^{177}Lu-PSMA-617 for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies

For Public: Contains no confidential information

Technology appraisal committee B [15 September 2022]

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Company: Advanced Accelerator Applications, a Novartis company

NICE National Institute for Health and Care Excellence

Key unresolved issues

Issue	Resolved?	ICER impact
PSMA testing	No	Unknown
Broadening population to include people for whom taxanes are not suitable	No	Unknown
Excluding radium-223 as a comparator for people with bone metastases	No	Unknown
Company's network meta-analysis • Fixed effects versus random effects model • Studies included in the network meta analysis	No	Large when using NMA rather than RWE to estimate cabazitaxel overall survival
Overall survival estimates for cabazitaxel in the model	No	
Cabazitaxel utility values	No	Large
Pre-medication and concomitant medication costs for cabazitaxel	No	Large (primary driver G-CSF costs)

Abbreviations: ICER: incremental-cost effectiveness ratio; NMA: network meta-analysis; RWE: real world evidence

Background

Metastatic hormone-relapsed prostate cancer associated with poor outcomes and low quality of life

Prostate cancer

- 45,885 new cases in England and Wales in 2019-20
- 13% present with metastatic disease at diagnosis

Hormone sensitive = responding to androgen deprivation therapy (ADT) → Progression → 'Hormone-relapsed' also known as 'metastatic castration-resistant prostate cancer' (mCRPC)

PSMA-positive

- Prostate cancers can express a transmembrane protein called prostate-specific membrane antigen (PSMA)
- PSMA expression is increased in poorly differentiated, metastatic, and hormone-relapsed prostate cancers

Prognosis

- 10-20% people with prostate cancer develop hormone-relapsed cancer after around 5 years of follow-up
- mCRPC is associated with significant negative impacts on health-related quality of life
- Prostate cancer mortality is associated with increasing age and metastatic disease
- Skeletal involvement in mCRPC is common and results in significant morbidity and mortality
- People with visceral metastases are likely to have a worse prognosis than those with bone metastases alone

What proportion of people with mCRPC would have bone metastases alone?

Treatment pathway for prostate cancer

Androgen deprivation therapy (ADT) continues despite hormone relapsed

Docetaxel can be offered twice; abiraterone OR enzalutamide only once; so fewer options

Taxane

ARPI

	Hormone sensitive	Hormone relapsed		
Non-metastatic	ADT → Progression → ADT Radical therapy- surgery or radiotherapy	Enzalutamide + ADT in high risk (TA580) Darolutamide + ADT in high risk (TA660) Apalutamide + ADT in high risk (TA740)		
Metastatic	ADT (NG131) Docetaxel + ADT (NG131) ~~Abiraterone + ADT in high risk~~ (TA720) Apalutamide + ADT (TA741) Enzalutamide + ADT (TA712)	**Chemotherapy 'not yet indicated'** Abiraterone (TA387) Enzalutamide (TA377) Watchful waiting	**Chemotherapy indicated** Docetaxel (TA101) – Karnofsky performance score 60% or more Olaparib (no prior taxane) - ongoing	**Post-docetaxel** Abiraterone (TA259) Enzalutamide (TA316) Cabazitaxel (TA391) Radium-223* (TA412) Docetaxel re-treatment Olaparib (prior taxane) - Ongoing appraisal **^{177}Lu vipivotide tetraxetan**

*Radium-223: For symptomatic bone metastases and no known visceral metastases

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; NG: NICE guideline; TA: technology appraisal

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

Marketing authorisation August 2022	"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"
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	Patients 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 required • ^{177}Lu only used in special controlled areas in hospital, administration by people who are trained and qualified to use it safely
Price	• [redacted] per vial (list price) • Confidential simple patient access scheme discount is applicable

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ^{86}Ga: gozetotide; MBq: megabecquerel; mCi: millicurie; mCRPC: metastatic castration-resistant prostate cancer; MHRA: Medicines and Healthcare products Regulatory Agency; PSMA: protein-specific membrane antigen

Patient and professional organisation perspectives

Submissions from Prostate Cancer UK; TACKLE Prostate Cancer; British Nuclear Medicine Society

Impact of prostate cancer

Affects everyone differently, symptoms include: fatigue, chronic and acute pain, bone urinary and bowel problems, low mood or depression

"Treatment affected my ability to lead an active life"

Significantly poor quality of life, despite all attempts at symptom control

Bone metastases may result in spinal cord compression, pain and potential paralysis

Living with cancer and no curative treatments difficult emotionally

What people would like from treatment

Avoid severe side-effect burden of further chemotherapy

Options for people who have exhausted current therapies, particularly people with bone and soft tissue metastases

Treatment options outside palliative care

Live longer and prevent possible painful symptoms or death

Fewer symptoms, improved quality of life for a longer period of time

^{177}Lu

Novel, precise, and can target lymph nodes

Offers a benefit in survival, valuable time with families

Visceral metastases after radium-223 could be avoided if ^{177}Lu used first

"The quality of life while on the treatment is very high; I was able to work and exercise while undergoing treatment"

To consider:

- Logistics with nuclear medicine therapy
- Chemotherapy restrictions during COVID-19 reduced number of people having prior taxane therapy

Clinical expert perspectives

Unmet need

- Significant unmet need both for patients and healthcare professionals
- Unmet need for more effective treatments – high number of patients ineligible or do not want chemotherapy
- No standard guidelines defining chemotherapy ineligibility
- "This innovative technology has increased optimism for patients in mCRPC setting who have limited options"

^{177}Lu clinical trial

- ^{177}Lu is innovative, effective, less toxic and led to better quality of life and survival
- "Likelihood of benefit for patients who are unsuitable for taxanes and have PSMA positive disease should be on par with the benefits seen with ^{177}Lu in VISION…feasible that as these patients have not had multiple lines of therapy, they may have a better response"
- Patient feedback and trial data show ^{177}Lu is well tolerated and has overall benefit on quality of life

^{177}Lu in clinical practice

- Less frequent administration, may reduce demand on chemotherapy resources
- Relatively few hospitals have experience for radioligand therapies – but upscale possible for centres with experience
- Training, facilities needed e.g. PET-CT scans, and ^{177}Lu has limited shelf-life because short half-life
- "I have treated over 200 patients using this technology and there are very little treatment related or induced side effects"

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Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; PSMA: prostate specific antigen

Key issue: PSMA testing

Testing needed for ^{177}Lu use, current options limited with future options developing

A PET scan uses a low dose of radiation to check the activity of cells in different parts of the body

Company: PSMA testing is needed for people having ^{177}Lu but limited options currently available

