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Lead team presentation

Padeliporfin for treating localised prostate cancer [ID866]

1st Appraisal Committee meeting

Committee B

Chair: Amanda Adler

Lead team: John Cairns and Sarah Wild

Company: Steba Biotech

ERG: Aberdeen HTA Group

NICE technical team: Sharlene Ting, Jasdeep Hayre

6th June 2018

Key issues

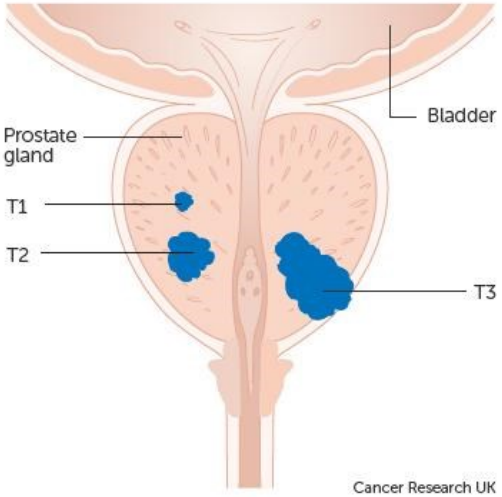
- Treatment pathway and positioning of padeliporfin
  - relevant comparators
    - active surveillance and/or radical therapies?
- How to define ‘disease progression’?
- Is the company’s assumption that all treatments have the same risk of metastatic progression clinically plausible?
- The company adjusted ‘time to metastasis’ and ‘overall survival’ for general population all-cause mortality. Should ‘time to radical therapy’ also be adjusted?
- Which distribution for ‘time to radical therapy’ extrapolation should the company use?
- Which adverse event rates are more plausible?
  - Company’s (Ramsay 2015) or ERG’s (ProtecT)?
- Should adjuvant and salvage therapies be included in the model?
- Innovation and equality issues

Prostate cancer

Localised disease

Risk of progression split broadly into 4 categories

- Very-low risk
- **Low risk (17%) T1 to T2a**
- Intermediate risk T2b
- High risk* ≥T2c

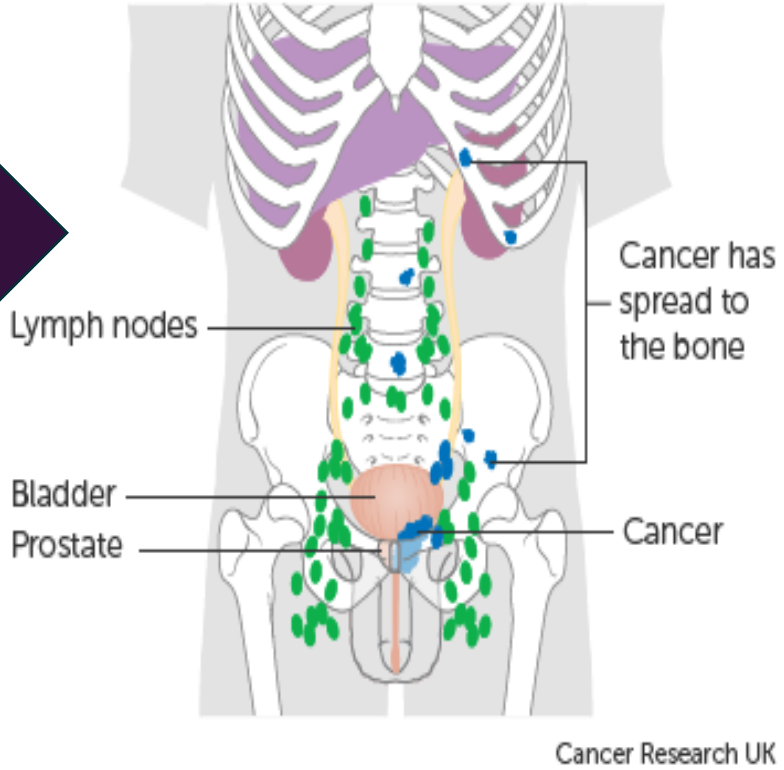


*can be locally advanced disease

Disease progression

Metastatic disease

Cancer spreads to other parts of the body



Padeliporfin (Tookad®)

*Indication population: unilateral, low-risk prostate cancer (**not** very-low-risk)*
***Focal therapy** given using Vascular-Targeted Photodynamic therapy*

Marketing authorisation

➢ **monotherapy** for adults with previously **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 no more than 5 mm in any 1 core) or 1-2 positive cores with ≥ 50% cancer involvement in any 1 core or a PSA density ≥ 0.15 ng/mL/cm^3

Mechanism of action

- administered using Vascular-Targeted Photodynamic (VTP) therapy
  - padeliporfin is activated by laser light → kills cancer cells over several days

Administration and dose

- dose based on body weight
- single dose of 3.66 mg/kg (intravenously)
- VTP under general anaesthetic
- retreatment of same lobe or treatment of contralateral lobe **not** recommended

*Differences with low-risk definition in NICE CG175: PSA **<** 10ng/mL; clinical stage **T1** to T2a

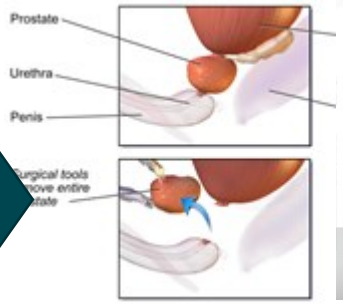
Treatments for localised prostate cancer

Several options available

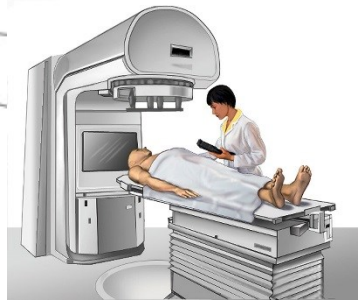
Active surveillance
- **monitors** for disease progression
- delays radical therapies

Multi-parametric magnetic resonance imaging (MRI), PSA testing, digital rectal examination, re-biopsy

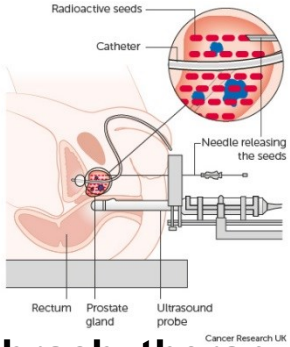
Radical therapies
- **treat** cancer → affect **whole** prostate
- risk of side effects → may affect quality of life



prostatectomy (surgery)



external beam radiotherapy*



brachytherapy*

Focal therapy/padeliporfin?**
- **treats** cancer by **targeting main lesion** → preserves prostate
- reduces risk of side effects

*Intermediate- and high-risk: radiotherapy plus androgen deprivation therapy (NICE CG175); ****Available on the NHS by special arrangements or in trials:** cryotherapy (NICE IPG423), high-intensity focused ultrasound (NICE IPG424); PSA, prostate-specific antigen

Clinical perspective

NHS clinicians recommend 'active surveillance' for low-risk disease

- Goal of treating localised disease: stop progression outside prostate while minimising adverse effects (bowel, urinary and sexual dysfunction)
- Regarding stratifying risk: threshold between low and intermediate risk disease not well established and changing
  - low volume Gleason 3 + 4 may have lower risk than high volume Gleason 3 + 3
- Padeliporfin has safe adverse effect profile
  - may reduce resource use (avoid active surveillance) and need for radical therapies with associated side effects
- Variable access to current focal therapies in the NHS

Gleason score: grade tumour (≤ 6 – relatively favourable; ≥ 8 – relatively aggressive)

Treatment pathway, company's positioning of padeliporfin and relevant comparators

NICE's prostate cancer guideline update ongoing

Active surveillance

↓

Evidence of disease progression or patient choice

↓

Radical therapies
surgery, external beam radiotherapy, brachytherapy

Company's positioning of padeliporfin in pathway

Padeliporfin is not an alternative for clinically insignificant* disease

Padeliporfin is an alternative for people **choosing** radical therapy
No clinical evidence for this comparison from key trial

- ***What determines switch from surveillance to treatment?***
- ***Where would padeliporfin fit in the treatment pathway for 'low-risk' disease in the NHS?***
- ***What are the relevant comparators?***

