



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1686 – ¹⁷⁷Lutetium PSMA i&t for metastatic castrate resistant prostate cancer

Applicant: **A group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists (AANMS)**

Date of MSAC consideration: **28-29 July 2022**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

A codependent application was received by the Department of Health from a group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists (AANMS), requesting, in the context of progressive metastatic castrate-resistant prostate cancer (mCRPC), Medicare Benefits Schedule (MBS) listing of:

- (i) prostate specific membrane antigen positron emission tomography/computerised tomography (PSMA PET/CT) to determine eligibility for
- (ii) ¹⁷⁷Lutetium PSMA imaging and therapy (¹⁷⁷Lu PSMA i&t) and 24-hour post-therapy single-photon emission/computed tomography/computerised tomography (SPECT/CT).

Although the Applicant Developed Assessment Report (ADAR) did not specify post-therapy SPECT/CT after each treatment cycle in the proposed item descriptor for ¹⁷⁷Lu PSMA i&t, the description of the intervention in the ADAR states “The Applicant proposes post-treatment SPECT/CT be included within the ¹⁷⁷Lu PSMA MBS descriptor as part of routine treatment.” The proposed fee is also stated to include post-treatment SPECT/CT.

2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of 1) ¹⁷⁷Lu PSMA i&t therapy for treatment of progressive mCRPC and 2) whole body PSMA PET/CT to identify those eligible for ¹⁷⁷Lu PSMA i&t. MSAC acknowledged the high clinical need for this population with advanced disease, and the consumer preference for ¹⁷⁷Lu PSMA therapy over its comparators of best supportive care and cabazitaxel. MSAC noted the limitations in the evidence

comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products, but concluded from the evidence available that these two products are mutually noninferior and thus considered the evidence for ¹⁷⁷Lu PSMA-617 to be relevant for ¹⁷⁷Lu PSMA i&t. MSAC accepted the high certainty from the evidence that ¹⁷⁷Lu PSMA i&t therapy is acceptably safe and effective, but that the incremental cost-effectiveness ratio (ICER) was too high and uncertain.

Consumer summary

This is an application from a group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine, requesting Medicare Benefits Schedule (MBS) listing of a ¹⁷⁷Lutetium prostate-specific membrane antigen imaging scan and therapy (¹⁷⁷Lu PSMA i&t) to treat patients with metastatic castrate-resistant prostate cancer.

Metastatic castrate-resistant prostate cancer is a type of advanced prostate cancer that has spread to other parts of the body. In Australia, 3,000 men die each year from this cancer.

A new therapy is proposed for the treatment of metastatic castrate-resistant prostate cancer which no longer responds to standard treatments called PSMA-targeted radionuclide therapy. This therapy uses a radioactive chemical (called a radionuclide) that is linked to a molecule that targets the PSMA receptor on prostate cancer cells. When the molecule binds to the PSMA receptor, the radioactive chemical can enter the prostate cancer cell and kill it. ¹⁷⁷Lu PSMA i&t is a type of PSMA-targeted radionuclide therapy. Whole body PSMA positron emission tomography/computed tomography is used to select those eligible for ¹⁷⁷Lu PSMA i&t therapy.

MSAC acknowledged the clinical need for this therapy, and that patients prefer it over other last-line options. MSAC also considered it to be a safe and effective therapy option for men with metastatic-resistant prostate cancer who have failed most other standard available therapies. However, MSAC was not convinced that, as proposed and on the basis of the available evidence, this therapy was good value for money.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support public funding of 1) ¹⁷⁷Lu PSMA i&t therapy for metastatic-resistant prostate cancer and 2) whole body PSMA positron emission tomography/computed tomography to identify those eligible for ¹⁷⁷Lu PSMA i&t therapy. MSAC considered ¹⁷⁷Lu PSMA i&t therapy to be a safe and effective treatment, but was concerned that, as proposed and on the basis of the available evidence, it did not represent good value for money.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from a group of academic specialists, co-sponsored by the AANMS, is for MBS listing of ¹⁷⁷Lu PSMA i&t to treat patients with progressive mCRPC. MSAC noted that ¹⁷⁷Lu PSMA i&t is currently available under the Therapeutic Goods Administration's (TGA's) Special Access Scheme and funded by the Department of Veterans' Affairs (DVA). MSAC noted that an alternative product, ¹⁷⁷Lu PSMA-617, is not currently registered by the TGA in Australia.

MSAC noted that ¹⁷⁷Lu PSMA i&t therapy is delivered by appropriately trained and accredited nuclear medicine specialists in specialist outpatient facilities. MSAC noted that the proposal also includes PSMA PET/CT to allow appropriate patient selection, and SPECT/CT for post-treatment monitoring and assessment (for each cycle of ¹⁷⁷Lu PSMA i&t therapy). MSAC noted that after consideration by the PICO Advisory Subcommittee (PASC), the applicant removed the

requirement (and proposed MBS item) for confirmatory testing with whole body ¹⁸F-fluorodeoxyglucose (FDG) PET/CT for appropriate patient selection.

MSAC noted that the proposed population is patients with mCRPC after progressive or symptomatic disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor. MSAC noted 3,000 patients die each year in Australia from mCRPC and the significant morbidity associated with bone metastasis requiring analgesia and skeletal related events. MSAC noted that the pre-MSAC response highlighted limitations with current standard of care, notably cabazitaxel, with many patients with advanced disease opting to forego cabazitaxel due to its toxicity and electing instead to commence palliative care. MSAC acknowledged the high clinical need for effective new therapies for progressive mCRPC.

MSAC noted that all consumers, specialists and the majority of organisations who provided input were supportive of the application. The Royal Australian and New Zealand College of Radiologists (RANZCR) raised a concern that there is no policy framework in place for theranostics before MSAC's consideration of this application, and it did not support the AANMS Position Statement of Practice of Theranostics. MSAC also noted from public consultation feedback that there is currently inequitable access to ¹⁷⁷Lu PSMA i&t therapy due to its limited availability and high costs.

MSAC noted in the clinical management algorithm that patients eligible for ¹⁷⁷Lu PSMA i&t are those who have had a positive PSMA PET/CT (maximum standardised uptake value [SUV_{max}] of >15 at ≥ 1 disease site and $SUV_{max} >10$ at all measurable sites) and have adequate marrow/liver/renal function. Patients receive up to six cycles of ¹⁷⁷Lu PSMA i&t therapy at six-weekly intervals.

MSAC noted that the comparator for the diagnostic test is no testing with PSMA PET/CT, while the comparators for the therapy are cabazitaxel, or standard care if prior cabazitaxel or unable/unwilling to undergo treatment with cabazitaxel. MSAC considered these to be appropriate and that ¹⁷⁷Lu PSMA i&t therapy would replace or displace cabazitaxel and would displace best supportive care.

MSAC noted the Evaluation Sub-Committee (ESC) advice for the item descriptors and agreed with the suggestions, including for the therapeutic item to be amended to specify "followed 24 hours later by whole body PSMA single-photon emission computed tomography (SPECT)" (see Table 2). MSAC noted that as requested by ESC, the pre-MSAC response included a breakdown of the proposed fee of \$8,000 for ¹⁷⁷Lu PSMA i&t. The applicant also reiterated that the fee of \$8,000 per dose would be sufficient to cover the costs of safe delivery of the service across all settings in Australia.

MSAC noted that the primary supporting clinical trial data for ¹⁷⁷Lu PSMA i&t provided in the application consisted of two randomised trials that used the product ¹⁷⁷Lu PSMA-617. MSAC noted that ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 have related, but not identical, structures, with the differences being their chelators and linking portions. ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 have been shown to have high specific PSMA receptor binding in mice, with similar IC_{50} values, similar tumour uptake, and some features suggesting slightly less uptake of ¹⁷⁷Lu PSMA-617 in kidneys and salivary glands.¹ MSAC noted the results of a tissue kinetics and radiation dose study involving empirical testing of the differences between ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 in a direct comparison in 138 patients. MSAC considered that the radiation doses delivered to tumours and normal tissues were similar, MSAC noted the results of a safety and response study

¹ Ruijgrok EAM, van Vliet N, Dalm SU, de Blois E, van Gent DC, Haeck J et al. (2020). Extensive preclinical evaluation of lutetium-177-labeled PSMA-specific tracers for prostate cancer radionuclide therapy. *European Journal of Nuclear Medicine and Molecular Imaging* **48**(5):1339-1350.

involving in a matched pair analysis of 110 patients (55 for ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617, respectively). MSAC considered that the rate of clinically relevant toxicities was low for both compounds, and there were no relevant differences for overall survival (OS). Moreover, based on the results from five studies provided in the ADAR and an additional study added by the commentary, MSAC considered ^{177}Lu PSMA i&t and ^{177}Lu PSMA-617 to be radioequivalent, having similar efficacy, biodistribution and safety. Thus, MSAC concluded from the evidence available that these two products are mutually noninferior for patient outcomes and thus considered the evidence for ^{177}Lu PSMA-617 to be relevant for ^{177}Lu PSMA i&t which was required for its subsequent acceptance of the results of the clinical evaluation and the clinical aspects of the modelled economic evaluation across these two ^{177}Lu PSMA products. However MSAC was not prepared to generalise this conclusion to include other ^{177}Lu PSMA products. Instead MSAC considered it necessary for an MBS item descriptor to appropriately define the ^{177}Lu PSMA therapy (if subsequently supported). Throughout this document, MSAC has therefore referred to specific ^{177}Lu PSMA products, either ^{177}Lu PSMA i&t or ^{177}Lu PSMA-617.

MSAC noted from the ADAR that ^{177}Lu PSMA i&t is currently produced under Good Laboratory Practice (GLP), not Good Manufacturing Practice (GMP). MSAC noted that in Australia, radiopharmaceuticals can be produced onsite for use in nuclear medicine facilities in hospitals under a TGA exemption. MSAC noted that it was unclear when or if the manufacturer of ^{177}Lu PSMA-617 might apply for approval or funding in Australia. MSAC noted the differences between GMP and GLP standards, but concluded that the available evidence did not suggest that ^{177}Lu PSMA i&t produced under GLP would necessarily be clinically inferior to ^{177}Lu PSMA-617 produced under GMP.

MSAC noted that eligibility for the VISION trial was set at uptake greater than liver activity (a threshold which the submission considered to be typically an SUV_{max} of 5, however, MSAC considered this to be approximate, and may vary across patients in the range of 2–7). The VISION trial did not use post-therapy SPECT/CT (but did have eight-weekly diagnostic CT plus bone scans for 24 weeks, then 12-weekly up to two years to assess progression), and the control arm was best supportive care. Eligibility for the TheraP trial was set at $\text{SUV}_{\text{max}} \geq 20$ at disease site and >10 at all measurable sites, used post-therapy SPECT/CT, and the control arm was cabazitaxel.

Noting the differences in SUV_{max} thresholds used in the trials, MSAC queried whether the thresholds chosen in the application (>15 at ≥ 1 disease site and >10 at all measurable sites) were appropriate. MSAC noted from the ADAR that PSMA PET/CT using a PSMA SUV_{max} threshold of ≥ 15 results in at least similar effectiveness compared with an SUV_{max} greater than liver activity. MSAC noted from a conference abstract presented at the [2022 American Society of Clinical Oncology \(ASCO\) Annual Meeting²](#) that an SUV_{mean} of 10 (which is similar to an SUV_{max} of 15) is highly predictive of patient response to therapy. MSAC also noted that there were no significant differences in reported health outcomes using different SUV_{max} thresholds (based on naïve comparisons), and the ESC advice that a higher and more restrictive SUV_{max} threshold is a practical and safe approach when introducing a novel therapy. Overall, based on the available evidence, MSAC considered the proposed SUV_{max} thresholds in the application to be appropriate, noting that this could be reviewed and adjusted if higher certainty evidence becomes available.

MSAC noted that the pre-MSAC response addressed ESC's request to provide additional evidence supporting the use of SPECT/CT 24 hours after ^{177}Lu PSMA i&t therapy. The applicant indicated that SPECT/CT is used to detect limited or exceptional response, so may be used to reduce futile

² [TheraP: \$^{177}\text{Lu}\$ -PSMA-617 \(LuPSMA\) versus cabazitaxel in metastatic castration-resistant prostate cancer \(mCRPC\) progressing after docetaxel—Overall survival after median follow-up of 3 years \(ANZUP 1603\). | Journal of Clinical Oncology \(ascopubs.org\)](#)

or unnecessary treatment cycles. The applicant referred to the LuPIN trial that showed that SPECT imaging parameters correlated with patient outcomes such as PSA progression-free survival (PFS), while the Australian-based RE-SPECT trial demonstrated that SPECT/CT could be used to personalise treatment for mCRPC, reducing the number of futile cycles without compromising patient outcomes. MSAC noted that SPECT/CT is currently being used in Australian clinical practice following ¹⁷⁷Lu PSMA i&t therapy as a baseline for future comparisons, to implement treatment holidays in exceptional responders (which reduces futile radiation exposure and saves these doses, restricted to a maximum of six cycles, for later) and to consider therapy change if there has been significant disease progression. MSAC noted that SPECT/CT also enables radiation dosimetry of metastases and kidneys, which facilitates an adjustment of administered activity if this is considered appropriate. Overall, MSAC considered it appropriate for an MBS item descriptor for the ¹⁷⁷Lu PSMA therapy (if subsequently supported) to retain the proposed specification “followed 24 hours later by whole body Lu PSMA single-photon emission computed tomography (SPECT)”.

For comparative safety, MSAC noted from the trials that treatment with ¹⁷⁷Lu PSMA-617 was associated with a low incidence of adverse events (AEs) that led to dose reduction, interruption or discontinuation. MSAC noted that there were no deaths attributed to study treatment in the TheraP trial. In the VISION trial, less than 0.1% of patients experienced a fatal AE that was considered to be related to ¹⁷⁷Lu PSMA-617 therapy. MSAC considered that ¹⁷⁷Lu PSMA-617 (and thus ¹⁷⁷Lu PSMA i&t) is inferior in safety compared with best supportive care, as there were more short-term AEs for ¹⁷⁷Lu PSMA-617 in the TheraP trial. MSAC considered that the different short-term side-effect profiles of ¹⁷⁷Lu PSMA-617 and cabazitaxel made direct comparison difficult (e.g. diarrhoea is worse with cabazitaxel) but that the safety of ¹⁷⁷Lu PSMA-617 (and thus ¹⁷⁷Lu PSMA i&t) is at least noninferior (and likely superior as claimed) to cabazitaxel.

For clinical effectiveness, MSAC considered from the trials that ¹⁷⁷Lu PSMA-617 (and thus ¹⁷⁷Lu PSMA i&t) is superior for PSA response, overall response rate, PFS, and several quality of life domains and patient reported outcomes (e.g. pain scores) compared with cabazitaxel and best supportive care. Similarly, MSAC considered that ¹⁷⁷Lu PSMA-617 (and thus ¹⁷⁷Lu PSMA i&t) is superior to best supportive care for median OS and has similar OS at three years compared with cabazitaxel.

MSAC noted that the economic evaluation was a cost-effectiveness analysis incorporating a cost-utility analysis. MSAC noted that the partitioned survival model had three health states: PFS (utility value 0.74), progressed disease (utility value 0.59), and dead (utility value 0) and adopted a proportional hazards approach. MSAC noted that in the TheraP trial, patient reported outcomes and quality of life were better with ¹⁷⁷Lu PSMA-617 than cabazitaxel, suggesting that the utility of PFS should be higher with ¹⁷⁷Lu PSMA i&t than cabazitaxel. However, MSAC noted that ESC considered the utilities to be appropriate and noted the ICER was not overly sensitive to changes in utility values (see Table 12).

MSAC noted that there were three key drivers of the economic model. The first was cabazitaxel OS, which the ADAR assumed to be the same as the OS hazard ratio (HR) of ¹⁷⁷Lu PSMA-617 versus best supportive care (HR=0.62). The second key driver was extrapolation, where the treatment effect continued beyond 20.9 months in the trial period for up to 10 years. The third key driver was the time horizon, which was 10 years in the base case.

