HTA Austria
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177Lu-PSMA Radioligand Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer

Update 2023
Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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List of abbreviations

177Lu 177Lutetium
68GA ..... Gallium
ADT ..... androgen deprivation therapy
AE ..... adverse event
AMG ..... Arzneimittelgesetz
ARDT ..... androgen receptor-directed therapy
BE ..... Belgium
BPI-SF ..... Brief Pain Inventory-Short Form
BSC ..... best supportive care
bzgl. ..... bezüglich
CAD ..... Canada
CADTH ..... Canadian Agency for Drugs and Technologies in Health
CG ..... control group
CI ..... confidence interval
CNS ..... central nervous system
CR ..... complete response
CT ..... computer tomography
CTCAE ..... Common Terminology Criteria for Adverse Events
DE ..... Germany
DNK ..... Denmark
ECOG ..... Eastern Co-operative Oncology Group
EMA ..... European Medicines Agency
EORTC QLQ-C30 ... European Organisation, for Research and Treatment of Cancer Quality of Life Questionnaire
ESMO ..... European Society for Medical Oncology
EUnetHTA ... European Network for Health Technology Assessment
FACT-P ..... Functional Assessment of Cancer Therapy-Prostate
FDA ..... Food and Drug Administration
FDG ..... fluorodeoxyglucose
FRA ..... France
GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
HR ..... hazard ratio
HRQoL ..... health-related quality of life
HRRm ..... homologous recombination repair gene
IG ..... intervention group
IQR ..... interquartile range
ITT ..... intention to treat
IV ..... intravenous

LHRH .....luteinizing hormone-releasing hormone
LKF .....Leistungsorientierte Krankenanstaltenfinanzierung
n .....number
NR .....not reported
MCBS.....Magnitude of Clinical Benefit Scale
MCMD.....minimal clinically meaningful differences
mCRPC.....metastatic castration-resistant prostate cancer
mHSPC .....metastatic hormone-sensitive prostate cancer
MRI .....magnetic resonance imaging
NCCN-FACT-FPSI-17....National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Prostate Symptom Index-17 Questionnaire
NL .....Netherlands
NR .....not reported
NRCT.....non-randomised controlled trial
OR .....odds ratio
ORR .....objective response rate
OS.....overall survival
PARP.....poly-ADP ribose polymerase
Pat. .....Patienten
PC.....prostate cancer *(German: Prostatakrebs)*
PCWG3 .....Prostate Cancer Clinical Trials Working Group-3
PET..... positron emission tomography
PFS ..... progression-free survival
PP..... per protocol
PPI ..... present pain intensity
PR ..... partial response
PRI..... Puerto Rico
PSA ..... prostate-specific antigen
PSMA ..... prostate-specific membrane antigen
QALY..... quality-adjusted life year
QoL ..... quality of life
RCT ..... randomised controlled trial
RECIST..... Response Evaluation Criteria In Solid Tumors
RLT ..... radioligand therapy *(German: Radionuklidtherapie)*
RoB ..... risk of bias
RR..... relative risk
SABR ..... Stereotactic Ablative Body Radiotherapy
SR..... systematic review *(German: systematische Übersichtsarbeit)*
s.s. ..... statistically significant
SWE..... Sweden
SWISS..... Switzerland
UK..... United Kingdom
USA..... United States of America

Executive Summary

Introduction

Health Problem

With an estimated 1.4 million new cases globally, prostate cancer (PC) is the second most common incident cancer in men in 2020. The incidence of PC differs over 50-fold among various world populations. In Austria, 150 per 100,000 males were newly diagnosed with PC in 2022, and 39 per 100,000 males died of it.

2020: PC is the second most common cancer in men globally

The growth of PC is driven by male sex hormones called androgens. Even though 80-90% of patients respond to androgen therapy, approximately 10-50% of cases develop metastatic castration-resistant PC (mCRPC). None of the current standard treatment options (e.g. hormonal agents or chemotherapy regimens) are proven to be associated with prolonged survival and/or improved patients' health-related quality of life.

novel target treatments for mCRPC needed

Description of Technology

177Lutetium (177Lu) is, to date, the most widely used radioisotope for targeted therapy in PC. Prostate-specific membrane antigen (PSMA), a protein expressed on prostate cells, is a target for radionuclide therapy of PC and its metastases. Labelling PSMA onto 177Lu can be done in various ways using different PSMA ligands, e.g. PSMA-617 and PSMA-I&T.

most widely used radioligand therapy: 177Lu-PSMA

On March 23, 2022, 177Lu-PSMA-617 (Pluvicto®), produced by Endocyte, a Novartis company, received marketing authorisation from the U.S. Food and Drug Administration (FDA) for PSMA-positive mCRPC patients who were previously treated with at least one androgen receptor pathway inhibitor and one or two taxane-based chemotherapy regimens. On December 9, 2022, the European Medicines Agency (EMA) approved 177Lu-PSMA-617 (Pluvicto®) in combination with androgen deprivation therapy (ADT) with or without androgen receptor pathway inhibition for the treatment of adult PSMA-positive mCRPC patients who have been previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy. The claimed benefits of 177Lu-PSMA-radioligand therapy (RLT) are potential survival benefits concerning progression-free survival and overall survival, reducing prostate-specific antigen (PSA), and less grade ≥3 adverse events.

2022 FDA and EMA approval of 177Lu-PSMA-617 (Pluvicto®)

expected benefits in overall & progression-free survival, PSA & a safe profile with minimal grade ≥3 adverse events

177Lu-PSMA-RLT is currently not included in the Austrian hospital benefit catalogue. The intervention is expected to be given to up to 400 men in Austria annually.

177Lu-PSMA-RLT not included in benefit catalogue

Methods

This assessment presents an update of the evidence comprised in the previous systematic review from 2019 about the efficacy and safety of 177Lu-PSMA-RLT compared to standard care in adult male patients with PSMA-positive mCRPC.

project aim: update of the 177Lu-PSMA-RLT evidence

The systematic literature search was conducted in four databases on the 12th of December, 2022. It was limited from December 2018 to December 2022 and in Medline and Embase to only articles published in English or German. After deduplication, 871 citations were identified. The additional manual

systematic search in 4 databases limited to December 2018-2022: 871 hits

search and the contact with the manufacturers did not reveal any further potentially relevant references.

selection, extraction & quality appraisal conducted by 2 researchers

The study selection, data extraction and assessment of the methodological quality of the studies with the Cochrane risk of bias (RoB) tool were performed by two independent researchers. GRADE (Grading of Recommendations Assessment, Development and Evaluation) was further used, and the evidence was qualitatively synthesised. Only randomised controlled trials (RCTs) were included in the qualitative synthesis.

critical outcomes for efficacy & safety

The following critical outcomes were used for a recommendation: Overall and progression-free survival, general and health-related quality of life, treatment-related death (grade 5) and grade 3-4 adverse events.

Results

Available evidence

available evidence for efficacy & safety: 3 RCTs with a high RoB

Three RCTs were included. In two RCTs, 177Lu-PSMA-617 monotherapy was compared to chemotherapy, namely Cabazitaxel (n=200) and Docetaxel (n=40). The third RCT (n=831) compared 177Lu-PSMA-617 in combination with standard care (without cytotoxic chemotherapy) to standard care alone. The RCTs were classified with a high RoB.

Clinical efficacy

1 RCT with statistically significant improvements in overall & progression-free survival & health-related quality of life

One RCT showed statistically significant differences in overall survival (+4.0 months), progression-free survival (+5.3 months) and regarding the duration to worsening of functionality and pain (+3.5 and +3.7 months, respectively) in favour of the 177Lu-PSMA-617 plus standard care group compared to the group receiving standard care alone. Another RCT reported a statistically significant difference in health-related quality of life 12 weeks after the first treatment cycle, favouring the 177Lu-PSMA-617 compared to the chemotherapy group. However, the study did not report absolute or relative differences. The third RCT showed statistically significant health-related quality of life improvements for specific sub-domains after 51 weeks, favouring the 177Lu-PSMA-617 compared to the chemotherapy group. None of the included RCTs reported on generic quality of life.

Safety

monotherapy with fewer grade ≥3 adverse events compared to chemotherapy

combination therapy with more grade ≥3 events than standard care without chemotherapy

The RCTs did not show statistically significant differences in treatment-related deaths and grade ≥3 adverse events. One RCT reported no treatment-related deaths in any study group after 18 months. In contrast, the other two RCTs reported minimally more treatment-related deaths in the 177Lu-PSMA-617 monotherapy than the chemotherapy group (2 vs. 1), and in the 177Lu-PSMA-617 combination therapy than in the standard care alone group (5 vs. 0). Regarding grade ≥3 adverse events, fewer events were reported in the 177Lu-PSMA-617 groups than in the chemotherapy groups (30-33% vs. 50-53%), but more in patients receiving 177Lu-PSMA-617 in combination with standard care than in the group receiving standard care alone (52.7% vs. 38.0%).

Upcoming evidence

8 ongoing RCTs for mCRPC, 5 ongoing RCTs for mHSPC & extended follow-up of TheraP trial (abstract)

Thirteen ongoing RCTs were identified investigating the efficacy and safety of different 177Lu-PSMA-RLTs as monotherapy or combination therapy compared to different standard therapies in pre-treated PSMA-positive patients with mCRPC (n=8) or metastatic hormone-sensitive prostate cancer (mHSPC) – another evolving population. In addition, there is the completed three-year follow-up of the TheraP trial with overall survival data; however, only the abstract was available when writing this report.

Discussion

further evidence regarding combination with chemotherapy & survival outcomes needed

Further research is needed regarding 177Lu-PSMA-RLT combined with standard care, including chemotherapy, as chemotherapy is a standard of care for eligible patients. In addition, overall and progression-free survival data for comparing 177Lu-PSMA-617 monotherapy to chemotherapy is essential.

very low to moderate certainty of evidence

The results should be interpreted with caution owing to the following factors: The certainty of the evidence for the critical outcomes for each comparison presented was very low to moderate owing to difficulties with the study comparators, missing data and limitations of the open-label study design. A further potential applicability issue includes the population of the included studies. Only patients with an ECOG performance status of ≤2 were included in the RCTs. In clinical practice, patients with higher performance status scores might also receive 177Lu-PSMA-RLT.

high costs associated with 177Lu-PSMA-617: cost-effectiveness analyses are necessary

Besides, the high costs of 177Lu-PSMA-617 (Pluvicto®) and additional costs of special training and equipment may induce alternative considerations regarding the intervention (e.g. "self-synthesised" 177Lu-PSMA-RLTs) and settings (e.g. outpatient). Given the high prevalence of mCRPC, cost-effectiveness analyses of 177Lu-PSMA-RLT are needed.

Conclusion

recommendation: inclusion of 177Lu-PSMA-RLT combination therapy in the hospital benefit catalogue restricted to selected patients & specialised centres

The evidence of moderate certainty regarding overall survival indicates superiority of 177Lu-PSMA-617 in combination with standard care (without cytotoxic chemotherapy) versus standard care alone. In addition, the evidence shows a potential superiority of the 177Lu-PSMA-617 combination therapy with respect to progression-free survival and health-related quality of life. However, the results should be interpreted with caution owing to the low certainty of the evidence for these outcomes. Including 177Lu-PSMA-RLT combined with standard care (without cytotoxic chemotherapy) in the hospital benefit catalogue should thereby be restricted to selected patients and limited to specialised centres. Thereby, close monitoring of the efficacy and safety of 177Lu-PSMA-RLT is recommended. In addition, "self-synthesised" 177Lu-PSMA-RLTs of radiopharmaceutical units could be considered.

results of the extended follow-up of the TheraP trial & further ongoing RCTs are to be awaited

The results of the extended follow-up of the TheraP trial (abstract already available) and further ongoing RCTs will shed more light on the efficacy and safety of different 177Lu-PSMA-RLTs as monotherapy or combination therapy compared to standard care, including chemotherapy, in mCRPC patients. Re-evaluation for the mCRPC population is recommended not before 2025.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

2020: Prostatakrebs ist die zweithäufigste Krebsart bei Männern weltweit

2022: 150/100.000 Männer mit neuer Prostatakrebsdiagnose in Österreich

Mit schätzungsweise 1,4 Millionen neuen Fällen weltweit war Prostatakrebs die zweithäufigste Krebserkrankung bei Männern im Jahr 2020. In Österreich wurde im Jahr 2022 bei 150 von 100.000 Männern Prostatakrebs neu diagnostiziert; 39 von 100.000 Männer starben daran. Die Inzidenz von Prostatakrebs steigt proportional mit dem Alter. Zusätzliche Faktoren, die das Risiko erhöhen, an Prostatakrebs zu erkranken, sind beispielsweise genetische Faktoren, Ernährung und Adipositas.

für Patienten mit mCRPC fehlt bis dato eine wirksame Therapie

Das Fortschreiten von Prostatakrebs wird von männlichen Geschlechtshormonen, Androgenen, angetrieben. Obwohl 80-90 % der Patienten auf eine Androgentherapie ansprechen, entwickeln zirka 10-50 % einen metastasierten kastrationsresistenten Prostatakrebs (mCRPC). Keine der derzeit verfügbaren Standardbehandlungen (z. B. Hormonpräparate oder Chemotherapie) führt nachweislich zu einer Verlängerung des Gesamtüberlebens und/oder zu einer Verbesserung der gesundheitsbezogenen Lebensqualität.

Beschreibung der Technologie

die am häufigsten eingesetzte Radioligandentherapie bei Prostatakrebs: 177Lu-PSMA

177Lutetium (177Lu) ist bis heute das am häufigsten verwendete Radioisotop für die Therapie von Prostatakrebs. Über das prostataspezifische Membranantigen (PSMA) – ein Protein, das auf Prostatazellen exprimiert wird – gelangt die Radionuklidtherapie gezielt zu den Krebszellen und Metastasen, um sie von innen zu zerstören. Die Synthese von 177Lu mit PSMA kann auf verschiedene Weise mit unterschiedlichen PSMA-Liganden erfolgen, z. B. PSMA-617 und PSMA-I&T.

2022: FDA- und EMA-Zulassung von 177Lu-PSMA-617 (Pluvicto®)

erwartete Vorteile hinsichtlich dem progressionsfreien Überleben, Gesamtüberleben, PSA-Werte & ein sicheres Profil mit minimalen Grad 3-4 Toxizitäten

Am 23. März 2022 erteilte die US-amerikanischen Arzneimittelbehörde (FDA) die Marktzulassung für 177Lu-PSMA-617 (Pluvicto®), hergestellt von Endocyte – einem Novartis Sub-Unternehmen – bei erwachsenen PSMA-positiven mCRPC-Patienten, die zuvor mit mindestens einem Androgenrezeptor-Signalweg-Inhibitor und einem oder zwei Taxan-basierten Chemotherapie-Regimen behandelt wurden. Am 9. Dezember 2022 erteilte die Europäische Arzneimittelagentur (EMA) die Zulassung für 177Lu-PSMA-617 (Pluvicto®) in Kombination mit einer Androgenentzugstherapie mit oder ohne Hemmung des Androgenrezeptorwegs für die Behandlung erwachsener PSMA-positiver mCRPC-Patienten, die zuvor mit einem Androgenrezeptor-Signalweg-Inhibitor und einer Taxan-basierten Chemotherapie behandelt wurden. Der Hauptnutzen der 177Lu-PSMA-Radioligandentherapie (RLT) besteht in einer potentiellen Verbesserung des progressionsfreien Überlebens und des Gesamtüberlebens, der Senkung des PSA-Wertes und in weniger Grad 3-4 Toxizitäten.

177Lu-PSMA-RLT aktuell nicht im Leistungskatalog enthalten

177Lu-PSMA-RLT ist bis dato nicht im österreichischen Krankenhausleistungskatalog (LKF-Katalog) enthalten. Es wird erwartet, dass jährlich bis zu 400 Männer in Österreich mit 177Lu-PSMA-RLT therapiert werden sollen.

Methoden

Ziel der vorliegenden Arbeit war es, die in der systematischen Übersichtsarbeit aus dem Jahr 2019 dargelegte Evidenz zur klinischen Wirksamkeit und Sicherheit einer 177Lu-PSMA-RLT im Vergleich zur Standardbehandlung bei erwachsenen Patienten mit PSMA-positivem mCRPC zu aktualisieren.

Projektziel: Aktualisierung der 177Lu-PSMA-RLT Evidenz

Die systematische Literatursuche wurde am 12. Dezember 2022 in vier Datenbanken durchgeführt. Sie wurde auf den Zeitraum von Dezember 2018 bis Dezember 2022 beschränkt und in Medline und Embase nur auf Artikel, die in englischer oder deutscher Sprache verfügbar waren. Insgesamt wurden nach Deduplizierung 871 Zitate identifiziert. Die zusätzliche manuelle Suche und die Kontaktaufnahme mit den Herstellern ergab keine weiteren potentiell relevanten Referenzen.

systematische Suche in 4 Datenbanken begrenzt auf Dezember 2018-2022: insgesamt 871 Treffer

Die Studienauswahl, die Datenextraktion und die Bewertung der methodischen Qualität der Studien mit Hilfe des Cochrane Risk of Bias Tools Version 2 wurden von zwei Forscherinnen unabhängig voneinander durchgeführt. Darüber hinaus wurde mit Hilfe des Grading of Recommendations Assessment, Development and Evaluation (GRADE)-Schemas die verfügbare Evidenz qualitativ zusammengefasst. Nur randomisierte kontrollierte Studien (RCTs) wurden in die qualitative Synthese einbezogen.

Studienauswahl, Extraktion & Qualitätsbeurteilung: von 2 Forscherinnen durchgeführt

Die folgenden entscheidungsrelevanten Endpunkte wurden für eine Empfehlung herangezogen: Gesamtüberleben und progressionsfreies Überleben, allgemeine und gesundheitsbezogene Lebensqualität, Therapie-bedingter Tod (Grad 5) und Grad 3-4 Toxizitäten.

entscheidungsrelevante Endpunkte für klinische Wirksamkeit & Sicherheit

Ergebnisse

Verfügbare Evidenz

Drei RCTs aus 2021 wurden für dieses Update herangezogen: Zwei RCTs verglichen 177Lu-PSMA-617 Monotherapie mit Chemotherapie-Regimen, nämlich Cabazitaxel (n=200) und Docetaxel (n=40). Das dritte RCT (n=831) untersuchte 177Lu-PSMA-617 in Kombination mit Standardbehandlungen (ohne zytotoxische Chemotherapie) im Vergleich zu Standardbehandlungen alleine. Die RCTs wurden mit einem hohen Verzerrungsrisiko bewertet.

verfügbare Evidenz für die klinische Wirksamkeit & Sicherheit: 3 RCTs mit hohem Verzerrungsrisiko

Klinische Wirksamkeit

Ein RCT zeigte statistisch signifikante Unterschiede zugunsten der 177Lu-PSMA-617 Kombinationstherapie hinsichtlich des Gesamtüberlebens (+4,0 Monate), des progressionsfreien Überlebens (+5,3 Monate) und der Dauer bis zur Verschlechterung der Funktionalität bzw. des Schmerzes (+3,5 bzw. +3,7 Monate). Ein weiteres RCT berichtete ebenfalls einen statistisch signifikanten Unterschied bezüglich der gesundheitsbezogenen Lebensqualität zugunsten der 177Lu-PSMA-617 Monotherapie gegenüber der Chemotherapie Gruppe 12 Wochen nach dem ersten Behandlungszyklus. In dieser Studie wurden jedoch keine absoluten oder relativen Unterschiede angegeben. Das dritte RCT zeigte statistisch signifikante Lebensqualitätsverbesserungen hinsichtlich der „sozialen Funktionsfähigkeit“, „Durchfall“, „Müdigkeit“ und „Schlaflosigkeit“ nach 51 Wochen zugunsten der 177Lu-PSMA-617 Gruppe im Vergleich zur Chemotherapie Gruppe. Keines der eingeschlossenen RCTs berichtete zur allgemeinen Lebensqualität.

