Lutetium-177 vipivotide tetraxetan for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more treatments

For public – contains no confidential information

Technology appraisal committee B – 6 September 2023

3rd committee meeting (ACM3)

Chair: Baljit Singh

Lead team: Nigel Westwood, David McAllister, Gabriel Rogers

Evidence assessment group: School of Health and Related Research Sheffield (ScHARR), University of Sheffield

Technical team: Emilene Coventry, Christian Griffiths, Janet Robertson

Company: Advanced Accelerator Applications, a Novartis company

Project history

- September 2022 – appraisal committee meeting 1:
  - Lu177 vipivotide tetraxetan not recommended, draft guidance issued
  - Committee's preferred assumptions set out in the draft guidance for consultation – further analyses based on these required
  - End of life likely to be met for the comparison with best supportive care, but updated model and survival estimated needed to draw conclusions versus other comparators
- January 2023 – appraisal committee meeting 2:
  - Company submitted new base case and increased patient access scheme discount but not the committee's preferred analysis
  - Main conclusions and recommendations did not change
  - Second consultation on draft guidance. Rationale:
    - new analyses had been presented that had not been previously consulted on
    - the committee still had not seen an analysis that reflected its preferences
    - the company agreed to provide the required analysis

Key issues

Impact on ICER: Small, Large, Unknown

Issue	Question for committee	Impact on ICER
Estimate of relative effect between ^{177}Lu and cabazitaxel	***Which analysis do you think is most appropriate: the company or the EAG's?***	Large
RWE to inform cabazitaxel efficacy; HR derived from unanchored MAIC to estimate ^{177}Lu overall survival	***Which analysis do you think is most appropriate: the company or the EAG's?***	Large
Utility analysis	***Which approach is more appropriate?***	Large
Generalisability of base case to people 'medically unsuitable' for taxanes	***Should ^{177}Lu be considered for this population given there is no evidence for this population?***	Unknown
End of life	***Does ^{177}Lu meet end of life criteria in the relevant populations?***	

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ^{177}Lu, Lu vipivotide tetraxetan; MAIC, matching-adjusted indirect comparison; RWE, real-world evidence

Recap from second meeting

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Summary of committee's earlier conclusions on key issues

Issue	ACD 2 conclusion

Estimate of relative effect between ^{177}Lu and cabazitaxel	• Appropriate to adjust for bias introduced in VISION by informative censoring and withdrawal rates
	• NMAs associated with uncertainty. Committee preferences were:
	  • Include TheraP and exclude studies in people who have not had an anti-androgen
	  • Random effects model

Estimation of overall survival	• Real-world evidence (RWE) to estimate absolute event estimates for cabazitaxel • Hazard ratio from the NMA to estimate relative effect for survival for ^{177}Lu
Utility	• Treatment-dependent utility values may be appropriate • Scenarios including treatment-dependent and treatment-independent utilities helpful
Generalisability to taxanes 'medically unsuitable' group	• Likely worse prognosis in this subgroup • Useful to have scenario analyses using relative treatment effect for wider population but with higher baseline risk (so worse overall survival
End of life	• ^{177}Lu meets end of life criteria compared with standard care but comparison with cabazitaxel is uncertain

Lutetium-177 prostate-specific membrane antigen-617 (Pluvicto, Advanced Accelerator Applications)

Marketing authorisation	"Adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes" • MHRA August 2022
Mechanism of action	^{177}Lu binds to a protein called PSMA (prostate specific membrane antigen) that is found on the surface of prostate cancer cells. Radiation is emitted from ^{177}Lu causing prostate cancer cells to die
Eligibility	People should be identified by PSMA imaging
Administration	• 7400 MBq intravenous injection, approximately every 6 weeks for up to a total of 6 doses • Monitoring before and after treatment needed • ^{177}Lu only used in special controlled areas in hospital, administration by people who are trained and qualified to use it safely
Price	• List price: £20,000 per vial • Confidential simple patient access scheme discount is applicable

Abbreviations: ^{177}Lu: lutetium-177 vipivotide tetraxetan; MBq: megabecquerel; mCRPC: metastatic castration-resistant prostate cancer; MHRA: Medicines and Healthcare products Regulatory Agency