MSAC noted the ESC’s concerns with the proportional hazards approach and extrapolation method for OS and PFS, but the applicant maintained in its pre-MSAC response that the methods used in the ADAR base case were appropriate, as the parametric curves used showed the best statistical (lowest AIC/BIC) fit (i.e. aligned best to the trial data) and also produced clinically plausible long-term estimates, as validated by results from other trials and local expert opinion.

MSAC noted that the applicant's pre-MSAC response responded to an ESC request by providing all available updated results from the TheraP trial including replacing assumption-based parameters in the model with the updated data. This resulted in amending the ¹⁷⁷Lu PSMA i&t: cabazitaxel OS and PFS HR to 1 (i.e. from 0.62 in the base case) and 0.62 (from 0.63), respectively based on the three-year follow-up data from the TheraP trial.

MSAC noted that the pre-MSAC response also responded to an ESC request by providing multivariate sensitivity analyses with a time horizon respecified to seven years (reduced from 10 years) and using the three-year follow-up data from the TheraP trial. This increased the ICER from \$81,650 per quality-adjusted life year (QALY) in the ADAR base case to \$202,659 per QALY (see Table 13). However, MSAC also noted that the applicant considered the comparator should be weighted more towards best supportive care due to the toxicity of cabazitaxel, so used a comparator split of 75% best supportive care to 25% cabazitaxel. MSAC noted that this was also similar to the comparator split in olaparib in mCRCP (March 2021 Pharmaceutical Benefits Advisory Committee (PBAC) Public Summary Document [PSD]). Based on available evidence, MSAC considered this was appropriate. MSAC noted that removing the assumed effectiveness in terms of OS of cabazitaxel in the pre-MSAC model meant that the weighting of cabazitaxel versus standard care had a significant influence on the economic model, decreasing the ICER from \$202,659 per QALY to \$111,405 per QALY. MSAC noted the ICER was further improved to \$98,551 per QALY when compared with best supportive care alone. However, MSAC considered this time horizon used in these sensitivity analyses to be inappropriate for the proposed population, noting that it is not consistent with previous advice from the PBAC for medicines in later-line mCRPC treatment (Olaparib March 2021 PSD). MSAC advised that a time horizon of five years would be more appropriate in the base case model, noting that this change would increase the ICER.

In relation to the financial implications, MSAC noted the pre-MSAC response also responded to an ESC request by providing recalculations which assumed 18% of patients receiving Lu-PSMA would then receive cabazitaxel, 15% of eligible patients would receive Lu-PSMA (uptake) and a comparator split of 75% best supportive care: 25% cabazitaxel (consistent with the pre-MSAC economic model). On this basis, the estimated maximum financial implications to the Government health budget would be \$13.3 million in Year 1 to \$28.6 million in Year 6 (see Table 15).

MSAC considered that training standards and accreditation that adequately protect patients would be essential. MSAC noted that the Department supports the Royal Australasian College of Physicians (RACP) and the RANZCR approving training and accreditation. MSAC noted that the Committee for Joint College Training (CJCT) has members appointed by RANZCR and RACP and is the body that sets training requirements for nuclear medicine. It has already ratified the training and accreditation standards for theranostics proposed by the AANMS, which are being incorporated into the nuclear medicine training program. MSAC noted that while the Department supports the AANMS's proposed "grandparenting" arrangements, the Department did not consider the training requirements to be practical or achievable, and would restrict use. MSAC considered that, as the requirements were for multiple types of radionuclide therapy (which is a standard part of nuclear medicine and not a novel technology) and not restricted to Lu PSMA, it should be readily available and achievable.

Overall, MSAC noted the limitations in the evidence comparing ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 products, but concluded from the evidence available that these two products are mutually noninferior and thus considered the evidence for ¹⁷⁷Lu PSMA-617 to be relevant for ¹⁷⁷Lu PSMA i&t. MSAC accepted the high certainty from the evidence that ¹⁷⁷Lu PSMA i&t therapy is acceptably safe and effective, but that the economic model generated an ICER per QALY close to \$100,000 for several potentially plausible scenarios which was unacceptably high for the

proposed population and expected utilisation and was underestimated if a more appropriate 5-year time horizon were adopted. MSAC advised that an ICER in the range of those for other treatments accepted by PBAC using a 5-year time horizon in later-line mCRPC would be more likely to be acceptable. MSAC advised that the applicant consider how the ICER may be reduced including whether the proposed intervention should be placed after cabazitaxel and against best supportive care, a subgroup in which it demonstrated more favourable cost effectiveness. MSAC also had concerns that the ICER was too uncertain due to the model sensitivity to OS differences between ¹⁷⁷Lu PSMA i&t and cabazitaxel, as well as the time horizon used. MSAC advised that any resubmission should be considered through the standard pathway via ESC.

Other matters

MSAC noted that patent-related issues were raised in the public consultation. MSAC noted that advising on patent matters is not within its Terms of Reference and considered this to be a matter for government.

4. Background

MSAC has not previously considered PSMA PET/CT for this purpose, nor ¹⁷⁷Lu PSMA i&t with subsequent SPECT/CT.

5. Prerequisites to implementation of any funding advice

Consistent with other radiopharmaceutical products for which the administration is funded through the MBS, the proposed product for the therapeutic intervention (¹⁷⁷Lu PSMA i&t), is produced under Good Laboratory Practice (GLP) in Australia. GLP-compliant production of ¹⁷⁷Lu PSMA i&t is the current standard of care for the provision of radiopharmaceutical treatments for mCRPC across Australia, within trials and clinically. It is routinely used in nuclear medicine departments for radiopharmaceutical production across Australia. GLP production of ¹⁷⁷Lu PSMA i&t is currently available through the TGA exemption for production of radiopharmaceuticals in public or private hospitals for local use and not for on-sale.

6. Proposal for public funding

The key change from the ratified PICO Confirmation was that the ADAR removed the requirement (and proposed MBS item) for confirmatory testing with FDG PET/CT as a diagnostic component to help determine eligibility for the therapeutic intervention.

The proposed item descriptor for PSMA PET/CT requested in the ADAR is provided in Table 1, with suggestions from the Department identified as deleted text being struck out and inserted text being in italics.

Table 1 Proposed item descriptor for PSMA PET/CT with subsequent suggestions

Category 5 - Diagnostic Imaging Services
MBS item XXXX Whole body prostate specific membrane antigen (PSMA) positron emission tomography (PET)/ computerised tomography (CT) study, performed for the assessment of suitability for ¹⁷⁷ Lutetium 177 PSMA therapy in a patient with metastatic castrate resistant prostate cancer <i>after progressive disease has developed while on at least one who has previously received a taxane chemotherapy and at least one androgen receptor signalling inhibitor.</i>
(R) (Anaes)
Patient must be referred by oncology specialist.
Fee: \$1,300 \$1,400 Benefit: 85% = \$1,190

The request for PSMA PET/CT was radiotracer agnostic. The ADAR noted that ⁶⁸Ga or ¹⁸F labelled tracers are often used in Australia; ⁶⁸Gallium (⁶⁸Ga)-PSMA-11 was used in all trials presented in the ADAR for determining patient eligibility. The ADAR claimed PSMA radiotracers used for PSMA PET/CT for patients with mCRPC to determine eligibility for ¹⁷⁷Lu PSMA i&t are considered interchangeable for the following reasons:

- The PSMA PET/CT scan requested in this application is the same as that in Application 1632 from which a tracer agnostic PSMA PET/CT was accepted by MSAC in early-stage prostate cancer.
- MSAC advised in Application 1632 that it would be preferable not to specify any radiopharmaceutical tracers in the MBS item descriptors, “to allow clinicians and nuclear medicine physicians the choice of radiopharmaceutical tracer, and to allow for any future improved radiopharmaceutical tracers to be used as well” (MSAC PSD 1632, 2021, p.4).
- Compared to gallium 68 (⁶⁸Ga), ¹⁸F has a longer half-life of 110 minutes compared to 68 minutes for ⁶⁸Ga, making it more suitable for distribution from centralised GMP manufacturers. ⁶⁸Ga-based radiotracers are more commonly produced at the PET/CT location (“in-house”) with no, or very limited distribution.
- PET instrumentation and resultant maximum standardised uptake value (SUV_{max}) measurement is consistent for patients with mCRPC across available PSMA radiotracers in Australia. This is because all operating PET instrumentation which are listed on the Location Specific Practice Number (LSPN) for Medicare purposes undergo regular quality control/quality assurance program to ensure that SUV measurements are within acceptable limits.

The ADAR additionally summarised the results of Hoberück (2021)³ who reported a retrospective analysis of 46 prostate cancer patients (median age: 71 years) who underwent consecutive ⁶⁸Ga PSMA 11 and ¹⁸F PSMA 1007 PET/CT or PET/MRI within a mean of 12 ± 8.0 days. There was no significant difference between ¹⁸F PSMA 1007 and ⁶⁸Ga PSMA 11 in the SUV_{max} locally (31.5 vs 32.7; p=0.658), in lymph node metastases (28.9 vs 24.9; p=0.30) or in bone metastases (22.9 vs 27.6; p=0.286). The authors also reported that “[i]n [¹⁸F]-F-PSMA-1007 PET, more patients featured presumable unspecific uptake in the lymph nodes (52.2% vs. 28.3%; p<0.001), bones (71.7% vs. 23.9%; p<0.001) and ganglia (71.7% vs. 43.5%; p<0.001). Probable unspecific, exclusively [¹⁸F]-F-PSMA-1007-positive lesions mainly occurred in the ribs (58.7%),

³ Hoberück S, *et al.* Intraindividual comparison of [⁶⁸ Ga]-Ga-PSMA-11 and [¹⁸F]-F-PSMA-1007 in prostate cancer patients: a retrospective single-center analysis. EJMNM Res. 2021 Oct 19;11(1):109.

axillary lymph nodes (39.1%) and cervical ganglia (28.3%)". Hoberück (2021) concluded that "it appears reasonable to choose the PSMA radiotracer depending on local availability with attention to the greater occurrence of nonspecific bone findings with [¹⁸F]-F-PSMA-1007".

PASC noted that "although MSAC accepted that all available diagnostic PSMA agents may be equivalent (MSAC 1632 PSD), it is not established that all will give the same lesional SUV_{max} values as required in the PICO. PASC also noted that SUV can vary dependent on the camera and software used. The assessment report for this application will need to provide analytical concordance data across diagnostic PSMA ligand options available in Australia against the different PSMA criteria as proposed in the item descriptor and as defined in the trials." [PICO, p14].

The data from Hoberück (2021) did not provide concordance data across diagnostic PSMA ligand options available in Australia against the different PSMA criteria as proposed in the item descriptor (SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease) nor as defined in the two trials included as the main evidentiary basis of the ADAR (TheraP: PSMA PET/CT SUV_{max} ≥20 at a site of disease and >10 at all other measurable sites of metastatic disease or VISION: PSMA PET/CT SUV_{max} uptake greater than that of liver parenchyma (approximately SUV_{max} threshold of 5 (IQR 4-7)) in one or more metastatic lesions of any size in any organ system). Hoberück also included only six patients (13.0%) undergoing imaging for follow-up of known metastases or evaluation for PSMA-targeted radioligand therapy; the remainder had biochemically recurrent disease (n=30; 65.2%) or were undergoing primary staging (n=10; 21.7%).

The proposed item descriptor for treatment with ¹⁷⁷Lu PSMA i&t requested in the ADAR is provided in Table 2. Suggested changes in strikethrough and italicised text were added to be consistent with the ratified PICO Confirmation and subsequent Departmental advice.

Although the item descriptor in the ADAR did not include post-therapy SPECT/CT, the proposed fee was described in the ADAR to be "based around an assumption of \$5,500/dose for the labelling of ¹⁷⁷Lu to PSMA i&t peptide by a certified radiopharmaceutical scientist using the current TGA exemption for GLP compliant production. Administration costs of \$2,500 include the time required for safe administration by a theranostics medical specialist, nurse, medical radiation scientist, and medical physicist, and 30 minutes on a SPECT/CT machine following treatment." The Pre-ESC response confirmed that the proposed cost of ¹⁷⁷Lu PSMA i&t is inclusive of the production and preparation of ¹⁷⁷Lu, administration, immediate aftercare and post-treatment SPECT/CT. The applicant agreed with the explicit inclusion of post-treatment SPECT/CT in the item descriptor as suggested by the commentary if deemed appropriate by MSAC. The Department advised that "¹⁷⁷Lu emits a spectrum of radiation, including beta rays, which treat the malignancy, and, in addition, two low energy gamma rays which are useful for imaging with SPECT. The latter is an integral part of the theranostic service and does not require separate reimbursement", indicating that post SPECT/CT should be included. The ADAR stated the use of SPECT/CT may be an early indicator of limited response to ¹⁷⁷Lu PSMA-617 therapy based on serial imaging analysis after cycles 1 and 3 that indicated an increase in SPECT/CT total tumour volume was associated with shorter PSA PFS. The ADAR suggested that SPECT/CT may reduce the number of unnecessary subsequent Lu PSMA treatment cycles for patients. Post-treatment SPECT/CT was utilised in the TheraP trial, but not in VISION. In VISION, patients were reassessed after four cycles before receiving further cycles; only patients with evidence of response, signs of residual disease (on CT with contrast/MRI or bone scan) and good tolerance

to treatment could receive cycles five and six. Patients in both trials had a median of 5.0 cycles of treatment.

Table 2 Proposed item descriptor for ¹⁷⁷Lu PSMA with subsequent suggestions

<p>Category 3 - Therapeutic Procedures T3. Therapeutic Nuclear Medicine</p> <p>MBS item ZZZZ</p> <p>Administration of ¹⁷⁷Lutetium 177 PSMA i&t followed 24 hours later by whole body Lu PSMA single-photon emission computed tomography (SPECT) for treatment of a patients with progressive metastatic castrate resistant prostate cancer, after disease progression on chemotherapy and at least one androgen signalling inhibitor who is are PSMA-positive as determined by PSMA PET/CT defined as SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease, after progressive disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor</p> <p>Patients are A patient is eligible to claim once per cycle up to receive a maximum of 6 cycles in each course of therapy. Treatment can be ceased before 6 cycles if there is evidence of disease progression, unacceptable toxicity or if the patient is no longer deriving clinical benefit in the opinion of the treating Nuclear Medicine Specialist.</p> <p>Fee: \$8,000 Benefit: 85% = \$6,800</p>
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The item descriptor proposed by the ADAR specified ¹⁷⁷Lu PSMA i&t (unlike the ratified PICO Confirmation) which was ¹⁷⁷Lu PSMA product agnostic. The TheraP and VISION trials (the main evidentiary base for the ADAR) assessed ¹⁷⁷Lu PSMA-617; thus the ADAR was reliant on the acceptance that ¹⁷⁷Lu PSMA i&t and -617 are non-inferior.

The proposed item descriptor limited ¹⁷⁷Lu PSMA i&t use to those with ‘progressive’ mCRPC, however ‘progressive’ was not defined. ‘Progressive’ disease was defined as by a rising PSA as per Prostate Cancer Working Group 3 (PCWG3) criteria in TheraP. Other studies included in the ADAR stipulated that progression be additionally demonstrated with new sites of disease on conventional imaging (CT and bone scan). Although both the TheraP and VISION trials employed PSMA PET/CT for determining eligibility to the trials (see above for eligibility criteria), neither enrolled patients based on the maximum standardised uptake value (SUV_{max}) proposed in this ADAR (SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease).

The proposed item descriptor for ¹⁷⁷Lu PSMA i&t did not specify how ‘evidence of disease progression’ should be measured for treatment with ¹⁷⁷Lu PSMA i&t to cease before 6 cycles (i.e, prostate specific antigen (PSA) or radiographic progression as per TheraP or image-based progression only as per VISION). There is a marked difference between PFS reported in the ¹⁷⁷Lu PSMA-617 arms in TheraP (5.1 months) versus VISION (8.7 months), however similar radiologic/ radiographic PFS was observed in TheraP (approximately 9 months) compared with 8.7 months in VISION. The definition of PFS had implications for the cost-effectiveness and overall cost of listing ¹⁷⁷Lu PSMA i&t on the MBS.

