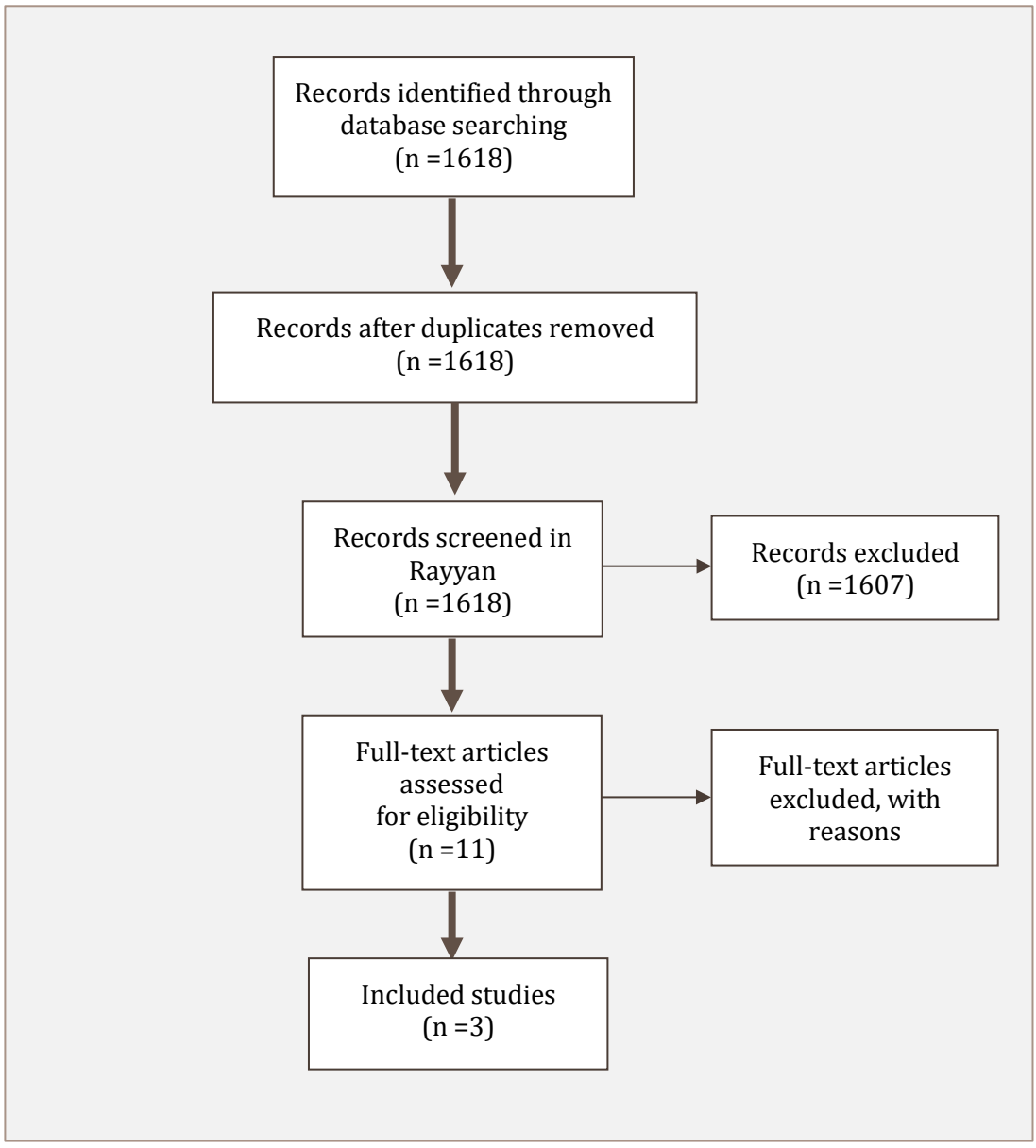

Figure 1: Flow chart of article selection

Included studies

We included three RCTs in total, that are presented in *Table 5* (39-41). Two of the studies compared the effect of ^{177}Lu-PSMA-617 to a taxane-based chemotherapeutic agent, i.e., cabazitaxel (39) and docetaxel (41). The third study (the VISION study) compared the effect of ^{177}Lu-PSMA-617 in combination with standard of care therapy, to standard of care therapy alone (40). The standard of care therapy in the VISION study (used in both groups) was not permitted to include the use of any cytotoxic chemotherapeutic agent (e.g., taxanes), systemic radioisotopes (e.g., radium-223), immunotherapy, or drugs that were considered investigational at the start of the study (e.g., olaparib) (40).

Table 5: Included RCTs for effect analyses

	Sartor 2021 (40)		**Hofman 2021 (39)**		**Satapathy 2021 (41)**	
Study name	VISION		TheraP			
Study number	NCT03511664		NCT03392428		CTRI/2019/12/022282	
Study type	RCT		RCT		RCT	
Study phase	Phase 3		Phase 2		Phase 2	
Follow-up (median)	20.3 months		18.4 months		n.a.	
Population	Men with mCRPC, previously treated with ≥1 approved anti-androgen therapy, and 1-2 taxane regimens.		Men with mCRPC, previously treated with docetaxel and anti-androgen therapy. Cabazitaxel considered next appropriate standard treatment.		Men with mCRPC, chemotherapy-naïve patients. Prior treatment with novel anti-androgen drugs (abiraterone and enzalutamide) was allowed	
Intervention vs. comparator	^{177}Lu-PSMA-617 + SoC†	SoC†	^{177}Lu-PSMA-617	Cabazitaxel	^{177}Lu-PSMA-617	Docetaxel
Number of participants	n=551	n=280	n=99	n=101	n=20	n=20
Age of participants *median (range)*	70.0 (48-94)	71.5 (40-89)	72.1 (66.9 -76.7)*	71.8 (66.7 -77.3)*	68 (54-85)	68 (50-84)
Years since diagnosis *median (range)*	7.42 (0.9-28.9)	7.37 (0.7-26.2)	n.a.	n.a.	3 (2-7)	2 (1-6)

n.a.: not available, RCT: randomised, controlled trials, SoC: standard of care therapy
**Interquartile range*
†The standard of care therapy in the VISION study was not permitted to include the use of any cytotoxic chemotherapeutic agent (e.g., taxanes), systemic radioisotopes (e.g., radium-223), immunotherapy, or drugs that were considered investigational at the start of the study (e.g., olaparib)

The VISION study is a phase 3 RCT that included a total of 831 patients (40). The study population consisted of men with mCRPC who were previously treated with docetaxel and (possibly) anti-androgen therapy, and where cabazitaxel was considered the next appropriate treatment step (40). In fact, patients who had received one prior taxane-based treatment and were candidates for a second taxane-based treatment, were considered ineligible for inclusion in the VISION study (40). The TheraP study is a phase 2 RCT that included a total of 200 patients (39). The study population consisted of men with mCRPC who were previously treated with at least one approved anti-androgen therapy (39). The study by Satapathy et al. is a phase 2 RCT that included a total of 40 patients (41). The study population consisted of men with mCRPC who were chemotherapy-naïve, i.e., not previously treated with chemotherapy agents such as taxanes, but they could have been treated previously with anti-androgen therapy (41). As the studies differ in terms of intervention and comparator, as well as having included

different populations in terms of previous treatments, we did not perform a meta-analysis of the data. More features of the three studies are presented in *Appendix 4*.

Excluded studies

The full list of excluded studies, with reasons for why they were excluded, is presented in *Appendix 3*. In brief, the main reasons for exclusion were because the study populations were not randomised and/or there were no comparators.

Ongoing studies

The list detailing relevant ongoing clinical trials is found in *Appendix 6*. In brief, we found 39 ongoing trials, of which six were phase 3 RCTs and nine were phase 2 RCTs. In total, all ongoing trials represent 6057 planned participants, and all include treatment with ^{177}Lu-PSMA for mCRPC patients. One of the ongoing studies have results that have been included in this HTA (*Appendix 6*) (40).

Risk of bias assessment

Two researchers independently assessed the studies using the Cochrane risk of bias tool (32). Each study was rated as being at low, unclear, or high risk of bias on seven domains: selection bias (random sequence generation and allocation bias), performance bias, detection bias, attrition bias, reporting bias, and other bias. Any disagreements were resolved through discussion.

The overall risk of bias assessments are shown in *Figure 2* and *Figure 3*. In brief, we assessed all three studies to have low risk of bias concerning random sequence generation (domain 1) and reporting bias (domain 6), and unclear risk of bias concerning allocation concealment (domain 2). Though none of the three studies were blinded in any capacity (neither patients nor personnel), we still assessed all studies to have low risk of bias in terms of performance bias and detection bias (domains 4 and 5). The reason for this is that we believe that the lack of blinding would not influence the main outcome, i.e., overall survival, as it is measured objectively. This is in line with the Cochrane handbook, i.e., to not draw for systematic biases (32).

Concerning attrition bias (domain 5), we only assessed the study by Satapathy et al to have low risk of bias (41). We assessed the TheraP study (Hofman et al) to have high risk of bias, due to high withdrawal rate of participants assigned to the control group (cabazitaxel treatment) before receiving the treatment (39). Similar tendency was seen in the VISION study (Sartor et al), but the study personnel initiated relevant adjustments to avoid bias (40). They also provided results of the ITT study population, in addition to the results of the randomised subpopulation (40). We therefore assessed the VISION study to have low risk of attrition bias. Concerning other bias, (domain 7), we assessed the TheraP and the VISION studies to have low risk of bias (39;40), whereas the study by Satapathy et al to have unclear risk of bias due to challenges with the administration of the study treatment due to COVID-19 (41).

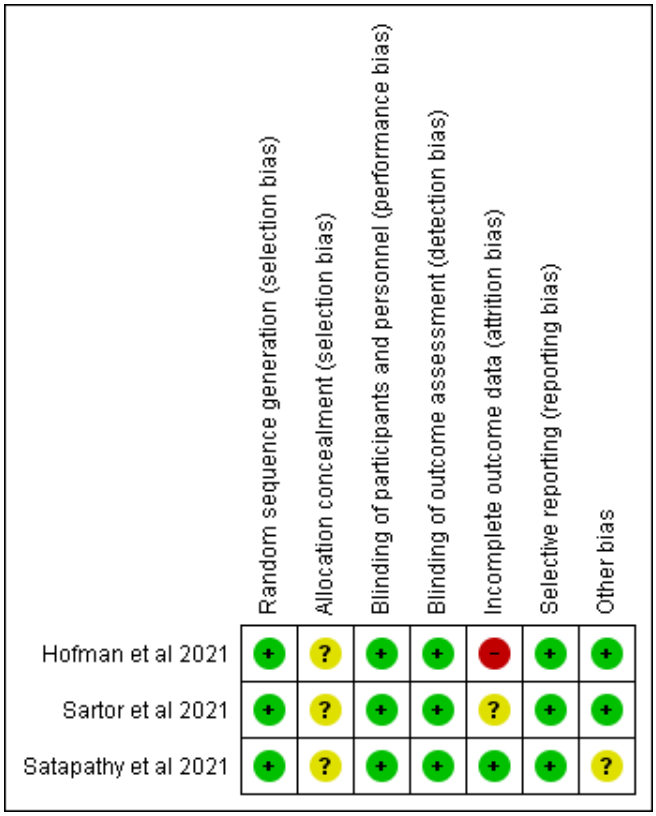

Figure 2: Risk of bias tables for each included study

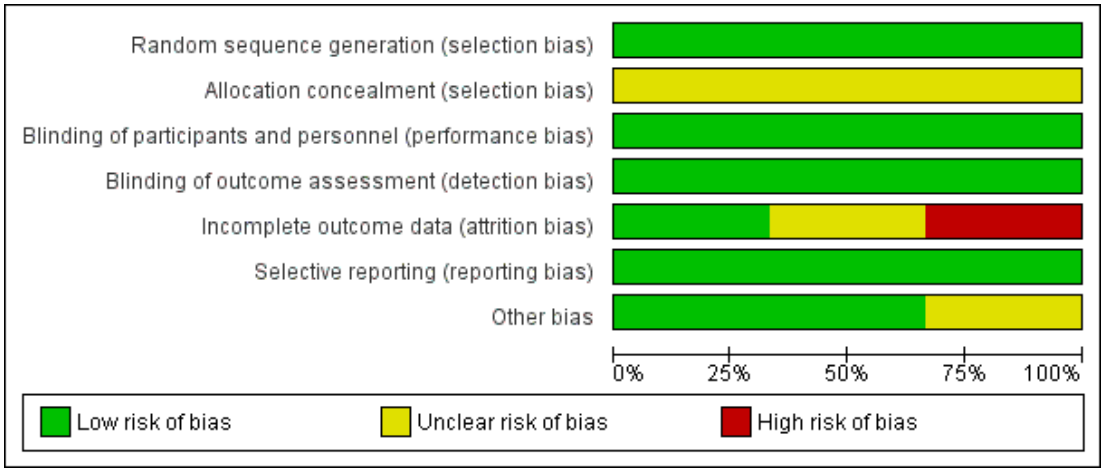

Figure 3: Risk of bias graphs across included studies

Data analysis

Both studies by Hofman et al (TheraP) and Satapathy et al analysed the data according to the ITT-principle (39;41), whereas the study by Sartor et al (VISION) used a randomised subpopulation for their data analysis, i.e., all patients randomised after a specific date and who had disease that could be evaluated according to RECIST version 1.1 (40;42). This was done to avoid biased results due to high withdrawal rates of patients in the comparator arm (standard of care therapy only). However, the authors did analyse progression-free survival according to the ITT population and found little to no difference between the ITT population and the randomised subpopulation (40). All three studies analysed adverse events in the safety population, i.e., all randomised patients that received at least one dose of study drug.

Because each comparison was supported by only one study, we did not conduct a meta-analysis. We present our results in summary of findings tables and forest plots. The forest plots were made using GraphPad Prism 9 (43), and GRADEpro was used to prepare summary of findings tables (44).

Efficacy outcomes

For the outcomes overall survival, progression-free survival, and first symptomatic skeletal event, the results are presented as hazard ratios with 95% confidence interval (CI). For progression-free survival, Sartor et al had published 99.2% CI which we imputed to 95% CI (40). Hazard ratio is the ratio of the hazard rates for the intervention and comparator (under the assumption of proportional hazards). A hazard rate quantifies how many events, e.g., progression or deaths would be expected to occur at a given moment for patients receiving a specific treatment. In this report, a hazard ratio less than one (HR<1) favours the intervention, while greater than one (HR>1) favours the comparator.

For confirmed ≥50% reduction of PSA-level, the results were calculated as risk ratios, based on the results presented in the studies. Risk ratio is the ratio of the probability of an outcome for the intervention versus the comparator during a defined time-period. For confirmed reduction of PSA-level, risk ratios less than one (RR<1) favour the comparator, while risk ratios greater than one (RR>1) favour the intervention.

Safety outcomes

According to our protocol, we planned to extract data on both severe adverse events grade 3 and 4, and serious adverse events. In our report, we present data on severe adverse events ≥grade 3, calculated as risk ratios, based on the results presented in the studies. For severe adverse events ≥grade 3, risk ratios less than one (RR<1) favour the intervention, while risk ratios greater than one (RR>1) favour the comparator. We found no data on total numbers of serious adverse events in the three included studies, but we present narrative data on serious adverse events as presented in the included studies, as well as the most common adverse events, to further elucidate on the adverse events associated with ^{177}Lu-PSMA-617 therapy.

Quality of life outcome

For quality of life, we present the results in accordance with the different quality of life questionnaires on which the results were based on 1) the Functional Assessment of Cancer Therapy - Prostate (FACT-P), 2) National Comprehensive Cancer Network - Functional Assessment of Cancer Therapy – FACT Prostate Cancer Symptom Index - 17 Item Version (NCCN-FACT-FPSI-17), and 3) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – cancer 30 (EORTC QLQ-C30). The results are presented as 1) hazard ratio (95% CI) of time to worsening, defined as the earliest occurrence of a ≥10 point decrease relative to baseline, disease progression, or death (FACT-P), and 2) median score change from baseline with p-value for the difference between groups (NCCN-FACT-FPSI-17), and 3) mean score (95% CI) for Global Health Status, with a calculated mean difference (95% CI) (EORTC QLQ-C30). Mean difference less than 0 (MD<0) favours the comparator, while mean difference greater than 0 (MD>0) favours the intervention.

Certainty of evidence

We evaluated the certainty of the estimates of all outcomes using the GRADE approach, as described in the Method chapter (*GRADE: assessing the certainty of evidence*). Our GRADE judgements are presented in the summary of findings tables for all outcomes, as well as in *Appendix 5*.

Results – overall survival

^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone

Overall survival was only reported in the VISION study and was defined as "*time from randomization to death*" (40). The time perspective for overall survival was 32 months, as presented in the overall survival curve in the VISION study (time from randomisation) (40). The median overall survival was 15.3 months for patients treated with ^{177}Lu-PSMA-617 in combination with standard of care therapy, and 11.3 months for patients treated with standard of care therapy alone (40). The published hazard ratio (95% CI) for overall survival was 0.62 (0.52 to 0.74), which is statistically significant in favour of ^{177}Lu-PSMA-617 in combination with standard of care therapy (40). In other words, patients who received ^{177}Lu-PSMA-617 in combination with standard of care therapy, died at 62% of the rate of patients who received only standard of care therapy (*Figure 4*, *Table 6*).

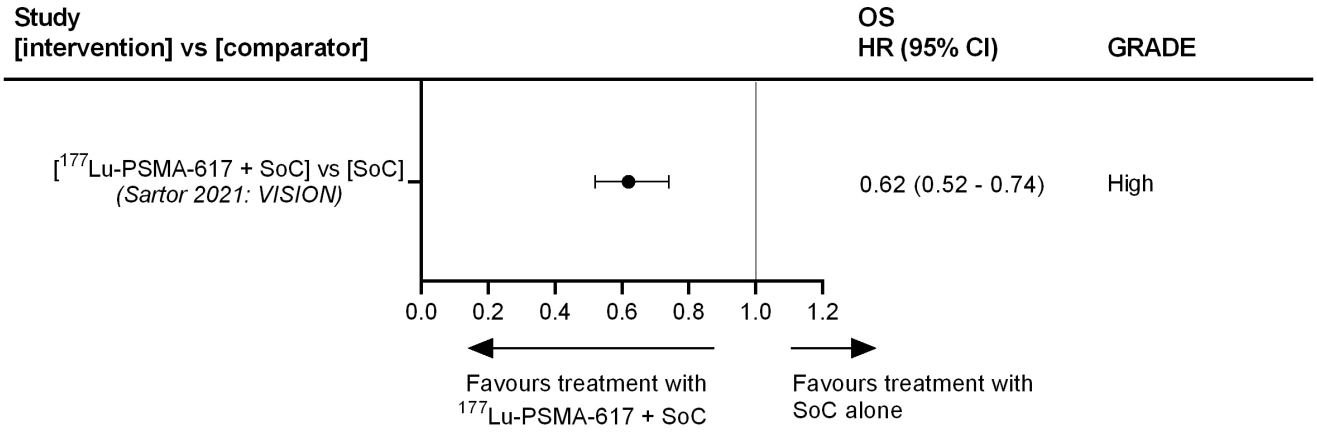

Figure 4: Forest plot of overall survival - VISION study

Values <1: death is less likely to occur, values >1: death is more likely to occur.
CI: confidence interval, HR: hazard ratio, SoC: standard of care therapy.

If we assume that 251 of 1000 patients treated with standard of care therapy alone have died within a year, then the estimated hazard ratio would correspond to 56 fewer patients (i.e., 195 patients) treated with ^{177}Lu-PSMA-617 plus standard of care therapy having died within a year. The 95% CI shows that it is statistically possible that between 87 fewer patients (i.e., 164 patients) and 41 fewer patients (i.e., 210 patients) would be anticipated to die within a year when receiving ^{177}Lu-PSMA-617 in combination with standard of care therapy than when receiving standard of care therapy alone (*Table 6*).

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Table 6: Summary of findings table of overall survival

Author, (study name) Participants	Hazard ratio (95% CI)	Anticipated absolute risk of OS per year†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with SoC	Risk difference with ^{177}Lu-PSMA-617 + SoC		
Sartor 2021 (VISION) n=831	**HR 0.62** (0.52 to 0.74)	251 per 1000	**56 fewer per 1000** (87 fewer to 41 fewer)	⊕⊕⊕⊕ High	^{177}Lu-PSMA-617 + SoC improves overall survival (High certainty of evidence)

†Computed as dichotomous data using GRADEpro,and imputed the anticipated number of deaths per 32 months to anticipated number of deaths per year. CI: confidence interval: n: total number of participants in the study; OS: overall survival; SoC: standard of care therapy

Based on the assumed threshold of minimal clinically important difference of 2 months and our GRADE assessment, we can summarise the hazard ratio result (using a standardised sentence) as follows:

- ^{177}Lu-PSMA-617 in combination with standard of care therapy improves the overall survival of patients with mCRPC more than treatment with standard of care therapy alone (high certainty evidence) (*Table 6*).

Results – progression-free survival

^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone

In the VISION study, progression-free survival was defined as "*time from randomization to centrally reviewed imaging-documented disease progression, defined according to PCWG3 guidelines, or death*" (40;45). The time perspective for progression-free survival was 22 months, as presented in the progression-free survival curve in the VISION study (time from randomisation) (40). The published median progression-free survival was 8.7 months for patients treated with ^{177}Lu-PSMA-617 in combination with standard of care therapy, and 3.4 months for patients treated with standard of care therapy alone (40). The hazard ratio with imputed 95% confidence interval was 0.40 (0.31 to 0.51), which is statistically significant in favour of ^{177}Lu-PSMA-617 in combination with standard of care therapy. In other words, patients who received ^{177}Lu-PSMA-617 in this study either experienced disease progression or died at 40% of the rate of patients who received standard of care therapy (*Figure 5*, *Table 7*).

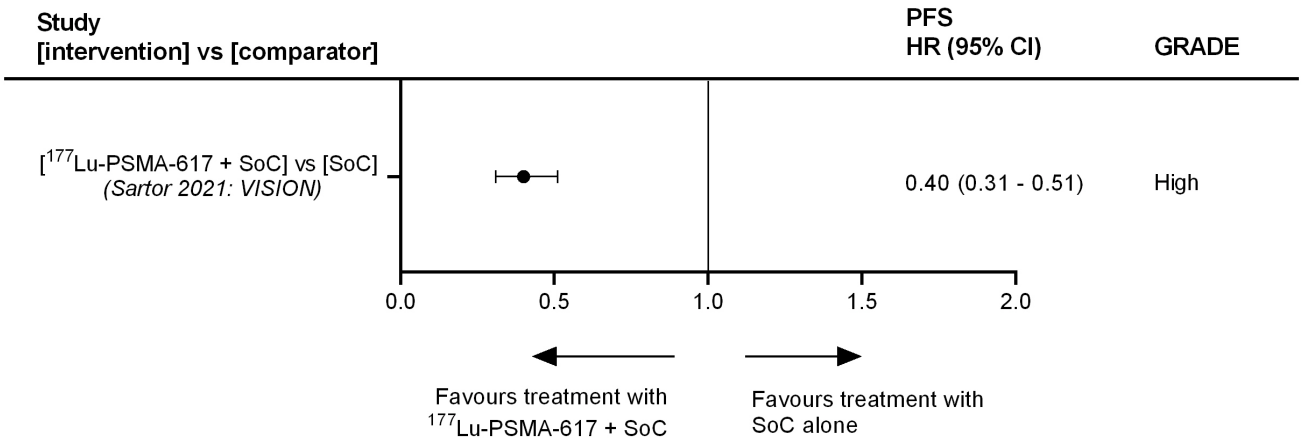


Figure 5: Forest plot of progression-free survival - VISION study

Values <1: disease progression or death is less likely to occur, values >1: disease progression or death is more likely to occur. CI: confidence interval, HR: hazard ratio, PFS: progression-free survival, SoC: standard of care therapy

If we assume that 258 of 1000 patients treated with standard of care therapy alone have progressed or died within a year, then the estimated hazard ratio would correspond to 135 fewer patients (i.e., 123 patients) treated with ^{177}Lu-PSMA-617 plus standard of care therapy having progressed or died within a year. The 95% CI shows that it is statistically possible that between 160 fewer patients (i.e., 98 patients) and 106 fewer patients (i.e., 152 patients) would be anticipated to progress or die within a year when receiving ^{177}Lu-PSMA-617 in combination with standard of care therapy than when receiving standard of care therapy alone (*Table 7*).

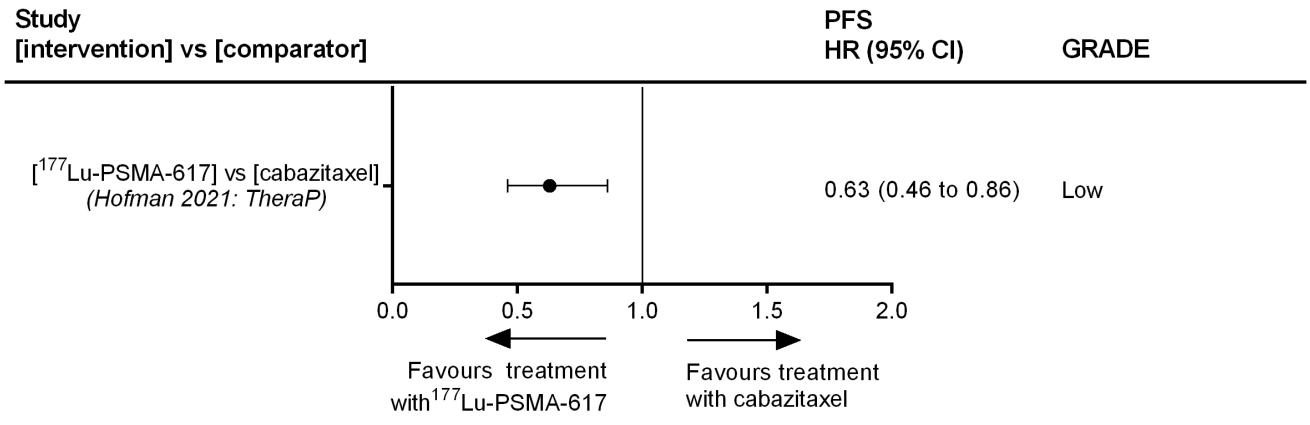
Table 7: Summary of findings table of progression-free survival - VISION study

Author, (study name) Participants	Hazard ratio (95% CI)	Anticipated absolute risk of PFS per year†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with SoC	Risk difference with ^{177}Lu-PSMA-617 + SoC		
Sartor 2021 (VISION) n=581	**HR 0.40** (0.31 to 0.51)*	258 per 1000	**135 fewer per 1000** (160 fewer to 106 fewer)	⊕⊕⊕⊕ High	^{177}Lu-PSMA-617 + SoC improves PFS (high certainty of evidence)

*†Computed as dichotomous data using GRADEpro,and converted from anticipated number of deaths per 22 months to anticipated number of deaths per year. *Calculated from 99.2% CI. CI: confidence interval: n: total number of participants in the study; PFS: progression-free survival; SoC: standard of care therapy*

^{177}Lu-PSMA-617 versus cabazitaxel

In the TheraP study, progression-free survival was defined as "*the interval from randomisation to first evidence of PSA progression defined by an increase of at least 25% and at least 2 ng/mL after 12 weeks (as per PCWG316), radiographic progression using locally reported CT and bone scanning ([RECIST] 1.117 and PCWG3 criteria for bone lesions), commencement of non-protocol anticancer treatment, or death from any cause*" (39;42;45). The time perspective for progression-free survival was 18 months, as presented in the progression-free survival curve in the TheraP study (39).The published median progression-free survival (95% CI) was 5.1 months (3.5 to 5.7) for patients treated with ^{177}Lu-PSMA-617, and 5.1 months (2.8 to 6.0) for patients treated with cabazitaxel[5] (39). However, the hazard ratio (95% CI) for progression-free survival was 0.63 (0.46 to 0.86), which is statistically significant in favour of ^{177}Lu-PSMA-617 (39). In other words, patients who received ^{177}Lu-PSMA-617 in this study either progressed or died at 63% of the rate of patients who received cabazitaxel (*Figure 6*, *Table 8*).



death is more likely to occur. CI: confidence interval, HR: hazard ratio, PFS: progression-free survival

[5] The progression-free survival at 12 months was 12% in the ^{177}Lu-PSMA-617 group and 3% in the cabazitaxel group (40)

If we assume that 584 of 1000 patients treated with cabazitaxel have progressed or died within a year, then the estimated hazard ratio would correspond to 106 fewer patients (i.e., 478 patients) treated with ^{177}Lu-PSMA-617 having progressed or died within a year. The 95% CI shows that it is statistically possible that between 165 fewer patients (i.e., 419 patients) and 33 fewer patients (i.e., 551 patients) would be anticipated to progress or die within a year when receiving ^{177}Lu-PSMA-617 than when receiving cabazitaxel (*Table 8*).

Table 8: Summary of findings table of progression-free survival - TheraP study

Author, (study name) Participants	Hazard ratio (95% CI)	Anticipated absolute risk of PFS per year†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with cabazitaxel	Risk difference with ^{177}Lu-PSMA-617		
Hofman 2021 (TheraP) n=200	**HR 0.63** (0.46 to 0.86)	584 per 1000	**106 fewer per 1000** (165 fewer to 33 fewer)	⊕⊕ Low	^{177}Lu-PSMA-617 may improve PFS (low certainty evidence)

†Computed as dichotomous data using GRADEpro,and converted from anticipated number of deaths per 22 months to anticipated number of deaths per year. CI: confidence interval: n: total number of participants in the study; PFS: progression-free survival

^{177}Lu-PSMA-617 versus docetaxel

In their study, Satapathy et al defined radiographic progression-free survival as "*per RECIST 1.1*" (41;42). The published median progression-free survival (95% CI) was 4.0 months (1.8 to 6.2) for patients treated with ^{177}Lu-PSMA-617, and 4.0 months (3.6 to 4.4) for patients treated with docetaxel (41). The time perspective for progression-free survival was 20 months, as presented in the progression-free survival curve in the study (time since treatment initiation) by Satapathy et al. (41). The hazard ratio (95% CI) for progression-free was 0.90 (0.46 to 1.77), which indicates little or no difference in effect between the ^{177}Lu-PSMA-617 and docetaxel groups (41). In other words, patients who received ^{177}Lu-PSMA-617 in this study either experienced disease progression or died at 90% of the rate of patients who received docetaxel (*Figure 7*, *Table 9*). As the confidence interval includes values above 1, it is statistically possible that patients who receive

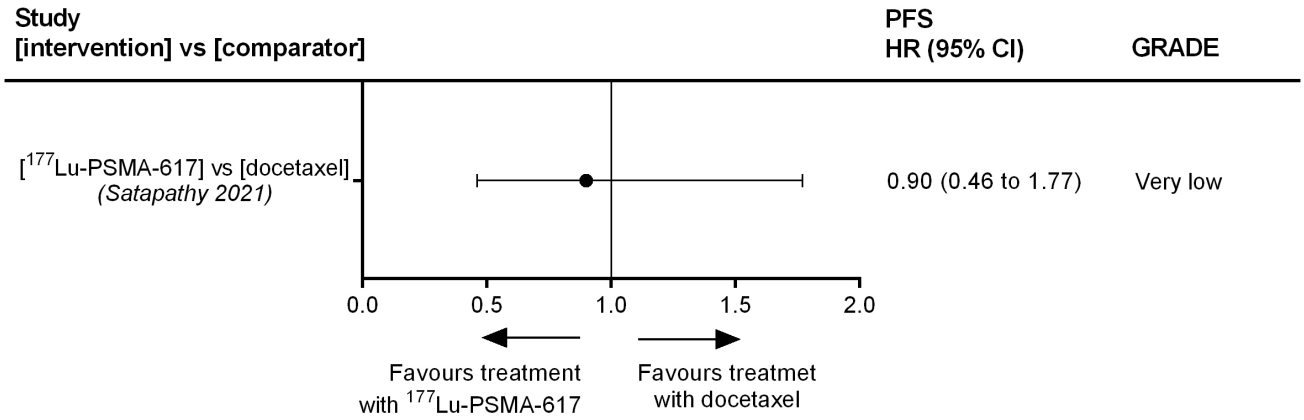


Figure 7: Forest plot of progression-free survival - Satapathy study

Values <1: disease progression or death is less likely to occur, values >1: disease progression or death is more likely to occur. CI: confidence interval, HR: hazard ratio, PFS: progression-free survival

^{177}Lu-PSMA-617 actually progress or die at the same rate or sooner than those who receive docetaxel (*Table 7*).

If we assume that 597 of 1000 patients treated with docetaxel have progressed or died within a year, then the estimated hazard ratio would correspond to 10 fewer patients (i.e., 587 patients) treated with ^{177}Lu-PSMA-617 having progressed or died within a year. The 95% CI shows that it is statistically possible that between 121 fewer patients (i.e., 476 patients) and 27 more patients (i.e., 627 patients) would be anticipated to progress or die within a year when receiving ^{177}Lu-PSMA-617 than when receiving docetaxel (*Table 9*).

Table 9: Summary of findings table of progression-free survival - Satapathy study

Author, (study name) study type, participants	Hazard ratio (95% CI)	Anticipated absolute risk of PFS per year†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with docetaxel	Risk difference with ^{177}Lu-PSMA-617		
Satapathy 2021 1 RCT n=40	**HR 0.90** (0.46 to 1.77)	597 per 1000	**10 fewer per 1000** (121 fewer to 27 more)	⊕ Very low	It is uncertain whether ^{177}Lu-PSMA-617 improves PFS because the certainty of this evidence is very low

†Computed as dichotomous data using GRADEpro,and converted from anticipated number of deaths per 22 months to anticipated number of deaths per year. CI: confidence interval: n: total number of participants in the study; PFS: progression-free survival

Based on the assumed threshold of minimal clinically important difference of 2 months and our GRADE assessments, we can summarise the results of the hazard ratios (using standardised sentences) as follows:

1) ^{177}Lu-PSMA-617 in combination with standard of care therapy improves the progression-free survival of patients with mCRPC more than treatment with standard of care therapy alone (high certainty evidence) (*Table 7*)
2) ^{177}Lu-PSMA-617 may improve progression-free survival in patients with mCRPC more than cabazitaxel (low certainty evidence) (*Table 8*)
3) It is uncertain whether ^{177}Lu-PSMA-617 improves progression-free survival in patients with mCRPC more than docetaxel because the certainty of this evidence is very low (*Table 9*)

Results – confirmed ≥50% PSA level reduction

^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone

For the comparison ^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone (the VISION study), our calculated risk ratio (95% CI) of confirmed ≥50% PSA level reduction was 6.4 (3.9 to 10.7) within 20 months, which is statistically significant in favour of ^{177}Lu-PSMA-617 plus standard of care therapy. In other words, patients who received ^{177}Lu-PSMA-617 in combination with standard of care treatment in this study were 5.2 times more likely to reduce the PSA level ≥50% within 20 months compared to patients who received standard of care treatment alone (*Figure 8*, *Table 10*).

