NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Padeliporfin for treating localised prostate cancer [ID866]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document** from the company:
   - Response to the ACD
   - Additional evidence
   -

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - the Royal College of Physicians on behalf of the NCRI/RCP/RCR/ACP
   - NHS England
     the Department of Health and Social Care stated that they had no comments

4. **Evidence Review Group critique of additional evidence**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Padeliporfin for treating localised prostate cancer [ID866]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee / Commentator	National Cancer Research Institute / Royal College of Physicians / Royal College of Radiologists / Association of Cancer Physicians	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. Our rationale for this is as follows: First, the radical treatment of low risk prostate cancer has been shown to have no cancer-specific or overall survival difference at 10 years in large randomised controlled trials in which the control has been watchful waiting or active monitoring. These studies, PIVOT and PROTECT, involved a lesser strategy of follow-up that did not involve the intense clinical and biopsy monitoring of active surveillance in the current era. Second, large prospective series have confirmed that active surveillance has extremely low mortality rates in the medium to long term. Third, whilst these series have shown transition to treatment of one-third to one-half of patients approximately, it is well accepted that this is on the whole due to mis-classification of disease risk at baseline transrectal systematic biopsy rather than progression. Therefore, the term progression to higher grade disease or higher volume of disease is on the whole due to such higher risk being missed at baseline biopsy and being found on subsequent repeat biopsy. It is therefore a correction of a miss-classification error rather than 'progression' in the manner in which we regard it. Fourth, as a result, the endpoint used in the RCT assessing padeliporfin compared to active surveillance is not a biological progression on the whole and therefore should be viewed with caution if the intervention reduces this endpoint which has no proven correlation to longer term survival. Fifth, the manner in which the many physicians tried to overcome the miss-classification error of transeptal systematic biopsies during the duration of this study was to include a confirmatory biopsy prior to active surveillance. In the NICE Clinical Guidance, there is also a pre-requisite to include multi-parametric MRI (mpMRI). 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.	Comments noted. Comments incorporated in sections 3.1, 3.2, 3.4, 3.7, 3.8, 3.9 and 3.12 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Sixth, over the last 5 years, the diagnostic pathway has changed. In the UK particularly, pre-biopsy mpMRI for all men with an elevated PSA as the initial diagnostic test followed by MRI-targeted biopsy means that the miss-classification error of the traditional transrectal systematic ('blind') biopsy is almost the norm in most units. NHS England have issued guidance to all regions and Trusts to bring in this diagnostic pathway. 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. In other words, as mpMRI before biopsy can identify 90% of significant cancers compared to approximately 50% by transrectal biopsy alone, men with low risk disease should have true low risk disease in 90% of the cases. In the current era of men diagnosed with a pre-biopsy mpMRI followed by targeted and systematic biopsies, 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. Lastly, there have been significant in-roads internationally with increasing proportions of men entering a programme of active surveillance rather than active treatment. This has been due to the recognition that any treatment in this group of men would confer some harm and no cancer control benefit. The mpMRI pathway will aid this further. The adage that only anxiety is being treated is correct when it comes to this group. 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 eligible for such a strategy. This would be an unacceptable regressive step in the field of prostate cancer. We would be happy to clarify any specific issues.	
2	Consultee	NHS England	1. These comments have been drawn up by [redacted] NHS England's Clinical Expert Group for prostate cancer. 2. [redacted] the NHS England Clinical Expert Group and the NCRI Prostate CSG agree with the NICE ACD conclusion that padeliporfin for low risk prostate cancer should not be recommended. 3. [redacted] was asked as to which focal therapies are used for localised prostate cancer. Currently under NICE Interventional Procedures Guidance IPG424 (high intensity focused ultrasound, HIFU) and IPG423 (cryoablation) and in certain centres which meet the requirements of the IPG guidelines , focal HIFU and cryotherapy are carried out. The UK Focal Therapy Users Group ([redacted]) has issued guidance to its members and users that 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 (ie use of focal therapies is mainly in intermediate risk patients). This is 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	Comments noted. Comments incorporated in sections 3.2 and 3.3 of the final appraisal document.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			disease. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, Bottomley D, Eggener S, Ehdaie B, Emberton M, Hindley R, Leslie T, Miners A, McCartan N, Moore CM, Pinto P, Polascik TJ, Simmons L, van der Meulen J, Villers A, Willis S, Ahmed HU. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol. 2015 Apr;67(4):771-7. doi: 10.1016/j.eururo.2014.09.018. 4. The majority (90%) of men treated with focal therapy historically in the UK are of intermediate and high risk. Of the 10% treated who are low risk, these cases are now uncommonly/rarely treated in the UK and are therefore mainly historical. There are occasionally exceptional cases in which some men with high volume Gleason 6 prostate cancer (>/=6mm of cancer on biopsy) are sometimes treated with focal therapy (these men generally would not be suitable for active surveillance either) or rarely in cases of strong patient refusal of active surveillance. 5. [redacted] was also asked as to how people with low-risk prostate cancer with and without disease progression are treated in NHS clinical practice. 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 (NPCA). "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 in this area of prostate cancer therapy." Quote from NPCA 2017 https://www.npca.org.uk/reports/npca-annual-report-2017/. This reassuring trend is as a result of: a) greater confidence in the attribution of a low risk status from MRI/targeted biopsies and transperineal saturation/mapping biopsies, b) long follow-up case series from Canada in which only transrectal systematic (inaccurate) biopsies were used and still show active surveillance has an extremely low risk of mortality (1.5% cancer-specific mortality and 2.8% metastases at median follow-up 6.4 years in 819 patients; Klotz et al, 2015), and c) the recent data from the PIVOT and PROTECT RCTs showing no benefit in treating low risk prostate cancer at 10 years follow-up compared to radical radiotherapy or radical prostatectomy.	
3	Consultee	Steba Biotech	We appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for the above appraisal. We have, via a separate document, and with the agreement of NICE, submitted additional analyses to address the uncertainties and questions raised by the Appraisal Committee. We have also clarified the position of padeliporfin in the treatment pathway, and highlighted the clinical benefits to the patient and economic value for the NHS. Our responses to the questions specified above are provided below:	Comments noted. Comments incorporated in sections 3.4, 3.10 and 3.11 of the final appraisal document.
4	Consultee	Steba Biotech	**Has all of the relevant evidence been taken into account?** We agree that all the relevant information has been taken into account.	Comments noted. No action required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
5	Consultee	Steba Biotech	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries are reasonable interpretations, and as stated above, we have submitted additional analyses to address the points raised by the Appraisal Committee, and clarified the position of padeliporfin in the treatment pathway along with its clinical benefit to the patient and economic value for the NHS. It is important to note that none of the comparators included in the appraisal have been assessed via the NICE appraisal process. Padeliporfin is the first technology for untreated localised prostate cancer to be formally assessed via the NICE appraisal process.	Comments noted. Comments incorporated in sections 3.4, 3.10 and 3.11 of the final appraisal document. The committee concluded that the relevant comparators are radical therapies because they are established practice in the NHS. See section 3.5 of the final appraisal document.
6	Consultee	Steba Biotech	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS**? We are disappointed that the provisional recommendations do not recommend padeliporfin for the treatment of localised prostate cancer. We believe that the additional analysis provided will reassure the Committee that padeliporfin is cost-effective when compared with radical prostatectomy and brachytherapy and can be recommended for use following the second Appraisal Committee meeting. Padeliporfin will provide patients and clinicians with an additional treatment option, the first pharmacological one in this disease setting. Based on the additional analysis provided padeliporfin could be offered • as alternative to radical prostatectomy and brachytherapy • to patients who refuse treatment with EBRT or are contraindicated for EBRT. in a specific group of patients: those who meet the indication criteria (unilateral low risk but not very low risk, based on 12-core TRUS biopsy), have been offered active surveillance and who want to proceed with an active treatment either at diagnosis or after an initial period on active surveillance. These patients are easily identifiable in clinical practice and would get a meaningful and significant clinical benefit by being offered padeliporfin. We believe that the additional analysis provided will reassure the Committee that padeliporfin cost-effective when compared with radical prostatectomy and brachytherapy and can be recommended for use in the above patients following the second Appraisal Committee meeting.	Comments noted. The committee concluded that the revised economic model is not suitable for decision-making for a comparison of padeliporfin with radical therapies. See section 3.12 of the final appraisal document.

