NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Contents:

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Consultation on the appraisal consultation document – deadline for comments 5pm on 2 November 2022 **Return via:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Advanced Accelerator Applications (AAA)**

NICE National Institute for Health and Care Excellence

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	**Stefan Palimaka**

Comment number	Comments
Summary	AAA have presented detailed responses to address the Committee's key areas of uncertainty surrounding the Company's submission, as well as a revised economic base case and supporting scenario analyses. The Committee recognised the considerable unmet need associated with metastatic castration-resistant prostate cancer (mCPRC) in patients having previously received treatment with androgen receptor pathway inhibitors (ARPIs) and taxane-based chemotherapy, or are medically unsuitable for taxanes. This unmet need is multifaceted, with patients facing a poor prognosis and limited treatment options. Clinical experts further noted during the committee meeting that the primary treatment option at this stage of disease, cabazitaxel, is associated with debilitating side effects. ^{177}Lu vivipotide tetraxetan represents the first radioligand therapy in the treatment of prostate cancer, offering a more targeted approach to treatment able to improve survival benefits in patients with a much more tolerable safety profile than currently approved treatments. The Committee recognised the potential of ^{177}Lu vivipotide tetraxetan to improve survival of patients with few side effects, allowing patients to lead a high-quality life, as described by a patient expert during the committee meeting. In this response to the Appraisal Consultation Document (ACD), the Company has provided detailed responses to address the Committee's key areas of uncertainty surrounding the Company's submission: • Heterogeneity associated with the studies included in the Company's network meta-analysis (NMA) • The use of real-world evidence (RWE) to estimate relative treatment effects in overall survival between cabazitaxel and ^{177}Lu vivipotide tetraxetan

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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	• The unavailability of robust data to inform the comparison between ^{177}Lu vivipotide tetraxetan and standard of care (SOC) in the population of patients for whom taxanes are medically unsuitable • The exclusion of radium-223 as a comparator in the Company submission • The Company's estimates of health-state utility values associated with each of the treatments considered in the economic analysis • The exclusion of prostate-specific membrane antigen (PSMA) testing costs in the Company's submission In line with the feedback from the Committee, the Company has presented a revised base case where OS for cabazitaxel is informed by the results of the NMA (including IPCW-adjusted or interval imputed OS and rPFS data for ^{177}Lu vipivotide tetraxetan), including revised utility values for cabazitaxel, and where costs associated with additional treatments taken prior to treatment with cabazitaxel have been aligned with Committee preferences. This approach excludes robust, clinically meaningfully OS estimates for cabazitaxel derived from a large RWE cohort of patients generalisable to UK clinical practice suggesting poorer outcomes than trials included in the NMA. As discussed further below, this approach therefore likely represents a conservative approach to estimating the relative survival benefits of ^{177}Lu vivipotide tetraxetan compared to cabazitaxel. Alongside an updated base case approach, the Company has proposed a revised patient access scheme (PAS) price of £[redacted] for ^{177}Lu vivipotide tetraxetan. This revised base case is associated with an incremental cost-effectiveness ratio (ICER) versus cabazitaxel below the willingness-to-pay threshold of £50,000 for medicines which reach the end-of-life criteria and thus demonstrates ^{177}Lu vivipotide tetraxetan to be a cost-effective use of NHS resources. The Company has additionally explored scenario in order to address remaining uncertainty which provide validation for the base case approach. The Company therefore urges the Committee to reconsider the evidence presented and make ^{177}Lu vivipotide tetraxetan available to this patient population under routine commissioning.
1	**The NMAs for OS and rPFS have been updated to include data from VISION adjusted for informative censoring; results of these NMAs inform OS and rPFS for cabazitaxel in the base case economic analysis** The Committee acknowledge the ERG's view that informative censoring due to high withdrawal in the SOC arm of VISION may have introduced bias in the comparison of ^{177}Lu vivipotide tetraxetan and SOC. They further noted that this was not adjusted for in the company NMA, which may therefore have introduced bias in the company's relative efficacy estimates. The Company therefore conducted NMAs incorporating rPFS and OS data from the VISION trial that were adjusted for the high withdrawal rates in the SOC arm, in order to account for informative censoring that may be biasing the outcomes of the NMA. Full details of the methodology and results of the NMAs are presented in Appendix 3. These revised NMA analyses have subsequently been used to inform OS and rPFS for cabazitaxel in the revised base case

	economic analysis presented in Appendix 1. The company maintains that fixed effects models are most appropriate for use in the cost-effectiveness analysis. However, scenario analyses using random effects and random effects with DuMouchel priors have been presented in Appendix 2. **Baseline risk-adjusted NMAs were explored for both OS and rPFS to account for heterogeneity between included trials. However, no improvement in statistical fit was achieved. As such, the additional modelling complexity associated with baseline risk adjustment means it is more appropriate to use NMAs unadjusted for baseline risk** The Committee suggested accounting for inter-trial heterogeneity in the NMA by adjusting for baseline risk as its preferred approach. The Company therefore explored baseline-risk adjusted NMAs for both OS and rPFS; full details of the methodology and results of the NMAs are presented in Appendix 3, including model fit statistics. Across both fixed and random effects models at all timepoints, there was no improvement in residual deviance and no significant reduction in DIC for baseline risk-adjusted models, suggesting that adjusting for baseline risk did not improve model fit. Therefore, the results of the baseline risk-adjusted NMAs have not been used to inform the revised base case analysis. **Given the heterogeneity across the trials included in the NMA, in particular between VISION and CARD, the propensity score weighting (PSW) analysis comparing VISION to the RWE cohort remains a relevant source of comparative evidence for OS** As previously noted in the Company's response at the Technical Engagement stage, and confirmed by clinical experts consulted, the CARD trial patient population was generally healthier and less heavily pre-treated than that in VISION. Clinical experts at the Committee further also noted that patients in CARD were required to have previously experienced disease progression during 12 months of treatment with an ARPI, and as such the CARD patient population may be more likely be resistant to ARPI treatment.[1] CARD and VISION trials represent the key trials for the active treatments considered in this submission, ^{177}Lu vivipotide tetraxetan and cabazitaxel, and therefore form the key links in the NMA networks comparing these two treatments. The high levels of heterogeneity in patient populations between the two trials means that any relative treatment effect derived from an NMA including both trials may be biased. As discussed in the response to Issue 2 below, the propensity score weighting analysis conducted at Technical Engagement ensured that differences between the VISION trial and cabazitaxel RWE cohort for most characteristics were small and non-significant, indicating that the treatment arms were broadly well-balanced. Furthermore, the effective sample size for the cabazitaxel cohort remained high (n=[redacted]) and there was a reasonable overlap in propensity score distributions between the two studies. In addition, the variables selected for the propensity score model were consistent with the most important prognostic factors identified in a targeted literature review (TLR) conducted as part of this response to the ACD. Whilst the Company acknowledge that, as an unanchored comparison, this comparison may be subject to bias due to unobserved confounding, the relative efficacy estimate for ^{177}Lu vivipotide tetraxetan versus

	cabazitaxel from this analysis remains relevant and plausible considering the limitations of the NMA. Therefore, a scenario has been conducted where OS for cabazitaxel is informed by the propensity score-weighted OS data from the RWE cohort. This scenario is relevant for decision-making and should be considered alongside the base case analysis where OS for cabazitaxel is informed by the revised NMA. The Company notes that the revised base case approach means that the RWE study no longer plays a role in quantifying cost-effectiveness, despite its large sample size and relevance to UK practice. The incorporation of RWE in NMA networks is the subject of ongoing study, and it has been proposed that robustly conducted RWE studies can form important links to strengthen NMA networks.[2] The Company therefore considered incorporating the RWE study into the NMA network in order to provide a stronger link between the two interventions of interest in this submission. However, there is a lack of consensus as to the best method for weighting RWE cohorts appropriately in NMA networks, given they are typically much larger than trial cohorts, but may be more susceptible to selection bias.[2] Given the difference in relative effect estimates for ^{177}Lu vipivotide tetraxetan versus cabazitaxel derived from the Company's NMA and RWE PSW analysis, it is reasonable to expect a NMA incorporating the RWE study would likely yield a point estimate of the relative effect somewhere between these two approaches. The cost-effectiveness results informed by the OS NMA could therefore be considered a conservative estimate. Whilst the Company agrees that the RWE study is associated with limitations in deriving relative treatment efficacy, both the committee and clinical experts noted that it represents an important and robust source of efficacy data for cabazitaxel in NHS clinical practice. Whilst it no longer forms the Company's base case approach to informing the efficacy of cabazitaxel, it still forms an important scenario analysis in the company's response to the ACD. The company therefore encourages the committee to consider the cost-effectiveness results informed by the PSW RWE study for cabazitaxel when making its decision.
2	**The majority of clinically important prognostic variables were accounted for in the propensity score weighting (PSW) RWE analysis** The Committee raised concerns that prognostic variables were not appropriately adjusted for in the weighted comparison between cabazitaxel RWE OS estimates and ^{177}Lu vipivotide tetraxetan OS estimates from VISION. Prognostic variables accounted for in the PSW analysis of the RWE study of cabazitaxel were originally selected via univariable linear regression of each variable as being associated with cohort assignment. The company acknowledges that this approach may omit clinically important prognostic variables in its weighting of the cabazitaxel OS estimates. In order to address the Committee's concerns regarding the appropriateness of the PSW analysis, the Company carried out a TLR to identify characteristics that may represent clinically important prognostic variables affecting the survival of patients with mCRPC. The Embase® and MEDLINE® databases were searched for relevant literature reporting survival outcomes in

patients with mCRPC, using the Embase® platform. The search terms developed to search the database is listed below in Appendix 4. Eighty studies were ultimately included, which reported on nearly 25 prognostic variables impacting.

A comparison of the variables available from the RWE and VISION cohorts, those that were selected for adjustment in the PSW analysis and those that were identified in the TLR, is presented in Table 1. The majority of variables identified in the TLR and available in both the RWE and VISION cohorts were selected for inclusion in the propensity score model. Whilst previous therapies were not adjusted for, all patients in VISION and the RWE cohort had received a prior ARPI and a taxane, since the RWE analysis only included patients treated with cabazitaxel in the RWE dataset who had also received a prior taxane and ARPI, in line with the eligibility criteria for VISION (n=[redacted]).

The Company acknowledge that a number of factors identified in the TLR were not reported consistently across the RWE and VISION cohort, and therefore could not be compared or adjusted for. Therefore, as an unanchored comparison, the results of the PSW analysis may be subject to bias from unobserved confounding. However, given a large number of important prognostic factors were adjusted for, the relative efficacy for ^{177}Lu vivipotide tetraxetan versus cabazitaxel estimated from this analysis remains relevant and plausible.

Table 1: Summary of prognostic variables considered for adjustment in the PSW analysis

Characteristic	Available from the RWE and VISION cohorts	Adjusted for in the PSW analysis	Identified as an important prognostic factor
Median age	Yes	Yes	Yes
ECOG score 0 or 1	Yes	Yes	Yes
Median time since diagnosis	Yes	Yes	Yes
Gleason score (8–10, unknown)	Yes	Yes	Yes
Previous prostatectomy	Yes	Yes	No
Previous ARPI (such as abiraterone acetate and enzalutamide)	Yes	No	Yes – previous therapy
One previous regimen of taxanes (e.g., paclitaxel and docetaxel)	Yes	No	
Two previous regimens of taxanes (e.g., paclitaxel and docetaxel)	Yes	No	
Previous cabazitaxel	Yes	No	
PSA	No	N/A	Yes
Alkaline phosphatase	No	N/A	Yes
Bone scan index	No	N/A	Yes
Circulating tumour cell	No	N/A	Yes
Haemoglobin	No	N/A	Yes

LDH	No	N/A	Yes
Clinical stage	No	N/A	Yes
Serum albumin	No	N/A	Yes

Abbreviations: ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; PSA: prostate-specific antigen; PSW: propensity score weighting; RWE: real-world evidence.

Of the variables presented in Table 1, laboratory markers, in particular PSA expression, are likely to have important prognostic implications. However, due to limitations in data collection, these were not available for PSW, and could therefore not be adjusted for in any updated analysis of the RWE study.

Another important factor, clinical stage of disease, was not able to be explicitly adjusted for in the PSW analysis of the RWE. However, median time from diagnosis was accounted, which may be correlated with clinical stage of disease. The impact of matching for time since diagnosis would therefore likely account to a large extent for disease stage, meaning adjustment of this variable would likely have minimal impact on OS estimates for cabazitaxel.

It should be noted that an important factor which was not possible to adjust for in the PSW was the time since receipt of a previous ARPI. The RWE study suggests that patients starting treatment within 12 months of receipt of and failure with an ARPI have worse survival outcomes than those who received an ARPI more than 12 months prior to start of cabazitaxel treatment, with OS estimates of [redacted] and [redacted] months in each of these subgroups. Given that the population of interest in this submission is likely to initiate treatment soon after failure with an ARPI, the OS estimates for cabazitaxel of [redacted] months in the RWE PSW may be an overestimate for the population of interest in this submission.

A robust scenario could not be conducted where OS for ^{177}Lu vivipotide tetraxetan was derived by applying the NMA hazard ratio to the RWE study cabazitaxel OS reference curve

The Committee suggested using the cabazitaxel RWE study as the reference OS estimate, to which the hazard ratio between cabazitaxel and ^{177}Lu vipivotide tetraxetan resulting from the updated OS NMA should be applied to estimate OS for ^{177}Lu vipivotide tetraxetan (if appropriate). The committee considered that the RWE study was appropriate to estimate absolute OS for cabazitaxel in clinical practice, and should therefore be used as the reference curve, with the resulting OS for ^{177}Lu vipivotide tetraxetan better representing what might be expected in clinical practice.

