Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Application Number: 2023-004

^{177}Lutetium PSMA radioligand therapy for the treatment of metastatic castrate-resistant prostate cancer

Evidence synthesis to support a generic justification decision

Date of decision: 18 April 2024

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Foreword

The European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation (Euratom) were initially transposed into Irish law under SI 256 in January 2019.(1) These regulations named HIQA as the competent authority for medical exposure to ionising radiation. One requirement under the regulations is that new practices involving medical exposures must be justified by HIQA before they are generally adopted — this is known as generic justification.

This report sets out a review of prior evidence syntheses which provides the evidence base to inform HIQA's generic justification decision. The report also includes the consideration of this evidence by HIQA's multidisciplinary Medical Exposure to Ionising Radiation Expert Advisory Group which is formally reported using an evidence-to-decision framework. The review considers the net benefit for the identified patient population in the context of the medical exposure to ionising radiation; the potential for occupational and public exposure is also considered.

This review was undertaken by the Ionising Radiation Evidence Review Team from the HTA Directorate in HIQA and was supported by HIQA's Medical Exposure to Ionising Radiation Expert Advisory Group who advised on the preparation of this report and participated in the evidence-to-decision process. HIQA would like to thank the Evidence Review Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this report. Particular thanks are due to the members of the Medical Exposures to Ionising Radiation (MEIR) Expert Advisory Group (EAG), Mr Lee O'Hora, who provided advice and information, and to the Austrian Institute for Health Technology Assessment (AIHTA) for permitting the reproduction of tables in this report.

The findings of the evidence review prepared by HIQA informed the deliberations of the MEIR EAG in completing the evidence to decision framework. The output of the framework was reached through consensus.

The membership of the EAG is as follows:

Prof Mary Coffey, Chairperson	Independent Chairperson
Dr Mathilde Colombié**	Consultant Nuclear Medicine Physician, Irish Nuclear Medicine Association
Dr Jennie Cooke	Principal Physicist, Children's Health Ireland, Irish Association of Physicists in Medicine (Diagnostic Radiology)
Dr Agnella Craig	Regional Manager, Ionising Radiation Regulation Team, HIQA Healthcare Directorate
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Key: * Not a member of the standing Expert Advisory Group, but attended as an ad hoc member for the meeting where this practice was discussed.

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The following members of the HTA Directorate contributed to the management, technical writing or dissemination of this report:

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Conflicts of Interest

None reported.

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Plain language summary

Prostate cancer is the most common cancer in men. Radioligand therapy is a targeted cancer medicine that works by binding to receptors on cancer cells and releasing a small amount of radioactivity, which causes damage to the cells. A new radioligand therapy has been developed for some patients whose prostate cancer has spread to other parts of the body (metastatic disease) or who have been treated with other types of anti-cancer treatments such as chemotherapy or hormone therapy. This new radioligand therapy binds to prostate cancer cells that have a particular type of protein on the surface of their cells, called prostate-specific membrane antigen (PSMA). Once the radioligand binds, radiation is then released by a radionuclide called ^{177}Lutetium (^{177}Lu). The new targeted treatment is known as ^{177}Lu-PSMA radioligand therapy.

Under Irish law, any new practices which involve the exposure of patients to ionising radiation must be justified by the Health Information and Quality Authority (HIQA). Justification means making sure that the benefits of the practice outweigh the risks involved for the kind of patients undergoing this treatment. To decide if this practice is justified, HIQA has reviewed the available evidence in the medical literature, and sought input from a group of experts, including a patient representative. HIQA has also considered the occupational and public radiation safety issues in this review.

The available evidence indicates that ^{177}Lu-PSMA radioligand therapy is a safe and effective treatment for this group of patients. Data from three clinical trials suggest that patients receiving ^{177}Lu-PSMA radioligand therapy live at least as long or longer compared with those who receive standard treatments. However, those who receive this radioligand have a longer time after treatment before their cancer grows or spreads.

The most common side effects of this treatment include: tiredness, dry mouth, nausea (feeling sick), loss of appetite, changes in bowel movements (such as constipation or diarrhoea), vomiting, weight loss, abdominal (stomach) pain, low blood counts (for example, low white blood cells, which make it harder for someone to fight infection), and urinary tract (kidney) infection. There is also a small risk of more severe side effects, such as damage to the kidneys, shortness of breath and developing another cancer. However, overall, the benefits of this treatment, which involves an exposure to ionising radiation, seem to outweigh the risks. After reviewing the risks and benefits of the practice, and considering the recommendation from its Medical Exposure to Ionising Radiation Expert Advisory Group, HIQA decided to justify this practice of ^{177}Lu-PSMA radioligand therapy for patients with metastatic castrate-resistant prostate cancer.

Key Points

Application

- This review was conducted in response to an application submitted by a radiologist at the Mater Misericordiae University Hospital for the generic justification of lutetium (^{177}Lu) prostate-specific membrane antigen (PSMA) radioligand therapy for the treatment of metastatic castrate-resistant prostate cancer (mCRPC).
- In Ireland, prostate cancer accounts for, on average, 30% of all diagnosed invasive cancers and 12% of all cancer deaths in men.
- Patients with mCRPC are those whose prostate cancer has spread (or metastasised) beyond the prostate gland (for example, to bones), and which has also stopped responding to hormone therapy or low levels of testosterone. Globally, it is estimated that mCRPC accounts for up to 2.1% of all prostate cancer cases.
- Many patients with mCRPC will have previously received some combination of surgery, radiotherapy, hormone therapy and taxane-based chemotherapy as part of first- or second-line treatment.
- ^{177}Lu-PSMA radioligand therapies are radiopharmaceuticals which comprise a radionuclide component (^{177}Lu) and a targeted component (PSMA) which exploit the upregulation and overexpression of the PSMA protein on prostate cancer cells and tumour vascular cells, compared with normal prostate tissue.
- A number of ^{177}Lu-PSMA radioligand therapies have been developed internationally. These include ^{177}Lu-PSMA-617 (Pluvicto®, Novartis) which has been approved by the European Medicines Agency and ^{177}Lu-PSMA-Imaging and Therapy (I&T) from Curium Radiopharmaceuticals. In this assessment, these radioligand therapies were considered to be a single practice.

Summary of evidence synthesis process

- In accordance with HIQA's Methods for generic justification of new practices in ionising radiation, a review of prior evidence syntheses was conducted to establish the evidence base for this new type of practice.
- In total, five systematic reviews were identified.
- A systematic review undertaken as part of a 2023 health technology assessment (HTA) published by the Austrian Institute for Health Technology Assessment (AIHTA) was identified as the most recent summary of evidence relevant to the research questions posed.

- The AIHTA systematic review was appraised using the ROBIS tool by the Evidence Review Team (ERT) and found to be at a low risk of bias. Summary of findings and GRADE tables were extracted from this report.
- The AIHTA review identified three completed randomised controlled trials (RCTs).
    - An updated search by the ERT identified one additional completed RCT, updates to the three completed RCTs (identified by the AIHTA review) and a further eight ongoing or unpublished RCTs.

Clinical effectiveness evidence

- The body of evidence was underpinned by the most recent findings of three completed RCTs. All three trials related to ^{177}Lu-PSMA-617, but they differed in the dose (range: 6.0 to 8.5GBq per cycle), frequency (range: 6 to 8 weeks) and duration of treatment (range: 4 – 6 cycles maximum). They also differed in the comparator used:
    - VISION (n=831): ^{177}Lu-PSMA-617 plus standard care versus standard care alone randomised in a 2:1 ratio. Standard care excluded cytotoxic chemotherapy. Due to issues with the control group, a modified analysis was also reported for this trial (n=581).
    - TheraP (n=200): ^{177}Lu-PSMA-617 versus cabazitaxel
    - Satapathy RCT (n=40): ^{177}Lu-PSMA-617 versus docetaxel in a chemotherapy-naïve population.
- Median overall survival (OS) with ^{177}Lu-PSMA-617 was found to be either longer than VISION RCT (15.3 vs 11.3 months; p<0.001) or comparable to TheraP and Satapathy RCTs that seen in the control arm.
- Progression-free survival (PFS) was reported in all three RCTs:
    - Median radiographic PFS with ^{177}Lu-PSMA-617 was either longer than VISION (8.8 vs 3.6 months, HR 0.43, 95% CI 0.32–0.58) or comparable to that seen in the control arm (TheraP, 5.1 vs 5.1 months; Satapathy RCT 4.0 vs 4.0 months).
- Health-related quality of life (HRQoL) was reported by all three RCTs, using different tools (BFI SF, EORTC QLQ-C30, NCCN-FACT-FPSI) with data collected at different time points:
    - In the VISION trial, the median time to deterioration was significantly longer for ^{177}Lu-PSMA-617 plus standard care compared with standard care alone (FACT P: 5.7 vs. 2.2 months, HR 0.54, 95% CI: 0.45-0.66; BPI SF: 5.9 vs. 2.2 months, HR 0.52, 95% CI 0.43-0.63).
    - In the TheraP trial, there was no statistical difference in mean global health status scores between the groups at 51 weeks using the

EORTC-QLQ-C30 tool. Some of the sub-domains did favour ^{177}Lu-PSMA-617 including social functioning (p=0.030), diarrhoea (p<0.0001), fatigue (p=0.027) and insomnia (p=0.023).
    - The Satapathy RCT reported a statistically significant difference in the per protocol analysis favouring the ^{177}Lu-PSMA-617 group over the docetaxel group (p<0.01) at 12 weeks, using the NCCN-FACT-FPSI tool.

Adverse events and safety evidence

- No serious safety issues were raised by the three RCTs.
    - Treatment-related deaths were recorded in two of the three RCTs with a higher frequency noted in the ^{177}Lu-PSMA-617 intervention arm (VISION: 0.9% (n=5) vs 0% (n=0); Satapathy RCT: 10% (n=2) vs. 5% (n=1)); statistical significance and causality were not reported.
    - The TheraP RCT reported no treatment-related deaths after a median follow-up of 18.4 months.
    - When compared with standard care (without cytotoxic chemotherapy), a higher proportion of patients experienced Grade 3-4 AEs (52.7% vs 38%) and treatment-related AEs (28.4% vs 3.9%) in the ^{177}Lu-PSMA-617 group in the VISION RCT, but these differences were not statistically significant.
    - When compared with taxane-based chemotherapy (docetaxel or cabazitaxel), a lower proportion of patients in the VISION and Satapathy RCTs experienced Grade 3-5 (30% vs 50%) or Grade 3-4 AEs (33% vs 53%) respectively in the ^{177}Lu-PSMA-617 groups; these differences were not statistically significant.
- Frequent monitoring is needed to inform the management of patients receiving ^{177}Lu-PSMA radioligand therapies (for example, dose reduction and or blood product support).

Certainty of the evidence

- The certainty of the evidence was found to be low (OS, PFS, HRQoL, Grade 3-4 AEs) or very low (HRQoL and treatment-related death).
- Downgrading of the certainty of the evidence was predominantly on the basis that all three RCTs were at risk of bias due to the open label nature of the trials and due to missing data from two of the RCTs. The largest of the RCTs included a comparator that excluded cytotoxic chemotherapy which was considered not to represent standard of care.

Clinical significance of reported change in ionising radiation dose

- The applicant indicated the intention to use a fixed dose of 7.4 GBq (^{177}Lu PSMA-617) or 7.2GBq (^{177}Lu-PSMA-I&T) for four to six cycles administered intravenously.
- The product information for ^{177}Lu-PSMA-617 recommends a dose of 7.4GBq (+/-10%) administered every six weeks (± one week) for up to a total of six cycles, unless there is disease progression or unacceptable toxicity.
- Administered doses reported in the three RCTs in the AIHTA systematic review varied, ranging from 6GBq up to 8.5GBq per cycle.
- One study used a decreasing dose of 0.5GBq per cycle while another reduced the dose per cycle on the basis of clinical risk factors.
- The total ionising radiation dose incurred from this therapy would also include the dose from associated imaging. This includes PSMA PET/CT required for patient selection (approximately 5.68mSv for the PET component and 6.9mSv for the whole body CT component) and potentially the dose from imaging used to verify the biodistribution of the administered radioligand.
- Patients indicated for this treatment typically have a short life expectancy, making the risk for long-term radiation effects, such as radiation-induced malignancy, largely inconsequential.

Medical Exposure to Ionising Radiation Expert Advisory Group (MEIR EAG)

- Informed by the review of the above evidence, the MEIR EAG completed judgements under a modified GRADE evidence-to-decision making framework to arrive at a recommendation to HIQA on the generic justification of ^{177}Lu-PSMA radioligand therapy for the treatment of metastatic castrate-resistant prostate cancer.
- The MEIR EAG noted that one of the studies demonstrated a survival benefit of three to four months with ^{177}Lu-PSMA radioligand therapy relative to standard care. Such a survival benefit would be considered significant for this patient cohort. However, it was recognised that the choice of study comparator is important; no survival benefit was seen when compared with cytotoxic chemotherapy. Overall, the benefits of this practice were judged to be moderate.
- While recognising the potential for adverse events with ^{177}Lu-PSMA radioligand therapy, the EAG noted that the standard treatment (chemotherapy) is also associated with potential adverse events. It was acknowledged that while ^{177}Lu-PSMA radioligand therapy is associated with a risk of thrombocytopenia, this risk can be mitigated by appropriate

monitoring and management of patients. Overall, the harms were judged to be trivial.

- When considering the balance between the desirable and undesirable effects, the MEIR EAG agreed that the balance probably favours the use of ^{177}Lu-PSMA radioligand therapy. It was agreed that it would provide an important therapeutic alternative for this patient group.
- The MEIR EAG recommended that ^{177}Lu-PSMA radioligand therapy should be generically justified for the treatment of metastatic castrate-resistant prostate cancer.

Decision making

- Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.
- The practice of ^{177}Lu-PSMA radioligand therapy for the treatment of metastatic castrate-resistant prostate cancer is generically justified under SI 256/2018.
- The generic justification of this practice is effective from 18 April 2024.

List of abbreviations used in this report

ADT	androgen deprivation therapy
AIHTA	Austrian Institute of Health Technology Assessment
ARPI	androgen receptor pathway inhibitor
ASCO	American Society of Clinical Oncology
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
CR	complete response
CT	computed tomography
CTCAE	common toxicity criteria of adverse events
DNA	deoxyribonucleic acid
EAG	expert advisory group
EANM	European Association of Nuclear Medicine
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPA	Environmental Protection Agency
EPAR	European public assessment report
ERT	Evidence Review Team
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
^{177}Hf	hafnium-177
HIQA	Heath Information and Quality Authority
HRQoL	health-related quality of life

HTA	health technology assessment
HSE	Health Service Executive
I&T	Imaging and Therapy
ITT	intention to treat
keV	kiloelectron volt
^{177}Lu	lutetium-177
mCRPC	metastatic castrate-resistant prostate cancer
MEIR	medical exposure to ionising radiation
MeV	mega electron volt
NCCP	National Cancer Control Programme
NICE	National Institute of Health and Care Excellence
NIPH	Norwegian Institute of Public Health
OS	overall survival
PERCIST	positron emission tomography response criteria in solid tumours
PET	positron emission tomography
PFS	progression-free survival
PICOS	population, intervention, comparator, outcome, study design
PMSA	prostate-specific membrane antigen
PRISMA	preferred reporting items for systematic reviews and meta-analysis
QLQ C-30	quality of life questionnaire core-30
RCR	Royal College of Radiology
RCT	randomised controlled trial
RECIST	response evaluation criteria in solid tumours

ROBIS	Risk Of Bias In Systematic Reviews
RQ	research question
SI	statutory instrument
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	single-photon emission tomography
UK	United Kingdom
US	United States of America
WHO	World Health Organization

1 Introduction

1.1 Background to application

Radioligand therapy with ^{177}Lutetium (^{177}Lu) vipivotide tetraxetan was authorised by the US Food and Drug Administration (FDA) in March 2022 and by the European Medicines Agency (EMA) in December 2022. It is indicated as a treatment option for men with prostate-specific membrane antigen (PSMA)-positive, metastatic, castrate-resistant prostate cancer (mCRPC), who have previously been treated with a taxane-based chemotherapy and with androgen receptor pathway inhibition.(2) This treatment is also known as ^{177}Lu-PSMA-617 and has been marketed under the trade name Pluvicto® by Novartis. The radionuclide (^{177}Lu) can also be labelled with a different PSMA ligand. One of these is known as ^{177}Lu-PSMA Imaging and Therapy (I&T) from Curium Radiopharmaceuticals, and is currently the subject of Phase III clinical trials.(3) Other ^{177}Lu radioligands are in development.(4-6) These radioligand treatments will be referred to collectively within this report as ^{177}Lu-PSMA radioligand therapy. To date, ^{177}Lu-PSMA radioligand therapy has only been available in Ireland through a compassionate access programme to men who have had two or three lines of treatment for mCRPC.

An application was received from a radiologist from the Mater Misericordiae University Hospital, who has experience of providing this treatment through the compassionate access programme. They would like to offer ^{177}Lu-PSMA radioligand therapy more widely to men who have PSMA-positive mCRPC who have previously had two or more lines of treatment. The applicant indicated the intention to use a fixed dose of 7.4GBq (^{177}Lu PSMA-617) or 7.2 GBq (^{177}Lu-PSMA-I&T) per cycle, for four to six cycles with biodistribution imaging following each cycle of treatment. As this represents a new practice in Ireland, it requires generic justification before it can be generally adopted.