- ^{86}Ga gozetotide PET-CT scan available in 5 cities in England, MHRA marketing authorisation: August 2022 with further options in development
- Services expansion addressed by NHS Levelling Up agenda → anticipate future expansion of PET-CT
- Imaging techniques can be used at various parts of prostate cancer pathway

ERG: Clinical advisers to ERG acknowledge diagnostic resources needed to identify PSMA-positive people currently unavailable to all patients in the UK

Stakeholder: Cost of PSMA test based on PSMA-PET scan using ^{68}Ga (as in VISION) not included in cost-effectiveness analysis → could underestimate ICER against comparators not needing PSMA test

Patient group: Clinical trial used specific PET tracer which has limited availability, reducing access to treatment. Recommend any PSMA-PET scan using fluorine or gallium to determine treatment eligibility

- What proportion of people with mCRPC would have PET-CT scans?
- Of these people, what proportion get PSMA radiotracers?
- Would any PSMA-PET scan using a fluorine or gallium tracer be suitable?
- What are the cost implications of moving from choline-based radiotracers?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; MHRA: Medicines and Healthcare products Regulatory Agency; PSMA: protein-specific membrane antigen

Decision problem

Company submission excludes docetaxel and radium-223 as comparators

	NICE scope	Company submission
Population	Adult patients with PSMA-positive, hormone relapsed metastatic prostate cancer previously treated with ARPI and taxane-based chemotherapy or for whom taxanes are not suitable	
Intervention	^{177}Lu vipivotide tetraxetan	
Comparators	• Docetaxel • Cabazitaxel • Radium-223 dichloride for people with bone metastases • Best supportive care	• Cabazitaxel • Best supportive care
Outcomes	• Progression free survival • Skeletal-related events • Overall survival • Adverse effects of treatment • Health-related quality of life	Also includes (not in model): • Overall response rate • Disease control rate • Duration of response
Diagnostic testing	Costs associated with ^{177}Lu will be included	Not included

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor; HRQoL: health-related quality of life; PSMA: prostate specific membrane antigen; SSE: symptomatic skeletal event

Comparators

Docetaxel not relevant comparator; ERG concern with excluding radium-223 as comparator and expanding population for whom taxanes are not suitable

	Docetaxel	Cabazitaxel	Radium-223	Best supportive care
In scope?	✓	✓	✓	✓
In company submission?	X	✓	X	✓
Company comment	Exclude docetaxel: generally used earlier in pathway and re-challenge is in 2% of people with mCRPC	N/A	Exclude radium-223: • For symptomatic bone metastases without visceral metastases, and ^{177}Lu intended regardless of metastasis site • Lack of evidence	N/A
ERG comment	Agree excluding docetaxel rechallenge as comparator – infrequent in UK practice	N/A	• Disagree excluding radium-223: used for bone metastases in post-ARPI and taxane (if suitable) setting • Agree with lack of evidence, remains unresolved	N/A
Clinical experts + Stakeholders	More benefit when used in hormone sensitive setting compared with hormone-relapsed	N/A	• Minority of people who would have radium-223 in the post-ARPI and taxane setting	N/A

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Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor

Key issue: Exclusion of radium-223 as a comparator

Radium-223 considered relevant comparator for mCRPC with bone, but no visceral metastases

Company: Radium-233 not considered relevant comparator and limited comparability with ^{177}Lu

- Comparator for small subgroup – Symptomatic bone metastases but no visceral
- To treat bone pain, rather than tumour/metastases (as ^{177}Lu) → limited at extending survival (clinical advice)
- No suitable evidence found for radium-223 in post ARPI, post-taxane setting → prevent indirect comparison

ERG: Consider radium-223 as comparator for people with bone metastases

- TA412 recommend radium-223 if docetaxel is contraindicated or unsuitable (with bone metastases)
- Most clinical advisors: minority of people have radium-223 in post-ARPI and taxane setting
- ALSYMPCA data (radium-233) not generalisable to VISION (^{177}Lu) – No further evidence available to address this uncertainty

Clinical experts: Comparator for symptomatic bone metastases with different mechanism of action

- Proportion with visceral/lymph metastases increases with treatment line progression (40-50%) and are not eligible for radium-223; VISION had 21.4% with visceral metastases → contraindicated for radium-223

Stakeholder: Any conclusions with other comparators should not be applied to this subpopulation

Patient group: Exclusion of radium-223 as a comparator seems appropriate - generally a palliative treatment with small life-extending potential, majority in VISION had bone metastases

Where does radium-223 fit in the treatment pathway? Is it used to prevent progression or alleviate bone pain?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor; mCRPC: metastatic castration-resistant prostate cancer

Treatment metastatic hormone relapsed guidance

Company submission includes three subgroups for the population of patients with mCRPC and possible placement of ^{177}Lu:

Subgroup	Pre-chemotherapy	2nd line / chemotherapy	3rd line	After cabazitaxel - 4th line
Eligible for further taxane treatment	ARPI	Docetaxel	Cabazitaxel Radium-223 ^{177}Lu	Standard care Radium-223 ^{177}Lu
Further taxane treatment unsuitable after docetaxel	ARPI	Docetaxel	Standard care Radium-223 ^{177}Lu	
Taxane treatment unsuitable	ARPI	Standard care Radium-223 ^{177}Lu		

Is ^{177}Lu positioning reflective of clinical practice?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor; mCRPC: metastatic castration-resistant prostate cancer

Key issue: Population for whom taxanes are unsuitable

Large subgroup that would benefit from added treatment option but no evidence of efficacy

Company: High unmet need, no treatment options for these people.

- 42% of total patient population eligible for ^{177}Lu at 2nd-line
- Acknowledge lack of clinical evidence – but mechanistically no reason efficacy and safety of ^{177}Lu significantly different for people who can't have taxanes → supported by clinical advice to company
- Reasons for taxane unsuitability include: Performance status; comorbidities; patient choice
- Potential to explore managed access routes for this subpopulation:
  → PSMAfore open-label Phase 3 RCT comparing 177Lu with ARPI in PSMA-positive mCRPC (no prior taxane treatment in past 12 months) could provide additional clinical data but taxanes may not be completely contraindicated

ERG: VISION trial not representative of subgroup for whom taxanes are unsuitable

- Modelling uses evidence from trials where people with mCRPC have had both ARPIs and taxanes
- No evidence provided supporting the claim efficacy similar between subgroups
- Highly heterogeneous group: Some contraindicated due to comorbidities and some based on patient choice

Clinical experts: Options for this subgroup are very limited, so ^{177}Lu would be important option

- No guidelines defining taxane unsuitability – treatments earlier in pathway expected to show greater benefit

Would people who can't have taxanes be able to have ^{177}Lu? If so, what proportion?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor; ECOG: Eastern Cooperative Oncology Group; RCT: randomised controlled trial