The following consultees/commentators indicated that they had no comments on the Appraisal Consultation Document

Department of Health and Social Care

Padeliporfin for untreated localised prostate cancer [ID866]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 23 July 2018
email: TACommB@nice.org.uk/NICE DOCS

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

Comment number	**Comments** Insert each comment in a new row.

Please return using NICE Docs

Padeliporfin for untreated localised prostate cancer [ID866]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 23 July 2018
email: TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for the above appraisal. We have, via a separate document, and with the agreement of NICE, submitted additional analyses to address the uncertainties and questions raised by the Appraisal Committee. We have also clarified the position of padeliporfin in the treatment pathway, and highlighted the clinical benefits to the patient and economic value for the NHS. Our responses to the questions specified above are provided below:
2	**Has all of the relevant evidence been taken into account?** We agree that all the relevant information has been taken into account.
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries are reasonable interpretations, and as stated above, we have submitted additional analyses to address the points raised by the Appraisal Committee, and clarified the position of padeliporfin in the treatment pathway along with its clinical benefit to the patient and economic value for the NHS. It is important to note that none of the comparators included in the appraisal have been assessed via the NICE appraisal process. Padeliporfin is the first technology for untreated localised prostate cancer to be formally assessed via the NICE appraisal process.
4	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS**? We are disappointed that the provisional recommendations do not recommend padeliporfin for the treatment of localised prostate cancer. We believe that the additional analysis provided will reassure the Committee that padeliporfin is cost-effective when compared with radical prostatectomy and brachytherapy and can be recommended for use following the second Appraisal Committee meeting. Padeliporfin will provide patients and clinicians with an additional treatment option, the first pharmacological one in this disease setting. Based on the additional analysis provided padeliporfin could be offered • as alternative to radical prostatectomy and brachytherapy • to patients who refuse treatment with EBRT or are contraindicated for EBRT. in a specific group of patients: those who meet the indication criteria (unilateral low risk but not very low risk, based on 12-core TRUS biopsy), have been offered active surveillance and who want to proceed with an active treatment either at diagnosis or after an initial period on active surveillance. These patients are easily identifiable in clinical practice and would get a meaningful and

	significant clinical benefit by being offered padeliporfin. We believe that the additional analysis provided will reassure the Committee that padeliporfin cost-effective when compared with radical prostatectomy and brachytherapy and can be recommended for use in the above patients following the second Appraisal Committee meeting .

Insert extra rows as needed

Checklist for submitting comments

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

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

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

Steba Biotech© – Response to ACD consultation – 23 July 2018

ID866 – Padeliporfin for treating localised prostate cancer

We appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for the above appraisal, and to submit additional evidence to address the uncertainties and questions raised by the Appraisal Committee. We believe that this additional evidence will reassure the Appraisal Committee that padeliporfin is cost-effective and can be recommended for use following the second Appraisal Committee meeting.

Executive summary

In summary, in addressing the points raised by the Appraisal Committee, we have:

- Clarified the position of padeliporfin in the treatment pathway and its clinical benefit to the patient (ACD Sections 3.4, 3.5, 3.7, and 3.10)
- Revised the economic model as follows:
    - Removed active surveillance as a comparator in line with ACD Section 3.4.
    - Incorporated adverse event (AE) data from ProtecT study (ACD Section 3.14).
        - Applied the urinary incontinence and erectile dysfunction rates from ProtecT for external beam radiotherapy (EBRT) and for radical prostatectomy.
        - Applied the bowel dysfunction rates from ProtecT for EBRT and assumed bowel dysfunction rates to be equivalent to the one of padeliporfin, based on clinical plausibility.
    - Adjusted the ‘time to metastasis’, and ‘overall survival’ curve for general population mortality (ACD section 3.16).
    - Taken the general population mortality into consideration for ‘time to radical therapy’ by defining any death as events (ACD section 3.16).
    - Applied the ‘time to radical therapy’ from ProtecT for active surveillance as the baseline and estimated the curve for padeliporfin relative to this baseline based on the data from PCM 301 (ACD section 3.17 and as per answer to the ERG clarification question B4 – 04 April 2018)

- Updated the model to include disutility value of -0.1 for bowel dysfunction (ACD Section 3.18).
- Applied the bowel dysfunction management cost from Hummel et al. once only (ACD Section 3.19)
- Incorporated the cost of multiparametric MRI (£343) to padeliporfin and active surveillance (ACD Section 3.19).
    - The cost of multiparametric MRI was also applied for the radical therapies for consistency.
- In addition to the above we have incorporated the HRG costs for racial prostatectomy and EBRT (recommended by ERG in their report, Page 112, Section 5.3.2)
- Explained how wastage in the padeliporfin was already applied in the model (ACD Section 3.19).

- Applied a revised patient access scheme (PAS) of [redacted]

The ICERs for the revised base case based on ProtecT AE data and 'time to radical therapy' curve (Weibull distribution for active surveillance and lognormal distribution for padeliporfin), demonstrate that padeliporfin is a cost-effective treatment when compared with radical prostatectomy (£22,831) and brachytherapy (£9,807). When compared with EBRT the ICER is £48,841. It is important to note that none of the comparators included in the appraisal have been assessed via the NICE appraisal process. Padeliporfin is the first technology for untreated localised prostate cancer to be formally assessed via the NICE appraisal process.

Padeliporfin will provide patients and clinicians with an additional treatment option, the first pharmacological one in this disease setting. Based on the additional analysis padeliporfin could be offered

- as alternative to radical prostatectomy and brachytherapy
- to patients who refuse treatment with EBRT or are contraindicated for EBRT.

in a specific group of patients: those who meet the indication criteria (unilateral low risk but not very low risk, based on 12-core TRUS biopsy), have been offered active surveillance and

who want to proceed with an active treatment either at diagnosis or after an initial period on active surveillance.