Topic exploration performed by HIQA in advance of developing this report indicated that a number of evidence syntheses had recently been conducted on this topic and therefore, in keeping with HIQA's methods for generic justification of new practices in ionising radiation, a 'review of prior evidence syntheses' was undertaken.(7)

This review has three research questions (RQs) which focus on safety and efficacy, including health-related quality of life. Reference is also made to the potential for public and occupational exposure to ionising radiation arising from the use of ^{177}Lu-PSMA radioligand therapy.

1.2 Overall Approach

A standing multidisciplinary MEIR expert advisory group (EAG) has been convened by HIQA comprising representation from key stakeholders. A full list of the membership of the EAG is available in the acknowledgements section of this report. The terms of reference for the EAG are published on the HIQA website.

This review of prior evidence syntheses was prepared to provide an evidence base to inform the discussions of the MEIR EAG and its recommendation-making process as well as the subsequent decision-making by HIQA. The following summarises the steps which have or which will be taken:

- A review of prior evidence syntheses was performed by HIQA's Ionising Radiation Evidence Review Team (ERT) to provide the evidence base for a generic justification decision.
- This review systematically identified relevant evidence relating to the safety and efficacy including health-related quality of life of ^{177}Lu-PSMA radioligand therapy for adults with PSMA-positive mCRPC.
- A draft report summarising the benefits and harms associated with this practice was produced and was circulated to the MEIR EAG for review.
- Following a meeting of the MEIR EAG, a draft of the report was amended as appropriate and was circulated again to the MEIR EAG for review.
- The final report was sent to the Director of HTA, along with a recommendation from the MEIR EAG regarding the generic justification of the practice.
- Following HIQA's decision, the final report and generic justification decision was published on the HIQA website.

2 Description of technology

Prostate-specific membrane antigen (PSMA) radioligand therapies are radiopharmaceuticals intended for the treatment of metastatic castrate-resistant prostate cancer (mCRPC). This radioligand therapy has a radionuclide component, ^{177}Lutetium (^{177}Lu), which administers a therapeutic amount of radiation, and a targeting component (PSMA), which helps ensure that this radionuclide targets the cancer cells.[3] PSMA radioligand therapies exploit the upregulation and overexpression of the PSMA protein on prostate cancer cells and tumour vascular cells, compared with normal prostate tissue.[8] By using an antigen specific to prostate cancer cells, these therapies can target and treat prostate cancer, particularly when it has spread beyond the prostate.

^{177}Lu has a half-life of 6.647 days and decays via β-emission to stable hafnium (^{177}Hf). The electrons produced by β-emissions cause damage to the DNA of tumour cells and surrounding tissues. This decay may occur via a number of different pathways to produce electrons with different energies; however, a maximum electron energy of 0.498MeV occurs in approximately 78.6% of decays.[2, 9] Other decays may produce electrons with lower energies. Low-energy gamma radiation is also produced during these decays with an energy of 113keV or 208keV — this may require additional shielding in the physical infrastructure of the planned nuclear medicine site. Licensing by the Environmental Protection Agency (EPA) is required in order to carry out this practice. As with the introduction of other radionuclides, ^{177}Lu-PSMA radioligand therapy may require additional training of staff.

As of March 2024, one form of ^{177}Lu-PSMA radioligand therapy has received marketing authorisation from the European Medicines Agency (EMA), ^{177}Lu PSMA-617, which is being marketed by Novartis under the name Pluvicto®.[2] The recommended treatment regimen of ^{177}Lu-PSMA-617 is 7.4GBq intravenously every six weeks (±one week) for up to a total of six doses, unless there is disease progression or unacceptable toxicity.[2] This ^{177}Lu-PSMA-617 radioligand therapy has been available to a limited number of patients in Ireland via compassionate access programmes. The other most common form of ^{177}Lu-PSMA radioligand therapy is ^{177}Lu-PSMA-I&T which is used for both imaging and therapy.[10] A retrospective study from the Theranostics Center for Molecular Radiotherapy and Molecular Imaging in Bad Berka, Germany captured dosimetric and adverse event data on 138 patients with mCRPC treated with either ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T.[11] This study indicated that while the whole-body half-life, mean whole-body doses and absorbed doses to normal organs differed between the radionuclides, the mean absorbed tumour doses were comparable and both radioligand therapies had an acceptable adverse event profile.

Clinical trials investigating the use of other ^{177}Lu-PSMA radioligand therapies such as ^{177}Lu-rhPSMA-10.1 and ^{177}Lu-labelled anti-PSMA monoclonal antibodies such as ^{177}Lu-J591 are ongoing.[4-6]

A patient's suitability for ^{177}Lu-PSMA radioligand therapy is determined by carrying out a form of imaging which identifies sufficient expression of PSMA. A 2023 joint procedure guideline from the European Journal of Nuclear Medicine and Molecular Imaging and the Society of Nuclear Medicine and Molecular Imaging recommends that PSMA expression is assessed preferably using ^{68}Gallium- or ^{18}Fluorine-PSMA positron emission tomography (PET), or alternatively ^{99}mTc-PSMA single-photon emission computed tomography (SPECT)/scintigraphy.[12] Conventional imaging, such as computed tomography (CT), magnetic resonance imaging (MRI) or bone scan may also be required to rule out the presence of PSMA-negative disease. The therapeutic indication listed in the European Public Assessment report (EPAR) for the licensed form of ^{177}Lu-PSMA radioligand therapy (^{177}Lu-PSMA-617) is PSMA-positive mCRPC, noting that patients should be identified by PSMA imaging.[2]

3 Description of clinical condition and epidemiology

Prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide.[13] In Ireland, for the period 2018 to 2020, there were, on average, 3,941 new cases of prostate cancer each year corresponding to an average annual incidence rate of 211.4 cases per 100,000 males. Prostate cancer accounts for, on average, 30.2% of all invasive cancers diagnosed in males and 12% of all cancer deaths in men.[14]

Metastatic castrate-resistant prostate cancer (mCRPC) refers to prostate cancer which has spread (or metastasised) beyond the prostate gland, and at the same time has stopped responding to hormone therapy or low levels of testosterone (hence, it is called 'castrate-resistant').[15] The most common sites of metastasis include bones, lymph nodes, lungs and the adrenal glands.[16]

A systematic review of 12 studies with a total of 71,179 patients found that 10 to 20% of men with prostate cancer develop castrate-resistant prostate cancer within five years of initial prostate cancer diagnosis.[17] Another systematic review highlighted two UK-based studies which reported the proportion of non-mCRPC and mCRPC in the CRPC population as 84.3% to 91.2% and 8.8% to 15.7% (1,821–2,600), respectively, between 1998 and 2009.[18-20] The majority of new mCRPC cases (86%) progress from previously diagnosed non-mCRPC, while a minority (<15%) arise from non-castrate-resistant disease.[21] Many of these patients will have previously received some combination of surgery, radiotherapy, hormone therapy and taxane-based chemotherapy as part of first- or second-line treatment.[22] A small proportion of these patients may not have received previous treatment due to the advanced nature of their disease at diagnosis.

Although there appears to be limited data on the prevalence of mCRPC in Ireland, one systematic review estimated the prevalence to be about 1.2% to 2.1% of all prostate cancer cases globally.[20] This is roughly consistent with research based on a US claims database which estimated the prevalence of mCRPC to be about 1.1% of all prostate cancer cases diagnosed.[23] The lack of data from European countries (except for the UK up to 2009) has been highlighted as a research gap.[20] It is estimated by the applicant that approximately 70 to 100 patients in Ireland could benefit from this treatment per year in Ireland.

For this cohort of patients with mCRPC, the treatment options to date have included cabazitaxel chemotherapy, enzalutamide, abiraterone with prednisone, radium-223 (^{223}Ra) radionuclide therapy, and best supportive care which may include the use of bisphosphonates or denosumab.[24] The choice of therapy may depend on previous

treatment, as noted in the National Cancer Control Programme's (NCCP) prostate cancer guidelines.[24] As this technology is based on an antigen-receptor relationship, patients with mCRPC should undergo a PSMA scan during their clinical workup to determine eligibility for ^{177}Lu-PSMA radioligand therapy.[25]

4 Methods

The reporting of this review of prior evidence syntheses adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria where appropriate.

The generic justification process is informed by three research questions (RQs). RQ1 and RQ2 consider progression-free survival (PFS), overall survival (OS), quality of life and symptom control while RQ3 considers adverse events and toxicity. In Ireland, public and occupational exposure is primarily the responsibility of the Environmental Protection Agency. However, regulations require HIQA to consider public and occupational exposure as part of the justification of medical exposures.(1) The approach taken to this issue and the three RQs is outlined in the following sections.

4.1 Research questions

This evidence review to inform decision-making on generic justification comprised three distinct RQs:

RQ1 Does the use of ^{177}Lutetium (^{177}Lu) prostate-specific membrane antigen (PSMA) radioligand therapy lead to improved OS and PFS, compared with other available treatment(s) in patients with metastatic, castrate-resistant prostate cancer (mCRPC)?

RQ2 Does the use of ^{177}Lu-PSMA radioligand therapy lead to improved quality of life or symptom control, compared with other available treatment(s), in patients with mCRPC?

RQ3 What is the risk of adverse events and toxicity associated with ^{177}Lu-PSMA radioligand therapy, compared with other available treatment(s) in patients with mCRPC?

Table 1 outlines the Population, Intervention, Comparison, Outcomes, Study Design (PICOS), as well as details of the eligible records and languages.

Table 1: PICOS table

PICOS	Description
Patient/Problem:	Adults aged 18 years and older with metastatic, PSMA-positive, castrate-resistant prostate cancer.
Intervention:	^{177}Lu-PSMA radioligand therapy. This includes: ▪ ^{177}Lu-PSMA-617 ▪ ^{177}Lu-PSMA-I&T (imaging and therapy)
Comparison:	Taxane-based chemotherapy (e.g. docetaxel, cabazitaxel); ^{223}radium radionuclide therapy; palliative or best standard care; olaparib; androgen deprivation therapy
Outcomes:	▪ RQ1: Overall survival; progression-free survival ▪ RQ2: Quality of life; symptom control ▪ RQ3: Frequency and severity of adverse events and toxicities
Study Design:	Step 1: For identification of prior evidence syntheses: ▪ Systematic reviews ▪ Health Technology Assessments Step 2: For identification of primary evidence published after the documented search date in the selected prior evidence syntheses: ▪ Randomised controlled trials Observational studies will be excluded.
Languages:	Only articles for which an adequate English translation can be obtained will be included.

Key: ^{177}Lu - Lutetium-177; PSMA - prostate-specific membrane antigen; RQ - research question.

4.2 Search strategy

The full search strategy can be found on Zenodo open repository: https://doi.org/10.5281/zenodo.8276241. This was a two-step process. The first step was to identify relevant prior evidence syntheses (systematic reviews and HTAs), one of which was selected based on recency and relevance to the research questions and was quality assessed to ensure it was of adequate quality. The second step was to identify any relevant randomised controlled trials (RCTs) that had been published since the search date stated in the selected systematic review or HTA.

4.2.1 Step 1 Identifying prior evidence syntheses

This step involved identifying all relevant systematic reviews and HTAs.

Electronic searches were conducted in Medline (EBSCO), the Cochrane Library and clinicaltrials.gov. The full search strategy for the Medline (EBSCO) search is outlined in Table A.1 in the Appendix. A targeted grey literature search of publications from relevant organisations was also conducted. The full search strategy and a list of grey literature sites are presented in Table A.2 in the Appendix. The search was undertaken on 22 August 2023 and re-checked for updates on 17 January 2024. All citations were entered into Covidence for screening.

From topic exploration it was clear that there were a number of recently published systematic reviews and HTAs on this topic and that the evidence base was rapidly evolving; therefore, those reviews published before July 2022 were excluded. For the purpose of this report, a systematic review is considered to comprise reviews reporting on at least one outcome of interest with all of the following characteristics:

- a clearly stated set of objectives with an explicit, reproducible methodology
- a systematic search of at least two databases, carried out since July 2022, which attempts to identify all studies that would meet the eligibility criteria
- a systematic presentation and synthesis of the characteristics and findings of the included studies
- a critical appraisal of the available evidence
- ideally, the systematic review will have evaluated the certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[26]

All relevant systematic reviews and HTAs were compiled and evaluated for relevance to the review questions and the recency of the searches they performed. The most

relevant and recent evidence synthesis was selected and appraised with Risk of Bias in Systematic Reviews (ROBIS) tool.[27]

Clinical guidelines provide evidence that a practice is currently being undertaken in another country and can provide useful recommendations around the practice. For this reason, any relevant clinical guidelines that were identified in topic exploration or by the search were compiled and presented in Section 5.11.

4.2.2 Step 2: Identifying new evidence

The search strategy was identical to that of Step 1, with the exception that the filter for systematic reviews was replaced with a filter for RCTs. No filter was used to limit the dates in the search, but those identified prior to the search undertaken by the selected review in Step 1 were excluded at the title and abstract screening phase.

4.3 Record selection and data extraction

Returned citations from the collective search were added to Covidence. All citations (titles and abstracts) were screened independently by one reviewer as per the inclusion criteria. Full-text screening was conducted independently by two reviewers. A small number of minor disagreements were resolved by discussion. Reasons for exclusion following full-text review were documented and summarised in the PRISMA Flowchart (see Figure 1).

Standardised data extraction templates were developed in Covidence and piloted prior to undertaking data extraction. Data extraction was performed by one reviewer. The second reviewer checked all of the data extraction. A small number of minor disagreements were resolved by discussion.

4.4 Risk of bias assessment

4.4.1 Step 1

Two reviewers independently appraised the selected evidence syntheses from Step 1 using the ROBIS tool. A small number of minor disagreements were resolved through discussion and by consulting with a third reviewer.

4.4.2 Step 2

As the aim of this step was only to identify if any new studies contradicted what had been found in Step 1; no formal risk of bias assessment was carried out on these studies.

4.5 Data synthesis

Data obtained from Step 1 and Step 2 were narratively synthesised. Findings from Step 1 were presented and complimented by evidence identified in Step 2 in order to highlight evidence gaps or discordant findings.

4.6 Grading of Recommendations Assessment, Development and Evaluation (GRADE)

A summary of findings table, including the certainty of the evidence for the primary outcomes, was extracted from the systematic review selected in Step 1 after receiving permission from AIHTA to reproduce these tables. The summary of findings table was adapted to reflect the new evidence identified in Step 2. The summary of findings table was used to help populate the modified evidence-to-decision table for generic justification, as outlined in HIQA's methods document.[7] As per GRADE guidelines, evidence was graded as high, moderate, low or very low certainty, the definitions of which are outlined in Table 2 below.

Table 2: GRADE working group definitions of the evidence grades

Certainty rating	Definition
High	'We are very confident that the true effect lies close to 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 the effect.'

4.7 International practice and guidelines

An overview of current international practice and guidelines is provided in Section 5.11 based on the findings of the topic exploration exercise conducted by the ERT. The grey literature search included a search of national public health organisations, and of the websites of governmental departments and relevant agencies for countries where the applicant or literature suggested this practice was already in

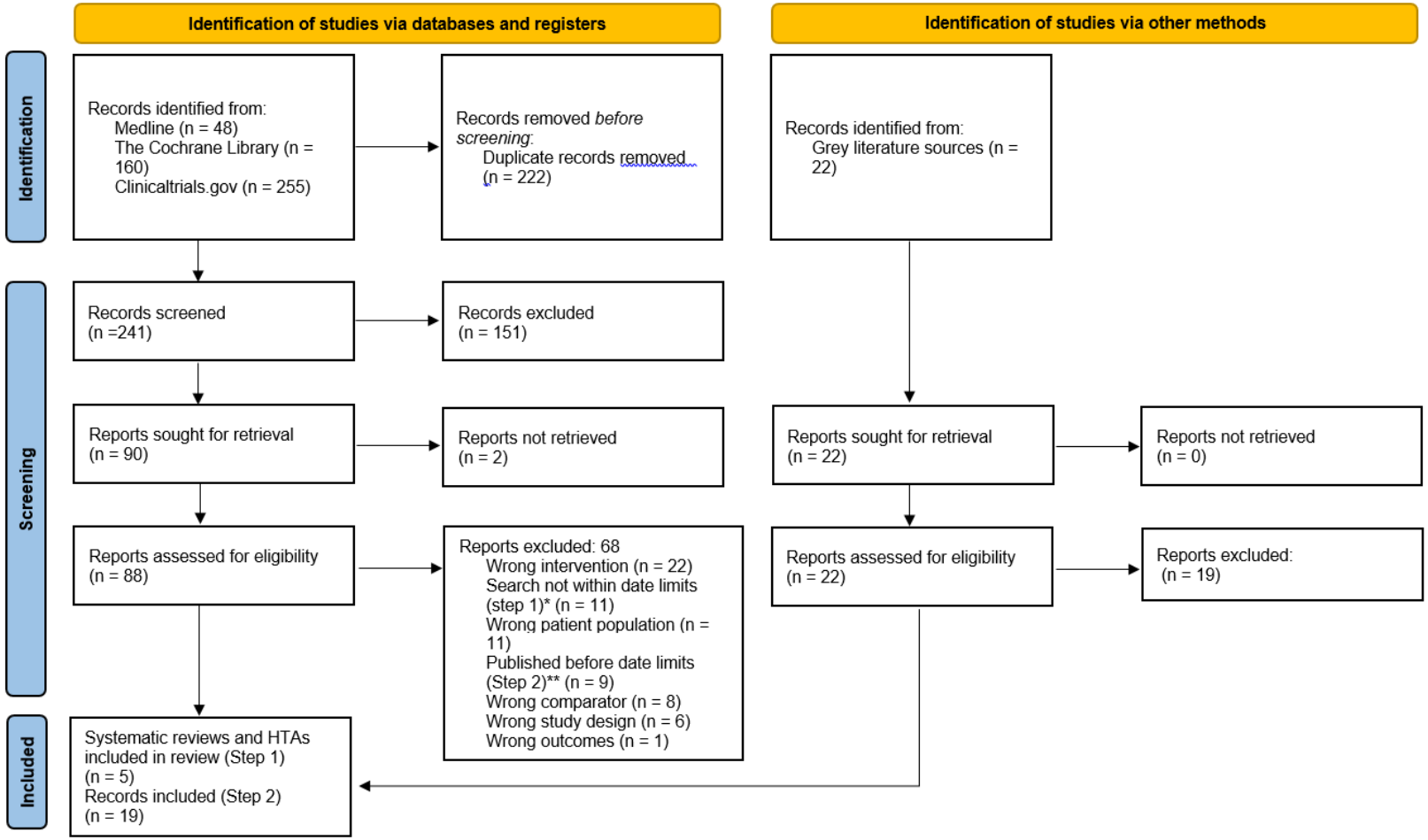
place. Any guidelines found and the associated recommendations are summarised in Section 5.11.