Although treatment with androgen signalling inhibitors (ASIs) should cease upon initiation of treatment with ¹⁷⁷Lu PSMA i&t based on the PBS restrictions for ASIs, there is a possibility that use of ASIs may continue in patients undertaking treatment with ¹⁷⁷Lu PSMA i&t, as observed in the VISION trial.

7. Population

Patients who have:

- progressive or symptomatic mCRPC, AND
- received:
 - at least one ASI (abiraterone / enzalutamide / darolutamide via PBS/RPBS), AND
 - at least one line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS).

Diagnostic test: PSMA PET/CT

If positive (SUV_{max} of >15 at ≥ 1 disease site AND $SUV_{max} >10$ at all measurable sites) and adequate marrow/liver/renal function, patients are then eligible for

Therapeutic intervention:

- ^{177}Lu PSMA i&t, 7.5-8.5 GBq IVI every 6 weeks for up to 6 cycles
- ^{177}Lu PSMA SPECT/CT 24 hours post-infusion for each cycle

The diagnostic test (PSMA PET/CT) will not replace any currently funded tests.

The intervention (^{177}Lu PSMA i&t) will replace or displace cabazitaxel and displace best supportive care.

8. Comparator

Diagnostic test: no testing with PSMA PET/CT

Therapy:

- cabazitaxel; or
- standard care (interchangeable with best supportive care) if prior cabazitaxel, or unsuitable/unwilling for cabazitaxel.

9. Summary of public consultation input

Consultation input was received from 18 organisations and 23 individuals prior to PASC consideration in December 2021. Ahead of the MSAC consideration, two additional individuals and four additional organisations provided input (22 organisations in total), and 8 organisations provided further input.

All individual consumers and specialists and most organisations that provided input were supportive of the application.

Advantages of the proposed therapy were said to include the following:

- LuPSMA i&t therapy is well tolerated by patients, improves progression-free and overall survival, and improves quality of life for patients with advanced prostate cancer.
- Consumers noted benefits relating to extension of life, improvement in quality of life and wellbeing for themselves, their carers, family and friends.
- Consumers and consumer organisations considered that public funding would make this treatment more accessible and affordable, which would provide more equitable access to this treatment.
- This treatment is already funded through the Department of Veterans' Affairs (DVA) and so Medicare funding would allow all men with advanced prostate cancer in Australia to be eligible for funding of the treatment.

Disadvantages of the proposed therapy were said to include the following:

- It was noted that there were no randomised controlled trials (RCTs) to confirm the safety, efficacy and favourable benefit-risk profile of this agent, nor any study investigating the optimum administered activity, number of cycles, or interval between cycles.
- Two commercial companies considered that there was insufficient evidence to support the application's claim that ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 are equivalent, and that the limited body of available data does not allow for a reliable clinical comparison between the two structurally different products.
- One commercial company noted that ¹⁷⁷Lu PSMA i&t is proposed to be produced under TGA exemption in public hospitals. It considered that this would limit the availability of the service and may result in variable service due to the lack of regulated quality standards and oversight.
- A cancer treatment organisation considered that the main disadvantage would be the need for specialised facilities to safely administer this treatment and enough practitioners trained in this specialised area of medicine.

Other comments raised regarding the proposed interventions were:

- It was noted that the treatment provides improved palliation, improved mobility and could lead to reduced hospital admission and reduced need for palliative care services.
- A clinical specialist organisation noted that this intervention would provide another layer of treatment for patients who received all available treatment.
- A clinical specialist organisation considered that until there is further evidence, the treatment should not be combined with other PBS-listed agents such as androgen signalling inhibitors, chemotherapy or PARP inhibitors. It also considered that in some circumstances where a patient's disease might disappear after only say two doses, only to relapse later on, that retreatment should be possible for these patients up to a maximum cumulative of 6 doses.
- A clinical specialist organisation considered that this treatment must be administered in collaboration with nuclear radiologists, radiation oncologist and medical oncologists as part of a multidisciplinary team.
- Other organisations and specialists noted that services associated with the proposed treatment would be routine pathology (blood) tests, monitoring PSA levels, and PSMA PET/CT and FDG PET/CT scans for confirmation and location of prostate metastases and to select that patients who are most likely to benefit from the treatment.
- A cancer treatment organisation noted that FDG PET is not routinely used and based on the VISION trial, not required in significantly improving patient outcomes. It considered the cut-off for platelets of $>75 \times 10^9/L$ for patients to be too low, as most trials have specified platelets to be $>100 \times 10^9/L$.
- A cancer treatment organisation considered that the costs were underestimated, as the cost of the isotope would be around \$6,000, and costs associated with the physician, physicist, nurse, IV fluids, facility fee and dosimetry imaging would also need to be considered. A specialist noted that the proposed fee appeared to be based on at-cost pricing of ¹⁷⁷Lu. Another organisation advised that its members have found the cost to be at least \$10,000 per cycle and that the DVA are already funding patients to receive this treatment at this cost.

- One organisation was concerned that there is no policy framework in place for theranostics before MSAC considers this application and does not support the AANMS Position Statement of Practice of Theranostics.
- A commercial organisation raised concern regarding patent issues arising from any manufacture, use or administration of ¹⁷⁷Lu PSMA i&t in Australia.

10. Characteristics of the evidence base

Table 3 presents a summary of the key features of the included evidence.

Table 3 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
¹⁷⁷ Lu PSMA i&t versus - 617	2 single ¹⁷⁷ Lu PSMA-617 arms from 2 RCTs 2 retrospective studies (one ¹⁷⁷ Lu PSMA i&t and one ¹⁷⁷ Lu PSMA-617) 2 registries (¹⁷⁷ Lu PSMA i&t) 1 matched analysis found during the evaluation (¹⁷⁷ Lu PSMA i&t and ¹⁷⁷ Lu PSMA-617)	☒ k=7 n=1,237	High, comparison of single arms across studies
SUV _{max} >15 at a single site of disease and SUV _{max} >10 at all sites of measurable disease	2 single ¹⁷⁷ Lu PSMA-617 arms from 2 RCTs 3 prospective studies (¹⁷⁷ Lu PSMA-617)	☒ k=5 n=584	High, comparison of single arms across studies
Change in patient management	2 single ¹⁷⁷ Lu PSMA-617 arms from 2 RCTs 3 prospective studies (¹⁷⁷ Lu PSMA-617)	☒ k=5 n=1,455	High, comparison of single arms across studies
Health outcomes	2 OL RCTs 1) ¹⁷⁷ Lu PSMA-617 versus cabazitaxel 2) ¹⁷⁷ Lu PSMA-617 + BSc versus BSc alone	☒ k=2 n=1,031	Low, although both open-label

¹⁷⁷Lu = ¹⁷⁷lutetium; BSc = best supportive care; k = number of studies; n = number of patients; OL = open label; PSMA = prostate specific membrane antigen; RCT = randomised controlled trial; SUV_{max} = maximum standardised uptake value

11. Comparative safety

¹⁷⁷Lu PSMA-617 versus cabazitaxel

Overall, a lower proportion of patients experienced an adverse event (AE) in the ¹⁷⁷Lu PSMA-617 arm compared to the cabazitaxel arm (86.7% vs 92.9%, respectively) in TheraP. Grade 3 and 4 AEs were lower in the ¹⁷⁷Lu PSMA-617 arm compared to the cabazitaxel arm (32.7% vs 52.9%, respectively).

The pre-MSAC response from the applicant noted that the safety results over the 3-year follow-up of the TheraP trial showed consistency with the earlier follow-up.

¹⁷⁷Lu PSMA-617 + best supportive care versus best supportive care alone

A numerically higher proportion of patients experienced an AE in the ¹⁷⁷Lu PSMA-617 + best supportive care arm compared to the best supportive care alone arm (98.1% vs 82.9%, respectively) in VISION. Grade 3 and 4 AEs were numerically higher in the ¹⁷⁷Lu PSMA-617 + best supportive care arm compared to the best supportive care alone arm (52.7% vs 38.0%, respectively) in VISION.

The median number of cycles per patient of ¹⁷⁷Lu PSMA-617 in both TheraP and VISION was 5.0.

In the ¹⁷⁷Lu PSMA-617 arm in both TheraP and VISION, fatigue (75.5% and 75.3% in TheraP and VISION, respectively), dry mouth (43.1% and 22.9%), nausea (40.8% and 35.3%) and anaemia (27.6% and 31.8%) were the most common AEs. Almost all of these frequent AEs were Grade 1 or 2, with less than 6.0% of patients experiencing a Grade 3 or 4 AE with the exception of pain in TheraP and anaemia in VISION. In TheraP a high proportion of patients experienced any grade pain (72.4% vs 65.9% in the ¹⁷⁷Lu PSMA-617 and cabazitaxel arms, respectively). This included any patient that had bone, buttock, chest wall, flank, neck, extremity, tumour pain or pelvic pain. Nonetheless, less than 11.0% of patients experienced a Grade 3 or 4 AE and therefore the majority of patients experienced pain that was mild to moderate in intensity. None of these common AEs were Grade 5.

Overall, treatment with ¹⁷⁷Lu PSMA-617 was associated with a low incidence of AEs that led to dose reduction, interruption or discontinuation. There were no deaths attributed to study treatment in TheraP. In VISION, less than 1.0% of patients experienced an AE that led to death that was considered by the investigators to be related to ¹⁷⁷Lu PSMA-617.

¹⁷⁷Lu PSMA i&t versus -617

The safety of ¹⁷⁷LuPSMA i&t and ¹⁷⁷Lu PSMA-617 was compared across single arms from the studies. Overall, the incidence of Grade 3–4 anaemia (≥5% of patients) was between 0–6.5% for patients treated with ¹⁷⁷Lu PSMA i&t and between 0–12.9% for patients treated with ¹⁷⁷Lu PSMA-617. The incidence of Grade 3–4 thrombocytopenia was between 1.9–3.4% for patients treated with ¹⁷⁷Lu PSMA i&t and between 0–11.2% for patients treated with ¹⁷⁷Lu PSMA-617. Similarly, the incidence of Grade 3–4 lymphopenia was 5.7% for patients treated with ¹⁷⁷Lu PSMA i&t and between 0–11.2% for patients treated with ¹⁷⁷Lu PSMA-617.

12. Comparative effectiveness

¹⁷⁷Lu PSMA i&t versus -617

The ADAR claimed that ¹⁷⁷Lu PSMA-617 is radio-equivalent (radiation delivery equivalent) to ¹⁷⁷Lu PSMA i&t on the following basis:

- ¹⁷⁷Lu PSMA-617 and ¹⁷⁷Lu PSMA i&t have near-identical chemical structures. The difference is in the chemical chelator.
- There is clinical evidence to support that this minor difference has negligible impact on the radiation dose delivered to tumour and non-tumour organs between the two agents.
- Patient outcomes in terms of response rates (see Table 4) and safety are comparable between the two agents (see above), demonstrated across multiple clinical settings. The PSA50 response rates show no statistically significant differences between the therapies, given all point estimates for ¹⁷⁷Lu PSMA i&t lie within the 95% CIs of at least one estimate for ¹⁷⁷Lu PSMA-617 (although just for GenesisCare and the Peter MacCallum Cancer Centre (PMCC) compared with TheraP) and vice versa.

Table 4 Comparison of response rates, PFS and OS between ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617

	¹⁷⁷ Lu PSMA i&t			¹⁷⁷ Lu PSMA-617	
	GenesisCare Meyrick et al. (2021) N=191	St. Vincent's Hospital Internal registry data N=103	Peter MacCallum Cancer Centre Internal registry data N=45 ^d	TheraP Hofman et al. (2021) N=99	VISION Sartor et al. (2021) N=551
Median cycles per patient (range) ^a	NR	3.0 (2–4)	3.0 (3–5)	5.0 (3–6) ^b	5.0 (1–6)
Average follow-up, months	7 (3–14) ^b	12 (8–18) ^b	NR	18.4	20.3
Efficacy					
PSA50, n (%) [95% CI] ^e	89 (56%) ^c [48, 64]	61 (59%) [49, 69]	25 (56%) [39, 70]	65 (66%) [56, 74]	177 (46.0%) [41, 51]
PFS, months (95% CI)	4 (3–8) ^b	NR	5.3 (NR)	5.1 (3.4, 5.7)	8.7 (NR)
OS, months (95% CI)	12 (5–18) ^b	NR	13 (NR)	NR	15.3 (NR)

Source: Sartor et al. (2021) Supplementary Appendix Table S8 p.24, Hofman et al. (2021) p.800, Meyrick et al. (2021) Table 1 p. 373, Medhurst et al. (2022)

^a Cycles per patient reported for the Safety population (patients who received any treatment) in TheraP (N=85) and VISION (N=529).

^b Interquartile range

^c 159 patients were assessed for a biochemical response

^d 46 patients received Lu PSMA therapy. However, one patient was excluded as PSA at baseline was undetectable despite a high burden of disease

^e 95% CI around proportions calculated during the evaluation using StatsDirect

Abbreviations: ¹⁷⁷Lu PSMA, ¹⁷⁷lutetium prostate-specific membrane antigen; CI, confidence interval; i&t, imaging and therapy; NR, not reported; OS, overall survival; PFS, progression-free survival; PSA50, prostate-specific antigen reduction of 50% or more from baseline

The ADAR suggested that the numerically lower PFS and OS results observed for ¹⁷⁷Lu PSMA i&t may be explained by the median doses administered (3.0 versus 5.0 for ¹⁷⁷Lu PSMA-617).

The commentary suggested that MSAC may wish to consider whether these biological arguments, together with a comparison of reported response rates, PFS and OS across different cohorts of patients is sufficient to support a claim of mutual non-inferiority, i.e., patient outcomes are sufficiently similar following treatment with either agent. This needs to be accepted by MSAC in order for the evidence for ¹⁷⁷Lu PSMA-617 to be considered relevant for ¹⁷⁷Lu PSMA i&t or other ¹⁷⁷Lu PSMA products and for subsequent acceptance of the results of the clinical aspects of the modelled economic evaluation. Ideally, a minimal clinically important difference (MCID) in each outcome would be nominated to assist this clinical judgement.

A further matched analysis⁴ comparing ¹⁷⁷Lu PSMA-617 (n=55) and ¹⁷⁷Lu PSMA i&t (n=55) was identified during the evaluation which appeared to be published after the search conducted for the ADAR. The dosing schedule for both products differed from that requested in the ADAR, with administration every 8 weeks and to a maximum of 8 cycles. However, given the matched nature of the study and the reporting of the patient relevant outcome of overall survival, the study is considered to be of value. Hartrampf et al. (2022) reported that OS was 12 months for patients treated with ¹⁷⁷LuPSMA i&t and 13 months for patients treated with ¹⁷⁷Lu PSMA-617 (P=0.89), after a median of 3.0 cycles.

⁴ Hartrampf PE, Weinzierl FX, Buck AK, et al. Matched-pair analysis of [¹⁷⁷Lu]Lu PSMA I&T and [¹⁷⁷Lu]Lu PSMA-617 in patients with metastatic castration-resistant prostate cancer [published online ahead of print, 2022 Mar 4]. *Eur J Nucl Med Mol Imaging*. 2022;10.1007/s00259-022-05744-6

Schuchardt et al. (2021)⁵ specifically compared the kinetics and dosimetry of ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 in a cohort of patients with mCRPC (n=138). ¹⁷⁷Lu PSMA-617 demonstrated a higher whole body absorbed dose and a higher lacrimal glands absorbed dose, but a lower renal absorbed dose as compared to ¹⁷⁷Lu PSMA i&t. This study also demonstrated that the tumour doses for ¹⁷⁷Lu PSMA i&t and ¹⁷⁷Lu PSMA-617 were identical, with the radiation dose delivered not statistically different between the two agents.

SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease

To assess the choice of SUV_{max} threshold, the ADAR similarly compared response rates, PFS and OS across single arms from studies, see Table 5. The ADAR stated that this demonstrated that using an SUV_{max} threshold of ≥5 compared to >15 is significant but is only marginal for >15 compared to ≥20. The ADAR oversimplified the eligibility criteria of the studies. Only TheraP specified SUV_{max} at the disease site versus sites of all measurable disease, “SUV_{max} of at least 20 at a site of disease and greater than 10 at all other measurable sites of metastatic disease”. Emmett (2019)⁶ specified “PSMA intensity at metastatic sites that was greater than or equal to that of their liver uptake”; VISION specified “uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system”; Hofman (2018) specified “site of metastatic disease with intensity significantly greater than normal liver (SUV_{max} of tumour involvement at least 1.5 times SUV of liver”); and LuPIN specified “SUV_{max} >15 on PSMA PET at ≥1 site, an SUV_{max} >10 at all measurable sites”. Further, all studies except VISION also required there be no significant site with PSMA-negative/FDG-positive discordant disease.

Table 5 Comparison of outcomes for patients treated with ¹⁷⁷Lu PSMA-617, by SUV_{max} threshold adopted

Trial/Study	SUV _{max} ^a	FDG PET/CT	Median follow-up, months	Median (max) doses	PSA50 n/N (%) [95% CI]	PFS, months [95% CI]	OS, months [95% CI]
Emmett (2019)	≥5 at metastatic sites	Yes ^b	NR	3.0 ^c (4.0)	5/14 (35.7) [13, 65]	NR	11.5 [7.5, 15.5]
VISION	≥5 in ≥1 metastatic lesion	No	20.3	5.0 (6.0)	177/385 (46.0) [41, 51]	8.7 [NR]	15.3 [NR]
Hofman (2018)	≥10 at metastatic sites	Yes ^b	25.0	3.0 ^d (4.0)	17/30 (56.7) [37, 75]	7.6 [6.3, 9.0]	13.5 [10.4, 22.7]
LuPIN	>15 at ≥1 site, >10 at all measurable sites	Yes ^b	21.8	5.0 (6.0)	34/56 (60.7) [41, 74]	7.5 [5.9, 9.0]	19.7 [9.5, 30.0]
TheraP	≥20 at disease site, >10 at all measurable sites	Yes ^b	18.4	5.0 (6.0)	65/99 (65.7) [56, 75]	5.1 [3.4, 5.7]	NR

^a at disease site or “all sites of measurable disease”; ≥5 is greater than liver parenchyma; ≥10 is greater than 1.5x liver parenchyma

^b where FDG PET/CT used, no significant site with PSMA-negative/FDG-positive discordant disease

^c estimated based on “14 completed 2 cycles, 8 completed 3 cycles, and 3 completed all 4 cycles” (p19 Emmett 2019)

^d estimated based on “all 30 patients received cycle 1 of LuPSMA, and 28 (93%), 24 (80%), and 14 (47%) patients received cycles two, three, and four, respectively” (p829 Hofman 2018)

Abbreviations: ¹⁷⁷Lu PSMA, ¹⁷⁷lutetium prostate-specific membrane antigen; CI, confidence interval; NR, not reported; OS, overall survival; PFS, progression-free survival; PSA50, prostate-specific antigen reduction of 50% or more from baseline

⁵ Schuchardt C, Zhang J, Kulkarni HR, Chen X, Mueller D & Baum RP. 2021. Prostate-specific membrane antigen radioligand therapy using (177)Lu PSMA I&T and (177)Lu PSMA-617 in patients with metastatic castration-resistant prostate cancer: comparison of safety, biodistribution and dosimetry. *J Nucl Med*.

⁶ Emmett L, Crumbaker M, Ho B, et al. 2019. Results of a Prospective Phase 2 Pilot Trial of (177)Lu PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. *Clin Genitourin Cancer*, 17, 15-22

There is a numerical trend in increasing PSA50 response rates with increasing SUV_{max} thresholds based on point estimates (although there were also numerical differences in response rates in studies restricting enrolment based on similar SUV_{max} thresholds i.e., Emmett 2019 [35.7%] and VISION [46.0%], which may be explained by differences in median number of doses, 3.0 and 5.0, respectively).

Most point estimates for PSA50 response lie within the 95% CIs for at least one other estimate, the exception to this is Emmett (2019) with a point estimate of 35.7% being lower than all lower 95% CIs reported. Moreover, PSA50 is an intermediate or surrogate outcome and the ADAR has not demonstrated a link between PSA50 and patient-relevant outcomes such as PFS and in particular, OS. PFS and OS did not show the 'same' trend in increasing PFS and OS with increasing SUV_{max} thresholds. This suggests there may be no difference in PFS or OS based on SUV_{max} threshold.

The ADAR highlighted that this (≥ 5 compared to >15 is significant but is only marginal for >15 compared to ≥ 20) is consistent with findings from Emmett et al. (2019). Emmett (2019) provided a comparison of those with SUV_{max} <15 and >15 , which demonstrated patients with an SUV_{max} <15 had no response to ¹⁷⁷Lu PSMA-617 treatment. Emmett (2019) had a small sample size (n=14) and included only three patients with SUV_{max} <15 . Although it is true that only those with SUV_{max} >15 demonstrated a PSA50 response, one of 11 patients (9.1%) with SUV_{max} >15 did not show a response and another (9.1%) had a minimal response. Only five of 11 patients (45.5%) with SUV_{max} >15 achieved PSA50. The ADAR stated this suggests patients with a SUV_{max} >15 have adequate levels of PSMA expression to warrant significant ¹⁷⁷Lu PSMA treatment response. This is a reasonable conclusion, but the results in Table 5 similarly suggest that patients with a SUV_{max} ≥ 5 (46.0% in VISION) have adequate levels of PSMA expression for response, that may not be statistically significantly different to those with a SUV_{max} >15 (45.5% in those with SUV_{max} >15 in Emmett 2019). Exclusion of patients with SUV_{max} between 5 and 15 from the treated population in the Australian setting may not be adequately justified based on the available data.

The ADAR describes the difference between response rates in LuPIN (60.7%) enrolling those with SUV_{max} >15 compared with the Emmett (2019; 35.7%) and VISION (46.0%) studies, enrolling patients with SUV_{max} >5 "is therefore significant", which is in contrast to the ADAR's description of the response rates as being similar across all studies with rates ranging from 46.0% to 66.0% in its interpretation of the data presented for the comparison of ¹⁷⁷Lu PSMA i&t versus -617.

Change in patient management

The ADAR similarly approached the assessment of change in management by assessing the proportion of patients who met eligibility criteria for various studies, according to SUV_{max} thresholds, see Table 6. The number ineligible for ¹⁷⁷Lu PSMA-617 in the studies were similar, however, inexplicably, a numerically greater proportion of patients were deemed eligible in TheraP (90%) despite more stringent PSMA PET/CT threshold criteria (SUV_{max} ≥ 20 at disease site and ≥ 10 at all sites of measurable disease) compared with 87.7%-89.9% at SUV_{max} ≥ 5 , 83.7% at SUV_{max} ≥ 10 and 87.0% at SUV_{max} ≥ 15 . The reason for this is unclear but could potentially be due to unobserved differences in the cohorts of patients from whom those enrolled were derived or from differences in 'reading' and interpreting the scans.

Table 6 Comparison of change in management, by SUV_{max} threshold adopted

	SUV _{max} ≥5 ^a		SUV _{max} ≥10 ^b	SUV _{max} ≥15	SUV _{max} ≥20
	Emmett 2019 N=18	VISION N=1003	Hofman et al. (2018) N=43	LuPIN N=100	TheraP N=291
Patients scanned, no.	18 (100)	1003 (100)	43 (100)	100 (100)	291 (100)
Patients excluded					
Inadequate PSMA intensity, n (%)	2 (11.1)	123 (12.3)	7 (16.3)	13 (13.0)	29 (10.0)
FDG/PSMA mismatch, n (%)	0	NA		13 (13.0)	51 (17.5)
Other	2 (0.1) ^c	8 (0.8) ^d	6 (13.4) ^e	18 (18.0) ^f	11 (3.8) ^g
¹⁷⁷ Lu PSMA-617 therapy eligible, n (%)	14 (77.8)	831 (82.9)	30 (69.8)	56 (56.0)	200 (68.7)

^a SUV_{max} ≥ liver parenchyma, approximately equivalent to SUV_{max} ≥5

^b SUV_{max} 1.5 x liver parenchyma, approximately equivalent to SUV_{max} ≥10

^c 4 patients were ineligible for Lu PSMA therapy. Of the 4 men excluded 2 (11%) of 18 had inadequate PSMA intensity and 2 (11%) had inadequate marrow function

^d 3 patients had progressive disease, 2 had an adverse event, 2 died and 1 withdrew consent

^e Excluded for reasons based on exclusion criteria in the trial

^f Scan fails were due to clinical deterioration (6%), concurrent illness (3%), low haemoglobin (7%) or personal reasons (2%)

^g Reasons for 'other' were not reported

Abbreviations: ¹⁷⁷Lu PSMA-617, ¹⁷⁷lutetium prostate-specific membrane antigen 617; FDG, fluorodeoxyglucose; NA, not applicable; PSMA, prostate-specific membrane antigen; SUV_{max}, maximum standardised uptake value

Sources: Pathmanandavel et al. (2021) p.9, Emmett et al. (2019) p.18, Hofman et al. (2021) Figure 1 p.800, Sartor et al. (2021) p.1094, Hofman et al. (2018) Figure 1 p.828

Health outcomes

Two open-label, randomised trials formed the evidentiary basis for health outcomes of the ADAR:

- TheraP; compared ¹⁷⁷Lu PSMA-617 (n=99) versus cabazitaxel (n=101) in patients with an SUV_{max} of at least 20 at a site of disease and greater than 10 at all other measurable sites of metastatic disease (as per ⁶⁸Ga PSMA-11 PET/CT), **AND** no sites of metastatic disease with discordant 2-[¹⁸F] FDG-positive (FDG PET/CT) and PSMA-negative findings; and
- VISION; compared ¹⁷⁷Lu PSMA-617 + best supportive care (n=551) versus best supportive care alone (n=280) in patients with ⁶⁸Ga PSMA-11 (PET/CT) uptake greater than that of liver parenchyma (approximately SUV_{max} threshold of 5 (IQR 4-7)) in one or more metastatic lesions of any size in any organ system.

The results of the trials are presented in Table 7. Kaplan-Meier (KM) curves for OS in VISION and PFS in TheraP and VISION are presented in Figure 1, Figure 2 and Figure 3, respectively.

Table 7 Summary of ¹⁷⁷Lu PSMA-617 efficacy

	TheraP		VISION	
	¹⁷⁷ Lu PSMA-617	Cabazitaxel	¹⁷⁷ Lu PSMA-617 + BSc	BSc
Median follow-up (months)	18.4	18.4	20.9	20.9
Response rate (PSA50)				
N	99	101	385	196
Events, n (%)	65 (66)	37 (37)	177 (46)	14 (7)
RD (95% CI)	29% (16%, 42%)		39% (33%, 45%) *	
p-value	<0.0001		<0.00001 *	
Overall/objective response (CR+PR)				
N	NR	NR	319*	120*
Events, n (%)	NR (49) ¹	NR (24) ¹	95 (30)	2 (2)
RD (95% CI)	25 (NR)		28% (23%, 34%)⁵	
p-value	NR		<0.00001⁵	
Overall survival				
N	99	101	551	280
Events, n (%)	NR	NR	343 (62)	187 (67)
Median (95% CI), months	NR	NR	15.3	11.3
HR (95% CI)	NR	NR	0.62 (0.52, 0.74)	
p-value	NR	NR	<0.001	
Progression-free survival				
N	99	101	385	196
Events, n (%)	90 (91) ⁴	83 (82) ⁴	254 (66) ²	93 (47) ²
Median (95% CI), months	5.1 (3.4, 5.7)	5.1 (2.8, 6.0)	8.7	3.4
HR (95% CI)	0.63 (0.46, 0.86)		0.40 (0.29, 0.57)³	
p-value	0.0028		<0.001	

Bold indicates statistically significant difference

* in patients with evaluable disease at baseline (Patients with at least one target lesion or at least one non-target lesion)

¹ in patients with measurable disease by RECIST criteria at baseline

² Imaging-based progression-free survival

³ 99.2% CI

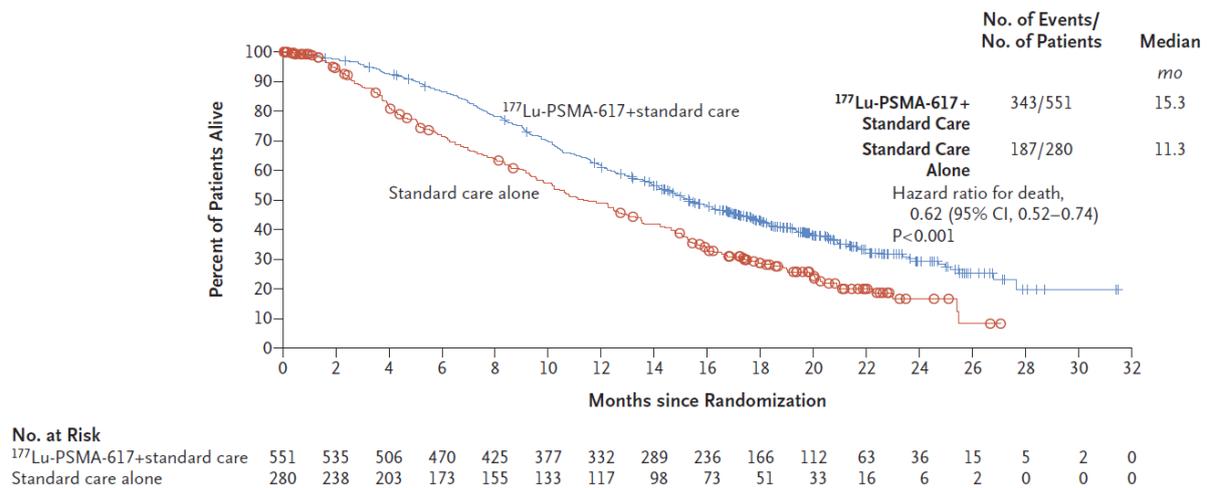
⁴ Radiographic or PSA progression-free survival

⁵ Calculated post-hoc using Review Manager 5.4.1 (Mantel-Haenszel, random effects)

Abbreviations: ADAR, applicant developed assessment report; BSc, best supportive care; CR, complete response; HR, hazard ratio; ¹⁷⁷Lu, lutetium-177; NR, not reported; PR, partial response; PSA50, prostate-specific antigen reduction of ≥50% from baseline; PSMA, prostate-specific membrane antigen; RECIST, Response Evaluation Criteria in Solid Tumours; RD, risk difference

Source: Section 2A of the ADAR

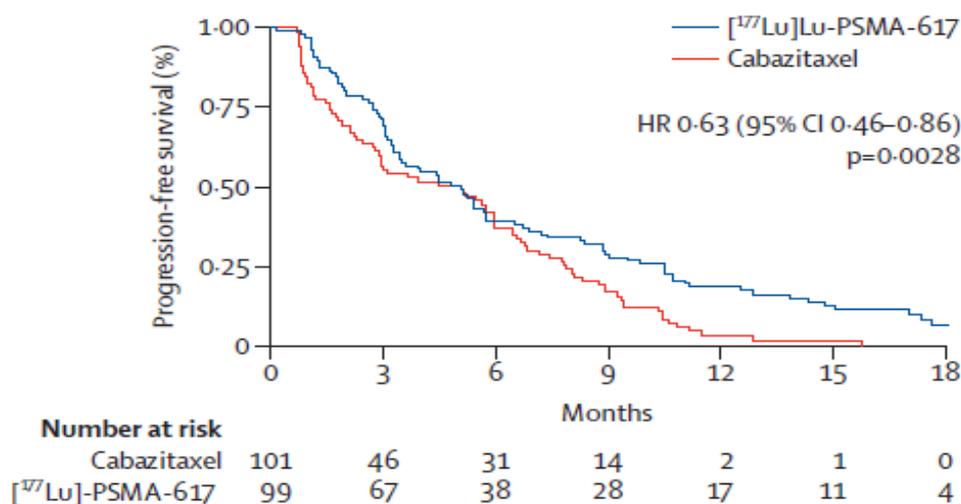
Figure 1 Overall survival in the VISION trial