Pivotal trial: VISION

Design	International (including UK sites), multicentre, phase 3 RCT, open-label FDA-approved education measure implemented mid-trial to reduce withdrawal rates
Population	mCRPC, progressed after treatment with 1 or more ARPI and 1 or 2 taxane regimens
Intervention	Lutetium 177 vipivotide tetraxetan plus standard care
Comparator	Standard care
Duration	Final datacut January 2021 Median follow up 20.9 months
Primary outcomes	Overall survival Radiographic progression-free survival
Secondary outcomes	**Key**: time to first symptomatic skeletal event, adverse events, health-related quality of life **Other**: overall response rate, disease control rate, duration of response

Abbreviations: FDA: US Food and Drug Administration; ARPI: androgen receptor pathway inhibitor; ; mCRPC: metastatic castration-resistant prostate cancer; RCT: randomised controlled trial

Clinical effectiveness: 177Lu vs cabazitaxel

Direct evidence: TheraP phase 2 trial (not in model)

TheraP multicentre, open-label, phase 2, randomised controlled trial	
Population	mCRPC progressed after prior docetaxel and ARPI
Intervention	^{177}Lu vipivotide tetraxetan (n=99) – dose 6.0 to 8.5 GBq
Comparator	Cabazitaxel (n=101)
Outcomes	**Primary:** PSA response (reduction of PSA ≥50% from baseline) **Secondary:** rPFS; response rates; pain; prognostic biomarkers
Duration	Median follow up 18.4 months
Pretreatment withdrawals	16% (16/101) for cabazitaxel; 1% (1/99) for ^{177}Lu

ARPI: androgen receptor pathway inhibitor; GBq: giga-becquerel; mCRPC: metastatic castration-resistant prostate cancer; PSA: prostate specific antigen; rPFS: radiographic progression-free survival

Cabazitaxel real-world evidence

Company did retrospective RWE study which combined data from major UK databases, identifying people with mCRPC from 2009 to 2018 (population most likely aligned with post-ARPI, post-taxane population)

- Datasets: NCR, SACT, Hospital Episode Statistics, Diagnostic Imaging Dataset and Radiotherapy Dataset
- Study assessed characteristics, current standard of care, clinical outcomes and healthcare resource usage
- Comparison then made with the VISION patient population

Baseline characteristics	RWE cabazitaxel (n=[redacted])	VISION (full analysis set) (n=831)
Median age*, years	[redacted]	[redacted]
White British† %	[redacted]	[redacted]
ECOG ≤1, n (%)	[redacted]	[redacted]
Bone metastases, n (%)	[redacted]	[redacted]

*RWE reported age at diagnosis, not cabazitaxel initiation
†VISION did not specify 'British'

Abbreviations: ^{177}Lu, lu vipivotide tetraxetan; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; NCR, National Cancer Registry; RWE, real-world evidence; SACT, Systemic Anticancer Therapy

Responses to second consultation

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Second ACD: consultation responses received

Company: Advanced Accelerator Applications

- Responded to committee conclusions, revised base case, scenario analyses

Stakeholders:

- British Nuclear Medicine Society (BNMS)
- British Uro-oncology Group (BUG)
- Prostate Cancer UK
- Royal College of Physicians (endorsed BNMS)
- TACKLE

Web comments

Stakeholder and web comments (1)

Patient need and benefits

- Lutetium-177 vipivotide tetraxetan ‘game changing’
- Clinically beneficial treatment
- Clear need for more lines of therapy with meaningful survival benefits for people whose disease has progressed and have few treatment options
- Strong support from patients: fewer grade 3+ side effects, better quality of life
- May result in fewer cabazitaxel chemotherapy treatments, fewer hospitalisations, less severe side effects and better quality of life
- If not recommended detrimental effect on development of molecular radiotherapy in England
- Allows patient-specific dosimetry that would inform treatment and may prevent unnecessary toxicities
- Already available in other countries and in private practice

I am much stronger, 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… I don’t really experience any other side effects

Stakeholder and web comments (2)