5 Results

5.1 Search results

After removal of duplicates, 241 title and abstracts were assessed for eligibility. Eighty-eight articles required full text review. An overview of the article selection process is presented in the PRISMA flowchart (Figure 1). After application of the inclusion and exclusion criteria, two systematic reviews and three health technology assessments (HTAs) relevant to step 1 were identified. An additional 19 records were identified that were relevant to Step 2; these included four reports of completed randomised controlled trials (RCTs) and 14 records of six ongoing RCTs (RCTs) and one long-term safety study.

Figure 1: PRISMA Flow Diagram



*Search was limited to systematic reviews and RCTs, at this stage any systematic review with a search conducted before July 2022 was excluded.
**In Step 1, systematic review identified with search up to December 2022. In Step 2 RCTs were excluded if published before December 2022

5.2 Review characteristics

5.2.1 Identifying prior evidence syntheses

A total of two systematic reviews and three HTAs[28-32] were identified for inclusion in this review of prior evidence syntheses. The characteristics of the included systematic reviews and HTAs are presented in Table 3. Of the five included records, one searched for evidence in relation to all ^{177}Lu-PSMA radionuclides, two searched for evidence in relation to both ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T and two searched for evidence solely in relation to ^{177}Lu-PSMA-617. All five of these documents concluded that the use of ^{177}Lu-PSMA-617 was of benefit in adults with mCRPC and that no serious safety issues were found. The findings from these systematic reviews and HTAs focused on ^{177}Lu-PSMA-617; no conclusions were presented in relation to other ^{177}Lu-PSMA radionuclides.

As described in the methods section (4.2.1), the systematic review from the Austrian Institute of Health Technology Assessment (AIHTA) was selected based on its relevance to the research questions and the recency of the literature search (December 2022). This review searched for evidence in relation to any ^{177}Lu-PSMA radioligand therapy and included a range of comparators.[28] This AIHTA systematic review focused on three RCTs,[33-35] detailed below, all of which showed ^{177}Lu-PSMA-617 to be beneficial or comparable in terms of overall survival (OS), progression-free survival (PFS) or health-related quality of life (HRQoL) when compared to standard care, cabazitaxel or docetaxel. No serious safety issues were raised by these studies.

5.2.2 Quality assessment of systematic review

The risk of bias of the AIHTA systematic review was assessed using ROBIS.[27] A summary of the results can be found in Table 4. Overall this review had a low risk of bias. However, some areas of concern included firstly the lack of a protocol; however, the authors were contacted and they indicated that the PICO was pre-specified and that the overall methods followed their standard published protocol. Secondly, AIHTA restricted the language of the search to English and German without describing the rationale for this; however, it was felt that it was unlikely studies had been missed as topic exploration conducted by the ERT had identified the same three RCTs included in this systematic review. Finally, the three RCTs included in the review were assessed as having a high risk of bias and there was no clear discussion of how this impacted on the findings of the review, although the GRADE certainty of evidence was discussed.

Table 3: Summary of characteristics of included HTAs and systematic reviews

Year published Title of document (Organisation)	Date of Search	PICO components	Number of studies (Total number of participants) Relevant to which RQ	Funding statement Author conflicts of interest	Author conclusions
HTAs					
2023[28] [177]Lu-PSMA Radioligand Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer: An Update 2023. Decision Support Document No. 118 Update (Austrian Institute for Health Technology Assessment (AIHTA)	December 2022	*Population:* Male patients (over 18 years old) with PSMA-positive mCRPC. *Radioligand:* Included any [177]Lu-PSMA therapy *Comparators:* Taxane-based chemotherapy; [223]radium radionuclide therapy; palliative or best standard of care; olaparib; ADT; next generation AR-directed therapy* *Outcomes:*	3 RCTs (n=40, n=200 and n=831) Relevant to: RQ1, RQ2 and RQ3	AIHTA is funded by the Austrian Ministry of Health, the Federation of Austrian social insurance institutions and the health funds of the nine regions of Austria. No COIs declared.	For OS, the evidence of moderate certainty indicated superiority of [177]Lu-PSMA-617 in combination with standard care (without cytotoxic chemotherapy) versus standard care alone. While there was low certainty of evidence in relation to PFS and health-related quality of life, the evidence showed potential superiority of the [177]Lu-PSMA-617 combination therapy for these outcomes. Conclusion: [177]Lu-PSMA radioligand therapy was recommended, restricted to selected patients and specialised centres.

		OS; PFS; Quality of life; Adverse events and toxicities. *Exclusion criteria:* Non-randomised controlled trials and registry studies.			
2023[31] ^{177}Lu-PSMA-617 for treatment of metastatic castration-resistant prostate cancer: a health technology assessment. (Norwegian Institute of Public Health (**NIPH**))	August 2022	*Population:* Men diagnosed with metastatic castrate-resistant prostate cancer patients. *Radioligand:* ^{177}Lu-PSMA-617. *Comparators:* All comparators: Standard of care treatment (e.g., antiandrogens, chemotherapy and/or radiotherapy); best supportive care, placebo, no treatment. *Outcomes:* OS; PFS; quality of life; adverse events and toxicities; other: time to first skeletal event and PSA level. *Exclusion criteria:*	3 RCTs (3 RCT studies: n=40, n=200 and n=831) Relevant to: RQ1, RQ2 and RQ3	NIPH is a government agency under the Ministry of Health and Care Services Report commissioned by the Regional Health Authorities. No COIs declared.	^{177}Lu-PSMA-617 plus standard of care therapy was found to improve OS and PFS. Most adverse events associated with ^{177}Lu-PSMA-617 were mild, but there was increased risk of Grade 3 adverse events.

		Non-RCTs.			
2023[30] ([177] Lu) Lutetium vipivotide tetraxetan (prostate cancer). Benefit assessment according to 35a SGB V Addendum to project A23-01 (dossier evaluation) Addendum A23-46 16.06.2023 [36] (Institute for Quality and Efficiency in Health Care (IQWiG))	Unclear when final search done. Bibliographic search 26.09.2022, study registry/ study results databases 26.9.2022, G-BA website 11.03.2022 Completeness of study pool checked by searching study registries on 25.01.2023	*Population:* Adult patients with progressive prostate-specific membrane antigen (PSMA)-positive, metastatic castrate-resistant prostate cancer previously treated with androgen receptor pathway pathway inhibition and taxane-based chemotherapy. *Radioligand:* [177]Lu-PSMA-617 *Comparators:* Abiraterone in combination with prednisone or prednisolone, enzalutamide, cabazitaxel, olaparib, best supportive care *Outcomes:* OS; health related quality of life, adverse events, morbidity and mortality *Exclusion criteria:* NR	1 RCT (VISION) (551 patients in intervention arm and 280 patients in comparator arm) Relevant to: RQ1, RQ2 and RQ3.	IQWIG undertakes work for the Federal Joint Committee or the Federal Ministry of Health No COIs declared.	For patients who have previously undergone androgen receptor pathway inhibition and taxane-based chemotherapy, and for whom abiraterone in combination with prednisone or prednisolone, enzalutamide, or BSC is deemed the most suitable treatment, there is evidence suggesting an unquantifiable additional benefit of [177]Lu compared to the relevant comparator therapy. However, for patients for whom cabazitaxel or olaparib is considered the most appropriate treatment, the additional benefit is not definitively established.

Systematic Reviews					
2023[32] Lutetium-177 PSMA for the treatment of metastatic castrate-resistant prostate cancer: a systematic review. (Patell et al.)	January 2010 – February 2023	*Population:* Metastatic castrate-resistant prostate cancer patients. *Radioligand:* ^{177}Lu-PSMA-617; ^{177}Lu-PSMA-I&T. *Comparator:* Any treatment for mCRPC. *Outcomes:* OS; PFS; quality of life; symptom control; adverse events and toxicities; other: PERCIST criteria, ECOG performance status, PSA decline >50% (% patients). *Exclusion criteria:* Prior to 2010, non-prostate cancer articles, local and metastatic castrate-sensitive prostate cancer, biomarker studies, non-English language articles, abstracts, editorials, single-patient case reports, replies, commentary.	40 Studies (16 retrospective, 3 real world studies, 9 phase I/II trials and 1 phase 3 trial, 11 ongoing clinical studies). Relevant to: RQ1, RQ2 and RQ3.	NR Some authors have received consultant fees, speaker's fees and or personal fees from various pharmaceutical companies and served on an advisory board and speaker's board. No other relevant affiliations or financial involvements declared.	^{177}Lu-PSMA-617 has shown promising results in patients with mCRPC. The therapy has a low toxicity profile and appears to be well tolerated. Both retrospective studies and prospective clinical trials have shown it to be an effective option for patients with mCRPC who have undergone treatment with novel hormonal agents and chemotherapy.

2023[29] ^{177}Lu-PSMA-Radioligand Therapy Efficacy Outcomes in Taxane-Naïve Versus Taxane-Treated Patients with Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Metaanalysis (Satapathy et al.)	December 2022	*Population:* Metastatic castrate-resistant prostate cancer patients with prior treatment with ADT and or chemotherapy. *Radioligand:* ^{177}Lu-PSMA-617; ^{177}Lu-PSMA-I&T. *Comparator:* Patients who received or did not receive taxane-based chemotherapy. *Outcomes:* PSA response rate; OS; PFS *Exclusion criteria:* Studies with <30 patients; records without full-length article; reviews; letters; abstracts; case reports; studies only reporting on dosimetry or toxicity.	13 studies; all were single-arm interventional studies; 11 retrospective; 2 prospective Relevant to: RQ1.	NR No COIs declared.	Improved response rate and long-term survival with ^{177}Lu-PSMA radioligand therapy in patients without prior taxane-based chemotherapy.

Key: ADT – androgen deprivation therapy; AR – androgen receptor; BSC – best supportive care; COI – conflict of interest; ECOG – Eastern Cooperative Oncology Group; HTA – health technology assessment; I&T – Imaging and Therapy; ^{177}Lu – Lutetium-177; mCRPC – metastatic castrate-resistant prostate cancer; NR – not reported; OS – overall survival; PERCIST – positron emission Tomography Response Criteria in Solid Tumours; PICO – population, intervention, comparator, outcome(s); PFS – progression-free survival; PSA – prostate-specific antigen; PSMA – prostate-specific membrane antigen; RCT – randomised controlled trial; RQ – research question.

Table 4: Risk of bias in systematic reviews (ROBIS): summary of judgements

	Domain summary				Overall risk of bias
Systematic review	**1. Study eligibility criteria**	**2. Identification & selection of studies**	**3. Data collection & study appraisal**	**4. Synthesis & findings**	**Overall risk of bias in the review**
AIHTA (2023)	Low concern	Low concern	Low concern	Unclear concern	Low concern

Key: AIHTA - Austrian Institute of Health Technology Assessment

5.2.3 Data synthesis and risk of bias of studies included in selected systematic review

The AIHTA HTA included three RCTs in their systematic review of the clinical effectiveness and safety of ^{177}Lu-PSMA radioligand therapy. The characteristics of these studies as summarised from the AIHTA systematic review are presented in Table 5. This systematic review was an update of a review carried out on the same topic in 2019. Although no RCTs of relevance were found for the original review of clinical effectiveness, AIHTA did include five prospective before-after studies in their safety analysis, the results of which are included in Section 5.7 for RQ3 Adverse events and toxicities.

The methodological quality of the three included RCTs were assessed by AIHTA using the Cochrane risk of bias (RoB) tool and the overall risk of bias was found to be high for each of these studies.[33, 34, 37] The main areas of concern were the open-label design in all three RCTs, missing outcomes in two of the RCTs,[34, 37] the lack of blinding of outcome assessors in all three RCTs and potential bias in the selection of the reported result.

The three RCTs included a total of 1,071 patients.[33, 34, 37] Evidence for all three RCTs were limited to a single ^{177}Lu-PSMA radioligand, ^{177}Lu-PSMA-617. The studies differed in terms of their comparators, population and dose of ^{177}Lu-PSMA-617 administered. The largest of the RCTs (VISION, n=831) included ^{177}Lu-PSMA-617 in the intervention arm along with standard care and compared this to a group who received only standard care (standard care could not include cytotoxic chemotherapy, radioligand therapies, immunotherapy or investigational drugs, but could include approved hormonal treatment, bisphosphonates and radiotherapy[34]), while the other two RCTs (TheraP, n=200 and the Satapathy RCT n=40) included ^{177}Lu-PSMA-617 in the intervention arm and a taxane-based chemotherapy in the comparator group (cabazitaxel and docetaxel, respectively).[33, 37] Although the population for all three RCTs were adult patients with mCRPC, the patients in two of the RCTs had been previously treated with one or two rounds of taxane-based chemotherapy regimens,[34, 37] while the third RCT was limited to chemotherapy-naïve patients.[33, 38] In all three RCTs, only patients with an ECOG performance status of two or less at baseline were included. PSMA-positivity determined by prior PET/CT imaging was a pre-requisite for entry into all three RCTs. However, for the VISION and Satapathy RCTs, only ^{68}Ga PSMA PET/CT imaging was required, while for the TheraP RCT, patients had to undergo imaging with both ^{68}Ga PSMA and ^{18}F FDG PET/CT scans to rule out the presence of discordant FDG-positive and PSMA-negative findings. Two of the RCTs were partly sponsored by the manufacturer,[34, 37] while the third did not report its funding source.[33]

The primary outcomes were OS and PFS for the largest RCT (VISION).[34] Two of the RCTs had PSA response rate as the primary outcome[33, 37] with one of these (n=40) powered to test non-inferiority of ^{177}Lu-PSMA-617 over docetaxel.[33] In the VISION RCT, 831 patients were included (551 intervention group vs 280 comparator group);[34] however, due to a high incidence of withdrawal from the trial in the control group, enhanced education measures were implemented at the trial site. Subsequently 581 patients (385 intervention group vs 196 in comparator group) were included in the modified intention-to-treat analysis (ITT). In one RCT, 40 patients (20 patients in ^{177}Lu-PSMA-617 arm vs 20 patients in docetaxel arm) were included in the ITT analysis, but a per protocol sensitivity analysis was also reported that included those patients who underwent at least half of their allocated treatment (15 vs 20 patients).[33]

Differences were observed between trials in terms of the administered dose and approach taken. In the VISION RCT, 7.4 GBq (200 mCi) ^{177}Lu-PSMA-617 plus standard care was administered once every six weeks for four to six cycles.[34] In the next largest RCT (TheraP), 8.5GBq of ^{177}Lu-PSMA-617 was administered once every six weeks with a decrease of 0.5 GBq per cycle, for a maximum of six cycles.[37] In the third RCT (by Satapathy et al.) 6.0 to 7.4 GBq of ^{177}Lu-PSMA-617 was administered every eight weeks (depending on patient weight, disease burden, renal and haematological factors) for up to four cycles.[33]

Longer-term follow-up studies have been published for two of the RCTs[33, 37] since the publication of the AIHTA systematic review, providing median follow-up of 36 months (TheraP) and 33.4 months (Satapathy et al) respectively.[38, 39] The largest RCT (VISION) had a median follow-up time of 20.9 months.[34] No longer-term follow-up data were identified for this trial; however, updates published since the AIHTA systematic review have provided results on HRQoL and pain outcomes.[40]

Table 5: Randomised controlled trials included in the AIHTA systematic review of clinical effectiveness and safety

Author and Year (Trial name and identification number) Country Sponsor/ Funding	Study Design Number of patients Median age of patients (range)	Population and inclusion criteria	Intervention (dose and number of cycles) Comparator	Follow-up	Outcome
Hofman 2021[37] (TheraP trial, NCT03392428) Australia Part funded by Endocyte (a Novartis company).	Prospective, multicentre, unblinded, randomised (1:1) phase 2 trial N=200 (99 vs 101) *Age* 72.1 (IQR 66.9-76.7) vs 71.8 (66.7-77.3)	*Population:* Male adults with metastatic castrate-resistant prostate cancer who had been previously treated with docetaxel and for whom cabazitaxel was considered the next appropriate standard treatment. *Inclusion Criteria:* - Adequate renal, haematological and liver function - Progressive disease with rising PSA level - Target or non-target lesions according to RECIST criteria - Significant PSMA avidity on ^{68}Ga-PSMA PET/CT - No sites of metastatic disease with discordant ^{18}F-FDG-positive and PSMA-negative findings - ECOG performance status ≤2 - Estimated life expectancy >12 weeks.	*Intervention*: ^{177}Lu-PSMA-617 IV (8.5 GBq once every 6 weeks, decrease of 0.5 GBq per cycle- maximum of 6 cycles) *Comparator:* cabazitaxel	18.4 months vs 18.4 months **Median 35.7 months	*Primary Outcomes:* Prostate-specific antigen response rate (PSA-RR). *Secondary Outcomes:* OS (death from any cause), HRQoL (QLQ-C30), Pain Response (McGill-Melzack Present Pain Intensity scale and analgesic score), PFS, PSA-PFS, PFS, Radiographic progression, ORR (CR or PR according to RECIST criteria, Frequency and severity of AEs assessed using the CTCAE (from first dose until 12 weeks after cessation of study treatment).