Source: Sartor et al. (2021) Figure 2B, p 1098

Abbreviations: ¹⁷⁷Lu PSMA-617, ¹⁷⁷Lutetium prostate-specific membrane antigen-617

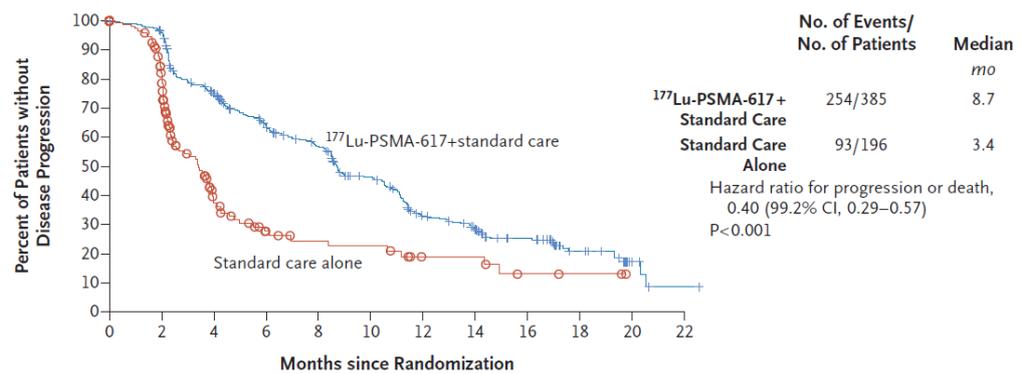
Figure 2 Radiographic or PSA PFS from the TheraP trial, ITT population



Source: Hofman et al. (2021) p. 801

Abbreviations: ¹⁷⁷Lu PSMA-617, ¹⁷⁷Lutetium prostate-specific membrane antigen 617; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival; PSA, prostate-specific antigen

Figure 3 Image-based PFS in VISION trial, rPFS population



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22
¹⁷⁷ Lu-PSMA-617+standard care	385	362	272	215	182	137	88	71	49	21	6	1
Standard care alone	196	119	36	19	14	13	7	7	3	2	0	0

Source: Sartor et al. (2021) Figure 2A, p 1098

Abbreviations: ¹⁷⁷Lu PSMA-617, ¹⁷⁷Lutetium prostate-specific membrane antigen 617; CI, confidence interval; PFS, progression-free survival

Across both TheraP and VISION, treatment with ¹⁷⁷Lu PSMA-617 was associated with statistically significantly prolonged PFS and overall/objective response rate compared to cabazitaxel and best supportive care (Table 7). Health-related quality of life for ¹⁷⁷Lu PSMA-617 also compared favourably compared to both cabazitaxel and best supportive care across multiple relevant instruments including FACT-P, EORTC QoL Questionnaire (QLQ-C30) and Patient DATA Form.

In VISION, treatment with ¹⁷⁷Lu PSMA-617 was also associated with a statistically significant OS advantage (HR=0.62 [95% CI: 0.52, 0.74]; p<0.001) when compared with best supportive care. After a median follow-up of 18.4 months, 90 deaths were documented in TheraP. Analysis of OS is planned to occur after 170 deaths.

Updated 3-year results from TheraP trial

As requested by ESC, the pre-MSAC response provided the available results from the TheraP trial, which were not evaluated. The applicant stated that OS results after median follow-up of three years for TheraP showed that for patients who received ¹⁷⁷Lu PSMA-617, OS was similar to those who received cabazitaxel (restricted mean survival time to 36 months was 19.1 months vs. 19.6 months in the ¹⁷⁷Lu PSMA-617 and cabazitaxel arm, respectively; HR=0.97 [95% CI: 0.70, 1.4]; p=0.99) (Table 8, Figure 4). Results for PFS remained consistent at 36 months follow-up in TheraP (HR=0.62 [95% CI: 0.45, 0.85]; p=0.0028) (Table 8, Figure 5).

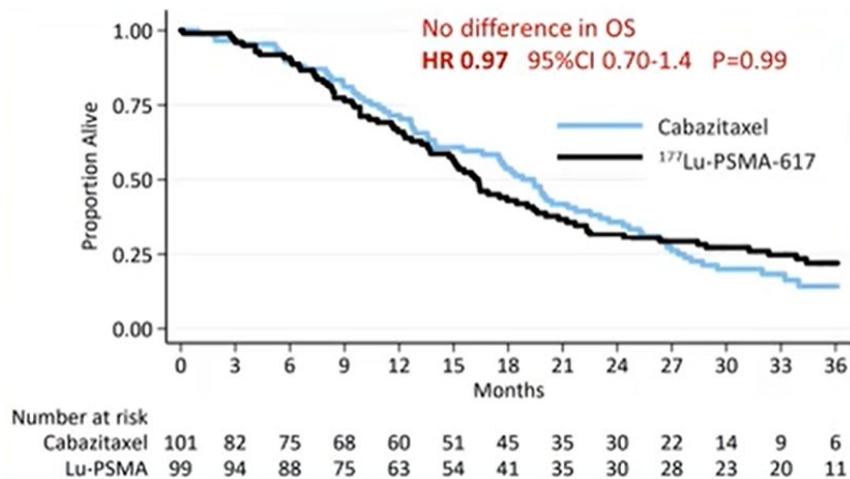
Table 8 Overview of OS and PFS in TheraP at median follow-up 36 months

	¹⁷⁷ Lu-PSMA-617 (n=99)	Cabazitaxel (n=101)
Median follow-up, months	36	36
Deaths, n (%)	77 (77.8)	70 (69.3)
OS (ITT)		
Restricted mean survival time to 36 months, months	19.1	19.6
Difference (95% CI)	-0.5 (-3.7 to +2.7)	
HR, 95% CI; p-value	0.97 (0.70, 1.4); 0.99	
PFS (PSA and radiographic) (ITT)		
Restricted mean survival time to 36 months, months	7.1	5.0
Difference (95% CI)	2.1 (NR)	
HR, 95% CI; p-value	0.62 (0.45, 0.85); 0.0028	

Source: Table 1, p6 of the Pre-MSAC response (conference abstract; Hofman et al., 2022; Attachment 1)

Abbreviations: ¹⁷⁷Lu-PSMA, ¹⁷⁷Lutetium prostate-specific membrane antigen; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NR, not reported; PFS, progression-free survival; PSA, prostate specific antigen

Figure 4 Kaplan-Meier of OS in TheraP at median follow-up 36 months (ITT)

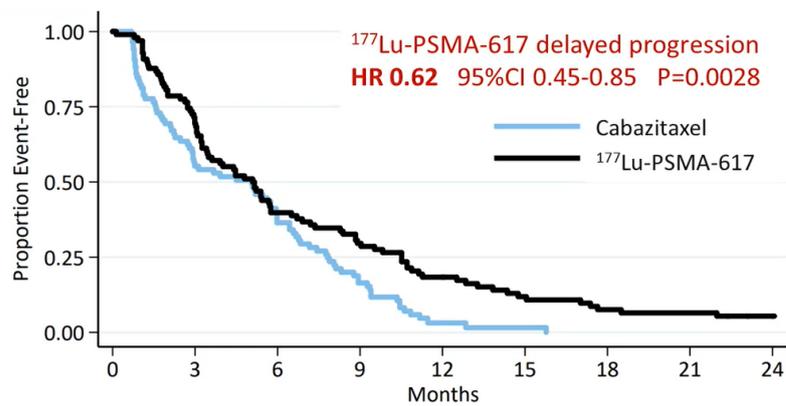


Source: Figure 1, p7 of the Pre-MSAC response (conference abstract by Hofman et al., 2022; Attachment 1)

Abbreviations: ¹⁷⁷Lu-PSMA, ¹⁷⁷Lutetium prostate-specific membrane antigen; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival

Note conference abstract was presented at the [2022 American Society of Clinical Oncology \(ASCO\) Annual Meeting](#)

Figure 5 Kaplan-Meier of PFS (PSA and radiographic) in TheraP at median follow-up 36 months (ITT)



Number at risk	0	3	6	9	12	15	18	21	24
Cabazitaxel	101	47	31	14	2	1	0	0	0
Lu-PSMA	99	68	39	29	17	11	7	6	3

Source: Hofman et al., 2022 (Attachment 1)

Abbreviations: ¹⁷⁷Lu-PSMA, ¹⁷⁷Lutetium prostate-specific membrane antigen; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival; PSA, prostate specific antigen

Note conference abstract was presented at the [2022 American Society of Clinical Oncology \(ASCO\) Annual Meeting](#)

Clinical claims

¹⁷⁷Lu PSMA i&t versus -617

The ADAR claimed that ¹⁷⁷Lu PSMA i&t can be considered radio equivalent (delivers the same radiation dose to cells) and delivers the same patient outcomes (efficacy and safety) as ¹⁷⁷Lu PSMA-617. The commentary noted that a comparison of reported PFS and OS across trials and studies may not be sufficient for making a claim of non-inferiority across the two radionuclides, which needs to be accepted by MSAC in order for the evidence presented for ¹⁷⁷Lu PSMA-617 to be considered relevant for ¹⁷⁷Lu PSMA i&t and for subsequent acceptance of the QALY results of the modelled economic evaluation. A minimally clinically important difference in PFS and OS should be nominated and a comparison should be made and considered against a nominated non-inferiority margin.

SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease

The ADAR claimed that the use of PSMA PET/CT using PSMA SUV_{max} threshold >15 (at a site of disease) results in at least similar effectiveness compared with the clinical utility standard (SUV_{max} ≥5 or SUV_{max} ≥20). The commentary considered this claim to be reasonably supported by the reported response rates in the evidence presented. However, the aim should have been to justify the nominated threshold which was not considered by the commentary to have been adequately supported by the evidence.

Health outcomes

The ADAR claimed that use of PSMA PET/CT and ¹⁷⁷Lu PSMA results in superior effectiveness compared with cabazitaxel and superior effectiveness compared with best supportive care. The commentary considered this would be better defined as:

The use of PSMA PET/CT and FDG PET/CT and ¹⁷⁷Lu PSMA-617 results in superior effectiveness compared with cabazitaxel among patients with mCRPC who have an SUV_{max} ≥20 at the disease site and >10 at all measurable sites of metastatic disease with no with PSMA-negative/FDG-positive discordant disease. The use of PSMA PET/CT and ¹⁷⁷Lu PSMA-617 results in superior effectiveness compared with best supportive care. The evidence presented in the ADAR supports these clinical claims.

The ADAR claimed that use of PSMA PET/CT and ¹⁷⁷Lu PSMA results in superior safety compared with cabazitaxel and inferior safety compared with best supportive care. The commentary considered this would be better defined as:

The use of PSMA PET/CT and FDG PET/CT and ¹⁷⁷Lu PSMA-617 results in superior safety compared with cabazitaxel among patients with SUV_{max} uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system. The use of PSMA PET/CT and ¹⁷⁷Lu PSMA-617 results in inferior safety compared with best supportive care. The evidence presented in the ADAR supports these clinical claims.

The commentary also noted that, as the MBS listing proposal relates to ¹⁷⁷Lu PSMA i&t or ¹⁷⁷Lu PSMA agnostic of product, the claims are dependent on MSAC accepting that:

- ¹⁷⁷Lu PSMA i&t is non-inferior to ¹⁷⁷Lu PSMA-617 for the evidence presented in the TheraP and VISION trials to be applicable to ¹⁷⁷Lu PSMA i&t.
- The results reported in the TheraP and VISION trials, among patients who are not entirely representative of the proposed population with respect to PSMA 'positivity' would be relevant to the proposed population:
 - TheraP excluded those with SUV_{max} >15 to <20 at a single site of disease and SUV_{max} >10 at all sites of measurable disease, which are included in the proposed population (SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease); and
 - VISION included those with SUV_{max} >liver parenchyma (approximately 5.4; IQR 4.2 – 7.6), some of whom would be excluded in the proposed population.
- The results reported in the TheraP and VISION trials, where PSMA PET/CT was conducted with ⁶⁸Ga for patient eligibility would be relevant under the proposed restriction which suggests that PSMA PET/CT be radiotracer agnostic.
- The results reported in TheraP, where eligibility further depended on FDG PET/CT where there were no significant sites with PSMA-negative/FDG-positive discordant disease would be applicable to a proposed population where FDG PET/CT would not be required for patient eligibility.
- The incremental benefit observed in the VISION trial, relied upon in the economic evaluation, which did not include post-treatment SPECT/CT would be applicable to the proposed population where post-therapy SPECT/CT would be used.

13. Economic evaluation

A cost-effectiveness analysis (incorporating a cost-utility analysis) was performed using a partitioned survival cohort approach using data from both VISION (Sartor et al., 2021) and TheraP (Hofman et al., 2021). A proportional hazards approach was adopted. The commentary considered that the use of a proportional hazards approach is a large cause of uncertainty in the model as the hazard ratios (HRs) seen over the trial durations may not be continued during the extrapolated time period. This is a particularly prominent issue given the proportion of the model's time horizon in the base case informed by extrapolation (approximately 85%). The impact this has on the ICER is unclear. A 10-year time horizon was applied. The commentary considered that the time horizon was excessive; the PBAC has previously considered that a 5 year time horizon would more appropriately represent later-line mCRPC treatment (paragraph 7.11, Olaparib March 2021 PSD) and the modelled economic evaluation presented for abiraterone was reported to be 7 years in duration (Abiraterone November 2012 PSD). The key components of the model are presented in Table 9.

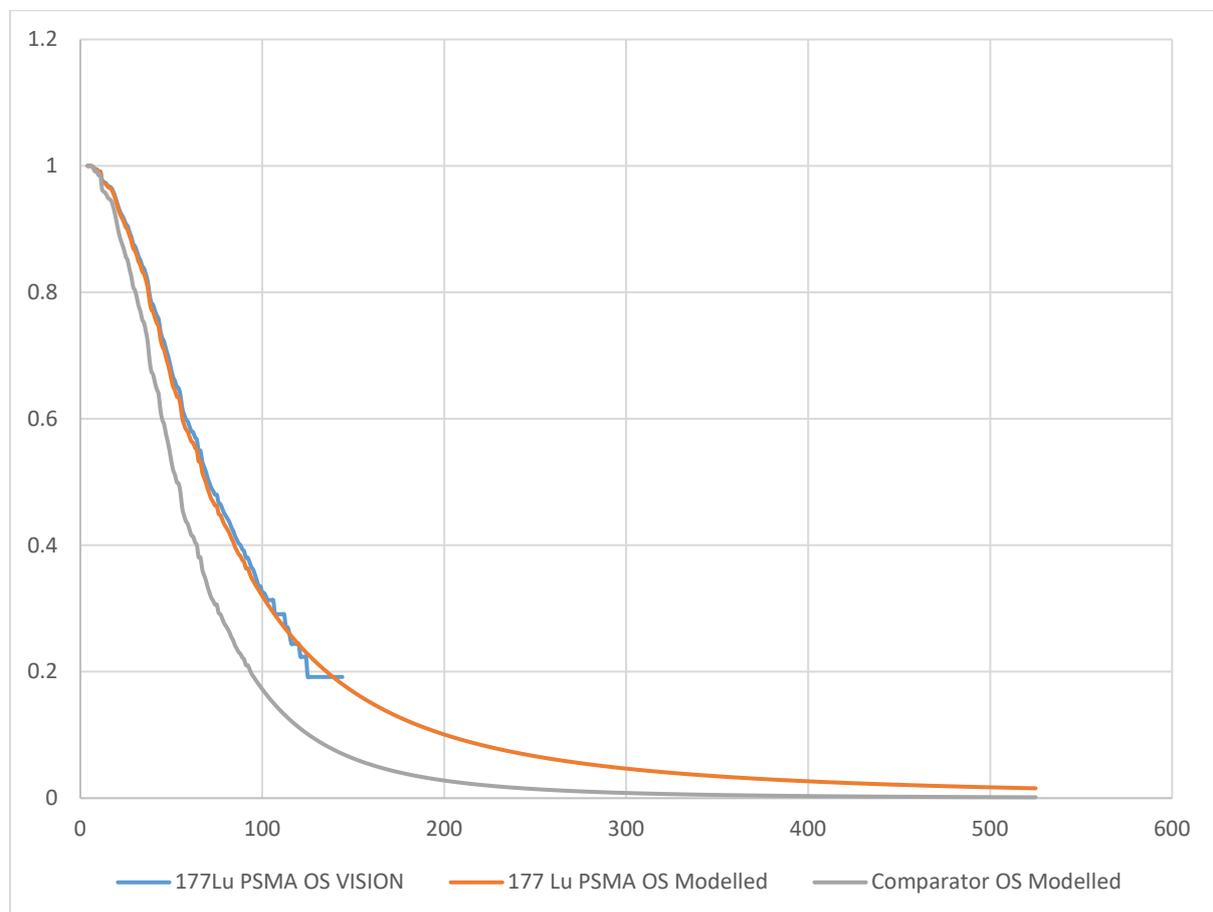
Table 9 Key components of the economic evaluation