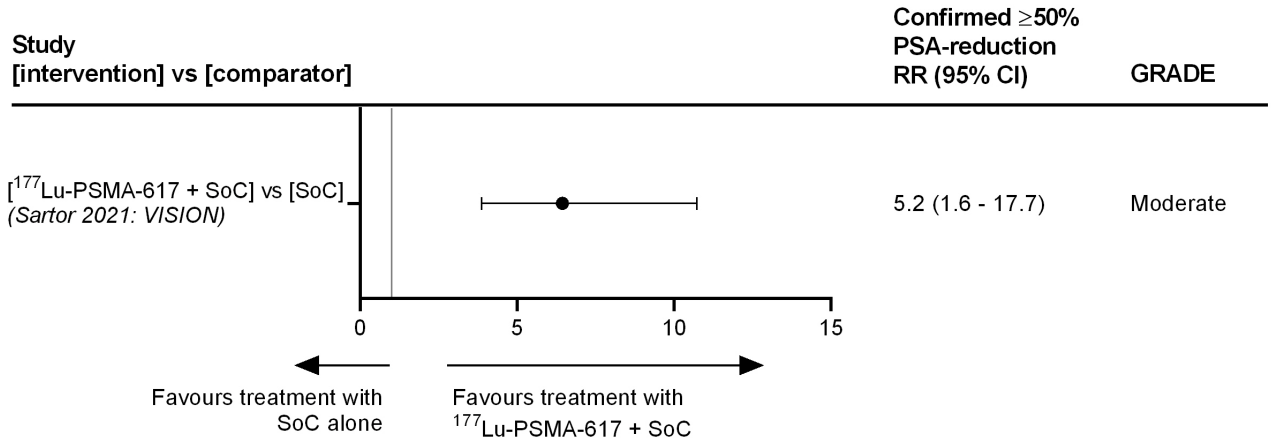


Figure 8: Forest plot of confirmed ≥50% PSA level reduction - VISION study

Values <1: reduction in PSA level is less likely to occur, values >1: reduction in PSA level is more likely to occur. CI: confidence interval, PSA: prostate specific antigen, RR: risk ratio, SoC: standard of care therapy

If we assume that 71 of 1000 patients treated with standard of care therapy alone have confirmed ≥50% PSA level reduction within 20 months, then the estimated relative risk would correspond to 389 more patients (i.e., 460 patients) treated with ^{177}Lu-PSMA-617 plus standard of care therapy having confirmed ≥50% PSA level reduction within 20 months. The 95% CI shows that it is statistically possible that between 205 more patients (i.e., 276 patients) and 694 more patients (i.e., 765 patients) would be anticipated to have a confirmed ≥50% PSA-level reduction within 20 months when receiving ^{177}Lu-PSMA-617 in combination with standard of care therapy than when receiving standard of care therapy alone (*Table 10*).

Table 10: Summary of findings table of confirmed ≥50% PSA level reduction - VISION study

Author, (study name) Participants Follow-up	Relative risk (95% CI)	Anticipated absolute risk of confirmed ≥50% PSA level reduction†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with SoC	Risk difference with ^{177}Lu-PSMA-617 + SoC		
Sartor 2021 (VISION) n=581 20 months*	**RR 6.4** (3.9 to 10.7)	71 per 1000	**389 more per 1000** (205 more to 694 more)	⊕⊕⊕ Moderate	^{177}Lu-PSMA-617 + SoC probably reduce PSA-level ≥50% (moderate certainty evidence)

†Computed as dichotomous data using GRADEpro.

*Median follow-up
CI: confidence interval, n: total number of participants in the study, PSA: prostate specific antibody

^{177}Lu-PSMA-617 versus cabazitaxel

For the comparison ^{177}Lu-PSMA-617 versus cabazitaxel (the TheraP study), our calculated risk ratio (95% CI) of confirmed ≥50% PSA level reduction was 1.80 (1.34 to 2.4) within 18 months, which is statistically significant in favour of ^{177}Lu-PSMA-617. In other words, patients who received ^{177}Lu-PSMA-617 in this study were 1.8 times more likely to reduce the PSA level ≥50% within 18 months compared to patients who received cabazitaxel (*Figure 9*, *Table 11*).

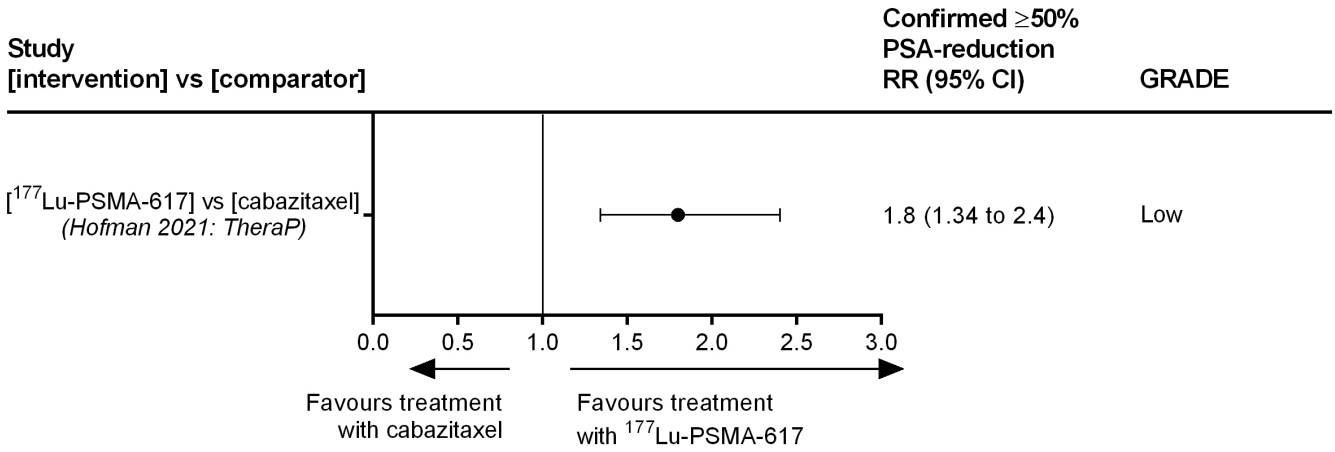


Figure 9: Forest plot of confirmed ≥50% PSA level reduction - TheraP study
Values <1: reduction in PSA level is less likely to occur, values >1: reduction in PSA level is more likely to occur.
CI: confidence interval, PSA: prostate specific antigen, RR: risk ratio

If we assume that 366 of 1000 patients treated with cabazitaxel have confirmed ≥50% PSA level reduction within 18 months, then the estimated relative risk would correspond to 293 more patients (i.e., 659 patients) treated with ^{177}Lu-PSMA-617 having confirmed ≥50% PSA level reduction within 18 months. The 95% CI shows that it is statistically possible that between 125 more patients (i.e., 491 patients) and 513 more patients (i.e., 879 patients) would be anticipated to have a confirmed PSA-level reduction of ≥50% within 18 months when receiving ^{177}Lu-PSMA-617 than those receiving cabazitaxel (*Table 11*).

Table 11: Summary of findings table of confirmed ≥50% PSA level reduction - TheraP study

Author, (study name) Participants Follow-up	Relative risk (95% CI)	Anticipated absolute risk of confirmed ≥50% PSA level reduction†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with cabazitaxel	Risk difference with ^{177}Lu-PSMA-617		
Hofman 2021 (TheraP) n=200 18 months	**RR 1.80** (1.34 to 2.40)	366 per 1000	**293 more per 1000** (125 more to 513 more)	⊕⊕⊕ Moderate	^{177}Lu-PSMA-617 probably reduce PSA-level ≥50% (moderate certainty evidence)

†Computed as dichotomous data using GRADEpro. CI: confidence interval, n: total number of participants in the study, PSA: prostate specific antibody

^{177}Lu-PSMA-617 versus docetaxel

For the comparison ^{177}Lu-PSMA-617 versus docetaxel (by Satapathy et al), our calculated risk ratio (95% CI) of confirmed ≥50% PSA level reduction was 1.5 (0.35 to 2.98) within 20 months[6], which indicated little or no difference in effect between the ^{177}Lu-PSMA-617 group and the docetaxel group. In other words, patients who received ^{177}Lu-PSMA-617 in this study were 1.5 times more likely to have a reduced PSA level of ≥50% within 20 months[6] compared to patients who received docetaxel (*Figure 10*). However, as the confidence interval includes values above 1, it is statistically possible that patients who receive ^{177}Lu-PSMA-617 are actually at equal or less probability of reducing the PSA-level ≥50% within 20 months[6] compared to those who receive docetaxel (*Figure 10*, *Table 12*).

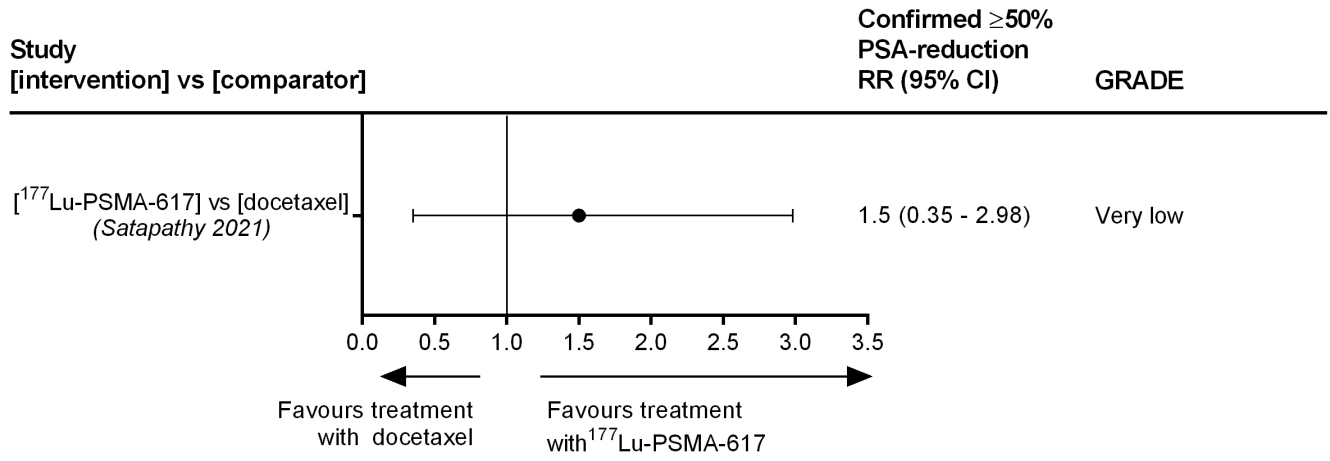


Figure 10: Forest plot of confirmed ≥50% PSA level reduction - Satapathy study

Values <1: reduction in PSA level is less likely to occur, values >1: reduction in PSA level is more likely to occur.

CI: confidence interval, PSA: prostate specific antigen, RR: risk ratio

If we assume that 400 of 1000 patients treated with docetaxel have confirmed ≥50% PSA level reduction within 20 months[6], then the estimated relative risk would correspond to 200 more patients (i.e., 600 patients) treated with ^{177}Lu-PSMA-617 having confirmed ≥50% PSA level reduction within 20 months[6]. The 95% CI shows that it is statistically possible that between 260 fewer patients (i.e., 140 patients) and 792 more patients (i.e., 1192 patients) would be anticipated to have a confirmed PSA-level reduction of ≥50% within 20 months[6] when receiving ^{177}Lu-PSMA-617 than when receiving docetaxel (*Table 12*).

Table 12: Summary of findings table of confirmed ≥50% PSA level reduction - Satapathy study

Author, Participants	Relative risk (95% CI)	Anticipated absolute risk of confirmed ≥50% PSA level reduction†	Standardised statements for the reporting of effect

[6] The study by Satapathy et al. reported no median follow-up time was reported, but we assume 20 months follow-up based on the survival curves (41)

Follow-up		Risk with docetaxel	Risk difference with ^{177}Lu-PSMA-617	Certainty of the evidence (GRADE)	
Satapathy 2021 n=35 20 months*	**RR 1.50** (0.35 to 2.98)	400 per 1000	**200 more per 1000** (260 fewer to 792 more)	⊕ Very low	It is uncertain whether ^{177}Lu-PSMA-617 reduces PSA-level ≥50% because the certainty of this evidence is very low

†Computed as dichotomous data using GRADEpro.
** No median follow-up time was reported in the study, but we assume 20 months follow-up based on the survival curves*
CI: confidence interval, n: total number of participants in the study, PSA: prostate specific antibody

Based on the assumed threshold of minimal clinically important difference of 20% relative improvement and our GRADE assessments, we can summarise the results of the risk ratios (using standardised sentences) as follows:

1) ^{177}Lu-PSMA-617 in combination with standard of care therapy probably reduce the PSA-level to ≥50% in more mCRPC patients than treatment with standard of care therapy alone (moderate certainty evidence) (*Table 10*)
2) ^{177}Lu-PSMA-617 probably reduce the PSA-level to ≥50% in more mCRPC patients than cabazitaxel (moderate certainty evidence) (*Table 11*)
3) It is uncertain whether ^{177}Lu-PSMA-617 reduce the PSA-level to ≥50% in more mCRPC patients than docetaxel because the certainty of this evidence is very low (*Table 12*)

Results – first symptomatic skeletal event

^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone

First symptomatic skeletal event was only reported in the VISION study and was defined as: "*time from randomization to first new pathological bone fracture, spinal cord compression, tumor-related orthopedic surgery, radiation therapy for bone pain, or death*" (40). The time perspective for time to first skeletal event was 22 months, as presented in the time to first skeletal event curve in the VISION study (time from randomisation) (40). The median time to first symptomatic skeletal event was 11.5 months for patients treated with ^{177}Lu-PSMA-617 in combination with standard of care therapy, and 6.8 months for patients treated with standard of care therapy alone (40). The published hazard ratio (95% CI) was 0.50 (0.40 to 0.62), which is statistically significant in favour of ^{177}Lu-PSMA-617 in combination with standard of care therapy (40). In other words, patients who were treated with ^{177}Lu-PSMA-617 in combination with standard of care therapy, developed the first symptomatic skeletal event (including death) at 50% of the

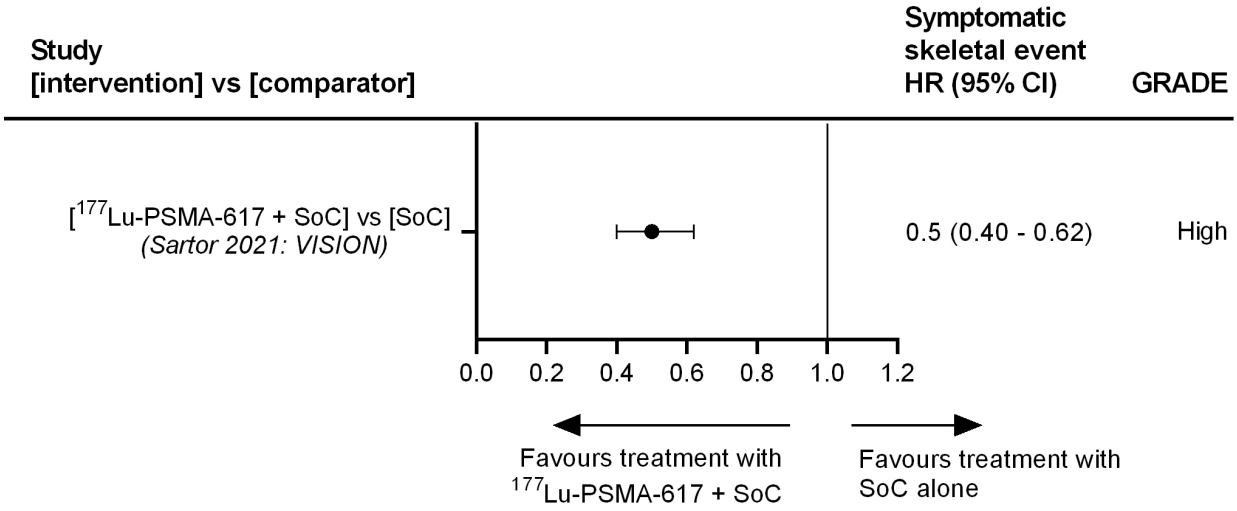


Figure 11: Forest plot of first symptomatic skeletal event - VISION study

Values <1: skeletal events are less likely to occur, values >1: skeletal events are more likely to occur. CI: confidence interval, HR: hazard ratio, SoC: standard of care therapy

rate of patients who were treated with standard of care therapy alone (*Figure 11*, *Table 13*).

If we assume that 381 of 1000 patients treated with standard of care therapy alone have developed a first symptomatic skeletal event (including death) within a year, then the estimated hazard ratio would correspond to 135 fewer patients (i.e., 246 patients) treated with ^{177}Lu-PSMA-617 plus standard of care therapy having developed a first symptomatic skeletal event (including death) within a year The 95% CI shows that it is statistically possible that between 173 fewer patients (i.e., 208 patients) and 95 fewer patients (i.e., 286 patients) would be anticipated to develop a first symptomatic skeletal event (including death) within a year, when receiving ^{177}Lu-PSMA-617 in combination with standard of care therapy than when receiving standard of care therapy alone (*Table 13*).

Table 13: Summary of findings table of first symptomatic skeletal event or death

Author, (study name) Participants	Hazard ratio (95% CI)	Anticipated absolute risk of first symptomatic skeletal event or death per year†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with SoC	Risk difference with ^{177}Lu-PSMA-617 + SoC		
Sartor 2021 (VISION) n=581	**HR 0.50** (0.40 to 0.62)	381 per 1000	**135 fewer per 1000** (173 fewer to 95 fewer)	⊕⊕⊕⊕ High	^{177}Lu-PSMA-617 + SoC reduces development of a first symptomatic skeletal event (high certainty of evidence)

†Computed as dichotomous data using GRADEpro,and converted from anticipated number of deaths per 22 months to anticipated number of deaths per year. CI: confidence interval, n: total number of participants in the study, SoC: standard of care therapy

Based on the assumed threshold of minimal clinically important difference of 20% relative improvement and our GRADE assessments, we can summarise the result of the hazard ratio using a standardised sentence as follows:

- ^{177}Lu-PSMA-617 in combination with standard of care therapy reduce development of a first symptomatic skeletal event in patients with mCRPC more than standard of care therapy alone (high certainty evidence) (*Table 13*).

Results – severe adverse events ≥grade 3 data analysis

According to the Common Terminology Criteria for Adverse Events, by the National Cancer Institute (National Institutes of Health, U.S. Department of Health and Human Services), adverse events are defined as: "*any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure*" (46). Based on the severity, adverse events are classified as follows (46):

Grade 1: mild symptoms, intervention not necessary
Grade 2: moderate symptoms, minimal, local or non-invasive intervention necessary
Grade 3: severe or medically significant, hospitalization necessary
Grade 4: life-threatening, urgent intervention necessary
Grade 5: death related to adverse events

^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone

In the VISION study, adverse events during treatment were defined as "*those occurring from the first dose of treatment up to and including 30 days after the last dose or before the receipt of subsequent anticancer treatment, whichever came first*" (40). For the comparison ^{177}Lu-PSMA-617 with standard of care therapy versus standard of care therapy alone, the calculated risk ratio (95% CI) for severe adverse events ≥grade 3 was 1.39 (1.14 to 1.69) within 20 months, which is statistically significant in favour of standard of care therapy treatment alone. In other words, patients who were treated with ^{177}Lu-PSMA-617 in combination with standard of care therapy in this study were 1.39 times more likely to experience severe adverse events ≥grade 3 within 20 months compared to patients who were treated with standard of care therapy alone (*Figure 12*, *Table 14*).

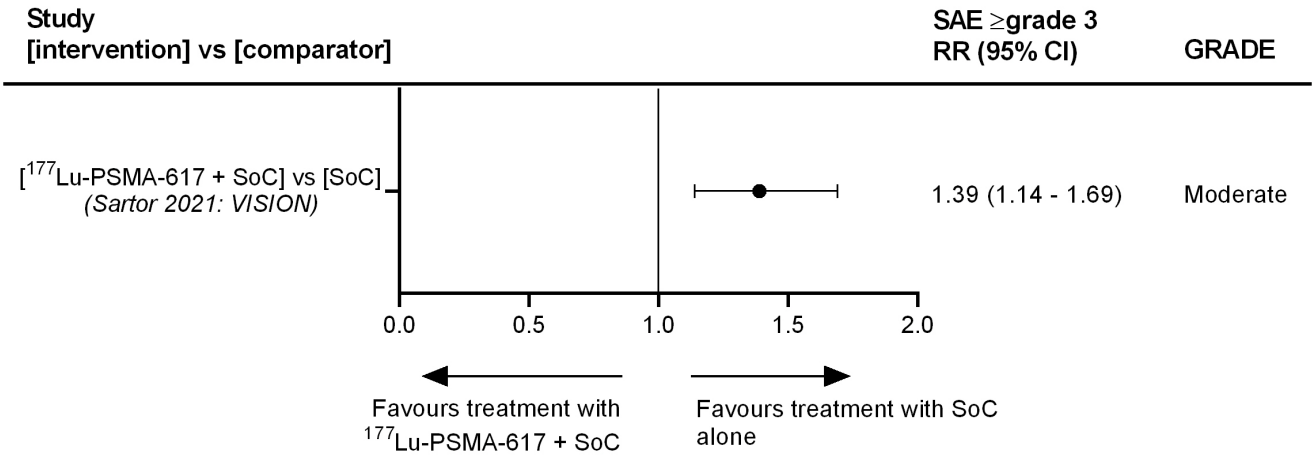


Figure 12: Forest plot of severe adverse events ≥grade 3 - VISION study
Values <1: severe adverse events ≥3 are less likely to occur, values >1: severe adverse events ≥grade 3 are more likely to occur. CI: confidence interval, RR: risk ratio, SAE: severe adverse events SoC: standard of care therapy.

If we assume that 380 of 1000 patients treated with standard of care therapy alone experience severe adverse events ≥grade 3 within 20 months, then the estimated relative risk would correspond to 148 more patients (i.e., 528 patients) treated with ^{177}Lu-PSMA-617 plus standard of care therapy experiencing severe adverse events ≥grade 3 within 20 months. The 95% CI shows that it is statistically possible that between 53 more patients (i.e., 433 patients) and 263 more patients (i.e., 643 patients) would be anticipated to experience severe adverse events ≥grade 3 within 20 months when receiving ^{177}Lu-PSMA-617 in combination with standard of care therapy than when receiving standard of care therapy alone (*Table 14*).

Table 14: Summary of findings table of severe adverse events ≥grade 3 - VISION study

Author, (study name) Participants Follow-up	Relative risk (95% CI)	Anticipated absolute risk of severe adverse events ≥grade 3†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with SoC	Risk difference with ^{177}Lu-PSMA-617 + SoC		
Sartor 2021 (VISION) n=734 20 months*	**RR 1.39** (1.14 to 1.69)	380 per 1000	**148 more per 1000** (53 more to 263 more)	⊕⊕⊕ Moderate	^{177}Lu-PSMA-617 + SoC probably increases adverse events ≥grade 3 (moderate certainty evidence)

†Computed as dichotomous data using GRADEpro.
**Median follow-up*
CI: confidence interval: n: total number of participants in the study; RCT: randomized controlled trial

^{177}Lu-PSMA-617 versus cabazitaxel

In the TheraP study, adverse events were "*reported according to the Common Terminology Criteria for Adverse Events version 4.03*" (39;47). For the comparison ^{177}Lu-PSMA-617 versus cabazitaxel (the TheraP study), the calculated risk ratio (95% CI) for severe adverse events ≥grade 3 was 0.73 (0.18 to 1.04) within 18 months. In other words, patients who received ^{177}Lu-PSMA-617 in this study were expected to have a 27% reduction in risk of severe adverse events ≥grade 3 within 18 months compared to patients who received cabazitaxel. However, the confidence interval includes values above 1, so it is statistically possible that patients who receive ^{177}Lu-PSMA-617 are actually at equal or greater risk of severe adverse events ≥grade 3 within 18 months compared to those who receive cabazitaxel (*Figure 13*, *Table 15*).

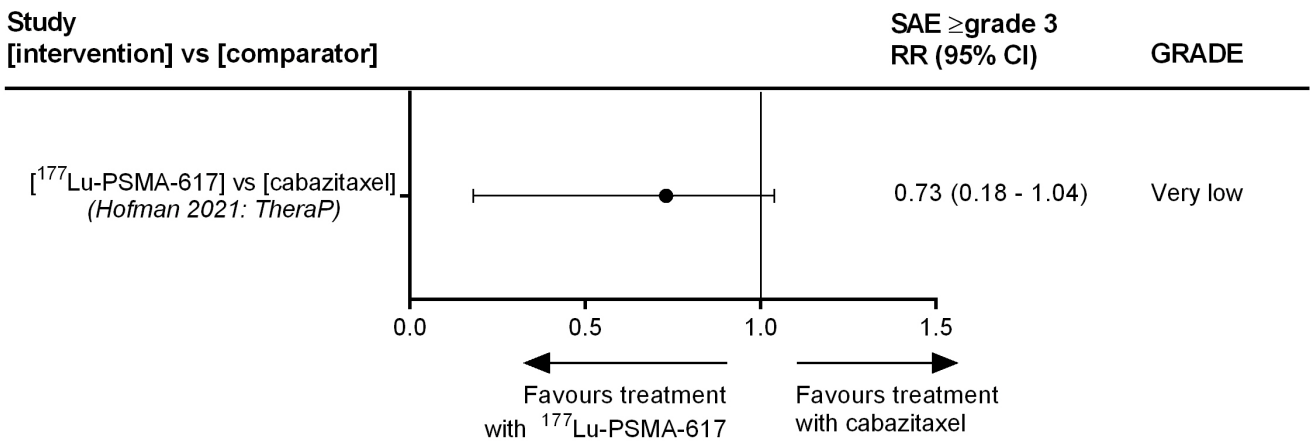


Figure 13: Forest plot of severe adverse events ≥grade 3 - TheraP study
Values <1: severe adverse events ≥grade 3 are less likely to occur, values >1: severe adverse events ≥grade 3 are more likely to occur. CI: confidence interval, RR: risk ratio, SAE: severe adverse events

If we assume that 529 of 1000 patients treated with cabazitaxel experience severe adverse events ≥grade 3 within 18 months, then the estimated relative risk would correspond to 143 fewer patients (i.e., 386 patients) treated with ^{177}Lu-PSMA-617 experiencing severe adverse events ≥grade 3 within 18 months. The 95% CI shows that it is statistically possible that between 434 fewer patients (i.e., 95 patients) and 21 more patients (i.e., 550 patients) would be anticipated to experience severe adverse events ≥grade 3 within 18 months when receiving ^{177}Lu-PSMA-617 than when receiving cabazitaxel (*Table 15*).

Table 15: Summary of findings table of severe adverse events ≥grade 3 - TheraP study

Author, (study name) Participants Follow-up	Relative risk (95% CI)	Anticipated absolute risk of severe adverse events ≥grade 3†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with cabazitaxel	Risk difference with ^{177}Lu-PSMA-617		
Hofman 2021 (TheraP) n=183 18 months*	**RR 0.73** (0.18 to 1.04)	529 per 1000	**143 fewer per 1000** (434 fewer to 21 more)	⊕ Very low	It is uncertain whether ^{177}Lu-PSMA-617 reduces adverse events ≥grade 3 because the certainty of this evidence is very low

†Computed as dichotomous data using GRADEpro.
**Median follow-up*
CI: confidence interval: n: total number of participants in the study; RCT: randomized controlled trial

^{177}Lu-PSMA-617 versus docetaxel

In the study by Satapathy et al., adverse events were "*assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0*" (41;47). For the comparison ^{177}Lu-PSMA-617 versus docetaxel (Satapathy et al), the calculated risk ratio (95% CI) for severe adverse events ≥grade 3 was 0.6 (0.27 to 1.34) within 20 months[6]. In other words, patients who received ^{177}Lu-PSMA-617 in this study were expected to have a 40% reduction in risk of severe adverse events ≥grade 3 within 20 months[6] compared to patients who received docetaxel. However, as the confidence interval includes values

above 1, it is statistically possible that patients who receive ^{177}Lu-PSMA-617 are actually at equal or greater risk of severe adverse events ≥grade 3 within 20 months[6] compared to those who receive docetaxel (*Figure 14*, *Table 16*).

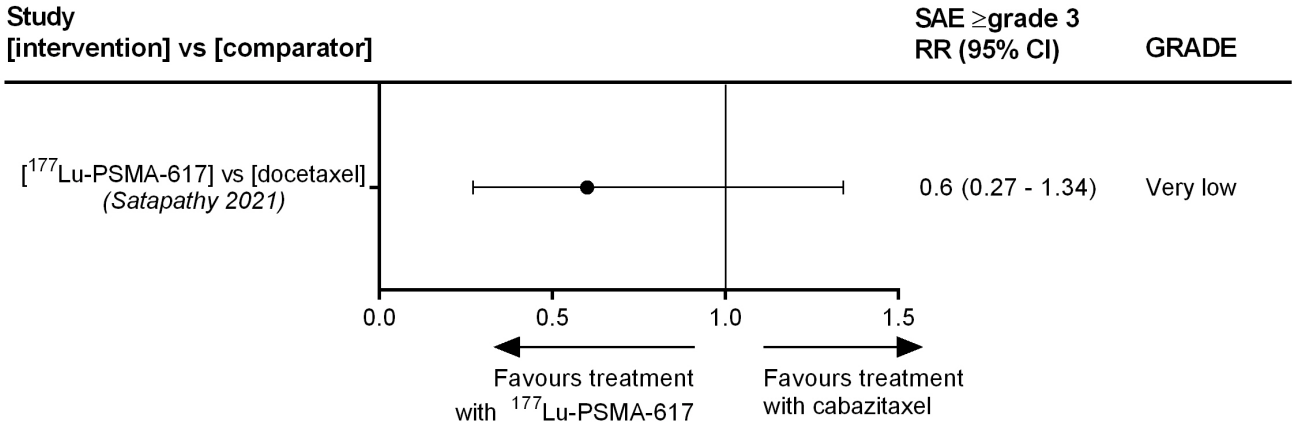


Figure 14: Forest plot of severe adverse events ≥grade 3 - Satapathy study
Values <1: severe adverse events ≥grade 3 are less likely to occur, values >1: severe adverse events ≥grade 3 are more likely to occur. CI: confidence interval, RR: risk ratio, SAE: severe adverse events

If we assume that 500 of 1000 patients treated with docetaxel experience severe adverse events ≥grade 3 within 20 months[6], then the estimated relative risk would correspond to 200 fewer patients (i.e., 300 patients) treated with ^{177}Lu-PSMA-617 experiencing severe adverse events ≥grade 3 within 20 months.[6] The 95% CI shows that it is statistically possible that between 365 fewer patients (i.e., 135 patients) and 170 more patients (i.e., 670 patients) would be anticipated to experience severe adverse events ≥grade 3 within 20 months[6] when receiving ^{177}Lu-PSMA-617 than when receiving docetaxel (*Table 16*).

Table 16: Summary of findings table of severe adverse events ≥grade 3 - Satapathy study

Author, (study name) Participants Follow-up	Relative risk (95% CI)	Anticipated absolute risk of severe adverse events ≥grade 3†		Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
		Risk with docetaxel	Risk difference with ^{177}Lu-PSMA-617		
Satapathy 2021 n=40 20 months*	**RR 0.60** (0.27 to 1.34)	500 per 1000	**200 fewer per 1000** (365 fewer to 170 more)	⊕ Very low	It is uncertain whether ^{177}Lu-PSMA-617 reduces adverse events ≥grade 3 because the certainty of this evidence is very low

†Computed as dichotomous data using GRADEpro.
** No median follow-up time was reported in the study, but we assume 20 months follow-up based on the survival curves*
CI: confidence interval: n: total number of participants in the study; RCT: randomized controlled trial

Based on the assumed threshold of minimal clinically important difference of 20% relative improvement and our GRADE assessments, we can summarise the results of the risk ratios using standardised sentences as follows:

1) ^{177}Lu-PSMA-617 in combination with standard of care therapy probably increase severe adverse events ≥grade 3 in patients with mCRPC when compared with

treatment with standard of care therapy alone (moderate certainty evidence) (*Table 14*)

2) It is uncertain whether ^{177}Lu-PSMA-617 reduce severe adverse events ≥grade 3 in patients with mCRPC more than cabazitaxel because the certainty of this evidence is very low (*Table 15*)
3) It is uncertain whether ^{177}Lu-PSMA-617 reduce severe adverse events ≥grade 3 in patients with mCRPC more than docetaxel because the certainty of this evidence is very low (*Table 16*)

Results – adverse events narrative summary

^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone

The registered adverse events in the VISION study were mostly mild (*Table 17*) (40). Examples of the most common adverse events of any grade with treatment of ^{177}Lu-PSMA-617 in combination with standard of care therapy and treatment with standard of care therapy alone, include fatigue (43% vs. 23%), dry mouth (39% vs. 1%), and pain from various locations (6-23% vs. 3-15%), in addition to several haematological events, including thrombocytopenia (17% vs. 4%) (40).