Sartor 2021[34] (Vision Trial, NCT03511664) Belgium, Canada, Denmark, France, Germany, Netherlands, Puerto Rico Sweden, Switzerland, UK, United States. Funded by Endocyte (a Novartis company).	Prospective, open-label, randomised (2:1), international, phase 3 trial N=831 (551 vs 280) *N=581 (385 vs 196) *Age* 70.0 (48-94) vs 71.5 (40-89) *71.0 (52-94) vs 72.0 (51-89)	*Population:* Male adults with castrate-resistant prostate cancer and at least one metastatic lesion on baseline CT, MRI, or bone scan imaging. *Inclusion criteria:* - PSMA-positive metastatic castrate-resistant prostate cancer was defined as at least one PSMA-positive metastatic lesion and no PSMA-negative lesions (based on ^{68}Ga PSMA PET/CT) - Diagnostic-grade CT scans were also available for all the patients. - Disease progression after the receipt of previous treatments, both with one or more approved androgen-receptor–pathway inhibitors and with either one or two taxane regimens. - An ECOG performance status score of 0 to 2 - A life expectancy of at least 6 months - Adequate organ and bone marrow function.	*Intervention*: ^{177}Lu-PSMA-617 IV + protocol-permitted standard care (7.4 GBq (200 mCi) once every 6 weeks - 4 cycles, up to 6 cycles in total possible in patients who had evidence of response) *Comparator:* Protocol-permitted standard care alone, e.g., approved hormonal treatments (abiraterone, enzalutamide), bisphosphonates, radiation therapy, denosumab, glucocorticoid at any dose.	20.3 months (19.8-21.0) vs 19.8 months (18.3-20.8)	*Primary Outcomes:* Imaging-based PFS and OS. *Secondary Outcomes:* HRQoL (FACT-P), pain (BPI-SF), ORR and disease control according to RECIST, PSA-response, time to first symptomatic skeletal event or death, SAEs and AEs (from first dose until 30 days after the last dose or before the receipt of subsequent anticancer treatment).
Satapathy 2022[33] (CTRI/2019/12/022282)	Randomised (1:1), parallel-group, open-label, phase 2 non-inferiority trial	*Population:* Male adults with biopsy-proven adenocarcinoma prostate and castrate-resistant disease *Inclusion criteria:* - Metastatic disease on ^{68}Ga-PSMA PET/CT with significant PSMA expression	*Intervention*: ^{177}Lu-PSMA-617 IV (6.0-7.4 GBq every 8 weeks, depending on the patient weight, disease burden, renal, and	**Mean 33.4 months	*Primary Outcomes:* PSA-RR *Secondary Outcomes:* HRQoL (NCCN-FACT-FPSI-17 questionnaire version 2, PFS, ORR CR + PR) according to RECIST 1.1, MRR

India **NR**	N=40 (20 vs 20) *Age* 68 (54-85) vs 68 (50-84)	- Chemotherapy-naïve - Prior treatment of NAADs - An ECOG performance score ≤2 - Adequate haematological, renal and liver function reserve.	haematological parameters; up to 4 cycles) *Comparator:* Docetaxel: 75mg/m^2 IV once every 3 weeks p to a maximum of 10 cycles.		(CR + PR) according to the adapted PERCIST, AEs assessed using the CTCAE.

Key: AE – adverse events; AIHTA – Austrian Institute of Health Technology Assessment; BPI-SF – brief pain inventory short form; CR – complete response; CTCAE – Common Toxicity Criteria of Adverse Events; CT – computed tomography; CTRI – Clinical Trials Registry of India; ECOG – Eastern Cooperative Oncology Group; FACT-P: functional assessment of cancer therapy, prostate; FPSI – functional prostate symptom index; 18F-FDG – Fluorine-18 Fluorodeoxyglucose; 68Ga – Gallium-68; GBq – Giga Becquerels; HRQoL – health-related quality of life; IV – intravenous; mCi – millicurie; MMR – molecular response rate; MRI – magnetic resonance imaging; NAAD – novel androgen axis drug; NCCN – national comprehensive cancer network; ORR – objective response rate; OS – overall survival; PERCIST – positron emission Tomography Response Criteria in Solid Tumours; PET- positron emission tomography; PFS – progression-free survival; PPI – present pain intensity; PR – partial response; PSA – prostate-specific antigen; PSA-PFS: prostate-specific antigen progression-free survival; PSA-RR – prostate-specific antigen response rate; PSMA – prostate-specific membrane antigen; PFS – progression-free survival; PII: present pain intensity; QLQ-C30 – quality of life questionnaire Core-30; RECIST – response evaluation criteria in solid tumours; SAE – serious adverse events; TRR – tumour response rate.
*After enhanced trial site education measures were implemented to reduce withdrawal from the control group
**Step 2 identified additional reports with longer follow-up

5.3 Identifying new evidence (Step 2)

Nineteen additional records were identified since December 2022 when AIHTA performed their search of the literature. This included longer-term follow-up reports for the VISION, TheraP and Sathapathy et al. RCTs and one additional completed RCT (the PSMAfore RCT).[38-41] Evidence from the PSMAfore trial was not included in the results, as only a conference abstract could be found. Six additional, ongoing RCTs were also identified, as well as a post-marketing, long-term follow-up study enrolling patients who have received at least one dose of ^{177}Lu-PSMA-617 through Phase I-IV Novartis studies. Relevant publications since December 2022 are listed in Table A.3 in the Appendix and are included in the narrative summary. These studies were not quality assessed as the main aim of this step was to look for findings that were discordant with the AIHTA systematic review.

5.4 GRADE

AIHTA assessed the certainty of the evidence for its critical outcomes using GRADE.[28] The AIHTA summary of findings table was extracted, adapted and presented in Table 6.

The certainty of the evidence ranged from very low to moderate depending on the outcome. The most common reasons for downgrading was risk of bias due to the open-label study design (all three RCTs) and missing outcomes (two RCTs), and indirectness, which was mainly due to one RCT (VISION) as the control group did not represent standard of care according to guidelines.[33, 34, 37]

For the outcome of OS, additional relevant data have been published since the AIHTA systematic review. This outcome was re-assessed by the ERT, and given the inconsistency of the data from the three RCTs for this outcome, it was downgraded from moderate to low certainty. This was the only outcome re-assessed by the ERT.

Table 6: Summary of findings table (adapted from AIHTA systematic review)

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of participants	Certainty	Comments
Efficacy					
OS	^{177}Lu-PSMA-617 & standard care vs standard care (ITT n=831, ITT[c] n=531): ITT: 15.3 vs 11.3, p<0.001 ITT[c]: 14.6 vs 10.4, p=NR ^{177}Lu-PSMA-617 vs cabazitaxel (n=200): ITT: 19.1 (16.9-21.4) vs 19.6 (17.4-21.8) (p=0.77) ^{177}Lu-PSMA-617 vs Docetaxel (n=40): ITT: 15 (9.5-20.5) vs 15 (8.1-21.9) p=0.905	ITT: HR 0.62 (0.52-0.74) ITT[c]: HR 0.63 (0.51-0.79)	3 RCTs: 1,071	Low[a,b,p]	Median OS in months.
Generic quality of life	NR				
Health-related quality of life	63 (60-67) vs 60 (57-64), p=0.20	NR	1 RCT: 176/200 (88%)	Low[d,e,f]	Mean global health status scores assessed with the EORTC-QLQ-C30: higher scores indicate better HRQoL.

	5.7 vs 2.2, p=NR	HR 0.54 (0.45-0.66)	1 RCT: ITT[c]: 385	Low[b,d]	Median months until deterioration in the FACT-P total score.
	5.9 vs 2.2, p=NR	HR 0.52 (0.43-0.63)			Median months until deterioration in the BPI-SF total score.
	S.s. improvement in the median total score in the [177]Lu-PSMA-617 arm compared to the Docetaxel arm (p<0.01). S.s. changes in sub-domains in favour of the intervention: Physical functioning (FPSI-DRS-P): p=0.02 Emotional functioning (FPSI-DRS-E): p=0.04 Treatment and side effects (FPSI-TSE): p<0.01		1 RCT: PP: 35	Very low[d,g,h]	Assessed with the NCCN-FACT-FPSI: a higher score indicates better HRQoL.
PFS	[177]Lu-PSMA-617 vs cabazitaxel (n=200): 5.1. vs 5.1, HR NR, p=NR [177]Lu-PSMA-617 & standard care vs standard care (n=581): 8.7 vs 3.4, HR 0.40, 99.2% CI 0.29-0.57, p<0.001 [177]Lu-PSMA-617 vs docetaxel (n=40): 4.9 vs 4.9, HR 0.90, 95% CI 0.46-17.77, p=0.98		3 RCTs: 1,071	Low[b,d,i]	Median PFS in months.
Safety					
Treatment-related deaths	n (%): [177]Lu-PSMA-617 vs cabazitaxel (n=183): 0 (0) vs 0 (0)		3 RCTs: 957	Very Low[b,d,j]	Number of Grade 5 treatment-related AEs according to CTCAE.

	[177]Lu-PSMA-617 & standard care vs standard care (n=734): 5 (0.9)[k] vs 0 (0) [177]Lu-PSMA-617 vs docetaxel (n=40): 2 (10) vs 1(5)[l,m]				
Grade 3-4 adverse events	Any AEs, n (%): [177]Lu-PSMA-617 vs cabazitaxel (n=183): 32 (33) vs 45 (53) [177]Lu-PSMA-617 & standard care vs standard care (n=734): 279 (52.7) vs 78 (38.0) Treatment-related AEs, n (%): [177]Lu-PSMA-617 vs cabazitaxel (n=183): NR [177]Lu-PSMA-617 & standard care vs standard care (n=734): 150 (28.4) vs 8 (3.9) Treatment-related SAEs, n (%): [177]Lu-PSMA-617 vs cabazitaxel (n=183): NR [177]Lu-PSMA-617 & standard care vs standard care (n=734): 43 (8.1) vs 5 (2.4)		2 RCTs: 917	Low[b,d]	Any AEs and treatment-related AEs according to CTCAE.
	n (%): 6 (30) vs 10 (50), p=0.20	Difference: 20% (-10-45)	1 RCT[m] ITT: 40	Low[d,n]	Treatment-emergent AEs Grades 3-5[o] according to CTCAE.

Abbreviations: AE – adverse events; BPI-SF – Brief Pain Inventory-Short Form; CI – confidence interval; CTCAE – Common Terminology Criteria for Adverse Events; OS – overall survival; PFS – progression-free survival; EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire; FACT-P – Functional Assessment of Cancer Therapy-Prostate; HR – hazard ratio; HRQoL – health-related quality of life; ITT – intention to treat; n – number; NCCN-FACT-FPSI-17 – National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Functional Prostate Symptom Index-17 Questionnaire; NR – not reported; PP – per protocol; RCT – randomised controlled trial; s.s. – statistically significant

Explanations:
[a] Considering the ITT analysis and overall survival as the outcome will not be affected by the "open-label" study design.
[b] The control group of one RCT received standard care without cytotoxic chemotherapy (e.g. cabazitaxel), which is standard care for this patient group according to guidelines.
[c] After the trial started (29 May 2018), a high incidence of withdrawal from the trial (56%) was noted in the control group at specific sites due to patient disappointment. On 5 March 2019, enhanced trial-site education measures were implemented to reduce the incidence of withdrawal.
[d] Open-label trial.
[e] Missing data.
[f] Reporting bias for certain domains of the EORTC-QLQ-C30 expected.
[g] Reporting bias as only the PP analysis was reported.
[h] The study did not report absolute or relative differences.
[i] The effect in the intervention group was higher in one RCT than the other, probably because of the combination therapy.
[j] The outcome results were different in the three RCTs.
[k] Pancytopenia, n=2; bone-marrow failure, n=1; subdural hematoma, n=1; intracranial haemorrhage, n=1.
[l] Persistent Grade 4 thrombocytopenia leading to treatment-related deaths.
[m] The follow-up time was not reported.
[n] Wide confidence intervals.
[o] The study did not report treatment-related adverse events as Grades 3-4 but 3-5.
[p] The effect of intervention was better in one RCT compared to the other two, probably due to comparators.

5.5 RQ1: Overall survival and progression-free survival

5.5.1 Overall Survival

Findings from the AIHTA systematic review

Overall survival (OS) was reported as a primary outcome by only one of the included RCTs.[34] This study (VISION trial) was the largest of the RCTs and had 831 patients (551 intervention group vs 280 comparator group). In the ITT analysis, the median OS was significantly longer in the group that received ^{177}Lu-PSMA-617 plus standard care compared with standard care alone (15.3 vs. 11.3 months; hazard ratio (HR): 0.62, 95% confidence interval (CI): 0.52-0.74), with a median follow-up of 20.9 months. As this trial had a high incidence of withdrawal from the control arm, an adapted ITT analysis based on 581 patients was also reported (385 vs 196). The adapted analysis produced similar results in favour of ^{177}Lu-PSMA-617 for OS (median OS 14.6 vs 10.4 months, HR: 0.63, 95% CI: 0.51-0.79).

The AIHTA GRADE assessment reported moderate certainty for this outcome.[28] They did not downgrade the certainty of the evidence due to the open-label design as it was unlikely to introduce bias for this outcome. However, they did downgrade the certainty of evidence for indirectness as the control group received standard care without cytotoxic chemotherapy (e.g., cabazitaxel or docetaxel). The AIHTA authors noted that this may have biased the results from the trial given that cytotoxic chemotherapy is considered standard of care for this cohort.[24]

Additional evidence

A follow-up report for the completed TheraP trial was published in 2023 which focused on the secondary outcomes from this study including OS.[39] OS was analysed using an ITT analysis and summarised as restricted mean survival time, with a 36 month median follow-up. There were 291 men enrolled in this study; however, after PSMA PET/CT and ^{18}F-FDG PET/CT imaging, 200 were eligible, and randomly assigned to ^{177}Lu-PSMA-617 (n=99) or cabazitaxel (n=101). After completing study treatment, 20% (n=20) of participants assigned cabazitaxel were given ^{177}Lu-PSMA-617, while 21% were given more cabazitaxel, 9% enzalutamide and 7% abiraterone. Further treatment was not recorded for the other 44 patients in this group. For patients assigned to ^{177}Lu-PSMA-617 group, 32% (n=32) subsequently received cabazitaxel, 5% more ^{177}Lu-PSMA-617, 5% abiraterone and 2% enzalutamide. The next line of therapy was not recorded for 55 of these patients. After a median follow-up of 35.7 months, 78% (n=77) of patients had died in the ^{177}Lu-PSMA-617 group and 69% (n=70) in the cabazitaxel group. No difference in OS was observed between the ^{177}Lu-PSMA-617 and cabazitaxel groups (19.1 months, 95% CI: 16.9 to 21.4 versus 19.6 months, 95% CI: 17.4 to 21.8;

p=0.77). Of the men excluded after PSMA imaging, 61 of these men had follow-up available and had a restricted mean survival time of 11.0 months (95% CI: 9.0 to 13.1), suggesting that OS may be shorter in men with low PSMA expression or discordant ^{18}F FDG–positive and PSMA-negative findings.