*little to no chance of disease progression in expected lifetime and unlikely to benefit from active treatments (Valerio 2014)

ERG clinical expert comments on positioning of padeliporfin

Padeliporfin has no place in treatment for low-risk disease
Padeliporfin should be compared with radical therapy

- Agree with company that padeliporfin is not an alternative to surveillance
- Padeliporfin may delay or avoid the need for radical therapy
  - but, future impact of delaying oncologically effective radical therapy is unclear
  - unclear if padeliporfin would affect effectiveness of delayed radical therapy
- Treating from diagnosis of low-risk disease not needed
  - would likely lead to 'over-treatment'
- To fit in the current pathway, padeliporfin should:
  - **be compared with radical therapy** in those who **progress** on active surveillance
    - outcomes should include not only adverse events, but also clinical and quality-of-life outcomes not provided in this appraisal
    - clinicians and patients would wish to see better outcomes

Decision problem – outcomes

NICE scope	Company submission and ERG comments
Outcomes: • disease-free survival • progression of disease • need for radical treatment • mortality • adverse effects of treatment • health-related quality of life	• Company: progression of disease = 'treatment failure' (histological cancer **progression** from low to intermediate/high **risk** or prostate cancer-related death) ➢ **ERG clinical expert: 'non-standard definition'** of 'progression'; other focal therapy studies used histologically proven **absence of disease.** Unlikely to affect relative treatment effectiveness • Company: need for radical treatment = '**notification** of start of radical therapy' ➢ **ERG:** 'notification' may not be appropriate. Potential for bias but unclear impact without information on how notification was done in treatment groups

Key clinical evidence

- **1 Phase 3 randomised controlled trial: PCM301**
  - padeliporfin *vs* active surveillance
  - **subgroup:** unilateral, low-risk (**not** bilateral or very-low-risk)
  - outcomes used in **economic model**: time to start of radical therapy and adverse events (bowel, urinary and sexual dysfunction)

- **Company did not provide a comparison with radical therapies**

PCM301 trial

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

✓ **Indication population (subgroup): 158 unilateral, low-risk disease**

Padeliporfin (n=80)

Phase 3, international with UK sites, multicentre, randomised, ***OPEN-LABEL****, parallel group (2011-2013)*

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

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

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

PSA, prostate-specific antigen

- Follow-up (**all**): biopsy at 12 and 24 months, PSA and rectal exam every 3 months

***Treatment failure:** histological cancer progression from low to intermediate/high risk or prostate cancer-related death

❖ ***Did patients on padeliporfin also have active surveillance?***

Comments from ERG and British Association of Urological Surgeons on PCM301

Patients on active surveillance were treated differently than in NHS
Some criteria in 'treatment failure' less likely to predict long-term clinical outcomes

- Men on active surveillance did not have multi-parametric MRI
  - in NHS, MRI will routinely be given to detect more significant disease
- Definition of 'treatment failure' may not predict long-term clinical outcomes
  - presence of ≥ 3 positive cores, cancer core length ≥ 5 mm and PSA rise on 3 consecutive measures
- Trial methods not in line with current practice guidelines
  - tumour localisation did not meet focal therapy requirements
  - risk of false negatives with biopsy sampling in padeliporfin is not adequately minimised by increasing sampling density

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

Baseline characteristics

Baseline characteristic	Padeliporfin (n=80)	Active surveillance (n=78)
Age (years)*	64 (6.3)	62 (6.3)
Caucasian, %	98%	100%
Time since diagnosis (months)*	5 (4.7)	5 (4.1)
T1c clinical stage, %	83%	91%
T2a clinical stage, %	18%	9%
Prostate-specific antigen (ng/mL)*	7 (1.8)	7 (1.7)
Estimated prostate volume (cm^3)*	37 (9.7)	38 (9.6)
1 positive core, %	19%	23%
2 positive cores, %	43%	42%
3 positive cores, %	39%	35%
Total cancer core length (mm)*	5.3 (2.6)	3.8 (2.7)

*Data are mean (standard deviation)

❖ ***Are patients representative of low-risk prostate cancer seen in NHS clinical practice?***

Results: co-primary endpoints

Patients on padeliporfin less likely to have definitive cancer or disease progression than patients on active surveillance

Outcomes	Padeliporfin (n=80, unless otherwise stated)	Active surveillance (n=78, unless otherwise stated)	Risk ratio (95% confidence intervals)
Absence of definitive cancer at 24 months			
Lobe diagnosed at baseline	71%	15%	4.6 (2.7 to 7.9)
Whole gland	45%	10%	4.4 (2.2 to 8.3)
Absence of disease progression[a] at 27 months			
Lobe diagnosed at baseline	90% of 71 patients	42% of 67 patients	2.2 (1.6 to 2.9)^
Whole gland	64% of 76 patients	25% of 71 patients	not available

^calculated by **ERG**; [a]no prostate cancer-related deaths in study

ERG: disease progression in active surveillance higher than in other trials*

❖ ***Is padeliporfin effective compared to active surveillance?***

*ProtecT (UK-based, 30% of 545 patients; 10 years) and PIVOT (US-based, 68% of 367 patients; 8 years)

Outcomes used in economic model

Patients on padeliporfin less likely to have radical therapies but more likely to have adverse events than patients on active surveillance

Outcomes at 24 months (unless otherwise stated)	Padeliporfin (n=79, unless otherwise stated)	Active surveillance (n=78)	Padeliporfin *vs* active surveillance
Proportion on radical therapy at 48 months[a]	28% of 80 patients	57%	HR: 0.3 (95% CI: 0.2 to 0.5)
Bowel dysfunction^	5%	0%	not available
Urinary dysfunction^	1%	1%	not available
Sexual dysfunction^	18%	3%	not available

[a]**Criteria to start radical therapy:** Gleason ≥ 7, PSA 10 ng/mL for 3 consecutive measures, clinical stage progression, > 3 positive cores and at least 1 core > 5 mm; ^Grade 2 or above adverse event needing treatment

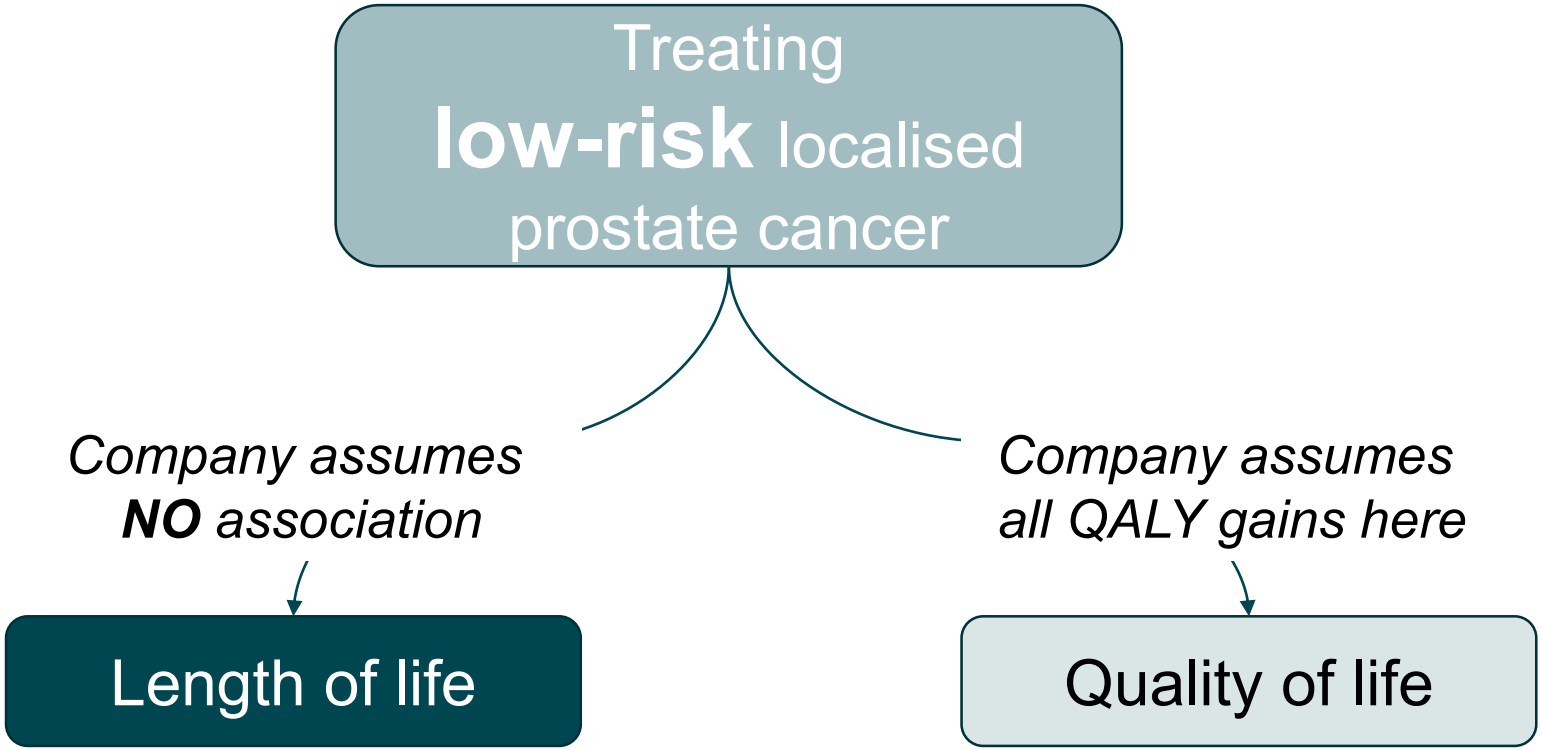
CI, confidence intervals; HR, hazard ratio; PSA, prostate-specific antigen