In addition to the base case, the following scenario analyses were performed (holding everything else equal to the base case above), with padeliporfin demonstrating to be cost-effective in each scenario compared with radical prostatectomy and brachytherapy (Table 1).

We believe that the additional analysis provided will reassure the Appraisal Committee that padeliporfin cost-effective when compared with radical prostatectomy and brachytherapy and can be recommended for use in the above patients following the second Appraisal Committee meeting.

Table 1: Deterministic analyses results for revised base case and scenarios

	Description	ICER (Cost/QALY) padeliporfin vs. radical prostatectomy	ICER (Cost/QALY) padeliporfin vs. brachytherapy	ICER (Cost/QALY) padeliporfin vs. EBRT
Revised base case	AS TTRT = Weibull, padeliporfin TTRT = lognormal	£22,831	£9,807	£48,841
Additional scenarios (changes made upon the revised base case)				
	AS TTRT = Weibull, padeliporfin TTRT = exponential	£22,805	£9,691	£49,206
	AS TTRT = Weibull, padeliporfin TTRT = Weibull	£25,657	£11,447	£52,803
	AS TTRT = Weibull, padeliporfin TTRT = loglogistic	£27,605	£12,518	£55,727
	AS TTRT = lognormal (second best fit), padeliporfin TTRT = lognormal	£21,821	£9,166	£47,637
	AS TTRT = lognormal (second best fit), padeliporfin TTRT =exponential	£22,706	£9,592	£49,230
	AS TTRT = lognormal (second best fit), padeliporfin TTRT =Weibull	£24,479	£10,766	£51,150
	AS TTRT = lognormal (second best fit), padeliporfin = loglogistic	£25,848	£11,544	£53,119
BD disutility	Age-adjusted multiplier for bowel dysfunction	£22,809	£10,477	£54,874
BD cost	Hummel 2010 data - annual cost	£22,993	£701	£32,898
AE data source	Ramsay AE prevalence + TTRT from PCM 301 only	£14,027	£24,349	£39,049
	ProtecT AE prevalence + TTRT from PCM 301 only	£65,958	£17,765	£113,214
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; AE, adverse event; TTRT, time to radical therapy; BD, bowel dysfunction.				

Section 1: Clarification on the position of padeliporfin in the treatment pathway and its clinical benefit to the patient

In response to the comments in sections 3.4, 3.5, 3.7, and 3.10 of the ACD we would like to clarify the patient population which should be offered and who will benefit from such padeliporfin. In particular it we would like to confirm:

- How patients can be identified for treatment within current clinical practice
- The clinical benefits required for a new treatment option in low-risk prostate cancer and the data available from padeliporfin VTP to support these
- Identification of a subgroup of low-risk patients who would benefit from padeliporfin VTP

Section 1.1: Identification of patients for treatment with padeliporfin

Padeliporfin is indicated as monotherapy for patients with unilateral low risk, but not very low risk disease, where:

- Low risk is defined as Gleason score ≤6 and PSA ≤10ng/mL and clinical stage T1 or T2a
- Very low risk is defined as low risk with the additional following criteria: maximum 2 positive cores and maximum 50% cancer involvement in any core and PSA density<0.15ng/ml/cm3

The pivotal Phase III padeliporfin study (PCM301) recruited patients based on the results of a 12-core transrectal ultrasound (TRUS) guided biopsy, which is the current recommended technique in the NICE guideline 'Prostate cancer: diagnosis and management' (CG175, published on January 2014 – Section 1.2.4) and the standard biopsy technique at the time of the study. As noted by the clinical experts (ACD Section 3.1) , practice is currently evolving towards diagnosis based on MRI-targeted biopsy, which is more sensitive and more specific.

It is important to note that while practice is still evolving:

- It is not yet universally adopted in the NHS, hence centers are still using and relying on 12-core TRUS biopsy to diagnose patients
- In centers which have adopted MRI-targeted biopsy patients with suspicious lesions detected on MRI who move to biopsy typically receive: a 12-core TRUS biopsy and additional biopsy of each suspicious lesion.

With clinical practice still evolving it is anticipated that patients eligible for treatment with padeliporfin will continue to be identified based on their 12-core TRUS biopsy results and their eligibility to padeliporfin will therefore be evaluated in the same way it was in the pivotal Phase III study (PCM301).

Section 1.2: The clinical benefits required for a new treatment option in low-risk prostate cancer and the data available from padeliporfin to support these

For patients with low-risk disease based on diagnosis using 12-core TRUS biopsy, the NICE clinical guideline recommends to *"offer active surveillance as an option to men with low-risk localised prostate cancer for whom radical prostatectomy or radical radiotherapy is suitable"* (CG175 – Section 1.3.7) and *"the decision to proceed from an active surveillance regimen to radical treatment should be made in the light of the individual man's personal preferences, comorbidities and life expectancy"* (CG175 – Section 1.3.9). These recommendations are in line with evolution of the medical practice over the last 10-15 years, which via active surveillance aim to avoid or delaying the use of radical therapies and their associated morbidities in men with low-risk prostate cancer.

More specifically, the Appraisal Committee for Medicinal Products for Human Use (CHMP) guidelines[1] on the evaluation of anticancer medicinal products (EMA/CHMP/703715/2012 Rev. 2 – 17 Dec 2015), identify the following three key benefits expected/required for new therapies in low-risk prostate cancer:

- Anti-tumour activity
- Reduction in the need for radical therapy
- Preservation of genitourinary function

Padeliporfin has proven benefits for each of these categories.

Anti-Tumour Activity

Padeliporfin has demonstrated that in its indication population, 65% of patients had a negative biopsy in the treated lobe and 45% of patients had negative biopsy in both lobes at 2 years (Table 3, Section A.7.1 in Form A of the original submission to NICE). Additionally, 90% of patients had absence of disease progression at 2 years (based on Gleason score upgrading, increase in tumour volume, PSA increase, or advanced disease). Both results where highly significant in comparison to the active surveillance group, as expected. These results cannot be compared even indirectly to anti-tumour activity of radical therapies, as this outcome is measured through biochemical recurrence rather than biopsy (biopsy is not possible after prostatectomy). However, based on biochemical recurrence studies have reported 3-year biochemical disease-free survival of 87% after radical prostatectomy and 95% after radiotherapy.[2] While limitations described above don't allow for true comparison of these results of radical therapy and radical prostatectomy with padeliporfin, clinical experts consulted by the company believe that the 2 vs. 3-year reporting it likely to have limited impact on results. In addition, they see biochemical recurrence after radical prostatectomy or radical therapy as a more severe form of progression than some of the events included in the endpoint for padeliporfin (e.g., progression to GS 3+4 or to more than 3 positive cores or to maximum cancer core length greater than 5mm).

Reduction in the need for radical therapy

A 29% absolute risk reduction has been reported at 4 years after padeliporfin in comparison to upfront management with active surveillance (28% vs 57%) (Page 45, Table 17,Section B.2.6, Form B). Here, the relative benefit of padeliporfin compared to upfront management with radical therapy can be evaluated de facto: as the conversion rate to radical therapy was 28% at 4 years, vs 100% for upfront radical therapy, ie, a 72% absolute risk reduction (Page 45, Section B.2.6, Form B).