A report on the final analysis of the smallest RCT (n=40) included in the AIHTA systematic review above (Satapathy et al.) was recently published and identified in Step 2.[38] The mean follow-up duration was 33.4 months, and post-trial treatments were given to 45% (9 out of 20) of the patients in the ^{177}Lu-PSMA-617 arm compared with 60% (12 out of 20) of those in the docetaxel arm. In the intervention group, 30% and 25% went on to receive docetaxel and enzalutamide, respectively, while in the comparator group 5% and 45% subsequently received ^{177}Lu-PSMA-617 and enzalutamide, respectively. In the intention-to-treat analysis, no difference (p=0.905) was seen in the median OS for the two arms (^{177}Lu-PSMA-617: 15 months (95% CI: 9.5 to 20.5 months) versus docetaxel: 15 months (95% CI: 8.1 to 21.9)). Similar results were reported in the per-protocol analysis. The conclusion from the authors was that long-term outcomes with ^{177}Lu-PSMA-617 and with docetaxel administered earlier in the pre-chemotherapy setting are comparable.[38] However, it should be noted that OS was a secondary outcome in this study and therefore the sample may have been under powered.

As there was additional evidence for this outcome, the ERT re-assessed this outcome using GRADE. The certainty of the evidence was found to be low. This was due to downgrading for inconsistency due to the difference in findings among the three RCTs and for indirectness as the control group of the VISION trial received standard care without cytotoxic chemotherapy (e.g., cabazitaxel or docetaxel).

5.5.2 Progression-free survival

Findings from the AIHTA systematic review

Median progression-free survival (PFS) was reported by all three RCTs,[33, 34, 37] but was the primary outcome in only one of these trials.[34] In the VISION trial (n=831), the median radiographic PFS was longer for the ^{177}Lu-PSMA-617 plus standard care group compared with the standard care alone group (8.8 vs 3.6 months; HR 0.43, 99.2% CI 0.32–0.58).[34] The modified ITT analysis from this RCT (n=581) had similar results (8.7 vs. 3.4 months; HR: 0.40, 99.2% CI: 0.29-0.57, p<0.001). No difference in median PFS was seen in either of the other two RCTs which compared ^{177}Lu-PSMA-617 with a taxane-based chemotherapy (5.1 months vs 5.1 months, p value not reported[37] and (4.0 vs 4.0 months, p=0.98).[33]

The AIHTA GRADE assessment reported a low certainty of evidence for this outcome.[28] They downgraded for risk of bias due to the open labelled design of all

three RCTs and also for indirectness as the effect in the intervention group was higher in one RCT than the others, which was probably due to the use of combination therapy. They also downgraded for indirectness due to the control group in one study receiving standard care which excluded cytotoxic chemotherapy, which may have biased the results from this trial. The AIHTA authors highlighted that as per clinical guidelines, cytotoxic chemotherapy would generally be considered standard of care for patients with mCRPC.

The AIHTA systematic review reported that one of the RCTs, TheraP, also reported on prostate-specific antigen (PSA) PFS, which was defined as the time from randomisation to PSA progression (an increase of at least 25% and at least 2 ng/ml after 12 weeks).[37] The group receiving ^{177}Lu-PSMA-617 had a significantly longer PSA-PFS compared with the cabazitaxel group (n=200, HR 0.60, 95% CI 0.44-0.83, p=0.0017).

Additional evidence

In the follow-up report for the TheraP trial (median follow-up time of 35.7 months), PSA or radiographic progression was reported for 177 out of 200 participants (n=93 in the ^{177}Lu-PSMA-617 intervention arm and n=84 in the cabazitaxel comparator group).[39] PSA or radiographic progression was delayed in the ^{177}Lu-PSMA-617 group compared with cabazitaxel (restricted mean survival time for PFS: 7.1 (95% CI: 5.9 to 8.4) months vs 5.0 (95% CI: 4.2 to 5.8) months; difference 2.1 months, 95% CI: 0.7 to 3.6, p=0.0050). The effect of treatment on PFS was not constant and was at its greatest after six months. Median PFS was unchanged and was as reported in AIHTA systematic review (5.1 months in each group).

5.6 RQ2 Health-related quality of life (HRQoL) and symptom control

Findings from the AIHTA systematic review

In the AIHTA systematic review, HRQoL was found to be reported in all three RCTs (secondary outcome).[33, 34, 37] However, there were no generic QoL tools used (e.g. EQ-5D) and each study used a different specific HR-QoL tool to collect the data and therefore the outcomes were considered separately.

In the VISION trial (n=581), the modified ITT analysis reported HRQoL using The Functional Assessment of Cancer Therapy – Prostate (FACT-P), which assesses the HRQoL of men with prostate cancer and includes 39 items with higher scores indicating better HRQoL.[28, 34, 42] They also used the Brief Pain Inventory-Short Form (BPI–SF) which assesses the severity of pain and its impact on functioning. Scores

range from 0 to 10 with lower scores representing lower levels of pain and better overall functioning.

The time to deterioration in the FACT-P total score was significantly longer for the ^{177}Lu-PSMA-617 plus standard care group than the standard care alone group (5.7 months vs 2.2 months, HR 0.54, 95% CI 0.45-0.66).[28, 34] Similarly, the time to worsening of pain and functioning measured using BPI-SF was longer for the ^{177}Lu-PSMA-617 arm (5.9 months vs 2.2 months, HR 0.52, 95% CI 0.43-0.63).

The GRADE certainty of this evidence was considered by the AIHTA to be low for this HRQoL outcome.[28] The certainty of the evidence was downgraded due to the open-label design of the study and due to indirectness, as the comparator group received standard care without chemotherapy (e.g., cabzitaxel or decetaxel), which would be considered standard of care for this patient group according to clinical guidelines.[24]

In the TheraP trial (n=176, out of 200), HRQoL was measured using the EORTC-QLQ-C30 questionnaire after 51 weeks.[28, 37] This tool was developed to assess HRQoL in cancer patients and included five functional, three symptom and a global health scale.[43] There was no statistically significant difference between the scores when comparing the ^{177}Lu-PSMA-617 and cabazitaxel groups (63 [95% CI 60 to 67] vs 60 [95% CI 57 to 64]; p=0.20). However, certain domains such as social functioning (score 79 vs 72, p=0.030), diarrhoea (score 9 vs 16, p<0.0001), fatigue (score 34 vs 40, p=0,027) and insomnia (score 23 vs 29, p=0.023) favoured ^{177}Lu-PSMA-617.

The AIHTA assessed the certainty of the evidence for this outcome to be low.[28] The certainty was downgraded twice for risk of bias based on the open-label design of the trial, missing data and expected reporting bias for certain domains of the EORTC-QLQ-C30 tool.

In the smallest of the RCTs (n=35), the HRQoL was assessed using the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Functional Prostate Symptom Index (NCCN-FACT-FPSI-17) questionnaire 12 weeks after the first treatment cycle.[33] This questionnaire assesses the functionality of men with prostate cancer and includes domains on disease-related physical and emotional symptoms, treatment side effects and function or wellbeing. Higher scores are associated with better levels of functioning.[28, 44] There was a statistically significant difference in the per protocol analysis favouring the ^{177}Lu-PSMA-617 group over the docetaxel group (p<0.01). Three out of four of the sub-domains favoured ^{177}Lu-PSMA-617, including physical functioning (p=0.02), emotional functioning (p=0.04) and treatment and side effects (p<0.01). No significant difference was found in the fourth sub-domain.

AIHTA assessed the certainty of the evidence for this outcome to be very low, after downgrading twice in the risk of bias domain due to the open-label design of this trial as well as for reporting bias, as only the per protocol analysis was reported.[28] The outcome was also downgraded for imprecision as the study did not report absolute or relative differences.

The VISION RCT also included an outcome on time to first symptomatic skeletal event or death (defined as: the time from randomisation to first new pathological bone fracture; spinal cord compression; tumour-related orthopaedic surgical intervention; requirement for radiotherapy to relieve bone pain; or death from any cause).[34, 40] Symptomatic skeletal events occurred at a similar rate in the intervention and comparator groups (16% [60/385] vs. 17% [34/196]). However, for the outcome of time to first symptomatic skeletal event or death, the median time to event was delayed in the ^{177}Lu-PSMA-617 plus standard care group compared with the standard care comparator group (11.5 [95% CI 10.3 to 13.2] months vs 6.8 (95% CI: 5.2 to 8.5) months; HR 0.5 (95% CI 0.40 to 0.62); p<0.001).

Additional evidence

In Step 2, an update on the VISION trial was identified that focused on HRQoL and pain outcomes (n=581, ^{177}Lu-PSMA-617 plus standard care intervention group n=385, standard care control group n=196).[45] In this study, a post-hoc analysis was included which allowed analysis for worsening of scores alone rather than the pre-specified composite outcome of worsening in FACT-P, EQ-5D-5L and BPI-SF or clinical disease progression or death. Time to worsening of HRQoL was delayed in the ^{177}Lu-PSMA-617 plus standard care group compared with the standard care alone control group on both the FACT-P (pre-specified analysis HR: 0.54 95% CI 0.45 to 0.66, post-hoc analysis HR: 0.46 95% CI: 0.35 to 0.61) and EQ-5D-5L (pre-specified analysis HR 0.65, 95% CI 0.54-0.78, post-hoc analysis HR 0.49, 95% CI: 0.40-0.62). Time to worsening of pain using the BPI-SF scales was also delayed in the ^{177}Lu-PSMA-617 plus standard care group compared with the standard care comparator group for both the pre-specified and the post-hoc analysis (pre-specified analysis HR 0.52, 95% CI 0.42-0.63, post-hoc analysis HR 0.45, 95% CI 0.33-0.60).

5.7 RQ3 Adverse events and toxicity

The AIHTA systematic review included three outcomes relevant to this question: treatment-related deaths, adverse events (AEs) Grade 3-4 and AE-related discontinuation of treatment.

The current AIHTA systematic review is an update of a systematic review it undertook in 2019. No studies were found in the 2019 review that reached the

inclusion criteria for clinical effectiveness, but for the safety analysis AIHTA identified five prospective before-after studies (n=141) that matched the inclusion criteria. A summary of these findings has been included below in the additional evidence section.[46-50]

5.7.1 Treatment-related death

Findings from the AIHTA systematic review

Treatment-related death was reported as a secondary outcome in all three RCTs.[33, 34, 37] This outcome was assessed using the Common Terminology Criteria for serious Adverse Events (CTCAE). In the VISION trial (n=734), five treatment-related adverse events led to the deaths of patients in the ^{177}Lu-PSMA-617 plus standard care arm of the trial (5 out of 551, 0.9%).[34] These deaths were due to pancytopenia in two patients, bone marrow failure in one patient, subdural haematoma in one patient and an intracranial haemorrhage in one patient. No treatment-related deaths occurred in the control group (standard care) after a median of 20.3 months follow-up. Statistical significance was not reported.

In another RCT (TheraP, n=183), no treatment-related deaths occurred after a median follow-up of 18.4 months.[37] In the smallest of the RCTs (n=40), 10% (n=2) of the patients in the ^{177}Lu-PSMA-617 group and 5% (n=1) in the docetaxel group died due to Grade 4 thrombocytopenia.[33] Statistical significance was not reported in either of these trials.

The AIHTA assessed the certainty of the evidence for this outcome to be very low. This was due to downgrading for bias due to the open-label nature of the trials; for inconsistency, as the three trials had different outcome results; and for indirectness, as the control arm of the VISION RCT excluded the use of cytotoxic chemotherapy, which would usually be considered one of the standard of care options according to guidelines.

Additional evidence

In the AIHTA 2019 systematic review, two of the five before-after studies reported on this outcome but no treatment-related deaths were reported in either study.[49, 51]

An update to the TheraP RCT reported no treatment-related deaths occurred after a median follow-up of 35.7 months.[39]

5.7.2 Adverse events (AEs)

Findings from the AIHTA systematic review

All three RCTs reported Grade 3-4 AEs, as assessed by CTCAE, as a secondary outcome.[33, 34, 37] In the largest RCT (VISION, n=734), more Grade 3-4 AEs were reported in the ^{177}Lu-PSMA-617 plus standard care group, compared with the standard care comparator group after a median of 20.3 months (52.7% vs 38.0%). This study also reported more treatment-related Grade 3-4 AEs (28.4% vs. 3.9%) and more treatment-related Grade 3-4 serious AEs (8.1% vs. 2.4%) in the ^{177}Lu-PSMA-617 plus standard care compared with the standard care group. The differences reported for this study were not statistically significant. In another RCT (TheraP, n=183, median follow-up time 18.4 months) there were fewer grade 3-4 AEs reported in the ^{177}Lu-PSMA-617 group compared with the comparator group who were treated with cabazitaxel (33% vs 53%).[37] This difference was not statistically significant.

The AIHTA assessed the certainty of the evidence for this outcome as low. This was due to downgrading for risk of bias as both of these trials were open label, and for indirectness due to the control group of the VISION study receiving standard care without cytotoxic chemotherapy, which would usually be considered one of the standard of care options according to guidelines.

In the Satapathy RCT (n=40), there were fewer treatment-emergent Grade 3-5 AEs in the ^{177}Lu-PSMA-617 arm compared with the docetaxel group (30% vs 50%); however, this difference was not statistically significant (difference 20%, 95% CI -10-45, p=0.20).[33]

The AIHTA assessed the certainty of the evidence for this outcome as low. This was due to downgrading for risk of bias as this RCT was open label and due to downgrading for imprecision due to wide confidence intervals.

Additional evidence

In the AIHTA 2019 systematic review, five before-after studies with relevant safety data were identified.[46, 47, 49-51] They included 141 patients (although data only reported for 116); clinical follow-up ranged from a mean of 13 to median of 25 months (two studies did not report length of follow-up).[47, 49, 51] The included studies listed a range of pre-specified outcomes they assessed. Four studies assessed nephrotoxicity, but no Grade 3-4 events were identified.[47-50] Haematological toxicity was assessed in all five studies.[46, 47, 49-51] More specifically, lymphopenia was assessed in three of the studies: two studies reported no events, the third study reported that Grade 3 lymphopenia attributed to ^{177}Lu-PSMA radioligand therapy occurred in 37% (n=11) of patients.[49-51] Treatment-related Grade 3-4 thrombocytopenia and anaemia were assessed in four studies;[46, 49-51] three reported no events; while one study reported 13% (n=4) had thrombocytopenia and 13% (n=4) had anaemia. Of the three studies that assessed neutropenia,[49-51] one

found cases (7%, n=2).[51] One study reported Grade 3 haematological toxicity in 3.2% (n=1) of patients.[47] In addition, one study also reported bone pain flare in 3% (n=1) of patients. Hepatotoxicity was assessed in two studies, but did not occur in either.[47, 50]

An update on the VISION study reported more Grade 3 or 4 haematological adverse events in those patients receiving intervention of ^{177}Lu-PSMA-617 plus standard care compared with standard care alone. This included anaemia in 15% (n=80) of 529 patients vs 6% (n=13) of 205 patients; lymphopenia in 51% (n=269) vs 19% (n=39) of patients; and thrombocytopenia in 9% (n=49) vs 2% (n=5) of patients.[40]

5.7.3 Discontinuation of treatment rates

Findings from the AIHTA systematic review

The AIHTA systematic review noted that all three RCTs reported on discontinuation of treatment.[33, 34, 37] The VISION trial (n=734) compared ^{177}Lu-PSMA-617 plus standard care with standard care alone. They reported that 63 patients (11.9%) and 37% (7%) discontinued ^{177}Lu-PSMA-617 treatment due to any AEs and due to Grade 3+ AEs, respectively.[34] Forty-five patients (8.5%) discontinued the standard care treatment in the ^{177}Lu-PSMA-617 plus standard care intervention group, compared with 16 patients (7.8%) in the standard care comparator group. Similar proportions of patients discontinued standard care due to Grade 3+ AEs (4.7% vs 5.9%). In the TheraP RCT (n=183), the absolute number of individuals who discontinued treatment was small: the AE-related discontinuation rate was slightly lower in the ^{177}Lu-PSMA-617 group (n=1, 1%) compared with the cabazitaxel group (n=3, 4%).[37] In the third RCT (n=40), treatment discontinuation rates due to Grade 3+ AEs were slightly higher in the ^{177}Lu-PSMA-617 group compared with the docetaxel group (n=2, 10% vs n=1, 5%; again, noting the absolute numbers were small).[33]

Additional evidence

In the AIHTA 2019 systematic review, only one of the five before-and-after studies included this outcome and they reported no occurrences for discontinuation of treatment.[51]

5.7.4 Radiation-induced malignancy

In general, an increased exposure to ionising radiation is associated with an elevated risk of radiation-induced secondary malignancy in the long term, typically decades after the exposure. Both the AIHTA and the Norwegian Institute of Public Health (NIPH) reviews highlighted that patients with mCRPC have a limited life expectancy.[28, 31] This was emphasised by the short median overall survival observed in the included RCTs (range: 11.3 to 21.8 months). Therefore, in this

context, the risk of developing secondary malignancy associated with ^{177}Lu-PSMA radioligand therapy may be considered inconsequential. However, it should be noted that if the cohort of patients referred for ^{177}Lu-PSMA radioligand therapy changes in the future — for example, to patients without metastatic disease — the risk of radiation-induced malignancy should be re-considered when judging the overall benefit-harm balance.