However, such a scenario would introduce inconsistencies between the source of OS and PFS data for ^{177}Lu vivipotide tetraxetan included in the economic model, which may result in logical inconsistencies. It should also be noted that the parametric model selected for extrapolating ^{177}Lu vivipotide tetraxetan OS (Stratified flexible Weibull [2 knots]) was closely aligned to clinical expert predictions of OS for patients receiving ^{177}Lu vivipotide tetraxetan in UK clinical practice, who estimated survival to be between 9–16% at three years, and 4–8% at four years for ^{177}Lu vipivotide tetraxetan; the Stratified flexible Weibull (2 knots) model predicts [redacted]% and [redacted]% survival

	for ^{177}Lu vipivotide tetraxetan at three and four years, respectively.[3] This extrapolation is therefore the most appropriate source of OS data for ^{177}Lu vipivotide tetraxetan for the base case analysis. In order to address the Committee's concerns regarding the uncertainty in the relative effect ^{177}Lu vipivotide tetraxetan versus cabazitaxel, OS for cabazitaxel in the revised base case economic analysis was based on the NMA. However, the company maintain that the scenario presented where OS for cabazitaxel is informed by propensity score-weighted RWE data is relevant for decision making. It should be noted that the Committee agreed with the use of the PSW RWE curve to inform the efficacy of cabazitaxel, with the lower survival estimates most likely to better reflect true survival in NHS practice. Its exclusion from the updated company's estimation of cabazitaxel survival is therefore likely to represent a conservative estimate for cabazitaxel survival.
3	**The base case analysis is generalisable to patients medically unsuitable for taxanes** The Committee acknowledged the lack of available evidence for the population of patients unsuitable for taxane therapy and proposed exploring a scenario where a higher baseline mortality risk was modelled for these patients to reflect a worse prognosis associated with medical unsuitability for treatment. The company acknowledge the Committee's concerns regarding the lack of clinical evidence for patients who are considered not medically suitable for taxanes. However, the Company would like to highlight that the current poor prognosis for patients not medically suitable for taxanes is a result of the lack of effective treatment options, and therefore may not be a good predictor of the ability of such patients to respond to treatment with ^{177}Lu vipivotide tetraxetan. As highlighted at Technical Engagement, reasons for medical unsuitability to taxanes may include but are not limited to: hypersensitivity to active substance or excipients, neutropenia <1,500 cells/mm^3, severe hepatic impairment, poor performance status (ECOG ≥3, ECOG ≥2) with substantial comorbidities, and lack of social support or impaired cognitive understanding sufficient to impact upon treatment compliance or toxicity monitoring.[4] Many of these factors relate to the risks associated with taxane treatment, given their substantial toxicity, and not the ability of the patient to respond to treatment. It should also be noted that in addition to the criteria for medical unsuitability for taxane treatment described above, clinical experts were in unanimous agreement that patient choice following appropriate education from a physician would also form part of the criteria for medical suitability for taxane treatment, and patient choice has previously been accepted as a criterion for medical unsuitability for treatment in other oncology indications.[5] The committee further noted that social factors, such as variable regional access to chemotherapy and associated treatment for sepsis, may prevent or deter patients from receiving chemotherapy in the first instance.[6] Therefore, for many patients who might be deemed medically unsuitable for taxanes, there is no mechanistic reason that they would not respond to a more tolerable, effective treatment, if it were made available, and thus the efficacy and safety of ^{177}Lu vipivotide tetraxetan is unlikely to

	be significantly different in such patients. Furthermore, receipt of prior taxane therapy was identified as an important prognostic factor in the TLR, and it is therefore plausible that some patients medically unsuitable for taxanes may in fact have a better prognosis on ^{177}Lu vipivotide tetraxetan than patients who have received and failed treatment with docetaxel. Clinical experts at Technical Engagement confirmed that despite the lack of clinical evidence, they would not expect patients deemed medically unsuitable for taxanes to respond significantly differently to ^{177}Lu vipivotide tetraxetan, compared with the VISION population. Therefore, the base case results presented in this response should be considered broadly generalisable to this patient population. Excluding these patients from treatment with ^{177}Lu vipivotide tetraxetan would create inequity biased against those patients who are not medically suitable for treatment with taxanes, a population for which there is particular unmet need, but who would be considered medically suitable for treatment with ^{177}Lu vipivotide tetraxetan.
4	**The lack of a robust comparison between ^{177}Lu vipivotide tetraxetan versus radium-223 in the small population of patients with symptomatic bone metastases but no visceral metastases should not be considered a significant source of uncertainty** The committee acknowledged that only a small number of patients would receive ^{177}Lu vipivotide tetraxetan as an alternative treatment to radium-223, and that both treatments had different mechanisms of action and clinical outcomes, radium-223 being predominantly used as palliative medication. However, the committee concluded that a subgroup analysis would be needed to determine the cost-effectiveness of ^{177}Lu vipivotide tetraxetan versus radium-223 in patients with symptomatic bone metastases only and no known visceral metastases. No alternative approach to resolve the uncertainty surrounding the comparison of ^{177}Lu vipivotide tetraxetan and radium-223 has been proposed. The Company have been unable to provide an appropriately robust analysis of the comparative cost-effectiveness of ^{177}Lu vivipotide tetraxetan and radium-223. This is for reasons previously highlighted in the Company's submission and response to key issues in the ERG report. The Company would like to reiterate that only a small overlap in patients considered for treatment with radium-223 and ^{177}Lu vivipotide tetraxetan would be anticipated in clinical practice. Firstly, there are strict restrictions associated with treatment radium-223, which requires bone metastases, but neither visceral nor lymph node metastases. Whilst no data was available for this combination of metastases, half of patients in the VISION trial presented with lymph node metastases, which would have precluded these patients being treated with radium-223.[7] The additional liver and lung metastases present in a smaller but significant number of patients would equally have precluded treatment with radium-223.[7] In addition, use of radium-223 is limited in clinical practice with only [redacted]% of all mCRPC patients in the RWE database reported to have received treatment with radium-223, whilst in the population of patients who received an ARPI and a taxane, only [redacted]% of patients when on to receive radium-223. Furthermore, its use in UK clinical practice appears to be predominantly at earlier stages of the treatment pathway, with a recent audit of the use radium-223 in patients with mCRPC

	suggesting that approximately 80% of patients receiving it as a first- or second-line treatment.[8] It is therefore likely that, as indicated by clinical experts, few patients would be considered for radium-223 at the stage of disease at which ^{177}Lu vivipotide tetraxetan is positioned. The lack of cost-effectiveness evidence for ^{177}Lu vivipotide tetraxetan in this population should not play an important role in the Committee's decision making. It however should be acknowledged that any such scenario may benefit ^{177}Lu vipivotide tetraxetan, given radium-223 would be associated with increased costs but clinical experts have confirmed that it is predominantly used palliatively in this setting and is therefore unlikely to be associated with a significant survival benefit. The key comparator for ^{177}Lu vipivotide tetraxetan in the post-ARPI and post-docetaxel setting is therefore cabazitaxel and a lack of a robust comparison between ^{177}Lu vipivotide tetraxetan and radium-223 should not be considered a significant source of uncertainty.
5	**The Company considered adjustment for informative censoring in its estimation of utility values using EQ-5D-3L data from the VISION trial. However, IPCW adjustment of the trial data was not feasible, and as such cannot be incorporated into the Company's estimation of treatment-dependent utility values** The committee agreed that differences in utilities between treatment arms were plausible, as were higher values for ^{177}Lu vipivotide tetraxetan at the same stage of progression. This approach was further supported by clinical experts, who noted the high psychological burden associated with either retreatment with taxane-based chemotherapy or a lack of active treatment (i.e. receiving SOC) following initial failure on docetaxel. The committee suggested that there was however uncertainty associated with these values due to informative censoring in the VISION trial, which may be biasing utility values in favour of ^{177}Lu vivipotide tetraxetan, given that early dropouts in the SOC arm of the VISION trial were generally healthier than those who continued. The Committee suggested that this uncertainty may be reduced by using EQ-5D-5L data from VISION adjusted for informative censoring via IPCW. The Company have investigated the possibility of conducting IPCW adjustment to account for informative censoring that may have occurred during the trial. However, this was not deemed feasible. For EQ-5D there were three sources of missing data in the VISION trial, which were dropouts, missed assessments and death. Patients that dropped out typically left the study before their second assessment and so did not have any change in EQ-5D data. The dropouts tended to be healthier patients so may not have deteriorated in health state as quickly as other patients. However, the reverse is likely to be true for missed assessments and there will also be missing deterioration in health data occurring before death for many patients. The Company are unaware of a method that can be used to address missing data in this situation. The Company recommend that little weight should be placed on the EQ-5D data. A deterioration in health state prior to death would be expected, with more deaths in the control arm. However, this information may not exist in the EQ-5D data from the VISION trial.

The company maintains that the use of treatment-dependent utility values is most appropriate

Whilst the Committee agreed that treatment-dependent utility values were plausible, these were associated with some uncertainty. As such, the Committee preferred to see a scenario in which treatment-independent utility values are used in order to address this uncertainty.

The Company maintains that this approach would not take into account the significant psychological burden of further chemotherapy, which was acknowledged by the committee and clinical experts. Further to this, disutility due to adverse events associated with cabazitaxel would not adequately reflect treatment burden, given the generally healthier and less-heavily pre-treated population in CARD as compared to VISION. The Company has therefore not carried out any further analyses in which treatment independent utility values are used.

However, the Company has attempted to address the Committee's concerns surrounding the use of treatment-dependent utility values, in particular the pre-progression utility value for cabazitaxel being lower than the post-progression value for ^{177}Lu vivipotide tetraxetan. The base case analysis has been updated in line with a scenario carried out by the ERG, in which the cabazitaxel utility values are assumed to be the average of the utility values for cabazitaxel and ^{177}Lu vivipotide tetraxetan. The resultant utility values for each treatment arm in each health state, derived from the company's updated utility values presented at the technical engagement stage, are shown in Table 2 below.

Table 2: Health state utility values used in scenario analysis

Health state	^{177}Lu vipivotide tetraxetan	Cabazitaxel	SOC
Pre-progression	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]

Abbreviations: SOC: standard of care.

6

The company maintains that PSMA-testing is becoming standard of care

The Committee concluded that costs of testing for PSMA-positivity should be included in the cohort of patients receiving ^{177}Lu vivipotide tetraxetan, given the eligibility for treatment stipulates PSMA-positivity determined by PSMA imaging. The Committee acknowledged that PSMA testing, either by positron emission tomography/ computed tomography (PET-CT) or single-photon emission computerised tomography (SPECT) scan, is already commonly used as part of the mCRPC diagnostic pathway. The Committee estimated that as many as 75% of patients will have received PSMA testing as part of their care prior to being considered for treatment with ^{177}Lu vivipotide tetraxetan. Clinical experts indicated the clinical practice was moving towards testing for PSMA-positivity earlier in the treatment pathway, and this number was increasing and would keep increasing.

The Company therefore maintains that excluding PSMA testing is the most appropriate approach, better reflecting current and near-future NHS practice. However, in order to alleviate

	Committee uncertainty with regards to PSMA testing, the Company have updated their base case economic analysis to include the cost of PSMA testing in the cohort of patients receiving ^{177}Lu vivipotide tetraxetan in the model. 25% patients in the ^{177}Lu vivipotide tetraxetan arm were assumed to incur additional costs associated with PSMA tests, in line with the Committee's upper estimate of 75% of patients receiving a PSMA test as part of their treatment history. All PSMA scans were assumed to be SPECT, given its already common usage in NHS practice. As per the Committee's recommendations, the cost of PSMA testing was adjusted proportionally to the rate of PSMA positivity, sourced from the VISION trial to account for the cost of PSMA-negative tests not leading to treatment with ^{177}Lu vivipotide tetraxetan. These changes have been incorporated into the company's updated base case analysis, the results of which are presented in Appendix 1. As per the Committee's preferences, a scenario has been presented in which all patients in the ^{177}Lu vivipotide tetraxetan arm are assumed to incur PSMA testing costs, the results of which are presented in Appendix 2. As can be seen in Table 4, this had a limited impact on the cost-effectiveness estimates.
7	**A 7-day treatment course of prophylactic granulocyte colony-stimulating factor (G-CSF) treatment with cabazitaxel has been included in the revised base case analysis. The greater incidence of neutropenia-related adverse events associated with lower usage of G-CSF should be considered** The Committee favoured using a 7-day treatment course for prophylactic treatment with G-CSF alongside each cycle of cabazitaxel. The committee acknowledged that there was variation in clinical practice regarding the administration, but favoured the 7-day cycle as this was the maximum commissioned by the NHS. The Committee also noted that this was the treatment course used in the appraisal of olaparib in a similar indication. The Company acknowledges that a 7-day treatment course of prophylactic treatment with G-CSF may better reflect the variation in UK clinical practice. The Company has therefore updated the costs associated with G-CSF treatment in its base case analysis to reflect a 7-day course of prophylactic treatment prior to each cycle of cabazitaxel therapy. The proposed approach to G-CSF treatment does not, however, take into account the increased incidence of neutropenia-related adverse events. The Company's original base case analysis derived incidence of neutropenia-related adverse events from the CARD trial, which specified a 14-day treatment course of G-CSF. Clinical expert feedback, as well as further literature evidence, suggests that a lower usage of G-CSF is associated with higher rates of neutropenia-related adverse events. Previously published studies have reported increased incidence of febrile neutropenia and neutropenic sepsis associated with shorter durations of G-CSF, as well as increased risk of hospitalisations.[9-12] Furthermore, the RWE study of patients receiving cabazitaxel in NHS practice suggests that [redacted]% of patients experience febrile neutropenia, compared with a rate of 3.2% (Grade 3 or 4) in the CARD trial.[1] Whilst no data are available for prophylactic G-CSF use in the RWE study, it is possible that this was closer to the 7-day course preferred by the committee than the 14-day course specified, resulting in higher rates of febrile neutropenia. This therefore suggest that patients receiving a shorter course of prophylactic G-

	CSF treatment experience a greater incidence of neutropenia-related events. The Company have been unable to source appropriate cost and utility data to model these increased neutropenia-related events. The updated Company base case includes incidence of adverse events for neutropenic sepsis and febrile neutropenia for ^{177}Lu vivipotide tetraxetan and cabazitaxel, sourced from the VISION and CARD trials, respectively.[1, 7] It should be however be noted that the combination of a 7-day course of G-CSF in combination of adverse event from CARD, which used a 14-day G-CSF course, represents a conservative approach modelling G-CSF in the cabazitaxel arm of the model.

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^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Consultation on the appraisal consultation document – deadline for comments 5pm on 2 November 2022 **Return via:** NICE DOCS

Appendix 1 Updates to company base case

The following updates were made in the revised company base case post ACD, in line with feedback from the Committee and clinical experts during the ACM:

- rPFS estimates for cabazitaxel are informed by the fixed effect NMA which includes the EAG's preference of including all trials (including TheraP), and uses VISION data adjusted for interval imputation
- OS estimates for cabazitaxel are now informed by the fixed effects NMA which includes all the trials included at technical engagement, with IPCW-adjusted VISION data
- The duration of G-CSF use has been lowered to 7 days, as per the Committee's preference
- Neutropenic sepsis and febrile neutropenia have been added as adverse events
- The cost of PSMA testing has been modelled for 25% of patients receiving ^{177}Lu vivipotide tetraxetan, adjusted for the rate of PSMA-negativity

The updated company base case following the ACD response, incorporating the above changes, is presented in Table 3. The ICERs demonstrate that ^{177}Lu vipivotide tetraxetan is a cost-effective use of NHS resources at a £50,000 willingness-to-pay threshold.

Table 3: Revised company base case results at ^{177}Lu vipivotide tetraxetan PAS price (deterministic)

Intervention	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
^{177}Lu vipivotide tetraxetan	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,828
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	117,362

Abbreviations: ^{177}Lu: Lutetium-177; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; QALY: quality-adjusted life year; SOC: standard of care.

Appendix 2 Additional scenario analysis results

Deterministic cost-effectiveness results for 177Lu vivipotide tetraxetan versus cabazitaxel resulting from a number of scenarios explored as part of the Company's response to the ACD are presented in Table 3 below. The use of the RWE study to inform OS for cabazitaxel in scenario greatly improves the cost-effectiveness estimates for ^{177}Lu vivipotide tetraxetan compared to cabazitaxel.

Table 4: Results of the scenario analysis at ^{177}Lu vipivotide tetraxetan PAS price (deterministic)

Scenario	Description	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	47,828
1	Exploring the use of random effects NMA to inform OS and rPFS	[redacted]	[redacted]	55,708
2	Exploring the use of the RWE PSW study to inform the OS estimate for cabazitaxel	[redacted]	[redacted]	29,334
3	Exploring the use of random effects NMA with DuMouchel priors	[redacted]	[redacted]	52,373
4	Exclusion of TheraP from the rPFS network	[redacted]	[redacted]	47,625
5	Inclusion SPECT-CT PSMA scans for all patients	[redacted]	[redacted]	49,448

Abbreviations: ^{177}Lu: Lutetium-177; ICER: incremental cost-effectiveness ratio; LYG: life years gained; PAS: patient access scheme; PSMA: prostate-specific membrane antigen; QALY: quality-adjusted life year.

Appendix 3 Revised NMA

Adjustment for informative censoring

In line with Committee preferences, data from VISION which had been adjusted for informative censoring potentially introduced by higher rates of dropout in the SOC arm were used in the revised NMA. As reported in Appendix J.3.4 of the Company submission, OS data were adjusted using inverse probability-of-censoring weighting (IPCW). For PFS, an interval-adjusted model was selected because it produced the most plausible predictions. The assumptions of this model may be more appropriate because is it likely that patients dropped out of the study for more than one reason; i.e., they may have dropped out during follow-up after progression occurred, or they may have dropped out at the start of the study because they were not happy at being in the control arm. Methods such as IPCW assume that patients leave a study early for the same reason and therefore may not perform well with the data from VISION.[13] Unadjusted and adjusted data for the subpopulation of patients who received ARPI as part of SOC in both VISION treatment arms (which was used within the NMA to maintain randomisation) are presented in Table 5; the adjusted data were used in all subsequent NMA analyses.