ERG: rate of radical therapy in active surveillance higher than another trial (ProtecT)*

Company: PCM301 monitoring was more stringent than ProtecT (which also had patients with 'very-low-risk' disease) → earlier detection and progression to radical therapy in PCM301

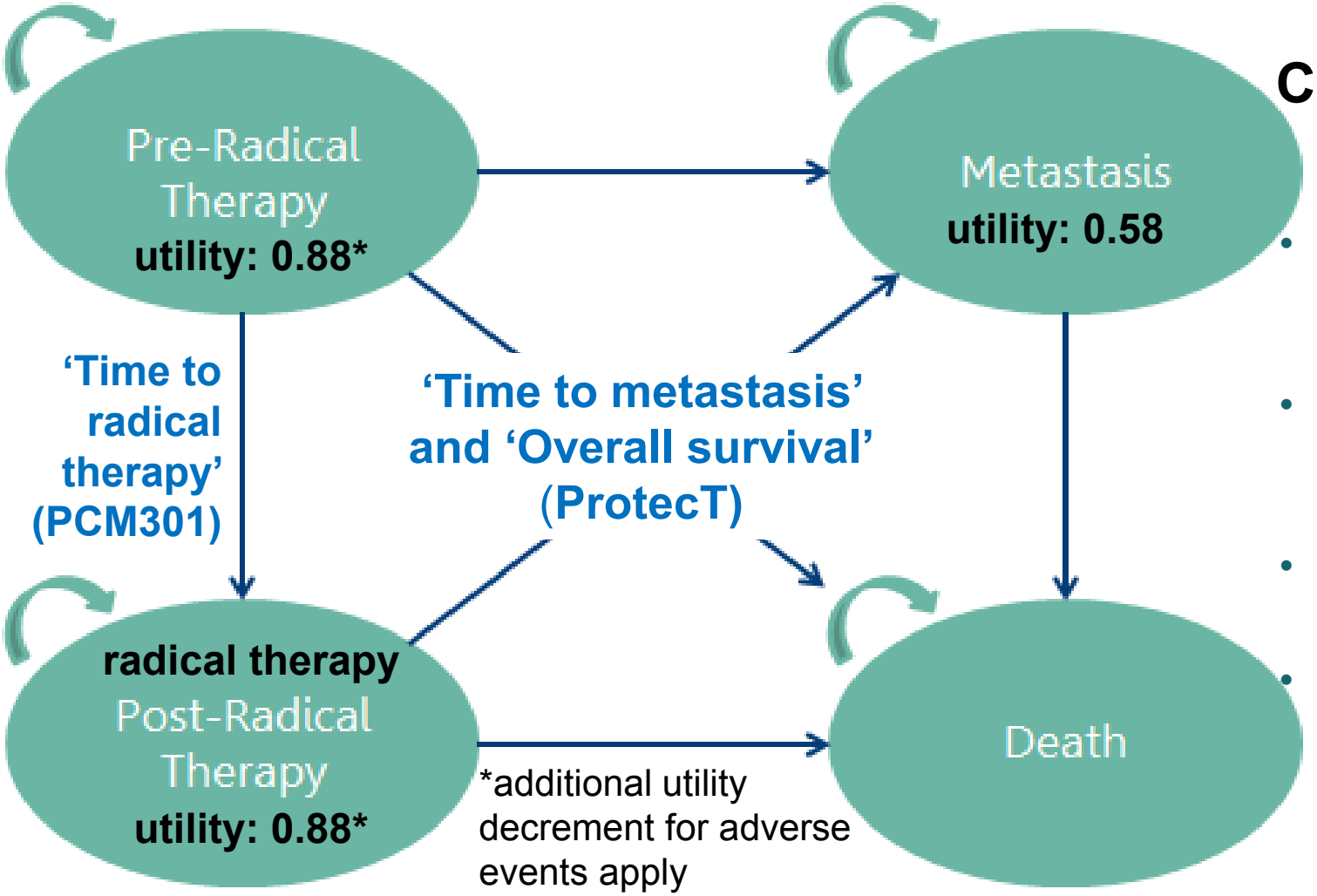
Cost effectiveness

Where do the QALY gains come from?



Increase in QALYs comes from improvement in ***quality of life associated with adverse events of treatments***

❖ ***Is it plausible that radical therapies (such as surgery) have no effect on length of life in low-risk disease?***



Company's model

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

- **Company assumed <u>all</u> treatments have same time to metastasis and overall survival**
- ProtecT: UK-based trial; active surveillance *vs* surgery *vs* radiotherapy in low and intermediate risk, few high risk; 10 years

❖ ***Is the assumption that all treatments have same time to metastasis and overall survival plausible?***

ERG comments on company's model

- Company adjusted the 'overall survival' and 'time to metastasis' curves for general population mortality but not 'time to radical therapy' curve → **overestimate** numbers in pre-radical therapy health state
- No long-term data to verify there is equal metastatic progression between:
  - padeliporfin and active surveillance
  - padeliporfin or active surveillance and radical therapies
- **Only driver in quality-adjusted life year differences are the key adverse events (bowel, urinary and sexual dysfunction)**

❖ ***Should 'time to radical therapy' curve be adjusted for general population mortality?***

Extrapolation of time to radical therapy for padeliporfin and active surveillance: PCM301 (1)

- **Company preferred log-normal**
- **ERG:** good fit in active surveillance driving log-normal choice → little difference between distributions based on fit statistics in padeliporfin
- extrapolations **uncertain** and **impact ICERs** (affects 12 years from baseline) → consider other distributions

Extrapolation of time to radical therapy for padeliporfin and active surveillance: PCM301 (2)

Company's rationale for choosing log-normal distribution for 'time to radical therapy' for active surveillance and padeliporfin

- Used fit statistics (Akaike Information Criteria, Bayesian Information Criteria) and visual inspection
- Clinical plausibility – in disease progression and progression to radical therapy after focal therapy:
  - most in-field progressions occur in first 2 years after treatment
  - most out-of-field progressions (other lobe) occur after this initial period at a fairly constant rate (typically 1-2% per year)
- ✓ Log-normal distribution has a steadier hazard of progression to radical therapy over time after the first few years than generalised gamma distribution