5.7.5 Common side effects

The VISION trial listed the most common adverse events that occurred in 10% of patients or more in either the intervention (^{177}Lu-PSMA-617 plus standard care, n=529) or the control (standard care only, n=205) arm.[40] The following occurred more frequently in the intervention arm: fatigue 43% vs 23%; dry mouth 39% vs <1%; nausea 35% vs 17%; anaemia 32% vs 13%; back pain 23% vs 15%; arthralgia 22% vs 13%; decreased appetite 21% vs 15%; constipation 20% vs 11%; diarrhoea 19% vs 3%; vomiting 19% vs 6%; thrombocytopenia 17% vs 4%; lymphopenia 14% vs 4%; leukopenia 12% vs 2%; bone pain 11% vs 8%; urinary tract infection 11% vs 1% and decreased weight 11% vs 9%.There was no difference in dyspnoea 10% vs 10%.

The TheraP trial similarly reported on adverse events (Grade 1-4) that occurred in 10% of patients or more in either the intervention (^{177}Lu-PSMA-617, n=98) or the control (cabazitaxel, n=85) arm.[37] The following Grade 3 or 4 adverse events occurred more frequently in the intervention arm: fatigue 5% vs 4%; pain 11% vs 5%; nausea 1% vs 0%; thrombocytopenia 11% vs 5%. Conversely, the following Grade 3 or 4 adverse events occurred less frequently in the intervention arm: diarrhoea 1% vs 5%; neuropathy 0% vs 1%; haematuria 1% vs 6%; neutropenia 4% vs 13%; insomnia 0% vs 1%; vomiting 1% vs 2%.

Satapathy et al. reported on both any grade and Grade 3+ adverse events in the intervention (^{177}Lu-PSMA-617, n=20) and the control (docetaxel, n=20) arm.[33] For Grade 3+ adverse events, while anaemia (25% vs 20%) and thrombocytopenia (10% vs 5%) were more common in the intervention arm, diarrhoea (0% vs 10%), palmar-plantar erythrodysesthesia syndrome (0% vs 5%), dyspnoea (0% vs 10%), febrile neutropenia (0% vs 5%) and nephrotoxicity (0% vs 5%) were less common.

5.8 Ongoing research studies

Six relevant ongoing RCTs involving ^{177}Lu-PSMA radioligand therapy in patients with mCRPC were identified in Step 2 of this review, as summarised in Table A.3 in the Appendix. Four of these ongoing RCTs include ^{177}Lu-PSMA-617 in the intervention arm and two RCTs incorporate ^{177}Lu-PSMA-I&T. The four RCTs involving ^{177}Lu-PSMA-617 are all Phase II multi-centre trials, recruiting in Australia,[52] Canada,[53] China[54]

and India,[55] with target accruals of 162, 200, 60, 100 participants, respectively.[52-54] The comparator for three of these trials is androgen receptor-directed therapy, while one involves the taxane-based chemotherapy, docetaxel. The primary outcomes for these trials differ and include PFS, PSA-PFS, radiographic PFS and OS. The ECLIPSE[56] and SPLASH[57] trials are Phase III multi-centre RCTs comparing ^{177}Lu-PSMA-I&T with abiraterone or enzalutamide in patients who have received prior androgen receptor-directed therapy. Both of these RCTs are currently recruiting, and list a primary endpoint of radiographic PFS. The target accruals are 400 and 415 participants for ECLIPSE and SPLASH, respectively, with study completion dates projected in 2027 and 2028.

Novartis, the manufacturer of ^{177}Lu-PSMA-617, has reported that the results from an additional post-marketing, long-term safety study will be available in 2033.[58] This study aimed to enrol 700 participants who have received at least one dose of ^{177}Lu-PSMA-617 as part of a Phase I-IV Novartis-sponsored study.[58]

5.9 Radiation dose to patients

The radiation dose received as part of this practice includes the dose from the administered therapy itself and the dose from the associated imaging. The dose from the associated imaging includes PSMA PET/CT imaging carried out as a required criterion for patient selection for ^{177}Lu-PSMA radioligand therapy. It may also include dose from imaging performed to verify the administered therapeutic dose.

Administered dose

The applicant indicated the intention to use a fixed dose of 7.4GBq (^{177}Lu-PSMA-617) or 7.2GBq of (^{177}Lu-PSMA-I&T) for four to six cycles administered intravenously. The product information for ^{177}Lu-PSMA-617 recommends a dose of 7.4GBq (+/-10%) administered every six weeks (± one week) for up to a total of six cycles, unless there is disease progression or unacceptable toxicity.[2] Recommended dose modifications are based on the severity of adverse clinical reactions.

As per Table 5, the three RCTs in the AIHTA systematic review reported differences in the administered dose ranging from 6GBq up to 8.5GBq in a single cycle. The VISION trial reported a fixed dose of 7.4GBq for up to six cycles.[34] The TheraP trial used a decreasing dose of 0.5GBq per cycle, with 8.5GBq delivered in the first cycle with a maximum of six cycles.[37] In the Satapathy RCT, they also reduced the dose per cycle on the basis of clinical risk factors such as patient weight, disease burden, renal, and haematological parameters.[33]

The organs at risk for ^{177}Lu-PSMA radioligand therapy include salivary glands, lacrimal glands, kidneys and bone marrow.[59] Excretory mechanisms contribute to kidney dose, with approximately 50% of the injected dose cleared within 48 hours. Table 7 outlines estimates of absorbed doses to critical organs after ^{177}Lu-PSMA radioligand therapy, based on guidance from the European Association of Nuclear Medicine (EANM).[60]

Table 7: EANM guidance on estimates of absorbed doses to organs at risk

Organ	Absorbed dose per unit activity (Gy/GBq) – mean ranges
Salivary glands	0.5 - 1.9
Lacrimal glands	0.4 - 3.8
Kidneys	0.4 - 0.8

Dose from associated imaging

PSMA PET/CT is used to determine patient selection for ^{177}Lu-PSMA radioligand therapy.[28, 61-66] A previous generic justification report from HIQA noted that while there is no national diagnostic reference level (DRL) for this imaging procedure, the estimated effective dose for ^{18}F-PSMA PET/CT is 5.68mSv for the PET component and 6.9mSv for the whole body CT component.[67] This compares with 13.47mSv for a (2021 DRL dose length product (DLP): 635Gy.cm) CT thorax, abdomen and pelvis and 3.07mSv for a bone scintigraphy scan.[67, 68] To note, patients with mCRPC may undergo PSMA PET/CT imaging as part of ongoing assessment and surveillance of their disease and therefore, additional PSMA PET/CT imaging may not be required to inform ^{177}Lu-PSMA radioligand therapy.

Verification imaging

Assessment of the administered dose with imaging is necessary due to significant inter-patient variability following the administration of a standard-activity dose of ^{177}Lu-PSMA radioligand therapy. Intrinsic patient characteristics leads to differing pharmaceutical uptake and washout, resulting in inter-patient variation in absorbed doses. The EANM recommends the use of planar or SPECT CT imaging up to seven days post-treatment delivery to verify and calculate critical organ and tumour dose.[60] The application received by HIQA for justification of this practice indicates the intention to use post-treatment imaging as part of the treatment pathway to assess biodistribution of the administered dose. The applicant intends to use whole body planar imaging for this assessment, which would incur no additional dose above the administered activity. However, should SPECT CT imaging be used for this

assessment, there would be an associated additional dose for the CT hybrid component of the procedure. While there is no national DRL for this particular procedure, to provide an indicative dose, HIQA's national DRL for the CT component of SPECT in oncology imaging (meta-iodobenzylguanidine (MIBG) and octreotide attenuation correction/localisation) is DLP=151 mGy.cm, which equates to 2.33mSv using conversion approximations.[69]

License for use

In accordance with regulatory requirements of S.I. 30 of 2019, all practices involving the use of ionising radiation must be authorised in advance by the Environmental Protection Agency (EPA).[70] All undertakings carrying out a radiological practice must fully comply with the relevant provisions of the regulations, and any conditions attached to a licence or registration are subject to compliance assessment, including inspection by the EPA. Undertakings carrying out therapeutic nuclear medicine, such as the practice outlined in this report, must hold a license for nuclear medicine giving rise to a medical exposure in a medical radiological installation from the EPA. Licensing is not nuclide specific; however, a prospective risk assessment is required prior to the installation and commissioning of all sources of ionising radiation information. Information on legislative requirements is provided in guidance for undertakings issued by the EPA.[71, 72]

5.10 Radiation protection of hospital staff and the public

^{177}Lu has a half-life of 6.7 days, emitting both β-particles and γ-photons. Therefore, patients who receive ^{177}Lu-PSMA radioligand therapy represent a public and occupational exposure risk. Dose constraints and limits for staff and public exposure are outlined in the regulations S.I. 30 of 2019 and must be adhered to.[70] To protect staff and members of the public, when planning for the implementation of a new nuclear medicine therapy, the service provider should have arrangements for logistics, facilities, procedures and staff training.

To ensure that dose constraints for staff and the public are not exceeded, service providers must consider the radiation characteristics of the radionuclide, the quantity of radioactivity, the excretion rate (biological half-life) and the total number of treatments to be carried out.[31] The differences between carrier-added and non-carrier-added preparations in the manufacturing process should also be considered, especially with respect to waste management.[73] The design stage of the risk assessment must be completed prior to the installation and commissioning of all sources of ionising radiation.[71] The room that the patient will stay in during and after the treatment delivery should have sufficient distance and or shielding from other patients and the general public. Transportation of the dose of nuclear medicine

therapy must also be considered. Staff training should ensure that staff have an awareness of the radiation protection issues and characteristics of all radioactive sources used in the clinical setting and in the safe handling of radioactive sources.(72)

Carers and comforters

Guidelines issued by HIQA outline the dose constraints to carers and comforters. Carers and comforters include family members who are in contact with the patient during or after the medical exposure.(74) In cases where a significant dose to the carer or comforter is anticipated, as may be the case in therapeutic nuclear medicine procedures, a meeting between the practitioner, patient, and carer or comforter should take place prior to the procedure to ensure that all risks are explained and understood. The exposure of carers and comforters of patients undergoing medical procedures involving ionising radiation should be subject to a prior risk assessment and where necessary the issue of control measures. Before the patient leaves the hospital or clinic, they should be given appropriate written instructions with a view to restricting the dose to persons in contact with them, including carers and comforters. Exceeding national dose constraints is considered a significant event, and HIQA must be notified when it occurs.(75)

Identified studies

The identified studies did not highlight any safety concerns for the public and occupational exposure. The NIPH HTA summarised the findings of two studies which evaluated radiation safety of ^{177}Lu-PSMA radioligand therapy as an outpatient procedure and the resultant dose to carers and comforters.(31) The patients were discharged at different time points from six to 72 hours after treatment delivery. The studies found that following each treatment cycle, the radiation doses to individual members of the public and or caregivers were around 0.25 mSv, with certain limitations on behaviour in place. In Ireland, current guidance indicates that the maximum dose which should be received by a carer or comforter per event or duration of exposure is 3mSv for an adult (not pregnant) and 15mSv for an adult over 60 years. The NIPH publication notes that the dose received by carers and comforters is largely dependent on the time from treatment administration to discharge.

5.11 International guidelines and reports

Three RCTs identified from the three HTAs and two systematic reviews included in this review of prior evidence syntheses originated from Australia, Belgium, Canada, Denmark, France, Germany, India, Puerto Rico, Sweden, the US and the UK.

In terms of international guidelines and reports, in addition to those described in the results above, seven relevant records were identified as part of the targeted grey literature search. These included:

- A reimbursement review for ^{177}Lu-PSMA-617 by Canada's Drug and Health Technology Agency (CADTH) published in March 2023.(76) The decision was to reimburse ^{177}Lu-PSMA-617 on the following conditions: it should not be reimbursed in combination with any other anticancer therapies except ADT; only six cycles should be reimbursed; the cost of ^{177}Lu-PSMA-617 should be reduced; and it should only be used for patients with PSMA-positive mCRPC who have had at least one treatment of an androgen receptor pathway inhibitor and at least one taxane-based chemotherapy regimen.

- A rapid recommendation on ^{177}Lu-PSMA-617 from the American Society of Clinical Oncology (ASCO) published in September 2022.(65) This report recommended that patients with PSMA-positive mCRPC who have progressed on one line of an androgen receptor pathway inhibitor and one previous line of chemotherapy receive 4 to 6 cycles of ^{177}Lu-PSMA-617 once every six weeks. Strength of recommendation: strong; evidence quality: moderate.

- A joint procedure guideline on the use of ^{177}Lu-PSMA radioligand therapy by the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging published in May 2023.(25) This guideline provided support to nuclear medicine personnel with regard to patient selection, performing the radioligand therapy in line with best practice, and the clinical management of possible side effects. The guideline also noted that while ^{177}Lu-PSMA-targeted radioligand therapy appears to be favourable for patients who have contra-indications to docetaxel, it is uncertain whether the benefits of ^{177}Lu-PSMA-targeted radioligand therapy outweigh the risks for those with good performance status, who are likely to tolerate docetaxel. No recommendation was provided regarding which radionuclide (^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T) was preferable, noting that both radiopharmaceuticals are the subject of ongoing RCTs.

- An update to the molecular radiotherapy guidance document for clinicians from the UK's Royal College of Radiologists published in 2019.(66) This document noted that ^{177}Lu-PSMA-targeted radioligand therapy had shown promise in initial studies, but that overall and disease-free survival were still the focus of ongoing clinical trials.

- An update to the prostate cancer guideline by the US National Comprehensive Cancer Network published in September 2023.(77) This guideline

recommended ^{177}Lu-PSMA-617 as a treatment option for patients with one or more PSMA-positive lesions and or metastatic disease that is predominantly PSMA-positive and with no dominant PSMA-negative metastatic lesions, who have had prior treatment with androgen receptor-directed therapy and a taxane-based chemotherapy.

- A rapid response report on ^{177}Lu-PSMA-targeted radioligand therapy by the Institute for Clinical Effectiveness in Argentina published in January 2022.(78) This report concluded that moderate quality evidence supports the use of ^{177}Lu-PSMA radioligand therapy, compared with placebo, in patients with PSMA-positive mCRPC who have progressed following two lines of treatment. Improvements were noted in OS, PFS and reductions in PSA level and symptomatic skeletal events. They reported low quality evidence supporting the use of ^{177}Lu-PSMA radioligand therapy compared with cabazitaxel as a third line therapy, in terms of reducing PSA levels and the incidence of Grade 3-4 adverse events.

- A clinical and cost-effectiveness assessment for ^{177}Lu-PSMA-617 from the UK's National Institute for Health and Care Excellence was published in November 2023.(64) This report concluded that clinical trial evidence indicates that ^{177}Lu-PSMA-617 improves PFS and OS compared with best supportive care. However, they did not recommend that new patients commence ^{177}Lu-PSMA-617 due to uncertainty in the evidence, when compared with cabazitaxel.

6 Discussion

For the purpose of this report and for the generic justification of ^{177}Lu-PSMA radioligand therapy, the ERT has compiled recent systematic reviews relevant to the three RQs, identified a suitable prior evidence synthesis (a 2023 HTA by AIHTA) which addresses these questions, and appraised this systematic review using a validated tool. The ERT subsequently undertook a search for additional publications and studies since the AIHTA systematic review literature search to ensure any newer evidence was included in this report. Despite searching for evidence on all ^{177}Lu PSMA radioligand therapies, only evidence relating to ^{177}Lu-PSMA-617 was identified.

Summary of RQ1 findings

For the outcome of OS, the AIHTA systematic review included only one RCT (VISION trial, n=831 patients), which reported a statistically significant improvement in median OS with ^{177}Lu-PSMA-617 plus standard care compared with standard care alone (15.3 vs 11.3 months). This trial excluded the use of therapies whose safety profile was not established when combined with ^{177}Lu-PSMA-617; this included cytotoxic chemotherapy, immunotherapy, ^{223}radium and investigational treatments. Since the publication of the AIHTA systematic review, follow-up reports have been published for two RCTs suggesting no difference in median OS between ^{177}Lu-PSMA-617 and taxane-based chemotherapy. Specifically, evidence from the TheraP trial suggests that median OS is similar with ^{177}Lu-PSMA-617 and cabazitaxel (19.1 vs. 19.6 months, p =0.77), with the authors concluding that ^{177}Lu-PSMA-617 provides an alternative to cabazitaxel for PSMA-positive mCRPC patients who are progressing after being treated with docetaxel and an androgen-receptor pathway inhibitor. Similarly, evidence from the Satapathy RCT suggests no difference in median OS between ^{177}Lu-PSMA-617 and docetaxel (15 vs. 15 months, p=0.905), with the authors concluding that ^{177}Lu-PSMA-617 administered earlier in the pre-chemotherapy setting to PSMA-positive mCRPC patients produces comparable OS to patients treated with docetaxel. It should be noted that OS was a secondary outcome for both TheraP and the Satapathy RCT and therefore the studies may not have been sufficiently powered for this outcome. Both trials also reported a substantial level of treatment crossover in the post-protocol regime, with Satapathy RCT suggesting that the better safety profile for ^{177}Lu-PSMA-617 resulted in more minimal side effects and allowed a higher proportion of patients in the intervention arm to cross over to docetaxel. The certainty of the evidence for OS was low.