Component	Description
Perspective	Australian healthcare perspective
Population	Patients with mCRPC who have received at least one ASI (i.e. abiraterone, enzalutamide or darolutamide via PBS/RPBS) as well as at least one line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS) in the setting of mCRPC.
Prior testing	Intervention: PSMA PET/CT (data informed by TheraP (Hofman et al., 2021)) Comparator: no prior testing
Comparator	Base case: weighted comparator of 75% cabazitaxel and 25% best supportive care. Alternative base case: weighted comparator of 25% cabazitaxel and 75% best supportive care. Alternative weightings were tested.
Type(s) of analysis	Cost-effectiveness analysis; cost-utility analysis
Outcomes	<ul style="list-style-type: none"> • Cost per life-year gained (cost/LYG) • Cost per quality-adjusted life year (cost/QALY)
Time horizon	10 years in the base case (vs median follow-up of 20.9 months in VISION (Sartor et al., 2021) and median follow-up of 18.4 months in TheraP (Hofman 2021)).
Computational method	Partitioned survival analysis, including proportional hazards approach
Generation of the base case	<p>Outcomes of PFS and OS for ¹⁷⁷Lu PSMA i&t were sourced directly from the ¹⁷⁷Lu PSMA-617 KM (ITT) data from VISION (Sartor et al., 2021). Parametric functions were fitted to ¹⁷⁷Lu PSMA-617 KM data (from t=0) to extrapolate PFS and OS to the model time horizon of 10 years.</p> <p>To model ¹⁷⁷Lu PSMA i&t outcomes: PFS and OS KM data for ¹⁷⁷Lu PSMA-617 were used until 20.9 months (median follow-up of VISION as reported in Sartor et al. (2021)). Beyond 20.9 months, parametric functions were used. The selection of parametric extrapolation was based on goodness-of-fit and clinical plausibility.</p> <p>To model cabazitaxel/best supportive care outcomes: Proportional hazards approach was adopted whereby hazard ratios for PFS and OS from TheraP and VISION (Hofman et al., 2021, Sartor et al., 2021)) were applied to the modelled PFS and OS in the ¹⁷⁷Lu PSMA i&t arm.</p>
Health states	Three health states: progression-free survival, progressed disease and death.
Utilities	<p>Progression-free survival: 0.74; Progressed disease: 0.59.</p> <p>The PBAC considered that the utility values used in the March 2021 olaparib submission (0.75 for progression-free; 0.70 for progressed disease) were higher than other utility value estimates in the literature (Olaparib March 2021 PBAC PSD). The abiraterone submission to the PBAC applied utilities from Sandblom et al (2004) (Abiraterone November 2012 PSD). The utilities reported in the publication were EQ5D scores of 0.538, 0.564 and 0.770 and EuroQOL VAS of 54.0, 53.2 and 70.0 for those who died of prostate cancer, died of other causes or were still alive on 31 Dec 2000, respectively. It is not clear which of these utilities were applied to each health state in the abiraterone submission, but these utility values are consistent with those used in the ADAR (if 0.77 was used for progression-free and 0.54 was used for progressed health states).</p>
Cycle length	1 week
Transition probabilities	<p>Health state allocation over time determined by PFS and OS data. In the base case, time on index treatment was approximated using PFS data.</p> <p>PFS and OS data for ¹⁷⁷Lu PSMA i&t were sourced from VISION (Sartor et al., 2021) representing a median follow-up of 20.9 months.</p>
Discount rate	5% for both costs and outcomes
Software	Microsoft Excel

Patients enter the model in the PFS state. In the base case, of those in the ^{177}Lu PSMA i&t arm, 90% are assumed to undergo treatment with ^{177}Lu PSMA i&t (the proportion meeting the PSMA PET/CT criteria in TheraP), with the remainder treated with cabazitaxel (75%)/best supportive care (25%). In the comparator arm, 75% are treated with cabazitaxel and are 25% treated with best supportive care. In each cycle, patients can either remain in the PFS health state, or transition to the PD or death health state. Patients who have progressed can remain in the PD state or transition to the death state but never go back to the PFS state. All patients eventually enter the death state.

Figure 6 presents the regenerated KM OS curve from the ^{177}Lu PSMA i&t arm from VISION and the extrapolated survival curves for ^{177}Lu PSMA i&t and comparator (75% cabazitaxel/25% best supportive care) applied in the model.

Figure 6 Kaplan Meier curve for overall survival for ^{177}Lu PSMA i&t from VISION, regenerated using WebPlotDigitizer, and the extrapolated survival curves for ^{177}Lu PSMA i&t and comparator (75% cabazitaxel/25% best supportive care) applied in the model base case (weeks)



Data from VISION was used to inform PFS and OS of ^{177}Lu PSMA i&t + best supportive care versus best supportive care alone. TheraP was used to inform the PFS of ^{177}Lu PSMA i&t versus cabazitaxel. In the absence of OS data from TheraP to inform the comparative effectiveness of ^{177}Lu PSMA i&t versus cabazitaxel, the ADAR base case assumed the comparative OS benefit for ^{177}Lu PSMA i&t versus cabazitaxel is the same for ^{177}Lu PSMA i&t versus best supportive care.

The use of the ^{177}Lu PSMA-617 + best supportive care versus best supportive care alone OS HR from VISION to inform the comparative effectiveness of cabazitaxel versus ^{177}Lu PSMA i&t in the model is an important issue creating a high level of uncertainty in the ICER given the inferred differences in effectiveness between best supportive care and cabazitaxel. This issue is

important given the base case analysis assumes 75% of patients in the comparator arm of the model are treated with cabazitaxel.

The approach used in the ADAR has the potential to underestimate the effectiveness of cabazitaxel on OS. The TROPIC trial⁷ provided a comparison of cabazitaxel 25 mg/m² once every three weeks plus prednisolone 10 mg daily with mitozantrone 12 mg/m² once every three weeks plus prednisolone 10 mg daily in patients with mCRPC with disease progression post docetaxel chemotherapy. Median overall survival was statistically significantly longer for patients treated with cabazitaxel than for those treated with mitozantrone (15.1 months versus 12.7 months; an incremental overall survival of 2.4 months [$p < 0.0001$]). The hazard ratio was 0.70 (95% CI: 0.59, 0.83) in favour of cabazitaxel (Cabazitaxel July 2011 PSD). In its consideration of abiraterone at the November 2011 PBAC meeting, the PBAC agreed that it was reasonable to assume that there is no overall survival benefit for mitozantrone and that placebo and mitozantrone are equivalent (Abiraterone November 2011 PSD).

Sensitivity analyses conducted during the evaluation using the upper and lower 95% confidence limits around the OS HR from VISION and applied to cabazitaxel only had substantial impacts on the ICER (decreased by 15.1%, increased by 24.5%, respectively). Further sensitivity analysis assuming a HR for OS of 0.885 ($0.62 * (1/0.70)$) and 1 (no difference) between ¹⁷⁷Lu PSMA i&t and cabazitaxel resulted in an increase of the ICER by 72.3% and 131.3%, respectively.

Costs relevant to PSMA PET/CT testing, ¹⁷⁷Lu PSMA i&t and cabazitaxel were appropriately included, as well as costs for treating Grade 3 or 4 adverse events. A price reduction for cabazitaxel came into effect on 1 April 2022, the results of the economic evaluation have been updated to reflect that price decrease. Although the model is predominantly based on VISION, where best supportive care therapies were reported, the ADAR did not apply costs related to those therapies. This may be an issue as there were differences in the relative use of various therapies between the groups. It is also notable that no costs associated with treatment of bone pain such as opioid use, ⁸⁹strontium (palliative isotope) and local radiotherapy were included.

The results of the economic evaluation (modified during the evaluation to reflect the recent price reduction of cabazitaxel) are presented in Table 10.

⁷ De Bono JS, et al. Prednisolone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; 376: 1147-54.

Table 10 Stepped derivation of the base case result of the economic evaluation (discounted)

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Step 1 (cost per LY – 90.8-week time horizon)					
¹⁷⁷ Lu PSMA i&t	\$63,127	\$24,074	1.154	0.173	\$139,283
Cabazitaxel/best supportive care	\$39,053		0.981		
Step 2 (cost per LY – 10-year time horizon)					
¹⁷⁷ Lu PSMA i&t	\$74,380	\$28,799	1.671	0.516	\$55,809
Cabazitaxel/best supportive care	\$45,581		1.155		
Step 3 (cost per QALY – 10-year time horizon)					
¹⁷⁷ Lu PSMA i&t	\$74,934	\$27,376	1.118	0.353	\$81,653
Cabazitaxel/best supportive care	\$47,558		0.765		

Abbreviations: ICER, incremental cost-effectiveness ratio; ¹⁷⁷Lu, lutetium-177; LY, life-year; PSMA, prostate specific membrane antigen; QALY, quality-adjusted life year

The key drivers of the model as summarised by the commentary are presented in Table 11.

Table 11 Key drivers of the model

Description	Method/value	Impact
		Base case: \$81,653/QALY gained
Cabazitaxel overall survival	Not reported in TheraP, so the ADAR assumed the overall survival hazard ratio of ¹⁷⁷ Lu PSMA i&t versus BSc (HR=0.62) is the same for cabazitaxel	High, favours ¹⁷⁷ Lu PSMA i&t Adjusting the hazard ratio by cabazitaxel versus mitozantrone to 0.89 increased the ICER to \$140,706/QALY gained.
Extrapolation	Treatment effect continued beyond 20.9-months in the trial period for up to 10 years	High, favours ¹⁷⁷ Lu PSMA i&t Using the second-best fitting function for overall survival increased the ICER to \$105,911/QALY gained.
Time horizon	10 years in the base case, which might be considered excessive	High, favours ¹⁷⁷ Lu PSMA i&t Reducing to 5 years increased the ICER to \$93,947/QALY gained.

Abbreviations: BSc, best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table 12 Sensitivity analyses for the modelled economic evaluation

	Incremental cost	Incremental QALYs	ICER	Impact
Base case	\$28,799	0.353	\$81,653	-
Discount rate 0% for costs and outcomes	\$30,080	0.408	\$73,675	-9.8%
Discount rate 3.5% for costs and outcomes	\$29,153	0.368	\$79,260	-2.9%
Time horizon of 7.5 years	\$28,528	0.334	\$85,319	+4.5%
Time horizon of 5 years	\$27,792	0.296	\$93,947	+15.1%
Testing				
Use PSMA PET/CT scanning data from VISION (86.6 87.7%)	\$28,089	0.334	\$81,759	+0.1%
Use PSMA PET/CT and FDG PET/CT scanning data from TheraP (90.0% and 80.5%, respectively) and FDG PET/CT cost (\$1,000)	\$24,365	0.284	\$85,788	+5.1%
Assume FDG PET/CT patient selection translates to OS benefit (HR decreased from 0.62 to 0.48 [0.62/1.3])	\$24,156	0.371	\$65,122	-20.2%

	Incremental cost	Incremental QALYs	ICER	Impact
Efficacy				
Next best statistically fitting PFS for ¹⁷⁷ Lu PSMA i&t (from log-normal to generalised gamma)	\$28,787	0.351	\$81,977	+0.4%
Next best statistically fitting OS for ¹⁷⁷Lu PSMA i&t (from log-logistic to generalised gamma)	\$29,290	0.277	\$105,911	+29.7%
Next best statistically fitting OS for ¹⁷⁷Lu PSMA i&t (from log-logistic to generalised gamma) AND time horizon of 5 years	\$28,756	0.266	\$108,293	+32.6%
Comparator				
Assume 0% cabazitaxel, 100% BSc	\$34,362	0.369	\$93,189	+14.1%
Assume 25% cabazitaxel, 75% BSc (alternative base case)	\$32,670	0.364	\$89,649	+9.8%
Assume 50% cabazitaxel, 50% BSc	\$30,827	0.359	\$85,823	+5.1%
Assume 100% cabazitaxel, 0% BSc	\$26,540	0.344	\$77,060	-5.6%
Lower bound 95% CI for OS HR (from 0.62 to 0.52) for both BSc and cabazitaxel	\$28,609	0.430	\$66,525	-18.5%
Upper bound 95% CI for OS HR (from 0.62 to 0.74) for both BSc and cabazitaxel	\$29,064	0.258	\$112,712	+38.0%
OS HR=0.62 versus BSc and HR=0.52 versus cabazitaxel	\$28,649	0.413	\$69,320	-15.1%
OS HR=0.62 versus BSc and HR=0.74 versus cabazitaxel	\$28,984	0.285	\$101,678	+24.5%
OS HR=0.62 versus BSc and HR=0.89 (0.62*(1/0.70)) versus cabazitaxel	\$29,221	0.208	\$140,706	+72.3%
OS HR=0.62 versus BSc and HR=1 versus cabazitaxel	\$29,396	0.156	\$188,854	+131.3%
Lower bound 95% CI for PFS HR vs cabazitaxel (from 0.63 to 0.46)	\$29,533	0.364	\$81,023	-0.8%
Upper bound 95% CI for PFS HR vs cabazitaxel (from 0.63 to 0.86)	\$28,083	0.340	\$82,567	+1.1%
Lower bound 99.2% CI for PFS HR vs BSc (from 0.40 to 0.29)	\$29,222	0.360	\$81,254	-0.5%
Upper bound 99.2% CI for PFS HR vs BSc(from 0.40 to 0.57)	\$28,406	0.346	\$82,117	+0.6%
Utilities				
15D utility values from Torvinen et al. (2013) (PFS: 0.80, PD: 0.67)	\$28,799	0.387	\$74,332	-9.0%
PFS: 0.86 (Krahn et al., 2007), PD: 0.635 (Wu et al., 2007) both sourced from Magnus et al. (2019)	\$28,799	0.400	\$71,922	-11.9%
Costs				
Allow vial sharing	\$29,814	0.353	\$84,530	+3.5%

Abbreviations: BSc, best supportive care; CI = confidence interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ¹⁷⁷Lu = lutetium-177; OS = overall survival; PSMA = prostate-specific membrane antigen; QALYs = quality-adjusted life years; PFS = progression-free survival

The commentary considered that the model was most sensitive to:

- the assumed effectiveness in terms of OS of cabazitaxel;
- the extrapolation functions used (predicting something we don't know); and
- the time horizon (questionable based on previous PBAC decisions).

Updated 3-year results from TheraP trial

As requested by ESC, the pre-MSAC response provided multivariate sensitivity analyses which were not evaluated. This analysis respecified the modelled time horizon and OS benefit vs. cabazitaxel (i.e. comparator OS). In addition, an alternative scenario is also presented varying the comparator weighting (Table 13).

Table 13 Results of scenario and sensitivity analyses

	Incremental cost	Incremental QALYs	ICER	Impact ²
Base-case presented in the PSCR ¹	\$28,798	0.353	\$81,650	N/a
As per base-case presented in PSCR + 7-year time horizon + incorporation of latest TheraP data ³ (MVS)	\$29,276	0.144	\$202,659	+148.2%
As per MVS + comparator split of 75% BSc: 25% cabazitaxel	\$32,493	0.292	\$111,405	+36.4%
As per MVS + comparator split of 100% BSc	\$34,000	0.345	\$98,551	+20.7%
As per MVS + assuming the average patient receives 3 ¹⁷⁷ Lu PSMA i&t cycles ⁴	\$16,994	0.144	\$117,640	+44.1%

¹ Base-case reflecting price reduction of cabazitaxel which came into effect on 1 April 2022. This was generated by changing the cabazitaxel AEMP in the CUA to \$946.16 to \$595.32. (It is unclear why these results are slightly different to those presented in Table 12.)