Table 17: Overview of adverse events - the VISION study

Sartor 2021 (VISION) (40)	**^{177}Lu-PSMA-617 + SoC (n=529)**		**SoC (n=205)**	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
All patients with AE	519 (98%)	279 (53%)	170 (83%)	78 (38%)
AE that led to a reduction in ^{177}Lu-PSMA-617 dose	30 (6%)	10 (2%)	n.a.	n.a.
AE that led to discontinuation of ^{177}Lu-PSMA-617	63 (12%)	37 (7%)	n.a.	n.a.
AE that led to death*	19 (4%)	19 (4%)	6 (3%)	6 (3%)
Examples of AE reported in the VISION study				
Fatigue	228 (43%)	31 (6%)	47 (23%)	3 (2%)
Dry mouth	205 (39%)	0	1 (1%)	0
Thrombocytopaenia	91 (17%)	42 (8%)	9 (4%)	2 (1%)
Pain – back	124 (23%)	17 (3%)	30 (15%)	7 (3%)
Pain – extremity	45 (9%)	3 (1%)	12 (6%)	0
Pain - bone	59 (11%)	13 (3%)	17 (8%)	5 (2%)
Pain - abdomen	32 (6%)	5 (1%)	7 (3%)	1 (1%)
Examples of treatment emergent AE reported in the VISION study				
Bone marrow suppression†	251 (47%)	124 (23%)	36 (18%)	14 (7%)
Hepatotoxicity††	54 (10%)	15 (3%)	16 (8%)	5 (2%)
Renal effects‡	46 (9%)	18 (3%)	12 (6%)	6 (3%)
QT prolongation§	9 (2%)	7 (1%)	1 (1%)	1 (2%)

AE: adverse events, n.a.: not applicable, SoC: standard of care therapy
** Death is considered grade 5 in the classification of adverse events (46).*
†Bone marrow suppression includes anaemia, thrombocytopaenia, lymphopenia, leukopenia, neutropenia, pancytopenia, febrile neutropenia, bicytopenia, bone marrow failure, normocytic anaemia
††Hepatotoxicity includes increased aspartate aminotransferase, blood alkaline phosphatase, alanine aminotransferase, gamma-glutamyltransferase, international normalised ratio, and transaminases, as well as hypoalbuminemia, hyperbilirubinemia, ascites, acute hepatic failure, cholestasis, hepatic encephalopathy, hepatic failure, hepatic lesion, hepatitis, hepatocellular injury, and jaundice.
‡Renal effects include acute kidney injury, proteinuria, and renal failure, as well as increased blood creatinine and blood urea, and decreased urine output
§QT prolongation includes syncope, ventricular tachycardia, loss of consciousness, and cardio-respiratory arrest

However, the VISION study also listed some treatment emergent adverse events of particular interest, including bone marrow suppression, hepatotoxicity, renal effects and QT prolongation (*Table 17*) (40). Of the patients who received ^{177}Lu-PSMA-617 in combination with standard of care therapy, 9% experienced treatment emergent renal adverse events of any grade, and only 3% experienced treatment emergent adverse

events ≥grade 3 (40). These numbers are similar to the group who received standard of care therapy alone (6% and 3%, respectively) (40).

Furthermore, 6% and 12% of patients who received ^{177}Lu-PSMA-617 in combination with standard of care therapy experienced adverse events of any grade that led to a reduction of the ^{177}Lu-PSMA-617 dose, and to discontinuation of ^{177}Lu-PSMA-617, respectively (*Table 17*) (40). Treatment related deaths were similar between the two groups (*Table 17*), with 19 registered treatment related deaths (4%) in the ^{177}Lu-PSMA-617 plus standard of care group, and six treatment related deaths (3%) in the standard of care therapy alone group (40).

^{177}Lu-PSMA-617 versus cabazitaxel

The registered adverse events in the TheraP study were mostly mild (*Table 18*) (39). Examples of the most common adverse events of any grade with treatment of ^{177}Lu-PSMA-617 and treatment with cabazitaxel, include fatigue (75% vs. 76%), dry mouth (60% vs. 21%), dry eyes (30% vs. 4%), and pain from various locations (4-29% vs. 5-24%), in addition to several haematological events, including thrombocytopenia (29% vs. 5%) (39).

Table 18: Overview of adverse events - the TheraP study

Hofman 2021 (TheraP) (39)	**^{177}Lu-PSMA-617 (n=98)**			**Cabazitaxel (n=85)**		
	Grade 1-2	**Grade 3-4**	**Grade 5**	**Grade 1-2**	**Grade 3-4**	**Grade 5**
All patients with AE	53 (54%)	32 (33%)	13 (13%)	34 (40%)	45 (53%)	6 (7%)
Examples of AE reported in the TheraP study*						
Fatigue	69 (70%)	5 (5%)	0	61 (72%)	3 (4%)	0
Dry mouth	59 (60%)	0	0	18 (21%)	0	0
Dry eyes	29 (30%)	0	0	3 (4%)	0	0
Thrombocytopaenia	18 (18%)	11 (11%)	0	4 (5%)	0	0
Pain – back	26 (26%)	3 (3%)	0	23 (24%)	0	0
Pain – extremity	13 (13%)	1 (1%)	0	5 (6%)	1 (1%)	0
Pain - bone	15 (15%)	1 (1%)	0	13 (14%)	0	0
Pain - abdomen	4 (4%)	0	0	4 (5%)	0	0
Cardiac disorders**	9 (9%)	3 (3%)	0	3 (4%)	4 (5%)	0
Acute kidney injury	0	1 (1%)	0	2 (2%)	1 (1%)	0
Hepatic failure	0	0	1 (1%)	0	0	0

AE: adverse events, n.a.: not applicable
Grade 5 is defined as death in the classification of adverse events (46).
***Cardiac disorders include acute coronary syndrome, atrial fibrillation, heart failure, myocardial infarction, palpitations, sinus tachycardia, supraventricular tachycardia*

However, both groups also experienced some more serious adverse events, including cardiac disorders, hepatic failure and acute kidney failure (*Table 18*) (39). Of the patients who received ^{177}Lu-PSMA-617, none experienced acute kidney failure events of grade 1-2, and only 1% experienced adverse events grade 3-4 (39). In the group who received cabazitaxel, the same numbers were 2% and 1%, respectively (39).

^{177}Lu-PSMA-617 versus docetaxel

The registered adverse events in the study by Satapathy et al. were mostly mild (*Table 19*) (41). Examples of the most common adverse events of any grade with treatment of ^{177}Lu-PSMA-617 and treatment with docetaxel, include fatigue (45% vs. 35%), dry

mouth (60% vs. 0%), and pain from various locations (5-30% vs. 10%), in addition to several haematological events, including thrombocytopenia (25% vs. 30%) (41).

Table 19: Overview of adverse events - the Satapathy study

Satapathy 2021 (41)	**^{177}Lu-PSMA-617 (n=20)**		**Docetaxel (n=20)**	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
All AE	n.a.	6 (30%)	n.a.	10 (50%)
AE that led to dose reduction	1 (5%)	1 (5%)	3 (15%)	3 (15%)
AE that led to drug discontinuation	2 (10%)	2 (10%)	1 (5%)	1 (5%)
AE that led to death*	2 (10%)	2 (10%)	1 (5%)	1 (5%)
Examples of AE reported in the Satapathy study				
Fatigue	9 (45%)	0	7 (35%)	0
Dry mouth	12 (60%)	0	0	0
Dry eyes	2 (10%)	0	0	0
Thrombocytopaenia	5 (25%)	2 (10%)	6 (30%)	1 (5%)
Pain - abdomen	1 (5%)	0	2 (10%)	0
Pain - generalised	6 (30%)	0	2 (10%)	0
Hepatotoxicity**	1 (5%)	0	2 (10%)	0
Nephrotoxicity	1 (5%)	0	4 (20%)	1 (5%)

AE: adverse events, n.a.: not available
**Death is considered grade 5 in the classification of adverse events (46).*
***Hepatotoxicity includes raised serum bilirubin and decreased serum albumin*

However, the study by Satapathy et al. also listed some more serious adverse events, including hepatotoxicity and nephrotoxicity (*Table 19*) (41). Of the patients who received ^{177}Lu-PSMA-617, one (5%) experienced renal adverse events of any grade, and none experienced adverse events ≥grade 3 (41). The corresponding numbers in the group who received docetaxel were 4 (20%) and one (5%), respectively (41).

Furthermore, one (5%) and two (10%) of patients who received ^{177}Lu-PSMA-617 experienced adverse events that led to a reduction of the ^{177}Lu-PSMA-617 dose, and to discontinuation of ^{177}Lu-PSMA-617, respectively (*Table 19*) (41). For patients who received docetaxel, these numbers were three (15%) and one (5%), respectively. The study also registered one (5%) treatment related death in the ^{177}Lu-PSMA-617 group, and two (10%) treatment related deaths in the docetaxel group (41).

Results – quality of life

^{177}Lu-PSMA-617 plus standard of care therapy versus standard of care therapy alone

In the VISION study, the published hazard ratio (95% CI) for time to worsening (i.e., earliest occurrence of a ≥10 point decrease relative to baseline, disease progression, or death) in FACT-P was statistically significant in favour of ^{177}Lu-PSMA-617 in combination with standard of care therapy: 0.54 (0.45 to 0.66) (40). In other words, patients who received ^{177}Lu-PSMA-617 in combination with standard of care therapy, experienced worsening, i.e., ≥10 point decrease relative to baseline, disease progression, or death, at 54% of the rate of patients who received only standard of care therapy (*Table 20*).

Table 20: Summary of findings table - quality of life in the VISION study

Author, (study name) study type, participants	FACT-P			Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
	Median time to deterioration (months)		Hazard ratio (95% CI)		
	^{177}Lu-PSMA-617 + SoC	SoC			
Sartor 2021 (VISION) 1 RCT	5.7	2.2	**HR 0.54** (0.45 – 0.66)	⊕⊕⊕ Moderate	^{177}Lu-PSMA-617 + SoC probably improves QoL (Moderate certainty evidence)

CI: confidence interval: FACT-P: functional assessment of cancer therapy – prostate, HR: hazard ratio, n: total number of participants in the study; RCT: randomized controlled trial, SoC: standard of care therapy

^{177}Lu-PSMA-617 versus cabazitaxel

In the TheraP study, the published mean scores (95% CI) for the patient-reported EORTC QLQ-C30 domain Global Health Status were 63 (60-67) in the ^{177}Lu-PSMA-617 group and 60 (57-64) in the cabazitaxel group (39). We calculated the mean difference (95% CI) on Global Health Status to be 3.2 (-1.5 to 7.8), which indicates that treatment with ^{177}Lu-PSMA-617 gives better overall quality of life than treatment with cabazitaxel (*Table 21*). However, the confidence interval includes values below 0, so it is statistically possible that patients who receive ^{177}Lu-PSMA-617 have equal or worse quality of life compared to those who receive cabazitaxel (*Table 21*).

Clinical meaningful improvements were also found for other patient-reported QLQ-C30 domains, including fatigue, diarrhoea, insomnia, and social functioning, in favour of ^{177}Lu-PSMA treatment (39). Data on all QLQ-C30 domains are shown in *Appendix 7: Quality of life – Hofman et al (TheraP study)*.

Table 21: Summary of findings table - quality of life in the TheraP study

Author, (study name) study type, participants	EORTC QLQ-C30 Mean global health status score (95% CI)		Mean difference (95% CI)	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
	^{177}Lu-PSMA-617	Cabazitaxel			
Hofman 2021 (TheraP) 1 RCT	**63** (60-67)	**60** (57-64)	**MD 3.2** (-1.5 to 7.8)	⊕ Very low	It is uncertain whether ^{177}Lu-PSMA-617 improve QoL because the certainty of this evidence is very low

CI: confidence interval: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- cancer 30, n: total number of participants in the study; MD: mean difference, RCT: randomized controlled trial.

^{177}Lu-PSMA-617 versus docetaxel

In their study, Satapathy et al used the NCCN-FACT-FPSI-17 questionnaire to measure the quality of life of the study participants. The results showed that the ^{177}Lu-PSMA-617 group had a median (interquartile range) score change from baseline of 7 (-4 to 15), indicating an improvement in quality of life, whereas the score change was -8 (-11 to 1) in the docetaxel group, indicating a worsening in quality of life (41). The difference in score change between the groups was statistically significant, with a p-value of 0.003, in favour of ^{177}Lu-PSMA-617 (*Table 22*).

Statistically significant differences in score changes between the two groups were also found for other NCCN-FACT-FPSI-17 domains, including emotional symptoms, physical symptoms, and treatment side-effects, in favour of ^{177}Lu-PSMA-617 treatment (41). Data on all NCCN-FACT-FPSI-17 domains are shown in *Appendix 7: Quality of life – Satapathy et al*.

Table 22: Summary of findings table - quality of life in the study by Satapathy et al

Author, (study name) study type, participants	NCCN-FACT-FPSI-17 Median change in score from BL (IQR)		p-value	Certainty of the evidence (GRADE)	Standardised statements for the reporting of effect
	^{177}Lu-PSMA-617	Docetaxel			
Satapathy 2021 1 RCT	**7** (-4 to 15)	**-8** (-11 to 1)	**0.003**	⊕⊕ Low	^{177}Lu-PSMA-617 may improve quality of life (Low certainty evidence)

BL: baseline, CI: confidence interval, IQR: interquartile range (1st quartile to 3rd quartile), n: total number of participants in the study; NCCN-FACT-FPSI-17: National Comprehensive Cancer Network - Functional Assessment of Cancer Therapy – FACT Prostate Cancer Symptom Index - 17 Item Version. RCT: randomized controlled trial

Based on the assumed threshold of minimal clinically important difference of absolute score change of 5 and our GRADE assessments, we can summarise the results of the mean difference and hazard ratio (using standardised sentences) as follows:

1) ^{177}Lu-PSMA-617 in combination with standard of care therapy probably improve the quality of life in patients with mCRPC more than treatment with standard of care therapy alone (moderate certainty evidence) (*Table 20*)
2) It is uncertain whether ^{177}Lu-PSMA-617 improves quality of life in patients with mCRPC more than cabazitaxel because the certainty of this evidence is very low (*Table 21*)
3) ^{177}Lu-PSMA-617 may improve quality of life in patients with mCRPC more than docetaxel (low certainty evidence) (*Table 22*)

Radiation safety and legislative aspects

Introduction

This chapter assesses radiation safety challenges and consequences associated with establishment of ^{177}Lu-PSMA-617 as a treatment option in Norway. We discuss aspects of radiation safety in connection with the Norwegian legislations where it is necessary. We also assess aspects about radiation protection that may have organisational or health economic consequences. According to the Radiation Protection Regulations, medical use of radiation is justified if the total diagnostic or therapeutic benefits, for the individual and society, is higher than the disadvantages with radiation (48). From a radiation safety perspective, the disadvantages with radioligand therapy (RLT) are the potential radiation exposure of hospital staff, the public, the environment, the family members of patients and the radiation risk for the patients. The Radiation Protection Regulations have requirements to ensure that the radiation exposure is as low as reasonably achievable and below dose limits, to ensure that the risk for harm from radiation exposure is minimized. In addition, Regulations on the application of the Pollution Control Act to radioactive pollution and radioactive waste has established clearance levels for discharge. Implementing the requirements in the legislations will reduce the risk of unintended exposure of staff, public and environment.

Methods

The assessment of radiation safety challenges and consequences is mainly based on international guidelines and recommendations, the Norwegian radiation protection legislation, experiences from administration of the regulations, and input from expert representatives. Keywords related to radiation safety were used to identify relevant publications from the systematic literature search performed by FHI. Two publications were used as examples of dose rate measurements and estimations in other countries. Medical physicist in the expert representatives' group have also contributed substantially to this chapter, with focus on dosimetry and practical implementations of the requirements in the Norwegian legislations and international guidelines.

^{177}Lu-PSMA radiation characteristics for radionuclide therapy

Lutetium-177 is a reactor-made isotope and decays with β- and γ-radiation with a half-life of 6.7 days. The β-particles deliver the cytotoxic radiation to the cells with a

maximum β⁻-energy of 498 keV and a maximum soft-tissue range of 1.7 mm, causing minimal effect on surrounding tissue. The γ-emission (113 keV [6%] and 208 keV [11%]) can be used for imaging and quantification with gamma camera (planar and single photon emission tomography/computed tomography [SPECT/CT]) (28;49;50).

Assessment of radiation safety challenges and consequences

License for use

Hospitals planning to acquire and administer radiopharmaceuticals or substances in connection with medical diagnostics and therapy need a license from the Norwegian radiation and nuclear safety authority (DSA). For medical therapy with radiopharmaceuticals or substances, the license is nuclide specific. That means that for a hospital to use ^{177}Lu-PSMA, a license for lutetium-177 is needed. Five hospitals have license for use of lutetium-177 in Norway today. Hospitals that do not have license for this use and wish to acquire and administer ^{177}Lu, need to apply for such a license. There is no fee for this application or license.

Holders of a Manufacturing and Importation Authorization (MIA) or a Wholesaler Distribution Authorization (WDA) issued within the EU/EEA can perform wholesaler activities in Norway for the products and activities covered by the MIA/WDA. The Norwegian Medicines Agency (NoMA) should be notified when such activities are planned. "Agilera Pharma AS" (formerly known as Institute for Energy Technology (IFE)) has this permit in Norway today. They also have, per 2023, a valid permission from DSA to import and distribute radiopharmaceuticals to hospitals.

Radiation protection of hospital staff, the public and family members of patients

To comply with the Radiation Protection Regulations regarding acquiring and administering radiopharmaceuticals or substances in connection with medical diagnostics and therapy, the hospitals must have arrangements established for logistics, facilities, and procedures as well as relevant expertise within the field of radiation protection and nuclear medicine.

Hospitals that already possess a license for the administration of radioactive substances have to reconsider the conditions when initiating new treatments and/or increasing the quantity of use, including design and shielding of the facilities, and competence and expertise. Logistics and work operations must be carefully planned to comply with national dose limits and other requirements in accordance with the Radiation Protection Regulations. In addition, practices are needed to secure compliance with the dose limits to the public and caregivers when discharging patients from the hospital after radionuclide therapy.

The Radiation Protection Regulations require that the hospitals shall plan the use of radiation and protective measures to ensure that exposure of the non-occupationally exposed workers and the public, shall not exceed an effective dose of 0.25 mSv/year.

When planning for implementation of a new nuclear medicine therapy, hospitals must consider the radiation characteristics of the nuclide, and the quantity of radioactivity, the excretion rate (biological half-life) and the total number of treatments to ensure that the above-mentioned dose constraint is not exceeded.

Facilities and logistics

Patients who receive ^{177}Lu-PSMA-617 will expose their surroundings to radiation for a certain amount of time. During and after the administration of the treatment, the patients must stay in a room with sufficient distance and/or shielding from other patients and the general public. The room must be designed in such a way that a person in a neighbouring room (below, above, next to) will not receive a dose exceeding the dose constraint of 0.25 mSv/year. The shielding assessment is normally done by a physicist that considers the following:

- The radiation characteristics of the nuclide
- The quantity of radioactivity, the excretion rate (biological half-life)
- The number of treatments
- The amount of radioactivity per patient,
- Time spent in the room
- Distance, shielding, and the occupation of the neighboring rooms

In general, hospitals receive single patient doses for nuclear medicine therapy. These doses must be carefully transported to the hospital and the reception and storage must be handled in a secure manner. Regulations regarding transport of radioactive materials has to be followed (51;52).

Radiation protection of staff

The Regulations on Radiation Protection and Use of Radiation has requirements on competence in radiation protection for employees involved in nuclear medicine, and employees who can be exposed for ionizing radiation in general. Relevant competence and training are important to ensure safe handling of radioactive sources and radiation protection of employees. The hospitals are responsible for employee competence and training concerning radiation protection and the use of radiation related to their work. As such, the hospitals must ensure adequate education and training of the employees involved, regarding radiation protection related to the characteristics of ^{177}Lu-PSMA-617. Relevant procedures must be established and available and should include radiation protection adapted to the use of ^{177}Lu-PSMA-617. In addition, the hospitals must ensure that personal protective equipment and technical safety systems is available when necessary.

General public and family members of the patient

Patients who receive ^{177}Lu-PSMA-617 will expose their surroundings to radiation for a certain amount of time. It is therefore necessary to install proper precautions to limit the exposure to members of the public, family members, and caregivers. Patients should be given radiation protection advice on how to limit the radiation exposure of others before discharge. The evaluation of when to discharge the patient from the hospital must be considered by the hospitals that is responsible for the treatment and should be based on a risk assessment. In some cases, hospitalization of patients might be necessary. Patients can be discharged once the radiation exposure of individual members of the public are assessed to be below the set limit (maximum 0.25 mSv per year). The expected duration of the hospital stay depends on several factors, including the dose and type of radiopharmaceutical given, excretion rate, patient's home situation and illness. Other factors, such as incontinence, nausea, or the patient's ability to comply with radiation protection advice should also be considered before discharge. In addition, there are

guidelines on dose constraints for caregivers of patients treated with radiopharmaceuticals. These guidelines presents an opportunity of allowing exposure of caregivers above given dose limits if this can be justified (53;54).

Some studies have investigated the outpatient treatment protocol, radiation safety and radiation characteristics of ^{177}Lu-PSMA (55;56). Radiation exposure to the public and/or caregivers were, amongst others, investigated. Discharge of patients were done at different timepoints after hospitalization (from 6 hours to 48 hours and 72 hours). In both studies the maximum doses to the individual members of the public and/or caregivers per treatment cycle was approximately 0.25 mSv, with some restrictions on behaviour. Details in radiation safety rules and requirements given to the patients and/or companions are not described. By giving the patients strict advice on behaviour for radiation protection of others, the time before discharge may be shortened. This includes restrictions such as limited close contact with family, children, and pregnant women, as well as keeping distance to others in public (public transportation etc).

Although the majority of patients most likely do not need hospitalization and can be discharged after some hours with restrictions on radiation protection, hospitals planning to establish ^{177}Lu-PSMA-617 as a treatment option should also have in mind the possibility that some patients may need hospitalization.

Radioactive waste management and permit for discharge

Using radiopharmaceuticals for therapy or diagnostics will lead to a wide range of radioactive waste, both in solid and liquid form. Liquid waste is mostly contaminated wastewater from the therapy ward consisting of bodily excretions discharged to the sewer system. Solid waste may include protective clothing, containers of used radiopharmaceutical, paper towels, and contaminated or used laboratory equipment. In the case of incontinent patients, solid waste may also include used incontinence pads and other urinary incontinence products that need to be stored and handled in a safe manner.

For legal and regulatory purposes, radioactive waste is material which no further use is foreseen, that contains or is contaminated with radionuclides at activity concentrations greater than clearance levels as established by the regulatory body (57). In Norway, clearance levels are given by Regulations on the application of the Pollution Control Act (58) to radioactive pollution and radioactive waste, which is regulated by DSA.

Implementing ^{177}Lu-PSMA-617 as a treatment option in Norway, with the foreseen increase in number of ^{177}Lu-RLT patients, will lead to an increase in radioactive discharge to the sewer system (liquid waste) and possibly an increase of solid waste. Discharge to the sewer system above the clearance limits is to be regarded as radioactive pollution and is not allowed without a permit from DSA. The permit can be issued after an application from the hospital against payment of a fee to cover the administrative costs. The fee rates can be found in Chapter 10 of Regulations relating to pollution control (59), in which the fees issued to hospitals are typically at the lower range of the values given at §39-4, between Rate 6 and 9 (i.e., between NOK 37 400 and NOK 7 500 in 2023). The fee rate relies mainly on the predicted amount of discharge, as well as the type of radionuclides in question. The hospital must be able to provide well founded evaluations regarding the impact of the given discharge of radioactive waste on the environment and human health, where they show that said impact is on an acceptable level. In existing

hospital buildings, current measures for reducing the radioactive pollution have low cost-benefit. If planning new hospital facilities involving patient treatments with radioactive substances, reduction of radioactive pollution, e.g., by the use of delay tanks, must be considered.

Hospitals should minimize the radioactive waste generated and ensure that it is kept separate from other waste. The dose rate outside storage room shall not exceed 7.5 μSv/t according to § 25e of Act on Radiation Protection and Use of Radiation (48). Waste that contains nuclides and is not discharged to the sewer system, should be set to decay before it can be disposed as ordinary waste, hazardous waste or others, depending on other contents of the waste (48). Waste containing nuclides that has not decayed below clearance limits within a year, must be declared and delivered to a facility that has a permit to handle such waste.

Dosimetry

Medical use of radiation must be optimised and planned to each individual patient (48). The European Association of Nuclear Medicine (EANM) encourages the practice of patient-specific dosimetry in therapy with ^{177}Lu-labelled compounds (60). For the purpose of organ and tumour dosimetry, planar and/or SPECT/CT imaging can be performed post therapy to achieve time-activity-curves (TACs) of the ^{177}Lu-PSMA-617 uptake. The time-integrated activity can then be calculated from the TAC and subsequently converted into absorbed doses to the specific target region. International dosimetry guidelines recommend 1-4 SPECT/CT scans (or possibly a planar-SPECT/CT imaging approach) up to 7 days post therapy for the basis of dose estimations of tumours and critical organs (like kidneys, salivary glands and lacrimal glands) (60). Dedicated dosimetry software may be beneficial to reduce the time needed to perform each dosimetry.

Absorbed doses, dose-related toxicities for organs at risk and long-term radiation effects

The salivary glands, lacrimal glands, kidneys, and bone marrow are the main organs at risk for therapy with ^{177}Lu-PSMA-617. Estimated absorbed doses for these organs are summarized in *Table 23*.

Salivary and lacrimal glands

Radiation exposure to the salivary glands (parotid, submandibular and sublingual glands) may cause xerostomia (dry mouth) (61). The salivary glands can be expected to achieve absorbed doses in the range of 0.5-1.9 Gy/GBq (60). Salivary gland toxicity causing xerostomia is a common side effect from ^{177}Lu-PSMA therapy with an estimated 22% of patients. However, only 2% of the patients experience grade 3 or 4 toxicity (61). It can be noted that xerostomia is often reversible for accumulated doses below 30 Gy (62). However, the tolerance level for salivary glands is inadequately identified. For the parotid glands an absorbed dose limit as low as 20 Gy has been proposed (60). Absorbed doses for the lacrimal glands are considerably higher than for salivary glands, with reported values of 0.4-3.8 Gy/GBq. However, despite the high reported doses to the lacrimal glands, no significant concern of xerophthalmia (dry eyes) has been reported (60-62).

Kidneys

The absorbed doses to the kidneys are expected to be in the order of 0.4-0.8 Gy/GBq (60). A dose of 23 Gy to the kidneys causes detrimental deterministic effects in 5% of patients within 5 years. However, studies from radionuclide therapy of neuroendocrine tumours have demonstrated that biological equivalent doses (correcting for the effect of dose fractionation) less than 40 Gy were safe for patients without any risk factors. The threshold is reduced to 28 Gy for patients with risk factors (such as hypertension, diabetes, age over 60 years, and previous chemotherapy) (63). Nephrotoxicity occurs in about 13% of patients receiving ^{177}Lu-PSMA, but only 1% grade 3 or grade 4 toxicities are reported (60;61;63). European guidelines recommends that a cumulative kidney absorbed dose of 40 Gy should not be exceeded in non-compromised patients with a life expectance > 1 year (64).

Bone marrow

The bone marrow is also considered a critical organ for radionuclide therapy in general. With ^{177}Lu-PSMA therapy, the absorbed dose to the red marrow is estimated to be 0.035 Gy/GBq (28). Hematologic toxicity is the most common adverse event after ^{177}Lu therapy, with the most frequent myelosuppression-related grade 3-4 toxicities being anaemia (12.9%), lymphopenia (7.8%), leukopenia (2.5%) and thrombocytopenia (7.9%) (40). Such toxicities may be attributed to the effects of ionizing radiation on sensitive precursor cells in circulation or in the bone marrow close to metastatic bone lesions (65). Generally, 2 or 3 Gy is considered to be the absorbed dose limit for the bone marrow to avoid hematologic toxicity (66;67). However, confirmation of the correct threshold is still needed for therapies using ^{177}Lu-PSMA (60).

Long-term radiation effects

Patients indicated for the ^{177}Lu-PSMA-617 (Pluvicto) treatment typically have a short life expectancy (68). The risk for long-term radiation effects, like radiation induced malignancy, is therefore neglectable (69). However, if the treatment is to be used at other patient papulations and stages of decease, the long-term radiation effects will need to be explored.

Individual assessments

In general, patients with mCRPC eligible for ^{177}Lu-PSMA-617 therapy have a high burden of disease and short overall survival. Higher doses to the organs-at-risk than the limits above may be justified after benefit-to-risk ratio evaluation for the individual patient (68).

Table 23: Estimated absorbed doses to critical organs after therapy with ^{177}Lu-PSMA

	Absorbed dose per unit activity (Gy/GBq)	Absorbed dose per unit activity (Gy/GBq)	Absorbed dose 1 treatment (7.4 GBq)	Absorbed dose 6 treatments (6 x 7.4 GBq)
Organ	*Sjögreen Gleisner et al. (60) Mean ranges*	*VISION sub-study (28;40) Mean ± SD*		
Salivary glands	0.5 - 1.9	0.63 ± 0.36	4.5 ± 2.6	28 ± 16
Lacrimal glands	0.4 - 3.8	2.1 ± 0.47	15 ± 3.4	92 ± 21
Kidneys	0.4 - 0.8	0.43 ± 0.16	3.1 ± 1.2	19 ± 7.3
Red marrow	-	0.035 ± 0.020	0.25 ± 0.15	1.5 ± 0.9

Gy: Gray, GBq: giga becquerel, SD: standard deviation

The EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA ligands states that ^{177}Lu-PSMA has a favourable safety profile with high response rates and low toxicity in patients with mCRPC (64). Multiple therapy cycles of ^{177}Lu-PSMA with a total cumulative activity of 32-40 GBq is suggested to be safe and justifiable (62;70).

Staff resources and expertise

An introduction of radioligand therapy for treating high-incidence cancer like prostate cancer may require an expansion of existing facilities. The higher activity levels needed for therapy, in combination with the different radionuclides involved, as well as the multiple steps in the process, demand a higher degree of expertise than for diagnostic nuclear medicine procedures (71).

Accessibility of a well-trained and experienced workforce may become a challenge in the possible implementation of radionuclide therapy with ^{177}Lu-PSMA in Norway.

In Norway, an oncologist or a nuclear medicine physician with medical and radiation protection competence are responsible to assess and verify eligibility and optimization for radionuclide therapies (48). Treatment initiation and continuation for ^{177}Lu-PSMA therapies is normally decided by a multidisciplinary team. The participation of nuclear medicine specialists in such a team is important to ensure acceptance and awareness of radioligand therapies (71).

There may be a need for an increase in technicians for dose preparations, injections/infusions of ^{177}Lu-PSMA, and increased number of ^{68}Ga/^{18}F-PSMA PET ~~and time spent on scanning procedures~~. The medical physicist may have a central role regarding radiation safety/protection procedures and dosimetry. There will most likely be a need for increase in physicists for dosimetry and general radiation protection assessments. Physicists may be involved in the evaluation of shielding needed, and the evaluation of when to discharge the patient.

Nurses and coordinators may be needed for patient handling and preparation procedures, monitoring the patients during a possible hospitalization and management of possible side-effects.

Organisational aspects

Introduction

The objective of this chapter is to provide information on organisational aspects of implementing ^{177}Lu-PSMA-617 treatment for mCRPC in Norway. How this treatment option will affect the allocation and organisation of different types of resources, structures, and processes in the health service is of major importance.

In case of implementing ^{177}Lu-PSMA-617 in Norway, there is a need for a higher degree of involvement of experts to consider organisational matters more precisely. The current investigation of organisational implications is part of the basis for the health economic evaluation in this HTA and is not detailed enough when it comes to certain important matters. In case of implementing ^{177}Lu-PSMA-617 in Norway, there is a need for a higher degree of involvement of experts to consider organisational matters more precisely.

To elucidate possible organisational aspects, we provide information on:

- Current organisation of health services and treatment options for patients with mCRPC
- The patient population eligible for ^{177}Lu-PSMA-617 treatment
- The anticipated treatment course of ^{177}Lu-PSMA-617 with emphasis on needed resources, which include:
    - Diagnostics, selection of patients and treatment planning
    - Execution of the treatment and patient follow-up during the treatment day
    - Follow-up between treatment cycles and after the final cycle
    - Follow-up after the treatment course has ended
    - Management of complications, adverse events and side effects
- Centralised versus decentralised organisation of ^{177}Lu-PSMA-617 treatment
- Work processes, equipment, staff and training
- Patient information, -involvement, and -practical implications
- Organisation of quality assurance and monitoring of the method

What concerns the practice of radiopharmacy, the diagnostic radiopharmaceuticals, and the expected radiation hygiene related to ^{177}Lu-PSMA-617 treatment, is presented in the chapter on *Radiation safety and legislative aspects*.

Methods

We have not found any previous documentation about possible organisational consequences with an introduction of ^{177}Lu-PSMA-617 in Norway – neither at a national level nor at a regional level. Therefore, we collected information from a variety of sources

to contour possible organisational implications of implementing ^{177}Lu-PSMA-617 treatment for mCRPC in Norway. We have used information from the following representatives for investigating organisational implications:

- The clinical experts (refered to as *the expert representatives* below), as mentioned in *Preface*
- Patient representatives, as mentioned in *Preface*
- The Norwegian Radiation and Nuclear Safety Authority *Preface*

At start-up of this HTA work, we arranged a joint digital meeting with the expert- and patient representatives, experts from DSA (i.e., The Norwegian Radiation and Nuclear Safety Authority) and the internal project group, to inform about the commission and the work process of this HTA. As part of the meeting, we collected some information about today's health services and the representatives' experiences and reflections of ^{177}Lu-PSMA-617 treatment for mCRPC. Next, we emailed a questionnaire to expert representatives and Novartis to ensure important information about possible organisational implications, and we arranged another digital meeting with organisational implications on the agenda. The experts from DSA also gave their comments to this part of the HTA in digital meetings we arranged with them and to the first written draft of this chapter. The expert group, the patient representatives, the DSA working group and the FHI project group were all invited to comment on the draft before completion.

As part of the information retrieval on organisational aspects, we also collected information from:

- Medication review from the European Medicines Agency (28)
- The Norwegian Pharmaceutical Product Compendium (72)
- Novartis documentation package on ^{177}Lu-PSMA-617 (73)
- Cancer Registry of Norway (74)
- Yearly report from the Norwegian Prostate Cancer Registry (2021) (2)
- The Norwegian national action program for diagnostics, treatment and follow-up of prostate cancer (7)

In addition, we included information form articles recommended by the experts and articles that we found through searches.

Current organisation of health services and treatment options

According to information in the yearly report from the Norwegian Prostate Cancer Registry (2), treatment and follow-up of prostate cancer is provided by 13 hospitals in Norway. In addition, there might be a few private hospitals offering treatment to patients with prostate cancer. In cases of mCRPC, diagnostics, treatment and follow-up are organized and provided by the same hospitals.

The Norwegian national action program with guidelines for diagnostics, treatment and follow-up of prostate cancer was updated in 2023 (7). The action program describes that hospitals investigating and treating prostate cancer are supposed to arrange interdisciplinary meetings to discuss the investigation and treatment options of their patients. According to action program, interdisciplinary meetings must be attended by urologist, radiologist, oncologist and pathologist" (i.e., a multidisciplinary team; MDT) (7). However, according to the expert representatives, the MDT should include

oncologist, specialist in nuclear medicine, radiologist, and medical physicist in cases of diagnostics, treatment, and follow-up of eligible patients for ^{177}Lu-PSMA-617 treatment. This needs to be further clarified if this treatment is to be introduced in Norway.

As previously described, the Norwegian national action program describes the current life-prolonging treatment options for mCRPC, which includes abiraterone or enzalutamide, olaparib (for patients with BRCA1/2 mutations), docetaxel, cabazitaxel and radium-223 (7). Choice of treatment is mainly based on progression of the disease, previous treatment, and tolerability (7). The action program briefly mentions ^{177}Lu-PSMA-617 treatment as a new treatment for mCRPC, and that the treatment is not available for use in clinical practice in Norway (as per January 2023) (7).