Table 5: VISION OS and rPFS outcomes adjusted for informative censoring

Population	Model	Outcome	Hazard ratio	Lower bound of 95% CI	Upper bound of 95% CI
ARPI subgroup	No adjustment	OS	[redacted]	[redacted]	[redacted]
		rPFS	[redacted]	[redacted]	[redacted]
	IPCW[a]	OS	[redacted]	[redacted]	[redacted]
	Interval imputation	rPFS	[redacted]	[redacted]	[redacted]

[a] Willems *et al.* (2018) method.
Abbreviations: ARPI: androgen receptor pathway inhibitor; CI: confidence interval; IPCW: inverse probability-of-censoring weighting; OS: overall survival; rPFS: radiographic progression-free survival.

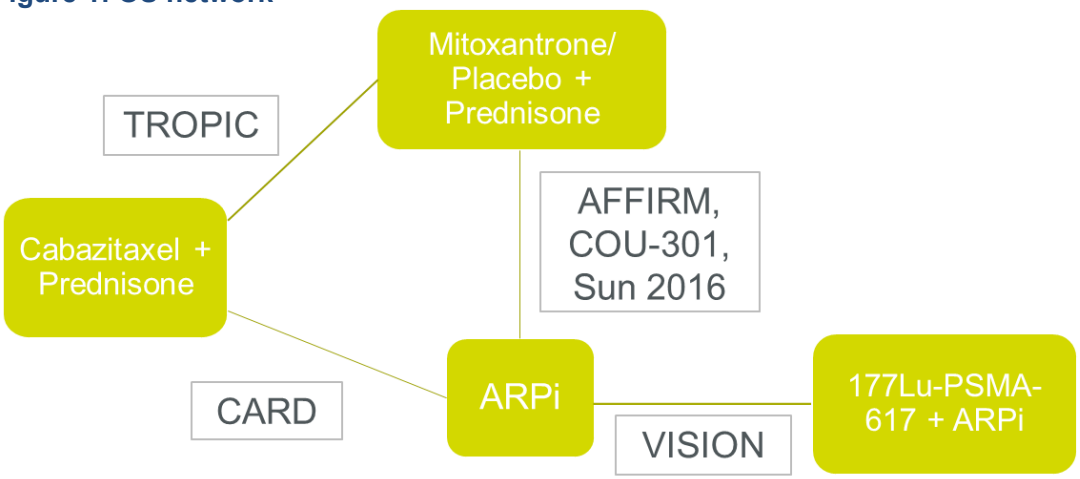
Included studies

The committee concluded that the NMAs were associated with uncertainty because all the trials had limitations and because of the heterogeneity between trial populations. Unlike patients enrolled in VISION, patients included in the TROPIC, COU-AA-301, AFFIRM and Sun *et al.* 2016 trials had not received prior treatment with an ARPI. Clinical experts consulted as part of this response also noted that the CARD population was generally healthier and represented a less heavily pre-treated population than patients in VISION, and that patients were required to have previously experienced disease progression during 12 months of treatment with an ARPI, and as such the CARD patient population may be more likely be resistant to ARPI treatment.[1] There were also key differences between TheraP and VISION, including differences in methodology, the diagnostic process, intervention production and dose, and study stratification factors.

Therefore, in line with the Committee's conclusions, baseline risk-adjusted network meta-analysis were explored including all studies, such that the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel is

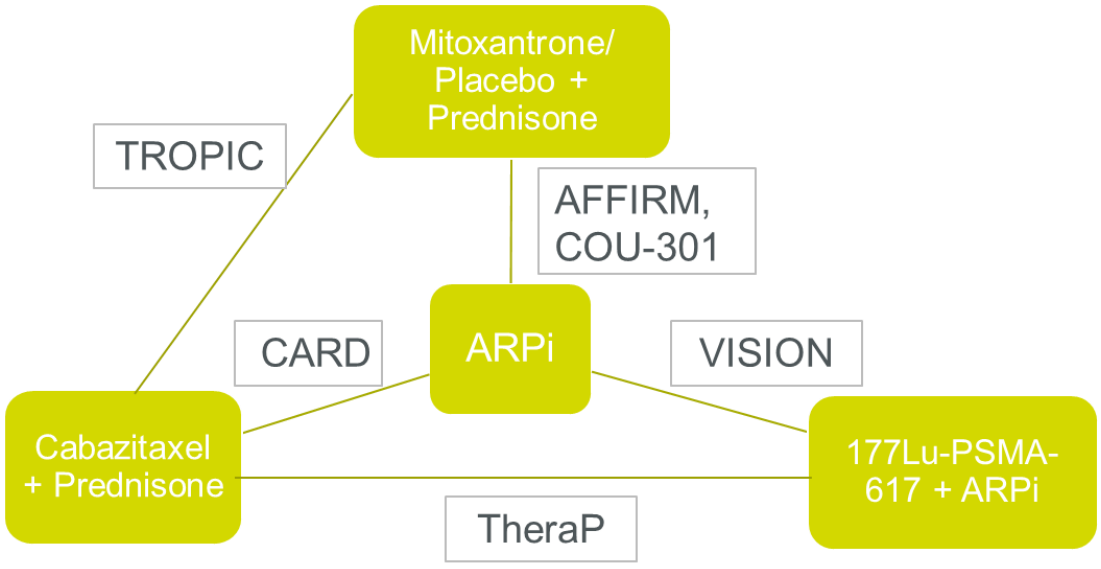
based on the largest possible evidence base, but ensuring that differences between the trials were accounted for; network diagrams are presented in Figure 1 and Figure 2 for OS and rPFS, respectively. Given the limitations associated with the TheraP trial, analyses were also explored where TheraP was excluded from the rPFS network (Figure 3).

Figure 1: OS network



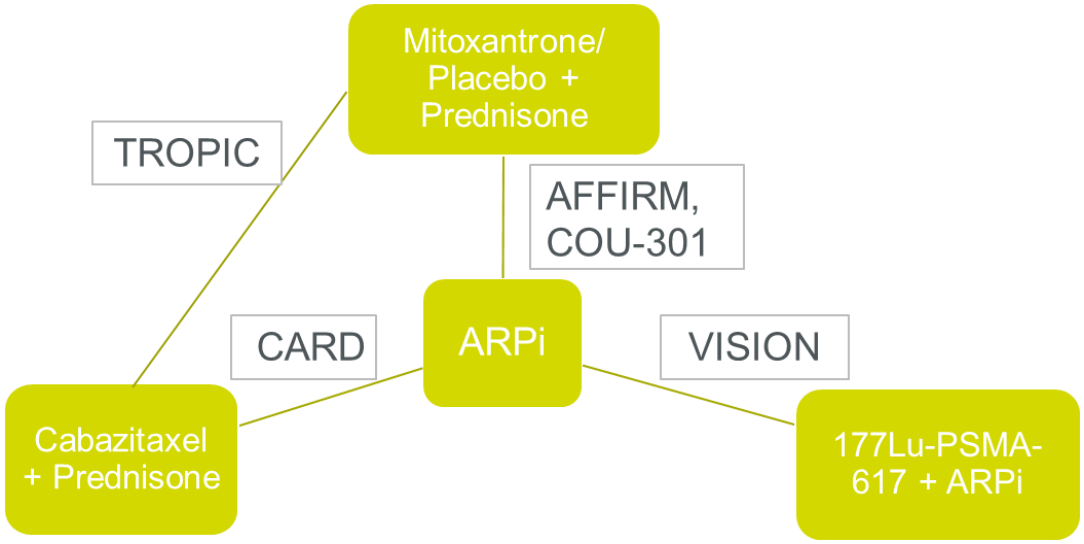
Abbreviations: ARPI: androgen receptor pathway inhibitor.

Figure 2: rPFS network (including TheraP)



Abbreviations: ARPI: androgen receptor pathway inhibitor.

Figure 3: rPFS network (excluding TheraP)



Abbreviations: ARPI: androgen receptor pathway inhibitor.

NMA without baseline risk-adjustment – Methods

The NMA was conducted using the summary results reported in study publications and included the synthesis of the HR of time to event endpoints of OS and rPFS. In this analysis, a linear model with normal likelihood distribution was used for the time to event outcomes (log HR and standard error [SE]). The NMA was performed using the MCMC software. This method includes the synthesis of all included data (direct and indirect comparisons), resulting in a single set of effective sizes. The NMA model inputs included natural log of HR (logHR) and SE of logHR. The results of the NMA were based on enough iterations (e.g., 100,000 iterations) on at least three chains, with a burn-in of 20,000 iterations. Convergence was assessed by visual inspection of trace plots. DuMouchel priors were also investigated as part of the random effects NMA, the results of which are presented alongside fixed and random effects NMA results in Table 9.

Table 6: DIC and residual deviance values for OS using fixed effects and random effects models

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

Table 7: DIC and residual deviance values for rPFS (including TheraP) using fixed effects and random effects models

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

Table 8: DIC and residual deviance values for rPFS (excluding TheraP) using fixed effects and random effects models

Value	Fixed Effects Model	Random Effects Model
DIC	[redacted]	[redacted]
Dbar	[redacted]	[redacted]
pD	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

NMA without baseline risk-adjustment – Results

The results of NMA are presented in terms of 'point estimates' (median of posterior) for the comparative treatment effects, along with the 95% credible intervals (95% CrI), as shown in Table 9.

Table 9: NMA results

Scenario	Model	HR – ^{177}Lu vipivotide tetraxetan vs		
		Cabazitaxel	ARPI	Mitoxantrone/ placebo
OS	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	DuMouchel priors	[redacted]	[redacted]	[redacted]
rPFS (including TheraP)	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	DuMouchel priors	[redacted]	[redacted]	[redacted]
rPFS (excluding TheraP)	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	DuMouchel priors	[redacted]	[redacted]	[redacted]

Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; FE: fixed effects; HR: hazard ratio; OS: overall survival; RE: random effects.

NMA with baseline risk-adjustment – methods

For each outcome, fixed and random effects models with and without baseline risk-adjustment were explored at 6-, 12- and 18-month timepoints and model fit statistics evaluated. Across both fixed and random effects models at all timepoints, there was no improvement in residual deviance and no significant reduction in DIC, suggesting that adjusting for baseline risk did not improve model fit.

Table 10: DIC and residual deviance values for OS using fixed effects and random effects models with and without baseline risk-adjustment

Timepoint	Value	No baseline risk-adjustment		With baseline risk-adjustment	
		Fixed Effects Model	Random Effects Model	Fixed Effects Model	Random Effects Model
	Beta (95% CI)		[redacted]		[redacted]

6 months			[redacted]		[redacted]
	SD (95% CI)			[redacted]	[redacted]
	Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
	DIC	[redacted]	[redacted]	[redacted]	[redacted]
12 months	Beta (95% CI)		[redacted]		[redacted]
	SD (95% CI)			[redacted]	[redacted]
	Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
	DIC	[redacted]	[redacted]	[redacted]	[redacted]
18 months	Beta (95% CI)		[redacted]		[redacted]
	SD (95% CI)			[redacted]	[redacted]
	Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
	DIC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; SD: standard deviation.

Table 11: DIC and residual deviance values for rPFS (with interval imputation, including TheraP) using fixed effects and random effects models with and without baseline risk-adjustment

Timepoint	Value	No baseline risk-adjustment		With baseline risk-adjustment	
		Fixed Effects Model	Random Effects Model	Fixed Effects Model	Random Effects Model
6 months	Beta (95% CI)			[redacted]	[redacted]
	SD (95% CI)		[redacted]		[redacted]
	Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
	DIC	[redacted]	[redacted]	[redacted]	[redacted]
12 months	Beta (95% CI)		[redacted]	[redacted]	
	SD (95% CI)		[redacted]		[redacted]
	Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
	DIC	[redacted]	[redacted]	[redacted]	[redacted]
	Beta (95% CI)			[redacted]	[redacted]

18 months				[redacted]	[redacted]
	SD (95% CI)		[redacted]		[redacted]
	Total residual deviance	[redacted]	[redacted]	[redacted]	[redacted]
	DIC	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DIC: Deviance information criteria; Dbar: Posterior mean of the deviance; pD: Effective number of parameters.

Appendix 4 TLR methodology

In order to validate the prognostic variables controlled for in the PSW analysis carried out on the RWE for cabazitaxel in the company's technical engagement response, a TLR was carried out to find evidence of the most relevant prognostic variables for patients with mCRPC. The search terms used to identify potentially relevant sources are detailed in Table 12, alongside the number of results hits for each search term.

Table 12: Search terms used in TLR (4th October 2022)

Number	Search term	Number of hits
1	mcrpc	6,677
2	'metastatic castration resistant prostate cancer'/exp OR 'metastatic castration resistant prostate cancer'	7,809
3	#1 OR #2	7,809
4	'treatment effect'	32,440
5	'effect modifier':	1,683
6	'prognostic factor':	80,322
7	'covariate'	28,136
8	#4 OR #5 OR #6 OR #7	141,388
9	#3 AND #8	252*
10	#3 AND #8 AND [humans]/lim AND [english]/lim	242

Response to the Appraisal Consultation Document from Prostate Cancer Research

Q. Has all of the relevant evidence been taken into account?

1. We are not aware of additional completed trials that should be taken into account. However, there are a number of ongoing trials and suggest that the TA is revisited as new evidence becomes available.

2. Though not included in the NICE scope, overall response rate, disease control rate and duration of response are highly relevant outcomes for patients and it is our view that these outcomes should have been taken into account.

3. Evidence pertaining to whether those withdrawing were more likely to be those with higher or lower QoL seems highly pertinent. Accepting that RWE is not the equivalent to an arm in the trial (and that trial data is extrapolated to 10 years, but RWE not) and that RWE only relates to overall survival and not progression free survival, it would be helpful to compare RWE on best supportive care vs trial arm best supportive care group? In the longer term it would be advantageous to examine the ways in which RWE can be generated to better meet the needs of HTA.

4. It appears that the hidden costs associated with carbazitaxel treatment have not been sufficiently well incorporated in the appraisal. Neutropenia (80-90% of patients at the upper end for data published in peer review journals), febrile nuetropenia and sepsis are significant and potentially life-threatening side effects of treatment with cabazitaxel. These side effects are significantly less frequent in patients who receive prophylactic G-CSF. The costs of prophylaxis and treatment of neutropenia and sepsis are therefore highly relevant. Accepting that there is a lack of data pertaining to these costs in clinical practice, and a wide range in terms of the percentage of patients experiencing these side effects in the published literature, might reasonable assumptions nevertheless be taken into account within the economic modelling.

Q. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

5. Key areas of uncertainty remain. It is unclear from the consultation documentation how the assumptions made in the evaluation have specifically addressed uncertainty and whether / to what extent the assumptions adopted have impacted the outcome of the TA, specifically:

    In relation to comparison with carbazitaxel, by necessity indirect but suggestive that lutetium-177 may be the more effective.

    Radium-223– may be a comparator for a few people but no evidence was submitted for this comparison so it could not be considered.

In any eventuality, we would be highly supportive of an agreement between the company and NICE that would permit the generation of evidence in practice, with a view to addressing uncertainty.

Q: Are the recommendations sound and a suitable basis for guidance to the NHS?

6. PMSA imaging limited access and not standard practice. Given the expectation (and expert opinion) that PSMA imaging will increase in use over time – we contend that the TA should have been grounded in the expectation of equity of access to PSMA imaging and that to do otherwise serves to compound inequity and to deny patients access to targeted treatment that offers better outcome. Provision of access to targeted treatments such as lutetium-177 could be considered a driver of service improvement rather than adopting the inverse position (i.e. that imaging should be universally available before a targeted treatment is introduced).

7. We would be highly supported of the NHS and the company reaching a commercial arrangement that provides access to Lut-177.