Clinical effectiveness

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Source of evidence for comparators

Only some comparators have ‘direct’ evidence

Direct evidence from randomised control trial	• **^{177}Lu compared with standard of care:** VISION Phase 3 trial • **^{177}Lu compared with cabazitaxel:** TheraP Phase 2 trial (not powered for survival). Used as supportive evidence in company submission
Indirect treatment comparison	• Network meta analysis (NMA) including VISION plus seven Phase 3 multicentre RCTs of alternative therapies compares **^{177}Lu** to **cabazitaxel** • Real-world evidence analysis from UK clinical practice on **cabazitaxel** used as supportive evidence for NMA and for modelling survival
Company provides no evidence	• Radium-223 • Taxanes contraindicated, or not tolerated • **PSMAfore** (n=450) is an open-label, Phase 3 RCT comparing ^{177}Lu with ARPI in PSMA-positive mCRPC, not exposed to prior taxanes in past 12 months. Primary completion October 2022; study completion: August 2023

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; RCT: randomised controlled trial

Clinical efficacy

^{177}Lu vipivotide tetraxetan vs Standard of Care

NICE National Institute for Health and Care Excellence

Direct clinical trial evidence: VISION

VISION informs key evidence for ^{177}Lu but concern with high risk of bias of trial

Design	International, multi-centre, phase 3 RCT, prospective, open-label including UK sites – FDA approved education measure implemented mid-trial to reduce withdrawal rates
Population	People with mCRPC, progressed after treatment with at least 1 ARPI and 1 or 2 taxane chemotherapy regimens
Intervention	^{177}Lu vipivotide tetraxetan plus standard of care
Comparator	Standard of care
Duration	Final data-cut: January 2021; median follow-up: 20.9 months
Primary outcome	Overall survival; radiographic progression-free survival
Key 2º outcomes	Time to first symptomatic skeletal event; adverse events; health related quality of life
Other 2º outcomes	Overall response rate; disease control rate; duration of response

ERG: Moderate quality (York CRD criteria), high risk of bias (Cochrane RoB criteria) – concerns with:

- Company use LDH as control for tumour burden but ERG concerned that it is not a robust prognostic marker and not routinely collected for people with mCRPC in NHS
- Imbalances between arms due to withdrawals – even after education measure intervention
- Open-label trial – result in risk of bias as may affect some outcomes (not overall survival)

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Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor; CRD: Centre for Reviews and Dissemination; LDH: lactase dehydrogenase; mCRPC: metastatic castration-resistant prostate cancer; RCT: randomised controlled trial; RoB: risk-of-bias

VISION study design

Phase 3, open-label, randomised controlled trial, completed January 2021

Inclusion criteria
- PSMA-positive
- Prior treatment with 1-2 taxanes, and an ARPI

Stratification factors
- Baseline LDH
- Liver metastases
- ECOG score
- ARPI as part of standard of care at baseline

Jun 2018 – Oct 2019
Randomisation 2:1
Open label

^{177}Lu + standard of care (N=551)

Standard of care (N=280)

Primary: Radiographic progression
Interim: overall survival analyses

Final survival analysis

Full Analysis Set (ITT): all randomised
^{177}Lu=551
SOC=280

PFS-Full Analysis Set: randomisation after 5th March 19
^{177}Lu=385
SOC=196

Safety Analysis Set: randomised with 1 treatment
^{177}Lu=529
SOC=205

High rate of withdrawals in control arm up to 5th March 2019:
- 56% (47/84) control arm discontinued trial without randomly assigned treatment
- 1.2% (2/166) intervention arm discontinued trial without randomly assigned treatment

After enhanced education measures on 5th March 2019 to reduce withdrawal
- 16.3% (32/196) control arm discontinued trial; 4.2% (16/385) intervention arm

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor; ECOG: Eastern Cooperative Oncology Group; ITT: intention-to-treat; LDH: lactate dehydrogenase; PFS: progression-free survival; PSMA: prostate-specific membrane antigen; SOC: standard of care

VISION baseline characteristics (1)

Comparable characteristics between arms; likely reflective of UK population

Characteristic		Full analysis set (N=831)		PFS-full analysis set (N=581)	
		^{177}Lu + SOC (N=551)	SOC (N=280)	^{177}Lu + SOC (N=385)	SOC (N=196)
Median age, years		70	71.5	71	72
Median time since diagnosis, years		7.4	7.4	7.3	7
ECOG ≤1, n (%)		510 (92.6)	258 (92.1)	352 (91.4)	179 (91.3)
Median PSA level, ng/ml		77.5	74.6	93.2	90.7
Site of disease, n (%)	Lymph node	274 (49.7)	141 (50.4)	193 (50.1)	99 (50.5)
	Bone	504 (91.5)	256 (91.4)	351 (91.2)	179 (91.3)
	Lung	49 (8.9)	28 (10)	35 (9.1)	20 (10.2)
	Liver	63 (11.4)	38 (13.6)	47 (12.2)	26 (13.3)

Clinical advice to ERG: VISION similar to likely population in UK practice – albeit probably younger and healthier

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ECOG: Eastern Cooperative Oncology Group; IU: international unit; LDH: lactate dehydrogenase; PFS: progression-free survival; PSA: prostate specific antigen; SOC: standard of care

VISION baseline characteristics (2)

People more heavily pre-treated in VISION having more than 1 ARPI

Characteristic		Full analysis set (N=831)		PFS-full analysis set (N=581)	
		^{177}Lu vipivotide tetraxetan + SOC (N=551)	SOC (N=280)	^{177}Lu vipivotide tetraxetan + SOC (N=385)	SOC (N=196)
Previous ARPI regimen, n (%)	1	298 (54.1)	128 (45.7)	213 (55.3)	98 (50)
	2	213 (38.7)	128 (45.7)	150 (39)	86 (43.9)
	>2	40 (7.3)	24 (8.6)	22 (5.7)	12 (6.1)
Previous taxane therapy regimen, n (%)	1	325 (59)	156 (55.7)	207 (53.8)	102 (52)
	2	220 (39.9)	122 (43.6)	173 (44.9)	92 (46.9)

Clinical expert comments: Overall results can be extrapolated to UK setting

- In VISION people could have 2 androgen receptor targeted agents but NICE approval is for 1 – likely benefits of ^{177}Lu in NHS setting could be more than in VISION

Are the baseline characteristics similar and generalisable to NHS clinical practice?