² Relative to the amended base case.

³ Amending ¹⁷⁷Lu PSMA i&t: cabazitaxel OS and PFS HR to 1 and 0.62, respectively.

⁴ Assumes a median of 18 weeks of treatment (1 dose every 6 weeks equating to 3 total doses)

Abbreviations: ¹⁷⁷Lu, lutetium-177; BSc, best supportive care; ICER, incremental cost-effectiveness ratio; MVS, multivariate scenario; PSCR, pre-subcommittee response; PSMA, prostate-specific membrane antigen; QALY, quality-adjusted life year

Source: Table 3, p8 of the pre-MSAC response

14. Financial/budgetary impacts

The financial implications to the MBS and PBS/RPBS resulting from the proposed listing of PSMA PET/CT and ¹⁷⁷Lu PSMA i&t are summarised in Table 14. As for the economic evaluation, the results below reflect the recent cabazitaxel price reduction.

The estimates were derived using the following assumptions:

- ‘Number of people who receive PSMA PET/CT’: 11.5% uptake in Year 1 (based on expert clinical opinion/applicant assumption), with a relative increase of 11.5% per year to determine the number of patients who undergo testing with PSMA PET/CT to determine ¹⁷⁷Lu PSMA i&t eligibility. The commentary considered that an initial uptake of 11.5% and relative increase of 11.5% per year for a last-line therapy in patients who are at the end of their clinical course appeared to be low. The ADAR appropriately tested this in sensitivity analyses, but only up to 15%. However, the uptake could be greater, although there may be constraints on growth in patient numbers given only certain centres can deliver the intervention.
- ‘Number of people who are eligible and receive ¹⁷⁷Lu PSMA i&t’: 90% of those undergoing PSMA PET/CT would meet eligibility criteria (SUV_{max} >15 at a site of disease and >10 at all other measurable sites of metastatic disease). Based on TheraP, where 262 of the 291 [90.0%] patients scanned with PSMA PET/CT showed adequate PSMA uptake [SUV_{max} ≥20 at a site of disease and >10 at all other measurable sites of metastatic disease]). Assume 100% of those who meet eligibility will receive ¹⁷⁷Lu PSMA i&t.
- ‘Number of people who would have otherwise had cabazitaxel’: 75% of those who are ‘eligible and receive ¹⁷⁷Lu PSMA i&t’, remainder would have otherwise received best supportive care (consistent with the base case of the modelled economic evaluation). All of this cabazitaxel use is assumed to be replaced, which is inconsistent with the modelled economic evaluation

that assumed 18% of patients had post ¹⁷⁷Lu PSMA i&t cabazitaxel treatment, reportedly based on TheraP. This could not be sourced from TheraP, however VISION reported subsequent use, 82 of 551 (14.9%) patients randomised to ¹⁷⁷Lu PSMA-617 in VISION underwent subsequent treatment with cabazitaxel.

Table 14 Net financial implications of PSMA PET/CT and ¹⁷⁷Lu PSMA i&t to the MBS and PBS/RPBS

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people eligible for PSMA PET/CT	3,004	3,043	3,083	3,124	3,165	3,206
Number of people who receive PSMA PET/CT	345	390	441	498	563	635
Netcost to the MBS for PSMA PET/CT (85% rebate applied)	\$411,092	\$464,379	\$524,574	\$592,571	\$669,382	\$756,150
Number of people who are eligible and receive ¹⁷⁷ Lu PSMA i&t	311	351	397	448	506	572
Net cost to the MBS for ¹⁷⁷ Lu PSMA i&t ^a (85% rebate applied)	\$9,961,141	\$11,252,340	\$12,710,908	\$14,358,542	\$16,219,748	\$18,322,211
Net cost to the MBS for PSMA PET/CT and ¹⁷⁷ Lu PSMA i&t ^a (85% rebate applied)	\$10,372,232	\$11,716,719	\$13,235,482	\$14,951,113	\$16,889,130	\$19,078,360
Change in use and cost of other health technologies						
Number of people who would have otherwise had cabazitaxel ^b	233	263	298	336	380	429
Net change in costs to the PBS/RPBS (minus co-pay)	-\$1,305,391	-\$1,474,601	-\$1,665,744	-\$1,881,664	-\$2,125,572	-\$2,401,096
Net change in cost to the MBS (85% rebate applied)	-\$163,577	-\$184,780	-\$208,732	-\$235,789	-\$266,353	-\$300,878
Net financial impact to MBS	\$10,208,656	\$11,531,938	\$13,026,750	\$14,715,324	\$16,622,778	\$18,777,482
Net financial impact to PBS/RPBS	-\$1,305,391	-\$1,474,601	-\$1,665,744	-\$1,881,664	-\$2,125,572	-\$2,401,096
Net financial impact Govt (MBS+PBS/RPBS)	\$8,903,264	\$10,057,337	\$11,361,006	\$12,833,660	\$14,497,206	\$16,376,386

^a assume 4.7 doses/patient

^b assume 7.3 doses/patient

Abbreviations: Lu, Lutetium; MBS, Medicare Benefits Scheme; PBS, Pharmaceutical Benefits Scheme; PET/CT, positron emission tomography/computed tomography; PSMA, prostate-specific membrane antigen; RPBS Repatriation Pharmaceutical Benefits Scheme

The financial implications may be underestimated if the uptake rate is higher than assumed by the ADAR. The cost savings to the PBS/RPBS for replaced cabazitaxel use is likely overestimated as cabazitaxel will be displaced rather than replaced in a proportion of patients. The table does not include the sensitivity analyses provided by the ADAR, including for FDG PET/CT.

As requested by the ESC, the pre-MSAC response provided additional analysis of the estimated financial impact, which was not evaluated. The applicant acknowledged that the PBS costs for post Lu PSMA cabazitaxel were not included in the base-case in the ADAR. Consistent with the economic model, 18% of patients receiving post-Lu PSMA cabazitaxel treatment was subsequently included. The applicant considered this had minimal impact on the net cost to the Government (MBS and PBS/RPBS). As also requested by ESC, the applicant also presented the scenario of maximal financial impact which was 15% uptake rate (considered the maximum uptake rate for Lu PSMA) and, consistent with the economic evaluation, a comparator split of 75% best supportive care: 25% cabazitaxel reducing the cabazitaxel cost offset (Table 15).

Table 15 Additional analyses of the estimated net financial implications to the MBS and PBS/RPBS

Scenario	2022	2023	2024	2025	2026	2027
Base-case (ADAR)	\$8,241,823	\$9,310,158	\$10,516,974	\$11,880,222	\$13,420,179	\$15,159,751
Post Lu-PSMA cabazitaxel from 0% to 18%	\$8,746,063	\$9,879,760	\$11,160,410	\$12,607,062	\$14,241,235	\$16,087,236
Post Lu-PSMA cabazitaxel from 0% to 18%, increasing uptake rate from 11.5% to 15%*	\$12,063,587	\$14,055,076	\$16,375,325	\$19,078,607	\$22,228,154	\$25,897,637
Post Lu-PSMA cabazitaxel from 0% to 18%, increasing uptake rate from 11.5% to 15% and reducing the proportion of eligible patients who would otherwise receive cabazitaxel treatment from 75% to 25%*	\$13,340,961	\$15,543,322	\$18,109,255	\$21,098,778	\$24,581,821	\$28,639,853

*These scenarios reflect the price reduction of cabazitaxel which came into effect on 1 April 2022

Abbreviations: ADAR, applicant developed assessment report; Lu, Lutetium; MBS, Medicare Benefits Scheme; PBS, Pharmaceutical Benefits Scheme; PSMA, prostate-specific membrane antigen; RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Table 4, p8 of the pre-MSAC response

15. Other relevant information

None.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

Incremental effectiveness – The evidence base consisted of high-quality randomised control trial (RCT) data, but only two trials were included and each had a different comparator. Results for response rates (PSA50) and progression-free survival (PFS) were significantly different in favour of ¹⁷⁷Lu PSMA-617, but the effect on overall survival (OS) was inconsistent across the two trials. Noting the recent results from the conference abstract from the TheraP trial against cabazitaxel presented at ASCO 2022, ESC requested that the applicant provide all of the available updated results from this trial, replace all assumption-based parameters in the model with this updated data, and discuss the consequences for the application.

¹⁷⁷Lu PSMA i&t versus ¹⁷⁷Lu PSMA-617 – There were no significant differences in reported health outcomes and biodistribution between these products, but these conclusions are based on naïve comparisons across different cohorts of patients.

PSMA diagnostic criteria – Both trials required whole body PSMA PET/CT to determine eligibility for ¹⁷⁷Lu PSMA-617. There were no significant differences in reported health outcomes using different SUV_{max} thresholds, but these conclusions are also based on naïve comparisons. In addition, there were applicability concerns as the PSMA criteria were different across the studies and compared with the proposed MBS population. Given this uncertainty in the evidence, MSAC may wish to consider that a higher and more restrictive SUV_{max} threshold is a practical and safe approach when introducing a novel therapy.

SPECT/CT post therapy – There was no convincing evidence presented to demonstrate whether SPECT/CT changes patient management, noting the VISION trial did not use SPECT/CT to assess treatment response. ESC requested that the applicant provide any additional evidence to support SPECT/CT providing clinical utility, for example, the extent to which use of SPECT/CT would reduce the number of treatment cycles administered and the circumstances by which this would occur.

Economic issues:

Modelled incremental benefit – MSAC may wish to consider whether the combination of assumptions around the time horizon, extrapolation method, comparator OS and proportional hazards for PFS and OS provide an appropriate basis for the modelling of incremental benefits. Sensitivity analyses indicate that the ICER may be considerably higher if less favourable assumptions are made. A multi-way sensitivity analysis would be informative in understanding how the ICER would react to simultaneous changes in the values of key driver variables.

MBS item fee for ¹⁷⁷Lu PSMA i&t – The justification of the proposed fee of \$8,000 is inadequate. ESC requested that the applicant provide an itemised breakdown of the ¹⁷⁷Lu PSMA i&t service to better justify the fee.

Financial issues:

ESC considers the estimated financial impacts to be uncertain and potentially underestimated, as PBS cost offsets are overestimated. Given this uncertainty, MSAC considerations could be facilitated by providing an estimate of the maximum financial impact that is likely to occur as a useful reference point.

Other relevant information:

Item descriptor frequency restrictions – MSAC may wish to consider whether there should be a lifetime restriction added to:

- the item descriptor for PSMA PET/CT, as there may be a risk of increased use for repeated staging scans unrelated to therapy. Accordingly, ESC requested further advice from the applicant on this matter.
- the item descriptor for ¹⁷⁷Lu PSMA, as the wording may need to ensure that no more than six cycles are claimed per patient per lifetime, given the lack of safety and efficacy data for ¹⁷⁷Lu PSMA therapy beyond six cycles.

Training accreditation – Before implementation, there needs to be agreement on training accreditation with AANMS/RANZCR.

ESC discussion

ESC noted that this application is requesting Medicare Benefits Schedule (MBS) listing for a ¹⁷⁷Lutetium prostate-specific membrane antigen imaging scan and therapy (¹⁷⁷Lu PSMA i&t) to treat patients with metastatic castrate-resistant prostate cancer (mCRPC). The ADAR stated that ¹⁷⁷Lutetium PSMA i&t is currently produced under Good Laboratory Practice (GLP) and is clinically

used in Australia under the Therapeutic Goods Administration's (TGA's) Special Access Scheme, funded by the Department of Veterans' Affairs (DVA) for veterans only. ESC noted the increasing profile of radiopharmaceuticals such as ¹⁷⁷Lu PSMA as theranostic products.

ESC noted that ¹⁷⁷Lu PSMA i&t therapy is delivered by nuclear medicine specialists in specialist outpatient facilities and involves up to six cycles at 6-weekly intervals.

ESC noted that an alternative product, ¹⁷⁷Lu PSMA-617 from Novartis, is not currently registered by the TGA in Australia.

ESC noted that this application is also requesting MBS listing for two codependent imaging technologies: whole body PSMA positron emission tomography/computed tomography (PET/CT) to help establish eligibility for the therapy and single-photon emission/computed tomography/computerised tomography (SPECT/CT) for post-treatment assessment. ESC noted that MSAC has supported (MSAC Application 1632) whole body PSMA PET/CT imaging in initial staging and restaging of prostate cancer and this will be implemented on 1 July 2022. These new items for PSMA PET/CT are agnostic of the type of PSMA and do not include reference to CT as CT attenuation item 61505 will generally be claimed with the items.

ESC noted that a key change from the Ratified PICO confirmation is that the ADAR removed the requirement (and proposed MBS item) for confirmatory testing with whole body 18F-fluorodeoxyglucose (FDG) PET/CT.

ESC noted that the proposed population is patients with mCRPC after progressive disease has developed while on at least one taxane chemotherapy and at least one androgen receptor signalling inhibitor. ESC acknowledged the clinical need of this population with advanced disease, noting about 3,000 patients die each year from mCRPC in Australia, and the significant morbidity associated with bone metastasis requiring analgesia and skeletal related events.

ESC considered the comparators of cabazitaxel and standard care (interchangeable with best supportive care in the applicant-developed assessment report [ADAR]), if prior cabazitaxel, or unsuitable/unwilling for cabazitaxel, to be appropriate.

ESC noted that, as for MSAC Application 1632, the proposed item descriptor for whole body PSMA PET/CT is agnostic of the type of PSMA. ESC considered this to be appropriate. ESC considered that there is a risk that practitioners could use the PSMA PET/CT item for repeated staging scans unrelated to therapy. Accordingly, ESC requested advice from the applicant as to whether the proposed PSMA PET/CT item should be restricted to once per lifetime noting that this would prohibit reassessment with PSMA PET/CT prior to subsequent ¹⁷⁷Lu PSMA treatment cycles.

ESC noted that patients who have a PSMA PET/CT and meet the PSMA criteria then undergo ¹⁷⁷Lu PSMA therapy. ESC noted that the item descriptor for ¹⁷⁷Lu PSMA is also agnostic of the type of ¹⁷⁷Lu PSMA, as it does not specify either ¹⁷⁷Lu PSMA i&t or ¹⁷⁷Lu PSMA-617, and considered this generic approach to be appropriate subject to MSAC's conclusions regarding the equi-effectiveness of these products. ESC noted that this item descriptor included a restriction of once per cycle up to a maximum of 6 cycles in each course of therapy, but that no lifetime limit was specified. ESC noted that chemotherapy does not have a frequency restriction, but the descriptor wording could allow more than six cycles per patient across more than one course. ESC considered that the wording of this item descriptor may need to be reviewed to ensure that no more than six cycles are claimed per patient per lifetime, as currently there is a lack of safety and efficacy data for ¹⁷⁷Lu PSMA therapy beyond six cycles.

ESC noted that the item descriptor for ¹⁷⁷Lu PSMA also includes SPECT/CT scans following each cycle (maximum of six) to measure the uptake of ¹⁷⁷Lu PSMA. The ADAR claimed that SPECT/CT may reduce the number of cycles if it detects evidence of a good response or no response. ESC

noted evidence provided in the ADAR from the LuPIN study that SPECT/CT-derived imaging parameters correlated with patient outcomes such as prostate-specific antigen progression-free survival (PSA PFS), but an increase in maximum standard uptake value (SUV_{max}) did not. ESC also noted advice from nuclear physicians that SPECT/CT can be used for diagnosis and treatment. However, ESC did not consider that the ADAR or pre-ESC response demonstrated how SPECT/CT would change subsequent management with ¹⁷⁷Lu PSMA. ESC also questioned whether SPECT/CT is needed with each cycle, noting one trial from the evidence (the VISION trial) did not use SPECT/CT. Also, although the median number of cycles used in the TheraP trial was 5, the minimum number of cycles received was 3, suggesting SPECT/CT did not alter management for the first 2 cycles. ESC requested that the applicant provide any additional evidence to support SPECT/CT providing clinical utility, for example, the extent to which use of SPECT/CT would reduce the number of treatment cycles administered and the circumstances by which this would occur.