Fit statistics – time to radical therapy

Treatment	Distribution	AIC	BIC	Mean (years)	Median (years)
Padeliporfin	Gompertz	194.76	199.52	4.65	5.61
	Weibull	194.94	199.70	7.13	6.39
	Log-logistic	195.27	200.03	10.44	6.91
	Log-normal	**196.35**	**201.11**	**12.47**	**8.03**
	Gamma	196.64	203.78	4.92	5.97
	Exponential	201.28	203.66	14.59	11.26
Active surveillance	Gamma	363.91	370.98	8.45	3.53
	Log-normal	**372.06**	**376.77**	**4.88**	**3.54**
	Log-logistic	375.94	380.65	5.12	3.49
	Weibull	380.96	385.68	3.53	3.70
	Gompertz	387.39	392.10	3.36	3.80
	Exponential	387.56	389.92	6.19	3.90

Source: PCM301 study; AIC, Akaike information criterion; BIC, Bayesian information criterion; **Company preferred log-normal distribution**

ERG: rate of radical therapy in active surveillance is higher than in ProtecT
Company's log-normal base case project [redacted] by 10 years *vs* 55% in ProtecT

❖ ***Which distribution fits best? (lower values are better)***

Health-related quality of life: utility values

Utility value or decrement	Company justification	ERG comments
Baseline: 0.88	Similar values in PCM301 and Ramsay (2015)	Likely source (Korfage 2005): Dutch men (average age 62 years), pre-surgery EQ-5D value for localised disease
Metastasis: 0.58	Unlikely to differ based on prior treatment	
Urinary incontinence: -0.05	Active treatment of prostate leads to urinary, erectile and bowel dysfunction, affecting quality of life	• Bowel dysfunction likely source (Hummel 2003): Originally, Japanese men with localised disease, EQ-5D values. Company did not apply multiplier to bowel dysfunction decrement → overestimate original value • Erectile dysfunction and urinary incontinence likely source (Volk 2004): US men (45-70 years), no history of prostate cancer, partners, time-trade off. Applied as constant decrements rather than age-adjusted multipliers
Erectile dysfunction: -0.04		
Bowel dysfunction: -0.16		

Adverse events rates (1)

- For padeliporfin and active surveillance, sourced from PCM301
- For radical therapies: Ramsay (2015) – based on all sources reporting adverse events (randomised controlled trials, non-randomised comparative studies, case series with >10 people)
  - Short term: median of rates before 6 months
  - Long term: mean of annualised rates after 6 months
- **ERG comments:**
  - Ramsay (2015) **not based on meta-analysis**; **naïve indirect comparison**, does not control for factors that may affect rates → uncertain comparability of adverse events rates applied for radical therapies
    - cross-checked rates for surgery and external beam radiotherapy against ProtecT → different results
    - applied rates for surgery and external beam radiotherapy compared to active surveillance from ProtecT (adjusted for baseline)

Adverse event rates (2): company and ERG changes

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

❖ ***Which adverse event rates are more plausible? Company's (Ramsay 2015) or ERG's (ProtecT)?***

Costs overview

- Pre-radical therapy and post-radical therapy health state: based on Ramsay (2015) study adjusted for inflation (2017-18 prices)
  - **ERG comments:** Ramsay (2015) used bottom-up* costings → low compared to Healthcare Resource Group-based reference costs
- Padeliporfin: acquisition and administration in cycle 1 (secondary care costs for physical examinations and nurse consultations); cycle-specific monitoring costs and 2nd padeliporfin treatment
- **Active surveillance: same monitoring cost structure as padeliporfin**
- Post-radical therapy health state: costs of radical therapy and monitoring (some receive adjuvant/salvage therapies)
- Monitoring costs for 3 key adverse events
- Metastasis state: one-off cost of treatment and maintenance
- Death state: one-off cost of end-of-life care

❖ ***Is monitoring with padeliporfin the same as active surveillance? Does this reflect PCM301? Did PCM301 collect costs?***

* 'bottom up' costing = detailed collection of resource use to inform costs

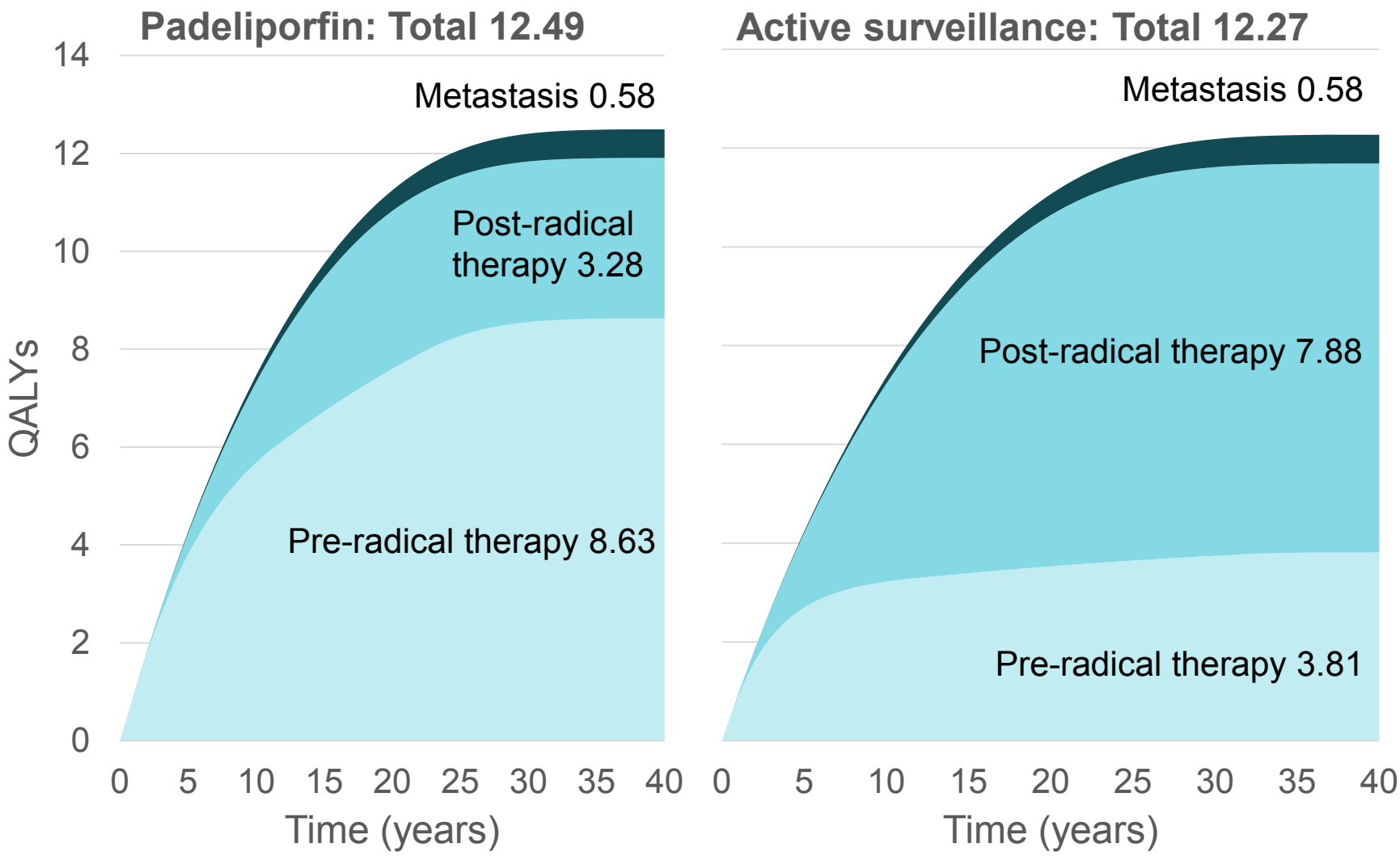
Costs – ERG comments

Costs	ERG comments
Padeliporfin administration costs	Company did not include multi-parametric MRI costs (£343) Company cost procedure as day case but patients in PCM301 stayed overnight (£276)
Adjuvant therapy costs	Company assumed some patients having surgery also have hormone therapy and external beam radiotherapy **ERG:** NICE CG175 does not recommend these treatments for **low risk**
Salvage therapy costs	Company assumed some patients having surgery (16%), external beam radiotherapy (6%) and brachytherapy (12%) also have salvage therapy (treatment to cure cancer after initial therapy does not work) **ERG:** rates based on Ramsay (2015) – unclear if rates are generalisable to PCM301 patients
Bowel dysfunction	Company applied cost on an annual basis **ERG:** original source used mean cost per patient → more suitable to apply as a one-off cost