Preservation of genitourinary function

Over a 4-year period compared to patients initially managed with active surveillance padeliporfin leads to a statistically significant reduction in time with erectile dysfunction (32% reduction) and with urinary incontinence (63% reduction) (Section A.7.5, Form A). While an indirect comparison with patients receiving upfront radical therapy could not be conducted, it can be assumed that padeliporfin is superior on the outcome of erectile dysfunction and urinary incontinence, given the multiple reports of genitourinary toxicities after radical

therapy, including the ProtecT study.[3] The avoidance of these toxicities is at the core of the active surveillance and padeliporfin strategies.

Based on this evidence, multiple clinical experts including experts from the UK, consulted by the company perceive that in its approved indication padeliporfin offers an attractive alternative to radical therapies for the treatment of low-risk prostate cancer.

Section 1.3: Identification of patients for treatment with padeliporfin

In clinical practice the clinical experts consulted by the company believe it is clinically relevant to offer padeliporfin to low-risk patients who:

- meet the indication criteria of padeliporfin (i.e. unilateral low risk but not very low risk, based on results of 12-core TRUS biopsy)
- have been offered active surveillance and want to proceed with an active treatment either at diagnosis or after an initial period on active surveillance

Based on recently published evidence, that there is still a significant burden of over-treatment with radical therapies among men with low-risk prostate cancer

- *At diagnosis:* a UK study has shown that in 2010 while ~70% of very low-risk and low-risk patients received conservative management (active surveillance or watchful waiting) after initial diagnosis ~30% elected to receive active treatment.[4]
- *After initial management with active surveillance*: studies report 37 to 65% conversion to radical therapy at 5 years for men initially diagnosed with low-risk disease, and 29 to 41% conversion at 5 years for men initially diagnosed with very low-risk disease (see company answer to ERG clarification question A8 - 04 April 2018). A significant portion of these men elect to radical therapy in absence of disease progression, as shown in the largest European study of an Active Surveillance cohort (PRIAS). This study reported that 22% (274/1,218) of patients who switched to an active therapy did so in absence of protocol-based progression, and only 59% of those who had a protocol-based reason remained with a Gleason score of 6[a].[5,6]

[a] NICE's clinical guideline on prostate cancer considers 'low-risk' disease to have a serum prostate-specific antigen (PSA) no more than 10 ng/ml, a Gleason score no more than 6, and a clinical stage of T1 to T2a.

In this context, and as stated above clinical experts consulted by the company believe it is clinically relevant to offer padeliporfin to low-risk patients who:

- meet the indication criteria of padeliporfin (i.e. unilateral low risk but not very low risk, based on results of 12-core resolution TRUS biopsy)
- have been offered active surveillance but who want to proceed with an active treatment either at diagnosis or after an initial period on active surveillance

The primary clinical benefit sought for these patients remains to avoid or delay radical therapies and their associated morbidities.

Importantly, the Appraisal Committee noted (ACD, Section 3.9) that patients who receive padeliporfin need to continue on active surveillance and questioned whether this would be an acceptable solution for patients who decided to discontinue active surveillance in the first place. Several clinical experts consulted by the company believe that active surveillance after padeliporfin is not equivalent to active surveillance in the absence of any treatment for patients with low-risk prostate cancer. One obvious difference is that padeliporfin addresses the anxiety experienced by some patients in absence of any cancer control.

In conclusion the patient population described above are easily identifiable in clinical practice and would get a meaningful and significant clinical benefit by being offered padeliporfin.

Section 2: Revised cost-effectiveness model

In summary and as stated above, in addressing the points raised by the Appraisal Committee, we have:

- Removed active surveillance as a comparator.
- Incorporated AE data from ProtecT study.
    - Applied the urinary incontinence and erectile dysfunction rates from ProtecT for EBRT and radical prostatectomy
    - Applied the bowel dysfunction rates from ProtecT for EBRT and assumed the bowel dysfunction rates post radical prostatectomy to be equivalent to the one of padeliporfin
- Updated the definition of 'time to radical therapy' curve from PCM 301 by defining any death as events
- Applied the 'time to radical therapy' from ProtecT for active surveillance as the baseline and estimate the curve for padeliporfin relative to this baseline based on the data from PCM 301
- Updated the bowel dysfunction utility decrement to -0.1
- Applied the bowel dysfunction management cost from Hummel et al. once only.
- Incorporated multiparametric MRI costs to padeliporfin and radical therapies.
- Incorporated the HRG costs for radical prostatectomy and EBRT
- Applied a revised patient access scheme (PAS) of [redacted].

Further information on the amends made is provided below and the results are provided below in Section 1.1.

Removed active surveillance as a comparator

In line with the Appraisal Committee (ACD Section 3.4) active surveillance was not an appropriate comparator for padeliporfin and therefore removed from the cost-effectiveness analysis.

Incorporated AEs from ProtecT study

In our original submission Ramsay et al.[7] was used as a source for AE data instead of ProtecT study due to the following reasons:

- By the end of the follow-up, only 85% of men assigned to radiotherapy or surgery had received a radical intervention. Therefore, we have reason to believe that the toxicity prevalence was underestimated in ProtecT.
- The Expanded Prostate Cancer Index Composite (EPIC) a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment was not used from the beginning of the study. Use of EPIC within the trial only started in 2005, which was in the middle of the study. This could have biased the quality of life results, as a significant portion of the patients did not report their score at baseline and during the initial study period, where the acute AE episodes occur.

However, in this response we have adopted the Appraisal Committee's preferred AE source of ProtecT study and have also assumed the bowel dysfunction rates after radical prostatectomy to be the same as after padeliporfin, instead of the same as active surveillance in ProtecT. This is because, based on clinical expert's input, it is clinically implausible that an invasive procedure like radical prostatectomy could have a lower bowel dysfunction rates than padeliporfin vascular-targeted photodynamic therapy procedure, which is a minimally invasive procedure. The short-term and long-term AE rates for active surveillance, radical prostatectomy and EBRT were extracted from ProtecT study and applied directly in the model. Considering that AE rates from ProtecT study came from a trial applied to the UK population and represented the AE profile in the real-world setting, it was more appropriate to adjust the AE rates observed in PCM301 in line with those in ProtecT study. Table 2 shows the AE prevalence in the revised base case.