Q. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

8. Given the high proportion of patients who may be in the unsuitable for taxane category (42%), and that this can be for both medical reasons (low red blood cell count; co-morbidity) and reasons of social inequity (lack of access to appropriate treatment facilities; certain common prostate cancer co-morbidities are more common with lower socio-economic status and non-white ethnicity), and the high unmet need of this group, it seems appropriate to give further consideration to both the benefits of the treatment vs BSC in this group, and the likely costs of leaving this group without the 177Lu treatment, given the patient experts' emphasis that anyone would choose 177Lu over chemo if they were aware of the results in terms of outcomes, QoL and lack of side effects.

ENDS

NICE National Institute for Health and Care Excellence

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 2 November 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Prostate Cancer UK]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	[redacted]

Please return to: **NICE DOCS**

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Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 2 November 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	**We are concerned with this recommendation as there is an unmet need for new treatments for PSMA-positive hormone-relapsed metastatic prostate cancer** Patients with metastatic castrate resistant prostate cancer (MCRPC) that has progressed after taxane-based chemotherapy and ADT have limited treatment options, as these patients are either treated with Radium-223, best supportive care, or retreated with taxanes. These treatments have however been associated with poor tolerability - including grade 3-4 adverse events. While, Cabazitaxel has become an additional treatment option for patients who are able to tolerate further chemotherapy, a proportion of patients who have progressed despite multiple prior therapies would not be suitable for further chemotherapy due to these patients being elderly and/or frail with significant disease and prior treatment-related comorbidities[1]. Further, Phase III trials for cabazitaxel and Radium 223 report that 56% of patients receiving these treatments experienced Grade 3 or higher adverse events. In addition, these treatment options have strict eligibility criteria and are only an option for a limited number of men. There therefore, remains a considerable unmet need for additional effective and well-tolerated, targeted therapeutic options for those with mCRPC- particularly to the population of men who are unsuitable for chemotherapy. Conversely, previous phase III trials demonstrate that Lutetium -177 vipivotide tetraxetan increases survival and maintains quality of life in patients with metastatic castrate resistant prostate cancer when compared to standard of care. Whole population data needs to be considered when evaluating Lutetium -177 vipivotide tetraxetan as a new treatment option to provide the maximum possible benefit to as many patients as possible. 1. Parker, C. A., Nilsson, S., Heinrich, D., Helle, S. I., O'sullivan, J. M., Fosså, S. D., ... & Sartor, O. (2013). Alpha emitter radium-223 and survival in metastatic prostate cancer. *New England Journal of Medicine*, *369*(3), 213-223. 2. de Wit, R., de Bono, J., Sternberg, C. N., Fizazi, K., Tombal, B., Wülfing, C., ... & Castellano, D. (2019). Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *New England Journal of Medicine*, *381*(26), 2506-2518. 3. Morris, M. J., De Bono, J. S., Chi, K. N., Fizazi, K., Herrmann, K., Rahbar, K., ... & VISION Trial Investigators. (2021). Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION).
2	**Statistically powered data for the medically unsuitable for taxane-based chemotherapy population is limited** The medically unsuitable for taxane-based chemotherapy population makes up a small subset of the MCRPC population and is unlikely to be well represented in clinical trials. This limits the statistical

[1] Droz, JP; Albrand, G; Gillessen, S et al. Management of Prostate Cancer in Elderly Patients: Recommendations of a Task Force of the International Society of Geriatric Oncology. Eur Urol. 2017;72(4):521-531.

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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	power of the results, and the ability to generate statistically significant findings. The VISION trial was not designed to include men who are medically unsuitable for taxane-based chemotherapy and requesting this level of evidence is unfair to men who are medically unsuitable for taxane-based chemotherapy. This also leaves those without bone metastases only, without alternative treatment options as only a small number of these men present with bone metastases and would be eligible to receive Radium-223. 1. Morris, M. J., De Bono, J. S., Chi, K. N., Fizazi, K., Herrmann, K., Rahbar, K., ... & VISION Trial Investigators. (2021). Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION).
3	**There is limited evidence to consider Radium-223 as a relevant comparator to Lutetium-177** Radium-223 dichloride is recommended as an option for treating adults with hormone-relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases. This limits its comparability with Lutetium -177 as the treatment is intended for use regardless of metastasis site. Radium-223 will therefore be a suitable comparator only for a small subset of patients who would be eligible for Lutetium-177 vipivotide tetraxetan. For example, in the VISION trial, 21.4% of patients had visceral metastases and were therefore unsuitable for Radium-223. Comparing Radium-223 to Lutetium-177 vipivotide tetraxetan requires a subgroup analysis of the VISION population with only bone metastases, however, the small simple size makes it difficult to provide statistically powered evidence on Radium-223 as a comparator. Parker, C. A., Nilsson, S., Heinrich, D., Helle, S. I., O'sullivan, J. M., Fosså, S. D., ... & Sartor, O. (2013). Alpha emitter radium-223 and survival in metastatic prostate cancer. *New England Journal of Medicine*, *369*(3), 213-223.
4	**Excluding patients who are medically unsuitable for taxanes leads to potential equality issues** We agree that broadening the population to include people who are not medically suitable for taxanes seems sensible as these groups of patients will have more limited options after ARPIs and will not have any active treatment beyond Radium-223.
5	**There is a need for novel targeted therapies** Additional treatment options with novel targeted mechanisms of action able to improve survival and preserve health related quality of life (HRQoL) in patients are urgently needed. VISION is the first Phase III clinical study demonstrating the value of targeted medicine for a large population within metastatic castrate resistant prostate cancer with an unmet need. It is also the first trial that provides evidence of the effectiveness of PSMA-targeted radioligand therapy for the management of metastatic castrate resistant prostate cancer. Lutetium -177 vipivotide tetraxetan sets the pace for a new class of novel therapies that deliver treatment straight to prostate cancer cells. If approved, Lutetium -177 vipivotide tetraxetan will transform treatment of incurable prostate cancer, improving the overall survival of patients while maintaining quality of life.
6	**Lutetium-177 has significant benefits** **Increase tolerability, limited 3+ side effects, QOL,** When added to standard of care, Lutetium-177 has been proven to improve overall survival and imaging-based progression free survival while also delaying the time to bone metastases and maintaining quality of life. A patient who is currently receiving Lutetium-177 under the PSMAfore clinical trial described his positive experience with the treatment. To quote, "*I am much stronger,*

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	and I feel much calmer and more relaxed because I am aware of the next steps and when my cycles are coming up. Also, other than the occasional dry mouth (which my doctor has given me something for), my experience with this treatment has been extraordinary as I don't really experience any other side effects". While another patient treated with Lutetium-177 has said: *"As the treatment is targeted, the side-effects are minimal enabling me to continue my work and bike riding. I will be taking part in the stage 2 of the Tour de France."* We believe that all patients with MCRPC should be able to experience these benefits and not just those patients involved in clinical trials.

Insert extra rows as needed

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Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Tackle Prostate Cancer**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NONE**
Name of commentator person completing form:	[redacted]

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	The comments from Tackle Prostate Cancer are listed below, using the main summary points from the ACD as reference.
1	***Lutetium-177 vipivotide tetraxetan is not recommended.....*** ***The committee did not see cost-effectiveness estimates using its preferred modelling assumptions or within the range considered an acceptable use of NHS resources. So, it concluded that it could not recommend lutetium-177 for treating PSMA-positive hormone-relapsed metastatic prostate cancer*** The decision by the committee is obviously one that Tackle Prostate Cancer finds very disappointing. Tackle Prostate Cancer campaigns for all patients to receive the best and most appropriate treatment for them - irrespective of the stage of their disease. For patients with advanced prostate cancer who have received all currently available therapies, the committee's decision effectively removes an option for further treatment and extension of life.
2	***There is an unmet need for new treatments for PSMA-positive hormone-relapsed metastatic prostate cancer*** There is undoubtedly a body of patients whose advanced disease is now progressing despite having had all currently available therapies. The statement by the committee that there is an unmet need is welcomed.
3	***Lutetium-177 is positioned appropriately in the treatment pathway*** Tackle would agree with this statement as it applies to current practice.
4	***It is appropriate to include the whole marketing authorisation, but there is no evidence for when taxanes are medically unsuitable*** Tackle are particularly pleased that the committee have recognised the needs of all patients irrespective of whether they have had taxane therapy previously. There could have been equality issues if a taxane unsuitable population were excluded from having Lutetium-177 therapy. There was a logical and cogent argument put forward by the clinical experts that patients who had not received taxanes would have an equal (if not potentially better) response to the Lutetium-177.
5	***Lutetium-177's adverse events in the trial reflect the experiences of people having it in clinical practice*** We agree with this statement. The acceptable side effect profile of this therapy was eloquently described by a patient expert. His experience matched that of patients described by the clinical experts.
6	***There are no equality issues to address in this technology appraisal*** The committee have agreed that therapy could be relevant to patients who are unsuitable for taxanes. Patient charities have always highlighted the potential for inequality when patients could be excluded from any new treatment because they had previously not received taxane therapy. it is very positive that this is not the case for this current appraisal.
7	***Eligibility is determined by PSMA imaging, but access to this is limited and not standard practice across the NHS*** Patients do report difficulty in accessing not only PSMA scanning but PET scanning in general.

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	However access is beginning to improve. Eligibility for Lutetium-177 treatment can also be achieved by the use of single photon emission (SPEC) technology which clinical experts indicate can be more widely available than PSMA-CT scanning.
8	***Cabazitaxel and best supportive care are relevant comparators for hormone-relapsed metastatic prostate cancer with metastases*** Tackle do not have the experience or expertise to be able to adequately comment upon this. However to the layman, Lutetium-177 therapy represents a totally innovative and unique mode of action in treating advanced prostate cancer. Therefore it would be logical to suggest that there can be no direct comparator as no other treatment involves a similar mode of action. It could be argued that, by definition, a truly innovative treatment may not have a direct comparator?
9	***Radium-223 dichloride may be a relevant comparator for people with symptomatic bone metastases but more evidence is needed*** At the appraisal were differences of opinion as to whether Radium-223 was an appropriate comparator. Strictly, Radium-223 is only indicated for the treatments of painful bone metastases. It's mode of action prevents it from being of benefit for soft tissue/visceral/lymph node metastases. Lutetium-177 is effective at all sites of metastasis. Clinical experts also stated there was a high incidence of progression to soft tissue/visceral/lymph node involvement in patients who had already been treated with Radium-223 (indeed it could be argued that these deposits were already present but unable to be identified with the scanning techniques used.) Thus logically and based purely on the mode of action, Lutetium-177 is highly likely to be superior to Radium 223. Is the latter therefore an appropriate comparator?
10	***Cost effectiveness:*** It is not appropriate for Tackle to be able to comment on statements in the ACD relating to this. Health economics are complex and, indeed, an organisation such as ours is excluded from Part 2 committee proceedings when this subject is discussed. This has to be one of the major reasons for the decision by the Committee not to recommend Lutetium-177.
11	***The committee acknowledged the innovative aspects of lutetium-177*** The treatment is based on PSMA technology. This is an entirely novel and innovative approach to both diagnosis and treatment. Lutetium-177 treatment is often termed as 'Molecular Radiotherapy'. This is indeed how it works – highly radio-active molecules are targeted specifically to cells expressing the PSMA antigen / receptor. Prostate cancer cells have a very high expression of the antigen/receptor and more so when hormone therapy has been used. No other treatment – pharmaceutical or physical – has this mode of action and thus specificity.
12	***What does the patient want?*** Tackle believe Lutetium-177 is a true step-change in treatment of advanced prostate cancer. A similar treatment utilising this molecue is already in use in certain neuro-endocrine cancers. We greatly regret that, at this time, a treatment capable of extending life with a low incidence of additional side effects will not be available to patients who literally have no other treatment left. The ideal treatment is one that is effective, with a low side effect profile and specifically targeted to *all* sites of metastasis - and not just bone as with Radium-223. It is counter-productive to initially use a treatment which does not have the ability to target all possible sites of metastasis – only for a need to arise to treat further soft tissue/visceral/lymph node metastases at a later stage. Not only is this an illogical treatment pathway but one which, for many patients, will be more costly to the NHS in the long run. Surely it is better to only use one initial treatment which has the potential to target *all* sites of metastasis?
13	***Where do we go from here?*** It would be a tragedy for patients with advanced prostate cancer if Lu-177 were never to be freely

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	available to them. The EAMS scheme has, until now, allowed many patients to receive treatment. It is disappointing that the committee have not recommended that this treatment could be made available via the Cancer Drugs Fund. Tackle sincerely hope that discussion will take place and that some compromise may be found.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**TACKLE PROSTATE CANCER**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NONE**
Name of commentator person completing form:	[redacted]

Comment number	Comments

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	Please add the comments below to our previous comments made:
1	Tackle Prostate Cnacer have just received the comments below from the patient who acted as a patient expert. We would like them added to our previous comments: 'As a patient expert, I am very concerned at the committee's decision not to recommend that Lutetium-177 becomes one of the treatment options for men suffering from metastatic prostate cancer. This is a treatment that has been successfully employed in Germany and Australia for a number of years and there is powerful data from the latter as to the drug's real-world efficacy. The UK is already falling behind other developed nations in its treatment of cancer and here is a drug which raises overall survival and does so with minimal side effects. While Lutetium-177 was unable to eradicate all my lesions, I have been able to lead a full and active life for the past year with no additional treatment. It makes no sense in treating men with relatively low volumes of disease to wait for that disease to spread further before employing a more prescriptive drug (Radium-223 which only treats bone metastases) or a debilitating taxane such as Cabazitaxel. Lutetium-177 is a breakthrough therapy capable of lengthening and enhancing the lives of men with prostate cancer and so deserves its place in the treatment arsenal against the disease. To me it would be a tragedy for patients with advanced prostate cancer if this innovative therapy was not made available to NHS patients. It would also be a travesty for our healthcare system that it would be available to those who could afford it.' Peter Isard, Lu-177 patient. 1st November 2022
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Nuclear Medicine Society
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that ……..
1	The British Nuclear Medicine Society advocates and strongly support implementation of [177Lu]Lu-PSMA treatment in clinical practice due to its clinical effectiveness, proven patients benefits and outcomes e.g., improved overall survival and better health-related quality of life. Thera(g)nostic PSMA molecule (used for both diagnosis and treatment) is a molecule of the last decade. Whilst patients in the USA and Europe have access to this treatment, NHS patients in the UK are having no or very limited early compassionate access to this novel innovative radiomolecular therapy. Patients who are not medically suitable for taxane are those patients with unmet need. They have either exhausted all the standard options of treatment or are also often unsuitable for 2nd line chemotherapy. The availability of 177Lu- vipivotide tetraxetan (PSMA) would provide a suitable option for treatment for patients with unmet need and reduced inequality in patients care. Patients with non-painful bone metastases who have received chemotherapy, 2-line chemotherapy and are not able to tolerate chemotherapy would have no access to any treatment if 177 Lu-PSMA is not approved. This would create overall inequality in care of patients with metastatic castration resistant prostate carcinoma (mCRPC) and can be perceived discriminatory.
2	No comment on the cost-effectiveness analysis can be given as it was not reported in the document due to the confidential commercial arrangements for lutetium-177, cabazitaxel and other postprogression treatments (pg 23).
3	BNMS agrees that an expansion of existing diagnostic and therapeutic services is required to reduce geographical inequality due to the need for some patients to travel long distances to receive treatment and potentially long waiting times. There is a need to improve the infrastructure to deliver this treatment and related diagnostic test for patients' selection fairly and equitably. The radiation doses delivered should be calculated and recorded and further optimisation of treatment using dosimetry can be achieved through future research.
4	Comparators: Cabazitaxel: More consideration about the much better toxicity profile of the Lu-177-PSMA compared to cabazitaxel on top of a higher response rate, as reported in the TheraP trial should be given. This is echoing clinical, and patients experiences in England, UK and abroad. Patients received Lu-177-PSMA treatment report very little toxicity and maintain good quality of life and PSMA treatment is much better tolerated than Cabazitaxel. 177Lu-PSMA compared with Cabazitaxel in men with metastatic castration-resistant prostate cancer led to a fewer grade 3 or 4 adverse events. In contrast to chemotherapy this treatment is very well tolerated with a favourable side-effect profile to cabazitaxel and hence would help in optimising patients' quality of life and expected to improve their OS.
5	Comparators: 223Ra-dicholoride The BNMS agrees that 223 Ra should not be used as a comparator. Further to pivotal ALSYMPCA trial, Radium-223 has been approved for mCRPC patients with painful skeletal metastases. Populations included in ALSYMPCA and VISION trials are different.
6	Comparing lutetium-177 with radium-223 dichloride for people with symptomatic bone metastases only (p.24) 223Ra and 177Lu-PSMA are likely to be complementary rather than exclusive. The mechanism of action of Lutetium-177 PSMA is different from that of Radium-223. Radium-223 is a bone targeting agent which mimicking calcium, while 177 Lutetium-PSMA targets PSMA expressing