1 RCT mit statistisch signifikanten Verbesserungen bzgl. Gesamtüberleben, progressionsfreies Überleben & gesundheitsbezogener Lebensqualität

Sicherheit

weniger Grad ≥3 Toxizitäten mit 177Lu-PSMA-Monotherapie im Vergleich zur Chemotherapie

mehr Grad ≥3 Toxizitäten mit Kombinationstherapie versus der alleinigen Chemotherapie-freien Standardbehandlung

Die eingeschlossenen RCTs wiesen keine statistisch signifikanten Unterschiede in Bezug auf Therapie-bedingte Todesfälle und Grad ≥3 Toxizitäten auf. In einem RCT wurden nach 18 Monaten keine Therapie-bedingten Todesfälle berichtet. Im Gegensatz dazu berichteten die beiden anderen RCTs minimal mehr Therapie-bedingte Todesfälle in der 177Lu-PSMA-617 Monotherapie im Vergleich zur Chemotherapie Gruppe (2 vs. 1) bzw. in der 177Lu-PSMA-617 Kombinationstherapie Gruppe im Vergleich zur alleinigen Standardtherapie Gruppe (5 vs. 0). Hinsichtlich der Grad ≥3 Toxizitäten wurden in den 177Lu-PSMA-617 Monotherapie Gruppen weniger unerwünschte Ereignisse als in den Chemotherapie Gruppen berichtet (30-33 % vs. 50-53 %). Bei den Patienten, die 177Lu-PSMA-617 in Kombination mit der Chemotherapie-freien Standardbehandlung erhielten, wurden nach 20 Monaten mehr Grad ≥3 Toxizitäten berichtet, als in der Gruppe, die nur die Standardbehandlung bekam (52,7 % vs. 38,0 %).

Laufende Studien

8 laufende RCTs zu mCRPC, 5 laufende RCTs zu mHSPC & längere Nachbeobachtung der TheraP-Studie als Abstract verfügbar

Insgesamt wurden 13 laufende RCTs identifiziert. Sie untersuchten die klinische Wirksamkeit und Sicherheit verschiedener 177Lu-PSMA-RLTs als Mono- oder Kombinationstherapie im Vergleich zu verschiedenen Standardtherapien bei vorbehandelten PSMA-positiven Patienten mit mCRPC (n=8) oder metastasiertem hormonsensitivem Prostatakrebs (mHSPC) – einer weiteren aufkommenden Population.

Darüber hinaus wurde kürzlich ein Abstract zur abgeschlossenen Drei-Jahres-Nachbeobachtung der TheraP-Studie mit Daten zum Gesamtüberleben veröffentlicht. Zum Zeitpunkt der Berichtserstellung war nur der Abstract verfügbar.

Diskussion

weitere Evidenz zur Kombination mit Chemotherapie & zum Gesamtüberleben erforderlich

Weitere Evidenz bezüglich 177Lu-PSMA-RLT in Kombination einer Standardbehandlung einschließlich Chemotherapie ist erforderlich, da Chemotherapie für geeignete Patienten zur Standardtherapie gehört. Darüber hinaus sind Daten zum Gesamt- und progressionsfreien Überleben für den Vergleich von 177Lu-PSMA-617 Monotherapie mit Chemotherapie ausstehend.

sehr geringe bis moderate Vertrauenswürdigkeit der Evidenz

Studienpopulation möglicherweise „gesünder" als in klinischer Praxis

Zudem sollten die vorliegenden Ergebnisse aufgrund der folgenden Aspekte mit Vorsicht interpretiert werden: Die Vertrauenswürdigkeit der Evidenz für die entscheidungsrelevanten Endpunkte für jeden vorgestellten Vergleich wurde sehr gering bis moderat eingeschätzt, da sich Limitationen bezüglich der Komparatoren der Studien, fehlender Daten und Einschränkungen des „open-label" Studiendesigns ergaben. Darüber hinaus wurden nur Patienten mit einem ECOG-Leistungsstatus von ≤2 in den Studien eingeschlossen. Dies repräsentiert möglicherweise nicht in vollem Umfang die klinische Praxis, da dort auch Patienten mit höheren Leistungsstatuswerten eine 177Lu-PSMA-RLT erhalten könnten.

hohe Kosten von 177Lu-PSMA-617: Kosteneffektivitätsanalysen sind notwendig

Darüber hinaus resultieren die hohen Kosten von 177Lu-PSMA-617 (Pluvicto®) sowie von speziellen Schulungen und Ausrüstungen zu alternativen Überlegungen hinsichtlich der Intervention (z. B. 177Lu-PSMA-RLTs aus Eigensynthese radiopharmakologischer Einheiten) und des Settings (z. B. ambulant). Angesichts der hohen Prävalenz von mCRPC sind Kosteneffektivitätsanalysen für 177Lu-PSMA-RLT erforderlich.

Zusammenfassung

Aus der verfügbaren Evidenz von moderater Vertrauenswürdigkeit hinsichtlich des Gesamtüberlebens ergab sich bei vorbehandelten mCRPC eine Überlegenheit von 177Lu-PSMA-617 in Kombination mit der Standardbehandlung (ohne zytotoxische Chemotherapie) gegenüber der Standardbehandlung alleine. Zusätzlich zeigt die Evidenz eine mögliche Überlegenheit der 177Lu-PSMA-617 Kombinationstherapie hinsichtlich des progressionsfreien Überlebens und der gesundheitsbezogenen Lebensqualität. Diese Ergebnisse sind jedoch mit Vorsicht zu interpretieren, da die Vertrauenswürdigkeit für Endpunkte als gering bewertet wurde. Die Aufnahme von 177Lu-PSMA-RLT in Kombination mit der Standardbehandlung (ohne zytotoxischer Chemotherapie) in den Krankenhausleistungskatalog sollte daher auf ausgewählte Patienten und auf spezialisierte Zentren beschränkt werden. Eine genaue Beobachtung der Wirksamkeit und Sicherheit wird dabei empfohlen. Darüber hinaus könnten 177Lu-PSMA-RLTs aus Eigensynthese von radiopharmazeutischen Einheiten in Betracht gezogen werden.

Empfehlung: Aufnahme der 177Lu-PSMA-RLT Kombinationstherapie in den Krankenhausleistungskatalog nur für ausgewählte Patienten & spezialisierte Zentren

Berücksichtigung von „Eigenproduktionen“

Für weitere randomisierte Evidenz zur klinischen Wirksamkeit und Sicherheit verschiedener 177Lu-PSMA-RLTs im Vergleich zur Standardbehandlung einschließlich Chemotherapie bei mCRPC-Patienten sind die Ergebnisse der längeren Nachbeobachtung der TheraP-Studie und laufende RCTs abzuwarten. Eine Re-Evaluierung für die mCRPC-Population ist daher nicht vor 2025 anzudenken.

Ergebnisse der längeren Nachbeobachtung der TheraP-Studie & weitere laufende RCTs sind abzuwarten

Updated background and summary of the clinical evidence from 2019

This chapter summarises the results of the systematic review from 2019 about 177Lu-PSMA radioligand therapy (RLT) in patients with metastatic castration-resistant prostate cancer (mCRPC) [1]. If necessary, we updated the description regarding the health problem, the target population and the technological characteristics.

Zusammenfassung des systematischen Reviews (SR) aus 2019

Health problem and characteristics of the technology (updated)

Overview of the disease, health condition and target population[1]

With an estimated 1.4 million new cases globally, prostate cancer (PC) is the second most common incident cancer in men in 2020 [2]. The incidence of PC differs over 50-fold among various world populations. Western countries like North America have the highest incidence rate, with more than 130 per 100,000 males in 2019, due to the routine screening of prostate-specific antigen (PSA) [2]. Similarly, 150 per 100,000 males were newly diagnosed with PC in Austria in 2022, and 39 per 100,000 males died of it [3].

Prostatakrebs (PC): häufigste Krebserkrankung bei Männern

The growth of PC is driven by male sex hormones called androgens. The natural course of PC is primarily dependent on tumour aggressiveness. PC can remain silent throughout a man's life without being detected; however, if PC grows to the stage of producing symptoms like bladder neck obstruction, invasion of adjacent organs, or distant metastasis, curative treatment is usually impossible [4].

Krankheitsverlauf ist abhängig von der Aggressivität des Tumors

Even though 80-90% of patients respond to androgen therapy, approximately 10-50% of cases develop mCRPC [5]. According to an analysis of the French nationwide healthcare database, the incidence of men with mCRPC was 21 cases per 100,000 men in 2014. The maximum mCRPC incidence was reported in men aged 80-89 (175 cases per 100,000 men), while less than one mCRPC case per 100,000 was observed in men aged between 40 and 49 years [6]. This shows that the incidence of mCRPC increases proportionally with age. In addition, genetic factors, family history, diet, and obesity play an essential role in the development of mCRPC [7].

10-50 % entwickeln eine metastasierende kastrationsresistente Form (mCRPC)

Risikofaktoren: Alter, Erbanlage, Ernährung, Übergewicht, etc.

[1] **A0001** – For which health conditions, and for what purposes is 177Lu-PSMA-RLT used? &
A0002 – What is the disease or health condition in the scope of this assessment? &
A0003 – What are the known risk factors for mCRPC? &
A0004 – What is the natural course of mCRPC? &
A0025 – How is mCRPC currently managed according to published guidelines and in practice? &
A0007 – What is the target population in this assessment? &
A0023 – How many people belong to the target population?

Current clinical practice

aktuelle Standardversorgung: BSC, Chemotherapie, Hormontherapie, Radiopharmazeutikum & PARP inhibitors

Currently, there are different standard of care treatments available for mCRPC patients, including:

- best supportive care (BSC), e.g. symptom management like pain killers, antiemetics and appetite stimulants,
- chemotherapies, e.g. Docetaxel or Cabazitaxel,
- novel hormonal agents such as androgen pathway inhibitors like Abiraterone or Enzalutamide),
- radiopharmaceuticals in case of bone metastases only, e.g. Radium-233 and
- PARP inhibitors, e.g. Olaparib is approved for mCRPC in BRCA1 and BRCA2 mutated patients.

If patients previously failed Docetaxel and novel hormonal therapy, the treatment options available are BSC, Cabazitaxel, Mitoxantrone, or Radium-233 (in case of bone metastases). Clinical judgments, patient performance status, comorbidities, and preferences determine treatment selection [8].

verlängerte Lebensdauer & verbesserte Lebensqualität dadurch nicht garantiert

None of these treatment options are proven to be associated with prolonged survival and/or improved patients' health-related quality of life (HRQoL) outcomes [8-10]. Therefore, there is a need for novel targeted treatments that can extend survival, minimise toxicities, and improve patients' quality of life (QoL), as mCRPC at this late stage is non-curative cancer.

Features of the intervention[2]

177Lu: das am häufigsten benutzte Radioisotop, PSMA: molekulares Target für die Radionuklidtherapie (RLT)

To date, 177Lutetium (177Lu) is the most widely used radioisotope for targeted therapy in PC. Prostate-specific membrane antigen (PSMA), which is a protein expressed on prostate cells, is a target for radionuclide therapy of PC and its metastases as PSMA is overexpressed (up to 1,000 times) in more than 90% of PC patients [7]. Labelling PSMA onto 177Lu can be done using different PSMA peptides and antibodies [11]. There are different PSMA ligands, although the most studied are PSMA-617 and PSMA-I&T [12].

177Lu-PSMA-RLT wird intravenös alle 4-6 Wochen für bis zu 6 Zyklen verabreicht; spezifische Vorkehrungen notwendig

Usually, 177Lu-PSMA-RLT is administered intravenously at a dose of around 7.4 GBq (200 mCi) every four to six weeks for up to six cycles under radioprotection precautions in the hospital's nuclear department. These precautions include specialised personnel (e.g. a medical oncologist, a radiation oncologist or a nuclear medicine physician, nurses and a radiation safety officer), specific equipment, an administration room and space for radiation waste storage. Different methods to apply the RLT include a syringe, an in-

[2] **B0001** – What is the technology and the comparator(s)? &
A0020 – For which indications has 177Lu-PSMA-RLT received marketing authorisation or CE marking? &
B0002 – What is the claimed benefit of 177Lu-PSMA-RLT in relation to the comparators? &
B0004 – Who administers 177Lu-PSMA-RLT and the comparators and in what context and level of care are they provided? &
B0008 – What kind of special premises are needed to use 177Lu-PSMA-RLT and the comparator(s)? &
B0009 – What supplies are needed to use 177Lu-PSMA-RLT and the comparator(s)? &
A0021 – What is the reimbursement status of 177Lu-PSMA-RLT? &
A0011 – How much 177Lu-PSMA-RLT utilised?

fusion using gravity, or a vial. However, before the treatment administration, patients need to undergo PSMA imaging to check if their cancer expresses PSMA as 177Lu-PSMA-RLT is administered only to those with PSMA-positive PC [13].

erwarteter Zusatznutzen: Lebensverlängerung & weniger Nebenwirkungen

The main claimed benefit of 177Lu-PSMA-RLT as targeted therapy is to have potential survival benefits concerning progression-free survival (PFS) and overall survival (OS), reducing PSA, with a safe profile that causes a minimal number of grade 3-4 toxicities. 177Lu-PSMA-RLT offers an additional non-curative therapeutic option for mCRPC patients [11].

März 2022: FDA-Zulassung für 177Lu-PSMA-617 Monotherapie

Dezember 2022: EMA-Zulassung für 177Lu-PSMA-617 plus Androgendeprivationstherapie mit oder ohne Hemmung des Androgenrezeptorwegs

On March 23, 2022, 177Lu-PSMA-617 (Pluvicto®) produced by Endocyte, a Novartis company, received marketing authorisation from the U.S. Food and Drug Administration (FDA) for PSMA-positive mCRPC patients who were previously treated with at least one androgen pathway inhibitor and one or two taxane-based chemo-regimens in the third-line settings and beyond. This application was granted priority review and breakthrough designation [14]. On December 9, 2022, the European Medicines Agency (EMA) approved 177Lu-PSMA-617 (Pluvicto®) in combination with androgen deprivation therapy (ADT) with or without androgen receptor pathway inhibition for the treatment of adult PSMA-positive mCRPC patients who have been previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy. This medicine is under additional monitoring by regulatory authorities to enhance reporting of suspected adverse drug reactions [15].

alternativ: "in-house" Produktion von 177Lu-PSMA-RLT möglich

Instead of using the final product, 177Lu-PSMA-617 (Pluvicto®), some radiopharmaceutical units also synthesis the 177Lu with a PSMA-ligand (PSMA-617 or PSMA-I&T) in-house, following specific standards.

ca. 400 erwartete Einsätze von 177Lu-PSMA-RLT pro Jahr in Österreich; aktuell nicht im Krankenhausleistungskatalog gelistet

According to information from submitting hospitals, 177Lu-PSMA-RLT is expected to be given to up to 400 men in Austria each year. Currently, only 177Lu-DOTA-Tate is included in the Austrian hospital benefit catalogue (Code ZN351); however, the intervention under investigation in this present systematic review, 177Lu-PSMA-RLT, is currently not included [16].

Results of the systematic review from 2019

Available evidence

keine Studie erfüllte Einschlusskriterien für die Analyse der klinischen Effektivität

No study fulfilled the inclusion criteria for assessing the clinical effectiveness of the 177Lu-PSMA-RLT. Randomised controlled trials (RCTs) and non-randomised controlled trials (NRCTs) were considered for inclusion but could not be identified through the systematic literature search.

5 prospektive Vorher-Nachher-Studie für die Sicherheitsanalyse mit 141 Pat. (116 berichtet) eingeschlossen

For the safety analysis, prospective observational evidence was also included. Hence, five prospective before-after studies that matched the inclusion criteria were included. The five studies comprised 141 patients. Yet, data were reported on 116 patients [17-21]. Without data from controlled trials, no comparisons could be made between 177Lu-PSMA-RLT and the comparators. Only treatment-related complications were considered for the safety analysis.

keine Studie wurde von einem Hersteller gesponsert

Nachbeobachtungszeitraum: 13-25 Monate

None of the included studies were explicitly sponsored by any of the manufacturers, but a member of the authoring team in one study was a shareholder at Scintomics, Germany [20]. One study had no funding [18]. The other studies were funded by the Peter MacCallum Foundation and Prostate Cancer Foundation [19], the University of Innsbruck and Medical University of Innsbruck [21], and the Paul Ramsey Foundation [17]. Clinical follow-up duration was unclear in two studies [17, 21] and ranged from a mean of 13 to a median of 25 months in the remaining three studies [18-20].

Clinical effectiveness

keine Evidenz erfüllte Einschlusskriterien

No comparative evidence was available to answer the question of the clinical effectiveness of 177Lu-PSMA-RLT.

Safety

keine schwerwiegenden Nebenwirkungen berichtet

Grad 3-4 Toxizitäten: 3-37 % der Pat. erlitten Hematoxizität & Hemoglobintoxizität

Concerning serious adverse events, the outcome of treatment-related death was reported in two studies, and it did not occur in either [12, 13]. Concerning adverse events (AEs), the outcomes of discontinuation rates were reported in one study where no patients discontinued treatment due to toxicities [19]. Regarding grade 3-4 toxicities, nephrotoxicity was reported in four studies but did not occur in any [18-21]. Hematotoxicity and lymphocytopenia were reported in three studies [19-21] and occurred in 37% of patients in one study [19]. Furthermore, thrombocytopenia and anaemia were both reported in four studies [19] [17, 20, 21], but both were reported in 13% of patients in one study [19]. Neutropenia was reported in three studies [19-21] but occurred in 7% of patients in one study [19]. In addition, hemoglobin toxicity was reported in one study in 3.2% of patients [18]. Hepatotoxicity was reported in two studies but did not occur in either [18, 21], while bone pain flare was reported in one study and occurred in 3% of patients [19].

PSMA-gerichtete Therapie kann auch Oberflächen anderer Organe angreifen

177Lu-PSMA-RLT is a therapy that targets a specific antigen expressed on the surface of PC tumour cells and can also target other cells, such as kidneys, liver, spleen, bone marrow, salivary, lacrimal, and parotid glands [22-26].

Recommendation

2019: Aufnahme in den Krankenhausleistungskatalog wurde nicht empfohlen

The evidence was insufficient to prove that the assessed technology, 177Lu-PSMA-RLT, was more effective and equally safe or equally effective, but safer than the comparators of BSC, hormonal therapy, chemotherapy, immunotherapy, radiopharmaceuticals, or steroids.

UPDATE 2021

1 Objectives and scope

1.1 PICO question

PIKO-Frage

Is 177Lutitium-labelled prostate-specific membrane-antigen inhibitor therapy compared to best supportive care or standard of care in adult male patients with PSMA-positive metastatic castration-resistant prostate cancer more effective and safe or equally effective and safer concerning overall survival, quality of life and grade ≥3 adverse events?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Updated inclusion criteria for relevant studies are summarised in Table 1-1.