Table 2: Revised AE rates used in the model

Treatment	Duration	Urinary incontinence	Erectile dysfunction	Bowel dysfunction
Padeliporfin	Short-term	0.000	0.240	0.050
	Long-term	0.010	0.261	0.013
Active surveillance	Short-term	0.000	0.078	0.000
	Long-term	0.010	0.174	0.000
Radical prostatectomy	Short-term	0.440	0.537	0.050
	Long-term	0.179	0.472	0.013
EBRT	Short-term	0.050	0.462	0.165
	Long-term	0.035	0.364	0.100
Brachytherapy	Short-term	0.332	0.268	0.055
	Long-term	0.363	0.262	0.116

Abbreviation: AE, adverse event; EBRT, external beam radiation therapy.
Sources: PCM301 trial[8]; Donovan 2016 (ProtecT study)[3]

The detailed calculation and adjustment of AE rates were, with the exception of adjusting the PCM301 AE data to the ProtecT study, conducted in a same way as recommended by ERG. The difference of AE rates between Month 6 and baseline was defined as the short-term rate, while the difference between the average rate after Month 6 and baseline was defined as the long-term rate. Urinary incontinence rates was based on the EPIC item of whether the patient had used one or more pads per day in past 4 weeks and the data were summarized in Table 25 of the Appendix 1. The erectile dysfunction rates came from the EPIC item of 'Erections firm enough for intercourse', which was used to calculate the percentages of patients with erection issue using 100% minus the proportion of patients with 'Erections firm enough for intercourse', see more details in Table 26 of the Appendix 1. The bowel dysfunction rates came from three EPIC items, 'Faecal incontinence more than once per week', 'Loose stools about half the time or more frequently' and 'Bloody stools about half the time or more frequently'. The ERG preferred assumption that the AE changes of short-term and long-term were zero was applied, see more details in Table 27 of the Appendix 1. The adjustment of AE rates for padeliporfin was based on the AE difference between padeliporfin and AS in PCM301 trial and AE rate derived in ProtecT study, see Table 28 of the Appendix 1.

Updated the definition of 'time to radical therapy' curve from PCM 301 by adding any death as events

The Appraisal Committee suggested adjusting the 'time to radical therapy' curves from PCM 301 with the general mortality (ACD Section 3.16). However, as the patient-level data was available, we think it is more accurate to change the definition of 'time to radical therapy' (including any death as events) and refit the curves. This way, the general mortality is taken into consideration and it is more accurate than adjusting the curves by the general mortality.

In the new 'time to radical therapy' curves, all deaths regardless of the reason were defined as events. With the new definition, only one death in the active surveillance arm was changed from censoring to event, while there were no deaths in the padeliporfin arm. The statistical fits are shown in Table 3 and the new parameters are shown in Table 29 of Appendix 2. Based on the sum of Akaike information criterion (AIC) and Bayesian information criterion (BIC) for padeliporfin and active surveillance, the best fit curve is gamma distribution. However, based on the clinician's opinion the gamma distribution was not deemed clinical plausible and the best fit distribution remained as lognormal.

Table 3: Goodness of statistical fits for new 'time to radical therapy' curves (defining any death as the events)

Treatment	Distribution	AIC	BIC
Padeliporfin	Gompertz	194.76	199.52
Padeliporfin	Weibull	194.94	199.70
Padeliporfin	Loglogistic	195.27	200.03
Padeliporfin	Lognormal	196.35	201.11
Padeliporfin	Gamma	196.64	203.78
Padeliporfin	Exponential	201.28	203.66
AS	Gamma	371.54	378.61
AS	Lognormal	379.28	383.99
AS	Loglogistic	383.10	387.82
AS	Weibull	388.35	393.06
AS	Gompertz	395.12	399.84
AS	Exponential	395.68	398.04
Sum	Gamma	568.18	582.39
Sum	Lognormal	575.63	585.11
Sum	Loglogistic	578.37	587.85
Sum	Weibull	583.29	592.77
Sum	Gompertz	589.88	599.36
Sum	Exponential	596.96	601.70
Abbreviation: AS, active surveillance; AIC, Akaike information criterion; BIC, Bayesian information criterion.			

Applied the 'time to radical therapy' from ProtecT for active surveillance as the baseline and estimate the curve for padeliporfin relative to this baseline based on the data from PCM 301

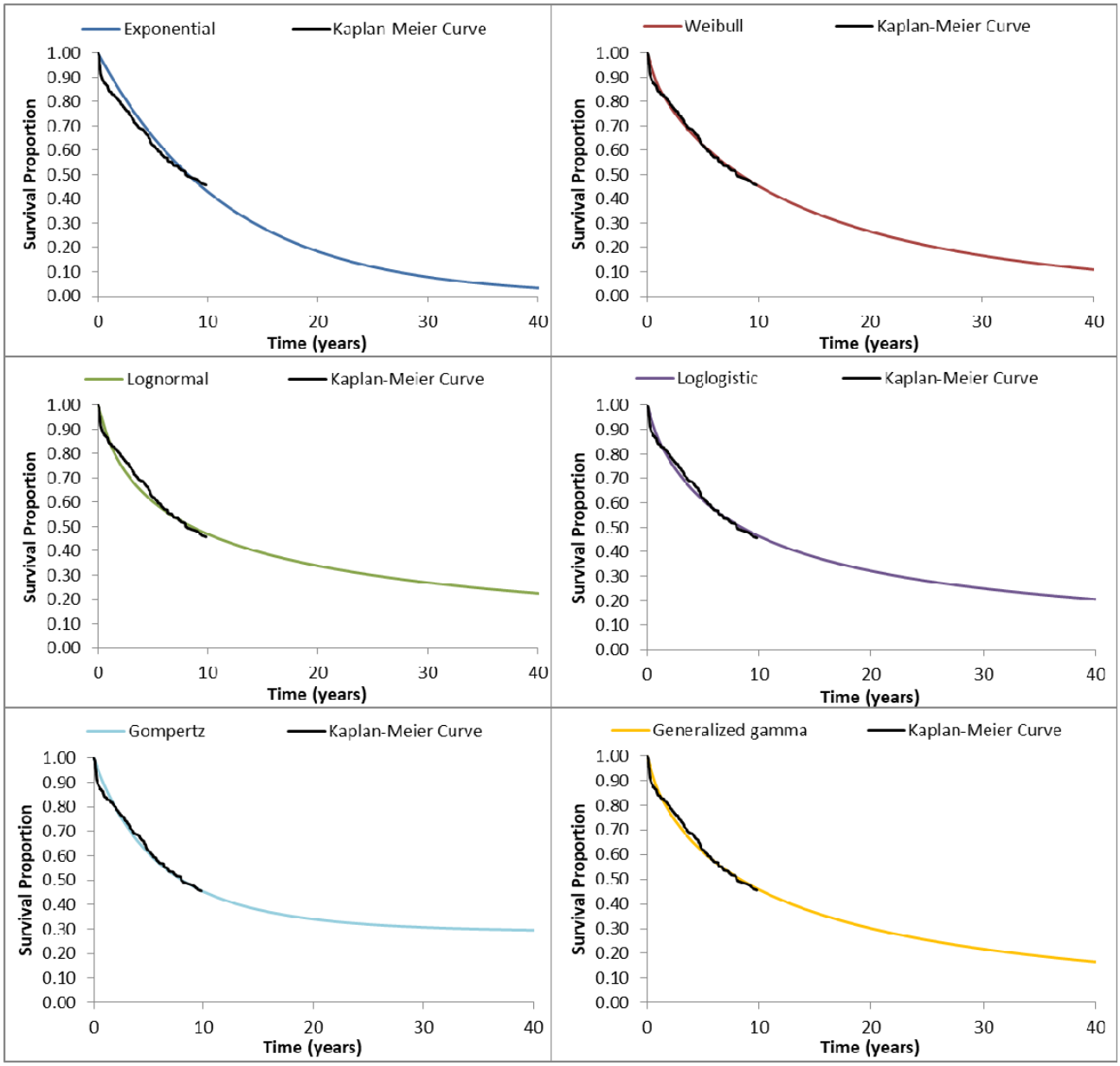
The Appraisal Committee expressed their concern about using lognormal distribution for 'time to radical therapy' extrapolation curves (ACD Section 3.17), as the lognormal curve predicted that most patients on active surveillance would have radical therapy, while ProtecT reported only 55% of patients would have radical therapy at Year 10 with lognormal distribution. We acknowledge the limitation of using 'time to radical therapy' extrapolation curves derived from PCM 301, therefore would propose that 'time to radical therapy' from ProtecT for active surveillance is used as the baseline with curve for padeliporfin relative to this baseline estimated by applying the 'time to radical therapy' data from PCM 301. This is a more consistent approach then directly applying the 'time to radical therapy' curves from PCM 301 as the 'time to radical therapy' curve of active surveillance from ProtecT was the most reliable evidence to the UK population in a real-world setting and the model also used the data from the ProtecT study estimating the curve of 'time to metastasis', 'overall survival' and the AE rates. This new approach was also requested by ERG in their clarification questions B4 – 04 April 2018.