As previously mentioned, per April 2023, at least two patients have been treated with ^{177}Lu-PSMA I&T for mCRPC in Norway, either funded by the regional health authorities or locally by hospital department. Furthermore, approximately 30 patients have received ^{177}Lu-PSMA treatment in Finland and Germany; ten persons in 2023, fourteen in 2022, and six persons prior to that. Some of these patients were referred by Norwegian clinicians, while an unknown number of the patients have taken the initiative themselves and applied for the treatment. If ^{177}Lu-PSMA-617 is approved as a routine treatment option of mCRPC in Norway, the start-up patient population will probably not be impacted by the small numbers that already started the treatment abroad.

The patient population

Expert representatives have estimated that around 400-500 new patients with PSMA-positive mCRPC per year will be eligible and thus candidates for ^{177}Lu-PSMA-617 treatment in Norway. This number is in line with the yearly report from the Norwegian Prostate Cancer Registry (2). In the VISION study), the intervention group received a maximum of six treatments with ^{177}Lu-PSMA-617, and an average of 4.46 ^{177}Lu-PSMA-617 treatments (40). Based on the average number of ^{177}Lu-PSMA-617 treatments, the health-services need to be prepared for about 2 200 treatments per year on average.

Table 24 summarises the approximate number of patients expected to be eligible for ^{177}Lu-PSMA-617 treatment distributed by region (and in the six university hospitals) in Norway, as informed by the expert representatives in the external working group.

Table 24: Estimated number of patients and ^{177}Lu-PSMA-617 treatments per health region (and university hospitals)

Health Authority	Patients per year	Treatments per year
Central Norway Regional Health Authority (St. Olav's university hospital)	60 –70	268 – 312
Northern Norway Regional Health Authority (University hospital of North Norway)	50	223
South-Eastern Norway Regional Health Authority (Oslo university hospital and Akershus university hospital)	200 –300	892 –1338
Western Norway Regional Health Authority (Haukeland university hospital* and Stavanger university hospital trust)	50 –100* 20 – 30**	223 – 446* 89 –134**
Total in Norway (range)	380 – 550	1695 – 2453

** Patients from Helse Fonna and Helse Førde adds to this. ** Numbers specifically for Stavanger.*

We have no prerequisite to make assumptions on the numbers of patients with mCRPC who will accept or reject the treatment, nor the numbers of patients who die before all the ^{177}Lu-PSMA-617 cycles have been carried out or discontinue the treatment for any reason.

The anticipated treatment course of ^{177}Lu-PSMA-617

^{177}Lu-PSMA-617 will constitute a new option in mCRPC therapy and will be an addition to the existing treatments that are available today. The expert representatives have conveyed pros and cons concerning the service distribution, i.e., some arguments are in favour of a "centralised" model (treatment provided at the six university hospitals), while others point to advantages with a "decentralised" model (i.e., treatment provided in university hospitals as well as and other relevant local hospitals). The experts highlighted the possibility of a centralised model, at least in the first years after the proposed treatment has been established in Norway. Due to regional differences in patient/treatment volume, challenges related to needed resources will most likely vary between the health regions, and we have not nuanced this in the presentation below.

As ^{177}Lu-PSMA-617 therapy is currently not available in Norway, the course of treatment with ^{177}Lu-PSMA-617 for persons with mCRPC has yet to be outlined in national guidelines (7). Still, ^{177}Lu-PSMA-617 treatment is mentioned in the guideline by the European Association of Urology (EAU), as a treatment option following docetaxel and one line of hormonal treatment (75). As the Norwegian action program is based on the EAU guidelines, it is reasonable to assume that the action program will be updated in line with the EAU guidelines following an implementation of ^{177}Lu-PSMA-617 in Norway. In this chapter, we have attempted to draw a contour of an approximate course of ^{177}Lu-PSMA-617 treatment and the potential needed resources, shown in *Table 25*, with some further descriptions in the following paragraphs. Importantly, the resources needed for the treatment, e.g., related to structure, equipment and staff are to a certain degree implemented in today's treatment course for this patient group. This means that the information on resources outlined below are not necessarily *additional* to what resources are currently in use. We have not been able to separate details on what organisational implications will be added to the current practice, with an implementation of ^{177}Lu-PSMA-617 treatment, as this is likely to vary depending on the individual hospitals that are relevant.

Based on the VISION study, ^{177}Lu-PSMA-617 therapy is typically given as four up to a maximum of six treatment cycles (40). We have chosen to describe the treatment course as various "phases" and tried to outline the anticipated needed resources in each treatment phase (*Table 25*). When treating patients, each case is unique, and the course of action must be adapted to the individual patient. As such, the drawn contour presented in this HTA should not be used as recommendation for practitioners and is only meant to be used for the overall considerations on organisational implications of introducing ^{177}Lu-PSMA-617 to the Norwegian health service.

Table 25: Contour of treatment phases and anticipated resources needed

Phases	Description and needed resources
Phase 1: Diagnostics, selection of patients, and treatment planning (Outpatient setting)	Description: - ECOG performance status (functional status) - Imaging (PSMA PET) - Laboratory test (haematology, chemistry and PSA, GFR) - Patient information - Scheduling, incl. drug ordering Needed personnel: Secretary, coordinator, MDT***, radiographer/ technologist, bioengineer Needed equipment: Machine capacity (PSMA PET); Laboratory (medical biochemistry)
Phase 2: Execution of the treatment (cycles 1 to maximum 6) and follow-up during the treatment day (Outpatient setting)	Description: - Preparations of ^{177}Lu-PSMA-617 - Prepare patient, incl. measures to minimize side effects (such as hydration, premedication for anti-emesis) - Drug administration; patient isolation - Patient observation during and after treatment (approximately 4 hours, until bladder emptying) - (when needed: imaging, possibly gamma camera (planar) and/or SPECT/CT; dosimetry) - Patient information Needed personnel: Secretary, coordinator, nurse, MDT***, (radiographer/ technologist) Needed equipment: Hotlab and further facilities for drug handling, incl. waste handling; Treatment rooms; Patient hotel after treatment to those traveling from a remote location (gamma camera when necessary)
Phase 3: Follow-up between each treatment cycle (4-6 cycles) (Outpatient setting)	Description: - Evaluation of treatment response and adverse effects; Laboratory test (haematology, chemistry and PSA) every 2. to 4. weeks - Further scheduling and drug ordering for next cycle - Evaluation with gamma camera (planar) and/or SPECT/CT might be necessary in some cases, and at least after the final treatment cycle (see phase 4); (dosimetry might be relevant in some cases) - Patient information Needed personnel: Secretary, coordinator, MDT***, (radiographer/ technologist), bioengineer Needed equipment: Diagnostic scanner capacity (gamma camera or SPECT/CT)
Phase 4: Follow-up after the treatment has ended (Outpatient setting)	Description: - Gamma camera (planar) and/or SPECT/CT for evaluation after treatment completion - Standard follow-up for patients with mCRPC (no additional follow-up) - Patient information Needed personnel: Oncologist, specialist in nuclear medicine, radiographer/ technologist; Else no additional resources needed (continue follow-up as usual). Needed equipment: Diagnostic scanner capacity (gamma camera or SPECT/CT); Else no additional resources needed.
Phases 2-4: Management of complications, adverse events, side effects (Outpatient setting and general practitioner)	Description: *A: Acute complications and adverse effects:* Management is like that of similar side effects after other medical treatment. *B: Subacute and long-term complications and side effects:* Management is like that of similar side effects after other medical treatment.

** Resources: The listed resources are indications, and will be decided upon by hospitals that will provide the treatment*

***ECOG: Eastern Cooperative Oncology Group*

****MDT: Multidisciplinary team, i.e., usually oncologist, specialist in nuclear medicine (nuclear medicine physician), radiologist, and medical physicist* (*according to the expert representatives and different from what is described in The Norwegian national action program* (7))

PSMA PET: PET (positron emission tomography) using a radioactive tracer called 68Ga-, 18F-marked PSMA-radioligand

Phase 1: Diagnostics, selection of patients and treatment planning

Phase 1 of ^{177}Lu-PSMA-617 treatment is the initiation of the treatment, and involves diagnostics, patient selection, and treatment planning. The anticipated need for resources for treatment phase 1 is outlined in *Table 25.* The organisational aspects will depend upon whether the treatment is centralised (i.e., at one of the six university hospitals) or decentralised. For example, with a centralised model, referrals for further judgement to decide on ^{177}Lu-PSMA-617 treatment, will probably come from many different hospitals. The initial execution of needed measures (PSMA PET and laboratory tests) can be performed in an outpatient setting. It will be necessary with routines for cooperation between non-university hospitals and university hospitals responsible for decision-making, patient communication, and treatment execution.

Highly specialized expertise and experience constituted by MDT will be required to decide upon the final selection of patients referred for ^{177}Lu-PSMA-617 treatment. Treatment planning for the initial cycle includes review of investigations and ordering ^{177}Lu-PSMA-617. Also, a tentative plan for subsequent treatment cycles and necessary measures will probably be outlined at the starting point. A thorough patient information about the treatment, including necessary radiation hygiene aspects and a clarification of the patient's expectations to the ^{177}Lu-PSMA-617 therapy, is important at the starting point, as well as in all following treatment phases.

Phase 2: Execution of the treatment and patient follow-up during the treatment day

Phase 2 involves the treatment execution, i.e., the administration of ^{177}Lu-PSMA-617 and the immediate patient follow-up after administration. The anticipated need for resources for treatment phase 2 is outlined in *Table 25*. The procedures on the treatment day can likely be performed in an outpatient setting, and the drug administration will be performed either as a slow injection or infusion (28;76). Procedures related to preventive initiatives, patient observation and measures during and after the treatment need to be established, but based on information from the expert representatives, we conclude that resources needed for this are modest. Treatment execution needs to be carefully organised at the day of treatment and must be in line with radiation safety requirements on ^{177}Lu-PSMA-617. The chapter on *Radiation safety and legislative aspects* includes descriptions about treatment rooms, facilities, and management of radioactive waste. Furthermore, as described in the *Radiation safety and legislative aspects* chapter, medical use of radiation must be optimized and planned to each individual patient (48), e.g., by using dosimetry. It is however unclear to us to which degree dosimetry will be needed for each patient treated with ^{177}Lu-PSMA-617.

Phase 3: Follow-up between treatment cycles and after the final cycle

Phase 3 involves the follow-up between treatment cycles and after the final treatment cycle. The anticipated need for resources for treatment phase 3 is outlined in *Table 25*. ^{177}Lu-PSMA-617 is given once every 6-8 weeks for a maximum of 6 doses (cycles) depending on the treatment response (39-41). A coordinator resource will be necessary for handling the logistics and administrative follow-up. Assessments of treatment response and adverse effects must be performed by the MDT, between the ^{177}Lu-PSMA-617 cycles as well as after the final cycle. Evaluation with PSMA PET and/or gamma camera with planar imaging (2D) or SPECT/CT (3D) is supposed to be conducted after the final treatment cycle and might also be necessary between treatment cycles (in

exceptional circumstances). To what extent these measures are required and where they can be performed (i.e., centralised, or decentralised), will influence the needed capacity, personnel resources, and costs, including PET tracers, patient travel and accommodation, medications, and other medical consumables. Blood sampling and -evaluations between treatments may be done at a local hospital or by the general practitioner (approximately every 3 weeks (2. to 4. week) during treatment and 3 weeks after the final cycle). MDT will likely decide upon the next steps in the treatment plan, with subsequent scheduling and drug ordering for the next cycle (7). A final evaluation regarding treatment response, toxicity and adverse effects are to be accomplished by the MDT.

Phase 4: Follow-up after the treatment course has ended

Phase 4 involves the follow-up after the ^{177}Lu-PSMA-617 treatment has ended. The anticipated need for resources for treatment phase 4 is outlined in *Table 25*. The involved experts (e.g., MDT) will decide upon the further follow-up after the ^{177}Lu-PSMA-617 treatment, and in line with the patient's preferences. Follow-up is expected to be according to the current existing routines for patients with mCRPC. Attention to long-term adverse effects of the ^{177}Lu-PSMA-617 treatment may be necessary. It is important that the general practitioner is informed about treatment results and about the plans for further follow-up, including what is expected from the general practitioner.

Phases 2-4: Management of patient complications, adverse events, and side effects

As outlined in *Table 25*, awareness to and management of patient complications, adverse events and side effects will be relevant during treatment execution and during follow-up (phases 2-4). This HTA has not investigated the *management* of complications and side effects thoroughly. Concerning radiation aspects, we expect low risk of acute side effects, and due to the limited life expectancy of patients with mCRPC, there are likely no long-term side effects due to radiation. According to the expert representatives, the frequencies of other *acute* side effects are probably low and mostly non-serious. However, as for any systemic- and RLT treatment, one should be prepared for complications during and after the treatment (76). The most common side effects are fatigue, dry mouth, nausea, anaemia, decreased appetite and constipation (28). As most patients with mCRPC are about 70 years old or older, the risk of other health issues also needs to be considered.

In total, the ^{177}Lu-PSMA-617 treatment will require many person- and structural resources on treatment days (1-6 cycles), and probably modest resources between the cycles and after the treatment has ended. The necessary investments will depend upon what structural, equipment and staff resources that are currently in place in the hospitals. Furthermore, as the patient load is expected to differ across Norway, the various health regions in Norway will be impacted differently, with different requirements to needed resources.

Centralised versus decentralised organisation of ^{177}Lu-PSMA-617 treatment

Ensuring equal treatment for all patients will necessitate the same service in all health regions and dissemination of the service provided to patients and all professionals involved, including general practitioners and cancer coordinators in the primary health

care services. We are under the impression that a centralised model will imply that the six university hospitals will be responsible for the ^{177}Lu-PSMA-617 treatment, whereas a decentralised model will involve the university hospitals in addition to various other local hospitals.

It is likely that university clinics in each health region will be responsible for the ^{177}Lu-PSMA-617 treatment of prostate cancer, at least in the initial phase of the implementation of the drug. Thus, the introduction of ^{177}Lu-PSMA-617 treatment in Norway will probably not affect the patient flow between health regions but may lead to increased centralisation within each health region. With a centralised "model", the professional expertise will be concentrated, and broad competence and experience can be built relatively quickly. However, depending on the increased patient load, it will also put pressure on needed resources, such as staff and equipment. Furthermore, the capacity for an increased patient load will likely differ between health regions in Norway today. The patient/treatment volume is expected to increase substantially, as most patients will have an average of four to five injections/infusions, and in addition – necessary measures must be accounted for. A close collaboration between departments, e.g., oncology, nuclear medicine, radiology, is needed. As ^{177}Lu-oxodotreotide (Lutathera) was introduced in 2018 for the treatment of neuroendocrine tumours (GEP-NETs), there has already been established routines and accumulated experience for peptide receptor radionuclide therapy (PRRT) in four of the six university hospitals in Norway (77). Nevertheless, a centralised "model" will increase the patient/treatment volume substantially in a few hospitals, resulting in higher volumes of radioactive waste to be handled, etc.

Decentralisation, i.e., a differentiation of service levels might be possible in the longer term when more experience with ^{177}Lu-PSMA-617 treatment has been accumulated. Some, if not all regions of Norway have decentralised treatment with radionuclide therapy and PSMA PET. As such, these departments already have some of the necessary equipment, facilities (e.g., injection rooms, Hotlab), and experienced personnel for administering treatment with ^{177}Lu-PSMA-617. However, this do not necessarily mean that all these departments have the required capacity for the added patient/treatment volume expected for the ^{177}Lu-PSMA-617 treatment. Importantly, lutetium-177 radiation characteristics are different from those of radium-223, and the shielding requirements for lutetium-177, waste management and the capacity for patient isolation, needs to be in place. Furthermore, a clear disadvantage of a decentralisation approach is that it may take more time to accumulate sufficient experience, especially for departments with low patient volumes. On the other hand, if ^{177}Lu-PSMA-617 treatment is offered in several hospitals in each health region, it would reduce travel time for the patients and optimize radiation hygiene for the public. The expert representatives anticipate that the ^{177}Lu-PSMA-617 treatment will also be approved for earlier stages of prostate cancer, thus possibly reducing and/or phasing out treatments that are used today, e.g., radiotherapy, surgery, etc. For primary health services, i.e., general practitioners and cancer coordinators, it is not likely that the implementation of ^{177}Lu-PSMA-617 will substantially affect their workflow. However, it is likely that a centralised scenario will require more resources at the primary health care level, e.g., blood sampling, than a decentralised scenario.

Work processes

The infrastructure for ordering, storage, administration, and waste management is already present in nuclear medicine departments in Norway. However, as the patient volume eligible for ^{177}Lu-PSMA-617 is expected to be about four times higher than the patient volume eligible for Lutathera, there is increased need for resources, i.e., facilities, staff, and capacity to perform necessary procedures on several levels. Parts of the work processes will likely be transferable from that of Lutathera. The treatment time for ^{177}Lu-PSMA-617 will likely be less than for Lutathera, seeing as there is no need for renal protective infusion with amino acids. Furthermore, according to their packet inserts ^{177}Lu-PSMA-617 (Pluvicto) can be injected (~ 1-2 minutes) as opposed to Lutathera, which requires a slow infusion (~30 minutes).

Imaging

In terms of imaging, implementation of ^{177}Lu-PSMA-617 is expected to increase the use of various imaging systems. However, we have not found any clear "guidance" to routines for the use of imaging in clinical practice with ^{177}Lu-PSMA-617 treatment. For SPECT/CT the estimated use is about 0.5-1 hours per scan with approximately 2 (1-4 scans, dependent on clinical decisions in each patient) scans per patient per treatment dose. It is further estimated at least one PSMA PET per patient, which again requires sufficient production of PSMA PET tracers (produced at all centres that have a cyclotron; Oslo/NMS, Haukeland, St. Olavs, UNN and/or at centres that have a gallium generator). For facilities that do not produce PSMA PET and need to order this, the transportation must follow the legal requirements. In total, PSMA PET will take about three hours per treatment (patient). Increased load on the various imaging systems warrants increased personnel resources, i.e., radiology technicians that can administer the radioactive tracer and operate the radiological imaging systems.

Dosimetry

In clinical studies, dosimetry (dose calculations after each treatment) is performed after each treatment with ^{177}Lu-PSMA-617. According to our investigations and the expert representatives, it is less clear how this is going to be handled in clinical practice, i.e., the amount of dosimetry needed. In case of implementing ^{177}Lu-PSMA-617 in Norway, there is a need for elaboration on this matter.

When performing dosimetry today, we expect each dosimetry to take approximately 2-3 hours. With dedicated software for dosimetry, this could probably be reduced to about 1.5 hours. Still, dosimetric analysis is very time-consuming, and will often span several days, images are taken two times, with the last imaging session often a day after treatment. Additional tasks include quality assurance, infusion or injection, and patient measurements. Again, a substantially increased patient load, as with implementation of ^{177}Lu-PSMA-617 treatment, warrants increased personnel resources. According to the expert representatives, there should be at least two medical physicists, preferably with nuclear medicine speciality, per health region who can do dosimetric analysis, and even more should have training in dosimetry. As dosimetric analysis requires extensive experience, one should allocate time specifically to educate physicists in dosimetry. See more about dosimetry in chapter on *Radiation safety and legislative aspects.*

Staff

Dependent on the patient/treatment volume load at the hospital, there will be a need for more oncologists and nurses in the cancer wards to take care of both the outpatients and those that need hospitalisation. Furthermore, specialists in nuclear medicine will have a key role in reviewing medical records for assessing indication for treatment, as well as assessing the PSMA PETs before MDT meetings, including demonstration of images, and other preparatory work. If dosimetry is to be assessed in terms of treatment response, this will also require additional time and effort from nuclear medicine specialists. As previously mentioned, MDT meetings are interdisciplinary. Given the increased patient/treatment load, it may be beneficial for these teams to have a dedicated coordinator responsible for handling the logistics and administrative follow-up regarding the ^{177}Lu-PSMA-617 treatment. It is assumed that there will be an increase in secretarial services. As long as the need for added resources are met, there should be no changes related to working hours or the working environment.

Although staff involved with radionuclide therapy have high expertise (education and experience) when it comes to patient treatment, patient safety, radiation hygiene, dosimetry, and waste management, some additional training and education (e.g., courses) will probably be needed with implementing ^{177}Lu-PSMA-617 treatment in Norway – to develop the right skills to ensure that the treatment is administered safely and competently. This will also be an opportunity to establish national networks for exchanging experience across health regions.

Facilities

The room capacity will depend upon each hospital's catchment area. When administering ^{177}Lu-PSMA-617, it is important to ensure adequate space for the treatment to be carried out securely, both for patients and treating personnel. This means either dedicated single treatment rooms (designed in such a way that a person in a neighbouring room will not receive a dose exceeding the dose constraint of 0.25 mSv/year) or larger treatment rooms, with space for more patients and the use of mobile lead screens between patients and other radiation hygiene requirements The facilities need to be suitable with separate toilets and shielding adapted for ^{177}Lu to ensure that patients are kept at a safe distance from each other and from treating personnel. Also see chapter on *Radiation safety and legislative aspects.* From the expert representatives' experience, in some hospitals there is a lack of sufficient space at the nuclear medicine departments, and relevant treatment rooms at oncology wards may therefore be an alternative for this purpose if these fulfil the needed requirements. In accordance with the radiation protection regulations, healthcare institutions must assess technical solutions for emission-reducing measures when planning significant changes in e.g., structures and/or changes in patient care, that include increased use of radioactive substances (see chapter on *Radiation safety and legislative aspects*).

In total, the capacity to provide ^{177}Lu-PSMA-617 treatment needs to be customized to an increased patient flow/treatment volume. This concerns required personnel, expert- and staff training and competence building, work processes, laboratory and measurement capacities, the "overall" facilities, and the higher volumes of radioactive waste to be handled and all required adaptions to ensure that the legal requirements are followed.

Depending on the existing resources in the hospitals, investments may, among others include PET and SPECT scanners, hotlab, license for use, radioactive waste management and permit for discharge, dosimetry software, thin-layer chromatography (TLC) for quality assurance of PET tracers, and treatment rooms (designed in such a way that a person in a neighbouring room will not receive a dose exceeding the dose constraint of 0.25 mSv/year). Although the treatment is supposed to be given in the outpatient setting, some extra capacity for hospitalization will be needed as well. Miscellaneous expenses will include Pluvicto airfreight, PET tracers, patient travel and accommodation, medications, and other medical consumables.

Patient information, -involvement, and practical implications

With introduction of ^{177}Lu-PSMA-617 treatment as an option to prolong life for persons with mCRPC in Norway, a plan for thorough patient information is needed. The plan should consider dissemination of information at the patient organisation level, as well as oral and written information to the individual patients who get this treatment. According to a systematic review by Connor et al (2022), there is currently limited understanding of patients' preferences for treatment, and thus trade-off decisions, following a new diagnosis of metastatic prostate cancer (78). Information for patients and relatives might be somewhat similar to what Lutathera patients receive today, in addition to specific information concerning radiation protection advice for lutetium-177. As mentioned above, patient information is also needed between treatment cycles, and after the final treatment cycle. Psychological reactions must be expected and should be mentioned as part of the patient information.

Patient's perspectives and experiences are elaborated on in a separate chapter in this HTA (see *Patient perspectives*). In short, practical implications for patients include transportation between hospital and home, and challenges regarding incontinence. Commonly, patient transport has limited toilet facilities, which can be a physical and mental challenge, especially when living a long distance from the hospital.

In total, it is expedient to involve the patient organisation during the planning of implementation of ^{177}Lu-PSMA-617 treatment in Norway to optimise user involvement and patient information.

Organisation of quality assurance and monitoring of the method

If ^{177}Lu-PSMA-617 is to be offered in Norway, a text describing the relevant diagnostics, treatment and follow-up processes is expected to be added to the Norwegian national action program for prostate cancer (7) and the "Package process for prostate cancer" (79). The quality assurance and monitoring of ^{177}Lu-PSMA-617 for mCRPC in Norway will need to be incorporated as part of the Norwegian Prostate Cancer Registry with yearly reports on key information on the treatment. In total, quality assurance and monitoring of the drug need to be planned for from the start if ^{177}Lu-PSMA-617 is introduced as a treatment option for mCRPC in Norway.

Health economic evaluation

Introduction

The basic aim of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration in an incremental analysis in which the differences in costs between an intervention and its comparator are compared with differences in consequences. Results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{intervention} - Cost_{comparator}}{Effect_{intervention} - Effect_{comparator}} = \frac{\Delta C}{\Delta E}$$

The health care sector, similarly, to society in general, is restricted by budget constraints. Therefore, economic evaluations are important tools for decision makers facing questions of how to prioritize treatments and maximize health benefits using limited resources. For an economic evaluation to be meaningful in a decision-making process, the ICER must be assessed according to a ceiling ratio that reflects the decision maker's maximum willingness-to-pay for a health gain. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda$$

where λ equals willingness-to-pay and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because the ICER has poor statistical properties due to its ratio nature, ICERs are often re-arranged to express either incremental net monetary benefit (INMB) or incremental net health benefit (INHB), which yields the following decision rules related to INMB or INHB.

$$INMB: \lambda \times \Delta E - \Delta C > 0$$

$$INHB: \Delta E - \frac{\Delta C}{\lambda} > 0$$

In other words, an intervention can be considered cost-effective if it yields a positive INHB or INMB.

Economic evaluations are often based on decision models (such as decision trees, Markov models, partitioned survival model, etc.) that calculate results based on various input parameters in the model. Because there are always uncertainties related to the

values of these parameters, sensitivity analyses are important in economic evaluations based on decision models. In short, sensitivity analyses illustrate how much the results vary when model parameters are changed. Probabilistic sensitivity analysis makes it possible to take the uncertainties of many model parameters into account simultaneously. The basic approach in probabilistic sensitivity analysis is to assign appropriate probability distributions to the model-parameters, which enables replacing the "fixed" values of the parameters with values generated by random draws from the distributions. Doing this repeatedly, with a specified number of iterations, allows to estimate the probabilities that alternative interventions are cost-effective subject to different ceiling values of willingness-to-pay. For each iteration, the alternative that renders the highest values of net monetary benefit or net health benefit is considered cost-effective. Results from probabilistic sensitivity analysis are often presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and as cost-effectiveness acceptability curves (CEACs), which show the probability of the alternatives being cost-effective subject to a range of values of willingness-to-pay.

In short, making a model probabilistic means that it is possible to estimate the uncertainty associated with a decision to implement alternative interventions, and it also provides a possibility of estimating the value of collecting additional information from new research.

Priority setting criteria

There are three primary criteria for setting priorities in the Norwegian health care sector: 1) the benefit criterion, 2) the resource criterion, and 3) the severity criterion (80).

Benefit

According to the benefit criterion, priority increases with the size of the expected health benefit of the intervention. The benefit criterion primarily refers to a technology's expected health gains: increased longevity and/or improved health-related quality of life. By combining these two types of health gains into a single outcome measure, the quality-adjusted life-year (QALY), it is possible to compare treatment outcomes across different diseases, patient groups and types of treatments. In practice, the benefit criterion is taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of interest.

Resources

According to the resource criterion, priority increase when fewer resources are needed for the intervention. The resource criterion focuses attention on how the health sector uses its limited resources. Introducing a new technology creates demands for personnel, equipment, facilities, etc. that could be used to provide treatments for other patients; a reality that is referred to as the "opportunity cost" of the new technology. The larger the quantity of resources allocated to a technology for one patient group, the fewer resources are available for treating others. In addition to resource use within the health sector, a technology may also impose costs for other parties. While potentially important for society, these resources are not considered for implementation of a new health intervention within the specialist health service in Norway (81), and therefore they are not included in our analysis. In practice, the resource criterion is taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of

interest. Resource use, measured as monetary costs, constitutes the numerator of the cost-effectiveness ratio (see "Cost-effectiveness" below). In addition to the cost-effectiveness analysis, a budget impact analysis may help inform decisions.

Severity

According to the severity criterion, priority increases with expected future health loss resulting from the disease. Severity is measured as "absolute shortfall", defined as the expected loss of future health (QALYs) associated with a specified diagnosis. For treatment of a diagnosed disease, severity is the average expected absolute shortfall for the relevant patient group given the current standard treatment. Generally, the greater the absolute shortfall associated with a disease, the more resources per QALY-gained the authorities may be willing to allocate (80).

Cost-effectiveness

Cost-effectiveness is an expression of the amount of health gains (in QALYs) created by a given amount of resources, or as seen from an opportunity cost perspective: the cost per additional QALY gained. A health economic analysis evaluates a new technology relative to a comparator. The ratio between the incremental (additional) cost of the new technology and its incremental effect is referred to as the ICER. The Norwegian White paper on priority setting (Meld. St. 34 2015-2016) indicates that weighting of resource use against utility should be based on the opportunity cost principle, and that priority should be further increased according to severity (absolute shortfall) (82). While there is no official Norwegian threshold value for willingness-to-pay for an additional QALY, the Magnussen group's proposal for how to operationalize the severity criteria suggests that threshold values for willingness-to-pay should increase with increases in disease severity, measured as absolute shortfall – the number of healthy life-years lost without treatment (83). There has been acceptance for linking willingness-to-pay to disease severity, but no general agreement on how increases in severity should affect willingness-to-pay. As part of the health-economic analysis, we calculate an absolute shortfall in order to provide decision-makers with a basis for applying the severity criterion. We recognize that the ultimate decision about the relevant willingness-to-pay for different levels of absolute shortfall rests with the decision-makers who evaluate this report.

Methods

General

We conducted a cost-utility analysis in order to assess the cost-effectiveness of ^{177}Lu-PSMA-617 for patients with mCRPC. All costs are measured in 2023 Norwegian kroner (NOK). Effects are measured as QALYs. Both costs and effects were discounted at an annual discount rate of 4% as recommended by the Norwegian Ministry of Finance and guidelines for health economic evaluation in the health sector (84;85). The analysis employed a health care perspective, which includes direct costs and effects related to the health care sector. This is the most appropriate perspective for prioritizing interventions when the decision maker's objective is to maximize health within a fixed health care budget.

We assumed a starting age in the model of 71 years, based on the mean age of patients included in the VISION trial (40) in the ^{177}Lu-PSMA-617 arm, and a 5-year time horizon.

We expressed results as mean ICERs. To examine uncertainty in model parameters, we performed probabilistic sensitivity analysis with 10,000 random draw Monte Carlo iterations. Probabilistic sensitivity analysis accounts for parameter uncertainty in a model by defining confidence intervals and a relevant statistical distribution for each parameter in the model. For each Monte Carlo iteration, a value is drawn from the distribution describing each parameter, resulting in new estimates of the benefits and costs of each treatment. We also performed a series of one-way sensitivity analyses in which model parameters were varied individually to determine the variables that had the largest impact on the deterministic cost-effectiveness results. Results of one-way sensitivity analyses were presented as Tornado diagrams.

The cost-effectiveness model was built and analysed using the TreeAge Pro Healthcare® 2023 (86). We used the R-Studio software for the statistical regression analyses for derivation of distributions for survival curves (87). We relied on the NICE Technical Document for appropriate use of partitioned survival analyses for decision modelling in health care (88).

Model structure

To assess the cost-effectiveness of ^{177}Lu-PSMA-617 for treatment of patients with mCRPC who were previously treated with AR pathway inhibition and taxane based chemotherapy, we developed a partitioned survival model. Partitioned survival model, often referred to as "Area Under the Curve" models, is a common tool for analysing cost-effectiveness for cancer treatments. As with other types of cost-effectiveness models, patients are tracked through different pre-defined health states. A typical partitioned survival model for cancer treatments includes three states, 1) progression-free, 2) progressed, and 3) dead, and is characterized by two survival curves, progression-free survival, and overall survival (*Figure 15*). State membership is derived from the survival curves at each model cycle. Note that the area under the overall survival curve includes all patients who are alive, but some are in the progression-free state (area under the progression-free survival curve) and others are in the progressed state (area between the progression-free survival and overall survival curves), i.e., the states, unlike in Markov models, are not mutually exclusive. State membership is determined as follows: the percent dead at any time is 1 minus the overall survival curve at each point in time. Similarly, membership in the progressed state is the difference between the overall survival and progression-free survival curves at each time point (88). In the partitioned survival models, it is the survival functions that determine how disease progresses and how patients move through the model.

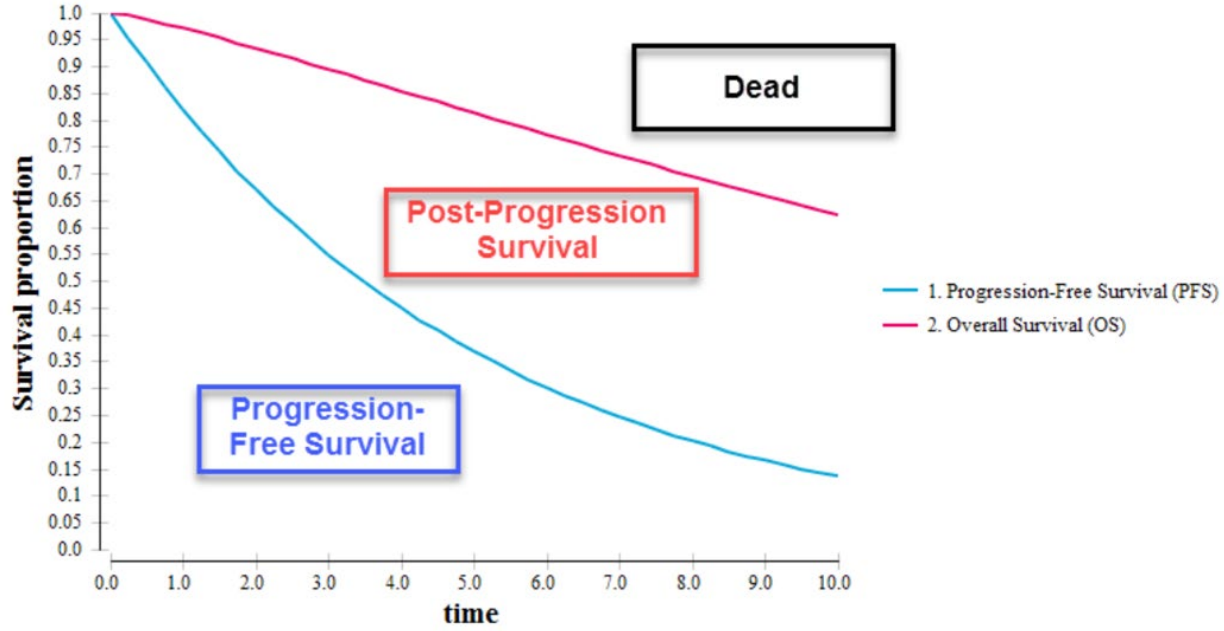


Figure 15: Survival Curves and Health States in Partition Survival Analysis, adapted from TreeAge User's Manual (86)

OS – PFS = Progressed, PFS = Progression Free, OS = Alive (Progressed + Progression Free)

As described in the chapter on *Efficacy and safety*, we have considered three RCTs where treatment with ^{177}Lu-PSMA-617 is directly compared to another treatment (*Table 5*). After a discussion with our expert representatives (89) we considered standard of care and cabazitaxel to be the most relevant comparators to ^{177}Lu-PSMA-617 in the Norwegian settings. In our health economic model, we relied on efficacy data from the VISION study (40), where standard of care was the comparator for ^{177}Lu-PSMA-617. The TheraP study (39), which is a multicentre, unblinded, randomised phase 2 trial, did not report on overall survival, which is necessary to have in order to calculate the area under the progression-free survival and overall survival curves in a partitioned survival analysis. In this health economic evaluation, we employed a partitioned survival model consisting of three health states:

1. Progression free-survival (PFS) - defined as the period before the patient has experienced disease progression. In this health state, the patient will receive either ^{177}Lu-PSMA-617 treatment in combination with standard of care or standard of care alone;
2. Progressed disease (PD) - defined as the period where the patient remains alive following disease progression where patients may receive treatment with subsequent anticancer therapy and supportive care;
3. Dead – defined as an absorbing state.