Evidence base

- Indirect comparisons vs cabazitaxel biased
- Real-world evidence from cabazitaxel NHS database should be used
- CARD study does not reflect NHS practice
- Suggestion that lutetium-177 vipivotide tetraxetan has no survival benefit based on only small number of studies
- In absence of robust clinical evidence, clinical expert opinion should be taken into account
- Evidence on patient imaging and dosimetry should be considered
- Radium-223 should not be a comparator – different mechanism of action
- Cabazitaxel should not be a comparator – place more evidence on evidence presented by patients and clinicians
- Can we provide access through the Cancer Drugs Fund while collecting more evidence

The company's updated base case

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Company updated base case

Issue	Company updated base case
Overall survival estimates	• OS estimates for cabazitaxel derived from RWE study used as reference • Hazard ratio from unanchored MAIC applied to this to derive OS estimates for ^{177}Lu • For ^{177}Lu vs standard care, the VISION data used directly
Patient population for 177Lu vs cabazitaxel	• Instead, relative effect for OS between ^{177}Lu and cabazitaxel based on unanchored MAIC between the ARPI-subgroup intervention arm of the VISION trial and the intervention arm of the CARD* trial
PSMA testing costs	• Applied to 62.5% of people in the ^{177}Lu vipivotide tetraxetan arm • Midpoint between the 50% to 75% Cancer Drugs Fund lead considered reflected the variation in access to routine testing in England and Wales • Includes PET-CT scan
Utilities	• Treatment-dependent utilities using company's original VISION utility analysis • Excluded additional utility decrements for adverse events (AEs) and symptomatic skeletal events (SSEs) • For cabazitaxel: average of the utility values for ^{177}Lu vipivotide tetraxetan and standard care in pre and post-progression states

*__CARD trial__: cabazitaxel vs enzalutamide or abiraterone plus prednisone; only enrolled people whose disease had progressed within 12 months on a prior ARPI (likely treatment effect modifier); also allowed second ARPI (not NHS practice)

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; ARPI, androgen receptor pathway inhibitor; MAIC, matching-adjusted indirect comparison; OS, overall survival; PET-CT, positron emission tomography CT; RWE, real-world evidence

Key issues

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Key issue: estimate of relative effect between ^{177}Lu and cabazitaxel (1)

ACD2

- The committee agreed that accounting for any bias introduced in VISION and withdrawal rates was appropriate
- Preference to include TheraP trial in NMA for direct evidence for 177Lu vs cabazitaxel but exclude trials in which people had not had an ARPI (TROPIC, COU-AA-301, AFFIRM, Sun et al.)

Company

- Timing of prior ARPI progression important confounder of relative treatment effect
- Addressed with 2 new indirect treatment comparisons:
  - Bucher indirect treatment comparison based on CARD and subgroup from VISION who had ARPI as standard care and progressed within 12 months of having previous ARPI
  - unanchored MAIC based on cabazitaxel arm from CARD and subgroup from ^{177}Lu arm of VISION who had ARPI as standard care

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; ARPI, androgen receptor pathway inhibitor; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis

Key issue: estimate of relative effect between ^{177}Lu and cabazitaxel (2)

Committee's preferences at ACM2	Company's new base case and scenarios at ACD2 response
Use TheraP trial for direct evidence for ^{177}Lu and cabazitaxel in NMA	Did not include TheraP. Did 2 new indirect analyses: Bucher ITC and unanchored MAIC
Analyses should adjust for withdrawal rates in VISION	Unadjusted data from VISION used in analyses
Exclude people who have not had an ARPI from NMA	Excluded from analyses

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; ACM, appraisal committee meeting; ARPI, androgen receptor pathway inhibitor; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis

Key issue: estimate of relative effect between ^{177}Lu and cabazitaxel (3)

Results of the company's Bucher ITC and unanchored MAIC, and EAG ACM2 NMA for OS and rPFS

Efficacy outcome	Bucher ITC (95% CI)	MAIC before weighting (95% CI)	MAIC after weighting (95% CI)	EAG ACM2 NMA (95% CrI)
OS	[redacted]	[redacted]	[redacted]	1.00 (0.44, 2.24)
rPFS	[redacted]	[redacted]	[redacted]	0.77 (0.47, 1.20)

In revised base case company used:

- hazard ratio from unanchored MAIC (after weighting) for OS – greater sample sizes and smaller confidence intervals than Bucher ITC
- hazard ratio from EAG-preferred NMA for rPFS, given the similarity in hazard ratios for rPFS from various methods