Contrasting results were also seen with respect to radiographic PFS. The VISION trial, which excluded the use of cytotoxic chemotherapy from standard care, reported a significantly longer median radiographic PFS with ^{177}Lu-PSMA-617 plus

standard care compared with standard care alone (8.8 vs 3.6 months). However, both the TheraP and Satapathy RCTs found no significant difference in PFS when comparing ^{177}Lu-PSMA-617 with taxane-based chemotherapy (cabazitaxel (5.1 vs 5.1) and docetaxel (4.9 vs 4.9), respectively). This outcome was reported to have a low certainty of evidence.

Summary of RQ2 findings

RQ2 related to HRQoL and symptom control. It is difficult to compare the findings of the three RCTs as they all used different tools to measure HRQoL and pain, and also reported their findings at different time points. In two of the RCTs (VISION and Satapathy RCTs),[33, 40] the ^{177}Lu-PSMA-617 intervention arm reported a longer time to deterioration in HRQoL or better HRQoL scores than the comparator group. In the third RCT (TheraP trial) there was no statistically significant difference between the overall mean global health status scores on the EORTIC-QLQ-C30 questionnaire, but ^{177}Lu-PSMA-617 was favoured in some of the sub domains such as social function (p=0.030), diarrhoea (p<0.0001), fatigue (p=0.027) and insomnia (p=0.023). The certainty of the evidence for these outcomes was very low to low.

Summary of RQ3 findings

Evidence in relation to RQ3, which addressed adverse events and toxicity, was mixed. In the VISION trial, after a median of 20.3 months follow-up, treatment-related deaths had been reported in 0.9% of the intervention group and none of the comparison group.[34] No treatment-related adverse events were reported in the TheraP trial after a follow-up of 35.7 months while the small Satapathy RCT reported 10% (n=2) in the ^{177}Lu-PSMA-617 group and 5% (n=1) in the docetaxel group died due to thrombocytopenia. The certainty of this evidence was very low.[33] Authors of the three RCTs conclude that ^{177}Lu-PSMA RLT has an acceptable toxicity profile. However, the number of treatment-related deaths (causality not reported) should be noted, particularly those related to thrombocytopenia and related events (e.g. haematoma, sub-dural haemorrhage). Authors agree that frequent monitoring is needed to inform the management of these patients (for example, dose reduction and or blood product support).

None of the three RCTs reported a statistically significant difference in Grade 3-4 AEs (2 RCTs) or treatment-related Grade 3-5 AEs (one RCT) between the intervention and comparator arms. A higher proportion of participants in the VISION trial (which excluded the use of chemotherapy as part of standard care) experienced more Grade 3-4 adverse events in the ^{177}Lu-PSMA-617 group compared with the standard care-only group. However, for the TheraP and Satapathy RCTs where the comparator was a taxane-based chemotherapy, the ^{177}Lu-PSMA-617 groups had a

lower proportion of Grade 3-4 AEs or treatment-related Grade 3-5 AEs compared to the cabazitaxel and docetaxel comparator groups respectively.

Considerations from existing evidence

Although all three RCTs provide evidence on the efficacy and safety of ^{177}Lu-PSMA-617, it should be noted that they differ substantially in terms of the population included, the comparators and their primary outcomes. Two RCTs included participants who had been pre-treated with taxane-based chemotherapy and androgen receptor pathway inhibitors,[34, 37] and one RCT comprised chemotherapy-naïve patients.[33] The comparator in two RCTs was taxane-based chemotherapy,[33, 37] while the other RCT had standard care as a comparator, defined as approved hormonal treatments (e.g., abiraterone), bisphosphonates, radiotherapy, denosumab and glucocorticoids, but excluding the use of cytotoxic chemotherapy.[34] While not explicitly reported, the other two RCTs (TherP and Satapathy RCT) likely also allowed standard care treatments in both arms. In terms of primary outcomes, one RCT had OS and PFS as the primary outcomes[34] and two RCTs had PSA response as the primary outcome.[33, 37] This outcome of PSA response is an indirect measure of disease progression and was not included in this report as an outcome of interest given the uncertainty regarding its relationship with clinical outcomes, and hence its usefulness in clinical decision-making. All three RCTs only included patients with an ECOG performance ≤2 suggesting that patients are at the very least ambulatory and capable of self-care. This was considered reflective of planned clinical practice, given the practical requirement for patients to be capable of self-care due to the risk of occupational exposure.

In the context of other studies

The results of this review of prior evidence are broadly in keeping with those of the other systematic reviews and HTAs identified in Table 3. This review focused mainly on the results of RCTs. In addition to reporting the results of RCTs, the systematic review by Patell et al. identified 16 retrospective studies and three 'real-world' studies which explored the use of ^{177}Lu-PSMA radioligand therapy in mCRPC.[32, 79] [59, 80-93] The retrospective studies varied in size from 10 to 145 participants who received between one and seven cycles of ^{177}Lu-PSMA radioligand therapy. While the endpoints of these studies varied, overall they concluded that ^{177}Lu-PSMA radioligand therapy showed promise in terms of biochemical response — that is, producing a reduction in PSA level, with acceptable toxicity levels. The first real-world study reported retrospectively-collected outcomes from 191 participants who underwent between one and five cycles of ^{177}Lu-PSMA-617 after the majority had received first and second line systemic therapies.[94] The median radiographic PFS, PSA-PFS (n=132) and OS (n=191) were reported as six months (range: 3-10

months), four months (range: 3-8 months) and 12 months (range: 5-18 months), respectively. Treatment-related Grade 3 or 4 adverse events consisted of haematological events (12%) and clinical events (5.7%) which included tiredness, bone pain, nausea, vomiting, proctitis, generalised seizures and dehydration. The second real-world study, the REALITY (Registry to Assess Outcome and Toxicity of Targeted RadionucLIde Therapy) study, incorporated data which were prospectively collected from 254 participants. These participants received a median of three cycles (range 1-13 cycles) of ^{177}Lu-PSMA-617 as salvage therapy following the failure of conventional treatments.(95) PSA-PFS and OS were reported as 5.5 months (CI: 4.4-6.6) and 14.5 months (CI: 11.5-17.5), respectively. No treatment-related deaths were noted, with the most common Grade 3 and 4 adverse events reported to be anaemia (7.1%), thrombocytopenia (4.3%) and lymphopenia (2.8%).The final real-world study reported data collected prospectively on 21 participants who received a median of two cycles of ^{177}Lu-PSMA-617 (range 1-4).(96) Biochemical recurrence, progression and stable disease were reported for 62%, 19% and 19% of participants, respectively. No Grade 3 or 4 adverse events were observed. All three real-world studies concluded that ^{177}Lu-PSMA radioligand therapy provides good response rates with an acceptable adverse event profile.

Other considerations from ongoing studies

Ongoing clinical trials with investigational products involving ^{177}Lu-PSMA

The three RCTs included in this review all used ^{177}Lu-PSMA-617 radioligand therapy; however, other ^{177}Lu-PSMA radioligands such as ^{177}Lu-PSMA-I&T and ^{177}Lu-PSMA-EB-617 are currently in various stages of clinical trials. Most are in early stages of clinical trials; however, ^{177}Lu-PSMA-I&T has been granted FAST Track designation by the FDA (April 2023) and is currently being tested in two phase III trials — ECLIPSE and SPLASH — which are due to be completed in 2029 and 2028, respectively.

Sequencing and combinations of treatments

Based on the European Public Assessment Report (EPAR), ^{177}Lu-PSMA-617 is currently licenced for use in men with mCRPC who have been previously treated with androgen receptor pathways inhibitors and taxane-based chemotherapy. ^{177}Lu-PSMA-617 should be given with androgen deprivation therapy with the option for patients also to receive androgen receptor pathway inhibitors. Standard care in this group of patients can vary depending on the individual and what is available, and there are a number of trials investigating the best treatment sequence and best combination of therapies for these patients. For example, the Satapathy RCT enrolled a population of chemotherapy-naïve men, and found the efficacy of the treatment to be comparable to docetaxel at a pre-chemotherapy stage with the added advantage of less frequent treatment cycles, less toxicity and better quality of

life. A 2023 systematic review by the same authors[29] (Table 3) found an improved response rate and long-term survival in patients treated with ^{177}Lu-PSMA radioligand therapy without prior taxane-based chemotherapy. Other examples include the sequencing of other radioligands with ^{177}Lu-PSMA radioligand therapy, such as ^{225}actinium labelled PSMA.[97]

Additional evidence identified in Step 2 from the PSMAfore trial was not included in the results, as only a conference abstract could be found. This phase III study[98] (n= 468) compared ^{177}Lu-PSMA-617 and androgen receptor pathway inhibitors in chemotherapy-naïve patients.

Hormone sensitive and non-metastatic population

The patient population for this report focused on the use of ^{177}Lu-PSMA radioligand therapy in a metastatic castrate-resistant population, however there is a move towards using ^{177}Lu-PSMA radioligand therapy in other populations, for example those with hormone-sensitive disease. PSMAddition (NCT04720157) is a phase III trial with ^{177}Lu-PSMA-617 plus standard care compared with standard care in a metastatic, hormone-sensitive, prostate cancer population, while other studies are exploring its use in in patients with locally recurrent prostate cancer, e.g., ROADSTER (NCT05230251).

Imaging associated with ^{177}Lu PSMA radioligand therapy

Several of the records identified in this review highlighted the role of PSMA PET/CT imaging in determining the suitability of patients for ^{177}Lu-PSMA-targeted radioligand therapy.[28, 31, 61, 63-66] PSMA PET/CT imaging is a non-invasive method of evaluating the whole body for the presence of disease with PSMA expression and has an established role in the staging and re-staging of some patients with prostate cancer.[67, 99] The therapeutic indication listed in the EPAR for the licensed form of ^{177}Lu-PSMA-targeted radioligand therapy (^{177}Lu-PSMA-617) is PSMA-positive mCRPC, noting that patients should be identified by PSMA imaging.[2] It should also be noted that the eligibility criteria for the three RCTs identified in this review of prior evidence syntheses were restricted to patients with PSMA-positive disease.[33, 34, 37]

Dosimetry

For radiotherapeutic exposures, the regulations indicate that exposures should be individually planned and their delivery verified, taking into account the doses to non-target volumes.[1] The product information for ^{177}Lu-PSMA-617 recommends a dose of 7.4GBq (+/- 10%) administered every six weeks (± one week) for up to a total of six cycles, unless there is disease progression or unacceptable toxicity. Dose modifications are suggested based on the grade of adverse reactions.

Legislation in Ireland mandates that all medical exposures are optimised. Furthermore, guidance from the EANM dosimetry committee encourages the practice of patient-specific dosimetry in ^{177}Lu-PSMA radioligand therapy beyond scaled administration based on parameters such as body surface area.(60) There is a growing body of available data on absorbed doses to critical organs and tumours with ^{177}Lu-PSMA radioligand therapy. This information may be used in the future to develop dosimetry-based personalised treatment determined by absorbed dose to both target and non-target organs.

The literature demonstrated a range of administered doses and number of cycles applied in clinical practice for this therapy, potentially reflecting the lack of a systematic approach in clinical practice. Some studies used a fixed dose per cycle, while others implemented a reduced dose per cycle based on clinical factors such as renal impairment. However, the rationale for determining the extent of dose reduction often lacked clarity, relying primarily on clinical judgement. While this approach represents some level of personalised therapeutic dosing, dosimetry-based personalised treatment was not applied. Although the studies included in this review did not demonstrate a dose-effect relationship, the evidence for other radionuclide therapy suggests a strong correlation between absorbed dose and toxicity and response.(100) Future studies involving dosimetry may provide more robust data on the dose-response relationship in ^{177}Lu-PSMA radioligand therapy.

The dose received by patients as part of this therapy includes PSMA PET/CT used for patient selection, as outlined above, noting that the incurred PET/CT dose is estimated in a previous report from HIQA.(67) Depending on the modality used, some patient dose may also be incurred as part of post-treatment imaging carried out to assess the distribution of the administered activity.

The applicant noted that patients may also receive another radionuclide therapy, ^{223}radium, for the treatment of painful bone metastases, either before or after ^{177}Lu-PSMA radioligand therapy. According to the EPAR, radium-223 dichloride should be administered with an activity of 55kBq per kg body weight, at four week intervals for a maximum of six doses.(101)

Conclusion

The practice for consideration is the use of ^{177}Lu-PSMA radioligand therapy and associated imaging for the treatment of mCRPC. The evidence to date suggests that ^{177}Lu-PSMA-617 provides an alternative to taxane-based chemotherapy and may be better than other treatment options normally available to patients with mCRPC in terms of OS and PFS. Those on ^{177}Lu-PSMA-617 have similar or better HRQoL scores compared with those on taxane-based chemotherapy or other types of standard care. In terms of adverse events, RCT data suggest there is no significant difference

in the proportion of patients experiencing Grade 3-4 AEs when compared with taxane-based chemotherapy or standard care. However, the relative proportions differ depending on the comparator. Overall no serious safety issues were raised. While higher numbers of treatment-related deaths were recorded with ^{177}Lu-PSMA-617, neither causality nor statistical significance were reported.

7 Evidence to decision

A draft of this report was submitted to the MEIR EAG for their consideration and feedback. Following this, a discussion was held at a meeting of the EAG on 22 February 2024, in which the evidence summary and additional contextual factors were considered. As per the HIQA Methods for generic justification of new practices in ionising radiation, a modified version of the GRADE evidence-to-decision (EtD) framework was used to support the MEIR EAG in coming to a recommendation regarding the generic justification of ^{177}Lu-PSMA radioligand therapy for the treatment of mCRPC.

7.1 Overview of MEIR EAG GRADE EtD discussion

Informed by the review of the above evidence, the MEIR EAG completed judgements under a modified evidence-to-decision (EtD) framework to arrive at a recommendation to HIQA on the generic justification of ^{177}Lu-PSMA radioligand therapy for the treatment of mCRPC. The full EtD framework including a summary of the panel discussion and the final judgements can be found in Table A.4 in the Appendix and Table 7, respectively. In terms of benefits and harms, the MEIR EAG considered the evidence for the outcomes listed in terms of both the magnitude of the effect and the certainty of the evidence. In accordance with the available GRADE guidance, the certainty of evidence was considered to be 'very low'.

In terms of the benefits of this practice, the MEIR EAG noted that one of the studies demonstrated a survival benefit of three to four months with ^{177}Lu-PSMA radioligand therapy relative to standard care. Such a survival benefit would be considered significant for this patient cohort. However, it was recognised that the choice of study comparator is important; no survival benefit was seen when compared with cytotoxic chemotherapy. The MEIR EAG agreed that a judgement of 'moderate' was appropriate for benefits.

The EAG noted that the standard treatment (chemotherapy) is associated with a number of potential adverse events. The risk of developing thrombocytopenia while undergoing ^{177}Lu-PSMA radioligand therapy was discussed; however, it was noted this risk can be mitigated by appropriate monitoring and management of patients. There was agreement among the MEIR EAG that the risk of developing secondary malignancy related to the radiation exposure from ^{177}Lu-PSMA radioligand therapy or associated imaging was not relevant to the decision to treat due to the limited life expectancy of this patient cohort. The MEIR EAG agreed that a judgement of 'trivial' was appropriate for harms.

When considering the balance between the desirable and undesirable effects, the MEIR EAG agreed that the balance probably favours the use of ^{177}Lu-PSMA

radioligand therapy. It was agreed that it would provide an important therapeutic alternative for this patient group. The MEIR EAG recommended to HIQA that [177]Lu-PSMA radioligand therapy for the treatment of mCRPC should be generically justified.

Table 8: ^{177}Lu-PSMA radioligand therapy for the treatment of mCRPC

	Summary of judgements						
Desirable Effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know
Certainty of evidence	**Very low**	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know

7.2 HIQA Decision

Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.

The practice ^{177}Lu-PSMA radioligand therapy for the treatment of metastatic castrate-resistant prostate cancer is generically justified under SI 256/2018.

The generic justification of this practice is effective from 18 April 2024. Under the Regulations, HIQA may review the generic justification of this practice if new and important evidence about the practice emerges. HIQA may also review this practice if new and important evidence about alternative techniques and technologies (including non-ionising practices) emerges.