Table 1-1: Inclusion criteria

Population	Male patients (≥18 years old) with PSMA-positive mCRPC It can also be called: ■ hormone-resistant prostate cancer (HRPC) or ■ androgen-insensitive/independent prostate cancer (AIPC) ICD-10 Code: Z19.2 MeSH terms: prostate, neoplasms, prostatic neoplasms, neoplasm metastasis, castration, castration-resistant
Intervention	177Lu-labelled PSMA inhibitor therapy administered intravenously: ■ The active substance is the radionuclide 177-Lutetium (177Lu) ■ Available agents of the RLT with PSMA: ■ 177Lu-PSMA-617 (Pluvicto®, Endocyte, a Novartis company, USA) ■ 177Lu-PSMA-I&T (Scintomics GmbH, Germany) ■ Agents synthesised by radiopharmacists MeSH-terms: lutetium, prostate, antigens, therapeutics, Lutetium-177, 177-Lu, 177Lu, Lu-177, PSMA, ligands, radioisotopes, radiopharmaceuticals No MeSH term: radioligand therapy
Control	**BSC:** including registered treatments of physician's choice and palliative care, such as pain mitigation, fatigue, weight loss, fear, and depression. **Best standard of care:** Chemotherapy, e.g.: ■ Docetaxel (Docefrez/Taxotere®) + prednisone ■ Cabazitaxel (Jevtana®) +prednisolone +/- carboplatin ■ Mitoxantrone (Novantrone®) +prednisolone ■ Estramustine (Emcyt®) + docetaxel + prednisolone Hormonal agents, e.g: ■ Enzalutamide (Xtandi®) ■ Abiraterone (Zytiga®) Radiopharmaceuticals, e.g.: ■ Radium 223 (Xofigo®) PARP inhibitors for HRRm, e.g.: ■ Olaparib MeSH terms: pharmaceutical preparations, drug therapy, antigens, prostatic neoplasms, bone and bones, palliative care, chemotherapy, best supportive care, antineoplastic agents, hormonal

Outcomes	
Efficacy	**Critical endpoints:** ■ **OS:** time from randomisation until death from any cause ■ **Generic QoL:** measurement of individual's sense of well-being and ability to carry out activities of daily living ■ **HRQoL:** measurement of individual's sense of well-being concerning both physical and mental health ■ **PFS:** time from random assignment in a clinical trial to disease progression or death from any cause **Important endpoints:** ■ **PSA-PFS:** PFS as measured by the prostate-specific antigen levels ■ **ORR and disease control,** according to the RECIST, measures patients' response to treatment[1] ■ **Time to first symptomatic skeletal event** **Relevant endpoint:** ■ **PSA-response**
Safety	**Critical endpoints:** ■ **Treatment-related grade 5 AEs (death)** as measured by CTCAE ■ **Grade 3-4 AEs** as measured by CTCAE **Important endpoint:** ■ **AE-related discontinuation**
Study design	RCTs
Language	English and German
Publication period	From December 2018 onwards

Abbreviations: AE – adverse event, BSC – best supportive care, CTCAE – Common Terminology Criteria for Adverse Events, HRQoL – health-related quality of life, HRRm – homologous recombination repair gene, mCRPC – metastatic castration-resistant prostate cancer, ORR – objective response rate, OS – overall survival, PARP – poly-ADP ribose polymerase, PFS – progression-free survival, PSA – prostate-specific antigen, PSMA – prostate-specific membrane antigen, QoL – quality of life, RCT – randomised controlled trials RECIST – Response Evaluation Criteria in Solid Tumours, RLT – radioligand therapy

[1] *When tumours improve = "respond", stay the same ="stabilise", or worsen ="progress" during treatment*

2 Methods

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [27].

EUnetHTA Core Model® Version 4.2. für SR herangezogen

2.1 Systematic literature search

The systematic literature search was conducted on the 12th of December 2022 in the following databases:

systematische Literatursuche in 4 Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library
- INAHTA database

The systematic search was limited to December 2018 to December 2022 and in Medline and Embase to only articles published in English or German. The specific search strategy employed can be found in the Appendix.

Suchzeitraum: Dezember 2018 bis Dezember 2022

Manufacturers of the most common products (177Lu-PSMA-617 [Pluvicto®] and 177Lu-PSMA-I&T) were contacted. However, they submitted no publications.

keine Dokumente von den Herstellern

By hand-search, no additional references could be identified, resulting in a total of 871 hits.

insgesamt 871 Treffer identifiziert

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 18th of January, 2023 resulting in 84 potential relevant hits.

Suche nach laufenden Studien (84 Treffer)

2.1.1 Flow chart of study selection

Literaturauswahl: 3 RCTs eingeschlossen

Overall, 871 hits were identified after deduplication. The references were screened by two independent researchers (SW and RF). In case of disagreement, a third researcher (GG) was involved in solving the differences. Out of the 871 hits, we included three RCTs for the qualitative synthesis. The selection process is displayed in Figure 2-1.

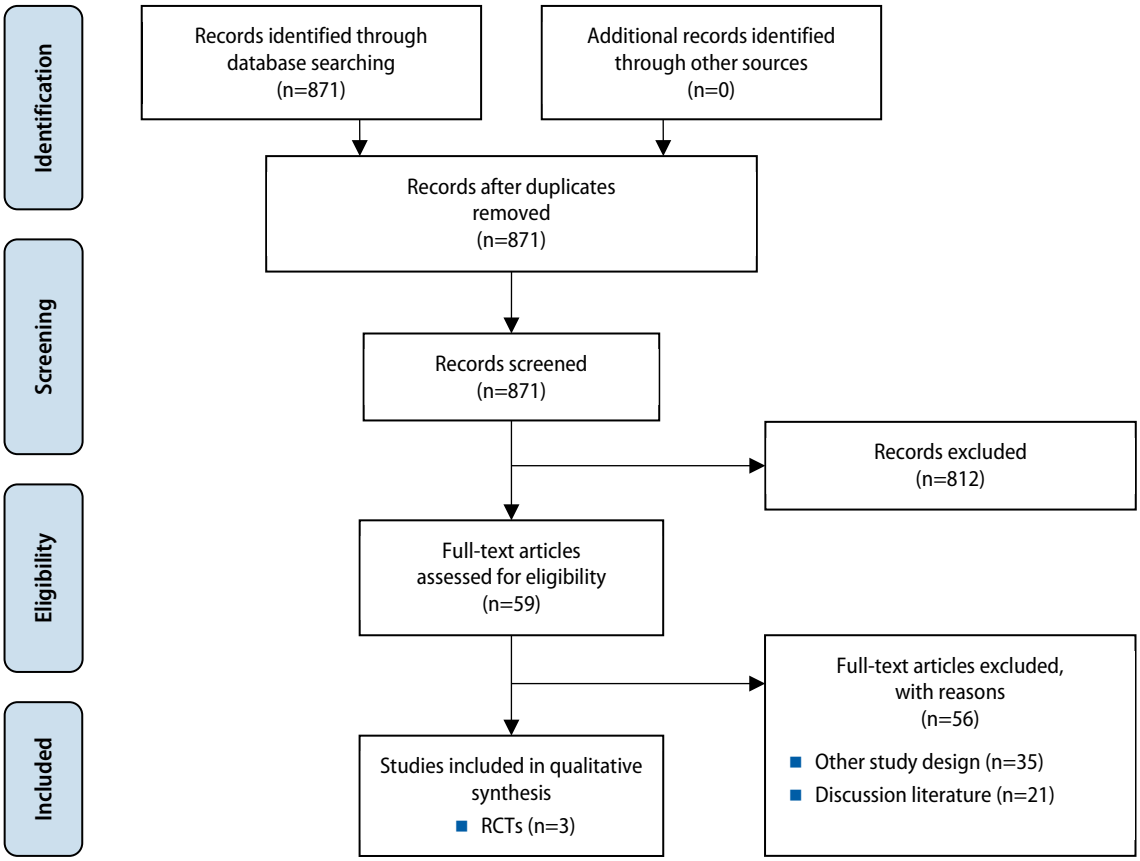

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.1.2 Analysis

Datenextraktion & Beurteilung der Studienqualität mit Cochrane RoB Tool (V.2) durch 2 Researcherinnen

Relevant data from the included RCTs were systematically extracted into a data extraction table (see Table A-1 in the Appendix). One researcher extracted the data of a study, and the other checked and verified the extracted data. SW did the data extraction for two RCTs, while RF extracted the data of the third RCT.

The two researchers (SW, RF) systematically assessed the risk of bias (RoB) of the included RCTs using the Cochrane RoB tool version 2 [28] (see Table A-2). All discrepancies were resolved by consensus.

2.1.3 Synthesis

qualitative Synthese der Evidenz

A qualitative synthesis of the evidence was performed. The research questions were answered in plain text format.

Zusammenfassung der Ergebnisse mit Hilfe des GRADE-Schemas

Furthermore, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scheme was used to synthesise the identified evidence [29]. Thereby, each endpoint was rated by two independent researchers (SW and RF). In disagreement, a third researcher (GG) solved the difference. A GRADE summary of findings table and an evidence profile table were compiled (see Table 4-1 and Table A-3). We conducted no inferential statistical analysis.

3 Results: clinical efficacy and safety

3.1 Outcomes

3.1.1 Efficacy outcomes

The following outcomes were defined as *critical* to derive a recommendation:

entscheidungsrelevante Endpunkte für die klinische Wirksamkeit:

- **Overall survival (OS)** was defined as the time from randomisation to death from any cause.

Gesamtüberleben (OS),

- **Generic quality of life (QoL)** was assessed with validated and standardised generic utility measures, such as EQ-5D or SF-6D.

allgemeine Lebensqualität (QoL),

- **Health-related quality of life (HRQoL)** was assessed with validated and standardised questionnaires to evaluate the individual physical and/or emotional functionality and pain level. The following questionnaires were used in the included studies:

gesundheitsbezogene Lebensqualität (HRQoL),

  - **The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)** was developed to assess the HRQoL of cancer patients. It includes five functional, three symptom and a global health and HRQoL scale. Higher functional scores indicate better function, and lower symptom scores indicate better HRQoL [30].
  - **The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire** assesses the HRQoL of life in men with PC. It includes 39 items, and the scores range from 1-153. Higher scores indicate better HRQoL [31].
  - **The National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17 Item Version (NCCN-FACT-FPSI-17)** assesses the functionality of men with PC. It includes 17 items under four domains: disease-related symptoms-physical (FPSI-DRS-P), disease-related symptoms-emotional (FPSI-DRS-E), treatment side effects (FPSI-TSE) and function/well-being (FPSI-F/WB). Response for each question ranged from zero (highly symptomatic) to four (no symptoms). Higher scores were associated with better functionality [32].
  - **The Brief Pain Inventory-Short Form (BPI-SF) questionnaire** assesses the severity of pain and its impact on functioning. It includes four items, and the scores range from 0-10. Lower scores represent lower levels of pain intensity and better overall function [33].

progressionsfreies Überleben (PFS)

- **Progression-free survival (PFS)** was the time from randomisation to independently centrally reviewed disease progressions or death.

Three further efficacy outcomes were defined as *important* but not critical to derive a recommendation:

weitere wichtige Endpunkte:

- **Prostate-specific antigen (PSA)-PFS** 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), according to the Prostate Cancer Clinical Trials Working Group-3 (PCWG3).

PSA-progressionsfreies Überleben (PSA-PFS),

- **Objective response rate (ORR) and disease control** were defined as the proportion of patients with a complete response (CR) or partial response (PR) to treatment within a specific time period, according to

objektive Ansprechrate (ORR),

the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. CR is defined as the disappearance of all target lesions, and any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10 mm. PR is defined as an at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Zeit bis zum ersten skelettalen Symptom

- **Time to first symptomatic skeletal event** was defined as the first use of external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or non-vertebral bone fractures, spinal cord compression, or tumour-related orthopedic surgical intervention.

weiterer relevanter Endpunkt: PSA-basierte Ansprechrate (PSA-RR)

An additional efficacy outcome was defined as *relevant*:

- **PSA response** was defined as the proportion of patients achieving a ≥50% decline in PSA from baseline, according to the PCWG3.

3.1.2 Safety outcomes

entscheidungsrelevante Sicherheitsendpunkte: Therapie-bedingter Tod (Grad 5), unerwünschte Ereignisse (Grad 3-4)

The following outcomes were defined as *critical* to derive a recommendation:

- **Treatment-related grade 5 adverse events (AEs, deaths)** were defined as any treatment-related deaths due to AEs, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.
- **Grade 3-4 AEs**: according to CTCAE version 5.0., grade 3 AEs were defined as severe or medically significant but not immediately life-threatening AEs leading to hospitalisation or prolonged hospitalisation, disabling, and limited self-care activities of daily living. Grade 4 AEs were defined as life-threatening consequences that require urgent intervention.

weiterer wichtiger Endpunkt: Abbruchquote aufgrund von unerwünschten Ereignissen

A further safety outcome was defined as *important*:

- **AE-related discontinuation** was defined as any AEs resulting in treatment discontinuation within a specific period.

3.2 Included studies for efficacy and safety

3 RCTs publiziert 2021 eingeschlossen; 2 RCTs von Novartis gesponsert, 1 RCT Sponsor unbekannt

To assess the efficacy and safety of 177Lu-PSMA-RLT in adult male patients with mCRPC, we identified three RCTs [19, 34, 35] published between February and November 2021, of which one is a non-inferiority RCT [35]. Two RCTs were (partly) sponsored by the manufacturer (Endocyte, a Novartis company) [19, 34]. In contrast, the third RCT [35] did not report the sponsor.

3 RCTs zu 177Lu-PSMA-617 (Pluvicto®) in unterschiedlichen Dosen, als Mono- oder Kombinationstherapie im Vergleich zur Chemotherapie-freien Standardbehandlung oder zu Chemotherapie-Regimen

The 177Lu-PSMA-617 (Pluvicto®) was administered in different doses and combinations in all three RCTs. In one RCT, 7.4 GBq 177Lu-PSMA-617 plus standard care was administered every six weeks for a maximum of six cycles compared to standard care alone. The standard care included approved hormonal treatments, bisphosphonates, and radiation therapy, but no cytotoxic chemotherapy, systemic radioisotopes, immunotherapy, or investigational drugs when the trial was designed, e.g. Olaparib [34]. In the other two RCTs, 6.0-8.5 GBq 177Lu-PSMA-617 was administered once every six [19] or eight weeks [35] for a maximum of four [35] or six [19] cycles. The two RCTs com-

pared 177Lu-PSMA-617 to chemotherapy, namely Cabazitaxel (20 mg/m² every three weeks for up to 10 cycles) [19] or Docetaxel (75 mg/m² every three weeks for up to 10 cycles with 5 mg prednisone twice daily) [35].

primäre Endpunkte: OS & PFS (1 RCT), PSA-basierte Ansprechrate (2 RCTs)

The primary outcomes of one RCT were OS and PFS [34]. The primary outcome of the other two RCTs was the PSA response rate [19, 35]. One of the two RCTs was powered to test the non-inferiority of 177Lu-PSMA-617 over Docetaxel in terms of this primary outcome with a non-inferiority margin defined as the lower limit of the 95% confidence interval (CI) for the absolute difference in the outcome between the study groups not exceeding -15% [35]. Detailed definitions of the outcomes can be found in chapter 3.1.

1 RCT zu Chemotherapie-naiven Pat.

in allen 3 RCTs Pat. mit ECOG Status ≤2

All three RCTs included adult male patients with mCRPC. However, while the patients of two RCTs were previously treated with taxane regimes (e.g. Docetaxel) [19, 34], the third RCT only included chemotherapy-naïve patients [35]. Furthermore, while one RCT included patients with an estimated life expectancy of more than 12 weeks [19], another RCT considered patients with a life expectancy of at least six months [34]. In all three RCTs, only patients with an ECOG performance status of ≤2 at baseline were considered for inclusion [19, 34, 35].

3 RCTs mit 1.071 Pat.:

größtes RCT mit 831 Pat. → Adaption der ITT-Analyse (n=581)

kleinstes RCT mit 40 Pat.

The three RCTs included a total of 1,071 patients. The largest RCT considered 831 (551 vs 280) patients in the intention to treat (ITT-) analysis. However, approximately one year after the trial started (on March 5, 2019), enhanced trial-site education measures were implemented due to a high incidence of withdrawal from the trial in the control group. Based on these adaptions, 581 (385 vs 196) patients were considered for the modified ITT analysis [34]. Another RCT included 200 (99 vs 101) patients [19], and the third RCT included 40 (20 vs 20) patients in the ITT analysis. In the latter RCT, a per protocol (PP) sensitivity analysis was additionally conducted by including only those patients who underwent at least half of the allocated treatment, e.g. at least two cycles of 177Lu-PSMA-617 or at least five cycles of Docetaxel (15 vs 20 patients) [35].

ähnliches medianes Alter zwischen den Studiengruppen (Range: 68-72 Jahre)

The median age of the patients receiving 177Lu-PSMA-617 ranged from 68 [35] to 72.1 years [19] and from 68 [35] to 70.0 years [34] for the control groups. In all three RCTs, at least 50% of the patients had a Gleason score of ≥8, and the majority had an ECOG performance status of 0 or 1 in both study groups [19, 34, 35].

ähnliches Follow-up in 2 RCTs (Range: 18,4-20,3 Monate); medianes Follow-up im 3. RCT nicht berichtet

The median follow-up was similar in two RCTs, with 18.4 [19] and 20.3 months [34]. The loss to follow-up in the two RCTs ranged from two [19] to four patients [34] in the 177Lu-PSMA-617 group and from four [34] to 17 patients [19] in the standard care or Cabazitaxel group, respectively. The follow-up duration and loss to follow-up were not reported in the third RCT [35]. In all RCTs, eleven (9 vs 2) patients [19], 496 (329 vs 167) patients [34] and 4 (3 vs 1) patients [35] discontinued the trial due to death.

alle 3 RCTs haben hohes Verzerrungsrisiko

Overall, the three RCTs were rated as having a high RoB (see chapter 4 and Table A-2 in the Appendix).

Detailed study and patient characteristics are displayed in Table A-1.

3.3 Results

Mortality

Mortalität:

The basis for assessing mortality built the outcome OS.[3]

1 RCTs berichtete OS (n=831): s.s. Unterschied von 15,3 vs. 11,3 Monate, HR 0,62

Only one of the three included RCTs [34] reported OS defined as a primary outcome. The study showed a statistically significant difference in OS in the ITT analysis (n=831, hazard ratio [HR] 0.62, 95% CI, 0.52-0.74, p<0.001). The median OS was longer in the 177Lu-PSMA-617 plus standard care group than in standard care alone (15.3 vs 11.3 months). In the adapted ITT analysis (n=581), the median OS was also longer in the 177Lu-PSMA-617 group plus standard care group (14.6 vs 10.4 months, HR 0.63, 95% CI, 0.51-0.79, p=not reported).

