NICE National Institute for Health and Care Excellence

Padeliporfin for treating localised prostate cancer [ID866]

Chair's presentation

2nd Appraisal Committee B meeting

2nd August 2018

Lead team: John Cairns, Sarah Wild

Evidence Review Group (ERG): Aberdeen HTA Group

NICE technical team: Sharlene Ting, Ross Dent, Jasdeep Hayre

Company: Steba Biotech

HTA, health technology assessment

Padeliporfin (TOOKAD®)

Marketing authorisation	Monotherapy for adults with untreated, unilateral, low-risk, adenocarcinoma of the prostate with a life expectancy ≥ 10 years: • prostate-specific antigen (PSA) ≤ 10 ng/mL AND • Gleason score ≤ 6 AND • Clinical stage T1c or T2a AND • **3 positive cancer cores (core length ≤ 5 mm in any 1 core) or 1 to 2 positive cores with ≥ 50% cancer involvement in any 1 core or a PSA density ≥ 0.15 ng/mL/cm^3** *(to exclude 'very-low-risk' disease)*
Administration and dose	• **single intravenous weight-based dose: 3.66 mg/kg** • **light via optical fibres inserted into the prostate activates the drug** • **retreating same lobe or treating other lobe not recommended**
Mechanism of action of therapy	• **focal therapy: targets tumour, not whole prostate** • **photodynamic: laser light activates padeliporfin → kills cancer cells**

PSA, prostate-specific antigen; Definition of 'low-risk' broadly in line with NICE prostate cancer guideline (CG175): PSA **<10 ng/ml and Gleason score ≤6 and Clinical stage T1–T2a**

Company's positioning of padeliporfin low risk disease

NICE Prostate Cancer guideline
update expected April 2019

Definition of 'active surveillance' in NICE guideline by year	
1	Multi-parametric MRI if not already performed
2 to 4	PSA every 3 to 4 months PSA 'kinetics' Rectal exam every 6 to 12 months At 12 months: rebiopsy
5 and every year after	PSA every 6 months PSA kinetics Rectal exam every 12 months

Active surveillance (comparator in only trial)

Disease progression

Radical therapies* (prostatectomy, external beam radiotherapy, brachytherapy)

Company

Padeliporfin?
Not an alternative to 'clinically insignificant' disease but for people who have 'surveillance fatigue'

Padeliporfin?
For people 'choosing' a radical therapy

MRI, magnetic resonance imaging; PSA, (plasma) prostate specific antigen

*Focal therapies available on the NHS by special arrangements or in trials: cryotherapy (NICE IPG423), high-intensity focused ultrasound (NICE IPG424)

PCM301 trial – comparator is active surveillance

Phase 3, international with UK sites, randomised, open-label, (2011-2013)

Adults with untreated, low-risk disease, diagnosed by biopsy < 12 months (Gleason ≤ 6, 5 mm maximum cancer core length)

Note: only a **subgroup** (n=158) determined marketing authorisation: **unilateral, low-risk disease**

Padeliporfin + active surveillance (n=80)

Active surveillance (n=78)
PSA and digital rectal exam every 3 months, biopsy every 12 months

Co-primary endpoints at 24 months
- absence of definitive cancer
- treatment failure*

Outcomes in economic model
- time to start of radical therapy
- adverse events: bowel, urinary, sexual dysfunction

PSA, serum prostate-specific antigen
*__Treatment failure:__ histological cancer progression from low to intermediate/high risk or prostate cancer-related death

Clinical experts at 1st committee meeting

Clinical experts explained that:

- people switch to radical therapy because of:
  - disease progression (increase in prostate-specific antigen levels or risk level or clinical stage)
  - 'surveillance fatigue'
- clinicians do not 'actively' treat low-risk disease without disease progression

[redacted]