The statistical fits of 'time to radical therapy' for active surveillance in ProtecT study is shown in Table 4 and Weibull was the best fitted distribution using the AIC and BIC. The Weibull distribution also has a good visual fit to the 'time to radical therapy' curve of active surveillance in ProtecT study (Figure 1).

Table 4: Goodness of fit statistics for parametric models fitted to 'time to radical therapy' curve in active monitoring group of ProtecT trial

Distribution	AIC	BIC
Weibull	1987.70	1996.30
Gamma	1988.36	2001.27
Lognormal	1989.14	1997.75
Loglogistic	1990.62	1999.22
Gompertz	2000.21	2008.82
Exponential	2020.10	2024.40
AIC, Akaike information criterion; BIC, Bayesian information criterion		

Figure 1: Comparison of ProtecT active surveillance 'time to radical therapy' curve with the fitted curves (six distributions)



The 'time to radical therapy' curve for padeliporfin was estimated relative to the curve of active surveillance from ProtecT study, which later was defined as the baseline. To estimate the curve for padeliporfin, a two-step approach was required: first the relative relation needed to be estimated between padeliporfin and active surveillance with 'time to radical therapy' data from PCM301 and second this relative relation was applied to the baseline, which is the curve for active surveillance in ProtecT study. The detailed calculation was described in Appendix 3.

Since lognormal distribution was the best fitted curve to the 'time to radical therapy' data in PCM 301, it was used as the base case to estimate the 'time to radical therapy' curve for padeliporfin relative to the baseline, together with Weibull distribution to model the curve for active surveillance.

Updated the bowel dysfunction utility decrement to -0.1

In the response to Appraisal Committee's comments on bowel dysfunction disutility (ACD, Section 3.18), we have adopted the Appraisal Committee's preferred utility decrement (-0.1) into the revised base case. In addition, we have added the scenario of using the age-adjusted multiplier for bowel dysfunction disutility, as suggested by the Appraisal Committee.

Incorporated multiparametric MRI costs to padeliporfin and radical therapies

As requested by the Appraisal Committee (ACD, Section 3.19) we have included the cost of multiparametric MRI to padeliporfin and active surveillance. Additionally, we have included this cost of multiparametric MRI to the radical therapies, as this test is becoming standard practice at diagnosis prior to any treatment.

Incorporated the HRG costs for radical prostatectomy and EBRT

In the ERG report (Page 112, Section 5.3.2), it was noted that the HRG based reference costs for radical prostatectomy and EBRT were applied in line with previous NICE models in the area of prostate cancer. We think that the use of such costs provide a more appropriate cost inputs than those used in our original submission.and have therefore included the HRG costs of radical prostatectomy and EBRT into the revised base case.

Applied a patient access scheme of [redacted]

The company has applied a patient access scheme (PAS) with a [redacted] discount applied to both padeliporfin and the other consumables used with padeliporfin, including the optical fibre, catheter and rectal probe.

Scenario Analyses

In addition to the revised base case results are provided for the following scenario analyses (holding everything else equal to the base case):

- 'Time to radical therapy' curve for active surveillance = Weibull distribution, for padeliporfin it was derived using:
    - Lognormal distribution (revised base case)
    - Exponential distribution
    - Weibull distribution
    - Loglogistic distribution
- 'Time to radical therapy' curve for active surveillance = lognormal distribution, for padeliporfin it was derived using (results reported in the Appendix 4):
    - Lognormal distribution
    - Exponential distribution
    - Weibull distribution
    - Loglogistic distribution
- Applying the age-adjusted disutility multiplier for bowel dysfunction
- Applying the bowel dysfunction cost from Hummel 2012[9] as the annual cost
- Apply the 'time to radical therapy' extrapolation curves from PCM 301 only and use the following AE data from Ramsay et al.[7] and ProtecT study. These two scenarios were added in order to provide a complete picture of the impact of the new 'time to radical therapy' approach on the ICER. However, we would like to emphasize the concern of long-term extrapolation to apply the 'time to radical therapy' curves from PCM 301 directly in the model.
    - Ramsay AE data
    - ProtecT AE data

Section 2.1: Results

Deterministic analyses

The ICERs for the revised base case based on ProtecT AE data and 'time to radical therapy' curve (Weibull distribution for active surveillance and lognormal distribution for padeliporfin), demonstrate that padeliporfin is a cost-effective treatment when compared with radical prostatectomy (£22,831) and brachytherapy (£9,807) (Table 5). When compared with EBRT the ICER is £48,841 (Table 6).

Table 5: Revised base case analysis for padeliporfin vs RP and BT; AS TTRT = Weibull, padeliporfin TTRT = lognormal