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	disease in the bone, nodes prostate and other viscera. So, two agents are entirely different in their mechanisms and hence may be used for different indications too. Prostate cancer is a heterogeneous disease. Patients with painful bone metastases benefit from 223Ra. There is evidence that PET-PSMA scan and 18FNaF bone scan can be discordant reiterating heterogeneity of metastatic disease. Therefore, it is essential to preselect patients for the best targeted precision treatment. (Harmon AS et el. Oncotarget 2018; 9;37676-88) Uprimny C et al.Eur J Nucl Med Mol Imaging. 2018 Oct;45(11):1873-1883). There is evolving evidence that alpha and beta emitters can be complementary or sequentially be used with benefit in OS and a favourable side-effect profile- Kambiz Rahbar et al. Safety and Survival Outcomes of Lutetium-177–Prostate-Specific Membrane Antigen Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer with prior Radium-223 treatment: The RALU Study. Journal of Nuclear Medicine, published on October 27, 2022 as doi:10.2967/jnumed.122.264456; Ahmadzadehfar H, et al. Eur J Nucl Med Mol Imaging. 2021;48(12):4067-4076 - WARMTH study). For patients with painful bone predominant mCRPC receiving 223Ra in routine care, subsequent 177Lu-PSMA treatment was clinically feasible and well tolerated, with limited myelosuppression. Survival outcomes reflected previous reports. In the absence of prospective evidence for a direct comparison between 223Ra and 177Lu-PSMA in patients with painful bone disease, sequential treatments could be viable option until further evidence emerges.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Bayer plc**]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Bayer broadly agrees with the summary outlined in the ACD and the provisional recommendations of the Committee regarding the use of Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies. We believe these are an accurate representation of the evidence submitted by the manufacturer. However, there is one key issue that is of high concern for Bayer and that we would like to highlight below for consideration during the second ACM.
2	On page 9 of the ACD, the following statements were made in regard to radium-223's clinical efficacy, intended use in practice and relevance as a comparator for this appraisal: *The company argued that radium-223 dichloride may be a relevant comparator for a* ***small subgroup*** *of people with symptomatic bone metastases alone. But it noted that radium-223 dichloride has a different mechanism of action from lutetium-177.* ***It is used to alleviate bone pain whereas lutetium-177 would be used to improve survival****. The clinical experts explained that ALSYMPCA (a trial that compared radium-223 dichloride plus best supportive care with placebo and best supportive care) found a survival benefit with radium-223 dichloride. They added that it looked at symptomatic bone metastases as a secondary outcome.* ***But they agreed that, in clinical practice, radium-233 dichloride is used palliatively to treat symptomatic bone pain****.* Bayer considers the above statements to contain multiple factual inaccuracies and represent a

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	erroneous interpretation of the radium-223 evidence and its associated positive NICE recommendation (TA412). ALSYMPCA was a large phase III international RCT investigating the efficacy and safety of radium-223 compared with placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases. **The primary end point was overall survival**. The main secondary efficacy end points included time to the first symptomatic skeletal event and various biochemical end points. The study showed that radium-223, as compared with placebo, significantly improved overall survival (median, 14.9 months vs. 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; P<0.001)[1]. Assessments of all main secondary efficacy end points also showed a significant benefit of radium-233 as compared with placebo. The development of radium-223 and its associated clinical evidence clearly shows it is not a **'palliative'** treatment, but a treatment that addresses the underlying mechanism of the disease and significantly prolongs survival. Secondly, the clinical experts attending the committee meeting did not use the word **'palliative'** treatment to describe the use of radium-223 in clinical practice. They actually highlighted the fact that radium-223 does provide a significant and meaningful survival benefit as observed in clinical trials and during its established use in NHS clinical practice, as any clinician using radium-223 in practice could substantiate. The experts did rightly point out that radium-223 is indeed indicated only in patients with **symptomatic** bone metastases, which is deemed to reflect the more advanced state of the disease for these patients that stand most to benefit from radium-223. As per radium-223's SmPC, symptomatic bone metastases are defined as the presence of any of the following: - hypercalcaemia - pathological fracture - newly onset or increased fatigue/generalised weakness - impaired mobility - anaemia, neutropenia, or thrombocytopenia - back pain (due to spinal cord compression) - pain and discomfort - reduced activity of daily living due to pain - sleep disturbance due to pain This highlights that the **symptomatic** bone metastases definition is broader than '**bone pain'**. At such, Bayer requests NICE to address any misleading terminology in the ACD regarding the clinical efficacy of radium-223 and its use in clinical practice. Radium-223 should not be referred to as a 'palliative' treatment i.e. a treatment used for relieving pain only **without dealing with the underlying mechanism of the condition (tumour growth and associated survival)**. Radium-223 is a highly efficacious and cost-effective treatment as demonstrated in the pivotal ALSYMPCA trial and reflected in the NICE positive recommendation regarding its use (TA412), and it has been long established in clinical practice as a reliable option to significantly prolong survival and delay progression of metastases in prostate cancer patients with symptomatic bone metastases only. Finally, the ALSYMPCA trial makes an indirect treatment comparison between radium-223 and lutetium-177 possible and this should absolutely be explored before making recommendations for this subgroup of patients with symptomatic bone metastases only, in which radium-223 is an established standard of care in the NHS as recommended by NICE (TA412). Despite the populations in ALSYMPCA and VISION not being fully aligned in terms of prior therapies, an indirect treatment comparison can still be performed, and the level of bias associated to imbalances in prior therapies and other prognostic characteristics of the two trials populations can be explored and adjusted for. Bayer estimates approximately 30% of mCRPC patients would have symptomatic bone metastases only following progression on two prior lines of systemic therapies (if eligible) and would be eligible

[1] Parker, C. al, et al. "Alpha emitter radium-223 and survival in metastatic prostate cancer." *New England Journal of Medicine* 369.3 (2013): 213-223.

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 2 November 2022. Please submit via NICE Docs.

	for radium-223. Hence the size of this subgroup is substantial, highlighting the high importance for the NHS to only commission treatments that are clearly shown to be cost-effective against all established standard of care comparators.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

UK MRT Consortium comments for NICE 177Lu-PSMA-617 appraisal consultation

November 2022

UK MRT Consortium Member	Comment/s
[redacted] (Tackle Prostate Cancer)	For patients with advanced prostate cancer who have received all currently available therapies, the committee's decision effectively removes an option for further treatment and extension of life. Our main message has been that this is a totally innovative technology, and provides potentially life extending treatment for patients who have already exhausted all current therapies for their advanced disease. It is also more logical to use Lu-177 and not Radium-223 at this advanced stage as the latter will only deal with bone METs and not soft tissue ones. A significantly proportion of patients with bone METs will then go on to develop soft tissue ones. Sadly finding patients to act as advocates is not easy because of the GDPR and confidentiality problems in identifying patients. Yes it will always be a ploy to reduce the price from the pharma companies. Here, also, I suspect they are worries about the collateral costs of increased input through radio-nuclear medicine facilities and the capital and other costs this may add to the actual cost of the Lu-177 itself?
[redacted] (Charing Cross Hospital)	See letter in Appendix
[redacted] (The Royal Marsden NHS Foundation Trust, The Institute of Cancer Research)	The main comment to make is that it is important that NICE is aware of the IR(ME)R regulations and CQC report on the necessity of dosimetry for PSMA treatments and that that should be accounted for on costings and recommendations. This is not mentioned at present.

[redacted] (Barts NHS Trust)	I think we should state there is a group of patients which have run out of other options and the TheraP trial showed Lu-177 PSMA was better tolerated than Cabazitaxel. It would be helpful if patient advocacy groups could get testimonials of those treated on VISION and overseas. NICE appears to take notice of these.
[redacted] (The Christie NHS Foundation Trust)	I think this evidence-based response to the supporting evidence provided by NICE is so key – whether quantitatively from TheraP or qualitatively from patient experience.
[redacted] (Swansea Bay University Health Board – Oncology)	Echoed Stephen Allen's comments: 'Yes it will always be a ploy to reduce the price from the pharma companies. Here, also, I uspect they are worries about the collateral costs of increased input through radio-nuclear medicine facilities and the capital and other costs this may add to the actual cost of the Lu-177 itself?' Noted that the ancillary costs especially, which NICE will be looking at, and if not NICE, then local commissioning organisations. These will include: • NM infrastructure • Extra imaging costs, capacity • Extra clinic space, lists • Staff training and recruitment
[redacted] (Prostate Cancer UK)	PCUK have submitted a response to Nice which included a patient perspective that described the benefits of the treatments. PCUK also spoke about the need for novel treatments like LU-177, the possibility of equality issues if patients who are medically unsuitable for taxanes are excluded, and the other points in the ACD doc.
[redacted] (Betsi Cadwaladr University Health Board – North Wales Medical Physics)	Probably worth noting that NICE haven't considered these costs at all so far – there's a nominal cost for 'administration' of Lu177-PSMA but this probably doesn't come anywhere near the real costs once you factor in NM infrastructure, extra imaging costs, capacity, extra clinic space, lists, staff training and recruitment, etc.

Appendix

[redacted]
MB ChB FRCP MSc FRCR MD MA MAE
Consultant Clinical Oncologist

[redacted] [redacted] [redacted]
Fulham Palace Road
London W6 8RF

Harrow
HA1 3RX

Cromwell Road
London SW5 0TU

Private Appointments/Correspondence: [redacted]
Email:

31st October 2022

[redacted] Clinical Lead for Urological Cancers
[redacted]

Dear [redacted],

Many thanks for asking me to provide comments with regards to the preliminary decision by NICE not to rule in favour for endorsing Lutetium PSMA therapy.
I note that they used the comparator of second line chemotherapy with Cabazitaxel to help inform their decision.

I would like to make the following points based on my experience with treating patients both with Lutetium and Cabazitaxel.

The most striking thing is the risk of myelosuppression with Cabazitaxel which is the dose limiting toxicity, and the majority of my patients require growth factor support. For the patients treated with lutetium so far, I have not observed myelosuppression and febrile neutropaenia requiring hospital admission.
In addition, the gastro-intestinal toxicity, and fatigue with Cabazitaxel is relatively common, and virtually negligible with Lutetium.

It is for these reasons that many of my patients decline Cabazitaxel, but perhaps of more importance is the peripheral neuropathy that patients initially experience with Docetaxel and can be exacerbated by using Cabazitaxel.

These real-life experiences echo what was reported in the Thera -P trial with a better side effect profile of Lutetium compared to Cabazitaxel.

Moreover, for those patients with poorly controlled diabetes, the avoidance which is necessary for Cabazitaxel.

Yours sincerely,

[redacted]
MBChB MRCP MSc FRCR MD MA MAE
Consultant Clinical Oncologist

[redacted] *Consultant Clinical Oncologist* [redacted]

Following on from our national UK MRT Consortium meeting 1st November 2022 at the RCR – the group further discussed the NICE judgement on 177-LuPSMA-617. We would like the committee to reconsider access to this therapy based on the TheraP trial results, which indicate that overall survival was not compromised by treatment, compared with Cabazitaxel and that 177-LuPSMA-617 actually helped to maintain a good quality of life versus Cabazitaxel chemotherapy, which will result in an improvement in QALY. Further to individual patient benefit, keeping patients out of hospital, particularly when we face unprecedented strain on our health care service is also economically beneficial and these results should also be considered.

Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Comments on the ACD received from the public through the NICE Website

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

3.15 The costs of PSMA testing for the whole population need to be included in the cost-effectiveness estimates

'testing'

"imaging" ?

3.3 Eligibility is determined by PSMA imaging, but access to this is limited and not standard practice across the NHS

'choline is typically used as a radio-isotope for PET-CT scans, but that fluorine and gallium are alternatives. Technetium-99m-labelled PSMA is used for single-photon emission computerised tomography (SPECT)'

Choline is not a radio-isotope. The radio-isotopes involved are fluorine-18, gallium-68, and technetium-99m.

These, with choline, and the various PSMA targeting molecules, are all different _radiopharmaceuticals_.

There are several PSMA radiopharmaceuticals (e.g. Ga-68 PSMA-111, Ga-68 PSMA-I&T, F-18 PSMA-1007, F-18 PSMA-DCFPyL, F-18 PSMA-rhPSMA-7.3, Tc-99m PSMA-RGS)

'choline is typically used'

The text appears to suggest choline is more popular than PSMA for imaging, but I am not sure this is true, and there is evidence that actual PSMA imaging is better than choline (and other alternatives). This section gives undue prominence to choline over PSMA imaging (there are commercial interests in pushing choline).

e.g. (from a very quick basic search)
Moghul M, Somani B, Lane T, et al. Detection rates of recurrent prostate cancer: 68Gallium (Ga)-labelled prostate-specific membrane antigen versus choline PET/CT scans. A systematic review. Environment and Planning E: Nature and Space. 2019;11. doi:10.1177/25148486211052860

Treglia G, Pereira Mestre R, Ferrari M, Bosetti DG, Pascale M, Oikonomou E, De Dosso S, Jermini F, Prior JO, Roggero E, Giovanella L. Radiolabelled choline versus PSMA PET/CT in prostate cancer restaging: a meta-analysis. Am J Nucl Med Mol Imaging. 2019 Apr 15;9(2):127-139. PMID: 31139496; PMCID: PMC6526363.

PSMA-targeted Radiotracers versus 18F Fluciclovine for the Detection of Prostate Cancer Biochemical Recurrence after Definitive Therapy: A Systematic Review and Meta-Analysis
Nelly Tan, Udochukwu Oyoyo, Niusha Bavadian, Nicholas Ferguson, Anudeep Mukkamala, Jeremie Calais, and Matthew S. Davenport
Radiology 2020 296:1, 44-55
https://pubs.rsna.org/doi/full/10.1148/radiol.2020191689

3.18 Lutetium-177 is not a cost-effective option for hormone-relapsed metastatic prostate cancer at the price chosen by the company
'testing'

"imaging" ?

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

There is real world evidence and data from NHSE which are additional evidence relevant to current practice.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Where this is positioned at failure of chemotherapy the impact of quality of life compared to retreatment or more other agents should be weighted.

Are the recommendations sound and a suitable basis for guidance to the NHS?
these are at variance with assessments of efficacy in the US and should be reassessed

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

this is a particularly aggressive malignancy in men of African background who are often diagnosed late. This constitutes a significant inequality. Data from South africa has shown efficacy and acceptability in this group.

Name	
Role	Heads of Radioisotope Physics, ICR
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

Account should be taken of the UK Ionising Radiation (Medical Exposure) Regulations 2017 (IR(ME)R), that require patient dosimetry to plan and verify the radiation doses delivered from therapeutic procedures within nuclear medicine. The regulations also highlight the need for treatment optimisation and the role of the medical physics expert. A recent IR(ME)R report from the Care Quality Commission explicitly states that 'patient-specific dosimetry should form part of the patient pathway for any non-standardised therapy radiopharmaceuticals, such as 177Lu-PSMA (prostate specific membrane antigen), to mitigate the risk to patients'.