Committee considerations: clinical trial

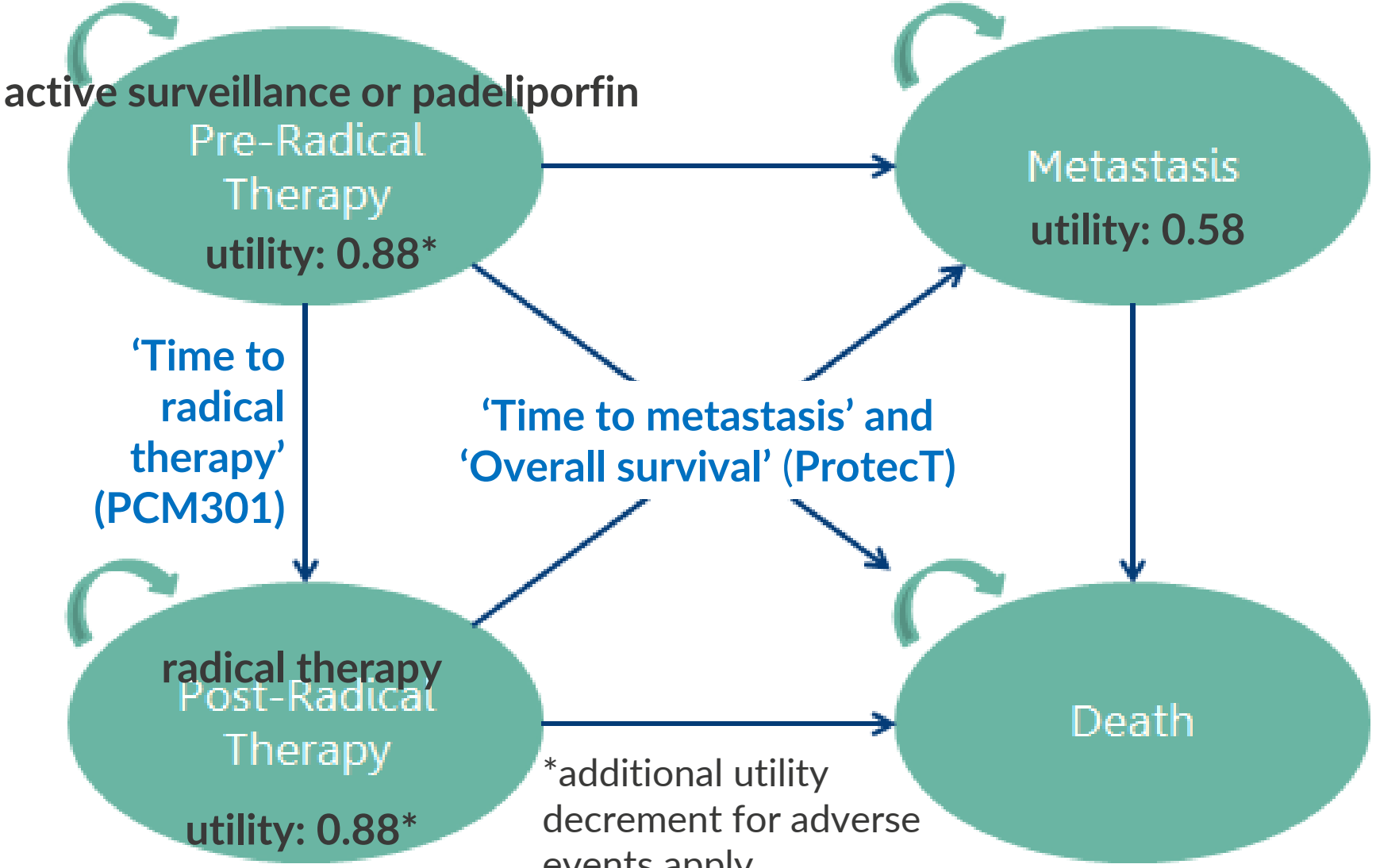
- Active surveillance does not reflect relevant comparator
- Population different from NHS patients
  - diagnostic criteria changed → Gleason 6 in PCM301 now likely Gleason 7
- Active surveillance in trial differs from NHS practice
  - PCM301 did not include multi-parametric MRI → standard NHS practice now
- Rate of 'disease progression' in people randomised to active surveillance higher than in another ProtecT UK-based randomised trial comparing active monitoring, prostatectomy and external-beam radiotherapy for localised disease over 10 years
  - 58% in PCM301 *vs* 30% in ProtecT
- No clinical evidence for padeliporfin compared with radical therapies
  - Company said indirect comparison of padeliporfin and radical therapies not possible because of 'incongruent' outcomes → ERG 'broadly agree'