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; ACM, appraisal committee meeting; ARPI, androgen receptor pathway inhibitor; CI, confidence interval; EAG, external assessment group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; rPFS, radiographic progression-free survival

Key issue: estimate of relative effect between ^{177}Lu and cabazitaxel (4)

EAG comments

Cautions interpretation of results from the Bucher ITC and unanchored MAIC because of limitations:

- use of unadjusted VISION data
- exclusion of the TheraP trial, not in line with committee's preference
- Bucher ITC is equivalent to a fixed effect NMA, which assumes no heterogeneity between the CARD trial and the subgroup in the VISION trial whose disease had progressed within 12 months of having a previous ARPI
- lack of adjusting for certain important covariates in the unanchored MAIC

Which analysis do you think is most appropriate: the company or the EAG's?

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; ARPI, androgen receptor pathway inhibitor; EAG, external assessment group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; rPFS, radiographic progression-free survival

Key issue: RWE to inform cabazitaxel efficacy and HR derived from unanchored MAIC to estimate ^{177}Lu overall survival

ACD2

- Committee preferred using RWE to estimate survival for people having cabazitaxel and the NMA to estimate relative treatment effect of cabazitaxel compared with ^{177}Lu

Company

- Revised base case uses RWE overall survival data to inform absolute efficacy of cabazitaxel
- Hazard ratio derived from unanchored MAIC applied to cabazitaxel RWE overall survival curve to estimate overall survival for ^{177}Lu in model
- Did scenario analysis using hazard ratio from EAG's preferred NMA

EAG comments

- Use of RWE overall survival data in line with committee's preferred analysis
- EAG did scenario analysis using hazard ratio from Bucher indirect treatment comparison (increases ICER)

Is the updated company approach appropriate?

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost effectiveness ratio; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RWE, real world evidence

Key issue: utility analysis (1)

ACD2

- Committee preferred treatment-independent utilities with AE decrements including grade 2 AEs
- Accepted that treatment-dependent utility values plausible as grade 2 AEs were not included
- Scenarios including treatment-dependent and independent utility values would be helpful

Company

- Used treatment dependent utilities in base case
- Treatment-independent utilities "unlikely to fully account for patients' experience of treatment, in particular with cabazitaxel"
- 3 extra scenario analyses for ^{177}Lu vs cabazitaxel using treatment-independent utility values from company's original utility analysis except for pre-progression health state for cabazitaxel

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; AE, adverse event

Key issue: utility analysis (2)

Treatment group	^{177}Lu			Cabazitaxel			
Analysis/AE	Asthenia	Fatigue	Neuropathy	Asthenia	Fatigue	Neuropathy	Duration of AE
Company's original approach to EAG preferred analyses at ACD1 response (when included) – grade 3 or above	[redacted]	[redacted]	[redacted]	4.0%	0.0%	3.2%	1 month
Company's updated base case (ACD2 response) – grade 3 or above	[redacted]		[redacted]	4.0%		3.2%	1 month
Company's scenario 5 (ACD2 response) – grade 3 or above	[redacted]		[redacted]	4.0%		3.2%	5.06 months for cabazitaxel
Company's scenario 6 (ACD2 response) – all grade AEs	[redacted]		[redacted]	53.2%		19.8%	1 month
Company's scenario 7 (ACD2 response) – all grade AEs	[redacted]		[redacted]	53.2%		19.8%	5.06 months for cabazitaxel

- Incidence and duration of other AEs not changed
- Company removed symptomatic skeletal events utility decrements for both treatment groups, which were included in the EAG's previous preferred analyses

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; ACD, appraisal consultation document; AE, adverse event; EAG, external assessment group

Key issue: utility analysis (3)

EAG comments

- Including all-grade neuropathy and fatigue/asthenia not committee preference
- Likely overestimates impact on cabazitaxel (includes grade 1 AEs)
- Mild fatigue/asthenia or neuropathy assumed to incur same disutility and costs as moderate, severe or potentially life-threatening AEs
- Unclear what proportion additional patients in CARD and VISION included in company's new scenarios had moderate (grade 2) AEs that would require treatment or would impact on overall health-related quality of life
- No clinical evidence on additional burden with cabazitaxel after docetaxel