ESC noted that the Department recommended a number of explanatory notes to be included in the item descriptor, including a definition of progressive disease; when treatment should cease before six cycles; that the service includes the supply/administration of medications, pathology and intravenous (IV) infusions; and that there should be no co-claiming of nuclear medicine consultation items. However, ESC was concerned that this would make the explanatory notes too clinically prescriptive, noting that few listings of medicines on the Pharmaceutical Benefits Scheme (PBS) include this degree of detail.

ESC noted that the proposed fee for the PSMA PET/CT should be reduced from \$1,400 to \$1,300 in recognition that the CT attenuation item 61505 at a fee of \$100 will be claimed with the PSMA PET/CT item (consistent with the new items for initial staging and restaging to be implemented 1 July 2022). ESC noted that the proposed fee of \$8,000 for the ¹⁷⁷Lu PSMA i&t is \$5,500 for PSMA preparation and \$2,500 for service (consult, IV access, nursing, SPECT/CT). ESC noted that this was a fee increase of \$1,000 from the original [application form](#). ESC noted that the applicant stated the treatment is 'at cost' and the proposed costs are "the absolute minimum to deliver this service safely to patients". ESC also noted that the applicant stated that there was a large cost difference between the therapeutic products, with the cost per cycle being \$8,000 for Lu PSMA i&t and \$57,000 for ¹⁷⁷Lu PSMA-617 (estimated based on costs from the United States being US\$43,000, excluding treatment administration). ESC requested that the applicant provide a more detailed breakdown of the costs of the proposed ¹⁷⁷Lu PSMA i&t service (including to separate out the SPECT/CT component) to better justify the proposed fee.

ESC noted that the Department supports the Royal Australasian College of Physicians (RACP) and the Royal Australian and New Zealand College of Radiologists (RANZCR) approving training and accreditation. The Committee for Joint College Training has developed accreditation, but this needs formal approval by RACP/RANZCR. ESC noted that the Australasian Association of Nuclear Medicine Specialists (AANMS) requires that trainees have experience with more than 50 administrations of a therapy in the previous 3 years and participate in multidisciplinary team discussion of more than 50 cases. ESC noted that the Department supports the AANMS proposed grandfathering arrangements but did not consider the trainee requirements to be practical or achievable and would restrict use. ESC considered that issues relating to accreditation need to be resolved before this service is implemented.

ESC noted public consultation feedback received to date indicated that there is currently inequitable access to ¹⁷⁷Lu PSMA i&t therapy due to its limited availability and associated costs. ESC noted that those who cannot access this therapy have a low quality of life and live in pain, and that it is not equitable if it is only available for those who can afford it. Consumers consider that there is a great need for this therapy because of its benefits relating to extension of life, improvement in quality of life, and improved pain control compared with chemotherapy. ESC noted feedback from a specialist that the treatment is well tolerated, improves survival and reduces the need for pain medication. ESC also noted that the need for specialised facilities and trained operators was identified as an issue.

ESC noted the supporting clinical trial data available for ¹⁷⁷Lu PSMA i&t consisted of two randomised trials included in the application but using the pharmaceutical product ¹⁷⁷Lu PSMA-617. A claim of mutual noninferiority therefore needs to be accepted by MSAC in order for the evidence for ¹⁷⁷Lu PSMA-617 to be considered relevant for ¹⁷⁷Lu PSMA i&t or other ¹⁷⁷Lu PSMA products and for subsequent acceptance of the results of the modelled economic evaluation. ESC acknowledged that the data available are limited because ¹⁷⁷Lu PSMA is a novel treatment, and Australia is a worldwide leader in its use.

ESC noted that both ¹⁷⁷Lu PSMA i&t and -617 products have near-identical chemical structure, with the difference being the chemical chelator that binds the radionuclide with the receptor. ESC noted that the ADAR claims that best available evidence shows that ¹⁷⁷Lu PSMA i&t and -617 are radioequivalent, having similar efficacy, biodistribution and safety. ESC noted from the five studies, as well as an additional paper by Hartrampf et al. 2022⁸ (added by the commentary) that performed a matched pair analysis, that efficacy outcomes (PSA50, PFS and OS) were similar between the products. ESC also noted that the risk of bias was high across the naïve comparisons across different cohorts of patients. In addition, ESC also noted a dosimetry study from Schuchardt et al. 2021⁹ that showed some differences in body/organ uptake and tumour dosimetry, including ¹⁷⁷Lu PSMA-617 having a higher whole-body retention and half-life in salivary glands, but in the pre-ESC response, the applicant considered that there was an equivalent delivery of radiation dose to the tumour and organs. ESC noted that the studies reported no difference in adverse events (including grade 3–4 adverse events) or treatment-related deaths between the two products.

ESC noted that the two randomised trials had different comparators: the TheraP trial¹⁰ (an Australian multicentre, randomised, phase 2 trial) compared ¹⁷⁷Lu PSMA-617 with cabazitaxel, and the VISION trial¹¹ (a US/European multicentre phase 3 trial) compared ¹⁷⁷Lu PSMA-617 with best supportive care. ESC noted although both were open-label trials the risk of bias was low, and considered this evidence to be of high quality. ESC noted that all eligible populations required PSMA-positive disease on imaging. The enrolled patients were similar in both trials, although prior cabazitaxel use in the ¹⁷⁷Lu PSMA-617 arm was 0% for the TheraP trial and 38% for the VISION trial. Both trials used a median of five cycles of ¹⁷⁷Lu PSMA-617. ESC noted the commentary considered that both trial populations were largely similar to the proposed MBS population.

Although, ESC noted that there was a difference in the PSA eligibility between the trials, the use or not of FDG PET/CT to further determine patient eligibility (TheraP used FDG PET/CT whereas VISION did not), as well as a difference in the PSMA criteria which was used to identify patients suitable for therapy. Eligibility for the TheraP trial was set at an $SUV_{max} \geq 20$ at disease site and >10 at all measurable sites, while the VISION trial used an $SUV_{max} \geq 5$ (uptake greater than liver activity). ESC also noted that the PSMA criteria is different in the item descriptor with an $SUV_{max} >15$ at a single site of disease and >10 at all sites of measurable disease. ESC noted that results from several studies suggesting that a higher SUV_{max} results in a greater PSA response but there

⁸ Hartrampf PE, Weinzierl F-X, Buck AK, Rowe SP, Higuchi T, Seitz AK et al. (2022). Matched-pair analysis of [¹⁷⁷Lu]Lu PSMA I&T and [¹⁷⁷Lu]Lu PSMA-617 in patients with metastatic castration-resistant prostate cancer. *European Journal of Nuclear Medicine and Molecular Imaging*.

⁹ Schuchardt C, Zhang J, Kulkarni HR, Chen X, Mueller D & Baum RP (2021). Prostate-specific membrane antigen radioligand therapy using (¹⁷⁷Lu) PSMA I&T and (¹⁷⁷Lu) PSMA-617 in patients with metastatic castration-resistant prostate cancer: comparison of safety, biodistribution and dosimetry. *Journal of Nuclear Medicine*.

¹⁰ Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC et al. (2021). [¹⁷⁷Lu]Lu PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *The Lancet* **397**(10276):797-804.

¹¹ Sartor AO, Morris MJ, Messman R & Krause BJ (2020). VISION: An international, prospective, open-label, multicenter, randomized phase III study of ¹⁷⁷Lu PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). *Journal of Clinical Oncology Conference* **38**(6 Suppl).

is no significant difference following an SUV_{max} of 15 or 20. ESC noted that there were no PFS or OS trends with increasing SUV_{max} (see Table 5).

ESC noted a claim from the ADAR that using a PSMA SUV_{max} threshold of >15 results in at least similar effectiveness with SUV_{max} ≥5 or ≥20. ESC considered this to be reasonable but noted that the risk of bias was high because it relied on naïve comparisons across different cohorts of patients. ESC also noted concerns from the commentary that different numbers of cycles were used in the studies and that the ADAR did not demonstrate a link between the intermediate outcome of PSA50 and the more patient-relevant outcomes such as PFS or OS. Additionally, ESC noted a concern about excluding patients with an SUV_{max} between 5 and 15. Overall, ESC acknowledged the lack of quality data assessing SUV_{max} but considered that there was no convincing data to indicate any differences in health outcomes from using different SUV_{max} eligibility thresholds. However, given this uncertainty in the evidence, ESC advised that MSAC may wish to consider whether a higher and more restrictive SUV_{max} threshold (as proposed) is a practical and safe approach when introducing a novel therapy.

ESC noted that PASC had a concern with the measurement of SUV_{max} and questioned if instruments are standardised to allow accurate measurement. ESC noted that the ADAR provided evidence from Hoberück et al. (2021)¹² that SUV_{max} was comparable between different PSMA tracers, but that not all participants in the study were patients with mCRPC.

ESC noted from the trials that PSA response, overall response rate and PFS were all superior with ¹⁷⁷Lu PSMA-617 compared with either cabazitaxel or best supportive care. ESC noted that median OS was a key endpoint of the VISION trial, finding that Lu PSMA was superior compared with best supportive care (a 4-month incremental survival gain). ESC also noted that ¹⁷⁷Lu PSMA-617 was superior to cabazitaxel for several quality of life domains, including diarrhoea, fatigue, social functioning and insomnia. ESC noted that OS results were not reported for the TheraP trial, but recently a conference abstract was presented at the [2022 American Society of Clinical Oncology \(ASCO\) Annual Meeting](#) showing there is similar OS from using ¹⁷⁷Lu PSMA-617 compared with cabazitaxel. Noting the availability of this new evidence, ESC requested that the applicant provide all of the available updated results from the TheraP trial, replace all assumption-based parameters in the model with this updated data from these recently published results and discuss the consequences for the application (which may include any applicability issues arising noting the model also includes inputs from the VISION trial).

For comparative safety, ESC noted from the evidence that ¹⁷⁷Lu PSMA-617 had a lower number of adverse events compared with cabazitaxel, including Grade 3–4 adverse events. However, ¹⁷⁷Lu PSMA-617 had a higher number of adverse events compared with best supportive care, including Grade 3–4 adverse events. Most side effects of ¹⁷⁷Lu PSMA-617 were grade 1–2, and included fatigue (75%), nausea (35–40%), dry mouth (23–43%) and anaemia (27–32%). Grade 3, 4 and 5 side effects included anaemia (12.9%), pain (11.2%), thrombocytopenia (7.9–11.2%), leukopenia (7.8%) and death (1%).

ESC noted the clinical claims that the use of PSMA PET/CT and ¹⁷⁷Lu PSMA results in superior safety and effectiveness compared with cabazitaxel, and inferior safety and superior effectiveness compared with best supportive care. ESC considered these clinical claims to be reasonable, but the incremental OS benefit was not conclusive (vs. cabazitaxel).

ESC considered the economic evaluation (cost-effectiveness analysis and cost-utility analysis) to be appropriate. ESC noted that the proportions of positive and negative PSMA PET/CT test results

¹² Hoberück S, Löck S, Borkowetz A, Sommer U, Winzer R, Zöphel K et al. (2021). Intraindividual comparison of [⁶⁸Ga]-Ga-PSMA-11 and [¹⁸F]-F-PSMA-1007 in prostate cancer patients: a retrospective single-center analysis. *European Journal of Nuclear Medicine and Molecular Imaging Research* **11**(1):109.

to determine eligibility for ¹⁷⁷Lu PSMA i&t used in the Markov model were based on data from the TheraP trial, and alternative data were used in a scenario analysis.

ESC noted that a proportional hazards assumption was adopted for modelling PFS and OS from the trials. ESC noted the uncertainty raised for this approach as per the commentary. ESC noted that the ADAR base case assumed the incremental OS benefit for ¹⁷⁷Lu PSMA i&t over cabazitaxel is the same as for ¹⁷⁷Lu PSMA i&t over best supportive care. ESC considered this key assumption for the model needed to be reviewed in light of the recent OS results reported from the TheraP trial.

ESC noted that the model time horizon was 10 years. ESC considered that this may not be reasonable due to the inconsistent OS gain and the long extrapolation period beyond the median follow-up of 20.9 months from the VISION trial. Consistent with previous PBAC advice for medicines in later-line mCRPC treatment, ESC also considered that a time horizon of 5–7 years was more reasonable for the base case results of the model.

ESC considered the utilities to be appropriate and the costs to be broadly appropriate. ESC noted minor issues identified by the commentary around the costs of best supportive care and bone pain, but ESC did not consider these to be major issues.

ESC noted that, following an update from the commentary to incorporate the price reduction in cabazitaxel, the base case ICER is \$81,653/quality-adjusted life year (QALY) for the 10-year time horizon. ESC noted that the cabazitaxel OS, the time horizon and extrapolation are all drivers of the model, and favour ¹⁷⁷Lu PSMA i&t (see Table 10). ESC also noted that increasing the OS hazard ratio for cabazitaxel from 0.62 to 0.89 and 1.0 (i.e. no OS benefit) substantially increased the ICER to \$140,706/QALY and \$188,854/QALY gained, respectively (see Table 11). ESC noted that, in the pre-ESC response, a sensitivity analysis was provided that combined several scenarios and sensitivity analyses. Considering all scenario and sensitivity analyses provided, ESC questioned why multivariate sensitivity analyses were not performed to understand how the ICER would react to simultaneous changes in the values of the key driver variables.

ESC noted that the utilisation uptake of PSMA PET/CT was assumed to be 11.5% in Year 1, with a relative increase of 11.5% per year. ESC considered this approach to be overly specific and uncertain, and noted that the uptake could potentially be higher. However, ESC considered that there could be a constraint on the growth in patient numbers, as only certain centres can deliver the intervention. ESC also noted that all cabazitaxel use was assumed to be replaced, but considered this assumption to not be appropriate as it was inconsistent with the modelled economic evaluation that more reasonably assumed 18% of patients had post-¹⁷⁷Lu PSMA i&t cabazitaxel treatment (reportedly based on the TheraP trial). The VISION trial reported that 14.9% of patients randomised to ¹⁷⁷Lu PSMA-617 underwent subsequent treatment with cabazitaxel.

For the financial impact, ESC noted that the base case used the mortality approach and a scenario was tested using the PBS item script approach (slightly higher volumes). Consistent with the revised economic evaluation, the commentary provided revised financial estimates based on the reduced price of cabazitaxel. The estimated net financial impact to the MBS ranged from \$10,208,656 in Year 1 to \$18,777,482 in Year 6. ESC considered that this was subject to doubt regarding several parameters, including eligible patient numbers, uptake rate, impact of patient co-payment (not being accounted for), and cabazitaxel being displaced rather than replaced. Overall, ESC considered that the estimated financial impacts to be uncertain and likely underestimated, as PBS cost offsets are overestimated. Given this uncertainty, ESC considered that an estimate of the maximum financial impact that is likely to occur may provide a useful reference point for MSAC deliberations.

17. Applicant comments on MSAC's Public Summary Document

The applicants for MSAC 1686 are pleased that MSAC has concluded that ¹⁷⁷LuPSMA-I&T therapy is safe and clinically efficacious, as well as being equivalent to ¹⁷⁷LuPSMA-617. The applicants believe that it is important MSAC has decided that the proposed indication is an unmet need, and agree that there is strong support for this therapy amongst consumers because it is well tolerated and effective in controlling symptoms.

The applicants would like to highlight the fact that this proposal to MSAC is currently the least expensive proposal for delivery of ¹⁷⁷LuPSMA therapy in the world. Despite this, ¹⁷⁷LuPSMA (both I&T and 617) is now funded in Europe and the USA at significantly higher cost than this proposal – but remains unavailable to many men in Australia. The issue of inequitable access to this treatment remains unaddressed.

Utilising the MSAC findings of equivalency, safety, efficacy and unmet need, the applicants look forward to engaging with government in a meaningful way to discuss the options available to provide access to this treatment to men with prostate cancer as appropriate. The applicants believe that Australia is in an excellent position to provide high quality treatment to men across Australia with an existing network of treatment capable sites established as part of internationally recognised multi-centre national trials which evaluated this therapy in recent years.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)