[redacted]

ERG, Evidence Review Group; MRI, magnetic resonance imaging

Company's model

Company assumed all treatments have same time to metastasis & death



- partitioned survival analysis
- lifetime horizon (**from 63 years**)
- 6 monthly cycle
- **no radical therapy after 75 years**

[redacted]

KEY DRIVER: quality of life and costs related to 3 adverse events (bowel, urinary and sexual dysfunction)

Committee considerations: economic model

- Time to radical therapy as a model outcome:
  - not appropriate for comparing padeliporfin *vs* radical therapies
  - not adjusted for general population mortality
  - log-normal extrapolation for active surveillance and padeliporfin time to radical therapy not clinically plausible
- Uncertainty about most appropriate rates of adverse event for radical therapies
  - Ramsay et al. (health technology assessment report) *vs* ProtecT trial
- Utility decrements of adverse events
  - bowel dysfunction decrement from ERG is preferred
  - should be adjusted multiplicatively
- Costs should:
  - include multi-parametric magnetic resonance imaging
  - apply bowel dysfunction costs only once
  - consider use of robotic prostatectomy
  - include wastage of padeliporfin

[redacted]

ERG, Evidence Review Group

Appraisal consultation document: preliminary recommendation

- Padeliporfin is **not** recommended, within its marketing authorisation, for untreated unilateral, low-risk prostate cancer in adults

Padeliporfin *vs* active surveillance (not a relevant comparator)

- Higher rates of 'absence of definitive cancer' and 'absence of disease progression'
- No evidence for delay of metastases or length of life
- Company and ERG's ICERs: £49,415 to £58,047 per QALY gained

Padeliporfin *vs* radical therapies (prostatectomy, external beam radiotherapy, brachytherapy)

- Company did not provide any clinical evidence
- Company and ERG's ICERs: £26,942 to £37,722 per QALY gained

[redacted]

ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Appraisal consultation document: comments

- **Company**
  - new analyses: different source of adverse event rates, inclusion of additional costs, different source of time to radical therapy data for active surveillance
  - No new evidence on comparison to radical therapies
  - Patient access scheme – not yet agreed
- NHS England's Clinical Expert Group for prostate cancer
- Collective response *RCP/RCR/ACP/NCRI*:
  - Royal College of Physicians
  - Royal College of Radiologists
  - Association of Cancer Physicians
  - National Cancer Research Institute
- Comments by topic:
  1. General comments
  2. PCM301 trial
  3. Support for active surveillance only in NHS for low risk disease
  4. Misclassification
  5. Who gets focal therapies in NHS
  6. Company's comments and new evidence

[redacted]

General comments

- "We agree with the conclusions of the ACD on padeliporfin for the treatment of low risk prostate cancer. Namely, that it should not be recommended for use in the UK for this indication." *RCP/RCR/ACP/NCRI*
- "Agree with the NICE ACD conclusion that padeliporfin …. should not be recommended" *NHS England Clinical Expert Group and the NCRI Prostate CSG*
- "…any treatment in this group of men would confer some harm and no cancer control benefit" *RCP/RCR/ACP/NCRI*
- "The adage that only anxiety is being treated is correct" *RCP/RCR/ACP/NCRI*
- "Any treatment, albeit with fewer adverse events than radical therapy, that continues the over-treatment burden of low risk prostate cancer would be a significant backward step and likely lead to a reversal in the trend towards active surveillance in most men" *RCP/RCR/ACP/NCRI*
- "This would be an unacceptable regressive step in the field of prostate cancer" *RCP/RCR/ACP/NCRI*