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Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARPI: androgen receptor pathway inhibitor; PFS: progression-free survival; SOC: standard of care

VISION primary outcome results – OS and rPFS

^{177}Lu significantly improves OS and rPFS compared with standard care

	Full analysis set (ITT population)		PFS Full Analysis Set (after withdrawal intervention)	
	^{177}Lu + SOC (N=551)	SOC (N=280)	^{177}Lu + SOC (N=385)	SOC (N=196)
Primary endpoint: overall survival – Jan 2021				
Events, n (%)	343 (62.3)	187 (66.8)	[redacted]	[redacted]
Median, months (95% CI)	15.3 [redacted]	11.3 [redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	0.62 (0.52, 0.74)		[redacted]	
Alternative primary endpoint: radiographic progression-free survival – Jan 2021				
Events, n (%)			254 (66)	93 (47.4)
Median, months (99.2% CI)			8.7 [redacted]	3.4 [redacted]
Hazard ratio (99.2% CI)			0.40 (0.29, 0.57)	

Does ^{177}Lu show clinical efficacy compared with standard of care?

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Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; OS: Overall survival; PFS: Progression-free survival

Adverse events results in VISION

Higher rate of adverse events in ^{177}Lu arm compared with SOC

AE, n (%)	^{177}Lu + SOC (N=529)	SOC (N=205)	Analysis
All	519 (98.1)	170 (82.9)	
• Drug-related	451 (85.3)	59 (28.8)	
Serious (≥1% people)	192 (36.3)	57 (27.8)	[redacted]
• Drug-related	49 (9.3)	5 (2.4)	
Grade ≥3	[redacted]	[redacted]	• No Grade ≥3 in >5% people for SOC arm • Highest rates Grade ≥3 in ^{177}Lu: [redacted]
• Drug-related	[redacted]	[redacted]	
Fatal	19 (3.6)	6 (2.9)	[redacted]

- Most common events leading to dose interruption/reduction in ^{177}Lu arm → Anaemia and thrombocytopenia
- **TEAEs:** Higher rates of **fatigue** and **myelosuppression** in ^{177}Lu for any Grade and Grade 3-5
  Higher rates of **dry mouth**, **nausea**, **vomiting**, **hypersensitivity** in ^{177}Lu for Grade 1-2

Clinical experts: ^{177}Lu seems well tolerated from patient feedback and trial results – similar rates of AEs

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; AE: adverse event; SOC: standard of care; TEAEs: treatment-emergent adverse events

Clinical efficacy

^{177}Lu vipivotide tetraxetan vs Cabazitaxel

Cabazitaxel direct evidence: TheraP Phase 2 trial

TheraP not included in model and not powered for OS; ERG assess high risk of bias

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 6.0-8.5 GBq
Comparator	Cabazitaxel (N=101)
Primary outcome	PSA response (reduction of PSA ≥50% from baseline)
Secondary outcomes	rPFS; response rates; pain; prognostic biomarkers
Duration	Median follow-up 18.4 months
Pre-treatment withdrawals	16% (16/101) for cabazitaxel; 1% (1/99) for ^{177}Lu

Outcome (^{177}Lu vs cabazitaxel)	Results
PSA response	66% vs 37% (95% CI: 16-42%)
rPFS	HR: 0.64 (95% CI: 0.46, 0.88)
*OS (restricted mean to 36 months)	19.1 vs 19.6 (95% CI: -3.7, 2.7)
Adverse events	• ^{177}Lu: More Grade 1-2 (54% vs 40%); • Cabazitaxel: More Grade 3-4 (53% vs 33%)

Company: TheraP not included in NMA or model because:

- Differences in diagnostic process, ^{177}Lu production and dose, and patient stratification
- Not powered for OS

ERG: High-risk of bias

- Imbalances and missing data between arms – leading to high risk of bias in at least 1 domain
- Open-label trial – can affect outcomes

*OS is from extended follow-up (Hofman et al., 2022, Journal of Clinical Oncology)

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Abbreviations: ARPI: androgen receptor pathway inhibitor; GBq: giga-becquerel; HR; Hazard Ratio; mCRPC: metastatic castration-resistant prostate cancer; NMA: network meta-analysis; OS: overall survival; PSA: prostate specific antigen; rPFS: radiographic progression-free survival; SOC: standard of care

Cabazitaxel real-world evidence

RWE comparable to VISION but OS for cabazitaxel shorter than SOC in VISION

Company did retrospective RWE study which combined data from major UK databases, identifying people with mCRPC 2009-18 → 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 (FAS) (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'

Results: (no rPFS results)

- Median OS cabazitaxel: [redacted]
- Restricted mean OS: [redacted]

Company: Median OS for cabazitaxel in RWE shorter than median OS in SOC arm of VISION ([redacted] vs 11.3 months)

- Patients have enhanced monitoring with more visits to healthcare professionals and imaging, so may have longer OS compared to real-world

ERG: Argument of enhanced care in clinical trials applies equally to both treatment arms in VISION

- PSWA analyses from company post TE, results in similar OS estimates but prognostic factors may not be included

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ECOG: eastern Cooperative Oncology Group; mCRPC: metastatic castration-resistant prostate cancer; NCR, National Cancer Registry; OS: overall survival; PSWA: propensity score weighted analysis; rPFS: radiographic progression-free survival; RWE: real-world evidence; SOC: standard of care; SACT, Systemic Anticancer Therapy

Studies included in the network meta-analysis

Company and ERG have different preferences for inclusion/exclusion of TROPIC, COU-AA-301, AFFIRM, Sun et al., 2016 and TheraP trials in network meta-analysis

	Company NMA	ERG NMA	Study Population (all mCRPC)	Intervention (per arm)	Previous ARPI?	N
TROPIC	✓		Refractory to hormone therapy and previous treatment with docetaxel	**Mitoxantrone** + prednisone vs. **cabazitaxel** + prednisone	No	755
COU-AA-301	✓		Previous docetaxel treatment	**Abiraterone** + prednisone/prednisolone vs. **placebo** + prednisone/prednisolone	No	1195
AFFIRM	✓		Previous docetaxel treatment	**Enzalutamide** vs. **placebo**	No	1199
Sun et al. 2016	✓		≥ 18 years old	**Abiraterone** + prednisone vs. **placebo** + prednisone	No	214
CARD	✓	✓	Progressive and previously treated with 3 or more cycles of docetaxel	**Cabazitaxel** vs. **enzalutamide** or **abiraterone** + prednisone	1	255
VISION	✓	✓	Pre-treated with taxane regimens - subpopulation of patients who received ARPI as part of SOC	**^{177}Lu vipivotide tetraxetan** + **SOC** vs. SOC	1 or more	831
TheraP		✓	Pre-treated with taxane regimens	**^{177}Lu vipivotide tetraxetan** vs. **cabazitaxel**	1 or 2	200

Company: Note some relatively similar baseline characteristics between trials (age, ECOG score), but some differences too (disease characteristics, prior therapies, trial duration)