- ***Should adjuvant therapy costs be included? Did they contribute to results of PCM301?***
- ***Are the proportion of patients having salvage therapy plausible?***

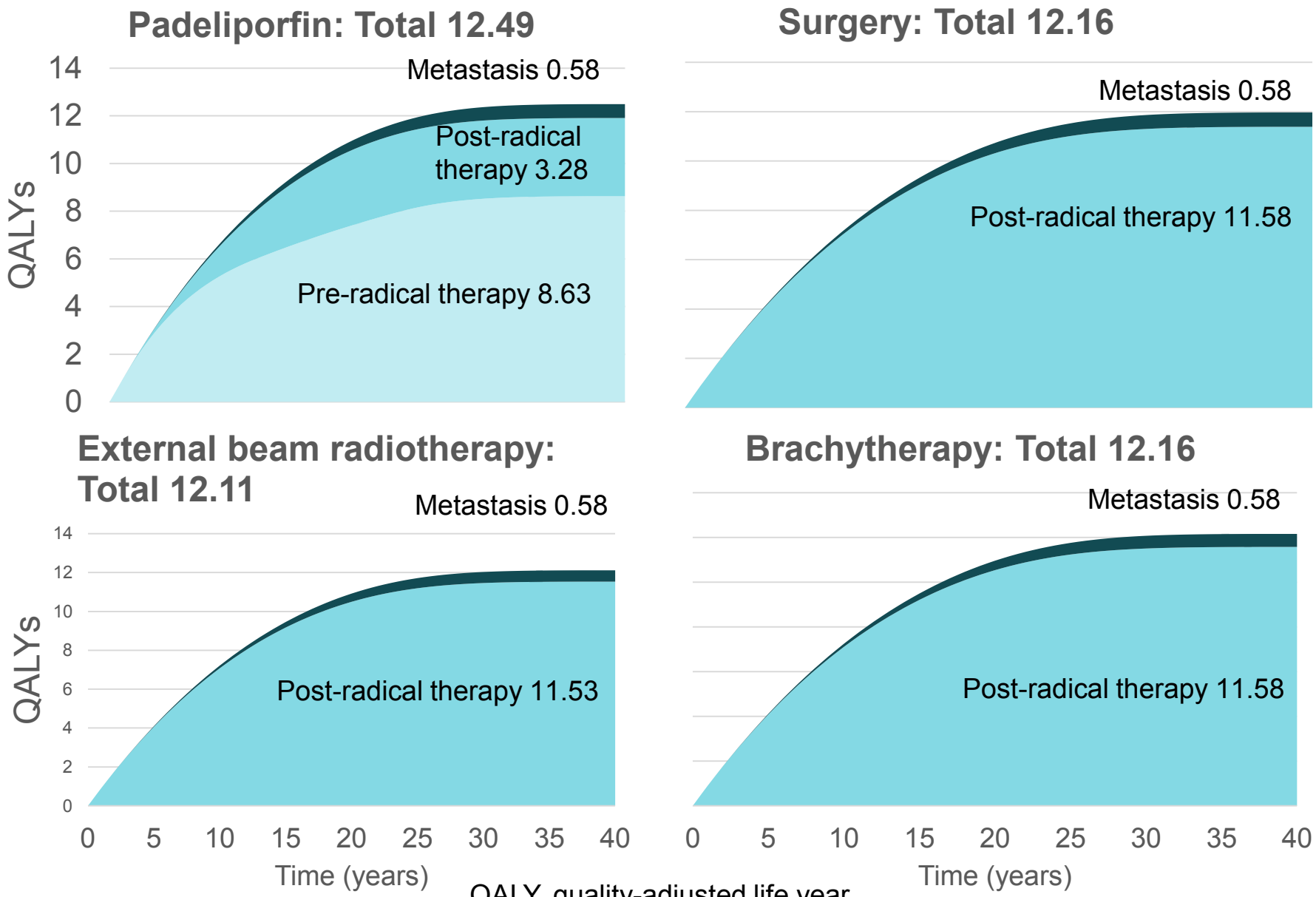
Company's base case: QALYs (1)

All treatments give the same benefit in metastasis health state



QALY, quality-adjusted life year

Company's base case: QALYs (2)



QALY, quality-adjusted life year

Company base case deterministic results – fully incremental analysis with active surveillance and pairwise comparisons against padeliporfin

ICERs are sensitive to adverse event rates and time to radical therapy distribution

If active surveillance is a relevant comparator:

Treatment	Total costs (£)	Total QALYs	ICER (£/QALY)	ICER *vs* padeliporfin (£/QALY)
Active surveillance	16,650	12.27	-	49,415
External beam radiotherapy	17,522	12.11	AS dominates EBRT	26,728
Surgery	19,334	11.97	AS dominates surgery	15,946
Brachytherapy	20,554	12.16	AS dominates brachytherapy	21,533
Padeliporfin	27,652	12.49	**49,415**	**-**

All costs are at list price; company did not submit Patient Access Scheme; AS, active surveillance; EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Company base case deterministic results – fully incremental analysis without active surveillance provided by ERG

If active surveillance is <u>not</u> a relevant comparator:

Treatments	Total costs (£)	Total QALYs	ICER (£/QALY)
External beam radiotherapy	17,522	12.11	-
Surgery	19,334	11.97	EBRT dominates surgery
Brachytherapy	20,554	12.16	EBRT extendedly dominates brachytherapy
Padeliporfin	27,652	12.49	**26,728**

All costs are at list price; company did not submit Patient Access Scheme; EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Blended comparison: 'World with and without padeliporfin' – company's base case results

Treatment	World without padeliporfin	World with padeliporfin
Padeliporfin	0%	[redacted]
Active surveillance	51%	[redacted]
Surgery	25%	[redacted]
External beam radiotherapy	12%	[redacted]
Brachytherapy	12%	[redacted]

Company's base case

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
World without padeliporfin	17,889	12.16	-	-	-
World with padeliporfin	20,263	12.30	2,373	0.14	**17,287**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

❖ ***Which analysis is preferred? Fully incremental analysis with or without active surveillance or 'blended comparison' analysis?***

Scenario analyses ('time to radical therapy' distributions) – deterministic results for pairwise comparison of padeliporfin and active surveillance

Scenarios		Total cost (£)		Total QALYs		ICER
		Padeliporfin	AS	Padeliporfin	AS	
Base case (log-normal distribution)*		27,652	16,650	12.49	12.27	**49,415**
Time to radical therapy distributions*	Log-logistic	28,991	16,518	12.43	12.28	**80,580**
	Weibull	30,905	17,384	12.34	12.23	**125,830**
	Exponential	26,103	15,841	12.56	12.31	**41,617**
Active surveillance time to radical therapy curve based on ProtecT (Weibull)^	Time to radical therapy: padeliporfin relative to ProtecT AS	23,864	11,217	12.65	12.56	**139,042**
Generalized gamma to model time to radical therapy*^	Active surveillance and padeliporfin time to radical therapy curves converge	29,452	14,427	12.40	12.39	**803,382**

*For padeliporfin and active surveillance; ^ERG scenarios; All costs are at list price; company did not submit Patient Access Scheme; AS, active surveillance; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Scenario analyses ('time to radical therapy' distributions) – deterministic results for pairwise comparisons of padeliporfin and radical therapies

Scenarios		ICER vs surgery	ICER vs external beam radiotherapy	ICER vs brachytherapy
Base case (log-normal distributions)*		15,946	26,728	21,533
Time to radical therapy distributions*	Log-logistic	21,101	36,287	31,561
	Weibull	31,753	60,001	59,368
	Exponential	11,394	19,050	13,885
Active surveillance time to radical therapy curve based on ProtecT (Weibull)^	Time to radical therapy: padeliporfin relative to ProtecT active surveillance	6,642	11,757	6,754
Generalized gamma to model time to radical therapy*^	Time to radical therapy curves for active surveillance and padeliporfin converge	23,356	41,054	36,891

*For padeliporfin and active surveillance; ^ERG scenarios; All costs are at list price; company did not submit Patient Access Scheme; AS, active surveillance; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG exploratory analyses