Abbreviations: AE, adverse event; EAG, external assessment group

Key issue: utility analysis (4)

Company scenario	Description	Effect on ICER vs company's new base case at ACD2 response
5	Treatment-independent utility values: grade ≥3 neuropathy and fatigue Disutility duration for cabazitaxel aligned to mean treatment duration from CARD	Small increase
6	Treatment-independent utility values: all-grade neuropathy and fatigue Disutility duration unchanged	Small decrease
7	Treatment-independent utility values: all-grade neuropathy and fatigue Disutility duration for cabazitaxel aligned to mean treatment duration from CARD	Small decrease

Abbreviations: ACD, appraisal consultation document; ICER, incremental cost effectiveness ratio

Key issue: utility analysis (5)

EAG scenario	Description	Effect on ICER vs company's new base case at ACD2 response
1	EAG's NMA estimates for OS and rPFS, treatment-independent utilities	Very large increase
2	Company's MAIC after weighting estimates for OS and rPFS, treatment-independent utilities	Small increase
3	Company's Bucher indirect treatment comparison estimates for OS and rPFS, treatment-independent utilities	Increase
4	EAG's NMA estimates for OS and rPFS, treatment-dependent utilities	Large increase
5	Company's MAIC after weighting estimates for OS and rPFS, treatment-dependent utilities	Very small decrease
6	Company's Bucher ITC estimates for OS and rPFS, treatment-dependent utilities	Small increase

EAG's approach included disutilities associated with symptomatic skeletal events and grade ≥3 AEs, and 5.06 months duration for cabazitaxel fatigue/asthenia and neuropathy AEs

Are utilities modelled appropriately?

Abbreviations: ACD, appraisal consultation document; AE, adverse event; EAG, external assessment group; ICER, incremental cost effectiveness ratio; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; rPFS, radiographic progression-free survival

Key issue: generalisability of base case to people ‘medically unsuitable’ for taxanes (1)

ACD2

- Appropriate to consider the whole population in the marketing authorisation, including when taxanes are ‘medically unsuitable’
- Likely worse prognosis in this subgroup
- Useful to have scenario analyses using relative treatment effect for wider population but with higher baseline risk (so worse overall survival)

Company

- Failure of previous taxane treatment important prognostic factor – people may actually have improved prognosis on lutetium 177 vipivotide tetraxetan
- Provided additional evidence for people who have not had taxanes suggesting improved prognosis for this group with lutetium 177 vipivotide tetraxetan

Key issue: generalisability of base case to people ‘medically unsuitable’ for taxanes (2)

Company’s scenario analysis for lutetium-177 vipivotide tetraxetan vs standard care

Scenario	Description	Effect on ICER vs company's new base case at ACD2 response
1	Decreased hazard of progression and death applied to both model arms as a proxy for better prognosis in medically unsuitable population, based on Ahmadzadehfar et al. (2021) **multivariate** analysis (weighted HR = 0.673)	Decreased
2	Decreased hazard of progression and death applied to both model arms as a proxy for better prognosis in medically unsuitable population, based on Ahmadzadehfar et al. (2021) **univariate** analysis (weighted HR = 0.649)	Decreased

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio

Key issue: generalisability of base case to people ‘medically unsuitable’ for taxanes (3)

EAG comments

- Company did not provide the analysis preferred by committee
- Considers that additional analyses from company should be considered with extreme caution because of
  - potential for lag-time bias
  - retrospective nature of Ahmadzadehfar et al. (2021) study used to adjust for overall survival and progression-free survival
- Considerable uncertainty over applicability of cost-effectiveness estimates for lutetium 177 vipivotide tetraxetan to people 'medically unsuitable' for taxanes because of lack of clinical data on effectiveness for this group

Should lutetium 177 vipivotide tetraxetan be considered for this population given there is no evidence for this population?