ERG: Most comparator trials, population seem to be less heavily pre-treated than in VISION

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; SOC: standard of care

Key issue: studies included in NMA

Company updated after TE to exclude ALSYMPCA and PROfound trials but still differ from ERG preferred NMA

	Company after technical engagement	ERG after technical engagement
TROPIC **COU-AA-301** **AFFIRM** **Sun et al.**	• Inclusion allows comparison based on largest possible evidence base • Acknowledge heterogeneity as patients less heavily pre-treated vs VISION	• Excluded based on substantial differences between populations and CARD • Trials contain ARPI-naïve patient population → ARPI-sensitivity could be a confounding factor • Analysis of direct evidence (CARD) and indirect evidence, found limited overlap for OS & rPFS for cabazitaxel vs ARPI
CARD	• Substantial differences to VISION • Population generally healthier and less heavily pre-treated • Population progressed during 12 month ARPI treatment → resistant to ARPI may bias effect for cabazitaxel	• 0% (CARD) vs 41% (VISION) had 2 lines of taxanes, • [redacted] in OS or rPFS in VISION for 1 vs. 2 taxanes → may not be significant treatment modifier • Around half people in VISION arms progress after 2 or 3 ARPI – may have similar ARPI resistance as CARD
TheraP	• Disagree including – bioequivalence of study drug to ^{177}Lu not established; different dosing • Potential bias in allowing treatment suspension if exceptional response	• Acknowledge differences with VISION but important to include head-to-head evidence for unbiased treatment effect estimates → scenario excluding TheraP • Consistency check → no inconsistency when including the direct evidence (TheraP) in NMA

Stakeholder: TheraP should be included to maximise evidence base

Clinical expert: CARD trial not suitable comparison due to inclusion criteria, RWE more suitable

Which studies should be included and excluded in the NMA?

Abbreviations: ARPI: androgen receptor pathway inhibitor; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression-free survival; RWE: real-world evidence

Key issue: NMA model, fixed vs random effects

Using a fixed-effect model could underestimate probabilistic ICERs

Post TE	Company NMA (5 studies)	
	Fixed-effect	Random-effects (non-informative prior*)
OS	[redacted]	[redacted]
rPFS	[redacted]	[redacted]

*informative priors reduced width of the Credible intervals

	ERG NMA (includes VISION and CARD) random effects, informative prior	
	Include TheraP	Exclude TheraP
OS	-	0.84 (0.37, 1.87)
rPFS	0.74 (0.47, 1.16)	0.98 (0.43, 2.20)

	VISION: ^{177}Lu vs SOC	CARD: Cab vs ARPI	TheraP: ^{177}Lu vs Cab
OS	0.62 (0.52, 0.74)	0.64 (0.46, 0.89)	N/A
rPFS	0.40 (0.29, 0.57)	0.54† (0.40, 0.73)	0.64 (0.46 to 0.88)

†Assessment for rPFS in CARD includes non-radiographic measures

Company: Fixed-effect NMA, assumes no heterogeneity
Post TE: Present random-effects model but note unlikely that random effects approach could accurately address heterogeneity within NMA

ERG: Prefer random-effects model with informative prior for realistic heterogeneity distribution

- Company acknowledge inter-trial heterogeneity
- Informative prior assumes HR in one study is no more than 5X HR in another → in-line with 2022 HTA guide estimating heterogeneity with sparse data
- Goodness of fit check of company's NMA does not show good fit for OS and rPFS
- Probability sensitivity analysis results sensitive to heterogeneity → Underestimate ICER in fixed-model

What NMA is most appropriate?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; Cab: cabazitaxel; HR: hazard ratio; HTA: health technology assessment; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression-free survival

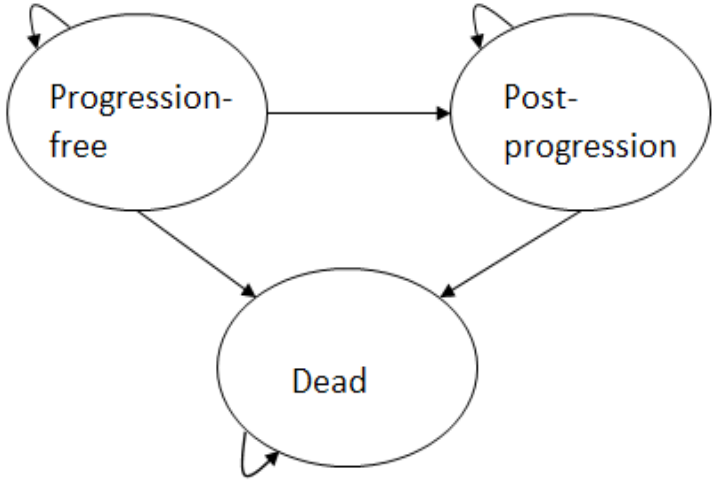
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model structure – Cost utility analysis

Partitioned survival model with 3 health states for ^{177}Lu compared with cabazitaxel and standard of care

Structure	Partitioned survival model – 3 health states
Intervention	^{177}Lu vipivotide tetraxetan
Comparators	Cabazitaxel, standard of care
Mean age	[redacted] years
Cycle length	Weekly. No half-cycle correction
Time horizon	10 years
Utilities	EQ-5D-5L mapped to 3L
Price year	Unit costs: 2019/2020 prices; Drug costs: 2021 prices
Discount rate	3.5% per year for cost and health effects
Treatment costs	^{177}Lu from VISION; cabazitaxel from CARD



Source: ERG report

ERG: Company present 1 cost-effectiveness analysis covering all patients in ^{177}Lu indication
→ Only relevant comparator differing across subgroups

- Modelled mortality rates never fall below age- and sex-matched estimates for UK general population – but no model constraints for this

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; EQ-5D-5L: EuroQol-5-Dimension 5-level

Modelling time-to-event parameters

Company efficacy data from VISION for ^{177}Lu and standard care; from RWE for cabazitaxel OS; and applied hazard ratio from NMA for cabazitaxel rPFS

	Company base case
^{177}Lu arm and standard of care arm	• Parametric or flexible spline models to time-to-event data (ITT cohort VISION data) • Lowest AIC/BIC: Stratified flexible Weibull (2 knots) used for OS and rPFS • Censoring explored in scenario analyses, unadjusted data used – only small differences
Cabazitaxel	• **OS** Kaplan-Meier estimate (Cabazitaxel cohort of **RWE study**) • No extrapolation as OS Kaplan-Meier curve reaches zero within the follow-up period • Scenario analysis uses network meta-analysis (NMA) hazard ratio • **rPFS:** Fixed effect hazard ratio from **NMA** applied to extrapolated ^{177}Lu arm