Initially, all individuals in the model are in the progression-free survival state, moving along to the progressed disease state and death according to the transition probabilities determined by the Kaplan-Meier curves available from the VISION trial (40). The analysis was conducted over a lifetime horizon, which we determined to be 60 months, with one-month cycle length. The model structure is shown in *Figure 16*. The model was populated with relevant data for costs, effects, and estimated the results of the economic evaluation.

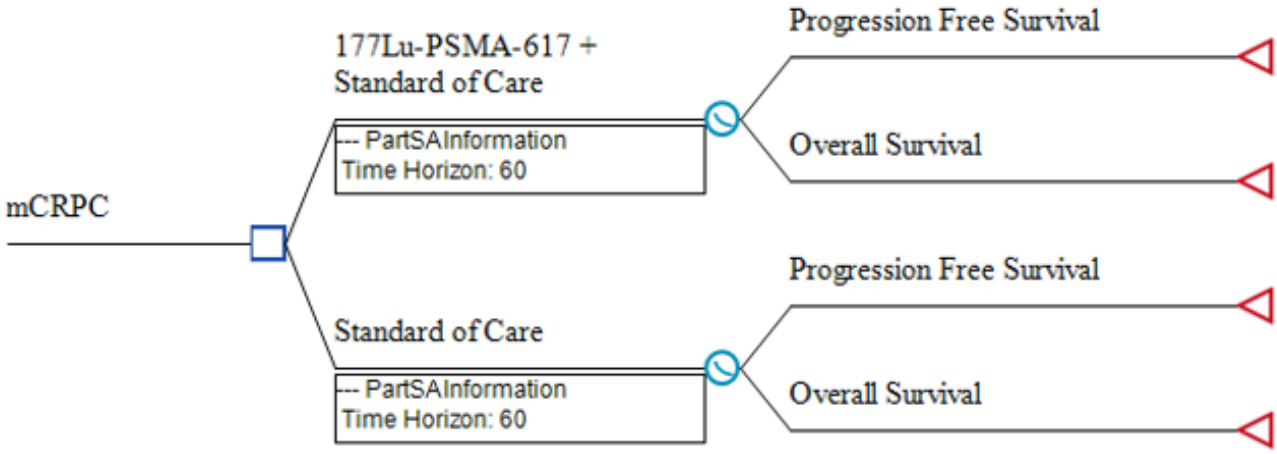


Figure 16: Partitioned Survival Analysis model structure

mCRPC: metastatic castration resistant prostate cancer; Time Horizon = Number of months

Model parameters

We describe the values we have used as inputs for our model parameters below.

Standard of Care

Patients in both treatment arms received at least one dose of their assigned treatment (standard of care therapy and/or ^{177}Lu-PSMA-617). The proportions of the patients receiving concomitant treatment were obtained from VISION study supplementary file (40). We only included treatments that affected at least five percent of the study population in one of the treatment arms. The proportions of patients receiving concomitant treatment are presented in *Table 26*.

Table 26: Proportion of patients receiving concomitant treatment. Adapted from the VISION study (40)

Drug	^{177}Lu-PSMA-617 + SOC	SoC	Reference
Abiraterone	0.250	0.351	VISION study (40)
Enzalutamide	0.297	0.424	VISION study (40)
Glucocorticoids	0.663	0.654	VISION study (40)
GnRG-agonist	0.885	0.859	VISION study (40)
Bisphosphonates	0.085	0.137	VISION study (40)
Denosumab	0.348	0.390	VISION study (40)

SoC: Standard of care therapy; GnRH-agonist: Gonadotropin-releasing agonist

Clinical Efficacy

As mentioned, the transitions probabilities and data regarding overall survival and progression-free survival were obtained from the Kaplan-Meier curves of the VISION trial (40). To define the overall survival and progression-free survival curves for each of the reference treatments, we relied on a survival fitting technique and associated Excel

spreadsheet proposed by Hoyle and Henley, which can be used to reconstruct the underlying patient-level data for number of events and censored patients from each trial (90). This technique makes it possible to determine the position of points more accurately on Kaplan-Meier plots so that they can be expressed as parametric survival curves for use in the cost-utility model. We used WebPlotDigitizer Version 4.6 (91) to extract data from the Kaplan-Meier plots that defined the survival curves by recording the number of patients on each survival curve at each time point where that information was shown on the Kaplan-Meier plot. Because it is difficult to determine the exact position of points on published survival plots using WebPlotDigitizer, we entered this data into the Excel worksheet from the Hoyle and Henley article (90) to determine more precisely the number of events and censored patients in a given time interval. To ensure that the point estimates were extracted accurately, we checked for the censored patients and events between intervals and calibrated the points manually to adjust for any corrections. We then imported the patient level data into R Studio (87) to conduct parametric survival regression analyses. We derived several distributions for each of the four survival curves (progression-free survival and overall survival for both intervention and comparator) using Lognormal, Exponential and Weibull distributions. Based on the Akaike Information Criterion (AIC) and visual inspection we assessed their goodness of fit. For each of the curves we selected a distribution which would best fit the trial data, as presented in *Table 27*.

Table 27: Survival probabilities derived from VISION study (40)

Survival probabilities	Distribution parameters	Distribution
OS ^{177}Lu-PSMA-617+SoC	μ (mean of logs) = 2.72 (CI: 2.52 – 2.93) σ (standard deviation of logs) = 0.947 (CI: 0.88 – 1.013)	Lognormal
OS SoC	Shape = 1.349 (CI: 1.21 – 1.51) Rate = 0.0248 (CI: 0.018 – 0.033)	Weibull
PFS ^{177}Lu-PSMA-617+SoC	μ (mean of logs) = 2.16 (CI: 1.96 – 2.38) σ (standard deviation of logs) = 1.03 (CI: 0.95 – 1.113)	Lognormal
PFS SoC (≤ 4 months)	Shape = 1.369 (Fixed) Rate = 0.096 (Fixed)	Weibull
PFS SoC (> 4 months)	Rate = 0.1719 (Fixed)	Exponential

OS: overall survival, PFS: progression-free survival, SoC: standard of care therapy

To improve adjustment, the parametric survival of progression free survival in the standard of care group was reproduced as Weibull distribution the first 3.6 months, and exponential function thereafter. Age-related death adjustments were not made, as they were already accounted for by the overall survival. Figures with extrapolated survival curves and a table presenting the AIC scores can be viewed in *Appendix 9*.

Costs

We captured the average monthly cost per patient in the progression-free and progressed disease health states for both treatment options. We included the following costs in the model: drug costs (including the outpatient administration costs), medical imaging costs (nuclear medicine), patient monitoring costs, hospital costs associated

with treatment of adverse events, post-treatment cost (dosimetry), and end-of-life care were included in the model. All costs were measured in 2023 Norwegian kroner (NOK).

We relied on the following sources of unit costs: Novartis, the supplier of ^{177}Lu-PSMA-617 radiopharmaceutical (73), Sykehusinnkjøp (Norwegian national agency for procurement of hospital supplies) (92), diagnosis-related group (DRG) codes (93), tariffs, unit costs database from the Norwegian Medicines Agency (94), and our earlier HTA publication on drugs for treatment of patients with mCRPC (95). Since costs for some of the relevant procedures are not yet available in public databases, we have procured them directly from the hospitals that perform them (89). All costs have been measured in 2023 Norwegian kroner (NOK). To capture uncertainty around cost estimates we have calculated ±25% and used gamma distributions for the probabilistic sensitivity analysis in the model.

Drug costs – therapeutic interventions

We used pharmacy maximum retail price (AUP) excluding value-added tax (VAT) to calculate the monthly drug cost included in the model. For the main intervention, ^{177}Lu-PSMA-617, we received this price directly from the company, Novartis (73). Many of the suppliers of the other relevant drugs have an "agreement price" that we obtained from Sykehusinnkjøp HF (92). We also included injection/infusion costs associated to zoladex, zoledronic acid, denosumab, cabazitaxel, docetaxel, carboplatin, ^{177}Lu-PSMA-617 and radium-223 (94). *Table 28* presents monthly drug costs and the calculated recommended doses. We assumed that patients receive the drugs only in progression-free health state.

Table 28: Drug costs per patient, excluding VAT (NOK)

Drug	Dosage and treatment regime	Dosage form	Package AUP (NOK)	Unit per package	Monthly drug cost (NOK)	Reference
^{177}Lu-PSMA-617 (Pluvicto)	7.4 Gbq every 6 weeks	Vial	[redacted]	1	[redacted]*	Novartis (73)
Abiraterone (Qilu)	1,000 mg daily	Tablet 500 mg	[redacted]	56	[redacted]	Sykehusinnkjøp HF (92)
Enzalutamide (Xtandi)	160 mg daily	Tablet 40 mg	[redacted]	112	[redacted]	Sykehusinnkjøp HF (92)
Zoledronic acid (Zoledron)	100 ml every 3 weeks	Vial	[redacted]	1	[redacted]*	Sykehusinnkjøp HF (92)
Prednisolone (Alternova)	10 mg daily	Tablet 5 mg	88	100	53	The Norwegian Pharmaceutical Product Compendium (72)
Dexamethasone (Krka)	12 mg daily	Tablet 4 mg	626	100	72	The Norwegian Pharmaceutical Product Compendium (72)
GnRH-agonist (Zoladex)	10.8 mg every 3 months	Vial	2,743	1	2,067*	The Norwegian Pharmaceutical Product Compendium (72)
Denosumab (Prolia)	60 mg every 6 months	Vial	1,738	1	866*	The Norwegian Pharmaceutical Product Compendium (72)

Drug	Dosage and treatment regime	Dosage form	Package AUP (NOK)	Unit per package	Monthly drug cost (NOK)	Reference
Cabazitaxel (Stada)	25 mg every 3 weeks	Vial	[redacted]	60 mg/ 3 ml	[redacted]*	Sykehusinnkjøp HF (92)
Docetaxel (Kabi)	75 mg every 3 weeks	Vial	[redacted]	160 mg/ 8 ml	[redacted]*	Sykehusinnkjøp HF (92)
Radium223 (Xofigo)	50 kBq per kg every 4 weeks	Vial	[redacted]	1	[redacted]*	Agira Pharma AS (96)
Carboplatin (Kabi)	360 mg every 4 weeks	Vial	[redacted]	600 mg/ 60 ml	[redacted]*	Sykehusinnkjøp HF (92)

mg: milligram; kg: kilogram; Gbg: gigabecquerel; kBq: kilobecquerel; AUP: Pharmacies' maximal retail price; NOK: Norwegian kroner: GnRH-agonist: gonadotropin-releasing hormone agonist;
**injection cost is included*

We used the proportions of patients receiving concomitant treatment (*Table 27*) to estimate the weighted costs of concomitant treatment for both treatment arms. The weighted costs of concomitant treatment are presented in *Table 29*.

Table 29: Weighted costs of concomitant treatment, all weights derived from the VISION study (40)

Drug	^{177}Lu-PSMA-617 + SoC (NOK)	SoC (NOK)	References
Abiraterone (Qilu)	[redacted]	[redacted]	Sykehusinnkjøp HF (92)
Enzalutamide (Xtandi)	[redacted]	[redacted]	Sykehusinnkjøp HF (92)
Glucocorticoids**	41	42	The Norwegian Pharmaceutical Product Compendium (72)
Gn-RH agonist (Zoladex)	1,829	1,734*	The Norwegian Pharmaceutical Product Compendium (72)
Zoledronic acid (Zoledron)	[redacted]	[redacted]*	Sykehusinnkjøp HF (92)
Denosumab (Prolia)	302*	338*	The Norwegian Pharmaceutical Product Compendium (72)
Total	[redacted]	[redacted]	

NOK: Norwegian kroner; GnRH-agonist: Gonadotropin-releasing hormone agonist;
**injection cost is included;*
***average of prednisolone and dexamethasone*

Monitoring costs

To account for follow-up costs including regular physician consultations, blood tests, and imaging diagnostics, we have applied average monitoring costs separately for progression free state and progressed disease. We have used estimates from our earlier HTA report on medications for mCRPC (95) and updated these into the present value with an Statistics Norway price index (*Table 30*) (97).

Table 30: Monthly monitoring costs, adapted from HTA of four drugs for patients with mCRPC (95)

	Progression-free status	Progressed disease status
Monthly monitoring costs (NOK)	6,935	5,500

Costs of treatment-related severe adverse events

We have included costs related to treatment of severe adverse events ≥grade 3 in the specialist health care by calculating an average cost for each arm in the model. We have assigned weights to each of the included adverse events according to the frequencies on which they occurred in the VISION trial (40) and linked them to unit costs of treatment taken from the Norwegian DRG-system (93). *Table 31* shows the list of severe adverse events ≥grade 3 included in the analyses, their incidence, treatment unit costs and the calculated average costs for each arm as applied in the model as one-time costs at the end of the active treatment period. Table A in *Appendix 8* lists treatment unit costs of the included adverse events with their description.

Table 31: Costs of treatment of the included adverse events and weighted average costs used in the model

Included severe adverse events grade ≥ 3	Incidence in the VISION study (40)		Treatment unit cost – NOK (DRG 2023) (93)
	^{177}Lu PSMA-617 + SoC	SoC	
Abdominal pain	0.0090	0.0050	1,930
Anaemia	0.1285	0.0488	24,841
Asthenia	0.0113	0.0098	3,068
Back pain	0.0321	0.0341	39,142
Bone pain	0.0250	0.0240	39,389
Dyspnea	0.0130	0.0150	2,573
Fatigue	0.0586	0.0146	1,435
Hypokalaemia	0.0095	0.0000	38,647
Muscular weakness	0.0000	0.0049	14,919
Musculoskeletal pain	0.0000	0.0000	4,948
Neutropenia	0.0340	0.0049	3,068
Thrombocytopenia	0.0794	0.0098	24,816
Lymphopenia/ lymphocytopenia	0.0775	0.0049	36,000
Leukopenia	0.0246	0.0049	43,793
Urinary tract infection	0.0378	0.0049	34,020
Haematuria	0.0246	0.0049	36,717
Renal effects (AKI, renal failure, proteinuria, blood urea, etc)	0.0340	0.0290	78,680
Spinal cord compression	0.0000	0.0050	2,078
Hypertension	0.0321	0.0146	2,078
Weighted average cost (NOK)	**16,842**	**6,979**	

AKI: acute kidney injury, DRG: diagnosis related group, SoC: standard of care therapy

PSMA PET/CT, SPECT/CT, and Dosimetry

Both in the intervention (^{177}Lu PSMA-617 + SoC) and comparator (SoC alone) arm of the model, we have applied a cost of an initial PSMA PET/CT scan, which is crucial for optimal selection of patients. In addition, we have included a cost of another PSMA PET/CT scan in the intervention arm for assessment of clinical response following 5th treatment with ^{177}Lu PSMA-617 as a one-time cost (89).

In Norway, two traces are in use for this purpose: ^{68}Ga-PSMA and ^{18}F-PSMA. Resource use varies according to the type of tracer used. Based on cost data and information on time use we received from the expert representatives (89), we have calculated an average estimate of NOK 24,113 per patient per scan. . This estimate includes purchase and transport of the tracers, gallium generator/cyclotron, personnel time, and overheads.

According to the European guidelines on dosimetry of ^{177}Lu-labelled somatostatin-receptor- and PSMA-targeting ligands (60), each treatment with ^{177}Lu-PSMA-617 should be followed by a dosimetry procedure (more on dosimetry in the *Radiation and legislative aspects* chapter). To calculate an average cost estimate related to these procedures, we have assumed a dosimetry schedule comprising of three SPECT/CT scans following the first treatment and one SPECT/CT scan after each of the remaining treatments. The average number of treatments is 4.5 per patient (40). That gives on average 4.5 dosimetry procedures with 6.5 SPECT/CT scans, with a cost of NOK 7,700 each (89). Based on the information received from the expert representatives, we assumed that each dosimetry takes on average 3.5 hours of a specialist worktime (depending on the used software), and the working hour of a medical physicist costs NOK 1,800 (inclusive of social costs) (89). The average cost related to the necessary dosimetry procedures for the whole treatment sequence sums up to NOK 78,400 per patient and has been applied as a one-time cost in the model. There however uncertainty around the exact dosimetry routines that will be in place in the Norwegian clinical practice. We therefore explored the impact of this cost parameter on the results in a separate scenario analysis.

Radiotherapy

In line with the VISION trial (40), we have applied costs of radiotherapy that patients received after the main active treatment. In the VISION study 8.9% of patients in the intervention arm and 11.1 % of patients in the control arm received radiotherapy. We have calculated an average cost of radiotherapy based on the DRG 851N (*Poliklinisk ekstern strålebehandling ved svulst i mannlige kjønnsorganer*) (93) and information of average number of sessions taken from Kreftlex (98) to amount to the total of NOK 60,568. We have calculated a one-time cost of radiotherapy for both arms (as shown in the *Table 32*) and included it in the analyses.

Table 32: Cost of radiotherapy included in the model

Radiotherapy	^{177}Lu PSMA-617 + SoC	SoC
Proportion of patients receiving therapy (40)	8.9%	11.1%
Average cost (NOK)	5,390	6,723

NOK: Norwegian kroner, SoC: standard of care therapy

Subsequent treatment after discontinuation of treatment with 177Lu PSMA-617 + SoC and Standard of Care

We have included costs related to subsequent treatment that patients received after discontinuation of treatment with either ^{177}Lu PSMA-617 + SoC or standard of care. We adapted the proportions of patients receiving additional treatment from VISION study (40). We only included subsequent treatments that affected at least 2 % of the study population in one of the treatment arms. We have assumed that all patients were receiving these for 4 cycles on average, in line with dosage recommendations for two most costly medications, i.e., cabazitaxel and radium 223. The monthly weighted average cost of subsequent treatment is presented in *Table 33*.

Table 33: Cost of subsequent treatment included in the model (following first-line treatment)

Drug	^{177}Lu PSMA-617 + SoC, weighted	^{177}Lu PSMA-617 + SoC (NOK)	SoC, weighted	SoC (NOK)	Reference
Cabazitaxel (Stada)	0.149	[redacted]*	0.189	[redacted]*	Sykehusinnkjøp HF (92)
Docetaxel (Kabi)	0.049	[redacted]*	0.036	[redacted]*	Sykehusinnkjøp HF (92)
Radium 223 (Xofigo)	0.025	[redacted]*	0.054	[redacted]*	Agilera Pharma AS (96)
Carboplatin (Kabi)	0.073	[redacted]*	0.096	[redacted]*	Sykehusinnkjøp HF (92)
Enzalutamide (Xtandi)	0.022	[redacted]	0.025	[redacted]	Sykehusinnkjøp HF (92)
Denosumab (Prolia)	0.029	25*	0.079	68*	The Norwegian Pharmaceutical Product Compendium (72)
Total cost		[redacted]		[redacted]	

NOK: Norwegian kroner; SoC: Standard of care

**Injection costs associated to cabazitaxel, docetaxel, radium 223, carboplatin and denosumab are included in the total cost*

End-of-Life costs

We have applied a one-time lump cost estimate of NOK 145,285, that includes costs incurred during the final three months of life to all patients progressing into the dead state in the model. We have used the previously calculated (95) estimate and updated into the present value with a Statistics Norway price index (97). The estimate includes doctor and nurse visits, nursing home stays, palliative outpatient treatment, palliative inpatient care at a hospital and stay in a palliative care center during the final two weeks of life.

Health-Related Quality of Life

Health-related quality of life (HRQoL) refers to the impact a person's health status has on their overall quality of life. It is a measure of how physical, emotional, and social well-being are affected by an individual's health condition, treatment, and healthcare experiences. In order to obtain QALY weights that would best represent both patients and health states in our model, we searched for published articles with HRQoL values. We considered the utility weights used in an earlier cost-effectiveness analysis of

abiraterone, cabazitaxel and enzalutamide by Barqawi et al. (99) to be representative for the populations in our model. We reused the health state utility data associated with Progression-Free Disease (Progression-Free Survival) and Progressed Disease (Overall Survival) in both arms of the model, independent of treatment (*Table 34*). In addition, we have included impact of the adverse events and radiotherapy on HRQoL by calculating weighted average values for disutility related to adverse events. Like with adverse events cost, the weights assigned to each of the included adverse events were determined by their incidence in the VISION trial (40). The calculated average disutilities are included in *Table 34*. We have assumed that all adverse events resolve within four months on average, we therefore applied the calculated disutilities for the duration of four months. Details about the included adverse events, and related unit disutilities together with their sources are included in Table B in *Appendix 8*.

Table 34: Utility values related to health state and disutility values related to adverse events

Utility value	Base case value	Range	Distribution (parameters)	Reference
Progression free disease	0.617	(0.55 - 0.68)	Beta (α=132; β=82)	Barqawi et al. (99)
Progressed disease	0.370	(0.33 - 0.41)	Beta (α=207; β=252.6)	Barqawi et al. (99)
Disutility related to AE: ^{177}Lu PSMA-617 + SoC	-0.071	(-0.09 - 0.05)	Normal	Table B in *Appendix 8*
Disutility related to AE: SoC	-0.033	(-0.04 – 0.02)	Normal	Table B in *Appendix 8*

AE: adverse events; SoC: standard of care therapy; Beta: type of distribution α: and β: parameters of beta distribution function

Severity considerations – absolute shortfall (AS)

We estimated absolute shortfall (AS) based on projections about life expectancies. The AS computation is elaborated in the Norwegian Medicines Agency's submission guidelines for pharmaceutical reimbursements, which is derived from the White Paper on Priority setting, and a Norwegian life table and age adjusted HRQoL information from a general Swedish population (80;100-102). AS denotes the variation between quality-adjusted life expectancies at a given age (A) in the absence of the disease ($QALYs_A$) and the prognosis with the disease while receiving the current standard of care (P_A).

$$AS = QALYs_A - P_A$$

In the calculations, undiscounted numbers for $QALYs_A$ and P_A are used for prognosis (i.e., QALYs remaining for patients with standard of care in absence of intervention at mean diagnosed age) and QALY (A), which refers to the total amount of remaining QALYs for a healthy population at the mean diagnosed age (84).

Probabilistic sensitivity analysis

The base case utilised 10,000 Monte Carlo simulations to generate probabilistic results that capture the impact of uncertainties across multiple parameters on cost-effectiveness estimates in the model. Standard distributional forms were taken to describe the probability distribution functions relating to input parameters: costs were characterized by gamma distribution; utilities were characterized by beta distribution

(*Table 34*) and the survival curves distributions are described in *Table 27*. Scatterplot (*Figure 18*) and cost-effectiveness acceptability curves (*Figure 19*) were also presented, illustrating the probability that a modality would be considered optimal for a range of willingness-to-pay thresholds.

One-way sensitivity analyses

In addition to performing probabilistic sensitivity analysis to get the base case results, we carried out a series of one-way sensitivity analyses to investigate how uncertainty around single parameters affects cost-effectiveness results. In *Appendix 10* we present list of parameters for the series of one-way sensitivity analyses. We present results of the one-way sensitivity analyses as a tornado diagram in the results chapter.

Scenario analyses

In order to investigate assumptions on key parameters such us cost of the intervention and cost of comparator; we performed the following scenario analyses:

1. We explored how eventual discounts in price of the radiopharmaceutical ^{177}Lu-PSMA-617 would impact the results. We have therefore analysed the model with 20%, 40% and 60% discounts on the ^{177}Lu-PSMA-617 price.
2. We assummed that cabazitaxel is given in addition to standard of care in the comparator arm. We have made an assumption that survival curves remain equal to those from the base case. We have used the price of NOK [redacted] (excl. VAT) for cabazitaxel 60 mg as received from Sykehusinnkjøp (92). We have assumed the following dosage: 25 mg/m^2 every third week combined with oral prednison or prednisolon 10 mg daily during the treatment (72). We further assumed that patients received cabazitaxel for 5.1 months on average, in line with the CARD trial (103). We calculated an estimate of 2.07 m^2 for body surface of participants of the VISION trial (40) using the tool on Onco website (104), and used it to calculate the average dose cost. We have removed the effects (cost of disutilities) of adverse events in this scenario, since due to toxicity of taxane-based therapy, we couldn't assume similar safety profile between cabazitaxel and medications included in standard of care.
3. Due to uncertainty around the dosimery schedule that will be applicable for patients receiving ^{177}Lu-PSMA-617 treatment in the Norwegian clinical practice, we investigated how costs related to dosimetry impact cost-effectiveness results. In this scenario we removed these costs from the analysis.

Budget impact analysis

Budget impact analysis is a type of economic evaluation used to estimate potential financial impact of a new intervention at an aggregate population level. In other words, budget impact is the additional total cost of introducing the new intervention minus the total costs of not doing it. Budget impact analysis is commonly used by decision-makers to assess the feasibility and affordability of implementing a new intervention, and to understand its potential impact on healthcare resource allocation. Following the guidelines on budget impact analysis from the Norwegian Medicines Agency (101), we used undiscounted costs which included the Maximum Drug Retail Price (including VAT). To capture the likely changes in expenditure, we used a five years' time horizon. To estimate the additional total cost of introducing of ^{177}Lu-PSMA-617 for the treatment of mCRPC in Norway, we included the direct costs associated to ^{177}Lu-PSMA-617 only.

The direct costs included the cost of intervention itself, such as the cost of the radiopharmaceutical drug, as well as the administration cost. We did not include health state costs (monitoring cost), transportation costs, or costs of treating adverse events that we used in the partitioned survival model. The cost included in the budget impact analysis is listed in *Table 35*.

Table 35: Cost included in the budget impact analysis

Costs (NOK)	^{177}Lu-PSMA-617 + SoC	SoC
Intervention	[redacted]	NA
Administration	19,278	NA
PSMA	30,142	30,142
SoC	[redacted]	[redacted]
Sum total cost incl. VAT (annually)	[redacted]	[redacted]

VAT: Value Added Tax; NOK: Norwegian kroner, NA: not available, PSMA: prostate specific membrane antigen, SoC: standard of care therapy

On a national level, number of potential patients relevant for ^{177}Lu-PSMA-617 ranged between 380-550 patients annually. Number of potential patients relevant for ^{177}Lu-PSMA-617 is taken from the chapter of *Organisational aspects* (*Table 24*). By introducing ^{177}Lu-PSMA-617 in Norway, we assumed an increasing proportion of patients each year, from 100 new patients will be treated with ^{177}Lu-PSMA-617 the first year, and 500 patients in the fifth year. Further, according to our health economic model we assume that all relevant cost associated with ^{177}Lu-PSMA-617 occurs within month six. This means that all costs associated with the introduction of ^{177}Lu-PSMA-617 are the same each year in our budget impact analysis.

Results – health economics

Incremental cost–effectiveness estimates in the base case scenario

The base case cost-utility results of the partitioned survival model based on the probabilistic analyses (10,000 iterations) is presented in *Table 36*; demonstrating lifetime expected costs and QALYs, incremental costs and QALYs, as well as the ICER. Treatment with ^{177}Lu-PSMA-617 plus standard of care was associated with a health gain of 0.44 QALY and NOK [redacted] higher costs when compared with standard of care alone. This results in an ICER equal to over NOK [redacted] per QALY.

Table 36: Results of the base case cost-utility analysis

Intervention	Total costs (NOK)	Incremental cost (NOK)	Effects (QALY)	Incremental effect (QALY)	ICER (NOK/QALY)
SoC	[redacted]		0.63		
^{177}Lu-PSMA-617 + SoC	[redacted]	[redacted]	1.07	0.44	[redacted]

ICER: incremental cost-effectiveness ratio, NOK: Norwegian kroner, QALY: quality-adjusted life year, SoC: standard of care therapy

The same results can also be presented as a cost-effectiveness graph, as in *Figure 17* below.

Figure 17: Cost-effectiveness graph of ^{177}Lu-PSMA-617 + standard of care therapy (SoC) versus standard of care therapy alone, base case analysis
QALY: quality-adjusted life-years

Probabilistic sensitivity analysis

The results of the probabilistic sensitivity analysis are illustrated in *Figure 18*. The results are based on 10,000 iterations of Monte Carlo simulations from the base case analysis. *Figure 18* show the uncertainty associated with the results in the base case analysis. The red dots show cases where ^{177}Lu-PSMA-617 + SoC has an ICER higher than NOK [redacted] per QALY when compared to standard of care therapy alone.

Figure 18: Scatterplot for base case-analysis
WTP: Willingness-to-pay; set here to NOK [redacted]/QALY for illustration only

Figure 19 presents cost-effectiveness acceptability curves at willingness to pay for one additional QALY between [redacted] and [redacted] Norwegian kroner per QALY. It is apparent that standard of care has a higher probability of being cost-effective than ^{177}Lu-PSMA-617 + SoC in the range of NOK [redacted] per QALY, when considering all parameter uncertainty simultaneously.

Figure 19: Cost-Effectiveness Acceptability Curves
SoC: standard of care therapy

One-way sensitivity analysis

The tornado tornado diagram is a visual tool for presenting a set of one-way sensitivity analyses, demonstrating how variations in individual model parameters affect cost-utility results, as represented by the ICER. In this diagram, the blue bar indicates the lower end of the parameter estimate, while the red bar represents the higher end of the parameter estimate. In *Figure 20* we can observe that the result is most affected by variation in cost of the intervention, i.e., ^{177}Lu-PSMA-617.

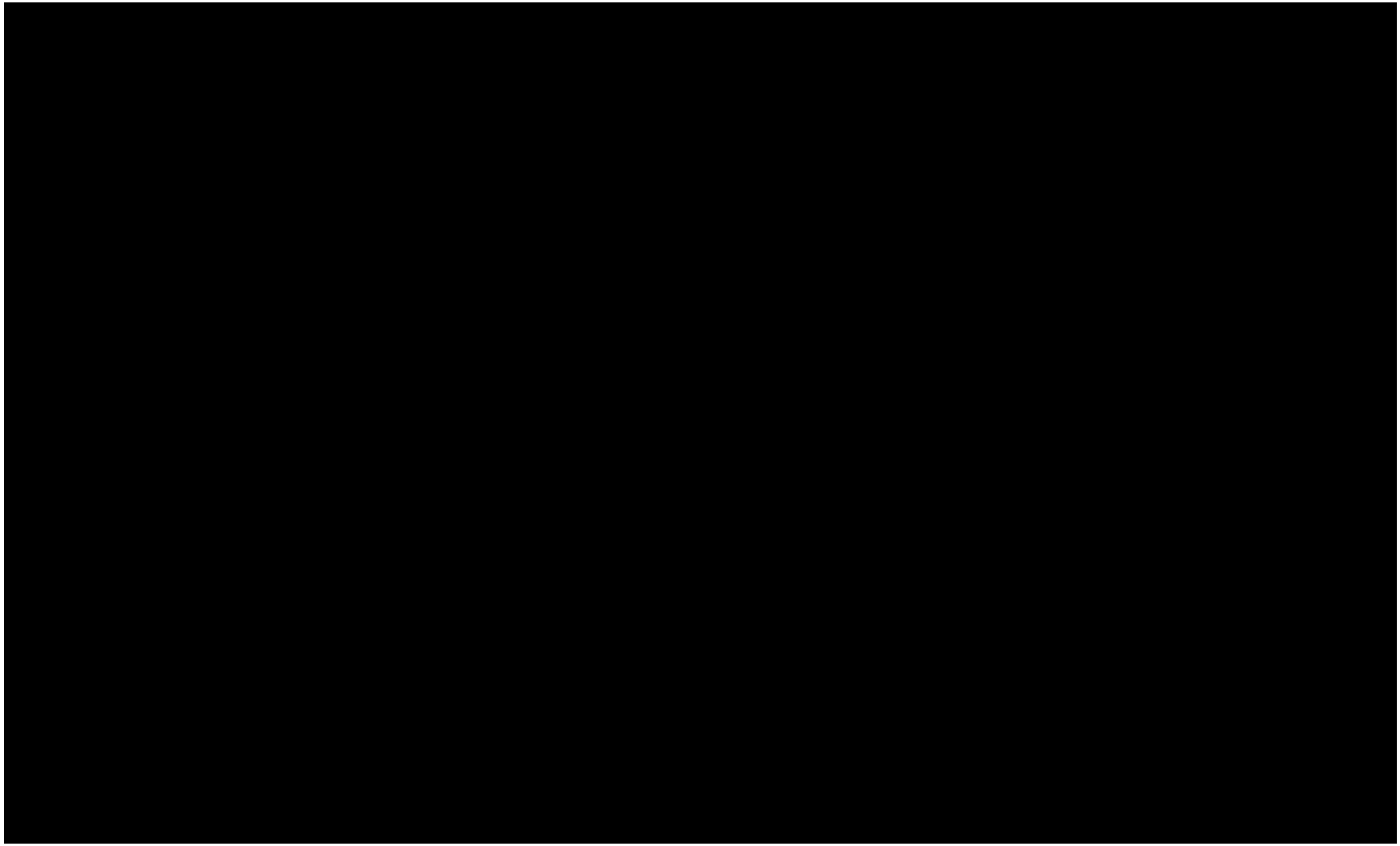


Figure 20: Tornado diagram revealing possible impact of variation in main parameters on the ICER of treatment with ^{177}Lu-PSMA-617 compared with standard of care therapy

For more parameter details, see Appendix 10. EV: expected value, Inv: intervention, Lu: lutetium, OS: overall survival, PD: progressed disease, PFS: progression-free survival, SC: subcutaneous, sd: standard deviation

Scenario analyses

1. Scenario analyses show that reduction in price of ^{177}Lu-PSMA-617 would result in gradual fall in ICER, see *Table 37*.
2. Scenario analysis with cabazitaxel as comparator (assumption about unchanged effect, only changed prices for comparator compared with base case), as presented in *Table 38*.
3. Scenario analysis without dosimetry costs, results presented in *Table 39*.