Morbidity

Morbidität:

The basis for assessing morbidity built the outcomes PFS, PSA-PFS, ORR, PSA-response and time to first skeletal event.[4]

1 RCTs (n=581) berichtete s.s. Unterschied bzgl. PFS: 8,7 vs. 3,4 Monate, HR 0,40

2 RCTs (n=280) zeigten keinen s.s. Unterschied zwischen 177Lu-PSMA-617 & Chemotherapie

The median PFS was reported in all three RCTs; however, it was only reported as a primary outcome in one study [34]. For the modified ITT analysis (n=581), a statistically significant difference in the median PFS was reported favouring the 177Lu-PSMA-617 plus standard care group compared to the standard care alone group (8.7 vs 3.4 months, HR 0.40, 99.2% CI 0.29-0.57, p<0.001). For the original ITT analysis (n=831), the median PFS was also longer for the 177Lu-PSMA-617 plus standard care group, and the difference was statistically significant (8.8 vs 3.6 months, HR 0.43, 99.2% CI 0.32-0.58, p=not reported) [34]. In the two other RCTs (n=240) [19, 35], the median PFS was similar between the 177Lu-PSMA-617 and the Cabazitaxel group (n=200: 5.1 vs 5.1 months, p=not reported [19]) or Docetaxel group (n=40: 4.0 vs 4.0 months, p=0.98 [35]).

1 RCT (n=200) berichtete s.s. Unterschied bzgl. PSA-PFS: HR 0,60

PSA-PFS was reported in only one RCT as a secondary outcome [19]. The study (n=200) reported a statistically significant difference in PSA-PFS between the 177Lu-PSMA-617 group and the Catazitaxel group (difference not reported, HR 0.60, 95% CI 0.44-0.83, p=0.0017).

3 RCTs berichteten ORR, nur 1 RCT (n=200) zeigte s.s. Unterschied nach 18,4 Monaten: 49 % vs. 24 %, RR 2,12

ORR and disease control were reported in all three RCTs as a secondary outcome; however, only one RCT (n=200) reported a statistically significant difference in the ORR favouring the 177Lu-PSMA-617 group compared to the Cabazitaxel group after a median of 18.4 months (49% vs 24%, relative risk [RR] 2.12, 95% CI 1.10-4.08, p=0.019) [19]. In another RCT (n=248), 17 patients (9.2%) in the 177Lu-PSMA-617 plus standard care group reached a CR, while none in the standard care alone group. Similarly, more patients in the 177Lu-PSMA-617 plus standard care group did achieve a PR (77 [41.8%] vs 2 [3.1%]) after a median of 20.3 months [34]. In the third RCT (n=40) [35], the number of patients showing the best ORR was similar between the 177Lu-PSMA-617 and the Docetaxel group (5 [39%) vs 6 [32%], with a difference of 7%, 95% CI -24-28, p=0.69)[7].

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[3] **D0001** – What is the expected beneficial effect of 177Lu-PSMA-RLT on mortality?

[4] **D0005** – How does 177Lu-PSMA-RLT affect symptoms and findings (severity, frequency) of mCRPC? &
D0006 – How does 177Lu-PSMA-RLT affect progression (or recurrence) of mCRPC?

All three RCTs also reported on the PSA response rate. Two RCTs defined it as a primary outcome [19, 35]. One of the two RCTs (n=200) reported a statistically significant difference in the PSA-response rate favouring the 177Lu-PSMA-617 group compared to the Cabazitaxel group after a median of 18.4 months (65 [66%] vs 37 [37%], difference 29%, 95% CI 16-42, p<0.0001) favouring the 177Lu-PSMA-617 group. In the second RCT (n=40), in the PP-analysis (n=35), the study showed non-inferiority of 177Lu-PSMA-617 compared to Docetaxel regarding the PSA response rate because the lower CI was greater than the specified non-inferiority margin of -15% (9 [60%] vs 8 [40%], difference 20%, 95% CI -12-47, p=0.25)[7] [35]. The third RCT (n=431) defined the PSA response as a secondary outcome. After a median of 20.3 months, more patients in the 177Lu-PSMA plus standard care group compared to patients with standard care alone reached a confirmed decrease in PSA by more than 50% (177 [46.0%] vs 14 [7.1], odds ratio [OR] 11.19, 95% CI 6.25-20.04) and by more than 80% (127 [33.0%] vs 4 [20.0%], OR 23.62, 95% CI 8.57-65.11). However, the differences between the study groups were not statistically significant [34].

1 RCT (n=200) berichtete s.s. Unterschied bzgl. PSA-RR nach 18,4 Monaten: 66 % vs. 37 %

1 RCT (n=35) zeigte Nichtüberlegenheit von 177Lu-PSMA-617 im Vergleich zu Docetaxel in Bezug auf PSA-RR

Only one of the three RCTs (n=581) reported the time to first symptomatic skeletal event or death, defined as a secondary outcome. The time to first symptomatic skeletal event or death was statistically significantly higher in the 177Lu-PSMA-617 plus standard care group compared to the standard care alone group (11.5 vs 6.8 months, HR 0.50, 95% CI 0.40-0.62, p<0.001) [34].

1 RCT (n=581) berichtete s.s. Unterschied bzgl. Zeit bis zum ersten skelettalen Symptom: 11,8 vs. 6,8 Monate, HR 0,50

Health-related quality of life and function

The outcome HRQoL was reported in all three RCTs as a secondary outcome using four different questionnaires:[5]

HRQoL mit 4 Fragebögen erhoben:

In one RCT (n=176), the HRQoL was measured by the EORTC-QLQ-C30 after 51 weeks. The study did not identify a statistically significant difference in the mean global health status scores between the 177Lu-PSMA-617 and Cabazitaxel groups (mean global score: 63 vs 60, p=0.20). However, statistically significant improvements favouring the 177Lu-PSMA-617 group were reported for the sub-domains “social functioning” (score: 79 vs 73, p=0.030), “diarrhea” (9 vs 16, p<0.0001), “fatigue” (34 vs 40, p=0.027) and “insomnia” (23 vs 29, p=0.023) [19].

1 RCT (n=176) zeigte s.s. Unterschiede bzgl. 4 Sub-Domänen nach 51 Wochen im Vergleich zur Chemotherapie

In another RCT (n=581), the HRQoL was assessed with the FACT-P and the BPI-SF questionnaires. The study reported that the time to deterioration in the FACT-P total score – indicating a deterioration in the HRQoL – was statistically significantly longer in the 177Lu-PSMA-617 plus standard care group compared to the standard care alone group (5.7 vs 2.2 months, HR 0.54, 95% CI 0.45-0.66, p=not reported). Similarly, the study showed that the time to deterioration in the BPI-SF total score – indicating a deterioration in pain levels and overall functioning – was statistically significantly longer in the 177Lu-PSMA-617 plus standard care group (5.9 vs 2.2 months, HR 0.52, 95% CI 0.43-0.63, p=not reported) [34].

1 RCT (n=581) berichtete s.s. längere Dauer bis HRQoL & Schmerz-Verschlechterung in Pat. mit 177Lu-PSMA-617 + Standardbehandlung

[5] **D0011** – What is the effect of 177Lu-PSMA-RLT on patients’ body functions? &
D0012 – What is the effect of 177Lu-PSMA-RLT on generic health-related quality of life? &
D0013 – What is the effect of 177Lu-PSMA-RLT on disease-specific quality of life? &
D0016 – How does the use of 177Lu-PSMA-RLT affect activities of daily living?

1 RCT (n=35) zeigte s.s. Unterschied in der Gesamtscore und in 3 Sub-Domänen 12 Wochen nach dem 1. Therapiezyklus, jedoch keine absoluten & relativen Unterschiede

In the third RCT (n=35), the HRQoL was measured using the NCCN-FACT-FPSI-17 questionnaire 12 weeks after the first treatment cycle. The PP analysis showed a statistically significant improvement in the median total score, favouring the 177Lu-PSMA-617 group compared to the Docetaxel group ($p<0.01$). Further, statistically significant differences favouring the intervention were reported for three of the four sub-domains, including physical functioning ($p=0.02$), emotional functioning ($p=0.04$) and treatment side effects ($p<0.01$). The study did not report absolute or relative differences [35].

keine Evidenz zur allgemeinen Lebensqualität

None of the included RCTs reported on the critical outcome generic QoL.

Patient safety

unerwünschte Ereignisse:

The basis for assessing patient safety built the outcomes treatment-related deaths, grade 3-4 AEs and AE-related discontinuation.[6]

1 RCT (n=183) berichtete keine Therapie-bedingten Todesfälle

in 2 RCTs (n=774) starben etwas mehr Pat. in der 177Lu-PSMA-617 (+ Standardbehandlung) Gruppe

All three included RCTs [19, 34, 35] reported treatment-related deaths as a secondary outcome. In one RCT (n=183), no treatment-related deaths were reported in the study groups after a median of 18.4 months [19]. In contrast, another RCT (n=734) reported five treatment-related AEs (0.9%) (two pancytopenias, one bone-marrow failure, one subdural hematoma and one intracranial hemorrhage) in the 177Lu-PSMA-617 plus standard care group after a median of 20.3 months but no treatment-related deaths in the standard care alone group [34]. In the third RCT (n=40), three patients (10%) in the 177Lu-PSMA-617 group and 1 (5%) in the Docetaxel group developed persistent grade 4 thrombocytopenia that led to treatment-related deaths [35].[7]

2 RCTs (n=223) berichteten weniger Grad ≥3 AEs in 177Lu-PSMA-617- vs. Chemotherapie-Gruppen

1 RCT (n=734) zeigte mehr Grad ≥3 AEs in Pat. mit 177Lu-PSMA-617 + Standardbehandlung

All three RCTs reported grade 3-4 AEs as a secondary outcome. In one RCT (n=183), fewer grade 3-4 AEs were reported in the 177Lu-PSMA-617 group compared to the Cabazitaxel group (32 [33%] vs 45 [53%]) after a median follow-up of 18.4 months [19]. In contrast, in the other RCT (n=734), more grade 3-4 AEs were reported in 177Lu-PSMA-617 plus standard care group compared to the standard care alone group (279 [52.7%] vs 78 [38.0%]) after a median of 20.3 months. In addition, the same study reported more drug-related grade 3-4 AEs in the 177Lu-PSMA-617 group (150 [28.4%] vs 8 [3.9%]) and more drug-related grade 3-4 SAEs (43 [8.1%] vs 5 [2.4%]) [34]. Both studies did not show a statistically significant difference in grade 3-4 AEs between the study groups. The third RCT (n=40) reported fewer treatment-emergent grade 3-5 AEs in the 177Lu-PSMA-617 group compared to the Docetaxel group; however, the difference was also not statistically significant (6 [30%] vs 10 [50%], difference 20%, 95% CI -10-45, $p=0.20$)[7] [35].

3 RCTs berichteten inkonsistente Abbruchquoten aufgrund von unerwünschten Ereignissen

Also, all three RCTs reported AE-related treatment discontinuation as a secondary outcome. In one RCT (n=183), the AE-related discontinuation rate was slightly lower in the 177Lu-PSMA-617 group compared to the Cabazitaxel group after a median follow-up of 18.4 months (1 [1%] vs 3 [4%]) [19], while it was minimally higher in another RCT (n=40) compared to Docet-

[6] D0003 – What is the effect of 177Lu-PSMA-RLT on the mortality due to causes other than mCRPC? &
C0008 – How safe is 177Lu-PSMA-RLT in comparison to the comparators? &
C0004 – How does the frequency or severity of harms change over time or in different settings? &
C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of 177Lu-PSMA-RLT?

[7] The follow-up time was not reported for this outcome in the Satapathy trial.

axel group (grade ≥3 AEs leading to discontinuation: 2 [10%] vs 1 [5%])[7] [35]. The third RCT (n=734) reported that 63 patients (11.9%) and 37 patients (7.0%) discontinued 177Lu-PSMA-617 therapy due to any AEs and grade ≥3 AEs, respectively, after a median follow-up of 20.3 months. In contrast, 45 patients (8.5%) of 177Lu-PSMA-617 plus standard care and 16 patients (7.8%) of the standard care group discontinued standard care due to any AEs. So did 25 patients (4.7%) of 177Lu-PSMA-617 plus standard care and 12 patients (5.9%) of the standard care group due to grade ≥3 AEs [34].

4 Certainty of evidence

Verzerrungsrisiko mit Cochrane RoB V.2 bewertet

The RoB for the included RCTs was assessed with the Cochrane RoB tool version 2 [28]. All three RCTs [19, 34, 35] were ranked as having a high RoB. The main reason for the high RoB in the RCTs was the open-label design in all three studies. Furthermore, there were missing outcomes in one RCT [19], as HRQoL and safety data were not reported for all patients. Besides, the third RCT did not report its sponsorship [35]. In addition, it was unclear in the RCT at which follow-up the safety data was assessed. The detailed RoB assessment is presented in Table A-2.

RCTs mit hohem Verzerrungsrisiko aufgrund des open-label Studiendesigns, fehlenden Daten, etc.

Vertrauenswürdigkeit der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE scheme for each endpoint individually. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [29].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

sehr niedrige bis moderate Vertrauenswürdigkeit der Evidenz zur Wirksamkeit; niedrige Vertrauenswürdigkeit der Evidenz zur Sicherheit

Overall, the certainty of the evidence for the efficacy of 177Lu-PSMA-617 as monotherapy or in combination with standard care compared to standard care or chemotherapy was rated as very low to moderate. The certainty of the evidence for safety was rated as low. No evidence was available to compare 177Lu-PSMA as monotherapy or combination therapy with radiopharmaceuticals or PARP inhibitors.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and the evidence profile in Appendix Table A-3.

Table 4-1: Summary of findings table of Lu177-PSMA-617 as monotherapy or combination therapy in patients with metastatic castration-resistant prostate cancer

Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of participants	Certainty	Comments
Efficacy					
Overall survival	**ITT:** 15.3 vs 11.3, p<0.001 **ITT[e]:** 14.6 vs 10.4, p=NR	**ITT:** HR 0.62 (0.52-0.74) **ITT[e]:** HR 0.63 (0.51-0.79)	**1 RCT** [34]: **ITT:** 831 **ITT[e]:** 385	Moderate[b,c]	Median overall survival 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** [19]: 176/200 (88%)	Low[f,g,h]	**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** [34]: **ITT[e]:** 385	Low[c,f]	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 177Lu-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** [35]: **PP:** 35	Very low[f,I,j]	Assessed with the **NCCN-FACT-FPSI**: a higher score indicates better HRQoL.
Progression-free survival	■ **177Lu-PSMA-617 vs Cabazitaxel (n=200):** 5.1. vs 5.1, HR NR, p=NR ■ **177Lu-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 ■ **177Lu-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** [19, 34, 35]: 1,071	Low[c,f,k]	Median progression-free survival in months.
Safety					
Treatment-related deaths	n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel (n=183):** 0 (0) vs 0 (0) ■ **177Lu-PSMA-617 & standard care vs standard care (n=734):** 5 (0.9)[m] vs 0 (0) ■ **177Lu-PSMA-617 vs Docetaxel (n=40):** 2 (10) vs 1(5)[n,o]		**3 RCTs** [19, 34, 35]: 957	Low[c,f,l]	Number of grade 5 treatment-related AEs according to CTCAE.
Grade 3-4 adverse events	Any AEs, n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel (n=183):** 32 (33) vs 45 (53) ■ **177Lu-PSMA-617 & standard care vs standard care (n=734):** 279 (52.7) vs 78 (38.0) Treatment-related AEs, n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel (n=183):** NR ■ **177Lu-PSMA-617 & standard care vs standard care (n=734):** 150 (28.4) vs 8 (3.9) Treatment-related SAEs, n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel (n=183):** NR ■ **177Lu-PSMA-617 & standard care vs standard care (n=734):** 43 (8.1) vs 5 (2.4)		**2 RCTs** [19, 34]: 917	Low[c,f]	Any and treatment-related AEs according to CTCAE.
	n (%): 6 (30) vs 10 (50), p=0.20	Difference: 20% (-10-45)	**1 RCT** [35][o]: **ITT:** 40	Low[f,p]	Treatment-emergent AEs grades 3-5[Q] according to CTCAE.

Abbreviations: AE – adverse events, BPI-SF – Brief Pain Inventory-Short Form, CI – confidence interval, CTCAE – Common Terminology Criteria for Adverse Events, 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-Prostate Symptom Index-17 Questionnaire, NR – not reported, PP – per protocol, RCT – randomised controlled trial, s.s. – statistically significant

Explanations:

[b] *Considering the ITT analysis and overall survival as the outcome will not be affected by the "open-label" study design.*

[c] *The control group of one RCT received standard care without cytotoxic chemotherapy (e.g. Cabazitaxel), which is one of the standard care for this patient group according to guidelines [36].*

[e] *After the trial started (May 29, 2018), a high incidence of withdrawal from the trial (56%) was noted in the control group at specific sites due to patient disappointment. On March 5, 2019, enhanced trial-site education measures were implemented to reduce the incidence of withdrawal.*

[f] *Open-label trial.*

[g] *Missing data.*

[h] *Reporting bias for certain domains of the EORTC-QLQ-C30 expected.*

[i] *Reporting bias as only the PP analysis was reported.*

[j] *The study did not report absolute or relative differences.*

[k] *The effect in the intervention group was higher in one RCT than the other, probably because of the combination therapy.*

[l] *The outcome results were different in the three RCTs.*

[m] *Pancytopenia, n=2; bone-marrow failure, n=1; subdural hematoma, n=1; intracranial hemorrhage, n=1.*

[n] *Persistent grade 4 thrombocytopenia leading to treatment-related deaths.*

[O] *The follow-up time was not reported.*

[p] *Wide confidence intervals.*

[Q] *The study did not report treatment-related adverse events as grades 3-4 but 3-5.*

5 Discussion

In 2021, the first published RCTs assessed the efficacy and safety of 177Lu-PSMA-617 as monotherapy or combination therapy compared to standard treatments. These RCTs initiated the present re-assessment of the evidence on 177Lu-PSMA-RLT. Overall, this update report captures evidence from three RCTs. In two RCTs [19, 35], 177Lu-PSMA-617 was compared to chemotherapy, namely Cabazitaxel [19] and Docetaxel [35]. The third RCT [34] compared 177Lu-PSMA-617 plus standard care to standard care alone, based on which the FDA (US-American) and EMA (European) approved 177Lu-PSMA-617 (Pluvicto®) for mCRPC [14, 15].

Veröffentlichung der ersten RCTs zu 177Lu-PSMA-RLT (n=3) veranlasste Re-Assessment der Evidenz

Summary of the main findings

The overall certainty of the evidence was rated as very low due to high indirectness (the control group of one RCT did not fully reflect the standard care according to guidelines), imprecision (e.g. wide confidence intervals), and RoB (e.g. open-label study design and missing outcomes).

Vertrauenswürdigkeit der gesamten Evidenz sehr niedrig & hohes Verzerrungsrisiko

Efficacy: One of the three RCTs (n=831) [34] showed a statistically significant difference in the critical outcomes OS, PFS and HRQoL, favouring 177Lu-PSMA-617 plus standard care arm over the standard care alone arm. Another RCT (n=40) also showed a statistically significant difference in HRQoL, favouring the study group receiving 177Lu-PSMA-617 compared to chemotherapy. However, the study did not report absolute or relative differences [35]. The third RCT (n=176) [19] reported statistically significant HRQoL improvements, favouring the 177Lu-PSMA-617 compared to the chemotherapy group, for the sub-domains "social functioning", "diarrhea", "fatigue" and "insomnia". None of the included RCTs reported on the critical outcome generic QoL.