ACD, appraisal consultation document

Comments on PCM301 trial

- "The RCT on padeliporfin did not include confirmatory biopsy or mpMRI directed biopsies prior to entry into the study. This will artificially inflate the re-classification rates of low risk disease to high risk disease." *RCP/RCR/ACP/NCRI*
  - ➢ That is, disease at end diagnosed as intermediate risk was always intermediate. Note: marketing authorisation includes low risk disease only
- Endpoint of trial, 'increase in risk' not a surrogate associated with clinical outcomes *RCP/RCR/ACP/NCRI*
- Because of misclassification of people as low risk, the trial overestimated any difference in treatment. "The group with low risk disease will not see the same reductions in transition to higher grade or burden of disease that might trigger radical or focal therapy" *RCP/RCR/ACP/NCRI*

mpMRI, multi-parametric magnetic resonance imaging; RCT, randomised controlled trial

Active surveillance only in low risk disease

- "Low risk prostate cancer is increasingly managed with active surveillance and the trend is going up as demonstrated by the recent National Prostate Cancer Audit."
  - "Only 8% of men with low-risk prostate cancer received potentially unnecessary radical treatment aimed at curing the disease in 2015-16 according to the fourth Annual Report of the National Prostate Cancer Audit (NPCA) published by the Royal College of Surgeons. This is an improvement on 2014-15 figures, when 12% of men treated by the NHS in England may have received unnecessary treatment for low risk disease. This reflects the international trend …" *NHS England Clinical Expert Group quoting from NPCA 2017*
- Supported by
  1. Less misclassification of low risk (as intermediate risk) MRI/targeted biopsies and transperineal saturation/mapping biopsies
  2. Follow-up of inaccurate transrectal biopsy showing low risk of death or metastases
  3. Randomised controlled trials PIVOT and PROTECT "showing no benefit in treating low risk prostate cancer at 10 years follow-up compared to radical radiotherapy or radical prostatectomy" *NHS England Clinical Expert Group*

[redacted]

MRI, multi-parametric magnetic resonance imaging

Misclassification: previously ‘low risk’ not actually low risk

- “Over the last 5 years, the diagnostic pathway has changed” *RCP/RCR/ACP/NCRI*
- With traditional transrectal systematic (‘blind') biopsy, misclassification error was “the norm” *RCP/RCR/ACP/NCRI*
- NHS England has issued guidance for pre-biopsy mpMRI for all men with an elevated PSA as the initial diagnostic test followed by MRI-targeted biopsy *RCP/RCR/ACP/NCRI*
- “This means that the miss-classification error of low-risk prostate cancer will be much lower than the rates of higher grade and higher volume disease seen in the padeliporfin RCT” *RCP/RCR/ACP/NCRI*
- mpMRI before biopsy much more sensitive – can identify 90% of significant cancers compared to approximately 50% by transrectal biopsy alone *RCP/RCR/ACP/NCRI*

[redacted]

mpMRI, multi-parametric magnetic resonance imaging; PSA, prostate-specific antigen

Who has focal therapies in NHS?