Table 37: Results of the scenario analyses with discounts on treatment with ^{177}Lu-PSMA-617 compared with standard of care therapy

	Base case results	Results with % discount:			
		20%	40%	60%	80%
ICER (NOK/QALY)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio, NOK: Norwegian kroner, QALY: quality-adjusted life year

Results of the scenario analyses with cabazitaxel as comparator

Table 38: Results of the scenario analyses with cabazitaxel as comparator, without adverse events effect

Intervention	Total costs (NOK)	Incremental cost (NOK)	Effects (QALY)	Incremental effect (QALY)	ICER (NOK/QALY)
Cabazitaxel	[redacted]		0.63		
^{177}Lu-PSMA-617	[redacted]	[redacted]	1.07	0.44	[redacted]

ICER: incremental cost-effectiveness ratio, NOK: Norwegian kroner, QALY: quality-adjusted life year

Table 39: Results of the scenario analyses without dosimetry costs

Intervention	Total costs (NOK)	Incremental costs (NOK)	Effects (QALY)	Incremental effect (QALY)	ICER (NOK/QALY)
Standard of care	[redacted]		0.63		
^{177}Lu-PSMA-617	[redacted]	[redacted]	1.07	0.44	[redacted]

ICER: incremental cost-effectiveness ratio, NOK: Norwegian kroner, QALY: quality-adjusted life year

Severity considerations - Absolute shortfall

In accordance with the economic model, we assume that patients are 71 years of age when entering the model. For men at this age, the expected quality-adjusted life expectancy in the general population is equal to 12.3 QALYs (101). The prognosis for patients with mCRPC is expected to be 0.63 QALYs (undiscounted) for standard of care alone, based on simulations from the health economic model with lifetime (5 years) time horizon. The absolute shortfall with these assumptions is:

$$AS = 12.3 - 0.63 = 11.67\ QALYs$$

This puts patients with mCRPC in severity class 3 (see severity class in glossary; *Appendix 1*) (83).

Budget impact analysis

We calculated the budgetary impact of introducing ^{177}Lu-PSMA-617 plus standard of care for patients with mCRPC in Norway. As mentioned in chapter on *Methods – health*

economics, we did not include costs associated with potential investments (e.g., PET). We assume an increasing number of new patients each year (from 100 new patients in year 2023 to 500 new patients in 2027) and that all relevant costs associated to these new patients occur in that one year only. *Table 40* presents the total added cost of introducing ^{177}Lu-PSMA-617 plus standard of care. We have not taken into account that an implementation of ^{177}Lu-PSMA-617 may affect the use of other treatment options for this population.

Table 40: Budget impact analysis (Base case analysis)

Cost per year (NOK)	Year				
	2023	2024	2025	2026	2027
Implementing ^{177}Lu-PSMA + SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not implementing ^{177}Lu-PSMA-617*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total added cost per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All costs are in Norwegian kroner (NOK); [redacted].
**Only standard of care therapy (SoC)*

Patient perspectives

Introduction

Patient perspectives relate to issues relevant for patients, individuals, and caregivers. Since patients with mCRPC can provide unique perspectives about experiences, attitudes, preferences, values, and expectations concerning health, illness, service delivery and treatments, their perspectives may extend far beyond the original setting of the proposed new method.

Methods

In this HTA, considerations regarding patients' experiences and perspectives were managed with the help of two patient representatives assigned by the Norwegian Prostate cancer patient association. We collected their perspectives through a questionnaire (105;106) and a digital interview. The patient representatives also participated as part of the external working group in digital meetings at start-up and mid-term in the project period.

The patient representatives provided their perspectives and experiences related to:

- The burden of living with mCRPC
- Reflections about the current course of treatment
- Expectations of the ^{177}Lu-PSMA-617 treatment

The burden of living with mCRPC

The patient representatives underline that the patient group eligible for ^{177}Lu-PSMA-617 treatment are men with a relatively large spread in age, in different life situations, with diverse backgrounds, and with various preferences for how they want life to be. The diagnosis of prostate cancer and the patients' following meetings with the health services are therefore experienced and handled very differently by those concerned. The patient representatives point to how important it is that health professionals understand each patient's overall situation. Clear and precise information and two-way communication with health care professionals are valuable for the patients and their relatives (i.e., partners and children).

Living with mCRPC means that everyday life is affected by a range of physical and psychological challenges related to the cancer itself, as well as the effects of various cancer treatments, e.g., surgery, radiation therapy, chemotherapy, hormonal therapy. Physical challenges include urinary incontinence, fatigue, and pain. The latter is often associated with skeletal metastases, and may result in reduced mobility, such as climbing

stairs. Patients will therefore require pain-relieving medications, and potentially mobility aids and help with transportation, e.g., stairlift. Treatments for prostate cancer also lead to loss of sexual function and reproductive capacity, which may be especially difficult to come to terms with for younger men with plans to start a family with their partners. In addition to the physical effects, experiencing a limitation in the ability and/or capacity to function "as normal" in everyday life, such as working and maintaining a social life, driving, and doing housework, is an additional mental burden for the patients. Such physical limitations will also cause additional work and responsibilities for the families of patients with mCRPC, in day-to-day life. On top of the extra physical load, both family and friends may experience mental challenges such as helplessness in caring for their loved ones, and fear for losing them too soon.

The first months after being diagnosed with mCRPC are particularly tough. For many, the psychological burden is the most challenging issue in living with this condition, and many struggle with symptoms of anxiety. This, combined with fatigue symptoms, could contribute to a feeling of helplessness and subsequent inaction. Several men live with their cancer diagnosis without being open with their partners about the physical and psychological difficulties it entails. This may cause strain and distress in the relationship,

As the age of men with mCRPC ranges from early thirties to well over 90, they will be in very different phases of life and the diagnosis will affect them differently. Issues relating to fertility and sexual functioning for example, may be of different importance for young men than for older men. Furthermore, younger men may be in a different financial situation than older men, e.g., starting their working career and entering the housing market with newly established loans. Conversely, men on the other side of the age scale have a very different life situation than younger men, e.g., being retired, and having established families with adult children that may have families of their own. However, many will also have experienced (natural) loss of family and friends due to age. According to the patient representatives, social visits and initiatives for socialisation needs to be prioritised for men with mCRPC of all age groups, but especially for older men. Furthermore, in contrast to younger men who usually are fit and healthy, old age is often accompanied by various other health challenges that also need treatment.

Reflections about the current course of treatment

According to the Norwegian national action program, prostate cancer is first treated with prostatectomy or radiation therapy, with subsequent drug therapy, i.e., hormone therapy and chemotherapy, for mCRPC (7). In Norway, patients have the right to proper information and participation through shared decision-making, throughout the entire course of treatment, as per the Patients' Rights Act (107). Although some patients may spend substantial time retrieving information and reading about the disease, others may fully trust their doctors as the experts, and will leave all treatment decisions to them, thereby choosing not to be an active participant in their own course of treatment. Some patients, especially older, may find it difficult to access information, especially as it is mostly available online. In the specialist healthcare, patients may experience that doctors have too little time for them, and that patient information often focus more on technical aspects that come across as dry, unsensitive and indifferent. This may cause

unassertiveness and affect the patient's mental health. Having a cancer coordinator is regarded as very important.

Patients have different experiences with the existing treatment options: Treatment is a must to prolong life and reduce pain, and it affects the quality of life in both positive and negative ways. The current treatments for prostate cancer have major implications on the patients' sex life and is something that seems to have been under-communicated. Furthermore, urinary incontinence is a common side effect of prostate cancer treatment. This requires the use of urine sheaths or pads to prevent drip. Concerns about urinary incontinence poses daily challenges and may cause the patients to limit their participation in everyday situations. As such, optimal access to toilets is important, and may be an added stress element when travelling, e.g., (long distance) to hospital for treatment, or visiting out of home.

Furthermore, pain due to metastatic disease is common among men with mCRPC, and is generally managed with strong opioid medications, often in high doses. As with all cancer treatments, opioids will cause side-effects, that may have a significant negative effect on quality of everyday life, such as fatigue symptoms. Patients also have concerns about long-term effects of the various medications that are available for mCRPC.

Expectations to ^{177}Lu-PSMA-617 treatment

Expectations related to the ^{177}Lu-PSMA-617 treatment may vary among patients. However, overall, there is a high expectation of ^{177}Lu-PSMA-617, as a new life prolonging treatment agent for mCRPC when other treatment strategies have not worked. Furthermore, patients also expect that the proposed treatment will reduce the metastatic disease, thereby relieving pain and lessen the use of pain medications such as opioids. By reducing the symptom burden and the subsequent need for symptom treating medication, the new treatment may have a positive impact on the patients' quality of life and result in better function and less use of municipal services.

Patients seem less concerned about the locations as to where the ^{177}Lu-PSMA- 617 treatment will be available, i.e., either centralised or decentralised organisation (see chapter on *Organisational aspects*), as long as the treatment is managed with high professional competence and experience. Easy access to the local (community) cancer coordinator would be of great help for patients and should therefore be included in the organisational planning of implementing ^{177}Lu-PSMA-617 treatment in Norway.

There are very few mCRPC patients in Norway that have direct experience with a ^{177}Lu-PSMA treatment (regardless of PSMA ligand, e.g., PSMA-617, PSMA-I&T, etc). As previously mentioned, only two patients have received the treatment in Norwegian hospitals, whereas others have travelled abroad to Finland or Germany for the treatment. According to the patient representatives, there are high hopes and expectations for ^{177}Lu-PSMA-617, but the treatment is so new that the available information is very technical and unintelligible for most patients to understand. As such, there is a need for clear and concise information specifically catered to patients and their next of kin, so that they are better suited to make informed decisions regarding their own course of treatment. Such information should first and foremost include specific selection criteria for the treatment (i.e., which patients can receive ^{177}Lu-PSMA-617), and the potential, anticipated effect, as well as side-effects, but also practical implications and consequences, such as radiation hygiene issues.

Discussion

Efficacy and safety discussion

Key findings summary

We have systematically reviewed the literature on clinical efficacy and safety of the ^{177}Lu-PSMA-617 treatment for mCRPC. The evidence base comprised of two phase 2 RCTs, studying the effect of ^{177}Lu-PSMA-617 compared with cabazitaxel (39) and docetaxel (41), and one phase 3 RCT studying the effect of ^{177}Lu-PSMA-617 in combination with standard of care therapy compared with standard of care therapy alone (40).

For the comparison of ^{177}Lu-PSMA-617 in combination with standard of care therapy versus standard of care therapy alone, we found that treatment with ^{177}Lu-PSMA-617 plus standard of care therapy improves both the overall survival and progression-free survival of patients with mCRPC[7] more than standard of care therapy alone (high certainty evidence). In addition, ^{177}Lu-PSMA-617 plus standard of care therapy also reduces the development of a first symptomatic skeletal event more than standard of care therapy alone (high certainty evidence). We also found that ^{177}Lu-PSMA-617 plus standard of care therapy probably reduces the PSA level in more mCRPC patients[7] than standard of care therapy alone (high certainty evidence), and probably improves the quality of life more than standard of care therapy alone (moderate certainty evidence). However, ^{177}Lu-PSMA-617 in combination with standard of care therapy probably increases the risk of severe adverse events ≥grade 3 in patients with mCRPC[7], more than standard of care therapy alone (moderate certainty evidence).

For the comparison of ^{177}Lu-PSMA-617 versus cabazitaxel, we found that ^{177}Lu-PSMA-617 may improve progression-free survival more than cabazitaxel (low certainty evidence) and probably reduces the PSA level in more mCRPC patients[8] than cabazitaxel (moderate certainty evidence). However, we are uncertain of the effect of ^{177}Lu-PSMA-617 in terms of severe adverse events ≥grade 3 and quality of life, compared with cabazitaxel, because the certainty of this evidence is very low.

For the comparison of ^{177}Lu-PSMA-617 versus docetaxel, we are uncertain of the effect with respect to progression-free survival, PSA level and severe adverse events ≥grade 3, because the certainty of the evidence is very low. However, we did find that ^{177}Lu-PSMA-

[7] The study population in the VISON study had previously been treated with hormone therapy and chemotherapy, including docetaxel and cabazitaxel.

[8] The study population in the TheraP study had previously been treated with docetaxel, but not cabazitaxel.

617 may improve quality of life in patients with mCRPC[9] more than docetaxel (low certainty evidence).

All three studies consistently presented fatigue, dry mouth and eyes, and pain as the most common adverse events linked to treatment with ^{177}Lu-PSMA-617. Although more serious adverse events, such as nephrotoxicity also were reported by all three studies, the incidence of these were generally low.

Survival data

We are aware that the TheraP study has published data on overall survival, that show no difference between the intervention group that received ^{177}Lu-PSMA-617 (median 19.1 months) and the comparator group that received cabazitaxel (median 19.6 months) (108). However, these data is published as a conference abstract, and not in a peer reviewed journal, and we therefore chose not to include it in our HTA (108). As the TheraP study and the VISION study differ with regards to the intervention and comparator used, as well as the study population recruited, we cannot compare the results directly. In the VISION study, both the intervention group and the comparator group received standard of care therapy which consisted mainly of hormone therapies, glucocorticoids and treatment with bone resorption agents (40). No cytotoxic chemotherapy, including taxan-based regimens were allowed (40). Based on this notion, one could argue that the lack of difference in overall survival seen in the TheraP study is because the effect of ^{177}Lu-PSMA-617 is compared with a cytotoxic agent; cabazitaxel, which is more potent than hormone therapy. Still, the TheraP study was not sufficiently powered to investigate overall survival, and the results may therefore change with a larger study population.

Adverse events

In assessing adverse events linked to treatment with ^{177}Lu-PSMA-617, we only used data from the three included studies, i.e., VISION, TheraP and the study by Satapathy et al. (39-41). Although we are aware that there exist several non-RCTs that have investigated adverse events following treatment with various ^{177}Lu-PSMA-variants, we were limited by our inclusion criteria of only RCTs. However, the most common adverse events related to ^{177}Lu-PSMA-617 treatment were consistently reported across the three included studies in this report. As the majority of patients with mCRPC are older men, some of the more common adverse events related to ^{177}Lu-PSMA-617 treatment, such as dry mouth and eyes, are also common signs of ageing. Furthermore, some of the reported adverse events, such as pain and fatigue, are also symptoms of the cancer itself, as well as common adverse events linked to other mCRPC treatments, including enzalutamide. As such, we cannot preclude that the most common adverse events linked to treatment with ^{177}Lu-PSMA-617 are in fact caused by other factors, and further exacerbated by ^{177}Lu-PSMA-617 therapy.

As mentioned above, treatment with ^{177}Lu-PSMA-617 in combination with standard of care therapy in the VISION study increased the risk of experiencing severe adverse

[9] The study population in the Satapathy 2021 study was chemotherapy-naïve.

events ≥grade 3 when compared with standard of care therapy alone. We find this result unsurprising, as the standard of care therapy in the VISION study did not include any treatment with a chemotherapeutic agent, such as taxanes, nor systematic radioisotope therapy (e.g., radium-223) (40). We also note that statistical significance is not necessarily reflected in clinical effect. As such, the statistical risk of adverse events as calculated based on clinical trials, may not reflect the clinical practice (see also the section on *Generalisability in a clinical setting*).

Safety

Radiation exposure is a well-known health hazard that may cause harm to the body by damaging the DNA. Depending on the exposure (e.g., dose and exposure time), radiation may cause serious damage such as organ failure, cancer, and even death. However, the harmful effect of radiation can also be exploited for cancer treatment, by aiming to cause damage specifically to the cancerous cells, and avoiding the surrounding, healthy tissue. The RLT treatment ^{177}Lu-PSMA-617, consists of the lutetium-177 radionuclide, which emits both β and γ-radiation, and the PSMA-617 ligand, which ensures specific binding to and thereby radiation of PSMA-positive cancer cells. Due to the limited capacity to penetrate the skin or tissue, β-radiation is considered to be most harmful if it enters the body. As ^{177}Lu-PSMA-617 is injected into the body to exert its effect, the treatment has a risk for some degree of systemic radiation damage. Furthermore, normal tissue that also express PSMA, e.g., lacrimal glands, salivary glands, and kidneys, will also be affected by the radiation through targeted binding of the ^{177}Lu-PSMA-617 compound. Indeed, studies have reported dry eyes and mouth to be common adverse events, but with mild severity, indicating little impact on patient safety (39-41;68). Risks that are considered important for patient safety include myelosuppression and renal toxicity. ^{177}Lu-PSMA-617 is mainly excreted though the kidneys, which also express PSMA, and there is therefore a risk of radiation damage to the kidneys. Although studies have shown few and relatively mild nephrotoxic events (mostly adverse events grades 1 and 2) (39;41), long-term nephrotoxicity of repeated administration with ^{177}Lu-PSMA-617 cannot be disregarded (68). Still, long-term radiation-induced malignancy of lutetium-177 can be considered "beyond the horizon of relevance" as the patients indicated for the ^{177}Lu-PSMA-617 (Pluvicto) treatment typically have a short life expectancy (68). However, if patients with earlier stages of the prostate cancer, e.g., non-metastatic, will be eligible for ^{177}Lu-PSMA-617 treatment in the future, long-term radiation effects and radiation-induced malignancies will need to be explored.

Strengths and weaknesses in this HTA

A general strength of this HTAs is that the work has been performed in a systematic manner and in accordance with our project plan (*Appendix 11*). Throughout the process, at least two researchers independently performed study selection, data extraction, and data analysis. In addition, they also independently assessed the methodological quality of the included studies (Cochrane risk of bias tool), and the quality of the outcome (GRADE). Based on this, we are confident that we have taken reasonable steps to produce a trustworthy HTA.

As our literature search was performed in August 2022, we cannot exclude the possibility that other relevant studies may have been published since that time.

However, our search strategy was thorough, and we are confident that we have identified all relevant studies published prior to August 2022.

Because only three studies were included, each with different intervention treatments (^{177}Lu-PSMA with or without standard of care therapy) and comparator treatments (standard of care therapy, cabazitaxel, and docetaxel), we did not perform a meta-analysis. We are aware that this limits our HTA, as synthesising results from multiple studies can yield more precise effect estimates and assess and potentially explain heterogeneity between studies and possible publication bias. In theory, we could have chosen to perform network meta-analysis, by pooling together the intervention treatments; ^{177}Lu-PSMA with or without standard of care therapy, as one common intervention, by assuming that standard of care therapy would have no additional effect. However, we were hesitant to make this assumption and we judged that such an analysis would be of limited benefit and a poor use of our resources. We therefore reported the results separate for each study.

Evidence quality with GRADE

As previously described, we used the GRADE approach in assessing the certainty of evidence. The main advantage of using GRADE is that it makes our judgements transparent and open to criticism. However, even though the GRADE approach provides a structure to evaluate the certainty of evidence in a systematic manner, the assessments are still made by subjective judgement. We therefore acknowledge that others may rate the certainty of evidence differently than we have.

Documentation package by Novartis

Our HTA differs somewhat from the submitted documentation package by Novartis. In terms of the systematic search strategy, we searched more broadly than the submission file. We focused on MeSH terms such as Prostatic Neoplasms and Lutetium, and used text words connected to these terms, in addition to variations of the term "PSMA antigen". As we did not limit our search further, it resulted in a maximum overview of relevant studies regarding lutetium. Furthermore, we included a search for ongoing studies, which the submission file did not.

The efficacy and safety data in the documentation package by Novartis, were mainly based on the VISION study (40), which is in line with our HTA. However, none of the other two studies in our HTA, i.e., the TheraP study (39) and the study by Satapathy et al (41), were included or mentioned in the documentation package.

Furthermore, in the documentation package, Novartis chose to perform a network meta-analysis to compare ^{177}Lu-PSMA-617 indirectly with cabazitaxel. In the literature search for the network, only phase 3 studies were included, which is seemingly the reason for why the TheraP study, where ^{177}Lu-PSMA-617 and cabazitaxel were compared directly, was excluded. As previously mentioned, we could have chosen to perform our own network meta-analysis, thereby allowing us to compare the effect of ^{177}Lu-PSMA-617 (indirectly) with cabazitaxel, as in the documentation package. However, that would have warranted a wider literature search to yield sufficient data to make a network, not only limited to lutetium-177 based therapy. This would then lead us to make assumptions about treatment regimens and study populations that could add additional

heterogeneity and uncertainties to the analysis. Seeing as we expected to find limited relevant literature, we found that the additional work in terms of making a network meta-analysis would be of limited benefit.

Generalisability of findings

The study populations in the three studies included in this HTA differ somewhat. First, all three studies used different inclusion criteria when recruiting study participants. In the VISION study, patients had to have been treated with one or two taxane based regimens (chemotherapy) (40). In the final study population, around 40-45% had been treated with two previous taxane based regimens, and almost 40% had used cabazitaxel (40). In the TheraP study, however, the study participants had to have been treated with docetaxel, and cabazitaxel should be the considered as the *next* appropriate standard treatment (39). In contrast, in the study by Satapathy et al, all study participants should be chemotherapy-naïve, i.e., none should have been treated with any taxane-based regimen (41). As such, the study participants within the different studies were in different stages of their treatment plan. In the Summary of Product Characteristics (SPC) in the Product Information for Pluvicto (^{177}Lu-PSMA-617), it is specified that Pluvicto is indicated for patients previously treated with taxane-based chemotherapy and androgen receptor pathway inhibitors (28). This is more in line with the study populations in the VISION and the TheraP studies than in the study by Satapathy et al.

Second, the patient populations in the three studies also differ in terms of race and ethnicities. In VISION and TheraP, the study participants were predominantly Caucasian ("white"), as the studies were conducted in Europe and North America, and Australia, respectively (39;40). Seeing as the Norwegian population is also predominantly Caucasian, the results from these studies are probably more transferable to a Norwegian setting. The study by Satapathy et al however, was conducted in India (41). There is growing evidence that incidence, morbidity, and mortality of prostate cancer is influenced, at least in part, by ethnicity and race (109). This is supported by the fact that several of the patients in the study by Satapathy et al seem to present with a more advanced disease or possibly a more aggressive disease (higher percentage of patients had higher ECOG and Gleason scores, with shorter time from diagnosis), than compared with patients in the VISION and the TheraP studies.

Third, the three studies were powered differently according to their main outcomes. The VISION study was the only study that was powered sufficiently to investigate overall survival, with 581 study participants. Both the TheraP study and the study by Satapathy et al was powered for investigating surrogate endpoints such as PSA response rate, and therefore had few study participants in total; n=200 and n=40, respectively. In contrast to the study by Satapathy et al however, the TheraP study was also sufficiently powered for progression-free survival.

In total, all these factors lead us to assess that the results from the study by Satapathy et al should be interpreted with caution in a Norwegian setting.

In terms of choice of comparator, all three RCTs differed from each other. Both the TheraP study and the study by Satapathy et al. compared the effect of ^{177}Lu-PSMA-617 to a chemotherapeutic agent, i.e., cabazitaxel and docetaxel, respectively (39;41). However, the VISION study used standard of care therapy as a comparator, as well as an

additional treatment in the intervention group. As previously described, the standard of care therapy in the VISION study was *not* permitted to include cytotoxic chemotherapeutic agents (e.g., cabazitaxel or docetaxel), systemic radioisotopes (e.g., radium-223), immunotherapy, or any drug that was considered investigational at the start of the study (e.g., olaparib). This differs from what would be considered as "standard therapy" in clinical practice in Norway today. As described in the Norwegian action program for treatment of prostate cancer, cytotoxic chemotherapy with docetaxel and cabazitaxel is a well-established treatment of patients with mCRPC. With this being omitted from the comparator treatment in the VISION study, we are unsure what effect this has on the results. One could argue that the TheraP study is a "better" study to explore the results of ^{177}Lu-PSMA-617, as it uses the more clinically "relevant" comparator of cabazitaxel. However, the study itself is quite small (n=200) and does not have sufficient power to investigate important outcomes, such as overall survival. As such, we caution against over-interpreting the results from all three studies, both in terms of efficacy and safety.

Generalisability in a clinical setting

The goal of a systematic review is to summarise available evidence that meet a defined set of criteria. Regardless of the amount and quality of evidence that can be included in a systematic review, it is important to remember that systematic reviews, as well as single studies, typically report treatment effects that do not necessarily reflect the treatment effect (i.e., clinical effect) for an individual patient. In other words, our findings are probably most usefully interpreted at the health system level, rather at an individual patient level.

Consistency with other reviews

As present time, we are not aware of any other systematic review or HTAs that has been conducted investigating the efficacy and safety of ^{177}Lu-PSMA-617. This is unsurprising seeing as ^{177}Lu-PSMA-617 (Pluvicto) just recently received marketing authorisation in USA and Europe, and that there are currently few RCTs with data on overall survival. We are however aware that Austria have started working on an HTA on ^{177}Lu-PSMA, though most likely with somewhat different selection criteria than used in this HTA. Novartis also informed us that they have submitted documentation packages to other Nordic countries.

Need for further research

^{177}Lu-PSMA-617 is a fairly new treatment for mCRPC, and as expected there is limited evidence especially on overall survival. In our HTA, we found only one RCT; the VISION study (40), that had published peer reviewed data on overall survival. As such, there is a need for more studies; preferably RCTs, to investigate the effect of ^{177}Lu-PSMA-617. We also expect that future studies will investigate long-term effect of the ^{177}Lu-PSMA-617 treatment, both on overall survival and other efficacy outcomes, as well as safety outcomes and quality of life. The VISION study is still ongoing and will likely produce longer follow-up data on overall survival and progression-free survival in the future. At the moment of this HTA, Pluvicto is indicated for treatment of adult patients with mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based

chemotherapy (28). It is likely that future studies will explore the effect and safety of ^{177}Lu-PSMA-617 in earlier stages of prostate cancer, as well as in combination with other treatments. It is also likely that future studies will investigate the effect of radioligand therapy on other cancer types, e.g., breast cancer. Radioligand therapy is still a fairly new treatment strategy and ^{177}Lu-PSMA-617 is to our knowledge only the second radioligand treatment to be marketed after Lutathera (^{177}Lu-oksodotreotid) for neuroendocrine cancer.

Implications for use

^{177}Lu-PSMA-617 present a new opportunity and a much-anticipated supplement in mCRPC therapy. As previously described, the Norwegian health-services need to be prepared for up to about 2 200 ^{177}Lu-PSMA-617 treatments per year, if this therapy is implemented in Norway. In the chapter on *Organisational aspects*, we have attempted to draw contours of organisational aspects that need to be further explored with a potential implementation of ^{177}Lu-PSMA-617 treatment in Norway. Although expert representatives have presented us with advantages and disadvantages of offering ^{177}Lu-PSMA-617 treatment in a centralised model, some have also argued for a decentralised model. It is our understanding that in a centralised model the ^{177}Lu-PSMA-617 treatment would be offered only at the six university hospitals in Norway, whereas in a decentralised model, the treatment would be offered at the six university hospitals in addition to various local hospitals. Furthermore, expert representatives have strongly advocated for the treatment to be given in an outpatient setting. It would still be reasonable to assume that some additional inpatient capacity will be needed. As such, type of organisational model will likely have an impact on the available capacity of resources needed for the ^{177}Lu-PSMA-617 treatment, especially due to regional differences in patient volume. It is important to note however, that required resources are not necessarily additional resources. Many hospitals may already have the required resources needed for ^{177}Lu-PSMA-617 treatment, e.g., facilities, equipment and staff, in today's treatment course for this patient group in Norway, but may lack the necessary capacity for the estimated increase in patient load. As the questions regarding required resources and capacity is complex, we see a need for expert involvement for more in-depth assessments on organisational matters.

It is also important to keep in mind that the treatment with, and therefore also the organisation of ^{177}Lu-PSMA-617 therapy, needs to be in line with requirements in the Norwegian radiation protection legislation. For example, expert representatives have argued that dosimetry would not be (very) necessary in the ^{177}Lu-PSMA-617 treatment. However, all medical use of radiation must be optimised and planned to each individual patient according to the Regulations on Radiation Protection and Use of Radiation and is also encouraged by the EANM for therapy with ^{177}Lu-labelled compounds (48;60).

From patients' perspective, the ^{177}Lu-PSMA-617 is first and foremost as a new option for life prolonging treatment for mCRPC. Thirty Norwegian patients have already received government-funded ^{177}Lu-PSMA-617 treatment abroad. We also know that patients have paid for ^{177}Lu-PSMA-617 treatment abroad themselves, although we are unaware to which degree. However, this illustrates how important some patients consider the ^{177}Lu-PSMA-617 treatment. If ^{177}Lu-PSMA-617 were not to be implemented as a treatment for mCRPC in Norway, expert representatives argue that well-off patients may travel abroad and pay for the treatment themselves. This could effectively cause a "class divide" in

Norwegian mCRPC patients, thereby challenging the equality principle that permeates the Norwegian Patients' Rights Act (107).

Health economics discussion

Strengths and weaknesses of the economic evaluation

In the decision-making process, the sections on clinical effect and health economics should be considered together in order to evaluate the treatment under consideration in terms of the three priority criteria (benefits, resource use and severity). The clinical efficacy and safety section of this report provides the necessary information for establishing the clinical benefit of treatments in terms of gains in overall and progression-free survival, and safety considerations. The health economic evaluation section combines that information in the health economic model with the cost of resources used in treatments, to determine health gains measured in terms of quality-adjusted life-years in relation to the costs, and severity, measured in terms of absolute shortfall.

In the economic evaluation, we assessed cost-effectiveness of ^{177}Lu-PSMA-617 as addition to standard of care therapy compared with standard of care alone for patients with mCRPC who have been treated with androgen receptor pathway inhibition and taxane based chemotherapy. We chose to use clinical data from the VISION trial (40) to inform the clinical effectiveness data in the analyses. This was the only study regarded as high certainty evidence for main outcomes that shaped our model, with data for both the overall survival and progression-free survival. While cabazitaxel, according to the clinical experts, is considered the most relevant treatment alternative for patients with mCRPC in the Norwegian clinical practice, we had some reservations from using data from the only study that directly compares ^{177}Lu-PSMA-617 with cabazitaxel, the TheraP trial (39). This comparison found that ^{177}Lu-PSMA-617 may improve progression-free survival more than cabazitaxel (low certainty evidence), however the data on overall survival has only been published as conference abstract, which was excluded from our systematic review as argued in the efficacy and safety discussion above. As mentioned, the TheraP study was not sufficiently powered to investigate overall survival, and the conclusions can differ in a larger population. We have considered using indirect comparisons to derive plausible effect between ^{177}Lu-PSMA-617 and cabazitaxel, however these came with numerous limitations, and we decided against it. We have nevertheless investigated impact of cost differences between therapies with ^{177}Lu-PSMA-617 and cabazitaxel by running a scenario analysis with cabazitaxel as a comparator. In this scenario, we have assumed survival curves were the same as these used in the base case scenario (possibly overestimating the effect size for ^{177}Lu-PSMA-617). We have also removed the adverse events effects (costs and disutilities associated with adverse events) from the analysis, as we could not assume the same safety profile for standard of care and a taxane based chemotherapy. We have used the actual price of cabazitaxel as supplied by Sykehusinnkjøp (92) in this analysis. The resulting ICER was very similar to that from the base case analysis, i.e., about NOK [redacted] per QALY. Another limitation with using cabazitaxel as a comparator was that some proportion of patients, in line with indication for ^{177}Lu-PSMA-617, will have been treated with it before being considered for treatment with ^{177}Lu-PSMA-617. About 40% of patients in the VISION trial have had a pervious therapy with cabazitaxel (40).

The results of the base case scenario in our cost-effectiveness analysis show that the total expected average intervention-related costs per patient in a 5-year perspective are about NOK [redacted] for patients who receive ^{177}Lu-PSMA-617 plus standard of care therapy

and NOK [redacted] for patients who receive standard of care therapy alone. These include costs of the active therapies, accompanying diagnostics, dosimetry, monitoring, treatment of complications and end of life costs. There is some uncertainty around cost estimates. For cost of the intervention, we have used the pharmacy list price (without VAT) as made available by the supplier (Novartis) (73). This price would be subject to negotiations between the supplier and Sykehusinnkjøp (procurement agency) preceding and/or accompanying decision making process about implementation of the ^{177}Lu-PSMA-617 therapy. The ultimate price is not therefore available at the time of this HTA, which constitutes a limitation to our analysis. We have explored how changes in the initial price would impact the results and presented them both in the sensitivity analysis (Tornado diagram) and separately in the scenario analysis. These results show that apart from the survival data, the cost of ^{177}Lu-PSMA-617 had the biggest impact on the results (ICER), and that with discounts the ratio of incremental costs to incremental effect goes moderately down improving relative cost-effectiveness.

The survival curves used in the model, were developed with use of relevant parametric distributions for both the comparator and intervention. The accuracy of our extrapolations was measured using both the AIC criterion and visual inspection of the fitted distributions and comparing them to the Kaplan Meier data from the Vision trial (40). However, there were some limitations with our approach, especially with regards to the choice of distribution for the progression-free survival curve for standard of care. Due to unavailability of individual level patient data, the number of censorships were considerably high for the short follow up time (22 months). Therefore, none of our parametric distributions was fitting the actual data adequately. Hence, the approach to combine two distributions and assumption that there was no variation in the parametric distribution of PFS (SoC) in order to avoid introducing additional uncertainty. Moreover, introducing additional uncertainty for our combined curves for the PFS would have led to misleading and contradictory outcomes for the survival probabilities. For instance, the parametric distribution for less than 4 months could have had a lower probability due to the random variation in our probabilistic simulation, whereas the probability for greater than 4 months could have exceeded probability for less than 4 months. Moreover, there was additional uncertainty on the extrapolations beyond the trial period and have few implications for our results, for e.g., if the actual proportion of patients are underestimated in our analysis it may indicate that the costs of SoC are underestimated along with the benefits for the SoC and vice versa if the proportion of PF patients are overestimated. Nonetheless, in an event of a relationship being present between the OS and PF states for the SoC, the model's discrepancy may be captured by the uncertainty in OS state (i.e., higher OS may suggest patients benefit from the treatment and gained extra QALYs and vice versa). Therefore, by assuming PFS to be fixed in our probabilistic sensitivity analysis we were able to avoid the issues associated with cross overs in our analysis which may have contributed to the consistency of the results. A similar approach was applied in another cost-effectiveness analysis of ^{177}Lu-PSMA-617 (110).

To minimize uncertainty around costs related to other pharmaceutical therapies, and to make our analysis as relevant as possible, we have used prices provided by Sykehusinnkjøp (92). As for the costs related to diagnostics with PSMA PET/CT or PET/MR, which are required for selection of patients eligible for treatment, we have chosen to apply these to all patients at the start of the model. For evaluation of treatment response, patients get regular PSA tests in all treatment alternatives. However for evaluation of expected effect of consecutive treatment rounds, it is necessary to monitor

uptake of the radiopharmaceutical in the lesions (89). We have therefore applied an additional PSMA PET/CT scan at the end of treatment round number 5 in the ^{177}Lu-PSMA-617-arm of the model. In clinical practice, other diagnostic imaging procedures can be used for evaluation of treatment effect, for example imaging with planar gamma camera (89).