Company's base case extrapolations

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: intention-to-treat; OS: overall survival; rPFS: radiographic progression-free survival; RWE: real-world evidence

Key issue: Cabazitaxel overall survival estimates

Differences in median OS for cabazitaxel in RWE and VISION – potential bias

ERG: Naïve unanchored indirect comparison modelling relative effect of ^{177}Lu vs cabazitaxel

- Company approach introduces bias estimating relative effect between cabazitaxel and ^{177}Lu
- Median OS for cabazitaxel from RWE lower than SOC in VISION
  - Company explanation trials have enhanced care does not justify modelling cabazitaxel arm independently
- Everyone in VISION would benefit from better care in a study – May bias ^{177}Lu OS estimates higher than clinical practice
- Prefer applying HR for OS from NMA to extrapolated ^{177}Lu arm

Company after technical engagement: VISION likely reflective of UK practice

- VISION SOC arm likely to benefit more from enhanced monitoring and have longer OS than in real-world – additional monitoring for ^{177}Lu to be mandated as per SmPC (clinical expert advice to company)
- Propensity score weighting analysis (PSWA) addressing population differences in RWE & VISION

Clinical expert: RWE true reflection of UK and should use for OS estimates – therapeutic landscape changed since cabazitaxel approval when ARTAs used post-chemotherapy – Now mainly pre-chemotherapy
Stakeholders: RWE may better reflect UK;
NMA should be used for cabazitaxel OS in absence of supporting RWE for ^{177}Lu to preserve randomisation and remove bias from baseline risk differences between populations

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ARTA: androgen receptor targeted agents; HR: hazard ratio; NMA: network meta-analysis; OS: overall survival; RWE: real-world evidence; SOC: standard of care: SmPC: summary of produce characteristics

Key issue: Cabazitaxel OS – Propensity score weighting

ERG have concerns with company's PSWA to address uncertainty in indirect comparison of RWE with VISION

Company after TE: Baseline characteristics in PSWA – Age; ECOG; time from diagnosis; gleason score 8-10; previous prostatectomy

- Analysis selected patients treated in line with eligibility criteria for VISION
- Median OS for people having cabazitaxel consistent with before PSWA: [redacted] months (95% CI: [redacted] months)

ERG after technical engagement: Propensity score weighting

Prognostic covariates identified by statistical hypothesis testing not by disease area or literature review

- Analysis shows RWE population similar to VISION – but may have missed prognostic factors
- Two RWE studies (cabazitaxel in mCRPC) in Netherlands and France show lower median OS than in CARD and TROPIC → suggest differences in patient population likely reason for discrepancy

Source of OS data for Cabazitaxel

- Treatment effects from VISION and CARD are unbiased estimates, used to generate NMA results
- Using RWE has strong assumption PSWA controlled for all effect modifiers and prognostic factors
- Treatment effect of cabazitaxel may be associated with treatment sequencing and prior ARPI response

Alternative approach:

- Use RWE as reference group, apply HR from NMA to estimate OS and rPFS for cabazitaxel and ^{177}Lu

What is the most appropriate way to estimate overall survival?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; NMA: network meta-analysis; mCRPC: metastatic castration-resistant prostate cancer; OS: overall survival; PSWA: propensity score weighted analysis; rPFS: radiographic progression-free survival; RWE: real-world evidence

Key issue: Cabazitaxel utility values (1)

Some evidence that cabazitaxel is associated with lower utilities than ^{177}Lu

Company: Prefer Treatment dependent utilities from VISION and TA391 (Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel)

- Taxanes associated with poor tolerability profile and considerable side effects
- Treatment-independent utility values may not capture psychological burden on people who have cabazitaxel

Health state utility	^{177}Lu	SOC	Cabazitaxel
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	0.627 ← TA391

ERG: Prefer company's scenario using treatment-independent utilities for pre- and post-progression

- Treatment-independent allow consistency across treatments → not subject to bias from withdrawal
- Possible psychological burden in SOC arm – unlikely cabazitaxel utility < SOC (after considering AEs)
- Potential informative censoring in EQ-5D analysis because higher baseline utilities in people withdrawing from study (higher rate in SOC arm) – likely bias results
- TheraP suggets^{177}Lu could have improved HRQoL post progression vs cabazitaxel but difference uncertain

Additional scenario after technical engagement: Treatment-dependent utility assuming utility for cabazitaxel is average between utility for ^{177}Lu vipivotide tetraxetan and utility for SOC

UK Early Access Programme: Results show utilities may be relatively stable post-cabazitaxel treatment → increase by 0.065 by cycle 10 (not statistically significant)

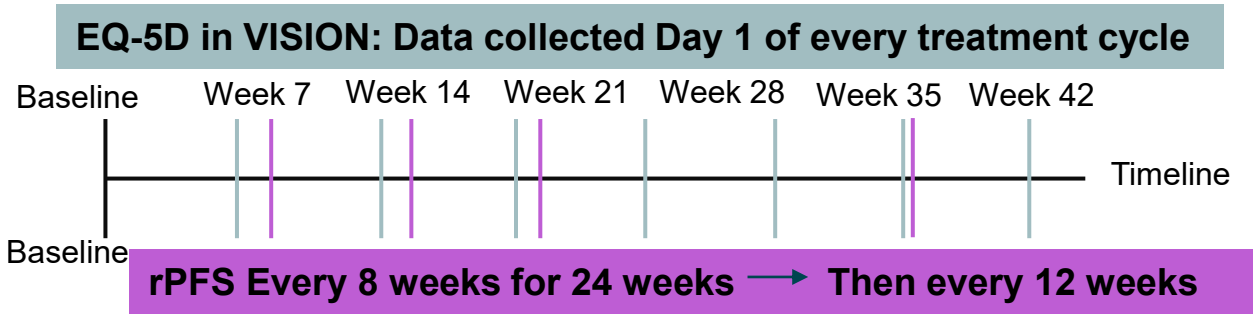
Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; AE; adverse event; EQ-5D: EuroQol-5-Dimension; HRQoL; health-related quality of life; OS: overall survival; SOC: standard of care

Key issue: Cabazitaxel utility values (2)

Company updated utilities after re-analysis of EQ-5D data but potential issues with excluding progression-free utility data and introducing informative censoring

Company after TE: Re-analysis of VISION EQ-5D to explore differences in utilities between treatment arms and address similar pre- and post-progression utilities in SOC arm

- Different assessment time-points for EQ-5D and rPFS may result in inaccuracies in individual categorisation
- Bigger impact expected on treatment arm with faster rate of progression (SOC)
- Updated utilities, excluding some EQ-5D data