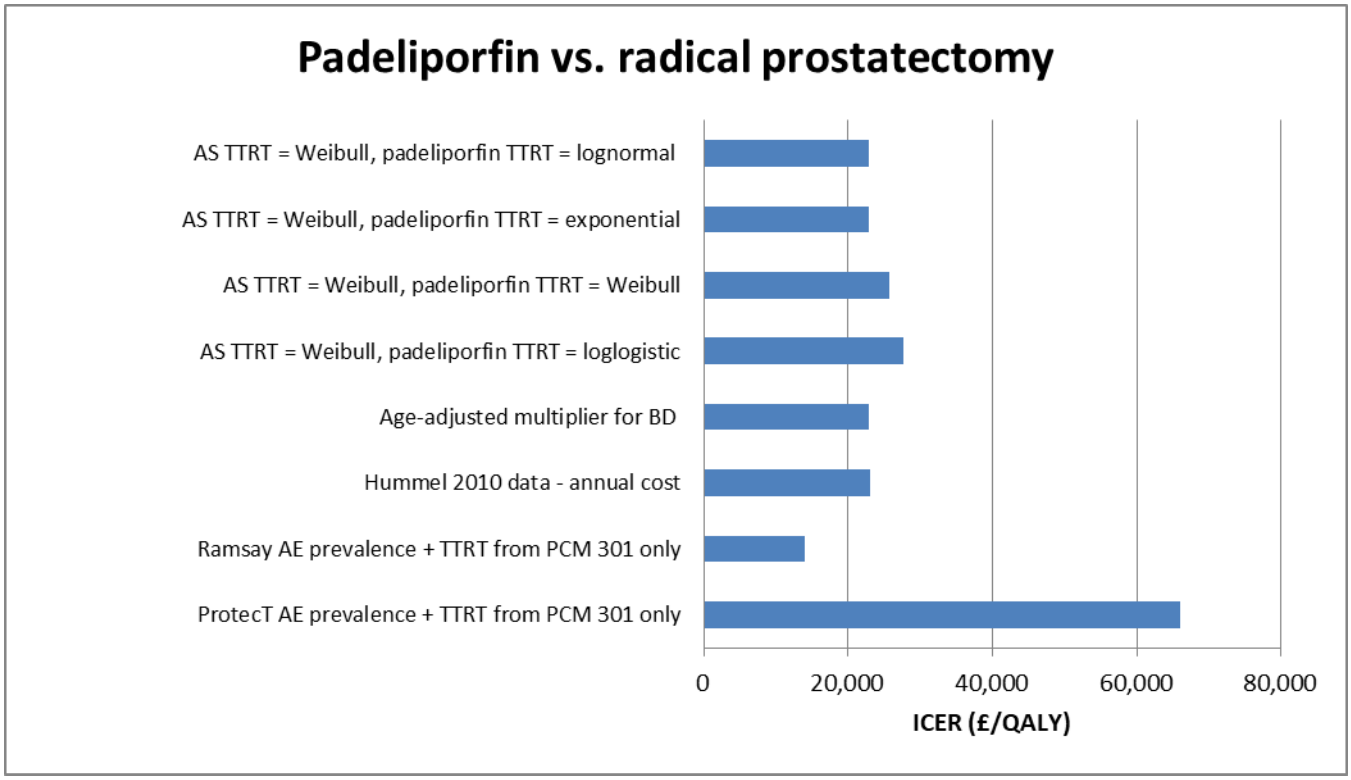
Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
Brachytherapy	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,871	0.213	0	22,831
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
Radical prostatectomy	[redacted]	[redacted]	[redacted]	-4,871	-0.213	0	22,831
Brachytherapy	[redacted]	[redacted]	[redacted]	-3,340	-0.341	0	9,807
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 6: Revised base case analysis for padeliporfin vs EBRT; AS TTRT = Weibull, padeliporfin TTRT = lognormal

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,483	-0.174	0	48,841
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

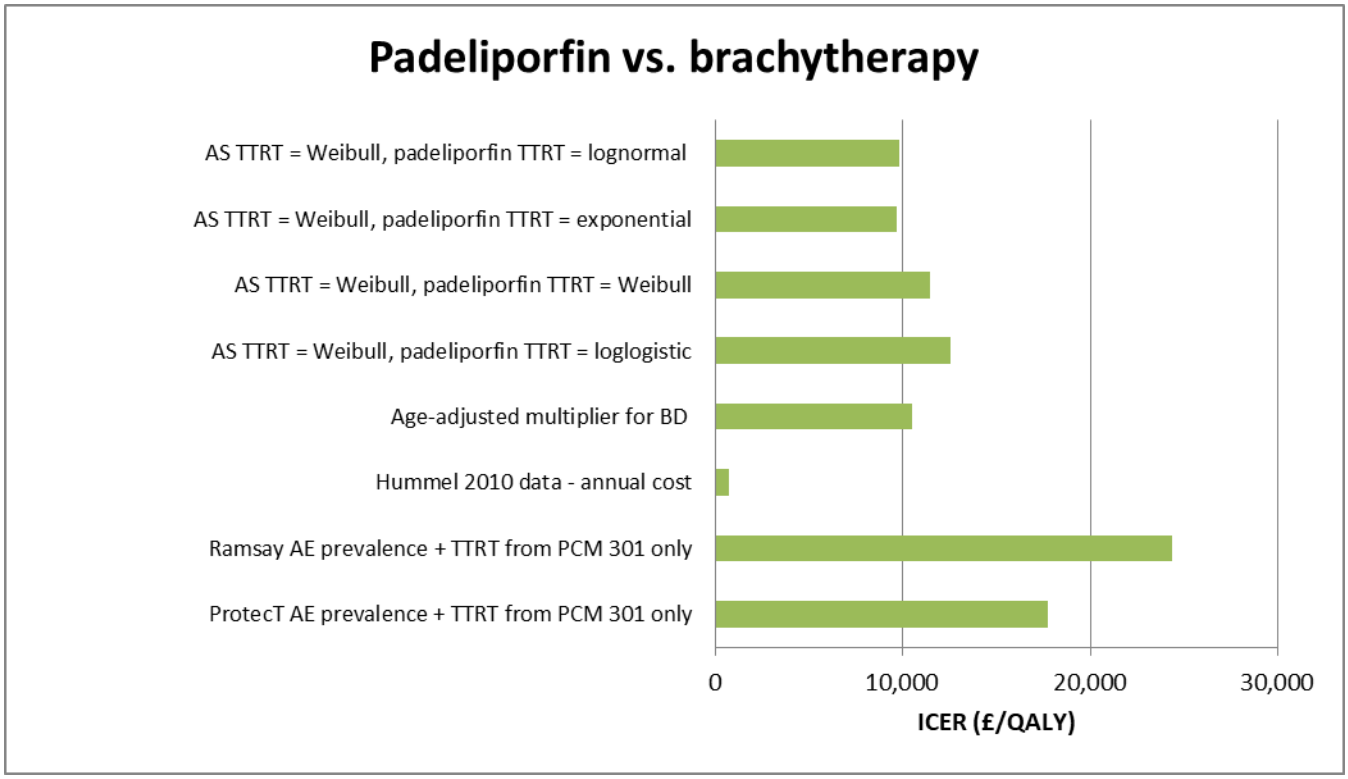
The overviews of the deterministic results for some scenarios as well as the revised base case are presented in Figure 2 - Figure 4 for the comparison of padeliporfin vs radical prostatectomy, brachytherapy and EBRT, respectively. The detailed results are presented in Table 7 - Table 20. The deterministic results for some further scenarios can be found in Appendix 4.