An aspect of the TheraP trial that should be considered is the inclusion of post-therapy SPECT/CT imaging to identify patients with low uptake/radiation. This may indicate ineffective treatments at an early stage. Patient dosimetry performed by the investigators of the TheraP trial (DOI: 10.2967/jnumed.118.219352) showed a correlation between tumour dose and PSA response. The VISION trial did not include imaging of the active drug, preventing comparison. EANM guidelines (https://doi.org/10.1007/s00259-022-05727-7) have detailed the methodology necessary. Treatment informed by imaging could have a significant impact on cost effectiveness and should be investigated.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

As the anticipated scale of delivery and cost-effectiveness analysis are not given in the evaluation, comments are based on the following projections: The Northern Cancer Alliance DRG Prostate Cancer Disease Landscape & Forecast (Nov 2020) estimate 390 patients per year will be eligible for PSMA-labelled treatment by 2029 in their region. Extrapolation to the UK population would therefore predict 7,800 patients per year with up to 46,800 administrations. This is in line with projections made for Germany and the Netherlands. At a cost of £20,000 per administration (excl. VAT) the total cost to the NHS may be up to £1bn per year.

In terms of clinical and cost effectiveness, outcomes from the VISION trial (DOI: 10.1056/NEJMoa2107322) demonstrated that PET PSMA imaging prevented 12% of unnecessary treatments. There were 9.3% drug related SAE (vs 2.4% for SoC), 3.6% drug related adverse events leading to death (vs 2.9% for SoC) and 0.9% drug related death (vs 0% SoC), the latter not reported in the committee papers. Complete or partial responses were seen in 51% of patients, implying little or no

benefit for 49% of patients (which would be at a cost of up to £459,000,000 p.a.). It is likely that, as reported in the TheraP trial, some or many unnecessary treatments would be avoided if post-therapy imaging and dosimetry are performed, at relatively inexpensive cost. Several centres are currently performing imaging and dosimetry for private patients or within the Early Access Scheme for regulatory compliance, although currently without reimbursement. Evaluation of the potential cost/benefit of performing post-therapy imaging and dosimetry should be performed, in the first place to indicate patients that are unlikely to benefit. Such infrastructure would support clinical trials to investigate the clinical effectiveness of personalised treatment.

The cost of service delivery should be fully considered. Reports from increasing experience at several centres indicate that this can be resource intensive in comparison with other radiotherapeutics. The cost of £1254 from the NHS schedule of costs (RN52Z) is insufficient. The costs for imaging and patient dosimetry should be included and may be taken from the NHS schedule of costs for radiotherapy. A possible code is SC48Z (£614).

Are the recommendations sound and a suitable basis for guidance to the NHS?

With the current evidence for clinical and cost effectiveness we agree with the current decision not to recommend Lu-177 PSMA. However, this is potentially a highly effective drug for many patients with the potential to be more clinically and cost effective with further development.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Name	
Role	
Other role	
Organisation	British Uro-Oncology Group
Location	
Conflict	
Notes	

Comments on the ACD:

1 We are concerned that this novel technology which has RCT evidence of improving overall survival in MCRPC will not be available to our patients as per the licensed indications

2 This recommendation will impact on the potential survival outcomes of eligible patients and this will lag behind other countries where this treatment would be funded

3 Despite significant advances in the field of MCRPC, the options for treatment remain limited and the role of theranostics in the treatment pathway is being increasingly recognised as an important strategy

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

177Lu-PSMA-617 is an important novel treatment in the field of molecular radiotherapy. Many UK patients can benefit from the treatment. We believe that patient access to molecular radiotherapy across the UK is of vital importance, and that molecular radiotherapy will continue to be a growth area, with many more novel treatments coming through to market over the next decade. The introduction of 177Lu-DOTA-TATE for the treatment of somatostatin-positive neuroendocrine cancer in the UK has been transformative for many patients and 177Lu-PSMA-617 has the potential to provide the same transformative effect as therapy for many patients with PSMA-positive metastatic prostate cancer, particularly as the treatment is well tolerated and maintains patients' quality of life.

The unique opportunity afforded by molecular radiotherapy, compared to other therapies are the ability to (i) screen patients for receptor expression by imaging them with a diagnostic version of the drug (ie. 68Ga-PSMA) so that only patients with high enough receptor expression to benefit from the treatment are treated (ii) use the radiation emitted by the treatment, to monitor the biodistribution of the therapeutic drug post-administration with gamma-imaging, to provide information about tumour targeting as well as off-target accumulation and dosimetry. These tools provide the opportunities for a personalised medicine approach to these treatments, like the personalised planning of treatments available with external beam radiotherapy, and we believe such an approach would optimise patient experience and outcome. We believe both screening and post-therapy imaging should be used to optimise patient selection and treatment response monitoring, which would drive improvements in both clinical outcomes and cost-effectiveness.

Diagnostic imaging to demonstrate PSMA expression is a vital tool to achieve effective patient screening and selection prior to the commencement of treatment. PSMA screening should be optimised to ensure value for money from treatment, and note should be taken of the opportunity to combine PSMA imaging with other molecular imaging agents such as FDG imaging to further improve the selection of patients and drive value for money as demonstrated in the TheraP trial (NCT03392428).

We hope that NICE recognises the benefits of this treatment and the importance of access for UK patients and continues to negotiate on cost

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

I believe that the THERAP trial data are more relevant than implied in the draft guidance. The data show significant improvements in PSA50 response compared with an active comparator (Cabazitaxel).

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

The challenge is that for this group of patients, especially if not fit for chemotherapy there are actually no real comparator, unless they are bone only and suitable for Radium-223.
Lu-177 PSMA-617 therapy offers OS improvement with better tolerability than Taxane chemotherapy.
More use of Lu-177 PSMA-617 will result in less use of Radium-223 and Cabazitaxel.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I hope that a way can be found through price negotiation to make this therapy available to patients in the UK

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

Name	
Role	
Other role	
Organisation	Institute of Physics and Engineering in Medicine
Location	
Conflict	
Notes	

Comments on the ACD:

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

On behalf of the Nuclear Medicine Special Interest Group of the Institute of Physics and Engineering in Medicine:

“In section 3.18 (p23), there should be inclusion of an allowance for verification imaging and single time point dosimetry within the costings. This is required to meet IRMER and the recommendations from ARSAC.

“This will increase the costs of the therapy slightly, but hopefully the supplier will reduce their price to make the overall costs acceptable for NHS use in the future. Having the costings considered at this point makes it more likely (in IPEM’s view) that, if the treatment is recommended in the future, the costs for the verification imaging/dosimetry will flow through to those performing that part of the service.”

^{177}Lu vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Addendum: EAG comments on the company's response to the Appraisal Consultation

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	29th November 2022

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

1 Introduction

In October 2022, the National Institute for Health and Care Excellence (NICE) issued a negative Appraisal Consultation Document (ACD) for ^{177}Lu vipivotide tetraxetan for the treatment of prostate-specific membrane antigen (PSMA)-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies.[1] The ACD states that the most likely cost-effectiveness estimates for ^{177}Lu vipivotide tetraxetan compared to standard of care (SOC) and to cabazitaxel are much higher than what NICE considers an acceptable use of NHS resources. The ACD also states that the Appraisal Committee acknowledged the uncertainties in the company's model but concluded that the model was suitable for decision making. Nonetheless, the Appraisal Committee noted the high level of uncertainty in the cost-effectiveness estimates which would be require several new analyses to address the Appraisal Committee's preferred assumptions.

In November 2022, the company submitted a response to the ACD.[2] The company's response includes a written document and an updated version of the base case model which includes some of the Appraisal Committee's preferred assumptions. The company's response document provides additional discussion around the following seven key points: (i) heterogeneity associated with studies included in the network meta-analysis (NMA); (ii) the use of real-world evidence (RWE) to estimate relative treatment effects on OS between cabazitaxel and ^{177}Lu vipivotide tetraxetan; (iii) generalisability of the base case analysis to patients medically unsuitable for taxanes; (iv) the exclusion of radium-223 as a comparator; (v) uncertainty around the utility estimates used in the model; (vi) the exclusion of PSMA testing costs; and (vii) premedication and concomitant medication costs for cabazitaxel (treatment duration of granulocyte-colony stimulating factor [G-CSF]).

Additional scenario analyses are presented around several of these issues. The company has also increased the Patient Access Scheme (PAS) discount for ^{177}Lu vipivotide tetraxetan to from [redacted] to [redacted] (new discounted cost per pack = [redacted]).

This EAG addendum provides a commentary on the company's ACD response[2] and should be read in conjunction with the External Assessment Group (EAG) report,[3] and the EAG's response to technical engagement (TE).[4] Section 2 provides a summary of the company's response to the ACD and the EAG's critique of these points. Section 3 presents the results of the company's revised base case model, including the new PAS for ^{177}Lu vipivotide tetraxetan. Section 4 presents additional exploratory analyses undertaken by the EAG including the new PAS.

2 Summary of the company's response to the ACD and EAG critique

This EAG addendum is structured around the seven issues discussed in the company's response to the ACD which are detailed in Sections 2.1 to 2.7. Each section summarises the company's position and also includes the EAG's opinion of the new data and/or assumptions.

2.1 Issue 1: Data used in the NMA

The company updated the NMA for overall survival (OS) with inverse probability of censoring weighting (IPCW)-adjusted VISION data, as preferred by the Appraisal Committee. The company also updated the NMA for radiographic progression-free survival (rPFS) using the interval imputed VISION data, and including the TheraP trial. A scenario analysis was also conducted excluding the TheraP trial. The EAG notes that in the ACD, the Appraisal Committee expressed a preference for including the TheraP trial in the NMA (Section 3.10) and also for using results from analyses which adjusted for the censoring of patients who withdrew from the trial (Sections 3.8 and 3.11). In the NMAs for both OS and rPFS, a fixed effect model was applied as the base case; scenario analysis using random effects and random effects with DuMouchel priors were also performed. Figure 1 and Figure 2 show the base case network diagram for OS and rPFS. Data used in the revised NMAs can be found in Table 1. Results of the company's revised NMAs can be found in Table 2.

The EAG notes that the results of the revised NMAs with adjusted OS and rPFS data from VISION have been subsequently used to inform OS and rPFS for cabazitaxel in the company's revised base case economic analysis, as described in the ACD response.

Figure 1: Base case network for OS (reproduced from the company's ACD response, Figure 1)

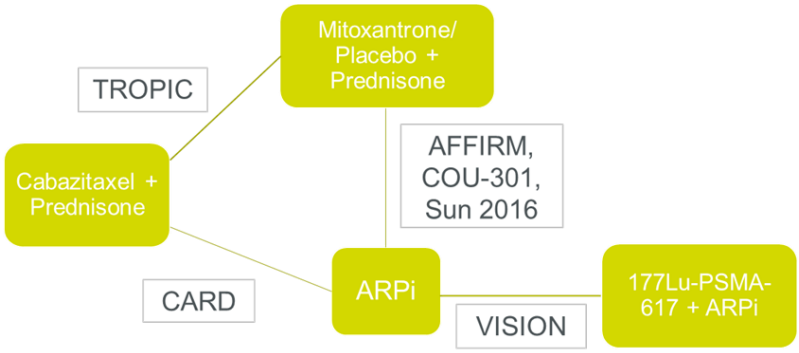

Figure 2: Base case network for rPFS (reproduced from the company's ACD response, Figure 2)

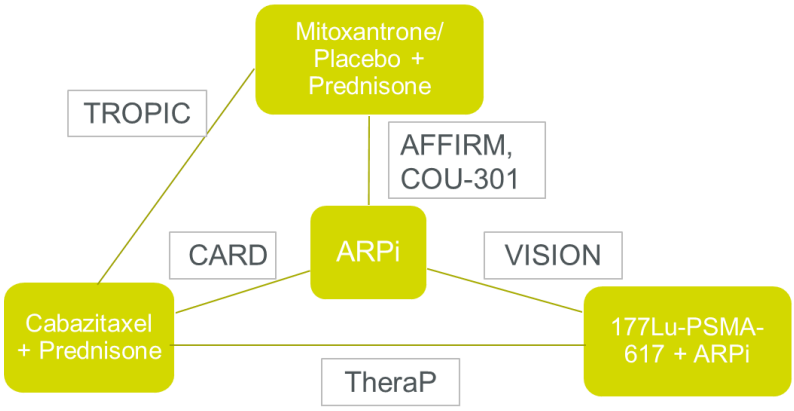

Table 1: Adjusted VISION OS and rPFS outcomes (reproduced from the company's ACD response, Table 5)

Population	Model	Outcome	Hazard ratio	Lower bound of 95% CI	Upper bound of 95% CI
ARPI subgroup	No adjustment	OS	[redacted]	[redacted]	[redacted]
		rPFS	[redacted]	[redacted]	[redacted]
	IPCW[a]	OS	[redacted]	[redacted]	[redacted]
	Interval imputation	rPFS	[redacted]	[redacted]	[redacted]

[a] Willems *et al.* (2018) method.
Abbreviations: ARPI: androgen receptor pathway inhibitor; CI: confidence interval; IPCW: inverse probability-of-censoring weighting; OS: overall survival; rPFS: radiographic progression-free survival.

Table 2: Updated NMA for OS and rPFS with adjusted VISION data (adapted from the company's ACD response, Table 9)

Scenario	Model	HR – ^{177}Lu vipivotide tetraxetan vs		
		Cabazitaxel	ARPI	Mitoxantrone/ placebo
OS	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	DuMouchel priors	[redacted]	[redacted]	[redacted]
rPFS (including TheraP)	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	DuMouchel priors	[redacted]	[redacted]	[redacted]
rPFS (excluding TheraP)	FE	[redacted]	[redacted]	[redacted]
	RE	[redacted]	[redacted]	[redacted]
	DuMouchel priors	[redacted]	[redacted]	[redacted]

Note: IPCW adjustment for OS and interval imputation adjustment for rPFS.
Abbreviations: ARPI: androgen receptor pathway inhibitor; CrI: credible interval; FE: fixed effect; HR: hazard ratio; OS: overall survival; RE: random effects.

The company also explored baseline risk adjusted-NMAs at 6-, 12- and 18-months for both OS and rPFS to account for heterogeneity between the included trials, as preferred by the Appraisal Committee. The company reports that "*there was no improvement in residual deviance and no significant reduction in DIC, suggesting that adjusting for baseline risk did not improve model fit.*"

The company also reiterates that "*the high levels of heterogeneity in patient populations between the two trials* [CARD and VISION] *means that any relative treatment effect derived from an NMA including both trials may be biased*" and the company "*encourages the committee to consider the cost-*

effectiveness results informed by the [propensity score weighting] *PSW RWE study for cabazitaxel when making its decision.*"

The EAG notes that no details of the method used for baseline risk adjusted-NMAs and DuMouchel prior were presented in the company's ACD response. As such, it is unclear how the baseline risk adjusted NMAs were performed or what informative prior was used. The EAG is therefore unable to comment on the appropriateness of the methods used.

The EAG used the node-split method[5] to check consistency in the company's revised NMA for both OS and rPFS. Tests for inconsistency show that there is a statistically significant difference between the direct and indirect evidence for the treatment comparison between cabazitaxel and ARPI (*p*-value = 0.02 for OS and *p*-value <0.001 for rPFS). The EAG believes that the inconsistency may be caused by anti-androgen sensitivity among the included trials as the populations in TROPIC, COU-AA-301, AFFIRM and Sun *et al.* were all anti-androgen naïve, but patients in CARD all failed ARPI within 12 months. Therefore, the EAG's view on excluding the indirect evidence (TROPIC, COU-AA-301, AFFIRM and Sun *et al.*) in the NMA remains unchanged. The EAG's preferred NMA only includes trials with ARPI experienced patients (CARD, VISION and TheraP).