We have also included costs associated with dosimetry in the intervention arm. As recommended by the European guidelines on dosimetry of ^{177}Lu-labelled somatostatin-receptor- and PSMA-targeting ligands (60), treatment with ^{177}Lu PSMA-617 should be followed by a dosimetry procedure. We have assumed a dosimetry schedule including three SPECT/CT scans following the first treatment and one SPECT/CT scan after each of the remaining treatments. However, there is uncertainty about how exactly dosimetry procedures will be organized and practiced in Norwegian hospitals, since there are no national guidelines on this, and the Regulations on Radiation Protection do not specify this issue. Recommendations related to dosimetry may also change over time. To investigate the impact of dosimetry costs on cost-effectiveness of the intervention, we have analysed an alternative scenario, where we have removed them from the analysis.

The therapy with ^{177}Lu-PSMA-617 is assumed to applied on an outpatient basis in our model. However, for some patients, hospital admissions will be unavoidable for various reasons. We have not accounted for additional costs related to these admissions; therefore, administration costs might be underestimated. Further, we have not included costs related to patients' travel and time, as many of these will be applicable for patients in both intervention and comparator arm, dependent on therapy regimen and on centralisation level of specific therapies.

We included costs of subsequent therapies following the active compared therapies as one-time costs at the end of the progression-free state. The therapies that constitute this element vary according to the type of pharmaceuticals individual patients had in the first and the consecutive lines of treatment.

Our analysis shows that therapy with ^{177}Lu-PSMA-617 in addition to standard of care therapy was more effective and produced 0.44 QALYs more than standard of care therapy alone. This reflects the significant improvements in terms of progression-free survival and overall survival achieved in the trial (40). In absence of published utility data from the VISION study, we have used utility weights from an earlier cost-effectiveness study that evaluated abiraterone, cabazitaxel and enzalutamide in patients with mCRPC by Barqawi et al (99) considering them to be representative for the populations in our model.

We carried out our analyses in a 5-year time perspective. We considered this time frame to be sufficient for capturing the most of differences in costs and health gains between compared treatment options. The median follow-up in the VISION trial was 20.9 months (40). In our model 96.15% of patients are deceased after 60 months.

In the budget impact analysis, we included costs associated with relevant treatment alternatives in annual time perspective. We have only included direct costs related to the therapy with ^{177}Lu-PSMA-617, i.e. the cost of the radiopharmaceutical and it's administration to the patient. We did not include costs related to adverse events or dosimetry costs.

We have not included any economic consequences of expanding the present capacity at nuclear medicine wards, that would be necessary upon introduction of ^{177}Lu PSMA-617 therapy as routine treatment for patients with mCRPC in the Norwegian hospitals. There is certain capacity in terms of infrastructure (building, equipment and processes), as well as competence already in place for possible introduction of new radioligand therapies. However, the expected increased patient load receiving both diagnostics and treatment with radioligands would most likely require development and expansion of the involved wards, new purchases, expanding personnel capacities and more.

In absence of an officially defined willingness-to-pay threshold for a QALY gained in Norway, we abstained from concluding about cost-effectiveness, as well as from performing a net benefits analysis. Such calculations require assuming a fixed value of willingness-to-pay as they combine both costs, effectiveness and willingness-to-pay into a single measurement.

Consistency with other cost-effectiveness analyses

Cost-effectiveness analysis in documentation package by Novartis (73)

The model used in the submitted documentation package assessed cost-effectiveness of Pluvicto in comparison with cabazitaxel and with standard of care and used partitioned survival analysis as a modelling tool. In absence of appropriate survival data for direct comparison with cabazitaxel, Novartis used indirect comparison from a network meta-analysis employing, among others, data from the CARD trial (cabazitaxel versus abiraterone or enzalutamide in mCRPC) (103). The comparison against standard of care was based on clinical data from the VISION trial (40). Novartis used treatment- and stage-specific unpublished utility values gathered for the VISION trial. The global model was otherwise adjusted with Norwegian unit costs and discounting. The price for Pluvicto used in the analyses was NOK [redacted] per package (we used the same price in our model in the base case scenario).

The documentation package assessed the effectiveness of the therapy by measuring the QALYs. Compared with cabazitaxel, Pluvicto was associated with an incremental QALY-gain of 0.44. The ICER was NOK [redacted] per QALY gained. Compared with standard of care the incremental QALY gain was equal to 0.43 QALY and the ICER was NOK [redacted] per QALY. These results do not differ substantially from our assessment.

Cost-effectiveness analysis of ^{177}Lu-PSMA-617 from Germany (110)

In January 2023, we found a German cost-effectiveness analysis of ^{177}Lu-PSMA-617 through a scoping search we performed in order to identify other relevant analyses. The study compared ^{177}Lu-PSMA-617 with standard of care and also used a partitioned survival analysis as a method and the VISION trial (40) to define clinical effectiveness in the model (110). Since the price for ^{177}Lu-PSMA-617 was not available, the included intervention costs were extrapolated from ^{177}Lu-DOTATATE. The ^{177}Lu-PSMA-617 gathered an average of 0.42 more QALY and costed USD 83,712 more than standard of care, resulting in an ICER of USD 200,708 per QALY (110).

We consider main traits in the methods as well as results of our analysis consistent with the two cost-effectiveness analyses described above. Unsurprisingly, since we have used results from the VISION trial (40) similarly to these two models, our analyses showed almost identical health benefit expressed as QALY gain. We have used the same cost estimates for ^{177}Lu-PSMA-617 as in the Novartis model, however when it comes to other

treatment costs the company's model used official price lists, while we had access to real world data on prices. Unlike these two analyses, we have included costs of additional diagnostics and dosimetry in the ^{177}Lu-PSMA-617-treatment arm. The German model used cost of ^{177}Lu-DOTATATE as a proxy for ^{177}Lu-PSMA-617 costs. Nevertheless, our results turned out to be comparable to the two models also in terms of costs.

Conclusion

In terms of efficacy, treatment with ^{177}Lu-PSMA-617 plus standard of care therapy[10] prolongs both overall and progression-free survival, when compared with standard of care therapy[10] alone in patients with mCRPC previously treated with hormone therapy and chemotherapy. We have high confidence in these results. ^{177}Lu-PSMA-617 also prolongs progression-free survival when compared with cabazitaxel in patients with mCRPC previously treated with docetaxel, although we have low confidence in this result. The combination of ^{177}Lu-PSMA-617 and standard of care therapy[10] also had beneficial effect on other efficacy outcomes, when compared with standard of care therapy alone.

In terms of safety, treatment with ^{177}Lu-PSMA-617 plus standard of care therapy[10] has a statistically higher risk of severe adverse events ≥grade 3, when compared with standard of care therapy[10] alone, in patients with mCRPC previously treated with hormone therapy and chemotherapy. We have moderate confidence in this result. When compared with cabazitaxel, ^{177}Lu-PSMA-617 seem to have lower risk of severe adverse events ≥grade 3, in patients with mCRPC previously treated with docetaxel, but we have very low confidence in this result. Still, treatment with ^{177}Lu-PSMA-617 in general has shown mostly mild adverse events, such as fatigue and dry eyes and mouth. Although one cannot disregard long-term toxicity with repeated administration, the relevant patient population in general has short life expectancy, and long-term radiation-induced malignancy of lutetium-177 can therefore be considered beyond the horizon of relevance.

From patients' perspective, it is evident that professional competence and experience related to issues relevant for patients, individuals, and caregivers are the most valued at all stages of the disease management. Their expectation to ^{177}Lu-PSMA-617 treatment is first and foremost as a new option for life prolonging treatment for mCRPC.

In terms of health economics, we assumed that the ^{177}Lu-PSMA-617 would take place in an outpatient setting. The cost-utility analysis indicates that the treatment with ^{177}Lu-PSMA-617 is more effective, but also more costly than standard of care therapy in mCRPC patients who previously been treated with AD and taxane based chemotherapy. The incremental cost per QALY is found to remain relatively high, although discounts on the

[10] The standard of care therapy in the VISION study was not permitted to include the use of any cytotoxic chemotherapeutic agent (e.g., taxanes), systemic radioisotopes (e.g., radium-223), immunotherapy, or drugs that were considered investigational at the start of the study (e.g., olaparib).

price of the intervention bring it somewhat down. Treatments are considered cost-effective if the willingness-to-pay per extra QALY gained is above the ICER. Implementation of ^{177}Lu-PSMA-617 treatment in Norway will also affect the current organisation and allocation of resources. The expected increase in patient volume will likely put a strain on the current capacity of resources to ensure that the treatment is managed in line with the Norwegian radiation protection legislation. With these circumstances, the added costs must be seen as an investment in building a solid foundation for future RLT treatment.

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Appendix 1

Glossary and abbreviations

Term	Definition
^{177}Lu	Lutetium-177
AIC	Akaike Information Criterion, an estimator of prediction error and relative quality of statistical models
AUP	The maximum pharmacy retail price (apotekenes utsalgspris)
AR	Androgen receptor
AS	**Absolute shortfall**. Expected loss of future health (in QALYs) associated with a specified diagnosis.
CI	**Confidence interval**. A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrower intervals, greater precision.
CUA	**Cost-utility analysis**. An economic evaluation where health consequences are measured in QALYs.
DRG	Diagnosis related
EQ-5D	**European Quality of Life-5 Dimensions**. EQ-5D is a standardized instrument for use as a measure of health outcome.
GRADE	Grading of Recommendations Assessments, Development, and Evaluation
GBq	**Giga-becquerel**. Measures the intensity of the radioactive source.
Gy	**Gray**. Measure of absorbed radiation.
HR	**Hazard Ratio**. Ratio of hazard rates. Ratio above 1 indicate increased instantaneous rate of an event. Ratios below 1 indicate a decrease in event rates.
HRQoL	Health related quality of life
HTA	Health Technology Assessments
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in
Ligand	A molecule, ion or functional group that binds to a receptor
mCRPC	Metastatic castration resistant prostate cancer
NHB	**Net Health Benefit**. In a decision-making process, a positive NHB suggests that the intervention represents good value for money
NMB	**Net Monetary Benefit**. In a decision-making process, a positive NMB suggests that the intervention represents good value for money.

Odds	The odds of an event happening is defined as the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.
OR	**Odds ratio**. The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
OS	Overall survival
PSA	Prostate specific antigen
ProbSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
PSMA	Prostate specific membrane antigen
Radioligand	A molecule where a radioisotope is labelled with a ligand
RR	**Relative risk**. The ratio of the risk of an outcome in one treatment group divided by the risk of the same outcome in a different treatment group.
Severity class	Diseases or conditions can be divided into six severity classes according to absolute shortfall (AS), as suggested by the Magnussen group (83). These classes range from: AS < 4 QALYs lost (severity class 1), 4-7, 9; 8-11, 9; 12-15, 9; 16-19, 9, and AS ≥ 20 QALYs (severity class 6).
Sv	**Sievert**. Unit of radiation absorption.
W (λ)	**Willingness-to.pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g., QALY or life year).

Appendix 2

Deailed search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 22, 2022>

Search Date: 04.08.22

1 exp Prostatic Neoplasms/ and Lutetium/ (288)

2 (((Lutetium-177* or Lutetium 177* or Lutetium177* or Lu177* or Lu-177* or 177Lu* or 177-Lu* or "Lu(177)" or "Lu-(177)" or "(177)Lu*" or "(177)-Lu*" or "Lu[177]" or "Lu-[177]" or "[177]Lu*" or "[177]-Lu*" or (Lu* adj1 "177*")) adj10 (PSMA* or prostate specific membrane antigen)) or LuPSMA* or Lu-PSMA*).mp,bt. (615)

3 1 or 2 (661)

Database: Embase <1974 to 2022 June 24>

Search Date: 04.08.22

1 Prostate Tumor/ and Lutetium 177/ (26)

2 (((Lutetium-177* or Lutetium 177* or Lutetium177 or Lu177* or Lu-177* or 177Lu* or 177-Lu* or "Lu(177)" or "Lu-(177)" or "(177)Lu*" or "(177)-Lu*" or "Lu[177]" or "Lu-[177]" or "[177]Lu*" or "[177]-Lu*" or (Lu* adj1 "177")) adj10 (PSMA* or prostate specific membrane antigen)) or LuPSMA* or Lu-PSMA*).mp. (1457)

3 1 or 2 (1474)

Database: Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2022

Search Date: 04/08/2022 12:06:15

ID Search Hits

#1 ([mh ^"Prostatic Neoplasms"] AND [mh ^Lutetium]) OR (((lutetium-177* OR lutetium177* OR Lu177* OR "Lu-177*" OR 177Lu* OR "177-Lu*" OR "Lu(177)" OR "Lu-(177)" OR "(177)Lu*" OR "(177)-Lu*" OR "Lu[177]" OR "Lu-[177]" OR "[177]Lu*" OR "[177]-Lu*" OR (Lu* NEXT 177) OR (177 NEXT Lu*)) NEAR/10 (PSMA* OR "prostate specific membrane antigen")) OR LuPSMA* OR Lu-PSMA*):ab,kw,ti

Number of hits: 112

Database: Epistemonikos

Search Date: 04.08.22

(((lutetium-177 OR lutetium177 OR Lu177 OR Lu-177 OR 177Lu* OR "177-Lu" OR "Lu(177)" OR "Lu-(177)" OR "(177)Lu" OR "(177)-Lu" OR "Lu[177]" OR "Lu-[177]" OR "[177]Lu" OR "[177]-Lu" OR Lu177-PSMA OR 177Lu-PSMA OR 177-Lu-PSMA Lu-177-PSMA OR LuPSMA OR Lu-PSMA OR 177Lu-PSMA-617 OR 177Lu-PSMA-R2) AND (PSMA* OR "prostate specific membrane antigen")) OR LuPSMA* OR Lu-PSMA*)

Number of hits: 35

[Advanced Search – Title/Abstract]

Database: Scopus

Search Date: 04.08.22

Advanced Search:

TITLE-ABS-KEY (((lutetium-177* OR "lutetium 177*" OR lutetium177 OR lu177 OR lu-177 OR 177lu* OR 177-lu* OR "lu(177)" OR "lu-(177)" OR "(177)lu*" OR "(177)-lu*" OR "lu[177]" OR "lu-[177]" OR "[177]lu*" OR "[177]-lu*" OR (lu* W/0 "177")) W/5 (psma* OR "prostate specific membrane antigen")) OR lupsma* OR lu-psma*)

Number of hits: 669

Database: EU Clinical Trials Register

Search Date: 04.08.22

(("prostate cancer" OR "prostate neoplasm" OR "prostate neoplasms" OR "prostatic neoplasm" OR "prostatic neoplasms" OR "prostate carcinoma" OR "prostate adenocarcinoma" OR mCRPC OR mHSPC) AND (lutetium OR 177Lutetium OR Lutetium177 OR 177Lu OR "177-Lu" OR Lu177 OR "Lu-177" OR LuPSMA OR Lu-PSMA))

Number of hits: 9

The references are listed in a separate text-file

Database: WHO ICTRP

Search Date: 04.08.22

Advanced Search:

Condition: prostate cancer OR prostate neoplasm OR prostate neoplasms OR prostatic neoplasm OR prostatic neoplasms OR prostate carcinoma OR prostate adenocarcinoma OR mCRPC OR mHSPC

Intervention: lutetium-177 OR lutetium177 OR Lu177 OR Lu-177 OR 177Lu OR 177-Lu OR LuPSMA OR Lu-PSMA

Recruitment status: ALL

Number of hits: 67

Database: Clinicaltrials.gov

Search Date: 04.08.22

Condition or disease: prostate cancer OR prostate neoplasm OR prostate neoplasms OR prostatic neoplasm OR prostatic neoplasms OR prostate carcinoma OR prostate adenocarcinoma OR mCRPC OR mHSPC

Other Terms: "Lu177-PSMA" OR "177Lu-PSMA" OR "177-Lu-PSMA" OR "Lu-177-PSMA" OR "LuPSMA" OR "Lu-PSMA" OR "177Lu-PSMA-617" OR "177Lu-PSMA-R2"

Number of hits: 42

Database: INAHTA

Search Date: 04.08.22

Search Term: ((("Lutetium"[mh] OR lutetium* OR 177Lu* OR 177-Lu OR Lu177* OR Lu-177*) AND ("Prostatic Neoplasms"[mhe] OR PSMA* OR "prostate specific membrane antigen" OR "prostate-specific membrane antigen")) OR LuPSMA* OR Lu-PSMA*)

Number of hits: 2

Treffliste:
https://database.inahta.org/search?limit=&terms=%28%28%28%22Lutetium%22%5Bmh%5D+OR+lutetium*+OR+177Lu*+OR+177-Lu+OR+Lu177*+OR+Lu-177*%29+AND+%28%22Prostatic+Neoplasms%22%5Bmhe%5D+OR+PSMA*+OR+%22prostate+specific+membrane+antigen%22+OR+%22prostate-specific+membrane+antigen%22%29%29+OR+LuPSMA*+OR+Lu-PSMA*%29&client=user

The literature search performed by: Gunn Eva Næss

Peer reviewed by: Elisabet Hafstad

Appendix 3

Excluded studies

List of 8 references excluded through full text screening, with reason for exclusion.

Reference	Reason for exclusion
Ahmadzadehfar H, Schlolaut S, Fimmers R, Yordanova A, Hirzebruch S, Schlenkhoff C, et al. Predictors of overall survival in metastatic castration-resistant prostate cancer patients receiving [177Lu]Lu-PSMA-617 radioligand therapy. Oncotarget 2017;8(61):103108-16.	Not randomised
Calais J, Czernin J, Thin P, Gartmann J, Nguyen K, Armstrong WR, et al. Safety of PSMA-Targeted Molecular Radioligand Therapy with 177Lu-PSMA-617: Results from the Prospective Multicenter Phase 2 Trial RESIST-PC (NCT03042312). Journal of Nuclear Medicine 2021;62(10):1447-56.	Not randomised
Calais J, Gafita A, Eiber M, Armstrong WR, Gartmann J, Thin P, et al. Prospective phase 2 trial of PSMA-targeted molecular RadiothErapy with 177Lu-PSMA-617 for metastatic castration-reSISTant Prostate Cancer (RESIST-PC): efficacy results of the UCLA cohort. Journal of Nuclear Medicine 2021;62(10):1440-6.	Not randomised
Crumbaker M, Pathman, avel S, Yam AO, Nguyen A, Ho B, et al. Phase I/II Trial of the Combination of 177Lutetium Prostate specific Membrane Antigen 617 and Idronoxil (NOX66) in Men with End-stage Metastatic Castration-resistant Prostate Cancer (LuPIN). European Urology Oncology 2021;4(6):963-70.	Not randomised
Emmett L, Crumbaker M, Ho B, Willowson K, Eu P, Ratnayake L, et al. Results of a Prospective Phase 2 Pilot Trial of 177Lu-PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. Clinical Genitourinary Cancer 2019;17(1):15-22.	Not randomised
Sayman HB, Gulsen F, Sager S, Akgun E, Yeyin N, Bilgic S, et al. Selective Intra-Arterial Lutetium-177-Labeled Prostate-Specific Membrane Antigen Therapy for Castration-Resistant Prostate Cancer: Initial Results. Journal of Vascular & Interventional Radiology 2022;33(3):342-5.	Not randomised
Schuchardt C, Zhang J, Kulkarni HR, Chen X, Muller D, Baum RP. Prostate-Specific Membrane Antigen Radioligand Therapy Using 177Lu-PSMA I&T and 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: Comparison of Safety, Biodistribution, and Dosimetry. Journal of Nuclear Medicine 2022;63(8):1199-207.	Not randomised
Zang J, Liu Q, Sui H, Wang R, Jacobson O, Fan X, et al. 177Lu-EB-PSMA Radioligand Therapy with Escalating Doses in Patients with Metastatic Castration-Resistant Prostate Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2020;61(12):1772-8.	Wrong comparator

Appendix 4

Characteristics of included studies

Detailed list of all three included articles.

Study	Intervention and comparator	Baseline characteristics	Follow-up	Eligibility criteria	Outcomes in analysis
Hofman 2021 ***(39)*** ***(TheraP)*** NCT03392428 Phase 2, non-blinded Multicenter, Australia	**^{177}Lu-PSMA-617** 8.5 GBq, i.v. reduced by 0.5 GBq/cycle, Every 6 weeks, Maximum 6 cycles	**n=99**, Age (mean (SD)): 71.7 years (7.9), ECOG status 0-1: 96%, Gleason score ≥8 at diagnosis: 53%, Bone metastases: 91%, Visceral metastases: 7%, Previous treatments: abiraterone only: 21%, enzalutamide only: 50%, both: 21%, prostatectomy: 43.4%	Median 18.4 months	mCRPC. Previous treatment with docetaxel. Cabazitaxel considered next appropriate standard treatment. Previous treatment with androgen receptor-directed therapy was allowed	PFS, PSA-level reduction, AE, QoL
	Cabazitaxel 20 mg/m^2, i.v.,3 weeks. Maximum 10 cycles	**n=101**, Age (mean (SD)): 71.5 years (7.0), ECOG status 0-1: 96%, Gleason score ≥8 at diagnosis: 50%, Bone metastases: 89%, Visceral metastases: 13%, Previous treatments: abiraterone only: 24%, enzalutamide only: 57%, both: 9%, prostatectomy: 43.6%			
Sartor 2021 (40) ***(VISION)*** NCT03511664 Phase 3, non-blinded International	**^{177}Lu-PSMA-617** 7.4 GBq, i.v. Every 6 weeks, Maximum 6 cycles Std.care: Medication: 100%* Radiation therapy: 14.9% Other interventions: 4.5%	**n=551**, Age (median (range)): 70.0 years (48-94), ECOG status 0-1: 92.6%, Gleason score ≥8 at diagnosis: 58.8%, Median time since diagnosis (range): 7.42 years (0.9-28.9), Bone metastases: 91.5%, Visceral metastases: 20.3%, Previous treatments: abiraterone: 33.9%, enzalutamide: 71.1%, docetaxel: 96.9%, cabazitaxel: 37.9%, prostatectomy: 43.6%	Median 20.9 months	mCRPC. Previous treatment with ≥1 approved androgen-receptor-pathway inhibitor, and 1-2 taxane regimens.	OS, PFS, PSA-level reduction, skeletal events, AE, QoL

Study	Intervention and comparator	Baseline characteristics	Follow-up	Eligibility criteria	Outcomes in analysis
	SoD, n=205 Medication: 100%* Radiation therapy: 16.6% Other interventions: 2.4%	**n= 280**, Age (median (range)): 71.5 years (40-89), ECOG status 0-1: 92.1%, Gleason score ≥8 at diagnosis: 60.7%, Median time since diagnosis (range): 7.37 years (0.7-26.2), 60.7%, Bone metastases: 91.4%, Visceral metastases: 23.6%, Previous treatments: abiraterone: 37.9%, enzalutamide: 73.6%, docetaxel: 97.5%, cabazitaxel: 38.2%, prostatectomy: 46.4%			
Satapathy 2021 (41) CTRI/2019/12/022282 Phase 2, non-blinded India	**^{177}Lu-PSMA-617, n=20** 6.0-7.4 GBq, i.v. Every 8 weeks, Maximum 4 cycles	Age (median (range)): 68 years (54-85), ECOG status 0-1: 75%, Gleason score ≥8 at diagnosis: 70%, Median time since diagnosis (range): 3 years (2-7), Bone metastases: 100%, Visceral metastases: 25%, Previous treatments: abiraterone only: 50%, enzalutamide only: 0%, both: 20%	n.a.	mCRPC Chemotherapy-naïve patients. Prior treatment with novel androgen-axis drugs (abiraterone and enzalutamide) were allowed.	PFS, PS-level reduction, AE, QoL
	Docetaxel, n=20 75 mg/m^2, i.v., Every 3 weeks. Maximum 10 cycles	Age (median (range)): 68 years (50-84), ECOG status 0-1: 70%, Gleason score ≥8 at diagnosis: 60%, Median time since diagnosis (range): 2 years (1-6), Bone metastases: 100%, Visceral metastases: 20%, Previous treatments: abiraterone only: 60%, enzalutamide only: 0%, both: 0%			

**SoC: standard care medication could consist of: gonadotropin-releasing hormone analogues, glucocorticoids, androgen receptor pathway inhibitors (enzalutamide, abiraterone, apalutamide, darolutamide), denosumab, bisphosphonates, testosterone 5α reductase inhibitors, degarelix acetate, degarelix, and oestrogens.*

Appendix 5

Detailed GRADE: overall survival

Table with detailed assessment of certainty of evidence (GRADE) for overall survival. The table also includes EPOC standard sentences according to importance of effect and GRADE-result.

Treatment A	Treatment B	Starting point for GRADE	GRADE assessment	Reasons for downgrading	Hazard ratio OS (95% CI)	Median survival difference – months	EPOC standard sentences
^{177}Lu-PSMA-617 + SoC	SoC	High	High	None	0.62 (0.52 to 0.74)	4 months	^{177}Lu-PSMA-617 + SoC improves overall survival (High certainty of evidence)

SoC: standard of care therapy

Detailed GRADE: progression-free survival

Table with detailed assessment of certainty of evidence (GRADE) for progression-free survival. The table also includes EPOC standard sentences according to importance of effect and GRADE-result.

Treatment A	Treatment B	Starting point for GRADE	GRADE assessment	Reasons for downgrading	Hazard ratio PFS (95% CI)	Median survival difference – months	EPOC standard sentences
^{177}Lu-PSMA-617 + SoC	SoC	High	High	None	0.40 (0.31 to 0.51)	5.3 months	^{177}Lu-PSMA-617 + SoC improves progression-free survival (high certainty of evidence)
^{177}Lu-PSMA-617	Cabazitaxel	High	Low	Study limitations, imprecision	0.63 (0.46 to 0.86)	0 months	^{177}Lu-PSMA-617 may improve progression-free survival (low certainty evidence)
^{177}Lu-PSMA-617	Docetaxel	High	Very low	Indirectness, imprecision	0.90 (0.46 to 1.77)	0 months	It is uncertain whether ^{177}Lu-PSMA-617 improves progression-free survival because the certainty of this evidence is very low

SoC: standard of care therapy

Detailed GRADE: confirmed ≥50% PSA reduction

Table with detailed assessment of certainty of evidence (GRADE) for confirmed ≥50% confirmed PSA reduction. The table also includes EPOC standard sentences according to importance of effect and GRADE-result.

Treatment A	Treatment B	Starting point for GRADE	GRADE assessment	Reasons for downgrading	Risk ratio PSA-level reduction (95% CI)	Relative improvement RR≥1.2?	EPOC standard sentences
^{177}Lu-PSMA-617 + SoC	SoC	High	Moderate	Imprecision	5.2 (1.6 to 17.7)	Yes	^{177}Lu-PSMA-617 + SoC probably reduce PSA-level ≥50% (moderate certainty evidence)
^{177}Lu-PSMA-617	Cabazitaxel	High	Moderate	Study limitations	1.80 (1.34 to 2.40)	Yes	^{177}Lu-PSMA-617 probably reduce PSA-level ≥50% (moderate certainty evidence)
^{177}Lu-PSMA-617	Cabazitaxel	High	Very low	Indirectness, imprecision	1.50 (0.35 to 2.98)	No	It is uncertain whether ^{177}Lu-PSMA-617 reduce PSA-level ≥50% because the certainty of this evidence is very low

PSA: prostate specific antigen, SoC: standard of care therapy

Detailed GRADE: time to first skeletal event

Table with detailed assessment of certainty of evidence (GRADE) for time to first skeletal event. The table also includes EPOC standard sentences according to importance of effect and GRADE-result.

Treatment A	Treatment B	Starting point for GRADE	GRADE assessment	Reasons for downgrading	Hazard ratio skeletal event (95% CI)	Relative improvement HR ≤0.8?	EPOC standard sentences
^{177}Lu-PSMA-617 + SoC	SoC	High	High	None	0.50 (0.40 to 0.62)	Yes	^{177}Lu-PSMA-617 + SoC improves the time to first skeletal event (high certainty of evidence)

SoC: standard of care therapy

Detailed GRADE: adverse events ≥grade 3

Table with detailed assessment of certainty of evidence (GRADE) for adverse events ≥grade 3. The table also includes EPOC standard sentences according to importance of effect and GRADE-result.

Treatment A	Treatment B	Starting point for GRADE	GRADE assessment	Reasons for downgrading	Risk ratio PSA-level reduction (95% CI)	Relative improvement RR≤0.8?	EPOC standard sentences
^{177}Lu-PSMA-617 + SoC	SoC	High	Moderate	Study limitation	1.39 (1.14 to 1.69)	No	^{177}Lu-PSMA-617 + SoC probably reduce severe adverse events ≥grade 3 (moderate certainty evidence)
^{177}Lu-PSMA-617	Cabazitaxel	High	Very low	Study limitation, imprecision	0.73 (0.18 to 1.04)	No	^{177}Lu-PSMA-617 probably reduce severe adverse events ≥grade 3 (moderate certainty evidence)
^{177}Lu-PSMA-617	Cabazitaxel	High	Very low	Study limitation, indirectness, imprecision	0.60 (0.27 to 1.34)	No	It is uncertain whether ^{177}Lu-PSMA-617 reduce severe adverse events ≥grade 3 because the certainty of this evidence is very low

SoC: standard of care therapy

Detailed GRADE: quality of life

Table with detailed assessment of certainty of evidence (GRADE) for quality of life. The table also includes EPOC standard sentences according to importance of effect and GRADE-result.