- In the NHS, "focal therapy should be used only in the setting of clinically significant prostate cancer that is likely to progress and not as an alternative to active surveillance in those men who are unlikely to progress" *NHS England Clinical Expert Group quoting from UK Focal Therapy Users Group guidance*
- "Use of focal therapies is mainly in intermediate risk patients" *NHS England Clinical Expert Group*
- "Supported by a UK led international consensus meeting published in 2015 (funded by Wellcome Trust) which also agreed that focal therapy should be directed towards intermediate risk disease" *NHS England Clinical Expert Group*
- "The majority (90%) of men treated with focal therapy historically in the UK are of intermediate and high risk" *NHS England Clinical Expert Group*
  - Note: outside of marketing authorisation

◉ *Would padeliporfin (a focal therapy) be used in NHS given that intermediate disease is outside padeliporfin's marketing authorisation?*

[redacted]

Company: Population for padeliporfin (1)

Committee

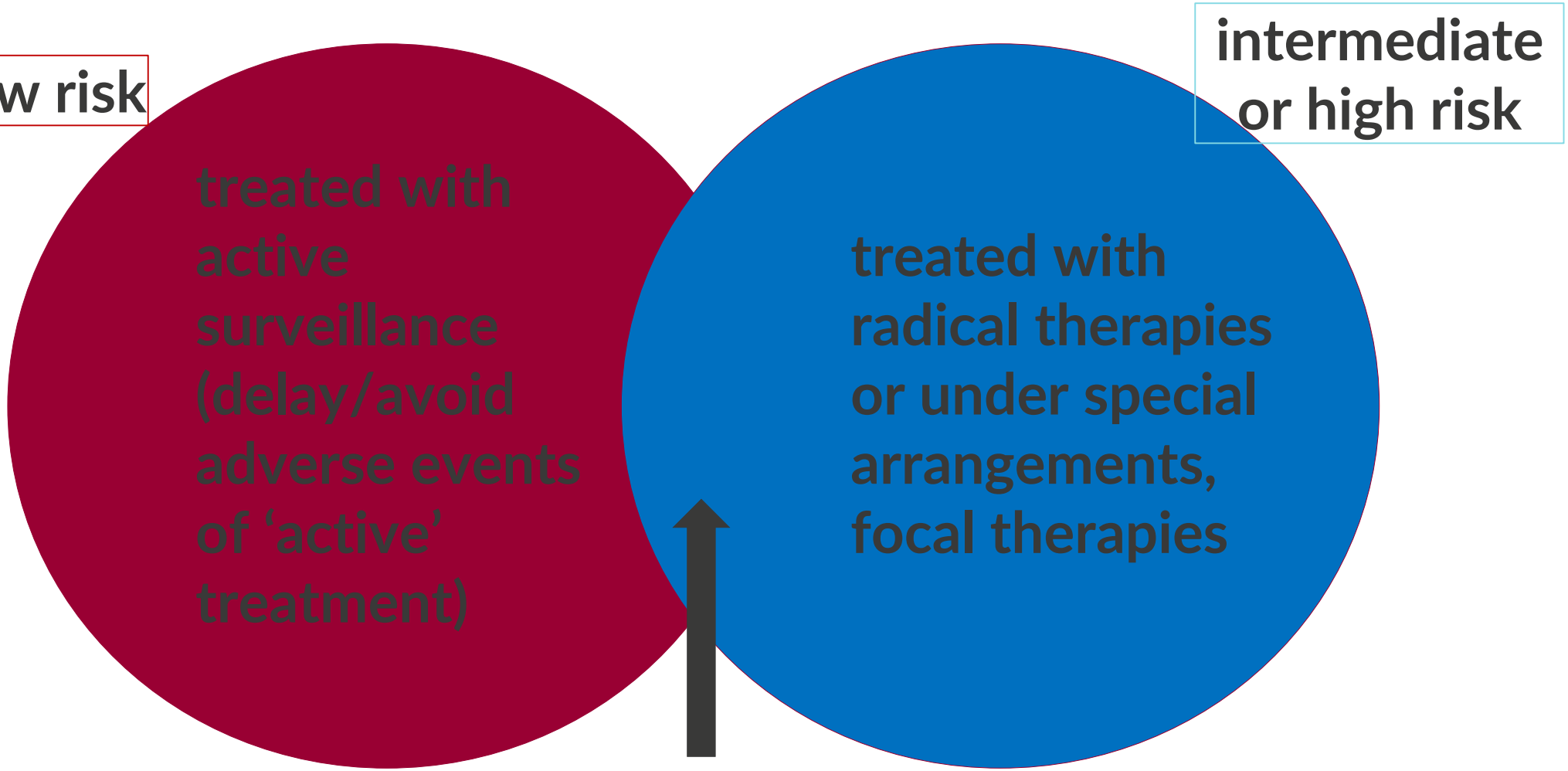
- Not an option when active surveillance is appropriate – low-risk disease without disease progression is not 'actively' treated in NHS
  - people with disease progression (increased PSA levels, or risk or clinical stage) would likely fall outside the marketing authorisation for padeliporfin
- Not an option for people with 'surveillance fatigue' – surveillance would continue after padeliporfin