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Appendix

Table A.1 Full search strategy – Medline

Database name			Medline Complete via Ebscohost	
Date search was run			18/10/2023	
#	Query	Limiters/Expanders	Last Run Via	Results
S15	S11 AND S14	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	44
S14	S12 OR S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,666,365
S13	MH "Randomized Controlled Trial" OR PT "Randomized Controlled Trial" OR TI random* N2 trial OR AB random* N2 trial OR TI placebo* OR TI "single blind*" OR TI "double blind*" OR TI "triple blind*" OR AB placebo* OR AB "single blind*" OR AB "double blind*" OR AB "triple blind*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	997,066
S12	MH "Systematic Review" OR MH "Meta Analysis" OR PT "systematic review" OR PT "Meta-Analysis" OR TI systematic* N1 (review* OR overview*) OR AB systematic* N1 (review* OR overview*) OR TI "meta analys*" OR TI "meta analyz*" OR AB "meta analys*" OR AB "meta analyz* OR TI literature N2 (review* OR overview*) OR AB literature N2 (review* OR overview*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	803,430
S11	S3 AND S10	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	634

S10	S4 OR S5 OR S6 OR S7 OR S8 OR S9	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,682
S9	TI (lu-dotatate OR lutetium OR "Lu 177" OR 177Lu) AND TI(PSMA OR "Prostate-specific membrane antigen")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	35
S8	AB(lu-dotatate OR lutetium OR "Lu 177" OR 177Lu) AND AB (PSMA OR "Prostate-specific membrane antigen")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	112
S7	AB (Lu-PSMA-617 OR 177Lu-PSMA OR '177lu DOTA vipivotide' OR '177lu psma 617' OR '177lu psma617' OR '177lu vipivotide DOTA' OR '177lu vipivotide tetraxetan' OR 'aaa 617' OR 'aaa617' OR 'DOTA vipivotide 177lu' OR 'DOTA vipivotide lu 177' OR 'DOTA vipivotide lutetium lu 177' OR 'pluvicto' OR 'psma 617 lu 177' OR 'psma617 lu177' OR 'vipivotide DOTA 177lu' OR 'vipivotide DOTA lu 177' OR 'vipivotide DOTA lutetium lu 177' OR 'vipivotide tetraxetan 177lu' OR 'vipivotide tetraxetan lu 177' OR 'vipivotide tetraxetan lutetium lu 177') OR TI (Lu-PSMA-617 OR 177Lu-PSMA '177lu DOTA vipivotide' OR '177lu psma 617' OR '177lu psma617' OR '177lu vipivotide DOTA' OR '177lu vipivotide tetraxetan' OR 'aaa 617' OR 'aaa617' OR 'DOTA vipivotide 177lu' OR 'DOTA vipivotide lu 177' OR 'DOTA vipivotide lutetium lu 177' OR 'pluvicto' OR 'psma 617 lu 177' OR 'psma617 lu177' OR 'vipivotide DOTA 177lu' OR 'vipivotide DOTA lu 177' OR 'vipivotide DOTA lutetium lu 177' OR 'vipivotide	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	329

	tetraxetan 177lu' OR 'vipivotide tetraxetan lu 177' OR 'vipivotide tetraxetan lutetium lu 177')			
S6	AB 177Lu-PSMA OR TI 177Lu-PSMA	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	73
S5	AB "Lutetium Lu 177 vipivotide tetraxetan" OR TI "Lutetium Lu 177 vipivotide tetraxetan"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	9
S4	(MH "Lutetium")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,397
S3	S1 OR S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	207,593
S2	(Prostat*) N4(neoplas* OR cancer* OR carcinoma* OR malignan* OR tumour* OR tumor* OR metasta* OR adenocarcinoma* OR angiosarcoma* OR sarcoma*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	207,593
S1	(MH "Prostatic Neoplasms, Castration-Resistant") OR (MH "Prostatic Neoplasms+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	149,766

Table A.2 Details of grey literature search

Organisation, country	Description	URL link
General grey literature sources		
Google and Google Scholar	The first five pages of each were checked. Key words: ("lu-dotatate" OR "lutetium" OR "Lu 177" OR "177Lu") AND "PSMA".	https://scholar.google.com/, https://www.google.ie
International organisations		
World Health Organization (WHO)		www.who.int/en
European Network for Health Technology Assessment (EUnetHTA)		https://www.eunethta.eu/
International HTA database (INAHTA)		https://database.inahta.org/
Guidelines International Network (G-I-N)	International guidelines library	https://g-i-n.net/international-guidelines-library
European Society of Radiology (ESR)		https://www.myesr.org/
European Society for Radiotherapy and Oncology		https://www.estro.org/Science/Guidelines
European Association of Nuclear Medicine		https://www.eanm.org/
European Medicines Agency (EMA)		https://www.ema.europa.eu/en/homepage
Country-specific organisations (only examples from selected countries)		
Canada		

Canadian Agency for Drugs and Technology in Health (CADTH)		http://www.cadth.ca
Ontario Health Technology Advisory Committee – Health Quality Ontario (HQO)		https://www.hqontario.ca/
Canadian Urological Association (CUA)		www.cua.org
Norway		
Norwegian Institute of Public Health (NIPH)		https://www.fhi.no
Ireland		
Department of Health (including National Clinical Guidelines)		health.gov.ie
Health Service Executive (HSE)		http://www.hse.ie/
National Cancer Control Programme HSE		https://www.hse.ie/eng/services/list/5/cancer/
Faculty of Radiologists Ireland		www.radiology.ie/
Health Products Regulatory Authority		https://www.hpra.ie/
United Kingdom		
COMARE		https://www.gov.uk/government/groups/committee-on-medical-aspects-of-radiation-in-the-environment-comare
The Royal College of Radiologists		https://www.rcr.ac.uk
National Institute for Health and Care Excellence (NICE)		https://www.nice.org.uk/

Health Technology Wales		https://healthtechnology.wales
Scottish Health Technologies Group		https://shtg.scot/
Scottish SIGN		https://www.sign.ac.uk/
National Institute for Health and Care Research, UK		Health Technology Assessment | NIHR
United States		
Agency for Healthcare Research and Quality (AHRQ)		https://www.ahrq.gov/
Food and Drug Administration (FDA)		http://www.fda.gov/cder/guidance/index.htm
American College of Radiology		https://www.acr.org
National Comprehensive Cancer Network		https://www.nccn.org/
American Association of Physicists in Medicine		https://www.aapm.org/pubs/ACRAAPMCollaboration.asp
Agency for Healthcare Research and Quality		https://www.ahrq.gov

Table A.3 RCTs identified in Step 2

Study: Reference (name/CT.gove number), country	Design	Population Inclusion/Exclusion criteria	Intervention Control	No of participants/target recruitment Primary/relevant outcome	Planned completion date of study Status
Completed trials/updated results					
NCT03392428 TheraP (OS results) Australia	Phase II RCT	Patients previously treated with Docetaxel and for whom cabazitaxel was considered the next appropriate standard treatment.	*Intervention*: ^{177}Lu-PSMA-617 IV *Control:* cabazitaxel	291 OS	Completed. No additional safety signals. Overall survival similar in both groups.
NCT03511664 VISION (HRQoL and pain outcome results) Belgium, Canada, Denmark, France, Germany, Netherlands, Puerto Rico, Sweden, Switzerland, UK, United States.	Phase III RCT	One or more approved AR-directed therapy & with 1-2 cycles of taxane-based regimens.	*Intervention*: ^{177}Lu-PSMA-617 IV + protocol-permitted standard care *Control:* Protocol-permitted standard care alone, e.g. approved hormonal treatments (abiraterone, enzalutamide), bisphosphonates, radiation therapy, denosumab,	581 (in this analysis) HRQoL (FACT-P) and EQ-5D-5L and pain (BPI-SF)	Completed. ^{177}Lu-PSMA-617 + protocol-permitted standard care extended time to worsening in HRQoL and time to skeletal events compared to protocol-permitted standard care alone.

			glucocorticoid at any dose.		
NCT04689828/ EUCTR2020-003969-19-NL PSMAfore Austria, Belgium, Canada, Czech Republic, Czechia, France, Germany, Netherlands, Poland, Slovakia, Spain, Sweden, Switzerland, UK, US.	Phase III RCT	Progressed only once on prior next generation AR-directed therapy*. Up to 6 prior doses of taxane-based chemotherapy permitted in the neoadjvuant or adjuvant setting.	*Intervention:* 100 GBq/ml of ^{177}Lu-PSMA-617 IV *Control:* Abiraterone 500mg or Enzalutamide 40mg	468 Radiographic PFS	Completed. Demonstrated an improvement in PFS compared with AR-directed therapy. Awaiting OS results.
CTRI/2019/12/022282 Satapathy et al. (OS results) India	Phase II RCT	Prior next generation AR-directed therapy*.	*Intervention:* ^{177}Lu-PSMA-617 IV *Control:* Docetaxel with prednisone 5 mg	40 PSA RR	Completed. No significant difference in OS compared to docetaxel.
Ongoing trials					

NCT05803941 US	Post-marketing study Long-term safety follow-up study from Phase I-IV Novartis sponsored studies	Must have received at least one dose of ^{177}Lu-PSMA-617.	*Intervention*: ^{177}Lu-PSMA-617 *Control:* *Various*	700	July 2033 Recruiting
NCT05204927 ECLIPSE France, Italy, Spain, US.	Phase III RCT	Must have received next generation AR-directed therapy*. No more than one previous AR-directed therapy. Up to 6 doses of prior docetaxel permitted.	*Intervention:* ^{177}Lu-PSMA-I&T *Control:* Standard of care hormone therapy (Abiraterone with prednisone or enzalutamide)	400 Radiographic PFS	June 2029 Recruiting
CTRI/2018/07/014703 India	Phase II RCT	Disease progression despite ADT or chemotherapy.	*Intervention:* ^{177}Lu-PSMA-617 IV *Control:* Abiraterone	100 OS	NR Not recruiting

NCT04419402 ANZUP 19001/eNZA-p Australia	Phase II RCT	Prior treatment with enzalutamide, darolutamide, or apalutamide not permitted. Prior treatment with abiraterone permitted. Prior chemotherapy not permitted except for docetaxel in the castrate-sensitive setting.	*Intervention:* 7.5 GBq of ^{177}Lu-PSMA-617 IV in 4 doses. *Control:* Enzalutamide 160mg	162 PSA-PFS	June 2024 Active, not recruiting
NCT05658003 China	Phase II RCT	Progressed only once on prior next generation AR-directed therapy*. Up to 6 prior doses of taxanes permitted in the neoadjvuant or adjuvant setting.	*Intervention*: 7.4 GBq of ^{177}Lu-PSMA-617 IV in 6 doses. *Control:* AR-directed therapy; BSC which may include ADT.	60 Radiographic PFS	April 2028 Recruiting
NCT04647526 SPLASH Canada, France, Netherlands, Sweden, UK, US.	Phase III RCT	Progressed only once on prior next generation AR-directed therapy*. Prior chemotherapy not permitted unless for hormone-sensitive prostate cancer.	*Intervention*: ^{177}Lu-PSMA-I&T every 8 weeks for 4 cycles *Control:* Abiraterone 1000mg or enzalutamide 160mg.	415 Radiographic PFS	March 2028 Active, not recruiting

NCT04663997 Canada	Phase II RCT	Must have received next generation AR-directed therapy*. Prior chemotherapy not permitted unless for hormone-sensitive prostate cancer.	*Intervention*: 7.4 GBq of ^{177}Lu-PSMA-617 IV in 6 doses. *Control:* Docetaxel 75mg/m^2 IV; maximum of 12 cycles	200 PFS	July 2025 Active, not recruiting

ADT – androgen deprivation therapy; AR – androgen receptor; BPI-SF – brief pain inventory short form; BSC – best supportive care; EQ-5D-5L – EuroQol 5 dimension-5 level; FACT-P: functional assessment of cancer therapy, prostate; GBq – Giga Becquerels; I&T – imaging & therapy; IV – intravenous; NR – not reported; OS – overall survival; PFS – progression-free survival; PSA – prostate specific antigen; PSMA – prostate-specific membrane antigen; RCT – randomised controlled trial; UK – United Kingdom; US – United States

* e.g. abiraterone, enzalutamide, apalutamide, darolutamide

Table A.4: Evidence-to-Decision Framework

Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Overall Survival (OS)** • VISION RCT: Median OS was significantly longer with ^{177}Lu-PSMA-617 + standard care vs standard care (15.3 vs 11.3 months; HR 0.62, 95% CI: 0.52-0.74). • TheraP RCT: comparable median OS for ^{177}Lu-PSMA-617 vs taxane-based chemotherapy (19.1 months, 95% CI: 16.9-21.4 vs 19.6 months 95% CI: 17.4-21.8; p=0.77). • Satapathy RCT: comparable median OS for ^{177}Lu-PSMA-617 vs taxane-based chemotherapy (15 months, 95% CI: 9.5-20.5 vs 15 months, 95% CI 8.1-21.9; p=0.905) in a chemotherapy-naïve population. **Progression-free survival (PFS)** • VISION: Median PFS with ^{177}Lu-PSMA-617 was longer than control arm (8.8 vs 3.6 months, HR 0.43, 95% CI 0.32–0.58). • TheraP & Satapathy RCTs: Median PFS comparable to control arm (5.1 vs 5.1 months; 4.0 vs 4.0 months). **Health-related quality of life (HRQoL)** • Reported by all three RCTs using different tools (BFI SF, EORTC QLQ-C30, NCCN-FACT-FPSI) with data collected at different time points. • Those on ^{177}Lu-PSMA-617 have similar or better HRQoL scores compared with those on taxane-based chemotherapy or other types of standard care.	Patients have previously travelled abroad to avail of this treatment.

Panel discussion:

The EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence. The EAG noted the eligible population for ^{177}Lu-PSMA radioligand therapy is patients with PSMA-positive, metastatic castrate-resistant prostate cancer, who have received prior treatment with androgen-based therapy and taxane-based chemotherapy. This population is estimated to be approximately 70 to 100 patients per year in Ireland. The MEIR EAG noted that one of the studies demonstrated a survival benefit of three to four months with ^{177}Lu-PSMA radioligand therapy relative to standard care. Such a survival benefit would be considered significant for this patient cohort. However, it was recognised that the choice of study comparator is important; no survival benefit was seen when compared with cytotoxic chemotherapy.

A judgement of 'moderate' was recorded by the EAG for this criterion.

Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Treatment-related death** • Reported in two of the three RCTs with a higher frequency noted in the ^{177}Lu-PSMA-617 intervention arm (VISION: 0.9% (n=5) vs 0% (n=0); Satapathy RCT: 10% (n=2) vs. 5% (n=1). **Grade 3-4 AEs** • No statistically significant differences between intervention and comparator arms. • VISION RCT- when compared with standard care (without cytotoxic chemotherapy), a higher proportion of patients experienced Grade 3-4 AEs (52.7% vs 38%) and treatment-related AEs (28.4% vs 3.9%) in the ^{177}Lu-PSMA-617 arm. • TheraP trial - when compared with cabazitaxel chemotherapy a lower proportion of patients experienced Grade 3-4 AEs (33% vs 53%) in the ^{177}Lu-PSMA-617 arm.	

	• Satapathy RCT – when compared with docetaxel chemotherapy a lower proportion of patients experienced Grade 3-5 (30% vs 50%) in the ^{177}Lu-PSMA-617 arm. **Dose** The dose incurred from this therapy would also include dose from associated imaging. This includes PSMA PET/CT required for patient selection (approximately 5.68mSv for the PET component and 6.9mSv for the whole body CT component) and potentially dose from imaging used to verify the biodistribution of the dose delivered. Patients indicated for this treatment typically have a short life expectancy, making the risk for long-term radiation effects, such as radiation-induced malignancy, largely inconsequential.	

Panel discussion:

The EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence.

While recognising the potential for adverse events with ^{177}Lu-PSMA radioligand therapy, the EAG noted that the standard treatment (chemotherapy) is also associated with potential adverse events. The risk of developing thrombocytopenia while undergoing ^{177}Lu-PSMA radioligand therapy was discussed; however, it was noted this risk can be mitigated by appropriate monitoring and management of patients.

It was noted that ^{177}Lu-PSMA radioligand therapy is indicated for patients with PSMA-avid disease. Therefore, patients would need to undergo PSMA PET/CT imaging to determine their suitability for treatment, so consideration of the radiation dose incurred by this radiation exposure is included in this criterion. However, there was agreement among the EAG that the risk of developing secondary malignancy related to the radiation exposure from ^{177}Lu-PSMA radioligand therapy or associated imaging was irrelevant due to the limited life expectancy of this patient cohort.

A judgement of 'trivial' was recorded by the EAG for this criterion.

Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of the evidence was found to be low (OS, PFS, HRQoL, Grade 3-4 AEs) or very low (HRQoL and treatment-related death). Downgrading of the certainty of the evidence was predominantly on the basis that all three RCTs were at risk of bias due to the open-label nature of the trials and due to missing data from two of the RCTs. The largest of the RCTs included a comparator that excluded cytotoxic chemotherapy, which was considered not to represent standard of care.	
Panel discussion: The finding for this criterion was noted to be based on the standard GRADE methodology, so no panel discussion around this criterion was required. The certainty of the evidence ranged from 'low' to 'very low'; therefore the overall certainty is 'very low'.		

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Panel discussion:

The EAG considered that the goal of therapy for this patient cohort is improved quality of life, and the evidence presented indicates that ^{177}Lu-PSMA radioligand therapy is associated with comparable or improved quality of life, progression-free and overall survival.

A judgement of 'probably no important uncertainty or variability' was recorded by the EAG for this criterion.

Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ favours the intervention ○ Varies ○ Don't know	See Summary of Findings Table - Table 6 in the report (above).	

Panel discussion:

After considering the balance between the desirable and undesirable effects, it was agreed that this balance probably favours the use of ^{177}Lu PSMA radioligand therapy. It was agreed that it would provide an important therapeutic alternative for this patient group.

A judgement of 'probably favours the intervention' was recorded by the EAG for this criterion.

Recommendation

On consideration of the balance between the benefits and harms, the MEIR EAG found that this favoured the use of ^{177}Lu-PSMA radioligand therapy. The MEIR EAG have recommended to HIQA that ^{177}Lu-PSMA radioligand therapy should be generically justified for patients with PSMA-positive, metastatic castrate-resistant prostate cancer.

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