Treatment A	Treatment B	Starting point for GRADE	GRADE assessment	Reasons for downgrading	Treatment effect (imprecision)	Relative improvement 20%?	EPOC standard sentences
^{177}Lu-PSMA-617 + SoC	SoC	High	Moderate	Study limitation	HR 0.54 (0.45 to 0.66)†	Yes	^{177}Lu-PSMA-617 + SoC probably improve quality of life (Moderate certainty evidence)
^{177}Lu-PSMA-617	Cabazitaxel	High	Very low	Study limitation, imprecision	MD 3.2 (-1.5 to 7.8)†	No	It is uncertain whether ^{177}Lu-PSMA-617 improve quality of life because the certainty of this evidence is very low
^{177}Lu-PSMA-617	Docetaxel	High	Low	Study limitation	^{177}Lu-PSMA: 7 (-4-5)* Docetaxel: -8 (-11-1)* p-value: 0.003	Yes	^{177}Lu-PSMA-617 may improve quality of life (Low certainty evidence)

HR: hazard ratio, MD: mean difference
†(95% CI)
**median score change from baseline (interquartile range)*

Appendix 6

List of ongoing trials

Study ID/name	Status/ Estimated end, study site	Treatments	Study design/ Enrollment (n)	Main outcome
NCT05204927/ Lu-177-PSMA-I&T for Metastatic Castration-Resistant Prostate Cancer	Recruiting/ 2029, USA	Arm 1: standard care hormone therapy (abiraterone/enzalutamide) Arm 2: ^{177}Lu-PSMA-I&T	RCT phase 3 crossover n=400	PFS
NCT04647526/ Study Evaluating mCRPC Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment (SPLASH)	Recruiting/ 2028, international	Arm1: ^{177}Lu-PNT2002 Arm 2: abiraterone or enzalutamide	RCT phase 3 n=415	PFS
NCT04720157/ An International Prospective Open-label, Randomized, Phase III Study Comparing 177Lu-PSMA-617 in Combination With SoC, Versus SoC Alone, in Adult Male Patients With mHSPC (PSMAddition)	Recruiting/ 2026, international	Arm1: ^{177}Lu-PSMA-617 Arm 2: standard care therapy	RCT phase 3 crossover n=1126	PFS
NCT03511664 (EudraCT 2018-000459-41)/ Study of 177Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer (**VISION**)	Active, not recruiting/ 2023, international	Arm 1: ^{177}Lu-PSMA 617 + standard care therapy Arm 2: standard care therapy	RCT phase 3 n=831	OS

Study ID/name	Status/ Estimated end, study site	Treatments	Study design/ Enrollment (n)	Main outcome
NCT04876651/ 177Lu-DOTA-rosopatamab With Best Standard of Care (SoC) for the Second Line of Treatment for Metastatic Castrate-resistant Prostate Cancer, Which Expresses PSMA (PROSTACT)	Not yet recruiting/ 2027, n.a.	Arm1: ^{177}Lu-DOTA-rosopatamb Arm 2: standard care	RCT phase 3 n=387	PFS
NCT04689828/ 177Lu-PSMA-617 vs. Androgen Receptor-directed Therapy in the Treatment of Progressive Metastatic Castrate Resistant Prostate Cancer (PSMAfore)	Active, not recruiting/ 2025, international	Arm 1: ^{177}Lu-PSMA-617 Arm 2: Androgen receptor-directed therapy	RCT phase 3 n=469	PFS
CTRI/2022/02/040221/ 177Lu-PSMA-617 plus low-dose rucaparib in metastatic castration-resistant prostate cancer: A randomized, controlled phase 2 trial (LuPlus)	Open to recruitment/ n.a., India	Arm 1: ^{177}Lu-PSMA-617 + rucaparib Arm 2: ^{177}Lu-PSMA-617	RCT phase 2 n=86	PSA response rate
NCT05150236/ EVOLUTION: 177Lu-PSMA Therapy Versus 177Lu-PSMA in Combination With Ipilimumab and Nivolumab for Men With mCRPC (ANZUP2001)	Recruiting/ 2024, Australia	Arm 1: ^{177}Lu-PSMA-617 + ipilimumab + nivolumab Arm 2: ^{177}Lu-PSMA-617	RCT phase 2 n=110	PFS
NCT00859781/ 177Lu Radiolabeled Monoclonal Antibody HuJ591 (177Lu-J591) and Ketoconazole in Patients With Prostate Cancer	Active, not recruiting/ 2025, USA	Arm 1: ^{177}Lu-J591+ketoconzole + hydrocortisone Arm 2: ^{111}In-J591 + ketoconazole + hydrocortisone	RCT phase 2 n=55	Proportion free of metastases
NCT04343885/ In Men With Metastatic Prostate Cancer, What is the Safety and Benefit of Lutetium-177 PSMA Radionuclide Treatment in Addition to Chemotherapy (UpFrontPSMA)	Recruiting/ 2024, Australia	Arm 1: ^{177}Lu-PSMA 617 + docetaxel Arm 2: docetaxel	RCT phase 2 n=140	Undetectable PSA rate
NCT04419402/ Enzalutamide With Lu PSMA-617 Versus Enzalutamide Alone in Men With Metastatic Castration-resistant Prostate Cancer (ENZA-p)	Recruiting/ 2023, Australia	Arm 1: ^{177}Lu-PSMA 617 + enzalutamide Arm 2: enzalutamide	RCT phase 2 n=160	PFS
NCT04443062/ Lutetium-177-PSMA-617 in Oligo-metastatic Hormone Sensitive Prostate Cancer (Bullseye)	Recruiting/ 2024, Netherlands	Arm1: ^{177}Lu-PSMA Arm 2: standard care therapy	RCT phase 2 n=58	Disease progression
NCT04663997/ 177 LuPSMA-617 vs Docetaxel in Metastatic Castration Resistant and PSMA-Positive Prostate Cancer	Recruiting/ 2025, Canada	Arm1: ^{177}Lu-PSMA-617 Arm 2: docetaxel	RCT phase 2 n=200	PFS
NCT05150236/ EVOLUTION: 177Lu-PSMA Therapy Versus 177Lu-PSMA in Combination With Ipilimumab and Nivolumab for Men With mCRPC (ANZUP2001)	Recruiting 2024, Australia	Arm 1: ^{177}Lu-PSMA-617	RCT phase 2 n=110	PFS

Study ID/name	Status/ Estimated end, study site	Treatments	Study design/ Enrollment (n)	Main outcome
		Arm 2: ^{177}Lu-PSMA-617 + ipilimumab and nivolumab		
NCT05230251/ Radioligand fOr locAl raDiorecurrent proStaTe cancER (ROADSTER)	Recruiting/ 2024, Canada	Arm 1: ^{177}Lu-PSMA + high dose radiation brachytherapy Arm 2: High dose radiation brachytherapy	RCT phase 2 n=12	Grade >3 toxicity
NCT03780075/ Lu177-EB-PSMA617 Radionuclide Treatment in Patients With Metastatic Castration-resistant Prostate Cancer	Recruiting/ 2022, China	^{177}Lu-EB-PSMA-617	RCT phase 1 n=50	PSA change
EudraCT 2017-004034-29/ A Phase 1/2 open-label, multi-center, dose-escalation study of safety, tolerability, pharmacokinetics, dosimetry, and response to repeat dosing of 177Lu-PSMA-R2 radio-ligand therapy in patients with prostate specific membrane antigen (PSMA) positive (68Ga-PSMA-R2) progressive metastatic castration-resistant prostate cancer, following previous systemic treatment.	Ongoing/ n.a., Spain	^{177}Lu-PSMA-R2	Non-RCT phase 1/2 n=96	Dose escalation
NCT05113537/ Abemaciclib Before 177Lu-PSMA-617 for the Treatment of Metastatic Castrate Resistant Prostate Cancer (UPLIFT)	Recruiting/ 2027, USA	^{177}Lu-PSMA-617 + abemaciclib	Non-RCT phase 1/2 n=30	SUVmax change
NCT03042468/ Phase I Dose-escalation Study of Fractionated 177Lu-PSMA-617 for Progressive Metastatic CRPC	Active, not recruiting/ 2023, USA	^{177}Lu-PSMA-617	Non-RCT phase 1/2 n=50	Dose Limiting Toxicity
NCT03658447/ PRINCE (PSMA-lutetium Radionuclide Therapy and ImmuNotherapy in Prostate CancEr) (PRINCE)	Active, not recruiting/ 2022, Australia	^{177}Lu-PSMA + pembrolizumab	Non-RCT phase 1/2 n=37	PSA response
NCT04430192/ Dosimetry, Safety and Potential Benefit of 177Lu-PSMA-617 Prior to Prostatectomy (LuTectomy)	Active, not recruiting/ 2023, Australia	^{177}Lu-PSMA-617 followed by prostatectomy	Non-RCT phase 1/2 n=20	Radiation absorbed dose in prostate
NCT04886986/ 225Ac-J591 Plus 177Lu-PSMA-I&T for mCRPC	Recruiting/ 2027, USA	^{225}Ac-J591 + ^{177}Lu-PSMA-I&T + ^{68}Ga-PSMA-11	Non-RCT phase 1/2 n=33	Dose Limiting Toxicity

Study ID/name	Status/ Estimated end, study site	Treatments	Study design/ Enrollment (n)	Main outcome
NCT05113537/ Abemaciclib Before 177Lu-PSMA-617 for the Treatment of Metastatic Castrate Resistant Prostate Cancer (UPLIFT)	Recruiting/ 2027, USA	^{177}Lu-PSMA-617 + abemaciclib	Non-RCT phase 1/2 n=30	Recommended dose
NCT05114746/ Study of 177Lu-PSMA-617 In Metastatic Castrate-Resistant Prostate Cancer in Japan	Recruiting/ 2026, Japan	^{177}Lu-PSMA-617	Non-RCT phase 1/2 n=28	Dose Limiting Toxicity
NCT05146973/ External Beam Therapy With Theranostic Radioligand Therapy for Oligometastatic Prostate Cancer (ProstACT TARGET)	Recruiting/ 2025, Australia	^{177}Lu-DOTA-TLX591	Non-RCT phase 1/2 n=50	PFS
NCT05340374/ Cabazitaxel in Combination With 177Lu-PSMA-617 in Metastatic Castration-resistant Prostate Cancer (LuCAB)	Recruiting/ 2026, Australia	^{177}Lu-PSMA-617 + cabazitaxel	Non-RCT phase 1/2 n=44	Max tolerated dose
NCT05383079/ Combination of Radium-223 and Lutetium-177 PSMA-I&T in Men With Metastatic Castration-Resistant Prostate Cancer (AlphaBet)	Recruiting/ 2026, Australia	^{177}Lu-PSMA-I&T + ^{223}Ra	Non-RCT phase 1/2 n=36	Max tolerated dose
NCT05398302/ Image-Guided Biopsies to Identify Mechanisms of Resistance in Patients With Metastatic Castration Resistant Prostate Cancer Treated With 177Lu-PSMA Radioligand Therapy	Not yet recruiting/ 2025, USA	^{177}Lu-PSMA-617	Non-RCT phase 1 n=30	Successful evaluable biopsy
NCT05162573/ EBRT + Lu-PSMA for N1M0 Prostate Cancer (PROQURE-1)	Recruiting/ 2023, Netherlands	^{177}Lu-PSMA-617 + EBRT	Non-RCT phase 1 n=18	Maximum tolerated dose
NCT03805594/ 177Lu-PSMA-617 and Pembrolizumab in Treating Patients With Metastatic Castration-Resistant Prostate Cancer	Active, not recruiting/ 2024, USA	^{177}Lu-PSMA-617 + pembrolizumab	Non-RCT phase 1 n=43	Objective response rate
NCT03874884/ 177Lu-PSMA-617 Therapy and Olaparib in Patients With Metastatic Castration Resistant Prostate Cancer (LuPARP)	Recruiting/ 2023, Australia	^{177}Lu-PSMA + olaparib	Non-RCT phase 1 n=52	Dose Limiting Toxicity
NCT04786847/ 177Lu-DOTA-TLX591 Safety, Biodistribution and Dosimetry Study (ProstACTSelect)	Recruiting/ 2024, Australia	^{177}Lu-DOTA-TLX591 + standard care therapy	Non-RCT phase 1 n=50	Adverse events
NCT05079698/ A Study of Stereotactic Body Radiotherapy and 177Lu-PSMA-617 for the Treatment of Prostate Cancer	Active, not recruiting/ 2024, USA	^{177}Lu-PSMA-617 + stereotactic body radiation therapy	Non-RCT pilot n=6	Dose Limiting Toxicity
NCT04996602/ Therapeutic Efficiency and Response to 2.0 GBq (55mCi) 177Lu-EB-PSMA in Patients With mCRPC	Recruiting/ 2022, China	^{177}Lu-EB-PSMA	Non-RCT n=30	PSA response

Study ID/name	Status/ Estimated end, study site	Treatments	Study design/ Enrollment (n)	Main outcome
NCT04769817/ ProsTIC Registry of Men Treated With PSMA Theranostics	Recruiting/ 2027, Australia	^{177}Lu-PSMA	Cohort n=400	PSA response rate
DRKS00027105/ Prospektive Studie zur Identifizierung adaptiver Resistenzmechanismen des metastasierten, kastrationsresistenten Prostatakarzinoms nach Therapie mit 177Lu-PSMA	Recruitment ongoing/ n.a., Germany	^{177}Lu-PSMA	Cohort n=60	Biomarkers for ^{177}Lu-PSMA
NCT05208229/ The Role of WB-MRI in the Evaluation of Prostate Cancer Patients Treated With Lutetium - Prostate Specific Membrane Antigen (Lu-PSMA) (WB-LuPSMA)	Recruiting/ 2024, Italy	^{177}Lu-PSMA	Cohort n=40	Disease progression
NCT05435495/ Mechanisms of Resistance to PSMA Radioligand Therapy	Recruiting/ 2023, USA	^{177}Lu-PSMA	Cohort n=125	Mean whole body tumor absorbed dose
EudraCT 2016-002732-32/ Radiometabolic Therapy (RMT) with 177Lu PSMA 617 in advanced castration resistant prostate cancer (CRPC): efficacy and toxicity evaluation	Ongoing/ n.a., Italy	^{177}Lu-PSMA-617	n.a. n=150	Disease control rate

EB: Evans blue, EBRT: external beam radiotherapy, Lu: lutetium, n.a.: not available, OS: overall survival, PFS: progression-free survival, PSA: prostate specific antibody, PSMA: prostate specific membrane antibody, Ra: radium, RCT: randomized, controlled trials, RLT: radioligand therapy, SUV_{max}: maximum standardized uptake value

Appendix 7

Additional results

Quality of life – Hofman et al (TheraP study)

Table with mean scores and mean difference of scores for each domain in the EORTC QLQ-C30 quality of life questionnaire from the TheraP study (39).

EORTC QLQ-C30 item	Mean score (95% CI)		Mean difference (95% CI)
	^{177}Lu-PSMA-617	Cabazitaxel	
Global health status score*	**63** (60 to 67)	**60** (57 to 64)	**MD 3.2** (-1.5 to 7.8)
Appetite loss†	**19** (17 to 24)	**22** (16 to 24)	**MD -3.3** (-9.1 to 2.5)
Constipation†	**13** (10 to 16)	**14** (9 to 16)	**MD -0.7** (-5.1 to 3.7)
Diarrhoea*	**9** (6 to 11)	**16** (13 to 19)	**MD -7.7** (-11.8 to -3.6)
Dyspnoea†	**24** (21 to 27)	**23** (20 to 27)	**MD 1.0** (-4.0 to 6.1)
Fatigue*	**34** (31 to 38)	**40** (36 to 43)	**MD -7.4** (-12.3 to -2.5)
Insomnia*	**23** (20 to 27)	**29** (25 to 33)	**MD -6.1** (-11.4 to -0.8)
Nausea and vomiting†	**7** (6 to 11)	**11** (6 to 12)	**MD -3.3** (-7.2 to 0.5)
Pain†	**25** (22 to 29)	**29** (23 to 31)	**MD -3.6** (-8.9 to 1.7)
Financial problems†	**12** (9 to 15)	**13** (9 to 16)	**MD -1.2** (-5.6 to 3.3)
Cognitive functioning†	**85** (82 to 87)	**81** (80 to 85)	**MD 3.4** (-0.4 to 7.2)
Emotional functioning†	**83** (80 to 85)	**78** (77 to 83)	**MD 4.3** (0.5 to 8.1)
Physical functioning†	**75** (72 to 77)	**72** (70 to 76)	**MD 2.8** (-1.3 to 6.9)
Role functioning†	**71** (66 to 74)	**67** (63 to 71)	**MD 3.8**

EORTC QLQ-C30 item	Mean score (95% CI)		Mean difference (95% CI)
	^{177}Lu-PSMA-617	Cabazitaxel	
			(-1.7 to 9.4)
Social functioning*	**79** (75 to 82)	**73** (69 to 77)	**MD 6.3** (1.1 to 11.5)

**Extracted mean (95% CI) from the study article [ref]*
†Calculated mean (95% CI) based on numbers extracted from QoL figures in the Hofman et al, using WebPlotDigitizer.
Functional domains: high score indicates high/healthy level of functioning
Symptom items: high score indicates high level of symptomatology/problems
Global health status: high score indicates high quality of life

Quality of life – Satapathy et al

Table with mean scores and mean difference of scores for each domain in the EORTC QLQ-C30 quality of life questionnaire from the study by Satapathy et al (41).

NCCN-FACT-FPSI-17 items	Change in score from baseline*		p-value
	^{177}Lu-PSMA-617	Docetaxel	
Physical disease-related symptoms	4 (-3 to 10)	-2 (-5 to 0.8)	0.023
Emotional disease-related symptoms	0 (0 to 2)	0 (-1 to 1)	0.043
Treatment side-effects	0 (0 to 1)	-2 (-4 to 0)	0.001
Functioning/well-being	0 (0 to 1)	-0.5 (-3 to 1)	0.191
Total FACT Prostate Symptom Index	7 (-4 to 15)	-8 (-11 to 1)	0.003

**Median (interquartile range: 1st quartile to 3rd quartile)*
NCCN-FACT-FPSI-17: National Comprehensive Cancer Network - Functional Assessment of Cancer Therapy – FACT Prostate Cancer Symptom Index - 17 Item Version

Appendix 8

Description of data used in economic model

Table A: Unit costs of treatment of the included adverse events

Adverse event	Treatment unit cost	DRG code	DRG code description (*Norwegian*)
Abdominal pain	1 930	906C	Poliklinisk konsultasjon vedr smerte i mageregionen (906C)
Anaemia	24 841	Average of 916O and 395	Poliklinisk konsultasjon vedr sykdommer ved bloddannelse eller i immunsystemet (916O) and Sykdommer i røde blodlegemer >17 år (395)
Asthenia	3 068	906C	Poliklinisk konsultasjon vedr smerte i mageregionen
Back pain	39 142	243	Rygglidelser, traumatiske tilstander og symptomer i ryggen
Bone pain	39 389	245	Andre beinsykdommer u/bk
Dyspnea	2 573	823U	Hyperbar oksygenbehandling
Fatigue	1 435	912A	Poliklinisk konsultasjon vedr ondartet svulst i mannlige kjønnsorgan
Hypokalaemia	38 647	297	Ernærings- og stoffskiftesykdommer ITAD >17 år u/bk
Muscular weakness	14 919	Average of 247 and 912A	Uspesifikke tilst og sympt fra muskel-skjelettsyst/bindevev ITAD (247) and Poliklinisk konsultasjon vedr ondartet svulst i mannlige kjønnsorgan (912A)
Musculoskeletal pain	4 948	980H	ØH-relaterte muskel- og skjelettilstander uten overnatting
Neutropenia	3 068	916O	Poliklinisk konsultasjon vedr sykdommer ved bloddannelse eller i immunsystemet
Thrombocytopenia	24 816	Average of 916O and 397	Poliklinisk konsultasjon vedr sykdommer ved bloddannelse eller i immunsystemet (916O) and Koagulasjonsforstyrrelser (397)
Lymphopenia/ lymphocytopenia	36 000	Average of 404 and 917A	Lymfom og ikke-akutt leukemi u/bk (404) and ol kons vedr lymfom, leukemi, myelomatose og visse andre benmargssykdommer (917A)
Leukopenia	43 793	399	Retikuloendoteliale og immunologiske sykd ITAD u/bk (399)

Adverse event	Treatment unit cost	DRG code	DRG code description (*Norwegian*)
Urinary tract infection	34 020	Average of 911O and 320	Poliklinisk konsultasjon vedr andre sykdommer i nyre og urinveier (911O) and Infeksjoner i nyrer og urinveier >17 år m/bk (320)
Haematuria	36717	325	Symptomer fra nyrer og urinveier >17 år m/bk
Acute kidney injury	78 680	316	Nyresvikt
Spinal cord compression	2 078	908F	Poliklinisk konsultasjon vedr lidelser og skader i rygg og nakke
Hypertension	2 078	905B	Poliklinisk konsultasjon vedr hypertensjon
DRG: diagnosis related			

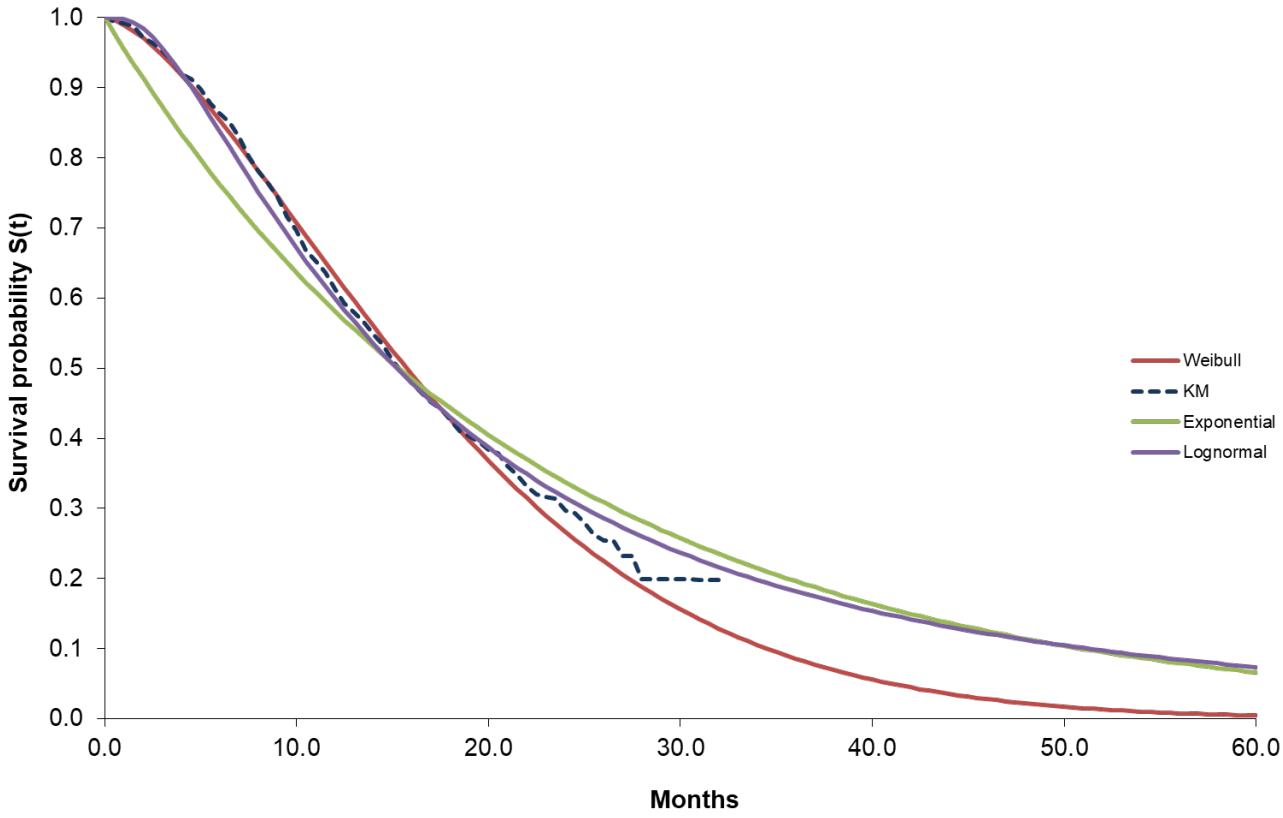
Table B: Disutilities related to treatment of serious adverse events and to radiotherapy included in the model

Included Adverse Event ≥grade 3 per Radiotherapy	Incidence in the VISION-trial (40;111)		Disutility	Source for disutility
	^{177}Lu-PSMA-617 + SoC	SoC		
Abdominal pain	0,0090	0,0050	0	Assumption
Anaemia	0,1285	0,0488	-0,119	(99)
Asthenia	0,0113	0,0098	-0,094	(112)
Back pain	0,0321	0,0341	-0,069	(112)
Bone pain	0,0250	0,0240	-0,069	(112)
Dyspnea	0,0130	0,0150	-0,219	(113)
Fatigue	0,0586	0,0146	-0,0734	(114)
Hypokalaemia	0,0095	0,0000	-0,09	Assumption
Muscular weakness	0,0000	0,0049	-0,067	(99)
Neutropenia	0,0340	0,0049	-0,131	(99)
Thrombocytopenia	0,0794	0,0098	-0,09	(114)
Lymphopenia/ lymphocytopenia	0,0775	0,0049	-0,09	Assumption
Leukopenia	0,0246	0,0049	-0,09	(114)
Urinary tract infection	0,0378	0,0049	-0,218	(113)
Haematuria	0,0246	0,0049	0	Assumption
Acute kidney injury	0,0340	0,0290	-0,218	(113)
Spinal cord compression	0,0000	0,0050	-0,22	(111)
Hypertension	0,0321	0,0146	-0,02	(113)
Radiation treatment	0,089	0,111	-0,06	(113)
Weighted average disutility	- **0,0707**	**-0,03325**		

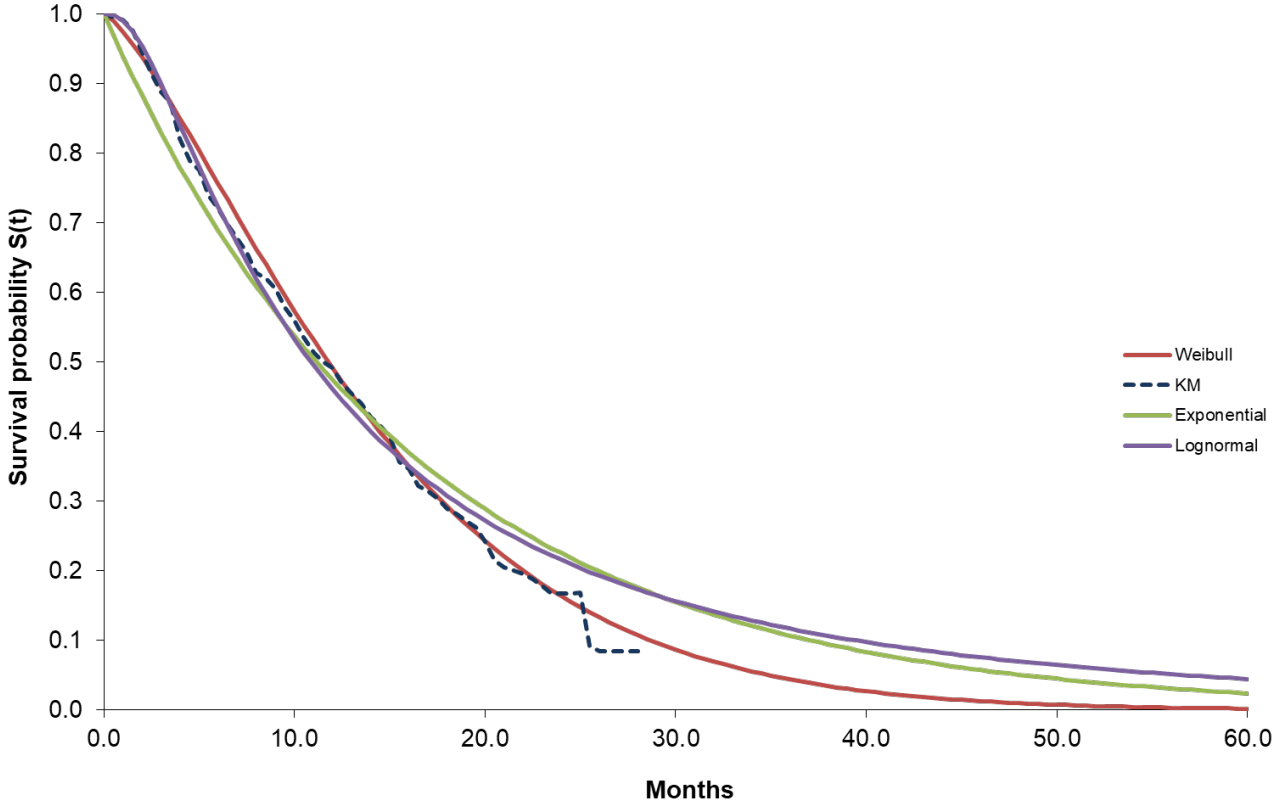
SoC: standard of care therapy

Appendix 9

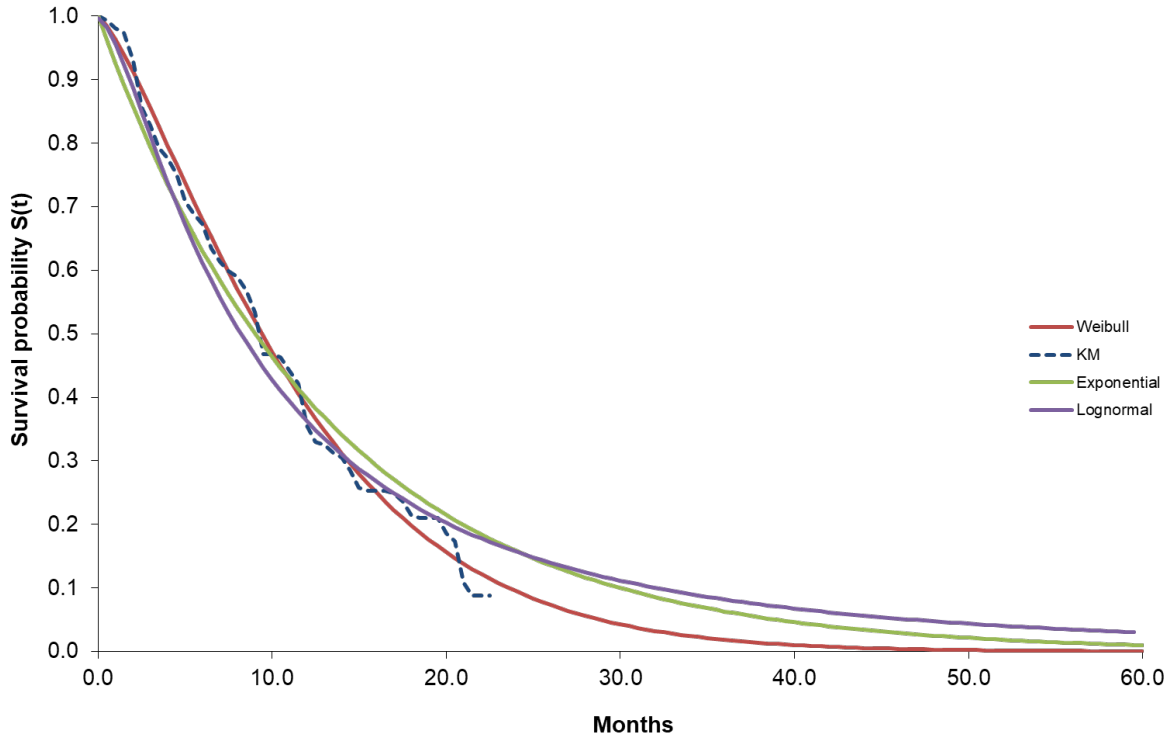
Extrapolated survival curves



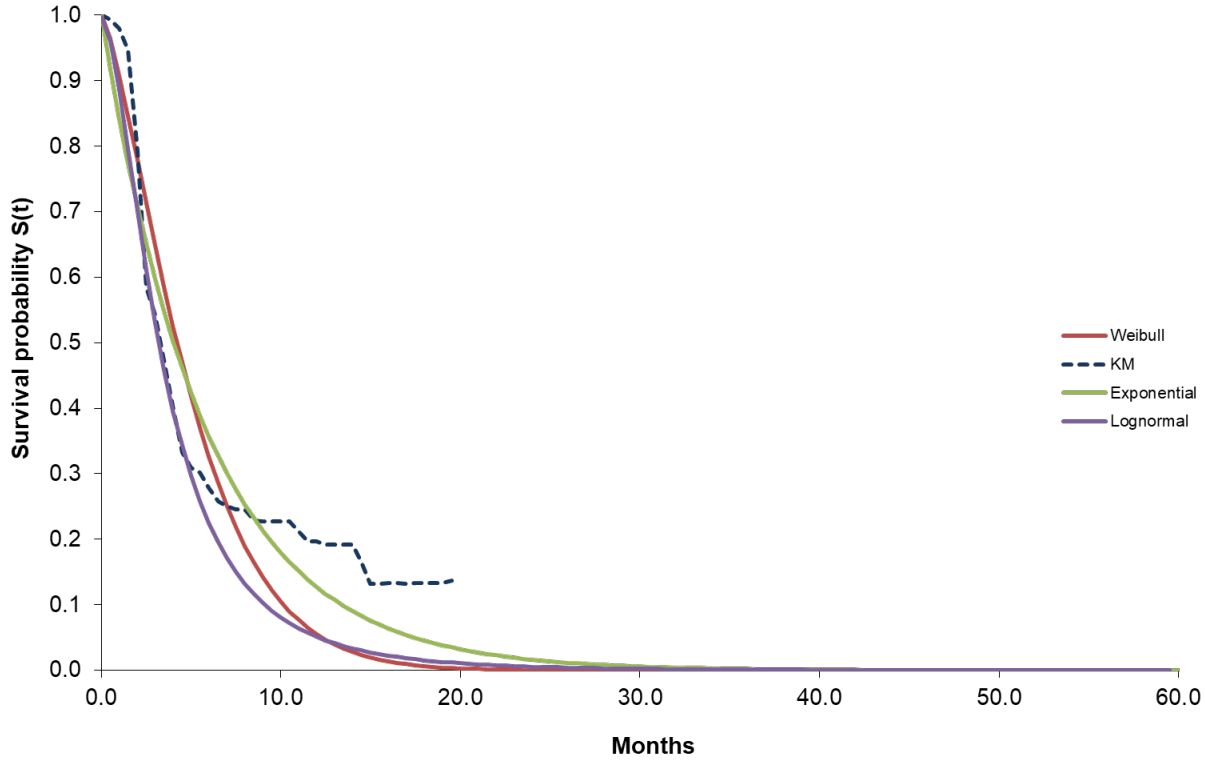
Overall survival for ^{177}Lu-PSMA-617



Overall survival for standard care therapy



Progression free survival for ^{177}Lu-PSMA-617



Progression free survival for standard of care therapy

AIC scores

PFS Intervention	AIC scores
Weibull	2077.027
Exponential	2097.801
Lognormal	2076.537
PFS SoC	
Weibull	690.4716
Exponential	706.7691
Lognorm	654.1771
OS Intervention	
Weibull	3297.001
Exponential	3230.984
Lognorm	3249.141
OS SoC	
Weibull	1346.49
Exponential	1361.814
Lognorm	-1339.1

Appendix 10

Description of parameters included in one-way (univariate) sensitivity analysis

Parameter name	Variable in model	Value	Low	High
^{177}Lu-PSMA-617 cost	Cost_Inv	159,698	111,789	207,608
Standard of care cost (^{177}Lu-PSMA-617)	Cost_SC_Inv	[redacted]	[redacted]	[redacted]
Monitoring cost (Progression free disease)	cost_monitoring_PF	6,935	4,855	9,016
Monitoring cost (Progressed disease)	cost_monitoring_PD	5,500	3,850	7,150
End of life cost	C_End_of_life	145,285	101,700	188,871
Infusion cost (^{177}Lu-PSMA-617)	C_Infusion_Inv	2,570	1,799	3,342
Infusion cost (SOC)	C_infusion_SC	3,458	2,421	4,495
PSMA PET cost	C_PSMA_PET	24,113	16,879	31,347
Adverse events cost (^{177}Lu-PSMA-617)	C_AE_Inv	26,687	11,790	21,895
Adverse events cost (SOC)	C_AE_SC	29,206	4,886	9,073
Dosimetry cost	C_dosimetry	15,680	10,976	20,384
Subsequent treatment cost	c_subtreat	45,376	31,763	58,989
Standard of care cost (SOC)	Cost_SC_SC	[redacted]	[redacted]	[redacted]
Radiotherapy cost (SOC)	c_Radiotherapy_SC	6,723	4,706	8,740
Radiotherapy cost (^{177}Lu-PSMA-617)	c_Radiotherapy_Inv	5,390	3,773	7,007
Utility (Progression free survival)	u_PFS	0.62	0.55	0.68
Utility (Progressed disease)	u_PD	0.37	0.33	0.41
Overall survival curve, mean (^{177}Lu-PSMA-617)	OS_Int_Lognormal_mean	2.732	2.72	2.732
Overall survival curve, standard deviation (^{177}Lu-PSMA-617)	OS_Inv_Lognormal_sd	0.947	0.945	0.947

AE: adverse events, Inv: intervention, OS: overall survival, PD: progressed disease, PFS: progression-free survival, SC: subcutaneous, sd: standard deviation, SOC: standard of care therapy

Appendix 11

Project plan

The project plan was published in November 2022 (30), and is found on NIPHs web page: https://www.fhi.no/cristin-prosjekter/aktiv/metodevurdering-av-177lu-psma-617-behandling-ved-metastatisk-kastrasjonsres/

Appendix 12

Progress log

Date	Milestone
18.06.2018	Proposal from Oslo University Hospital
27.08.2018	NIPH was commissioned by The Regional Health Authorities (RHA) to conduct a single technology assessment of ^{177}Lu-PSMA based on a documentation package from the Finnish producer MAP Medical Technologies Oy
22.10.2018	NIPH informed RHA that MAP Medical Technologies Oy would not send a documentation package. NIPH was commissioned by RHA to conduct a full health technology assessment (HTA).
03.04.2019	Start-up meeting with NIPH and external working group. Consensus: overall survival from randomised controlled trials (RCTs) is most important.
27.05.2019	NIPH informed RHA that there are no data on overall survival from RCTs. The commission was put on hold until such data were published
June 2021	NIPH was informed that a RCT published survival data on ^{177}Lu-PSMA-617
27.09.2021	NIPH informed RHA that there was not submitted any marketing application for ^{177}Lu-PSMA in Norway or Europe at that time. RHA instructed NIPH to start HTA as soon as application for ^{177}Lu-PSMA were available
16.02.2022	Novartis informed NIPH that an application for marketing ^{177}Lu-PSMA-617 was submitted to the European Medicines Agency.
04.04.2022	Meeting between NIPH and representatives from Novartis to discuss the HTA process and the possibility of submitting a documentation package
08.06.2022	Start-up meeting with the internal working group at NIPH
15.06.2022	Start-up meeting with the new external working group, of clinical experts, external experts, user representatives and representatives from the Norwegian Radiation and Nuclear Safety Authority. PICO was set.
August 2022	Systematic literature search finished
November 2022	Published project plan
16.12.2022	Received documentation package from Novartis
24.01.2023	Midway meeting with the external working group. Presented results, discussed health economy analysis and organisational aspects.
26.01.2023	Midway meeting with representatives from Novartis. Presented results, discussed health economy analysis and organisational aspects.
31.03.2023	Report draft sent to external working group, Sykehusinnkjøp and Novartis
08.05.2023	Report draft sent to internal review
25.05.2023	Submitted report

NIPH

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