Key issue: end of life (1)

1. *Treatment is indicated for people with a short life expectancy, normally less than 24 months*
2. *Sufficient evidence it can offer an extension to life, normally a mean value of at least 3 months extra, compared with current NHS treatment*

Committee should be satisfied that:

- *Estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival*
- *Assumptions used in the reference case economic modelling are plausible, objective and robust*

ACD2: ^{177}Lu meets end of life criteria compared with standard care but comparison with cabazitaxel is uncertain

- Committee did not see preferred estimates of ^{177}Lu compared with cabazitaxel
- No evidence on comparison of ^{177}Lu with radium-223 dichloride

Abbreviations: ACD, appraisal consultation document; ^{177}Lu, lutetium-177 vipivotide tetraxetan

Key issue: end of life (2)

Analysis	Standard care life years gained	^{177}Lu life years gained
Company's new base case and EAG's analyses	[redacted]	[redacted]

Analysis	Cabazitaxel life years gained	^{177}Lu life years gained
MAIC after weighting (company's base case and EAG scenario 2 and 5)	[redacted]	[redacted]
EAG-preferred NMA (EAG scenario 1 and 4)	[redacted]	[redacted]
Bucher (EAG scenario 3 and 6)	[redacted]	[redacted]

Does ^{177}Lu meet the end of life criteria in the relevant populations?

Abbreviations: ^{177}Lu, lutetium-177 vipivotide tetraxetan; EAG, external assessment group; MAIC, matching-adjusted indirect comparison

Other issues

Resolved

- ACD2: PSMA testing costs in 50% to 75% of population is appropriate
- Company: included costs for 62.5% of people having lutetium-177 vipivotide tetraxetan
- Scenario analyses varying proportion to 50% and 75%

Not resolved

- ACD2: radium-223 dichloride is a relevant comparator for people with bone metastases who do not have visceral metastases
- Excluded as a comparator by company
- Argue small patient group, lack of evidence

Abbreviations: ACD, appraisal consultation document; PSMA, prostate-specific antigen

Cost-effectiveness results

All results for incremental cost effectiveness ratios (ICER) are in part 2 slides because they include confidential comparator patient access scheme (PAS) discounts

EAG's preferred assumptions

EAG's pairwise comparisons against **cabazitaxel** (deterministic)

Scenario	Description	Effect on ICER vs company's new base case at ACD2 response
1	EAG's NMA estimates for OS and rPFS, treatment-independent utilities	Very large increase
2	Company's MAIC after weighting estimates for OS and rPFS, treatment-independent utilities	Large increase
3	Company's Bucher ITC estimates for OS and rPFS, treatment-independent utilities	Large increase
4	EAG's NMA estimates for OS and rPFS, treatment-dependent utilities	Very large increase
5	Company's MAIC after weighting estimates for OS and rPFS, treatment-dependent utilities	Large increase
6	Company's Bucher ITC estimates for OS and rPFS, treatment-dependent utilities	Large increase

EAG's pairwise comparisons against **standard care** (deterministic):

- grouped scenarios 1 to 3 and used treatment-independent utilities – increase in ICER
- grouped scenarios 4 to 6 and used treatment-dependent utilities – increase in ICER

Abbreviations: EAG, external assessment group; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis: OS, overall survival; rPFS, radiographic progression-free survival

Cost effectiveness conclusions

All ICERs were higher than what NICE normally considers an acceptable use of NHS resources, including the company's base case

- Key driver is approach to estimating hazard ratio for overall survival and radiographic progression-free survival
- Assumption of treatment-dependent utility values and about utility values for cabazitaxel also substantial impact on ICER vs cabazitaxel
- Approach for utilities vs standard care less impact on the ICER; both scenarios present ICERs over £100,000 per QALY gained

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Key issues

Impact on ICER: Small, Large, Unknown

Issue	Question for committee	Impact on ICER
Estimate of relative effect between ^{177}Lu and cabazitaxel	***Which analysis do you think is most appropriate: the company or the EAG's?***	Large
RWE to inform cabazitaxel efficacy; HR derived from unanchored MAIC to estimate ^{177}Lu overall survival	***Which analysis do you think is most appropriate: the company or the EAG's?***	Large
Utility analysis	***Which approach is more appropriate?***	Large
Generalisability of base case to people 'medically unsuitable' for taxanes	***Should ^{177}Lu be considered for this population given there is no evidence for this population?***	Unknown
End of life	***Does ^{177}Lu meet end of life criteria in the relevant populations?***	

Abbreviations: EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ^{177}Lu, Lu vipivotide tetraxetan; MAIC, matching-adjusted indirect comparison; RWE, real-world evidence

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Thank you