Company excluded data: EQ-5D after last progression assessment for progression-free; before rPFS assessment and radiographic progression shown; no HRQoL assessment with progression data or only 1 visit

ERG: Disagree with EQ-5D re-analysis → excluding progression-free utility data and informative censoring.
→ Preference for treatment independent utilities

Abbreviations: HRQoL: health-related quality of life; EQ-5D-5L: EuroQol-5-Dimension 5-level; rPFS: radiographic progression-free survival; SOC: standard of care

Key issue: Cabazitaxel utility values (3)

Company updated utilities after EQ-5D re-analysis but potential issues with excluding progression-free utility data and introducing informative censoring

	Company			ERG-preferred			Company updated (TE)			ERG exploratory		
	^{177}Lu	SOC	Cabazitaxel	^{177}Lu	SOC	Cabazitaxel	^{177}Lu	SOC	Cabazitaxel	^{177}Lu	SOC	Cabazitaxel
Utility												
Pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	0.63	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.63	[redacted]	[redacted]	[redacted]
QALY losses (one-off)												
Due to AE	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Due to SSEs	-	-	-	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-

Clinical expert: Progression post-cabazitaxel has utility detriments due to progression and side-effects
Stakeholder: Treatment-independent most reasonable when accounting for AE and SSE disutilities separately

- Lower utilities on chemotherapy often transient and associated with AE of chemotherapy
- Modelling artificially lower utilities for cabazitaxel on top of disutilities would double-count and overestimate potential negative impact of chemotherapy

What are the most appropriate utility values?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; AE: adverse event; SOC: standard of care; SSE: symptomatic skeletal events; TE: technical engagement

Key issue: Cabazitaxel pre-/concomitant medication costs (G-CSF)

G-CSF use varies in clinical practice, under use could increase risk of adverse events

Background: Company use G-CSF costs for 14 days of every 21-day cycle of cabazitaxel;
ERG comment G-CSF use is varied but when used, mainly 5-7 days → use 5 days in ERG approach

Company after Technical engagement: updated base case with 9 days G-CSF duration

- Further consultation with clinical experts – Accept 14 days G-CSF is overestimation
- Disagree with 5 days because severe AEs risk (neutropenic sepsis) – 7-9 days more appropriate

ERG after technical engagement: Unchanged preferred approach (5 days) but further clinical advice agree with fewer days of G-CSF risks → Conducted exploratory analysis using 7 days treatment

Clinical expert: 14 days (ASCO guidelines) – lower use likely increase neutropenia/neutropenic sepsis risk
Stakeholder: Clinical guidelines G-CSF for chemotherapy support one-off prophylaxis for 5-7 days

ID1640 Olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations: Committee concluded 7 days estimate of prophylactic G-CSF in cabazitaxel arm was appropriate

What is the most appropriate duration of G-CSF costs in the model?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; AE: adverse event; ASCO: American Society of Clinical Oncology; G-CSF: granulocyte-colony stimulating factor; SOC: standard of care

Key issue: Cabazitaxel pre-/concomitant medication costs

Further cost issues identified by the ERG

Cost issue	Company	ERG
Pre-medications and administration	Assume antihistamines, H2 antagonist and corticosteroids taken orally daily for duration of cabazitaxel treatment	Clinical advice to ERG: Pre-medications given intravenously on day of cabazitaxel and not continued daily (although likely variation) → Add granisetron on day of treatment and metoclopramide 3 days after treatment → Add prednisone/prednisolone – required continuously during cabazitaxel treatment (SmPC)
Costs involving chemotherapy	Apply Healthcare Resource Group costs for oral chemotherapy for each oral medication as part of SOC	Disagree with company approach because medications likely prescribed as part of routine care so likely captured by outpatient visits
ESA and G-CSF costs	1,000 unit dose for ESA, and 1 pack option for G-CSF (filgrastim)	Unit costs used not cheapest or most plausible: • Use 40,000 unit dose for ESA to reduce injections, and prefer cheaper 5 pack G-CSF
^{177}Lu dose estimate	Based on mean treatment duration in VISION (4.54 doses)	Estimate 4.46 based on data on distribution of doses → company may have over-estimated dose number

What are the appropriate costs to use in the model for each cost issue?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan ; ESA: erythropoietin stimulating agent; G-CSF: granulocyte-colony stimulating factor; SmPC: summary of product characteristics; SOC: standard of care

RESOLVED: ^{177}Lu and cabazitaxel standard of care costs and Symptomatic skeletal events estimation

Key issue	Conclusion
Standard of care costs applied to ^{177}Lu and cabazitaxel treatment arms 	**Company updated approach after technical engagement** Include standard of care costs to all treatment groups as in company scenario analysis (ERG preference), not just SOC treatment arm • Concomitant components of SOC based on VISION for ^{177}Lu and SOC arms • Cabazitaxel based on average frequencies in both VISION treatment arms • Small impact on ICER for ^{177}Lu vs cabazitaxel (£109); larger impact vs SOC (around £15K)
Symptomatic skeletal events estimation 	**Company updated approach after technical engagement** Use cumulative SSE incidence based on rates in VISION for ^{177}Lu and SOC, and CARD for cabazitaxel (as in company scenario analysis), rather than using log-normal survival to extrapolate SSE incidence from VISION • Minimal impact on ICER **ERG:** Greater impact on ICER when also using ERG approach to estimating utilities

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; ICER: incremental cost-effectiveness ratio; SOC: standard of care; SSE: symptomatic skeletal events

Overview of company and ERG survival modelling

Assumption	Company	ERG	Agree?
Treatment effect ^{177}Lu & SOC	VISION trial intention-to-treat population		✓
rPFS and OS HR cabazitaxel	Company's updated NMA	ERG's NMA	X
Survival ^{177}Lu and SOC arms	Stratified flexible Weibull (2 knots)		✓
Survival extrapolations Cabazitaxel	OS – adjusted RWE KM data rPFS – HR from NMA	OS and rPFS – HR from NMA applied to ^{177}Lu extrapolation	X
Utility values	Treatment-specific (no AE or SSEs) – new utility analysis	Treatment independent + decrements for AE and SSE	X
SSE incidence	Total incidence of SSEs reported in VISION and CARD		✓
SOC costs	Included for all treatments		✓
Cabazitaxel concomitant medication costs	9 days G-CSF duration	5 days G-CSF duration	X
Unit costs for epoetin alpha and filgrastim	Epoetin alpha: medicinal form needing many injections Filgrastim: pack of 1 pre-filled syringe	Epoetin alpha: unit cost from 40,000 form (less injections) Filgrastim: Cheaper option with 5 syringes	X
Cost of treatments	^{177}Lu mean treatment duration	Distribution of ^{177}Lu doses received	X