1) Different proportion of patients receiving surgery, external beam radiotherapy and brachytherapy after active surveillance or padeliporfin in each model cycle
2) Adjust time to radical therapy curves on active surveillance and padeliporfin for general population mortality
3) **Reduce utility decrement of bowel dysfunction from 0.16 to 0.1**
4) **Remove costs of adjuvant therapies after radical therapy**
5) **Set bowel dysfunction rate in surgery equal to rate in active surveillance**
6) **Set bowel dysfunction rate in surgery equal to rate in padeliporfin**
7) Use adverse event rates in surgery and external beam radiotherapy from ProtecT
8) Include costs for multi-parametric MRI before giving padeliporfin and active surveillance; £343
9) **Include cost of an overnight stay (£276) for padeliporfin**
10) **Apply cost of treating bowel dysfunction as a one-off to patients experiencing long-term bowel dysfunction**

❖ ***Which scenarios are preferred?***

ERG deterministic results – fully incremental analysis without active surveillance (1)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Company base case					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.14	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.05	Extended dominated
Padeliporfin	27,652	12.492	10,130	0.38	**26,728 (vs EBRT)**
Scenario 1 Recalculating the percentage of patients receiving surgery, EBRT and brachytherapy following active surveillance or padeliporfin in each cycle of the model					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.14	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.05	Extended dominated
Padeliporfin	27,733	12.492	10,211	0.38	**26,942 (vs EBRT)**
Scenario 2 Adjusting the time to radical therapy curves on active surveillance and padeliporfin for general population mortality					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.14	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.05	Extended dominated
Padeliporfin	27,931	12.452	10,409	0.34	**30,673 (vs EBRT)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy

ERG deterministic results – fully incremental analysis without active surveillance (2)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 3 Using bowel disutility value equal to -0.1					
EBRT	17,522	12.250	-	-	-
Surgery	19,334	12.065	1,812	-0.19	Dominated by EBRT
Brachytherapy	20,554	12.249	3,033	-0.001	Dominated by EBRT
Padeliporfin	27,652	12.530	10,130	0.28	**36,195 (vs EBRT)**
Scenario 4 Removing costs of adjuvant EBRT and hormone therapies					
EBRT	17,085	12.113	-	-	-
Surgery	18,242	11.970	1,156	-0.14	Dominated by EBRT
Brachytherapy	20,315	12.162	3,230	0.05	Extended dominated
Padeliporfin	27,248	12.492	10,162	0.38	**26,813 (vs EBRT)**
Scenario 5 Setting bowel dysfunction prevalence of surgery equal to active surveillance (ProtecT)					
Surgery	14,373	12.223	-	-	-
EBRT	17,522	12.113	3,149	-0.11	Dominated by surgery
Brachytherapy	20,554	12.162	6,181	-0.06	Dominated by surgery
Padeliporfin	26,929	12.529	12,555	0.31	**41,036 (vs surgery)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy

ERG deterministic results – fully incremental analysis without active surveillance (3)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 6 Setting bowel dysfunction prevalence of surgery equal to padeliporfin					
Surgery	14,930	12.195	-	-	-
EBRT	17,522	12.113	2,592	-0.08	Dominated by surgery
Brachytherapy	20,554	12.162	5,625	-0.03	Dominated by surgery
Padeliporfin	27,012	12.525	12,083	0.33	**36,612 (vs surgery)**
Scenario 7 Setting the adverse event rates for surgery and EBRT, based on the observed differences compared to active surveillance in ProtecT					
Surgery	12,996	12.479	-	-	-
EBRT	13,590	12.424	594	-0.06	Dominated by surgery
Brachytherapy	20,554	12.162	7,559	-0.32	Dominated by surgery
Padeliporfin	26,455	12.588	13,459	0.11	**124,345 (vs surgery)**
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of active surveillance and padeliporfin					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.14	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.05	Extended dominated
Padeliporfin	28,016	12.492	10,494	0.38	**27,688 (vs EBRT)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy; MRI, magnetic resonance imaging

ERG deterministic results – fully incremental analysis without active surveillance (4)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 9 Adding 1 inpatient excess bed day (£275.59) to padeliporfin treatment cost					
EBRT	17,522	12.113	-	-	-
Surgery	19,334	11.970	1,812	-0.14	Dominated by EBRT
Brachytherapy	20,554	12.162	3,033	0.05	Extended dominated
Padeliporfin	27,944	12.492	10,423	0.38	**27,500 (vs EBRT)**
Scenario 10 Treatment cost of bowel dysfunction as a one-off long term cost					
EBRT	11,817	12.113	-	-	-
Surgery	15,391	11.970	3,574	-0.14	Dominated by EBRT
Brachytherapy	16,956	12.162	5,139	0.05	Extended dominated
Padeliporfin	26,115	12.492	14,299	0.38	**37,727 (vs EBRT)**
Scenario 11 Applying scenarios 3,4,5,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,167	12.223	2,739	-0.03	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,525	12.553	14,097	0.30	**46,544 (vs EBRT)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy; HRG, Healthcare Resource Group

ERG deterministic results – fully incremental analysis without active surveillance (5)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
Scenario 12 Applying scenarios 3,4,6,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,277	12.205	2,848	-0.05	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,542	12.550	14,114	0.30	**47,016 (vs EBRT)**
Scenario 13 Applying scenarios 1,2,3,4,5,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,167	12.223	2,739	-0.03	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,565	12.524	14,137	0.27	**51,543 (vs EBRT)**
Scenario 14 Applying scenarios 1,2,3,4,6,9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
EBRT	12,428	12.250	-	-	-
Surgery	15,277	12.205	2,848	-0.05	Dominated by EBRT
Brachytherapy	16,717	12.249	4,288	-0.001	Dominated by EBRT
Padeliporfin	26,586	12.521	14,158	0.27	**52,235 (vs EBRT)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiation therapy; HRG, Healthcare Resource Group

Innovation

- First focal therapy with clinical trial data
- Unique solution to low-risk prostate cancer: addresses limitations of active surveillance and radical therapy
- Minimally invasive, targeted therapy aimed at area of cancer: preserve normal tissue, control disease progression and preserve quality of life (mainly urinary and erectile function)
- Reduce over-treatment:
  - ~17% low risk → ~49% elect to have radical therapy
  - of 51% choosing active surveillance, 25% to 60% switch to radical therapy within 5 to 10 years (large proportion stop active surveillance even without risk upstaging)

❖ ***Are there any substantial health-related benefits that have not been included in the quality-adjusted life year calculation?***
❖ ***Is padeliporfin a 'step-change' in the management of low-risk prostate cancer?***

Equality issues

- None identified by company or stakeholders

❖ ***Are there any equality issues to consider?***

END OF PART 1

Back-up slides

Ongoing studies

- PCM301 FU5 – extension study of PCM301
  - high drop outs
- ‘In-depth biopsy study’ planned
  - Phase IV study PCM401 – 7 year follow up observational cohort study of unilateral low risk localised prostate cancer treated with TOOKAD vascular targeted photodynamic therapy in clinical practice
  - Assess importance of tumour location in relation to toxicity and oncological outcome
  - Only baseline information in next 12 months
  - Data collection planned at 12 months after TOOKAD
- PCM402 – international registry to assess use of TOOKAD for localised prostate cancer
  - Only collects pre-treatment data

Data sources: PCM301 and ProtecT

- **Time to radical therapy** curves for padeliporfin and active surveillance: based on **PCM301**
- **Time to metastasis** and **Overall survival**: based on **ProtecT** (UK-based trial; low & intermediate risk, few high risk; 10 years)

Baseline characteristics of ProtecT

	Active surveillance (n=545)	Surgery (n=553)	Radiotherapy (n=545)
Mean age, years (SD)	62 (5)	62 (5)	62 (5)
Median PSA, ng/ml (IQR)	4.7 (3.7, 6.7)	4.9 (3.7, 6.7)	4.8 (3.7, 6.7)
PSA 10+ ng/ml (%)	10%	10%	11%
Gleason score 6, n (%)	77%	76%	78%
T1c clinical stage, n (%)	75%	74%	79%
T2 clinical stage, n (%)	25%	26%	21%