1 RCT: s.s. Unterschiede bzgl. OS & PFS

2 RCTs: s.s. Unterschied bzgl. HRQoL & 1 RCT s.s. Unterschiede in 4 Sub-Domänen

Safety: No statistically significant difference in the critical outcomes of treatment-related deaths and grade ≥3 AEs were reported in the included RCTs. While one RCT (n=183) [19] reported no treatment-related deaths in any study group, the other two RCTs (n=774) reported slightly more treatment-related deaths in the 177Lu-PSMA-617 plus standard care versus the standard care alone group [34] and the 177Lu-PSMA-617 monotherapy group compared to the Docetaxel group [35]. Regarding grade ≥3 AEs, fewer AEs were reported in 177Lu-PSMA-arm compared to chemotherapy (n=223) [19, 35], but more grade ≥3 AEs occurred in the 177Lu-PSMA-617 plus standard care group versus the standard care alone group [34].

3 RCTs: keine s.s. Unterschiede bzgl. Grad ≥3 AEs: weniger AEs im Vergleich zu Chemotherapie, aber mehr als bei der Standardbehandlung ohne Chemotherapie

Interpretation of the findings

The three included RCTs differ regarding the study population, intervention and comparators.

3 RCTs mit Unterschiede in der Population, Intervention & den Komparatoren:

Two RCTs [19, 34] included mCRPC patients pre-treated with androgen receptor pathway inhibitors and taxane-based chemotherapy. In contrast, the third RCT [35] assessed the non-inferiority of 177Lu-PSMA-617 in terms of efficacy and safety in chemotherapy-naïve mCRPC patients, which presents the administration of 177Lu-PSMA-RLT in a different treatment line than currently approved by the FDA and EMA.

2 RCTs zu vorbehandelten Pat. vs. 1 RCT zu Chemotherapie-naiven Pat. (≠ EMA-Zulassung)

2 RCTs verglichen 177Lu-PSMA-617 mit Chemotherapie

1 RCT: 177Lu-PSMA-617 plus Standardbehandlung → gewählte Standard-behandlung nicht Best Practice

Regarding both interventions and comparators of the included studies, two RCTs [19, 35] compared 177Lu-PSMA-617 monotherapy to chemotherapy, namely Cabazitaxel and Docetaxel. On the other hand, the one RCT [34] evaluated 177Lu-PSMA-617 in combination with standard care versus standard care alone. The standard care included but was not restricted to, approved hormonal treatments (e.g. Abiraterone or Enzalutamide), bisphosphonates, radiation therapy, Denosumab and glucocorticoid at any dose, but not cytotoxic chemotherapies (e.g. Cabazitaxel or Docetaxel), systemic radioisotopes, immunotherapies and investigational drugs, such as Olaparib. However, this standard of care is considered suboptimal: On the one hand, patients in the control group were enrolled and allocated to the abovementioned standard of care, which presents the same treatment under which they had already experienced disease progression [36]. On the other hand, some patients eligible for chemotherapy did not receive the best available care outside the trial setting [36].

1 RCT: OS & PFS als primäre Endpunkte, OS-Vorteil klinisch relevant; 2 RCTs: primärer Endpunkt nicht entscheidungsrelevant

Regarding the outcomes of the studies, one RCT [34] was powered for two primary endpoints, namely OS and PFS, that were considered critical for deriving a reimbursement recommendation. According to the Magnitude of Clinical Benefit Scale (MCBS) of the European Society for Medical Oncology (ESMO), the OS benefit of 177Lu-PSMA-617 combination therapy was rated as a substantial magnitude of clinical benefit (score 4) [37]. In the other two RCTs, the PSA response rate was the primary endpoint, considered a surrogate endpoint for disease progression and not highly relevant for a recommendation [19, 35].

1 RCT berichtete s.s. Unterschied bzgl. HRQoL, jedoch nur für kurzen Nachbeobachtungszeitraum

HRQoL, another critical endpoint, was measured in all three RCTs using different questionnaires, affecting the ability to compare the HRQoL results between the studies. One RCT [35] that reported a statistically significant difference in overall HRQoL only assessed it for a short follow-up period (12 weeks after the first treatment cycle). In addition, because no absolute difference in the HRQoL scores was reported, it remained unclear whether the difference was clinically relevant.

mehr Grad ≥3 AEs in Pat. mit 177Lu-PSMA-617 + Standardtherapie aufgrund der selbstlimitierenden Effekte, der Kombinationstherapie bzw. des Komparators erklärbar

Unexpectedly, in one included RCT [34], more grade ≥3 AEs were reported in the 177Lu-PSMA-617 plus standard care group compared to the standard care alone group (n=734). One reason could be the self-limited toxic effects of 177Lu-PSMA-RLT, including, e.g. xerostomia, xerophthalmia, fatigue, thrombocytopenia, anaemia, gastrointestinal upset and arthralgia. These toxic effects can be explained by the normal distribution of PSMA in the duodenal and jejunal brush border and the salivary or lacrimal glands [38]. Moreover, the higher grade ≥3 AE rate might be caused by the combination with standard care. Finally, the higher number of grade ≥3 AEs in the intervention group could also be because the control group did not receive chemotherapy as part of the usual standard care that is known to be associated with various AEs [39].

Nachbeobachtungs-zeiträume der Studien entsprechen der geschätzten Lebenserwartung von mCRPC Pat.

Concerning the follow-up durations of the included RCTs, the reported median duration of two RCTs (range: 18.3 to 21.0 months) can be considered suitable as they align with the estimated mean survival of mCRPC patients [19, 34]. It is reported historically as a range of nine to 39 months, varying according to the extent of metastases and symptoms [40]. The third RCT [35] did not report the median follow-up duration.

In terms of external validity, the generalisability of the study results to the Austrian context can be assumed, as the largest RCT (n=831) included was conducted as a multicenter study in different geographical regions (Netherlands, Germany, United Kingdom, Denmark, Sweden, France, Switzerland, Canada, Belgium, Puerto Rico, and the United States of America). However, it needs to be considered that in all three RCTs, only patients with an ECOG performance status of ≤2 at baseline were included. This might not be fully applicable to the clinical practice, as there, potentially also patients with higher performance status scores, could receive 177Lu-PSMA-RLT. Further aspects of the applicability of the included studies are summarised in the Appendix (see Table A-4).

Studienergebnisse generell auf österreichischen Kontext übertragbar, jedoch Studienpopulation möglicherweise „gesünder" als in klinischer Praxis

Existing evidence

The results of this systematic review are mostly aligned with the results from two other recent systematic reviews:

Einbettung in bestehendes Wissen:

The results of the present systematic review align with a systematic review [41] that followed less stringent inclusion criteria regarding the study design. It also included retrospective and prospective single-arm studies next to RCTs. Overall, it considered 69 papers with a total of 4,157 patients. At its publication, only two RCTs were available [19, 34]. The authors concluded that PSMA-targeted RLT resulted in a higher proportion of patients responding to therapy based on a ≥50% PSA decline compared to controls. Furthermore, data showed survival prolongation after PSMA-targeted RLT. Safety data and funding of the study were not reported.

1 SR mit weniger strikten Einschlusskriterien bzgl. Studiendesign: ähnliche Ergebnisse zum PSA-Rückgang & der Lebensverlängerung

Another systematic review [42] about the effectiveness of different third-line therapies in patients with mCRPC supported these results. The systematic review included seven RCTs with 3,958 patients and eight third-line treatments (Mitoxantrone, Ixapiletone, Cabazitaxel in two different doses, previous treatment with Abiraterone or Enzulatumide, BSC and PSMA-targeted RLT). The review concluded that treatment with PSMA-targeted RLT resulted in a 1.3-times-higher rate of median PSA decline ≥50% than treatment with Abiraterone, Enzalutamide, Mitoxantrone, or Cabazitaxel (p=0.00001). Regarding safety, PSMA-targeted RLT resulted in more severe thrombocytopenia but less often in severe leukopenia than Cabazitaxel. The study had no funding to disclose.

1 weiterer SR verglich mehrere 3. Linien-Therapien für mCRPC & bestätigte ebenfalls einen deutlichen PSA-Rückgang durch 177Lu-PSMA-RLT

Besides, Lu177-PSMA-RLT is not yet recommended in clinical guidelines, such as the NCCN guideline (last update 2019) [43], the ESMO guideline (last update 2020) [8] and the S3 guideline for prostate cancer (last update 2021) [44]. However, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a draft of the reimbursement recommendation about 177Lu-PSMA-617 for adult pre-treated PSMA-positive mCRPC in February 2023 [45].

Februar 2023: vorläufige Refundierungsentscheidung von kanadischem Institut veröffentlicht

Practical implications

All three included RCTs [19, 34, 35] assessed the efficacy and safety of the approved Novartis product, 177Lu-PSMA-617 (Pluvicto®). The costs of one solution of it are expected to be around 45,657 US dollars [46]. To save costs, some radiopharmaceutical units also synthesise the radionuclide (177Lu) with a PSMA-ligand (e.g. PSMA-617 or PSMA-I&T) according to in-house standards. Such "self-synthesised" radiopharmaceuticals have no marketing authorisation and can only be dispensed within specific legal frameworks. In

177Lu-PSMA-617 (Pluvicto®) mit hohen Kosten verbunden; es gibt Ausnahmeregelungen für nicht zugelassene RLTs gemäß § 8 AMG

Austria, they can be dispensed according to the exemption provision § 8 of the Austrian pharmaceutical law. This states that non-approved therapeutic options, such as in-house productions, can only be applied when approved diagnostic and therapeutic options have been exhausted, are out of the question for medical reasons, are unavailable, or for closing a gap in supply [47].

aktuell gibt es keine abgeschlossenen RCTs zur Wirksamkeit & Sicherheit von solchen in-house Synthesen von 177Lu mit PSMA-Liganden, jedoch einige einarmige Studien

To date, there are no completed RCTs about the efficacy and safety of such in-house-produced 177Lu-PSMA-RLTs; however, there are several single-arm studies from Europe (5 publications) [12, 48-51], Asia (n=8) [52-59] and Australia (n=3) [60-62]. With a focus on the European studies, the studies showed that the 177Lu was synthesised with the PSMA-617 ligand from ABX GmbH (Radeberg, Germany) or the PSMA-I&T from Scintomics Molecular, Applied Theranostics Technologies GmbH, Fuerstenfeldbruck, Germany. The studies showed a PSA response in 50% to 79% of the patients and that the most frequently reported grade ≥3 AEs were leukocytopenia, anaemia and lymphopenia. No RLT-related deaths were reported.

neben den Kosten für die RLT müssen weitere Kosten berücksichtigt werden, z. B. Schulungen, spezielles Equipment & Krankenhausaufenthalt

alternatives, ambulantes Setting könnte Kosten einsparen & Kapazitätsengpässe vorbeugen

Next to the costs for the RLT itself, the administration of 177Lu-PSMA-RLT has further economic implications that need to be considered, e.g. specialised personnel training and specific nuclear equipment [45]. In many countries and most available studies, 177Lu-PSMA-RLT is administered in an inpatient setting following radiation protection specifications, including hospitalisation in a controlled area for up to three days after the administration. A German supply analysis showed that in 2018, there were approximately 754 hospital beds (234,000 treatment days) available for nuclear medicine across Germany. The mCRPC population required a bed capacity of approximately 77,000 treatment days. Given the recent marketing approval of 177Lu-PSMA-617 (Pluvicto®) in Europe, capacity limits of nuclear hospital beds are expected to be reached or even exceeded in many countries, especially in rural areas [63]. One option to deal with these limited capacities is administering the intervention in an outpatient setting. As the patient-specific radiation dose of 177Lu-PSMA-RLT decreases below 25 µSv per hour after the administration at a one-meter distance, the intervention can also be applied in the outpatient setting. Patient education is essential in an outpatient setting, including warnings to stay away from children and pregnant women for approximately three days after the administration and clarifying specific hygiene rules to avoid contamination (e.g. daily showering). For example, in Austria and Australia, 177Lu-PSMA-RLT can also be applied in the outpatient setting [64].

Ongoing studies

zahlreiche laufende RCTs zu unterschiedlichen Indikationen & 177Lu-PSMA-RLT-Typen:

PSMA-targeted RLTs are an evolving treatment area for patients with PSMA-positive PC. Hence, several ongoing RCTs assess the efficacy and safety in different patient populations.

8 RCTs zu mCRPC Pat.:

Eight ongoing RCTs are assessing the efficacy and safety of different 177Lu-PSMA-RLTs as monotherapy or combination therapy compared to different standard therapies in patients with mCRPC – the population considered for the present systematic review:

3/8 RCTs zu 177Lu-PSMA-617 als Monotherapie im Vergleich zu ARDT oder Docetaxel

- Three of the eight RCTs (NCT04689828, NCT05658003, NCT04663997) evaluate **177Lu-PSMA-617** monotherapy compared to androgen receptor-directed therapy (ARDT) or Docetaxel. In all three RCTs, the primary endpoint is (radiographic) PFS. The primary completion date of two RCTs (NCT04663997, NCT05658003) is expected to be completed in 2024 and 2026, respectively. The primary completion date

of the third RCT (NCT04689828) was already in 2022, but no data has been published yet at the time of writing this report.

- Two ongoing RCTs (NCT04647526, NCT05204927) compare **177Lu-PSMA-I&T** monotherapy to either Abiraterone (with Prednisone) or Enzalutamide. Both studies have (radiographic) PFS as their primary endpoint. Their expected primary completion date lies between 2023 and 2024.

2/8 RCTs zu 177Lu-PSMA-I&T als Monotherapie im Vergleich zu Abiraterone oder Enzalutamide

- The remaining three ongoing RCTs did not specify the PSMA-targeting small-molecule inhibitors under investigation as a monotherapy compared to Docetaxel in 40 patients (CTRI/2019/12/022282) or as combination therapies, namely 177Lu-PSMA plus Enzalutamide versus Enzalutamide in 160 patients (NCT04419402) and 177Lu-PSMA plus Stereotactic Ablative Body Radiotherapy (SABR) versus SABR in 92 patients (NCT05560659). The studies' primary endpoints are PFS, PSA-PFS and PSA response rate. For one RCT (NCT04419402), the primary completion date was expected in 2022, but no data has been published.

3/8 RCTs zu 177-PSMA (ohne Angabe zum Ligand) als Monotherapie im Vergleich zu Docetaxel oder in Kombination mit Enzalutamide bzw. SABR im Vergleich zu Enzalutamide oder SABR alleine

Besides, five ongoing RCTs are assessing the efficacy and safety of different 177Lu-PSMA-RLTs as monotherapy or combination therapy in another evolving population, namely metastatic hormone-sensitive prostate cancer (mHSPC) patients:

5 RCTs zu Pat. mit metastasierender hormonsensitiver Form (mHSPC):

- One ongoing RCT (NCT04720157) assesses **177Lu-PSMA-617** as monotherapy compared to ARCT plus androgen deprivation therapy (ADT). The primary endpoint of this study is radiographic PFS, and the study completion date is in 2024. This study might be submitted to EMA for an indication extension of 177Lu-PSMA-617.

1/5 RCTs zu 177Lu-PSMA-617 als Monotherapie vs. ARCT + ADT

- Another ongoing RCT (NCT05496959) investigates **177Lu-PSMA-I&T** plus SBRT compared to SBRT alone. The primary endpoint of this study is the PSMA-based PFS, and the primary completion date is expected in 2024.

1/5 RCTs zu 177Lu-PSMA-I&T in Kombination mit SBRT vs. SBRT alleine

- The remaining three ongoing RCTs did not specify the PSMA-molecule they are investigating either as monotherapy compared to Abiraterone with Prednisolone (CTRI/2020/10/028341) and to ADT (NCT04443062) or as a combination with Docetaxel compared to Docetaxel alone (NCT04343885). These studies will assess PSA response and disease progression as their primary endpoints. All three RCTs are expected to be completed between 2023 and 2024.

3/5 RCTs zu 177Lu-PSMA (ohne Angabe zum Ligand) als Monotherapie oder in Kombination mit Docetaxel

Overall, the ongoing RCTs will shed more light on the efficacy and safety of different 177Lu-PSMA-RLTs as monotherapy or combination therapies for different pre-treated populations (mCRPC and mHSPC) compared to different standard treatments, including chemotherapy. However, none of the identified ongoing studies defined OS or HRQoL as the primary outcome. Detailed information about the ongoing RCTs is presented in Table A-5 in the Appendix.

keine der laufenden RCTs haben OS oder HRQoL als primären Endpunkt definiert

Next to the ongoing studies is the completed three-year follow-up of the TheraP trial [19]. However, at the time of writing this report, only the abstract was available. First insights into the results of the extended follow-up show that OS was similar in 177Lu-PSMA-617 versus Cabazitaxel groups after a median follow-up of three years (19.1 vs. 19.6 months, difference -0.5, 95% CI -3.7 to + 2.7). No additional safety signals were reported for the longer follow-up [65].

zusätzlich sind die Ergebnisse des 3-Jahres-Follow-up der TheraP Studie (inkl. OS-Daten) bald zu erwarten

Limitations of the report

nur RCTs eingeschlossen & z. B. große Registerstudien nicht berücksichtigt

The results of this review should also be seen in the context of its limitations. We excluded non-randomised controlled trials and registry studies and included RCTs as the best available evidence, which aligns with standard methodologies [64]. Excluding non-randomised and registry studies is not expected to affect the conclusion of this report, as proven in other systematic reviews mentioned previously (see "*Existing* evidence").

weitere wichtige Aspekte bzgl. der 177Lu-PSMA-RLT konnten nicht adressiert werden:

Moreover, there are crucial aspects concerning 177Lu-PSMA-RLT that were beyond the scope of the present systematic review and could not be addressed in more detail, for example:

Diagnostik mittels PET-Scan als Voraussetzung für die Intervention → Auswirkungen von möglichen Fehlerquoten?

Firstly, patients need to undergo a whole-body PSMA PET scan before administering 177Lu-PSMA-RLT. This scan serves as a pre-requirement for treatment eligibility (PSMA-positive). Concurrently, a FDG-PET scan is required to rule out PSMA-negative disease. Evidence showed that there is a specific screening failure rate of PSMA PETs. Given the high prevalence of PSMA expression in advanced prostate cancer and the expected screening failure rate of PSMA PETs should be taken into account: Probably more patients could have been suitable for the intervention and were not included (false-negative PSMA expression), or patients who were not suitable for the intervention were included (false-positive). Moreover, the burden of screening procedures, including long waiting times for PET scans due to limited availability and high imaging costs, needs to be discussed [66].

Kosteneffektivität von 177Lu-PSMA-617 bei mCRPC Pat.

Secondly, due to the high costs associated with the administration of 177Lu-PSMA-RLT and the high prevalence of mCRPC, the cost-effectiveness of the intervention needs also be considered [34, 67].

Conclusion

mögliche Überlegenheit von 177Lu-PSMA-617 Kombinationstherapie bzgl. OS, PFS & HRQoL gegenüber der alleinigen Standardbehandlung

The evidence of moderate certainty regarding OS suggests superiority of 177Lu-PSMA-617 in combination with standard care (without cytotoxic chemotherapy) versus standard care alone in pre-treated mCRPC patients. In addition, the evidence indicates a potential superiority of the 177Lu-PSMA-617 combination therapy with respect to the outcomes PFS and HRQoL. However, the results should be interpreted with caution owing to the low certainty of the evidence for these outcomes. Further evidence, preferably in terms of OS, PFS and HRQoL, is needed for 177Lu-PSMA-RLT monotherapy or combination therapy compared to standard care, including chemotherapy.