What are committee's preferred assumptions, including for PSMA testing?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; AE: adverse event; G-CSF: granulocyte-colony stimulating factor; NMA: network meta-analysis; RWE: real-world evidence; SOC: standard of care; SSE: symptomatic skeletal events

Scenario analyses to present in PART 2 slides

All ICERs reported in PART 2 slides because of confidential comparator discounts

Company	• Base case
ERG preferences	• Correction of model errors • ERG unit costs for epoetin alpha (ESA) and filgrastim (G-CSF) • ERG cabazitaxel pre- and concomitant medications (including 5 days G-CSF) • ERG costs for SOC concomitant medications • ERG costs for ^{177}Lu • Treatment-independent utilities (and utility decrements for adverse events and SSEs) • SSE disutilities from PREVAIL study • Cabazitaxel rPFS and OS estimates from ERG NMA
Sensitivity analyses	• Stratified flexible Weibull (2 knots) survival model for OS with IPCW adjustment • Stratified flexible Weibull (2 knots) survival model for rPFS with interval adjustment for interval censoring with original parametric survival model for rPFS • Alternative parametric survival curves for OS and rPFS
Exploratory analyses after TE	• 7 days G-CSF treatment • ERG NMA excluding TheraP

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; G-CSF: granulocyte-colony stimulating factor; NMA: network meta-analysis; OS: overall survival; rPFS: radiographic progression free survival; RWE: real world evidence; SSE: symptomatic skeletal events; TE: technical engagement

End-of-life

1. *Treatment is indicated for patients with a short life expectancy, normally less than 24 months*
2. *Sufficient evidence to indicate the treatment has the prospect of offering an extension to life, normally a mean value of at least added 3 months, 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*

Company: Consider ^{177}Lu to meet both end-of life criteria
Criteria 1. Median OS: VISION SOC: 11.3 months (95% CI: [redacted]); Cabazitaxel in UK practice: [redacted] months
Mean undiscounted life years predicted [redacted] (SOC) and [redacted] (cabazitaxel) in model
Criteria 2. Median OS: VISION ^{177}Lu: 15.3 months (95% CI [redacted]), P-value: <0.001
Mean undiscounted life years for ^{177}Lu: [redacted] months

ERG: End-of life met for people unable to have cabazitaxel and only treatment option is SOC
Criteria 1. Agree short life expectancy is met
Criteria 2. Extension to OS for ^{177}Lu vs. SOC meets criterion, but vs. cabazitaxel [redacted]

Clinical expert: Consider end-of-life is met

Is end-of-life considered to be met? Is this across all populations?

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; OS: overall survival; SOC: standard of care

Other considerations

Equality considerations

- Company and Tackle Prostate Cancer describe equality issues relating to mCRPC population who cannot have taxane-based chemotherapy, if recommendation limited to people who have had a taxane

Age (years)	Under 70	Over 70	Over 80
Proportion who have chemotherapy	63.6%	21.9%	5.7%

- PCUK: PHE 2019 data show indirect discrimination issue against older people in giving them access to a tolerable, life-extending treatment if limiting the scope to only people who have had a taxane
- Geographical inequality: Limited centres in UK able to do PSMA-positive testing and ^{177}Lu treatment Inequality could occur unless expansion of existing services is prioritised as some people will need to travel long distances for treatment

Innovation

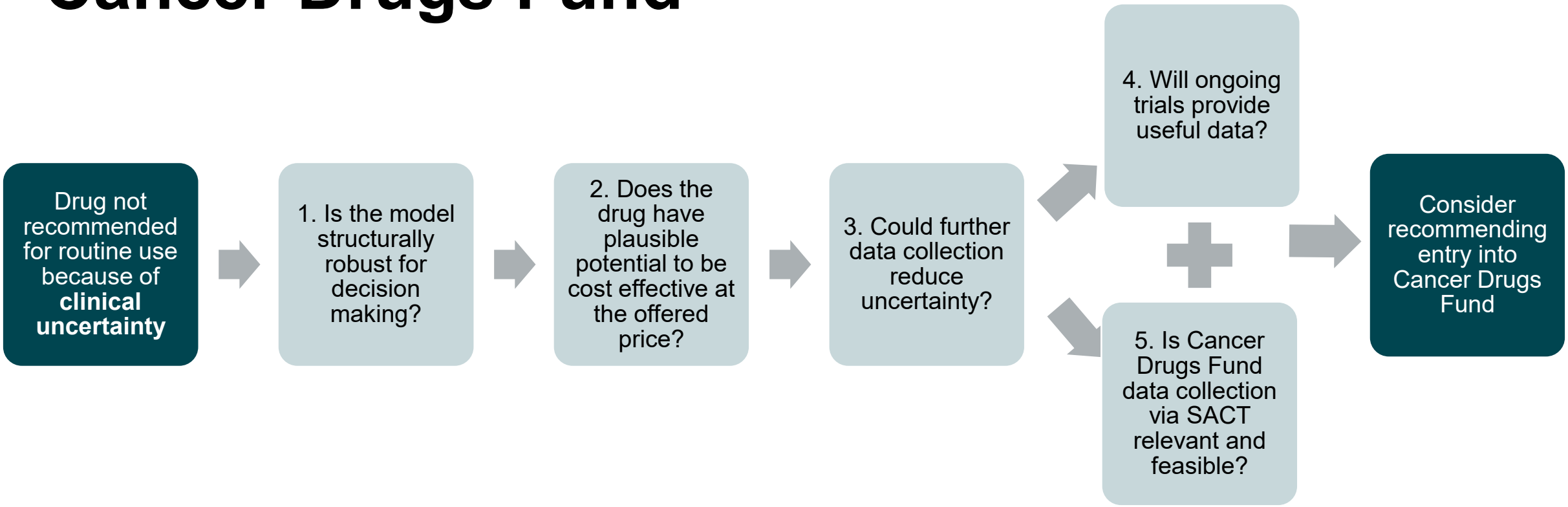
Company describe ^{177}Lu as having innovative potential because:

- Offers targeted approach to treating mCRPC and first radioligand therapy in treating prostate cancer,
- Shows clinical efficacy and addresses an unmet need

Clinical expert comment: Treatment will be a 'game changer' – uses new, targeted mechanism involving theranostics and very favourable tolerability profile

Abbreviations: ^{177}Lu: Lu vipivotide tetraxetan; mCRPC: metastatic castration-resistant prostate cancer; PSMA: prostate-specific membrane antigen; PCUK: Prostate Cancer UK; PHE: Public Health England

Cancer Drugs Fund



Define the nature and level of clinical uncertainty. Indicate the research question, analyses needed, and number of patients in the NHS in England needed to collect data.

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Thank you.