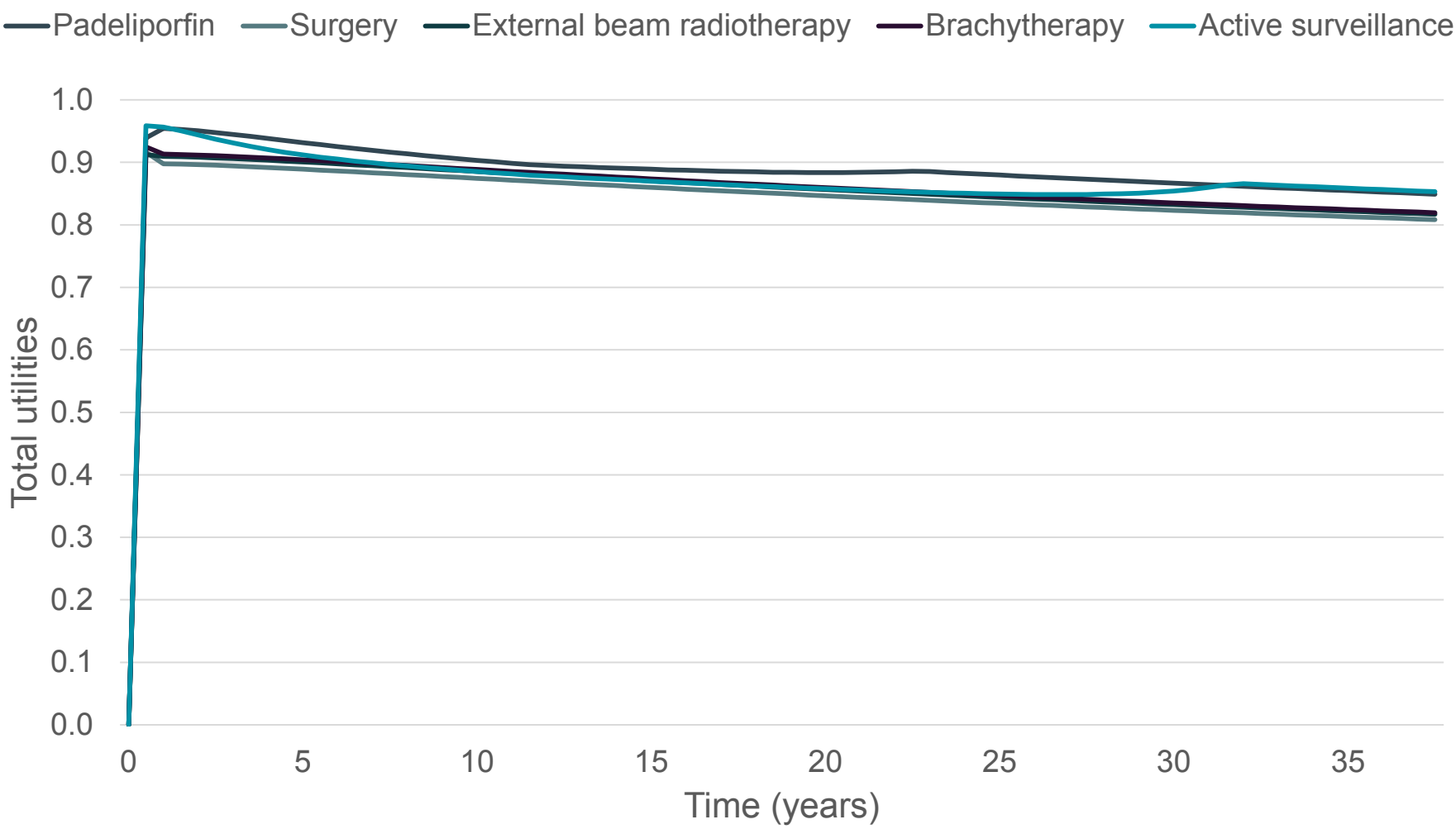
SD, standard deviation; IQR, inter-quartile range; PSA, prostate-specific antigen

Time to metastasis curves

- PIVOT trial (Observation *vs* surgery; 15 year follow up; Wilt 2017)
  - in very-low and low-risk disease, no significant difference in metastatic disease progression between observation and surgery (HR 0.54, 95% CI 0.18 to 1.62)
- Based on these additional data and the differences in populations between PCM301 and ProtecT, company concluded the following for the TTM curves:
  - for radical therapy (surgery, EBRT and brachytherapy), surgery arm of ProtecT is appropriate to describe expected disease progression in a UK, low-risk only population as differences in patient populations do not affect disease progression
  - for active surveillance (and padeliporfin), surgery arm of ProtecT is appropriate to describe expected disease progression in a UK, low-risk only population, taking into account the impact of excluding intermediate-risk patients on disease progression
- UK clinician agreed that radical therapy would have a similar effect on progression among patients with low risk and intermediate risk disease but patients on active surveillance with low risk *vs* intermediate risk would have different risk progression as no treatment is involved

Company's base case – total utility values

Patients start with same baseline utility of 0.88



Active surveillance resource use

Year	Resource inputs	NICE CG175 Multi-parametric MRI at start
1	• 4 nurse-led outpatient appointments • 4 PSA tests • 1 DRE • 1 MDT meeting	• 3-4 PSA tests • 1-2 DRE • 1 rebiopsy
2	• 1 biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2-4 PSA tests • 1-2 DRE
3	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2-4 PSA tests • 1-2 DRE
4	• 1 biopsy • 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2-4 PSA tests • 1-2 DRE
5	• 2 nurse-led outpatient appointments • 2 PSA tests • 1 DRE	• 2 PSA tests • 1 DRE
Annually thereafter	• 1 practice nurse appointment • 1 PSA test • 1 DRE	• 2 PSA tests • 1 DRE

PSA, prostate-specific antigen; DRE, digital rectal examination; MDT, multidisciplinary team; Source: Ramsay (2015)

Company's original base case and ERG's adjustment for general population all-cause mortality deterministic results – fully incremental analysis without active surveillance

Company's original base case model (before clarification): assumed that active surveillance and padeliporfin follow higher rate of progression to metastasis (active surveillance arm in ProtecT). After clarification, company assumed all treatments have equal time to metastasis and overall survival.

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
EBRT	16,999	11.340	-	-	-
Surgery	18,752	11.185	1,754	-0.155	Dominated by EBRT
Brachytherapy	19,871	11.393	2,873	0.053	Extended dominated
Padeliporfin	26,714	11.643	9,715	0.303	**32,082**

ERG's revision of company's original base case model – adjusted for general population all-cause mortality

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER * (£/QALY)
EBRT	17,522	11.089	-	-	-
Surgery	19,334	10.947	1,812	-0.143	Dominated by EBRT
Brachytherapy	20,554	11.139	3,033	0.049	61,372
Padeliporfin	27,621	11.083	7,067	-0.056	**Dominated by Brachytherapy**

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

World with and without padeliporfin

- Overall cost effectiveness: ICER of a population where padeliporfin is an option *vs* not

	Proportion of people having		
	Active surveillance	**Surgery**	**Radical radiotherapy**
Newly diagnosed low risk <60 years*	55.9%	27.3%	16.8%
Newly diagnosed low risk 60 – 69 years*	63.7%	16.6%	19.7%
'Indication' population <60 years^	14.8%	17.9%	7.4%
'Indication' population 60-69 years^	22.6%	7.1%	10.3%
Overall market share	51%	25%	24% (12% EBRT, 12% brachytherapy)

*Based on Greenberg (2015), adjusted by the company to exclude people who may have had hormone therapy (4.3%) and reallocated to the 3 treatment options; ^PCM301 distribution: 40% unilateral low risk ('indication' population), 37% unilateral very low risk, 23% bilateral low risk

ERG's exploratory analyses – world with and without padeliporfin (1)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1 recalculating the percentage of patients receiving surgery, EBRT and brachytherapy following active surveillance or padeliporfin in each cycle of the model					
World without padeliporfin	17,930	12.163	-	-	-
World with padeliporfin	20,327	12.301	2,398	0.137	**17,465**
Scenario 2 Adjusting the time to radical therapy curves on active surveillance and padeliporfin for general population mortality					
World without padeliporfin	17,855	12.157	-	-	-
World with padeliporfin	20,312	12.282	2,457	0.125	**19,596**
Scenario 3 Using bowel disutility value equal to -0.1					
World without padeliporfin	17,889	12.250	-	-	-
World with padeliporfin	20,263	12.371	2,373	0.121	**19,616**