Given the heterogeneity among the studies in the NMA, the EAG retains its view that it is more appropriate to use a random effects model than a fixed effects model. Hence, a random effects model with an informative prior was used for all the EAG's additional NMAs. Details of the prior used can be found in the EAG report.[3] Results of the EAG's additional NMAs can be found in Section 4.

The EAG notes that the EAG's NMA estimates the treatment effect of ^{177}Lu vipivotide tetraxetan versus cabazitaxel using trials where all included patients had received prior treatment with an ARPI, and in particular one study (CARD) where they had to have progressed within 12 months on their first ARPI. In contrast the company's NMA estimates the treatment effect of ^{177}Lu vipivotide tetraxetan versus cabazitaxel using some trials where patients had received prior ARPI and some trials where patients were ARPI naïve. It is therefore less generalisable to current clinical practice, where most patients would have received an ARPI before being offered cabazitaxel, and the company's proposed positioning of ^{177}Lu vipivotide tetraxetan and its marketing authorisation which is for use after an ARPI.

2.2 Issue 2: The use of RWE to estimate relative treatment effects on OS between cabazitaxel and ^{177}Lu vipivotide tetraxetan

The company acknowledges that their original PSW analysis of the RWE study of cabazitaxel which selected covariates to be included in the analysis via univariable linear regression may omit clinically important prognostic variables. In order to address the Appraisal Committee's concerns regarding the

appropriateness of the covariates included in the PSW analysis, the company carried out a targeted literature review (TLR) to identify characteristics that may represent clinically important prognostic variables affecting the survival of patients with metastatic castration-resistant prostate cancer (mCRPC). The TLR searched the Embase® and MEDLINE® databases, and included 80 studies which reported on "*nearly 25 prognostic variables [sic]*".

Four out of 13 variables identified as important prognostic factors in the TLR were adjusted for in the RWE analysis using PSW. However, 9 out of 13 identified important prognostic factors could not be adjusted for because they were not available from the RWE and VISION cohorts. The company acknowledges that the results of the PSW analysis may be subject to bias from unobserved confounding, but concludes that "*given a large number of important prognostic factors were adjusted for, the relative efficacy for ^{177}Lu vivipotide tetraxetan versus cabazitaxel estimated from this analysis remains relevant and plausible"*.

The company states that the Appraisal Committee's suggestion to use the cabazitaxel RWE study as the reference OS estimate and to derive the OS for ^{177}Lu vipivotide tetraxetan by applying the NMA hazard ratio to the reference OS estimate would introduce inconsistencies between the source of OS and rPFS data for ^{177}Lu vipivotide tetraxetan included in the economic model and may result in logical inconsistencies.

In order to address the Appraisal Committee's concerns regarding the uncertainty in the relative effect of ^{177}Lu vipivotide tetraxetan versus cabazitaxel, in the company's revised base case economic analysis the OS for cabazitaxel was based on the NMA. The company also presented a scenario where OS for cabazitaxel was informed by the PSW RWE analysis since it considers this source relevant for decision making.

The EAG acknowledges that electronic database searching for prognostic factor studies is challenging because of the difficulty of defining the search concept, poor and inconsistent indexing of studies (in MEDLINE and Embase), and the use of variable terminology between studies. It is apparent to the EAG that the company has carried out a focused search as opposed to a sensitive search for prognostic variables. The company's terms for the patient population were limited to the abbreviation, one indexed term, and a free-text statement, whereas in the systematic literature review company submission (CS) searches in Appendix D Table 1 (page 9) the evidence base is much larger at 42K (up to November 2021) compared to 7.8K previously. The company did not use any published search filter to identify prognostic factors but used four key statements "treatment effect", "effect modifier", "prognostic factor" or "covariate" to limit the search, which differs considerably from the published Hedges search filter.[6] Where a focused search is applied, the EAG suggests that the limitations of this approach and the risk

of bias in the studies retrieved could be mitigated by supplementing the search with other approaches such as reference and citation searching, and handsearching, or adopting an iterative search to improve the sensitivity of the search.[7, 8]

The EAG disagrees with the company's claim that a large number of important prognostic factors were adjusted for in the PSW as only four out of 13 important prognostic factors identified in the TLR were included in the PSW analysis. The EAG notes that because this is an unanchored indirect treatment comparison, both prognostic factors and effect modifiers should be included in the adjustment, not just the prognostic factors.[9] However, the company does not provide any justification regarding whether the appropriate effect modifiers were adjusted for in the analysis.

The EAG also disagrees with the company's justification for not providing the scenario analysis suggested by the Appraisal Committee (using the cabazitaxel RWE study as the reference OS estimate and deriving the OS for ^{177}Lu vipivotide tetraxetan by applying the NMA hazard ratio to the reference OS estimate) on the basis that this would introduce inconsistencies between the source of OS and rPFS data. The EAG believes that all the relevant evidence should be explored, and this scenario analysis would provide a reference OS estimate which would be likely to better reflect the true survival in current NHS practice. The EAG notes that the company's scenario analysis where OS for cabazitaxel is informed by the RWE data would also be subject to the same inconsistencies that are cautioned against in the company's ACD response. It is therefore unclear why the company chose to present its own scenario analysis, but not the Appraisal Committee's suggested scenario analysis.

Overall, the EAG's view of the robustness of the company's PSW RWE analysis remains unchanged. A detailed critique around this issue is presented in the original EAG report (Section 4.3.4, issue 3) and TE response (Section 4, key issue 4).[3, 4]

2.3 Issue 3: Generalisability of the base case analysis to patients medically unsuitable for taxanes

The Appraisal Committee acknowledged a likely worse prognosis in patients who are medically unsuitable for taxanes and *"agreed that scenario analyses using the same relative treatment effect as for the wider population but with a higher baseline risk, and so a worse overall survival would be useful*". Nonetheless, the Appraisal Committee *"concluded that it was appropriate to consider the whole population included in lutetium-177's marketing authorisation, including when taxanes are medically unsuitable. This is because a proportion of people for whom taxanes are medically unsuitable would be able to have lutetium-177."*

The company highlights that in its opinion the current poor prognosis for patients who are medically unsuitable for taxanes is a result of the lack of effective treatment options, and therefore may not be a good predictor of the ability of such patients to respond to treatment with ^{177}Lu vipivotide tetraxetan.

The company also comments that many of the reasons for medical unsuitability to taxanes relate to the risks associated with taxane treatment, given their substantial toxicity, and not the ability of the patient to respond to treatment. The company reiterates that individual patient choice would also form part of the criteria for medical unsuitability for taxane treatments.

The company argues that there is no mechanistic reason why many patients who might be deemed medically unsuitable for taxanes would not respond to a more tolerable, effective treatment, if it were made available, and thus the efficacy and safety of ^{177}Lu vipivotide tetraxetan is unlikely to be significantly different in such patients. In the company's view, it is plausible that some of these patients may in fact have a better prognosis on ^{177}Lu vipivotide tetraxetan compared to patients who have received and failed treatment with docetaxel. The company also mentions that clinical experts consulted by them would not expect patients deemed medically unsuitable for taxanes to respond significantly differently to ^{177}Lu vipivotide tetraxetan, compared with the VISION population.

Lastly, the company reiterates that excluding this group of patients from the recommendation for ^{177}Lu vipivotide tetraxetan would create inequity biased against those patients for which there is particular unmet need, but who would be considered medically suitable for treatment with ^{177}Lu vipivotide tetraxetan.

The EAG notes that the company has not provided any additional evidence to support the hypothesis that patients medically unsuitable for taxanes would obtain the same level of benefit from ^{177}Lu vipivotide tetraxetan, compared with patients from the VISION population who received at least one previous line of treatment with taxanes. As no further evidence has been presented to resolve this issue, the EAG's view of the available clinical evidence and uncertainty around the relative treatment effects of ^{177}Lu vipivotide tetraxetan in this subgroup remains unchanged. The EAG's critique around this issue is presented in the original EAG report (Section 4.3.4, issue 2) and TE response (Table 1, key issue 1).[3, 4]

2.4 Issue 4: The exclusion of radium-223 as a comparator

Clinical experts at the Appraisal Committee meeting explained that estimating what proportion of the eligible population for ^{177}Lu vipivotide tetraxetan has bone metastases alone is not straightforward. They estimated that about 80% to 90% of people receiving first-line treatment may have bone metastases alone, but the proportion of visceral metastases increases with progression and further lines of treatment,

and approximately 10% to 15% of patients who could have ^{177}Lu vipivotide tetraxetan would have isolated symptomatic bone metastases. The Appraisal Committee stated that radium-223 "*may be a relevant comparator for some people but that there was limited information available about the size of the relevant population*", and noted that comparative evidence for this group has not been presented. Hence, the Appraisal Committee concluded that it could not make any decision on the comparison between ^{177}Lu vipivotide tetraxetan and radium-223 for people with symptomatic bone metastases.

In the ACD response, the company states that they have not been able to provide an appropriately robust analysis of the comparative cost-effectiveness of ^{177}Lu vipivotide tetraxetan and radium-223 for reasons previously given in the CS and during technical engagement. The company reiterates that only a small number of patients in clinical practice would be anticipated to be considered for treatment with radium-223 and ^{177}Lu vipivotide tetraxetan. The company mentions that the use of radium-233 in UK clinical practice appears to be predominantly at earlier stages of the treatment pathway. The company indicates that approximately half of patients in the VISION trial would have been precluded from being treated with radium-223 for presenting with lymph node metastases, and that in the RWE database only [redacted] and [redacted] of all mCRPC patients and patients who received an ARPI and a taxane, respectively, have reported to have received treatment with radium-223. The company also reiterates that the key comparator for ^{177}Lu vipivotide tetraxetan in the post-ARPI and post-docetaxel setting is cabazitaxel; and a lack of a robust comparison between ^{177}Lu vipivotide tetraxetan and radium-223 should not be considered a significant source of uncertainty.

An additional ACD response was received from Bayer PLC,[10] where the manufacturer of radium-223 states that clinical evidence from the ALSYMPCA study shows a survival benefit associated with radium-223, and therefore this technology was not considered a 'palliative' treatment, but a treatment that addresses the underlying mechanism of the disease, which would have been highlighted by clinical experts attending the committee meeting. The ACD response from Bayer PLC also states that it estimated approximately 30% of mCRPC patients who have progressed on two prior lines of systemic therapies would be eligible for radium-233, and it is supportive of the possibility of an indirect comparison between radium-223 and ^{177}Lu vipivotide tetraxetan which adjusts for differences in the populations of the ALSYMPCA and VISION trials. On the other hand, comments received from the British Nuclear Medicine Society notes that populations included in ALSYMPCA and VISION trials are different, but also that treatment with ^{177}Lu vipivotide tetraxetan and radium-223 are likely to be complementary rather than exclusive due to their different mechanism of action, and that sequential treatments could be a viable option until further evidence for a direct comparison between these treatments emerges.[11]

Overall, the EAG maintains its view that radium-223 should be a comparator for the subgroup of patients with bone metastases who do not have visceral metastases in the post-ARPI and taxane setting and post-ARPI where docetaxel is contraindicated or unsuitable setting. The EAG's critique around this issue can be found in the original EAG report (Section 2.2) and TE response (Table 1, key issue 2).[3, 4] As the company has not presented any new evidence around this issue, the EAG's view remains unchanged.

2.5 Issue 5: Uncertainty around the utility estimates used in the model

Section 3.14 of the NICE ACD[1] states that in face of the different analyses presented by the company and the EAG, the Appraisal Committee considered:

(i) *"whether it was possible to adjust for withdrawal in the health- related quality-of-life results"*, and it may have been possible to apply IPCW analyses to account for withdrawals;

(ii) *"if there was still a meaningful difference in results between treatments, the uncertainty of using treatment-dependent utility values would be reduced"*.

The ACD also states that the Appraisal Committee *"concluded that all the utility values had uncertainty, although treatment-independent utilities had higher face validity across all treatments. It agreed that it preferred to see a scenario analysis to address the uncertainty."*

The company's ACD response[2] states that they have investigated the possibility of conducting IPCW adjustment to account for informative censoring on EQ-5D-5L data from the VISION trial, but concluded that this analysis is not feasible. The company presented the following supporting arguments:

(i) Those who withdrew from the control arm of VISION had greater baseline quality of life than people who continued.

(ii) There were three sources of missing EQ-5D data in the VISION trial: dropouts, missed assessments and death. Although patients who dropped out of the trial tended to be healthier, the reverse is likely to be true for those who had missed assessments; and deterioration in health before death for many patients may also not be fully captured due to missing assessments.

(iii) The company is unaware of any methods that could be used to address missing data in this situation. As such, the company recommends that little weight should be placed on the EQ-5D data.

The EAG notes that no details around the attempted IPCW analysis was presented by the company in its ACD response. Therefore, the EAG is unable to make any further comments on the IPCW analysis. The company maintains its position that their approach that uses treatment-dependent utility values is the most appropriate, since treatment-independent utilities would not take into account the significant psychological burden of further chemotherapy, which was acknowledged by the Appraisal Committee

and clinical experts. The company also considers that quality-adjusted life year (QALY) losses for cabazitaxel associated with adverse events (AEs) would not adequately reflect treatment burden, given that the population in CARD was generally healthier and less-heavily pre-treated compared with the population in VISION.

The company has not included any analyses using treatment independent utility values in its ACD response. In an attempt to address the Appraisal Committee's concerns regarding the utility values, the company included a new set of utility estimates in their updated base case. This revised approach presented by the company includes treatment-dependent utility values using the updated utility analysis presented at the technical engagement stage, excludes additional utility decrements for AEs and symptomatic skeletal events (SSEs), and applies for cabazitaxel pre- and post-progression health states the average of the utility values for ^{177}Lu vipivotide tetraxetan and SOC - similar assumption to the EAG exploratory analysis 3 presented at the technical engagement stage (TE-EA3)[4]. The utility values applied in the company's original base case analysis in the CS and their revised base case in the TE response and ACD response, and the EAG's preferred and additional exploratory analyses are presented in Table 3.

The EAG notes that, although the company has updated their approach regarding the utilities for cabazitaxel, the utility data used in the company's ACD response were not consistent with the EAG's TE-EA3 analysis, because the company used the utility analysis presented at the TE stage which the EAG believes was associated with informative censoring. In addition, this additional exploratory analysis (TE-EA3) was not included in the EAG's preferred base case analysis at technical engagement. It was instead presented as an exploratory analysis on the basis that there may be some psychological burden associated with patients receiving cabazitaxel post-docetaxel, but the level of this is difficult to quantify because it would be influenced by many other factors.[4] The EAG also notes that the company has not provided any further evidence on the additional burden associated with treatment with cabazitaxel.

Overall, the EAG's view remains unchanged from that presented in the original EAG report and TE response.[3, 4] A detailed critique around this issue is presented in these two documents (Section 4.3.4, issue 5 and Section 4, key issue 5, respectively).

The EAG also notes that the NICE ACD does not present a definitive conclusion regarding the Appraisal Committee's preferred assumption regarding the health state utility values. Although it states that treatment-independent utilities had higher face validity across all treatments, it agreed that it preferred to see a scenario analysis to address the uncertainty. In line with the previous EAG TE response,[4] the EAG presents its updated preferred analysis including treatment-independent utilities and accounting

for additional decrements for AEs and SSEs. In order to address the uncertainty around the utility estimates, the EAG also provides an additional scenario analysis as in TE-EA3, which uses treatment-dependent utilities and assumes the average of the utility values for ^{177}Lu vipivotide tetraxetan and SOC for cabazitaxel pre- and post-progression health states (see Section 4).