Ergebnisse des erweiterten Follow-up der TheraP Studie & laufender RCTs sind abzuwarten

The results of the extended follow-up of the TheraP trial and further ongoing RCTs will shed more light on the efficacy and safety of different 177Lu-PSMA-RLTs (e.g. 177Lu-PSMA-617, 177Lu-PSMA-I&T or non-specified 177Lu-PSMA) as monotherapy or combination therapy compared to standard care, including chemotherapy, in mCRPC patients. In addition, there is evolving evidence for mHSPC patients.

6 Recommendation

In Table 6-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 6-1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

The evidence of moderate certainty regarding OS suggests superiority of 177Lu-PSMA-617 in combination with standard care (without cytotoxic chemotherapy) versus standard care alone in pre-treated mCRPC patients. In addition, the evidence indicates a potential superiority of the 177Lu-PSMA-617 combination therapy with respect to the outcomes PFS and HRQoL. However, the results should be interpreted with caution owing to the low certainty of the evidence for these outcomes.

Empfehlung basierend auf aktueller Evidenz: Aufnahme von 177Lu-PSMA-RLT Kombinationstherapie in den Krankenhaus-leistungskatalog nur für ausgewählte Pat. & spezialisierte Zentren

Based on these results, we recommend the inclusion of 177Lu-PSMA-RLT in combination with standard care (without cytotoxic chemotherapy) in the hospital benefit catalogue restricted to selected patients and limited to specialised centres. Thereby, close monitoring of the efficacy and safety of 177Lu-PSMA-RLT is recommended. In addition, "self-synthesised" 177Lu-PSMA-RLTs of radiopharmaceutical units could be considered.

Berücksichtigung von „Eigenproduktionen"

The results of the extended follow-up of the TheraP trial (abstract already available) and eight ongoing RCTs will shed more light on the efficacy and safety of different 177Lu-PSMA-RLTs (e.g. 177Lu-PSMA-617, 177Lu-PSMA-I&T or non-specified 177Lu-PSMA) as monotherapy or combination therapy compared to standard care, including chemotherapy, in mCRPC patients. Re-evaluation for the mCRPC population is recommended not before 2025.

erweiterten Follow-up der TheraP Studie & laufende RCTs sind abzuwarten → Re-evaluierung nicht vor 2025

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: 177Lu-PSMA monotherapy or combination therapy: Results from randomised controlled trials

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
Study characteristics			
Country	Australia	UK, DNK, SWE, NL, BE, FRA, SWISS, DE, USA, CAD, PRI	India
Sponsor	Prostate Cancer Foundation of Australia, Endocyte (a Novartis company), Australian Nuclear Science and Technology Organization, Movember, The Distinguished Gentleman's Ride, It's a Bloke Thing, and CAN4CANCER[8]	Endocyte, a Novartis company	NR
Clinical identification number	NCT03392428	NCT03511664	CTRI/2019/12/022282
Study design	Prospective, multicentre, unblinded, randomised (1:1) phase 2 trial	Prospective, open-label, randomised (2:1), international, phase 3 trial	Randomised (1:1), parallel-group, open-label, phase 2 non-inferiority trial
Conducted between	02/2018-09/2019	06/2018 – 10/2019	12/2019 – 03/2021
Intervention	177Lu-PSMA-617 IV and 1.5 litre oral hydration on the day of administration	177Lu-PSMA-617 IV + protocol-permitted standard care	177Lu-PSMA-617 IV and adequate hydration (1.5-2 litre of oral fluids on the day of administration) and premedication for anti-emesis (IV ondansetron and dexamethasone)
Strength of radiation, GBq (range)	8.5 GBq once every 6 weeks, decrease of 0.5 GBq per cycle	7.4 GBq (200 mCi) once every 6 weeks	6.0-7.4 GBq every 8 weeks, depending on the patient weight, disease burden, renal, and hematological parameters
Total number of cycles, n	A maximum of 6 cycles	4 cycles; up to 6 cycles in total possible in patients who had evidence of response	Up to 4 cycles
Comparator	Cabazitaxel: 20 mg/m^2 every 3 weeks for up to 10 cycles	Protocol-permitted standard care alone, e.g. approved hormonal treatments (abiraterone, enzalutamide), bisphosphonates, radiation therapy, denosumab, glucocorticoid at any dose[9]	Docetaxel: 75 mg/m^2 IV once every 3 weeks, up to a maximum of 10 cycles, with prednisone 5 mg twice daily orally during chemotherapy course and prophylactic pegfilgrastim 6 mg subcutaneously on day 2
Average number of cycles per patient, median n (range)	■ **177Lu-PSMA-617:** 5 (IQR 3-6) ■ **Cabazitaxel:** 8 (IQR 5-10)	■ **177Lu-PSMA-617:** 5.0 (1-6) ■ **Standard care:** 5.0 (1-16) vs 2.0 (1-14)	■ **177Lu-PSMA-617:** NR (1-4)[10] ■ **Docetaxel:** NR (5-10)[11]

[8] The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

[9] Standard-care therapies could not include cytotoxic chemotherapy, systemic radioisotopes (e.g., radium-223), immunotherapy, or drugs that were investigational when the trial was designed (e.g., olaparib).

[10] All patients received at least one cycle; 15 patients (75%) received at least 2 cycles, thereof, 2 patients (10%) received 3 cycles and 6 patients (30%) received 4 cycles.

[11] All patients received at least 5 cycles, while 11 patients (55%) completed 10 cycles.

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
Co-interventions	NR	NR	■ Standard supportive care, e.g. blood transfusions, granulocyte colony-stimulating factor injections, bisphosphonates, or denosumab, as clinically indicated. ■ Patients continued to receive androgen deprivation therapy to maintain castrate levels of testosterone unless prior orchiectomy was done. ■ Patients who showed biochemical/radiological progression on follow-up or were unable to tolerate either treatment discontinued the study and were provided treatment with alternative approved therapeutic options as per guidelines.
Primary outcomes	Prostate-specific antigen response rate (PSA-RR)[12]	Imaging-based PFS[13] and OS[14]	PSA-RR[12] (non-inferiority margin: – 15%[15])
Secondary outcomes	■ OS (death from any cause) ■ HRQoL (QLQ-C30)[16] ■ Pain response (McGill-Melzack Present Pain Intensity scale and analgesic score)[17] ■ PFS[18] ■ PSA-PFS[19] ■ PPI (Present Pain Intensity)-PFS[20] ■ Radiographic progression[21]	■ HRQoL (FACT-P[22]) ■ Pain (BPI-SF[23]) ■ 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*)	■ HRQoL (NCCN-FACT-FPSI-17 questionnaire version 2[24]): baseline vs 12 weeks following the first treatment cycle ■ PFS[25] ■ ORR (CR + PR) according to RECIST 1.1 ■ MRR (CR + PR) according to the adapted PERCIST 1.0 ■ AEs assessed using the CTCAE version 5.0

[12] Defined according to the Prostate Cancer Clinical Trials Working Group-3 (PCWG3) as the proportion of patients achieving a ≥50% decline in PSA from baseline.

[13] Time from randomisation to independently centrally reviewed disease progression (defined according to the PCWG3) or death.

[14] Time from randomisation to death from any cause.

[15] Non-inferiority of the primary endpoint was defined as the lower limit of the 95% confidence interval for the absolute difference between the PSA-RRs of 177Lu-PSMA-617 and docetaxel was not less than – 15%.

[16] **EORTC Core Quality of Life Questionnaire (QLQ-C30)**: It includes 5 functional, 3 symptom and a global health and quality of life scale; higher functional scores indicate better function and lower symptom scores indicating better quality of life.

[17] **McGill-Melzack Present Pain Intensity scale** (scores 0-5, with 0 defined as no pain). Pain response was defined as a reduction of the present pain intensity (PPI) from baseline of ≥2 points. Outcome was restricted to men with a PPI score of ≥2 at baseline.

[18] Time from randomisation to first evidence of PSA progression defined by an increase of at least 25% and at least 2 ng/mL after 12 weeks (as per PCWG3), radiographic progression using locally reported CT and bone scanning (RECIST 1.1 and PCWG3), commencement of non-protocol anticancer treatment, or death from any cause.

[19] Defined according to the PCWG3 criteria.

[20] Time from randomisation to first evidence of an increase of ≥1 point from the nadir PPI score, commencement of non-protocol anti-cancer treatment, or death from any cause.

[21] Locally reported CT and bone scanning according to the RECIST 1.117 and PCWG3 criteria for bone lesions, commencement of non-protocol anticancer treatment, or death from any cause.

[22] **Functional Assessment of Cancer Therapy-Prostate (FACT-P)**: total score is the sum of the scores of 39 items of the questionnaire and ranges from 1-156, with higher scores indicating better quality of life.

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
Secondary outcomes *(continuation)*	■ ORR (CR or PR) according to RECIST 1.1. ■ Frequency and severity of AEs assessed using the CTCAE version 4.03 *(from first dose until 12 weeks after cessation of study treatment)*		
Inclusion criteria	Male adults with: ■ Metastatic castration-resistant prostate cancer who had been previously treated with Docetaxel and for whom cabazitaxel was considered the next appropriate standard treatment. ■ Adequate renal, haematological, and liver function. ■ Progressive disease with rising PSA level[26]. ■ Target or non-target lesions according to RECIST 1.1. ■ Significant PSMA avidity on 68Ga-PSMA PET/CT[27]. ■ ECOG performance status ≤2. ■ Estimated life expectancy >12 weeks.	Male adults with: ■ Castration-resistant prostate cancer and at least one metastatic lesion on baseline CT, MRI, or bone scan imaging. ■ PSMA-positive metastatic castration-resistant prostate cancer was defined as at least one PSMA-positive metastatic lesion and no PSMA-negative lesions [28]. ■ Diagnostic-grade CT scans were also available for all the patients[29]. ■ 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[30]. ■ An ECOG performance status score of 0 to 2 (on a scale from 0 to 5, with higher numbers indicating greater disability). ■ A life expectancy of at least 6 months. ■ Adequate organ and bone marrow function.	Male adults with: ■ Biopsy-proven adenocarcinoma prostate and castration-resistant disease. ■ Metastatic disease on Ga-PSMA-11 PET/CT with significant PSMA expression[31]. ■ Chemotherapy-naïve. ■ Prior treatment of NAADs. ■ An ECOG performance score ≤2. ■ Adequate haematological, renal and liver function reserve.

[23] **Brief Pain Inventory-Short Form (BPI-SF)**: scores range from 0-10, with lower scores representing lower levels of pain intensity and better overall functioning.

[24] **The National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Prostate Cancer Symptom Index – 17 Item Version (NCCN-FACT-FPSI-17)** includes 17 items under 4 domains: disease-related symptoms-physical (FPSI-DRS-P), disease-related symptoms-emotional (FPSI-DRS-E), treatment side effects (FPSI-TSE) and function/well-being (FPSI-F/WB). Response for each question ranged from 0 (highly symptomatic) 4 (no symptoms); higher score was considered to be good.

[25] Time from the start of the treatment regimen till documented biochemical or radiological progression, or death. Biochemical progression was defined as per the PCWG3 criteria and radiological progression was defined as per RECIST 1.1.

[26] Defined by PCWG3 criteria: sequence of 2 rising values above a baseline at a minimum of 1-week intervals; and PSA ≥20 ng/mL.

[27] Minimum uptake of SUVmax 20 at a site of disease, and SUVmax > 10 at sites of measurable disease ≥10 mm (unless subject to factors explaining a lower uptake, e.g. respiratory motion, reconstruction artefact).

[28] PSMA-positive status was determined with the use of centrally read gallium-68 (68Ga)–labeled PSMA-11 (68Ga-PSMA-11) PET–CT imaging at baseline.

[29] The presence of PSMA-positive lesions was defined in the protocol as 68Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system.

[30] There was no upper limit on the permitted number of previous androgen-receptor–pathway inhibitors (e.g., abiraterone and enzalutamide).

[31] Significant PSMA expression was defined as tracer avidity of at least 80% of the lesions being significantly (≥1.5 times) greater than that of normal liver with none of the lesions having uptake less than that of liver.

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
Exclusion criteria	■ Prostate cancer with known significant sarcomatoid or spindle cell or neuroendocrine small cell components ■ Site(s) of disease that are FDG-positive with minimal PSMA expression defined as FDG intensity > 68Ga-PSMA activity or 68Ga-PSMA SUVmax < 10. ■ Sjogren's syndrome. ■ Prior treatment with cabazitaxel or 177Lu-PSMA. ■ Contraindications to the use of corticosteroid treatment. ■ Active malignancy other than prostate cancer. ■ Concurrent illness, including severe infection that may jeopardise the ability of the patient to undergo the procedures with reasonable safety. ■ Serious psychological, familial, sociological or geographical condition that might hamper compliance with the study protocol and follow-up schedule. ■ Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception.	■ Patients with any PSMA-negative metastatic lesion[32]. ■ Previous treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 or hemi-body irradiation within 6 months prior to randomisation. Previous PSMA-targeted radioligand therapy is not allowed. ■ Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomisation. ■ Any investigational agents within 28 days prior to day of randomisation. ■ Known hypersensitivity to the components of the study therapy or its analogs. ■ Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy. ■ Transfusion within 30 days of randomisation. ■ History of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity; Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast). ■ A superscan as seen in the baseline bone scan. ■ Symptomatic cord compression or clinical or radiologic findings indicative of impending cord compression. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation. ■ Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. Patients with adequately treated non-melanoma skin cancer, superficial bladder cancer and patients with prior history of malignancy who have been disease-free for more than 3 years are eligible.	■ Patients with histological evidence of sarcomatous, spindle-cell or small-cell differentiation, and Sjogren syndrome.

[32] The presence of PSMA-negative lesions was defined in the protocol as PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis.

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
Follow-up, median months (95% CI)	18.4 (NR) vs 18.4 (NR)	20.3 (19.8-21.0) vs 19.8 (18.3-20.8)	NR
Follow-up imaging	CT of the chest, abdomen and pelvis, and technetium-^{99}m-phosphonate bone scans every 12 weeks until radiological progression	CT or MRI and technetium-99m-labeled methylene diphosphonate bone scans every 8 weeks for 24 weeks and then every 12 weeks after that	■ Post-therapy whole-body scans were acquired after 24h to look for the distribution of 177Lu-PSMA-617 in the lesions and normal tissues ■ Complete hemogram, liver and renal function tests, and PSA every 3 weeks ■ Interim Ga-PSMA-11 PET/CT at 6 weeks after the 2. cycle of 177Lu-PSMA-617 and 3 weeks after the 5. cycle of docetaxel ■ End of treatment Ga-PSMA-11 PET/CT performance after 6 weeks of the last treatment cycle
Patient characteristics			
Number of pts, n	**ITT:** 200 (99 vs 101)	**ITT:** 831 (551 vs 280) **ITT* on or after March 5, 2019**[33]**:** 581 (385 vs 196)	**ITT:** 40 (20 vs 20)[34] **PP:** 35 (15 vs 20)[35]
Discontinuation of the trial, n	Lost to follow-up: 2 vs 17 Discontinuation: 64 vs 72 ■ Patient decision: 4 vs 21 ■ Clinical decision: 9 vs 17 ■ PSA-progression: 10 vs 13 ■ Radiological progression: 18 vs 12 ■ Toxicity or safety: 1 vs 4 ■ Death: 9 vs 2 ■ Exceptional response: 7 vs 0 ■ Other: 6 vs 3	Discontinuation: 358 vs 221 ■ Lost to follow-up: 4 vs 4 ■ Withdrew consent: 29 vs 53 ■ Withdrawn by investigator: 0 vs 1 ■ Died: 329 vs 167	Discontinuation: 14 vs 9 ■ Progressive disease: 7 vs 7 ■ Treatment-related toxicity: 2 vs 1 ■ Disease-related deaths: 3 vs 1 ■ Exceptional response: 2 vs 0
Age, median yrs (range)	72.1 (IQR 66.9-76.7) vs 71.8 (66.7-77.3)	**ITT:** 70.0 (48-94) vs 71.5 (40-89) **ITT*:** 71.0 (52-94) vs 72.0 (51-89)	68 (54-85) vs 68 (50-84)
Gleason score ≥8, n (%)	53 (53) vs 50 (50)	**ITT:** 324 (58.8) vs 170 (60.7) **ITT*:** 226 (58.7) vs 118 (60.2)	14 (70) vs 12 (60)
ECOG performance status 0 or 1, n (%)	95 (96) vs 96 (96)	**ITT:** 510 (92.6) vs 258 (92.1) **ITT*:** 352 (91.4) vs 179 (91.3)	**Status 0:** 8 (40) vs 7 (35) **Status 1:** 7 (35) vs 7 (35)

[33] After the trial started (May 29, 2018), a high incidence of withdrawal from the trial was noted in the control group at certain sites due to patient disappointment. On March 5, 2019 enhanced trial-site education measures were implemented to reduce the incidence of withdrawal.

[34] 6/20 patients (30%) and 8/20 patients (40%) received 177Lu-PSMA-617 and docetaxel, respectively, as the first-line modality for mCRPC (no definition of "first-line modality" was reported).

[35] Per-protocol sensitivity analysis was also done by including only those patients who underwent at least half of the allocated treatment, i.e. received at least 2 cycles of 177Lu-PSMA-617 or at least 5 cycles of docetaxel.