Company feedback

- *At diagnosis*: a 2010 UK study showed that ~30% patients with very-low-risk or low-risk disease elected for active treatment
- *After being on active surveillance*: studies report that 1 in 3 to 2 in 3 people switch to radical therapy after 5 years
  - PRIAS (European study on active surveillance; **no UK centres**): 22% of 'switchers' have no "protocol-based progression", 59% with "protocol-based reason" had Gleason score 6
- Active surveillance after padeliporfin: different to active surveillance without treatment → addresses anxiety of having no cancer control
- NHS patients eligible for padeliporfin will be identified using transrectal biopsy that may or may not be MRI-targeted

MRI, magnetic resonance imaging; PSA, prostate-specific antigen

Company: Population for padeliporfin (2)



Padeliporfin?
Low-risk choosing radical therapies despite adverse events

◉ *Would padeliporfin be an option for this group of NHS patients, given clinical expert and consultation comments?*

Company comments on comparators

Committee

- Relevant comparators are radical therapies
- Not seen any evidence of effectiveness padeliporfin *vs* radical therapies

Company feedback

- Did not provide any clinical effectiveness evidence for padeliporfin compared with radical therapies
- Stated that padeliporfin meets criteria* for new therapies in low-risk prostate cancer:
  - anti-tumour activity: 90% on padeliporfin had no disease progression *vs* 87% on prostatectomy and 95% on radiotherapy had biochemical disease-free survival^
  - reduce need for radical therapy
  - preserve genitourinary function

ERG comments: no direct randomised comparison of padeliporfin *vs* radical therapies but can "infer significant benefits against immediate radical therapy" for genitourinary toxicities

*Appraisal Committee for Medicinal Products for Human Use guidelines on evaluating anticancer medicines;
^biochemical recurrence studies – clinical experts suggest biochemical recurrence is more 'severe' outcome than PCM301 endpoints, progression to Gleason score 7 or >3 positive cores or to maximum cancer core <5mm

Company's revisions to model

Issue (ACD section)	Committee's conclusions	Company revised
'Time to radical therapy' (3.13, 3.16)	Inappropriate outcome for padeliporfin *vs* radical therapies	✗
	Adjust for general population mortality	✓
'Time to radical therapy' extrapolation (3.17)	Log-normal curves for active surveillance and padeliporfin are not clinically plausible	✓
Urinary dysfunction (3.14)	ProtecT event rates are preferred	✓ (all AEs)
Utility decrements (3.18)	Bowel dysfunction: use ERG's 0.1	✓
	Adjust decrements multiplicatively	? (SA, age-adjusted)
Costs (3.19)	Include multi-parametric MRI costs	✓ (all therapies)
	Apply bowel dysfunction costs once only	✓
	Consider use of robotic prostatectomy	✗
	Wastage of padeliporfin	✓
Other	Use HRG based reference costs Applied patient access scheme	-

[redacted] ACD, appraisal consultation document; AE, adverse events; ERG, Evidence Review Group; HRG, Health Resource Group; MRI, magnetic resonance imaging; SA, sensitivity analysis