Table 3: Health state utility values used in scenario analysis

	Company's original approach (CS)			EAG-preferred approach (EAG report and EAG response)			Company's updated approach (TE response)			EAG's new exploratory analysis (TE-EA3)			Company's updated base case (ACD response)		
	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel	177Lu	SOC	Cabazitaxel
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	0.627	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.627	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY losses due to AE (one-off)	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-	-
QALY losses due to SSEs (one-off at the point of progression)	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-	-	-	-

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; AE: adverse events; CS - company submission; EAG: External Assessment Group; QALY: quality-adjusted life year; SOC: standard of care; SSE: symptomatic skeletal event; TE: technical engagement

2.6 Issue 6: The exclusion of PSMA testing costs

The NICE ACD document highlights that neither cost-effectiveness estimates by the company nor the EAG included the cost of PSMA testing, and that the Appraisal Committee concluded that this cost, which should account for PET-CT or SPECT scans and radiotracers and the proportion of PSMA-positive cancer in the relevant population, should have been included for the entire eligible population. The Appraisal Committee also thought that scenarios should be explored on the effect of up to 75% of people having either a PET-CT or SPECT scan as part of standard care.

The company maintains their view that excluding PSMA testing is the most appropriate approach, as this better reflects current and near-future NHS practice. The company notes that during the committee meeting, clinical experts indicated that clinical practice was moving towards testing for PSMA-positivity earlier in the treatment pathway. However, in order to reduce the uncertainty around the estimates of cost-effectiveness in relation to the costs of PSMA testing, the company has included it in their updated base case analysis. In the updated model, 25% of patients in the ^{177}Lu vipivotide tetraxetan arm were assumed to incur additional costs associated with PSMA tests, in line with one of the Appraisal Committee's scenarios where 75% of patients had already received a PSMA test and no additional imaging is needed. All PSMA scans were assumed to be SPECT, where unit costs were based on a weighted average from total HRG data for SPECT-CT tests associated with patients 19 years old and over, and the cost of PSMA testing was adjusted proportionally to the rate of PSMA positivity, based on data from the VISION trial.

The company also presents an additional scenario in which all patients in the ^{177}Lu vipivotide tetraxetan arm are assumed to incur PSMA testing costs. The company notes this had a limited impact on the cost-effectiveness estimates.

The EAG agrees with the inclusion of the PSMA testing costs. The company has only included the costs of SPECT-CT as a weighted average from the NHS Reference Costs, based on the total number of procedures for people with 19 years old and older. This procedure is in general cheaper than PET- CT scans. The EAG believes that the impact of PSMA testing may be underestimated in the company's updated model, and does not believe PET-CT scans should be excluded in estimating the cost of PSMA testing. The EAG has used a similar methodology to the company's to estimate the unit costs of the test, but including HRG codes for both PET-CT and SPECT-CT. This increases the cost for PSMA testing from £589.55 to £989.33 per test. The EAG has conducted their preferred base case analysis assuming all patients (100%) receive the test as per the NICE scope. However, as the committee concluded that scenarios on the effect of up to 75% of people having either a PET-CT or SPECT scan in standard care should be explored, the EAG has also presented a scenario in which only 25% of people require PSMA testing specifically to determine eligibility for ^{177}Lu vipivotide tetraxetan.

2.7 Issue 7: Premedication and concomitant medication costs for cabazitaxel

The company acknowledges that a 7-day treatment course of prophylactic treatment with G-CSF may better reflect the variation in UK clinical practice. The company included in its updated base case analysis the costs associated with a 7-day course of G-CSF treatment to each 21-day cycle of cabazitaxel therapy. The company notes, however, that this approach does not take into account the increased incidence of neutropenia-related AEs associated with treatment with cabazitaxel. The company also notes that the RWE study of patients receiving cabazitaxel in NHS practice suggests that [redacted] of patients experience febrile neutropenia, compared with a rate of 3.2% (Grade 3 or 4) in the CARD trial. The company notes that "*the combination of a 7-day course of G-CSF in combination of adverse event from CARD, which used a 14-day G-CSF course, represents a conservative approach modelling G-CSF in the cabazitaxel arm of the mode*l".

The EAG notes that the company has included one additional change in the model: inclusion of the costs of adverse events associated with neutropenic sepsis and febrile neutropenia for the ^{177}Lu vipivotide tetraxetan and cabazitaxel treatment groups, which the company introduced due to the shorter duration of G-CSF. For these neutropenic sepsis and febrile neutropenia they have included the incidence of these adverse events from VISION for ^{177}Lu vipivotide tetraxetan ([redacted] respectively) and the incidence from CARD for cabazitaxel (4.5% and 3.2%). They have applied reference costs of £5963.44 and £1082.72 respectively and utility decrements of 0.12 based on the utility decrement for febrile neutropenia in TA391.

The EAG notes that the inclusion of a 7-day treatment course of prophylactic treatment with G-CSF in the company's updated version of the model is in line with the committee's preference in the ACD (section 3.16). The EAG also notes that the impact on costs and QALYs of the additional adverse events incorporated by the company are small, and therefore the EAG has accepted the company's updated approach which includes adverse event data for neutropenic sepsis and febrile neutropenia.

3 Company's updated economic analyses

The company has submitted an updated version of the economic model as part of their ACD response, which includes a number of amendments related to some of the key issues raised by the EAG (see Table 4 below). The company has accepted most of the Appraisal Committee preferred analysis and assumptions. Nonetheless, the EAG notes that part of the correction of errors described in the EAG report Section 4.3.4 (Issue 1) and other proposed amendments have not been included by the company. During the verification of the new version of the submitted model, the EAG has identified that some of the other errors and remaining issues originally raised in the EAG report and TE responses, which have been included in the EAG preferred-analyses have been disregarded by the company, and are not mentioned by the company in the ACD response.

A comparison of the analyses presented by the company and the EAG during the appraisal process is summarised in Table 4.

Table 4: Summary of main remaining outstanding points from company's original base case (CS), EAG-preferred analysis (EAG report), company's updated base case (TE response), EAG-preferred analysis (TE response), Appraisal Committee's preferred scenario (ACD) and company's revised model (ACD response) – Excluding issues previously resolved

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's base case at TE response	EAG-preferred analysis (EAG TE response)	Appraisal Committee's preferred	Company's updated base case (ACD response)	Agreement between Committee-preferred and updated company's base case
EA1(a), (c), (d) and (g); Correction of various programming errors	Yes	Yes	Yes	Yes	✓
EA1 (b): Correction of zero health state occupancy in first model cycle	No	Yes	Yes	No	✗
EA1 (e): Correction of incorrect data on breakdown of opioids used as concomitant treatment	No	Yes	Yes	No	✗
EA1 (f): treatment duration of cabazitaxel pre-medication (GCSF, days)	9	5	7	7 (with additional AEs)	✓
EA2, EA3, EA4, EA5: Premedication and concomitant medication costs for cabazitaxel preferred by the EAG	No	Yes	Yes	No	✗
EA6: Approach for health state utility values	Treatment-specific (no AEs or SSEs) – new utility analysis	Treatment-independent + decrements for AEs and SSEs – original utility analysis	Treatment-independent + decrements for AEs had higher face validity, but would like to see scenario	Treatment-specific (no AEs or SSEs) – new utility analysis + cabazitaxel utilities assumed average between ^{177}Lu vipivotide tetraxetan and SOC	✗

Aspect of model/ issue identified in the EAG report Section 4.3.4	Company's base case at TE response	EAG-preferred analysis (EAG TE response)	Appraisal Committee's preferred	Company's updated base case (ACD response)	Agreement between Committee-preferred and updated company's base case
EA7: Approach for SSE incidence	total incidence of SSEs reported in VISION and CARD	total incidence of SSEs reported in VISION and CARD	total incidence of SSEs reported in VISION and CARD	total incidence of SSEs reported in VISION and CARD	✓
EA9: SSE disutilities (use of prevail data)	No	Yes	Yes	No	✗
EA10: Alternative rPFS and OS HR estimates for cabazitaxel	Company's new NMA (Studies included: TROPIC, COU-AA-301, AFFIRM, Sun *et al*, CARD and VISION Model: FE)	EAG's NMA (Studies included: CARD, TheraP and VISION Model: RE)	Further analysis was requested	Company's updated NMA (Studies included: TROPIC, COU-AA-301, AFFIRM, Sun *et al*, CARD, TheraP and VISION with adjusted OS and rPFS data Model: FE)	✗
EA11: Source of OS data for cabazitaxel	RWE – new analysis	NMA	NMA (or use RWE as benchmark to estimate ^{177}Lu vipivotide tetraxetan OS)	NMA	✓
Additional item: PSMA test costs included	No	No	Yes (SPECT and PET-CT, 25% to 100% patients receiving test)	Partially (25% of patients receiving tests but all are assumed to be SPECT not PET-CT)	Partially

Note: EA8 from the EAG report was a combination of EA6 and EA7 and so is not described separately in this table.
Abbreviations: ACD: Appraisal Consultation Document; CE: correction of errors; EA: exploratory analysis; EAG: External Assessment Group; HR: hazard ratio; KM: Kaplan-Meier; NMA: network meta-analysis; OS: overall survival; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression-free survival; SSE: symptomatic skeletal event; RWE: real world evidence.

The results of the company's revised base case analysis and additional scenario analyses are summarised in Table 5. The company's revised deterministic base case ICER for the comparison between ^{177}Lu vipivotide tetraxetan and cabazitaxel is £47,828 per QALY gained. The revised deterministic base case ICER against SOC is £117,362.

Table 5: Results of company's revised base case and scenario analyses presented in ACD response (pairwise comparisons)

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's revised base case model following ACD (deterministic)							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,828**
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£117,362**
Scenario 1: use of random effects NMA to inform OS and rPFS for cabazitaxel							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£55,708**
SOC*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£117,362**
Scenario 2: use of the RWE PSW study to inform the OS estimate for cabazitaxel							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,334**
SOC*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£117,362**
Scenario 3: use of random effects NMA with DuMouchel priors							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£52,373**
SOC*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£117,362**
Scenario 4: use of NMA excluding of TheraP from the rPFS network							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,625**
SOC*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£117,362**
Scenario 5: Inclusion of the costs of SPECT-CT PSMA scans for all patients							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,448**
SOC*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£118,656**

*Not reported by the company

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; SOC: standard of care; LYG: life year gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SA - scenario analysis; ACD; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression-free survival; PSMA: prostate-specific membrane antigen.

4 Additional analyses undertaken by the EAG

This section presents the additional analyses undertaken by the EAG. The EAG updated its NMA using the adjusted OS and rPFS data from VISION as reported in the company's ACD response. The EAG's NMA only includes the direct evidence to inform the relative effect of cabazitaxel and ARPI (the CARD trial). A random effects model with an informative prior[12] (truncated Turner prior assuming that the HR in one study could be no more than 5 times that of the HR in another) was used to inform the estimation of the between-study heterogeneity. The results of the EAG's additional NMAs are presented in Table 6.

Table 6: Results of the EAG's additional NMAs

	Using direct evidence to inform cabazitaxel versus ARPI
OS	1.00 (0.44, 2.24)
rPFS	0.77 (0.47, 1.20)

Abbreviations: OS: overall survival; rPFS: radiographic progression-free survival.

The EAG has also performed four additional exploratory analyses to explore the areas of uncertainty discussed in Section 2. Likewise in the original EAG report, the EAG adopted a number of approaches to explore and check the company's updated version of the model submitted at the ACD stage. The EAG believes the company's to be generally well programmed. However, the EAG notes that a number of amendments included in previous EAG preferred analyses (EAG report and TE response[3,4] have not been included by the company; see Section 3 and EAG report Section 4.3.4 [Issue 1]). Therefore, the EAG used the previous version of the model (used at the report and TE response) as a starting point to rebuild the company's updated base-case and the other exploratory analyses. The amendments included by the EAG involved:

- *Company's base-case + fix errors:* This scenario reflects the company's revised base case analysis, but also includes fixing of errors identified prior to the first committee meeting. These were: the links for oxycodone and tramadol to the appropriate model inputs; the health state occupancy in both the intervention and comparator arms for the progression-free health state; and ensuring health state related costs were accrued in the first model cycle (see EAG report Section 4.3.4 [Issue 1]);
- EAG preferred analysis at ACD: This analysis includes the fixed company's base case, but also includes some of the preferred settings that were originally included in the EAG report and EAG TE response:
    - Changing the unit costs for epoetin alpha and filgrastim in the model with the least expensive and/or more plausible combination available
    - Replacing the company's pre-/concomitant medications for cabazitaxel with EAG preferences
    - Removing the administration costs for oral medications given as part of SOC
    - Use the distribution of doses received in VISION rather than from the mean duration of treatment to estimate of costs for ^{177}Lu vipivotide tetraxetan
    - Use the treatment-independent approach to utilities using the original regression presented at CS, and including utility decrements for AEs and SSEs with the disutilities for SSEs obtained from the PREVAIL study

  Additionally, the EAG has also included in this analysis:
    - Use of the EAG updated NMA estimates (see Table 6)

- Unit cost for PSMA test which includes PET-CT from NHS Reference Costs using same approach the company used for SPECT-CT, and with the PSMA test being applied to 100% of patients in the ^{177}Lu vipivotide tetraxetan treatment group

The EAG also notes that in this analysis, an additional modification from the company's base-case comes into effect: the inclusion of the impact of febrile neutropenia and neutropenic sepsis on HRQoL associated with AEs,

The EAG undertook two additional exploratory analyses (EAs) which include changing some of the assumptions that be relevant for the Appraisal Committee in their decision-making. For each of these analyses, results are presented using the EAG's preferred analysis.

- *ACD EA1:* EAG's preferred analysis + treatment-dependent utility values from the original utility analysis, including utility decrements for AEs and SSEs and assuming cabazitaxel utilities are half-way between utilities for ^{177}Lu vipivotide tetraxetan and SOC (as in TE-EA3)
- *ACD EA2:* EAG's preferred analysis + costs of PSMA test applied to 25% patients in the ^{177}Lu vipivotide tetraxetan treatment group

The results of the EAG's additional analyses are presented as pairwise comparisons between ^{177}Lu vipivotide tetraxetan and cabazitaxel and SOC in

Table 7. Using the previous version of the model, the company's updated base case which includes fixing the errors leads to deterministic ICERs for ^{177}Lu vipivotide tetraxetan versus cabazitaxel of £47,722 per QALY gained and versus SOC of £116,950 per QALY gained.

Using the EAG preferred assumptions in the EAG preferred analysis leads to ICERs for ^{177}Lu vipivotide tetraxetan versus cabazitaxel and versus SOC of £1,253,078 per QALY gained and £150,511 per QALY gained, respectively. These ICERs are considerably higher than the company's revised base case ICER. The key driver of the higher ICERs relates to the HR estimates for OS and rPFS from the NMA. The assumption of treatment-dependent utility values and the assumption regarding the utility values for cabazitaxel also has an important impact on the ICER for the comparison against cabazitaxel, which is reduced to £318,260 per QALY gained. The scenario reducing the cost of the PSMA test for patients in the ^{177}Lu vipivotide tetraxetan treatment group has a smaller impact on the ICER.

Table 7: Results of additional exploratory analyses undertaken by the EAG (pairwise comparisons against cabazitaxel and SOC, deterministic)

Option	LYGs*	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. Costs	ICER
Company's revised base case model following ACD (deterministic)†							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,827**
SOC*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£117,360**
Company's base-case +fix errors identified prior to first committee meeting							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,722**
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£116,950**
EAG preferred analysis at ACD (new NMA + PSMA costs 100% pts + cost of additional AEs included)							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£1,253,078**
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£150,511**
EA ACD 1: EAG preferred at ACD + utility-dependent (as in TE-EA3)							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£318,260**
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£124,162**
EA ACD 3: EAG preferred at ACD + PSMA costs for 25% patients							
177Lu	[redacted]	[redacted]	[redacted]				
Cabazitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£1,181,177**
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£147,731**

Abbreviations: 177Lu: Lutetium-177 vipivotide tetraxetan; SOC: standard of care; LYG: life year gained; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

† The result presented in this table differs slightly from the equivalent analysis generated using the company's post-ACD model. The EAG is unclear about the exact source of this discrepancy, but is satisfied that it is minor.

5 References

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