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
Tumor stage (pT1/pT2/pT3/pT4), n (%)	NR	NR	NR
Site of disease, n (%)	■ **Lymph node only**: 7 (7) vs 9 (9) ■ **Bone metastases:** 90 (91) vs 90 (89) ■ **Visceral metastases**: 7 (7) vs 13 (13)	**ITT:** ■ **Lung:** 49 (8.9) vs 28 (10.0) ■ **Liver:** 63 (11.4) vs 38 (13.6) ■ **Lymph node:** 274 (49.7) vs 141 (50.4) ■ **Bone:** 504 (91.5) vs 256 (91.4) **ITT*:** ■ **Lung:** 35 (9.1) vs 20 (10.2) ■ **Liver:** 47 (12.2) vs 26 (13.3) ■ **Lymph node:** 193 (50.1) vs 99 (50.5) ■ **Bone:** 351 (91.2) vs 179 (91.3)	■ **Local nodes:** 15 (75) vs 15 (75) ■ **Distant nodes:** 8 (40) vs 10 (50) ■ **Skeletal:** 20 (100) vs 20 (100) ■ **Visceral:** 5 (25) vs 4 (20) ■ **Liver**: 2 (10) vs 1 (5) ■ **Lung:** 0 (0) vs 2 (10) ■ **Adrenal:** 2 (10) vs 0 (0) ■ **Others:** 1 (5) vs 1 (5)
Diagnosis, imaging procedure used	NR	CT, MRI, or bone-scan imaging	Ga-PSMA-11 PET/CT, biopsy
Previous interventions, n (%)			
Prostatectomy	43 (43.4) vs 44 (43.6)	**ITT:** 240 (43.6) vs 130 (46.4) **ITT*:** 159 (41.3) vs 82 (41.8)	NR
Radiotherapy	40 (40.4) vs 46 (45.5)	**ITT:** 415 (75.3) vs 217 (77.5) **ITT*:** 286 (74.3) vs 152 (77.6)	5 (25) vs 3 (15)
Androgen receptor pathway inhibitor	■ **Abiraterone only:** 21 (21) vs 24 (24) ■ **Enzalutamide only:** 49 (50) vs 58 (57) ■ **Both:** 21 (21) vs 9 (9)	**ITT:** ■ **Abiraterone:** 187 (33.9) vs 106 (37.9) ■ **Abiraterone acetate:** 210 (38.1) vs 114 (40.7) ■ **Enzalutamide:** 395 (71.7) vs 206 (73.6) ■ **Apalutamide:** 13 (2.4) vs 5 (1.8) **ITT*** ■ **Abiraterone:** 157 (40.8) vs 85 (43.4) ■ **Abiraterone acetate:** 110 (28.6) vs 62 (31.6) ■ **Enzalutamide:** 280 (72.7) vs 145 (74.0) ■ **Apalutamide:** 8 (2.1) vs 5 (2.6)	■ **Abiraterone only:** 10 (50) vs 12 (60) ■ **Enzalutamide only:** 0 (0) vs 0 (0) ■ **Both:** 4 (20) vs 0 (0)
Others	**Docetaxel:** 99 (100) vs 101 (100)	**ITT:** ■ **Docetaxel:** 534 (96.9) vs 273 (97.5) ■ **Cabazitaxel:** 209 (37.9) vs 107 (38.2) **ITT*:** ■ **Docetaxel:** 377 (97.9) vs 191 (97.4) ■ **Cabazitaxel:** 161 (41.8) vs 84 (42.9)	■ **Bisphosphonate and/or denosumab:** 20 (100) vs 20 (100) ■ **Androgen deprivation therapy:** 20 (100) vs 20 (100)

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
Outcomes			
Efficacy			
OS, median months	NR	**ITT:** 15.3 vs 11.3, HR 0.62 (95% CI, 0.52-0.74), p<0.001 **ITT*:** 14.6 vs 10.4, HR 0.63 (95% CI, 0.51-0.79), p=NR	NR
Generic QoL	NR	NR	NR
HRQoL			
EORTC-QLQ-C30 *(scores: 0-100, higher functional scores indicate better function; lower symptom scores indicate better HRQoL)*	n=176 ■ Mean global health status scores after 51 weeks: 63 (95%, CI 60-67) vs 60 (57-64), p=0.20 ■ QoL and symptoms clinically meaningfully[36] improved in the IG vs CG after 51 weeks in the following domains: ■ Social functioning: 79 (75-82) vs 73 (69-77), p=0.030 ■ Diarrhoea: 9 (95% CI, 6-11) vs 16 (13-19), p<0.0001 ■ Fatigue: 34 (31-38) vs 40 (36-43), p=0.027 ■ Insomnia: 23 (20-27) vs 29 (25-33), p=0.023	NR	NR
FACT-P *(scores: 1-156, higher scores indicate better HRQoL)*	NR	**ITT*:** Time to deterioration in the FACT-P total score was longer in the IG, median months: 5.7 vs 2.2, HR 0.54 (95% CI, 0.45-0.66), p=NR	NR
NCCN-FACT-FPSI *(scores: 0-4, higher scores indicate better HRQoL)*	NR	NR	**PP:** Significant improvement in the median total score in the 177Lu-PSMA-617 arm (p<0.01) at 12 weeks following the first cycle. Statistically significant changes in sub-domains in favour of the intervention[37]: ■ 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
BPI-SF *(scores: 0-10, lower scores represent lower pain levels & better overall function)*	NR	**ITT*:** Time to deterioration in the BPI-SF total score was longer in the IG, median months: 5.9 vs 2.2, HR 0.52 (95% CI, 0.43-0.63), p=NR	NR
PFS, median months	5.1 (range, 3.4-5.7) vs 5.1 (2.8-6.0)	**ITT:** 8.8 vs 3.6, HR 0.43 (99.2% CI, 0.32-0.58), p=NR **ITT*:** 8.7 vs 3.4, HR 0.40 (99.2% CI, 0.29-0.57), p<0.001	**ITT:** 4.0 (95% CI, 1.8-6.2) vs 4.0 (95% CI, 3.6-4.4), HR 0.90 (95% CI, 0.46-1.77), p=0.98 **PP:** 5.0 (95% CI, 3.3-6.7) vs 4.0 (95% CI, 3.6-4.4), HR 0.68 (95% CI, 0.32-1.44), p=0.30
PSA-PFS, median months	NR, HR 0.60 (95% CI, 0·44-0·83), p=0·0017	NR	NR

[36] A clinically meaningful difference was not defined in the study.

[37] Health-related quality of life was assessed at baseline and 12 weeks following the first treatment cycle.

Author, year Trial name [References]	Hofman et al., February 2021 TheraP trial [19]	Sator et al., June 2021 VISION trial [34]	Satapathy et al. November 2021 [35]
ORR and disease control according to RECIST, n (%)	49% (95% CI, 33-65) vs 24% (11-38), RR 2.12 (95% CI, 1.10-4.08), p=0·019	n=248 (184 vs 64)[38] **CR:** 17 (9.2) vs 0 (0) **PR:** 77 (41.8) vs 2 (3.1)	**ITT:** 5 (39, 95% CI, 12-65) vs 6 (32, 95%, 11-52), difference 7% (95% CI, -24-28, p=0.69) **PP:** 5 (46, 95% CI, 16-75) vs 6 (32, 95% CI, 16-75), difference 14% (95% CI, -19-45, p=0.45)
PSA-response, n (%)	**ITT:** 65 (66) vs 37 (37), difference 29% (95% CI, 16-42), p<0.0001 **By treatment received:** 65 (66) vs 37 (44), difference 23% (95% CI, 9-37), p=0.0016	n=471 (333 vs 138) Confirmed decrease: ■ ≥50%: 177 (46.0) vs 14 (7.1), OR 11.19 (95% CI, 6.25-20.04) ■ ≥80%: 127 (33.0) vs 4 (20.0), OR 23.62 (95% CI, 8.57-65.11)	**ITT:** Best response: 10 (50, 95% CI, 28-72) vs 8 (40, 95% CI, 19-61), difference 10% (95% CI, -19-37), p=0.53 **PP:** Best response: 9 (60, 95% CI, 35-85) vs 8 (40, 95% CI, 19-61), difference 20% (95% CI, **-12**[39]-47), p=0.25
Time to first symptomatic skeletal event or death, months	NR	**ITT*:** 11.5 vs 6.8, HR 0.50, 95% CI, 0.40-0.62, p<0.001	NR
Safety			
Treatment-related grade 5 AEs (death), n (%)	n=183 (98 vs 85): 0 (0) vs 0 (0)	n=734 (529[40] vs 205[41]): 5 (0.9)[42] vs 0 (0)	**ITT:** 2 (10) vs 1 (5)[43,44]
Grade 3-4 AEs, n (%)	n=183 (98 vs 85) **Any AEs:** 32 (33) vs 45 (53)	n=734 (529[40] vs 205[41]): ■ **Any AEs:** 279 (52.7) vs 78 (38.0) ■ **Treatment-related AEs:** 150 (28.4) vs 8 (3.9) ■ **Treatment-related SAEs:** 43 (8.1) vs 5 (2.4)	**Total treatment-emergent AEs grades 3-5**[45]**:** 6 (30, 95% CI, 10-50) vs 10 (50, 95% CI, 28-72), difference 20% (95% CI, -10-45), p=0.20
AE-related discontinuation, n (%)	n=183 (98 vs 85) 1 (1) vs 3 (4)	n=734 (529[40] vs 205[41]): **Discontinuation of 177Lu-PSMA-617:** ■ **AEs all grades:** 63 (11.9) vs NA ■ **AEs grades ≥3:** 37 (7.0) vs NA **Discontinuation of standard care:** ■ **AEs all grades** 45 (8.5) vs 16 (7.8) ■ **AEs grades ≥3:** 25 (4.7) vs 12 (5.9)	**ITT:** ■ **AEs all grades:** 2 (10) vs 1 (5) ■ **AEs grades ≥3:** 2 (10) vs 1 (5)

[38] Patients who had measurable target lesions according to RECIST version 1.1. on independent central review at baseline.

[39] The lower confidence limit was greater than the specified non-inferiority margin of -15%.

[40] Patients who received 177Lu-PSMA-617.

[41] 201 patients received standard care alone; in the safety analysis 205 patients were analysed in the control arm without explaining who the 4 additional patients were.

[42] Pancytopenia, n=2; bone-marrow failure, n=1; subdural hematoma, n=1; intracranial hemorrhage, n=1.

[43] The patients developed persistent grade 4 thrombocytopenia leading to treatment-related deaths.

[44] Adverse events were assessed at baseline and 12 weeks following the first treatment cycle. One cycle consisted of eight weeks.

[45] The study only reported grade 3-5 adverse events.

Abbreviations: AE – adverse event, BE – Belgium, BPI-SF – Brief Pain Inventory-Short Form, CAD – Canada, CG – control group, CI – confidence interval, CR – complete response, CNS – central nervous system, CT – computer tomography, CTCAE – Common Terminology Criteria for Adverse Events, DE – Germany, DNK – Denmark, ECOG – Eastern Co-operative Oncology Group, EORTC QLQ-C30 – European Organisation, for Research and Treatment of Cancer Quality of Life Questionnaire, FACT-P – Functional Assessment of Cancer Therapy-Prostate, FDG – fluorodeoxyglucose, FRA – France, HR – hazard ratio, HRQoL – health-related quality of life, IG – intervention group, IQR – interquartile range, ITT – intention to treat, MRI – magnetic resonance imaging, NCCN-FACT-FPSI-17 – National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Prostate Symptom Index-17 Questionnaire, NL – Netherlands, NR – not reported, OR – odds ratio, ORR – objective response rate, OS – overall survival, PCWG3 – Prostate Cancer Working Group version 3, PET – positron emission tomography, PFS – progression-free survival, PP – per protocol, PPI – present pain intensity, PR – partial response, PRI – Puerto Rico, PSA – prostate-specific antigen, PSMA – prostate specific membrane antigen, RECIST – Response Evaluation Criteria In Solid Tumors, RR – relative risk, SWE – Sweden, SWISS – Switzerland, UK – United Kingdom, USA – United States of America, 68GA – Gallium

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved in solving the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA [68] and in the Guidelines of EUnetHTA [69].

Table A-2: Risk of bias – study level (randomised studies), see [1]

Trial	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
TheraP trial, NCT03392428 [19]	Low	Some concern[a]	High[c]	High[d]	Low	**High**
VISION trial, NCT03511664 [34]	Low	High[a,b]	High[c]	High[d]	Low	**High**
CTRI/2019/12/022282 [35]	Low	Some concern[a]	Low	High[d,e]	High[f,g]	**High**[h]

Explanations:

[a] *Study participants, carers and people delivering the interventions were aware of the assigned intervention during the trial.*

[b] *The control arm was not implemented as intended due to non-adherence; however, it was solved in the way that the primary analysis of primary outcomes and key secondary outcomes were amended to include only patients who had undergone randomization on or after 5 March 2019. To maintain statistical power, the planned total sample size was increased from 750 to 814 in the protocol amendment on 8 July 2019.*

[c] *There were missing outcomes, e.g. for safety, and the percentage of missing data was not similar among both arms.*

[d] *The outcome assessors were aware of the intervention received by study participants.*

[e] *The non-inferiority margin was chosen through consensus after detailed inter-departmental discussions, which took into account the expected advantages with 177Lu-PSMA-617, e.g. the lesser number and frequency of cycles, potentially better safety profile and benefits in health-related quality of life outcomes.*

[f] *No information was reported about the median follow-up of the study. Health-related quality of life was assessed at baseline and 12 weeks following the first treatment cycle.*

[g] *Only the PP was reported showing a statistically significant improvement for the intervention arm; the non-inferiority margin of 177Lu-PSMA-617 was only reached in the PP analysis.*

[h] *The sponsor(s) of the study were not reported.*

Table A-3: Evidence profile: efficacy and safety of Lu177-PSMA-617 monotherapy or combination therapy in patients with metastatic castration-resistant prostate cancer

Quality assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	**177Lu-PSMA-617** (mono- or combination therapy)	Standard carea	Relative (95% CI)	Absolute (95% CI)	
Efficacy											
Overall survival (assessed in: median months)											
1	RCT [34]	Not serious[b]	Not serious	Serious[c]	Not serious	None	**ITT:** 551 **ITT[e]:** 385	**ITT:** 280 **ITT[e]:** 196	**ITT:** HR 0.62 (0.52-0.74) **ITT[e]:** HR 0.63 (0.51-0.79)	**ITT:** 15.3 vs 11.3, p<0.001 **ITT[e]:** 14.6 vs 10.4, p=NR	⊕⊕⊕◯ Moderate
Generic quality of life											
NR											
Health-related quality of life (follow-up: 51 weeks, assessed in: mean global health status scores of the EORTC-QLQ-C30 *[higher score indicates better HRQoL]*)											
1	RCT [19]	Very serious[f,g,h]	Not serious	Not serious	Not serious	None	176/200 (88%)		NR	63 (60-67) vs 60 (57-64), p=0.20	⊕⊕◯◯ Low
Health-related quality of life (assessed in: median months until deterioration in the FACT-P and BPI-SF total score)											
1	RCT [34]	Serious[f]	Not serious	Serious[c]	Not serious	None	**ITT[e]:** 385	**ITT[e]:** 196	**FACT-P:** HR 0.54 (0.45-0.66) **BPI-SF:** HR 0.52 (0.43-0.63)	**FACT-P:** 5.7 vs 2.2, p=NR **BPI-SF:** 5.9 vs 2.2, p=NR	⊕⊕◯◯ Low
Health-related quality of life (follow-up: 12 weeks after the first cycle, assessed with: NCCN-FACT-FPSI *[higher score indicates better HRQoL]*)											
1	RCT [35]	Very serious[f,i]	Not serious	Not serious	Serious[j]	None	**PP:** 15	**PP:** 20	S.s. improvement in the median total score in the 177Lu-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		⊕◯◯◯ Very low
Progression-free survival (assessed in: median months)											
3	RCTs [19, 34, 35]	Serious[f]	Not serious	Serious[c,k]	Not serious	None	670	401	■ **177Lu-PSMA-617 vs Cabazitaxel (n=200):** 5.1. vs 5.1, HR NR, p=NR ■ **177Lu-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 ■ **177Lu-PSMA-617 vs Docetaxel (n=40):** 4.9 vs 4.9, HR 0.90, 95% CI 0.46-17.77, p=0.98		⊕⊕◯◯ Low

Quality assessment							Summary of findings				
							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	**177Lu-PSMA-617** (mono- or combination therapy)	Standard carea	Relative (95% CI)	Absolute (95% CI)	
Safety											
Treatment-related deaths (assessed with: CTCAE)											
3	RCTs [19, 34, 35]	Serious[f]	Serious[l]	Serious[c]	Not serious	None	647	310	n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel after 18.4 months (n=183):** 0 (0) vs 0 (0) ■ **177Lu-PSMA-617 & standard care vs standard care after 20.3 months (n=734):** 5 (0.9)[m] vs 0 (0) ■ **177Lu-PSMA-617 vs Docetaxel (n=40):** 2 (10) vs 1(5)[n,o]		⨁◯◯◯ Very low
Grade 3-4 adverse events (follow-up, range: 18.4-20.3 months, assessed with: CTCAE)											
2	RCTs [19, 34]	Serious[f]	Not serious	Serious[c]	Not serious	None	627	290	Any AEs, n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel after 18.4 months (n=183):** 32 (33) vs 45 (53) ■ **177Lu-PSMA-617 & standard care vs standard care after 20.3 months (n=734):** 279 (52.7) vs 78 (38.0) Treatment-related AEs, n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel after 18.4 months (n=183):** NR ■ **177Lu-PSMA-617 & standard care vs standard care after 20.3 months (n=734):** 150 (28.4) vs 8 (3.9) Treatment-related SAEs, n (%): ■ **177Lu-PSMA-617 vs Cabazitaxel after 18.4 months (n=183):** NR ■ **177Lu-PSMA-617 & standard care vs standard care after 20.3 months (n=734):** 43 (8.1) vs 5 (2.4)		⨁⨁◯◯ Low
Grade 3-4 adverse events (follow-up: NR[o], treatment-emergent AEs grades 3-5[q] assessed with: CTCAE)											
1	RCT [35]	Serious[f]	Not serious	Not serious	Serious[p]	None	**ITT:** 20	**ITT:** 20	Difference 20% (-10-45)	**n (%):** 6 (30) vs 10 (50), p=0.20	⨁⨁◯◯ Low

Abbreviations: AE – adverse events, BPI-SF – Brief Pain Inventory-Short Form, CI – confidence interval, CTCAE – Common Terminology Criteria for Adverse Events, 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-Prostate Symptom Index-17 Questionnaire, NR – not reported, PP – per protocol, RCT – randomised controlled trial, s.s. – statistically significant

Explanations:

[a] *The comparator interventions in the studies involved different standard care treatments: chemotherapy (e.g. Cabazitaxel [19] or Docetaxel [35]) and approved hormonal treatments (abiraterone, enzalutamide), bisphosphonates, radiation therapy, denosumab or glucocorticoid at any dose [34].*

[b] *Considering the ITT analysis and overall survival as the outcome will not be affected by the "open-label" study design.*

[c] *The control group of one RCT received standard care without cytotoxic chemotherapy regimens (e.g. Cabazitaxel or Docetaxel), one of the standard care for this patient group according to guidelines [36].*

[e] *After the trial started (May 29, 2018), a high incidence of withdrawal from the trial (56%) was noted in the control group at certain sites due to patient disappointment. On March 5, 2019, enhanced trial-site education measures were implemented to reduce the incidence of withdrawal.*

[f] *Open-label trial.*

[g] *Missing data.*

[h] *Reporting bias for certain domains of the EORTC-QLQ-C30 expected.*

[i] *Reporting bias as only the PP analysis was reported.*

[j] *The study did not report absolute or relative differences.*

[k] *The effect in the intervention group was higher in one RCT than the other, probably because of the combination therapy.*

[l] *The outcome results were different in the three RCTs.*

[m] *Pancytopenia, n=2; bone-marrow failure, n=1; subdural hematoma, n=1; intracranial hemorrhage, n=1.*

[n] *Persistent grade 4 thrombocytopenia leading to treatment-related deaths.*

[o] *The follow-up time was not reported.*

[p] *Wide confidence intervals.*

[q] *The study did not report treatment-related adverse events as grades 3-4 but 3-5.*

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Within the included studies, this patient population was covered by three RCTs. The inclusion criteria of these studies reflect the intended patient population for the technology. One of the three RCTs [35] included chemotherapy-naïve patients, which represents an essential subpopulation at this stage according to the guidelines. Only patients with an ECOG performance status of 0 or 1 were included in all three RCTs. This is not fully applicable to the clinical practice as patients with higher performance status scores are also eligible. However, the patient population of the included studies reflects real-world conditions concerning age, sex, previous interventions received site of the disease and Gleason score.
Intervention	They included studies evaluated 177Lu –PSMA-617 produced by one manufacturer (Endocyte, a Novartis company). Noteworthy that two RCTs [19, 35] evaluated 177Lu-PSMA-617 as monotherapy, whereas one [34] evaluated this technology in combination with a different standard of care, including approved hormonal treatments (i.e. abiraterone, enzalutamide) and radiation therapy, but not cytotoxic chemotherapy, systemic radioisotopes, immunotherapy or investigational drugs, such as olaparib. Not including cytotoxic chemotherapy as a standard of care in this RCT could neglect an important subpopulation in the real world who are eligible to receive cytotoxic chemotherapy as part of their treatment regimen. Besides, there are other 177Lu-PSMA-RLTs (e.g. 177Lu-PSMA-I&T or in-house productions of hospital pharmacies) for which efficacy and safety still need to be clarified.
Comparators	Different standard of care treatments are established for this patient population, such as chemotherapy, hormonal therapy, radiopharmaceuticals, or best supportive care. Two of the included RCTs [19, 35] compared 177Lu-PSMA-617 to chemotherapy. On the other hand, the third RCT [34] did not include chemotherapy as one of the standard of care in the control arm. Overall, the comparator arms in all the RCTs are considered part of usual care routines in actual practice.
Outcomes	The critical outcomes for efficacy were overall survival, progression-free survival, quality-of-life, and health-related quality of life. All three RCTs reported progression-free survival and health-related quality-of-life, one reported overall survival, and none reported generic quality of life. Overall and progression-free survival was reported as alternate primary outcomes only in one RCT. Regarding the safety outcomes, the critical outcomes of treatment-related grade 5 AEs and grade 3-4 AEs were reported, not as the primary outcome measure, in all RCTs. Furthermore, follow-up duration was considerably similar among two of the included RCTs (18.3-21.0 months). On the other hand, one RCT did not report the median follow-up duration. The reported median follow-up durations were considered suitable as they align with the estimated mean survival of mCRPC patients, which is reported historically as a range of 9-36 months, varying according to the extent of metastases and symptoms [40].
Setting	One of the included RCTs was conducted as a multicenter study in different geographical regions (Netherlands, Germany, United Kingdom, Denmark, Sweden, France, Switzerland, Canada, Belgium, Puerto Rico, and the United States of America). However, the other two studies were conducted in one geographical region (Australia, India). Though only one of the included three RCTs was multinational, geographic settings are expected not to limit the results' applicability.