Company comments on 'time to radical therapy' adjusted for mortality of general population

Committee: 'time to radical therapy' should also be adjusted for general population mortality (but active surveillance is not a relevant comparator)

Company feedback

- Patient level data is available
- More accurate to change definition of 'time to radical therapy' to include any death as events and refit extrapolation curves
  - 1 death in active surveillance, no deaths in padeliporfin
- More accurate than adjusting curves by general mortality

ERG comments

- Approach is unreliable → small numbers of deaths and short-term follow-up
- Does not capture increasing mortality rate over time as cohort ages
- Inconsistent with approach used in the model to adjust for general population mortality for 'overall survival' and 'time to metastasis' curves → ERG prefers this approach
  - ➢ ERG has used this approach for all curves → modest impact on ICERs

◉ *Which approach to adjusting for general mortality does the committee prefer? Company's or ERG's?*

[redacted]

ICER, incremental cost-effectiveness ratio

Company comments on ‘time to radical therapy’ curves using ProtecT data

Committee: log-normal curves for active surveillance and padeliporfin not clinically plausible → at 10 years, log-normal curve predicted most people on active surveillance would have radical therapy *vs* 55% in ProtecT

Company feedback

- Accept limitation of using ‘time to radical therapy’ extrapolation curves based on PCM301 data
- Suggest using ProtecT data
  - UK population in a real-world setting
  - economic model also uses ProtecT data for ‘time to metastasis’, ‘overall survival’ and adverse event rates
- Use ‘time to radical therapy’ data from ProtecT for active surveillance (baseline)
- Use padeliporfin PCM301 ‘time to radical therapy’ log-normal curve adjusted relative to active surveillance ProtecT baseline (Weibull curve)

[redacted]

ERG comments on using ProtecT data for 'time to radical therapy' curves

ERG comments

- Revised modelling means fewer people have radical therapy after padeliporfin (40% at 10 years in the revised modelling *vs* 80% in the original modelling)
- Differences between PCM301 and ProtecT: active surveillance regimens and criteria for starting radical therapy
  - e.g. active surveillance regimen in ProtecT: no planned re-biopsies *vs* PCM301: re-biopies at 12 and 24 months
  - NICE guideline on active surveillance suggest re-biopsy only at 12 months and as needed

  → which study is more generalisable to NHS setting?
- People on active surveillance in ProtecT had higher risk of metastasis compared with radical therapies
  - → is it still reasonable to assume same 'time to metastasis' for all treatments now that ProtecT data is being used and the proportion of people starting radical therapy after padeliporfin is lower?

◉ *Does committee prefer company's original approach (using PCM301 data for padeliporfin 'time to radical therapy') or revised approach (adjusted using ProtecT data)?*

[redacted]

Company comments on adverse event rates

Committee: urinary dysfunction adverse event rates for radical therapies from ProtecT are more clinically plausible than from Ramsey et al used by the company

Company feedback

Revised analyses used adverse event rates from ProtecT:

- assume bowel dysfunction rates after prostatectomy same after padeliporfin
- use short and long-term adverse event rates for active surveillance, prostatectomy and external beam radiotherapy directly in model
- adjust adverse event rates for padeliporfin from PCM301 based on ProtecT (adverse event difference between padeliporfin and active surveillance in PCM301 plus adverse event rate from ProtecT)

ERG comments

- Company approach appropriate → adverse event rates more generalisable to NHS
- Adverse event rates for brachytherapy are the same as in company's original submission → ProtecT did not have brachytherapy, so potential bias in comparison
  - ERG exploratory analysis adjusts brachytherapy adverse event rates based on those observed for external beam radiotherapy in ProtecT

[redacted]

◉ *Should rates of adverse events with brachytherapy be based on the same source as all other adverse events (ProtecT)?*