All costs are at list price; company did not submit Patient Access Scheme

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG's exploratory analyses – world with and without padeliporfin (2)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 4 Removing costs of adjuvant EBRT and hormone therapies					
World without padeliporfin	17,218	12.163	-	-	-
World with padeliporfin	19,712	12.301	2,494	0.137	**18,170**
Scenario 5 Setting bowel dysfunction prevalence of surgery equal to active surveillance (ProtecT)					
World without padeliporfin	15,752	12.272	-	-	-
World with padeliporfin	18,901	12.370	3,148	0.098	**32,183**
Scenario 6 Setting bowel dysfunction prevalence of surgery equal to padeliporfin					
World without padeliporfin	16,000	12.259	-	-	-
World with padeliporfin	19,059	12.362	3,059	0.102	**29,885**

All costs are at list price; company did not submit Patient Access Scheme

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG's exploratory analyses – world with and without padeliporfin (3)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 7 Setting the adverse event rates for surgery and EBRT, based on the observed differences compared with active surveillance in ProtecT					
World without padeliporfin	14,355	12.446	-	-	-
World with padeliporfin	17,637	12.510	3,282	0.064	**51,157**
Scenario 8 Adding one-off cost of a pre-treatment multiparametric MRI scan to the cost of active surveillance and padeliporfin					
World without padeliporfin	18,056	12.163	-	-	-
World with padeliporfin	20,538	12.301	2,482	0.137	**18,082**
Scenario 9 Adding a weighted average cost of an inpatient excess bed day (£275.59) to the treatment cost of padeliporfin					
World without padeliporfin	17,889	12.163	-	-	-
World with padeliporfin	20,350	12.301	2,461	0.137	**17,927**

All costs are at list price; company did not submit Patient Access Scheme

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG's exploratory analyses – world with and without padeliporfin (4)

Treatments	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 10 Applying cost of bowel dysfunction as a one-off long term cost					
World without padeliporfin	14,284	12.163	-	-	-
World with padeliporfin	17,345	12.301	3,061	0.137	**22,297**
Scenario 11 Applying scenarios 3, 4, 5, 9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
World without padeliporfin	14,309	12.318			
World with padeliporfin	17,561	12.414	3,252	0.096	**33,763**
Scenario 12 Applying scenarios 3, 4, 6, 9 and 10 simultaneously and using a weighted average of HRG cost for surgery and EBRT					
World without padeliporfin	14,356	12.310			
World with padeliporfin	17,592	12.409	3,236	0.099	**32,661**

All costs are at list price; company did not submit Patient Access Scheme

EBRT, external beam radiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ERG deterministic results – fully incremental analysis with active surveillance (1)

Treatments	Total costs (£)	Total QALYs	ICER* (£/QALY)
Scenario 1: Different proportion of patients receiving surgery, EBRT and brachytherapy following active surveillance or padeliporfin in each cycle of the model			
Active surveillance (AS)	16,729	12.269	-
External beam radiotherapy (EBRT)	17,522	12.113	Dominated by AS
Surgery	19,334	11.970	Dominated by AS
Brachytherapy	20,554	12.162	Dominated by AS
Padeliporfin	27,733	12.492	**49,424 (vs AS)**
Scenario 2: Adjust time to radical therapy curves on active surveillance and padeliporfin for general population mortality			
Active surveillance	16,583	12.257	-
External beam radiotherapy	17,522	12.113	Dominated by AS
Surgery	19,334	11.970	Dominated by AS
Brachytherapy	20,554	12.162	Dominated by AS
Padeliporfin	27,931	12.452	**57,931 (vs AS)**
Scenario 3: Reduce utility decrement of bowel dysfunction from 0.16 to 0.1			
Active surveillance	16,650	12.340	-
External beam radiotherapy	17,522	12.250	Dominated by AS
Surgery	19,334	12.065	Dominated by AS
Brachytherapy	20,554	12.249	Dominated by AS
Padeliporfin	27,652	12.530	**58,047 (vs AS)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

ERG deterministic results – fully incremental analysis with active surveillance (2)

Treatments	Total costs (£)	Total QALYs	ICER* (£/QALY)
Scenario 4: Remove costs of adjuvant therapies following radical therapy			
Active surveillance (AS)	16,029	12.269	-
External beam radiotherapy	17,085	12.113	Dominated by AS
Surgery	18,242	11.970	Dominated by AS
Brachytherapy	20,315	12.162	Dominated by AS
Padeliporfin	27,248	12.492	**50,387 (vs AS)**
Scenario 5: Set bowel dysfunction rate in surgery equal to rate in active surveillance			
Surgery	14,373	12.223	-
Active surveillance	14,901	12.358	3,897
External beam radiotherapy	17,522	12.113	Dominated by AS
Brachytherapy	20,554	12.162	Dominated by AS
Padeliporfin	26,929	12.529	**70,562 (vs AS)**
Scenario 6: Set bowel dysfunction rate in surgery equal to rate in padeliporfin			
Surgery	14,930	12.195	-
Active surveillance	15,097	12.348	1,085
External beam radiotherapy	17,522	12.113	Dominated by AS
Brachytherapy	20,554	12.162	Dominated by AS
Padeliporfin	27,012	12.525	**67,651 (vs AS)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

ERG deterministic results – fully incremental analysis with active surveillance (3)

Treatments	Total costs (£)	Total QALYs	ICER* (£/QALY)
Scenario 7: Use adverse event rates in surgery and EBRT from ProtecT			
Surgery	12,996	12.479	-
External beam radiotherapy (EBRT)	13,590	12.424	Dominated by surgery
Active surveillance (AS)	13,758	12.501	35,340
Brachytherapy	20,554	12.162	Dominated by surgery & AS
Padeliporfin	26,455	12.588	**146,498 (vs AS & surgery)**
Scenario 8: Include costs for multi-parametric MRI for padeliporfin and AS; £343.42			
Active surveillance	16,975	12.269	-
External beam radiotherapy	17,522	12.113	Dominated by AS
Surgery	19,334	11.970	Dominated by AS
Brachytherapy	20,554	12.162	Dominated by AS
Padeliporfin	28,016	12.492	**49,588 (vs AS)**
Scenario 9: Include cost of an overnight stay (£275.59) in padeliporfin			
External beam radiotherapy	16,650	12.269	-
Active surveillance	17,522	12.113	Dominated by AS
Surgery	19,334	11.970	Dominated by AS
Brachytherapy	20,554	12.162	Dominated by AS
Padeliporfin	27,944	12.492	**50,730 (vs AS)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

ERG deterministic results – fully incremental analysis with active surveillance (4)

Treatments	Total costs (£)	Total QALYs	ICER* (£/QALY)
Scenario 10: Apply cost of treating bowel dysfunction as a one-off cost			
External beam radiotherapy	11,817	12.113	-
Active surveillance (AS)	13,696	12.269	12,019
Surgery	15,391	11.970	Dominated by AS
Brachytherapy	16,956	12.162	Dominated by AS
Padeliporfin	26,115	12.492	**55,782 (vs AS)**
Scenario 11: Apply scenarios 3, 4, 5, 9 and 10 simultaneously and using a weighted average of HRG cost for surgery and external beam radiotherapy			
External beam radiotherapy	12,428	12.250	-
Active surveillance	13,767	12.396	9,176
Surgery	15,167	12.223	Dominated by AS
Brachytherapy	16,717	12.249	Dominated by AS
Padeliporfin	26,525	12.553	**81,304 (vs AS)**
Scenario 12 Applying scenarios 3, 4, 6, 9 and 10 simultaneously and using a weighted average of HRG cost for surgery and external beam radiotherapy			
External beam radiotherapy	12,428	12.250	-
Active surveillance	13,805	12.389	9,882
Surgery	15,277	12.205	Dominated by AS
Brachytherapy	16,717	12.249	Dominated by AS
Padeliporfin	26,542	12.550	**79,376 (vs AS)**

All costs are at list price; company did not submit Patient Access Scheme; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; HRG, Healthcare Resource Group