Abbreviations: AE – adverse events, PSMA – prostate-specific membrane antigen, RCT – randomised controlled trial, RLT – radioligand therapy

List of ongoing randomised controlled trials

Table A-5: List of ongoing randomised controlled trials of Lu177-PSMA-617 monotherapy or combination therapy

Identifier/ Trial name	Patient population	Intervention/ Setting	Comparison	Primary Outcome	Primary completion date	Sponsor
Metastatic castration-resistant prostate cancer (mCRPC)						
NCT05560659/ POPSTAR II	(n=92) ■ Male aged ≥18 years with prostate adenocarcinoma ■ Prior definitive treatment with either radiotherapy or surgery, with no evidence of PSMA avid disease in the prostate/prostate bed ■ Significant PSMA expression in 68Ga – PSMA PET/CT	177Lu-PSMA + SABR inpatient	SABR	Biochemical PFS	November 2024	Peter MacCallum Cancer Centre
NCT04647526/ SPLASH	(n=415) ■ Male aged ≥18 years with progressive mCRPC ■ Ineligible or averse to chemotherapeutic treatment options. ■ Progression on previous treatment with one ARAT[46] ■ Positive PSMA-PET scan ■ Castrate circulating testosterone levels (<1.7 nmol/L or <50 ng/dL)	177Lu-PSMA-I&T (also called 177Lu-PNT2002) NR	Abiraterone/ Enzalutamide	Radiographic PFS	March 2023	POINT Biopharma
NCT04689828/ PSMAfore	(n= 469) ■ Male aged ≥18 years with progressive mCRPC ■ Positive 68Ga-PSMA-11 PET/CT scan ■ Castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L) ■ Progressed only once on ARDT ■ Candidates for change in ARDT[47]	177Lu-PSMA-617 NR	ARDT	Radiographic PFS	October 3, 2022, but no data has been published to date	Novartis Pharmaceuticals
NCT05204927	(n=400) ■ Male aged ≥18 years with progressive prostate adenocarcinoma ■ Previous treatment with ARDT ■ Positive PSMA PET scan ■ Castration with serum testosterone level of <50 ng/dL	177Lu-PSMA-I&T (also called 177Lu-PNT2002) NR	Abiraterone with Prednisone or Enzalutamide	Radiographic PFS	January 2024	Curium US LLC

[46] Androgen receptor-axis-targeted therapies include Abiraterone, Enzalutamide, Darolutamide or Apalutamide.

[47] Participants cannot have previously progressed nor had intolerable toxicity to both Enzalutamide and Abiraterone.

Identifier/ Trial name	Patient population	Intervention/ Setting	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT05658003	(n=60) ■ Chinese male aged ≥18 years with progressive mCRPC ■ positive [68Ga]Ga-PSMA-11 PET/CT scan ■ Castrate level of serum/plasma testosterone (< 50 ng/dl, or < 1.7 nmol/L) ■ Progressed only once on ARDT ■ Candidates for change in ARDT	177Lu-PSMA-617 NR	ARDT	Radiographic PFS	October 28, 2026	Novartis Pharmaceuticals
NCT04663997	(n=200) ■ Male aged ≥18 years with progressive mCRPC ■ Progression on ARDT ■ Positive PSMA metastatic disease	177Lu-PSMA-617 NR	Docetaxel	PFS	July 31, 2024	Canadian Cancer Trials Group
NCT04419402/ ENZA-p	(n=160) ■ Male aged ≥18 years with progressive mCRPC ■ Significant PSMA avidity on 68Ga-PSMA PET/CT	177Lu-PSMA + Enzalutamide NR	Enzalutamide	PSA-PFS	June 1, 2022, but no data published to date	Australian and New Zealand Urogenital and Prostate Cancer Trials Group
CTRI/2019/12/ 022282	(n=40) ■ Male aged ≥30 years with mCRPC ■ Significant PSMA expression in 68Ga – PSMA PET/CT ■ Chemotherapy naive patients.[48]	177 Lu-PSMA NR	Docetaxel	PSA response rate	Applicable only for Completed/ Terminated trials	Postgraduate Institute of Medical Education and Research
Metastatic hormone-sensitive prostate cancer (mHSPC)						
CTRI/2020/10/ 028341	(n=90) ■ Male aged ≥18 years with metastatic adenocarcinoma of the prostate ■ Patients who are planned for treatment with Abiraterone ■ PSMA-avid disease on Ga PSMA scan	177Lu-PSMA NR	Abiraterone with Prednisolone	PSA reduction at 24 weeks	NR	Tata Memorial Hospital
NCT04443062/ Bullseye	(n=58) ■ Male aged ≥18 years with adenocarcinoma of the prostate ■ No prior hormonal therapy[49] or taxane-based chemotherapy[50] ■ Radiotherapy or surgery appears to be no option ■ Positive 18F-PSMA-PET-CT	177Lu-PSMA NR	Deferred ADT	Disease Progression	January 1, 2023	Radboud University Medical Center

[48] Patients with prior treatment of new generation antiandrogens will be included.

[49] Including any androgen directed treatment such as Finasteride, Dutasteride, Bicalutamide, Apalutamide, Abiraterone or Enzalutamide.

[50] Including Docetaxel or Cabazitaxel.

Identifier/ Trial name	Patient population	Intervention/ Setting	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04343885/ UpFrontPSMA	(n=140) ■ Male aged ≥18 years with metastatic adenocarcinoma of the prostate ■ PSA > 10ng/ml	177Lu-PSMA+ Docetaxel NR	Docetaxel	PSA rate at 12 months	April 2024	Peter MacCallum Cancer Centre
NCT04720157/ PSMAddition	(n= 1,126) ■ Male aged ≥18 years with metastatic prostate cancer ■ Positive PSMA- disease. ■ Treatment-naïve OR minimally treated with LHRH agonist/antagonists[51]; if received, prior LHRH agonist/antagonist, adjuvant/neo-adjuvant setting must have been discontinued > 12 months before consent signature, CYP17 inhibitor, or ARDT	177Lu-PSMA-617 NR	ARDT + ADT	Radiographic PFS	August 28, 2024	Novartis Pharmaceuticals
NCT05496959/ LUNAR	(n=100) ■ Male aged ≥18 years with prostate adenocarcinoma ■ Oligorecurrent prostate cancer	177Lu-PSMA-I&T (also called 177Lu-PNT2002) + SBRT NR	SBRT	PSMA PET/CT-based PFS	September 1, 2024	Jonsson Comprehensive Cancer Center

Abbreviations: ADT – androgen deprivation therapy, ARDT – androgen receptor-directed therapy. CT – computer tomography, LHRH – luteinizing hormone-releasing hormone, mCRPC – metastatic castration-resistant prostate cancer, mHSPC – metastatic hormone-sensitive prostate cancer (mHSPC), PET – positron emission tomography, PFS – progression-free survival, PSA – prostate-specific antigen, PSMA – prostate-specific membrane antigen, SABR – stereotactic ablative body radiotherapy

[51] Luteinizing Hormone-Releasing Hormone (LHRH) agonist/antagonist could be with or without first generation anti-androgen (e.g. Bicalutamide or Flutamide).

Literature search strategies

Search strategy for Cochrane

Search Name: Lutetium177 PSMA therapy for prostate cancer	
Search date: 12/12/2022 18:41:00	
Comment: MEL Update 2023 (SW/R)	
ID	Search
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	(prostat* NEAR (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-carcinom* OR neoplasm*)) (Word variations have been searched)
#3	#1 OR #2 (Word variations have been searched)
#4	MeSH descriptor: [Lutetium] explode all trees
#5	(lutetium) (Word variations have been searched)
#6	(Lu* NEAR (177 OR 617 OR I&T OR PSMA)) (Word variations have been searched)
#7	(PSMA NEAR (Lu* OR 177 OR 617 OR I&T)) (Word variations have been searched)
#8	(J591) (Word variations have been searched)
#9	MeSH descriptor: [Prostate-Specific Antigen] explode all trees and with qualifier(s): [therapeutic use – TU]
#10	(radioligand*) (Word variations have been searched)
#11	(radio-ligand*) (Word variations have been searched)
#12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 (Word variations have been searched)
#13	#3 AND #12 (Word variations have been searched)
#14	#3 AND #12 with Cochrane Library publication date Between Dec 2018 and Dec 2022 (Word variations have been searched)
#15	#3 AND #12 with Publication Year from 2018 to 2022, in Trials (Word variations have been searched)
#16	#14 OR #15 (Word variations have been searched)
#17	(conference proceeding):pt
#18	(abstract):so
#19	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#20	#17 OR #18 OR #19
#21	#16 NOT #20
Total hits: 42	

Search strategy for Embase

Search Name: Lutetium177 PSMA therapy for prostate cancer		
Search date: 12.12.2022		
No.	Query Results	Results
#49.	#47 NOT #48	741
#48.	#47 AND 'Conference Abstract'/it	446
#47.	#46 AND [17-12-2018]/sd NOT [13-12-2022]/sd	1,187
#46.	#45 AND ([english]/lim OR [german]/lim)	1,920
#45.	#19 AND #44	1,930
#44.	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43	9,242
#43.	((radioligand* OR 'radio ligand*') NEAR/5 (therap* OR treat* OR regimen* OR program*)):ti,ab,de	1,065
#42.	'radioligand'/exp/dd_dt	140
#41.	'prostate specific antigen'/exp/dd_dt	213

#40.	j591:ti,ab,de	411
#39.	'monoclonal antibody j591'/exp	334
#38.	(psma NEAR/5 (lu* OR '177' OR '617' OR i&t)):ti,ab,de	1,562
#37.	(lu* NEAR/5 ('177' OR '617' OR i&t OR psma)):ti,ab,de	8,142
#36.	'lutetium prostate specific membrane antigen 617 lu 177'/exp	16
#35.	#26 AND #34	1,661
#34.	#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	85,249
#33.	'glutamate carboxypeptidas*':ti,ab,de	714
#32.	'glutamate carboxypeptidase ii'/exp	472
#31.	'folate hydrolas*':ti,ab,de	121
#30.	'folate hydrolase 1'/exp	18
#29.	psma*:ti,ab	14,852
#28.	(prostat* NEAR/2 antigen):ti,ab,de	72,519
#27.	'prostate specific antigen'/exp	66,926
#26.	#20 OR #21 OR #22 OR #23 OR #24 OR #25	7,817
#25.	'177 lu':ti,ab,de	3,944
#24.	177lu:ti,ab,de	1,666
#23.	'lu 177':ti,ab,de	3,350
#22.	lu177:ti,ab,de	808
#21.	(lutetium* NEAR/1 177):ti,ab,de	5,524
#20.	'lutetium 177'/exp	5,185
#19.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #17 OR #18	92,337
#18.	(('castration resistant' OR 'hormon* resistant' OR metasta* OR 'androgen insensitiv*') NEAR/5 ('prostat* cancer*' OR 'prostat* tumor*' OR 'prostat* tumour*' OR 'prostat* carcinom*' OR 'prostat* adenom*' OR 'prostat* adenoc*' OR 'prostat* adeno-c*' OR 'prostat* neoplasm*')):ti,ab,de	43,831
#17.	#11 AND #16	90,948
#16.	#12 OR #13 OR #14 OR #15	1,079,845
#15.	'androgen* insensitiv*':ti,ab,de	5,041
#14.	metasta*:ti,ab,de	1,067,466
#13.	'hormone resistant':ti,ab,de	1,082
#12.	'castration resistant':ti,ab,de	22,006
#11.	#9 OR #10	321,910
#10.	(prostat* NEAR/5 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm*)):ti,ab,de	321,735
#9.	'prostate cancer'/exp	254,413
#8.	aipc:ti,ab	336
#7.	hrpc:ti,ab	1,089
#6.	crprc:ti,ab	6
#5.	crpc:ti,ab	8,275
#4.	'androgen independent prostate cancer'/mj	11,013
#3.	'hormone resistant prostate cancer'/mj	11,013
#2.	'castration resistant prostate cancer'/mj	11,013
#1.	'metastatic prostate cancer'/mj	161

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 09, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to December 09, 2022>	
Search date: 12.12.2022	
ID	Search
1	exp Prostatic Neoplasms/ (174740)
2	(prostat* adj5 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*)).mp. (252986)
3	1 or 2 (252986)
4	exp Neoplasm Metastasis/ (252196)
5	metasta*.mp. (888142)
6	((castrat* or hormon*) adj resist*).mp. (21165)
7	androgen* insensitiv*.mp. (3964)
8	4 or 5 or 6 or 7 (911903)
9	3 and 8 (65306)
10	exp Prostatic Neoplasms, Castration-Resistant/ (9308)
11	((((castrat* or hormon*) adj resist*) or (metasta* or androgen* insensitiv*)) adj5 (prostat* adj5 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*))).mp. (38595)
12	CRPC.ti,ab. (6002)
13	CRPRC.ti,ab. (5)
14	HRPC.ti,ab. (786)
15	AIPC.ti,ab. (277)
16	9 or 10 or 11 or 12 or 13 or 14 or 15 (66129)
17	exp Lutetium/ (1840)
18	lutetium*.mp. (3922)
19	(Lu* adj5 "177").mp. (3003)
20	17 or 18 or 19 (4907)
21	exp Prostate-Specific Antigen/ (34188)
22	(Prostat* adj5 Anti?gen*).mp. (59358)
23	PSMA*.mp. (10765)
24	folate hydrolas*.mp. (121)
25	exp Glutamate Carboxypeptidase II/ (2402)
26	glutamat* carboxypeptidas*.mp. (2568)
27	21 or 22 or 23 or 24 or 25 or 26 (64576)
28	20 and 27 (864)
29	(Lu* adj5 ("177" or "617" or I&T or PSMA)).mp. (37921)
30	(PSMA adj5 (Lu* or "177" or "617" or I&T)).mp. (1510)
31	J?591.mp. (127)
32	exp *Prostate-Specific Antigen/tu [Therapeutic Use] (33)
33	radio?ligand*.mp. (32825)
34	"Therapeutic Use".fs. (2842967)
35	33 and 34 (1406)
36	radioligand therap*.mp. (929)
37	28 or 29 or 30 or 31 or 32 or 35 or 36 (40226)
38	16 and 37 (1398)
39	limit 38 to (english or german) (1384)
40	limit 39 to dt=20181217-20221212 (985)
41	limit 39 to ed=20181217-20221212 (794)
42	40 or 41 (1083)
43	remove duplicates from 42 (557)

Search strategy for HTA-INATHTA

14	((((radioligand*) OR (PSMA) OR ("Prostate-Specific Antigen"[mhe]) OR (Lu 177*) OR (lutetium*) OR ("Lutetium"[mhe])) AND (((prostat*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-carcinom* OR neoplasm*)) OR ("Prostatic Neoplasms"[mhe]))) FROM 2018 TO 2023) AND (English OR German)[Language],"5","2022-12-12T18:11:43.000000Z"
13	(((radioligand*) OR (PSMA) OR ("Prostate-Specific Antigen"[mhe]) OR (Lu 177*) OR (lutetium*) OR ("Lutetium"[mhe])) AND (((prostat*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-carcinom* OR neoplasm*)) OR ("Prostatic Neoplasms"[mhe]))) FROM 2018 TO 2023,"6","2022-12-12T18:11:19.000000Z"
12	((radioligand*) OR (PSMA) OR ("Prostate-Specific Antigen"[mhe]) OR (Lu 177*) OR (lutetium*) OR ("Lutetium"[mhe])) AND (((prostat*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-carcinom* OR neoplasm*)) OR ("Prostatic Neoplasms"[mhe])),"36","2022-12-12T18:10:27.000000Z"
11	((radioligand*) OR (PSMA) OR ("Prostate-Specific Antigen"[mhe]) OR (Lu 177*) OR (lutetium*) OR ("Lutetium"[mhe])) AND (((prostat*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-carcinom* OR neoplasm*)) OR ("Prostatic Neoplasms"[mhe])),"36","2022-12-12T18:07:50.000000Z"
10	(radioligand*) OR (PSMA) OR ("Prostate-Specific Antigen"[mhe]) OR (Lu 177*) OR (lutetium*) OR ("Lutetium"[mhe]),"48", "2022-12-12T18:07:06.000000Z"
9	radioligand*,"1","2022-12-12T18:06:35.000000Z"
8	PSMA,"3","2022-12-12T18:06:25.000000Z"
7	"Prostate-Specific Antigen"[mhe],"35","2022-12-12T18:05:36.000000Z"
6	Lu 177*,"13","2022-12-12T18:04:05.000000Z"
5	lutetium*,"7","2022-12-12T17:58:22.000000Z"
4	"Lutetium"[mhe],"4","2022-12-12T17:58:02.000000Z"
3	((prostat*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-carcinom* OR neoplasm*)) OR ("Prostatic Neoplasms"[mhe]),"389","2022-12-12T17:57:40.000000Z"
2	(prostat*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-carcinom* OR neoplasm*),"373","2022-12-12T17:57:23.000000Z"
1	"Prostatic Neoplasms"[mhe],"314","2022-12-12T17:55:12.000000Z"
Total hits: 5	

HTA Austria
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