Key driver in model: adverse event rates used in original and revised analyses

Treatment		Proportion of people having adverse events in each model cycle								
		Urinary incontinence			Erectile dysfunction			Bowel dysfunction		
		Company	ERG	CR	Company	ERG	CR	Company	ERG	CR
Padeliporfin*	Short	1%		0	2%		24%	5%		
	Long	0		1%	10%		26%	1%		
Active surveillance*	Short	1%		0	1%		8%	0		
	Long	0		1%	1%		17%	0		
Prostatectomy**	Short	25%	45%	44%	65%	47%	54%	4%	0	5%
	Long	28%	17%	18%	71%	31%	47%	13%	0	1%
External beam radiotherapy**	Short	9%	6%	5%	49%	38%	46%	15%	17%	17%
	Long	11%	3%	4%	41%	20%	36%	18%	10%	
Brachytherapy**	Short	33%			27%			6%		6%
	Long	36%			26%			12%		12%

*PCM301 grade 2+; **Ramsay 2015 (no mention of severity of adverse events, assumed grade 2+); ProtecT (ERG); Short-term = first 6 months, Long-term = after 6 months

CR, Company's revisions based on ProtecT; Urinary dysfunction: Expanded Prostate Cancer Index Composite (EPIC) item on incontinence pad use in past 4 weeks; Erectile dysfunction: EPIC item on erections firm enough for intercourse; Bowel dysfunction: EPIC 3 items on faecal incontinence more than 1x/week, loose stools at least half the time, and bloody stools at least half the time

[redacted]

Company revised base case

- deterministic and probabilistic results
- fully incremental and pairwise analyses
- includes proposed Patient Access Scheme discount

						Fully incremental analysis*	pairwise ICERs *vs* padeliporfin (£)	
	Total costs (£)	Total QALYs	Total LYs	Incremental Costs (£)	Incremental QALYs	ICER (£) cost/QALY	deterministic results	probabilistic results
External beam radiotherapy (EBRT)	[redacted]	[redacted]	[redacted]	-	-	-	48,841	35,258
Prostatectomy	[redacted]	[redacted]	[redacted]	3,613	-0.04	Dominated by EBRT	22,831	23,778
Brachytherapy	[redacted]	[redacted]	[redacted]	5,143	-0.17	Dominated by EBRT	9,807	10,423
Padeliporfin	[redacted]	[redacted]	[redacted]	8,483	0.17	48,841	-	-

[redacted]

ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; *provided by Evidence Review Group

Evidence Review Group scenario analyses

Deterministic pairwise results using the proposed Patient Access Scheme price

1. Adjustment of adverse event rates for brachytherapy relative to the adverse event rates observed for external beam radiotherapy in ProtecT
2. Same approach to adjust the 'time to radical therapy' curve for general population mortality as used to for the 'overall survival' and 'time to metastasis' curves
3. 'Time to radical therapy' curve based on PCM301 trial, rather than ProtecT as in company's original base case

	Deterministic pairwise ICERs *vs* padeliporfin (£)		
	External beam radiotherapy	Prostatectomy	Brachytherapy
Company revised base case	48,841	22,831	9,807
1. Adjustment of brachytherapy adverse event rates	48,680	22,759	25,057
2. Adjustment of 'time to radical therapy' curves for general population mortality	54,826	25,600	10,878
3. 'Time to radical therapy' curve based on PCM301 data (+ scenario 2)	130,307	63,065	25,999

Note: external beam radiotherapy dominates prostatectomy and brachytherapy in all fully incremental analyses

[redacted]

Equalities considerations

- Highlighted during scoping that there are age-related inequalities in access to radical therapies
  - people aged 80 years and over have lower rate of access than average

- At the first meeting, the committee noted that:
  - padeliporfin's marketing authorisation is for people with a life expectancy of 10 years or more
  - consideration of life expectancy should be driven by patient fitness rather than age
  - no evidence has been presented which would limit a recommendation based on age

Committee will continue to consider this issue when making recommendations

[redacted]