Figure 2: Overview of the deterministic results for scenarios for padeliporfin vs radical prostatectomy



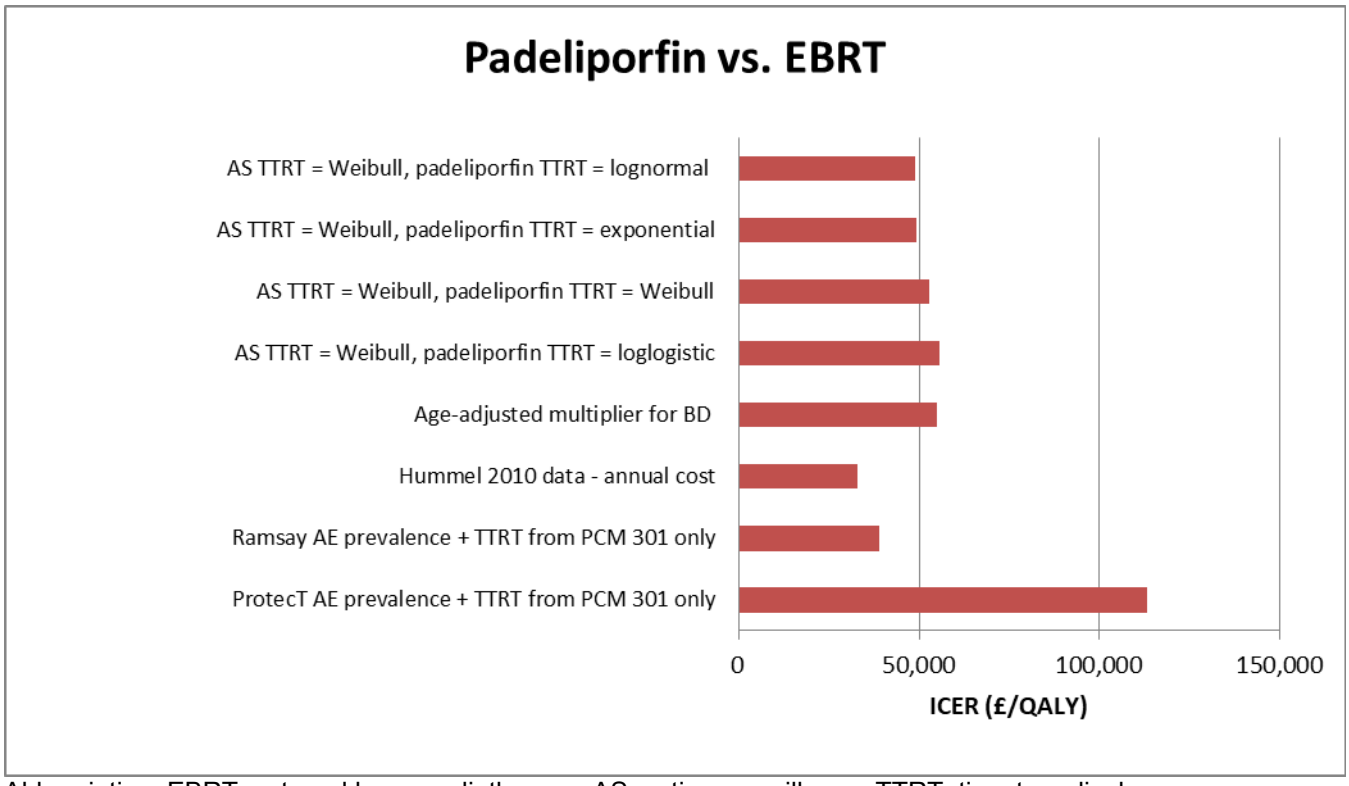
Abbreviation: AS, active surveillance; TTRT, time to radical therapy; BD, bowel dysfunction; AE, adverse event; ICER, incremental cost-effectiveness ratio.

Figure 3: Overview of the deterministic results for scenarios for padeliporfin vs brachytherapy



Abbreviation: AS, active surveillance; TTRT, time to radical therapy; BD, bowel dysfunction; AE, adverse event; ICER, incremental cost-effectiveness ratio.

Figure 4: Overview of the deterministic results for scenarios for padeliporfin vs EBRT



Abbreviation: EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy; BD, bowel dysfunction; AE, adverse event; ICER, incremental cost-effectiveness ratio.

Table 7: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = Weibull, padeliporfin TTRT = exponential

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,806	0.211	0	22,805
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-4,806	-0.211	0	22,805
BT	[redacted]	[redacted]	[redacted]	-3,276	-0.338	0	9,691

Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.

Table 8: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = Weibull, padeliporfin TTRT = exponential

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,419	-0.171	0	49,206
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 9: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = Weibull, padeliporfin TTRT = Weibull

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	5,393	0.210	0	25,657
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-5,393	-0.210	0	25,657
BT	[redacted]	[redacted]	[redacted]	-3,863	-0.337	0	11,447
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 10: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = Weibull, padeliporfin TTRT = Weibull

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-9,006	-0.171	0	52,803
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 11: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = Weibull, padeliporfin TTRT = loglogistic

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	5,715	0.207	0	27,605
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-5,715	-0.207	0	27,605
BT	[redacted]	[redacted]	[redacted]	-4,185	-0.334	0	12,518
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 12: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = Weibull, padeliporfin TTRT = loglogistic

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-9,328	-0.167	0	55,727
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 13: Revised scenario analysis for padeliporfin vs RP and BT; Age-adjusted multiplier for bowel dysfunction disutility

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Incremental Analysis							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.105	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,871	0.214	0	22,809
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-4,871	-0.214	0	22,809
BT	[redacted]	[redacted]	[redacted]	-3,340	-0.319	0	10,477
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy.							

Table 14: Revised scenario analysis for padeliporfin vs EBRT; Age-adjusted multiplier for bowel dysfunction disutility

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,483	-0.155	0	54,874
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy.							

Table 15: Revised scenario analysis for padeliporfin vs RP and BT; Hummel 2010 data used as the annual cost for bowel dysfunction management

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Incremental Analysis							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	4,667	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,905	0.213	0	22,993
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-4,905	-0.213	0	22,993
BT	[redacted]	[redacted]	[redacted]	-239	-0.341	0	701
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy.							

Table 16: Revised scenario analysis for padeliporfin vs EBRT; Hummel 2010 data used as the annual cost for bowel dysfunction management

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-5,714	-0.174	0	32,898
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy.							

Table 17: Revised scenario analysis for padeliporfin vs RP and BT; Ramsay AE prevalence + TTRT from PCM 301 only

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Incremental Analysis							
BT	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	322	-0.184	-1	Dominated by BT
Padeliporfin	[redacted]	[redacted]	[redacted]	6,838	0.281	0	24,349
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-6,516	-0.465	0	14,027
BT	[redacted]	[redacted]	[redacted]	-6,838	-0.281	0	24,349

Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AE, adverse event; TTRT, time to radical therapy.

Table 18: Revised scenario analysis for padeliporfin vs EBRT; Ramsay AE prevalence + TTRT from PCM 301 only

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-10,929	-0.280	0	39,049

Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AE, adverse event; TTRT, time to radical therapy.

Table 19: Revised scenario analysis for padeliporfin vs RP and BT; ProtecT AE prevalence + TTRT from PCM 301 only

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Incremental Analysis							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	2,073	-0.230	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	8,441	0.128	0	65,958
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-8,441	-0.128	0	65,958
BT	[redacted]	[redacted]	[redacted]	-6,367	-0.358	0	17,765

Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AE, adverse event; TTRT, time to radical therapy.

Table 20: Revised scenario analysis for padeliporfin vs EBRT; ProtecT AE prevalence + TTRT from PCM 301 only

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-11,947	-0.106	0	113,214
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AE, adverse events; TTRT, time to radical therapy.							

Probabilistic sensitivity analysis

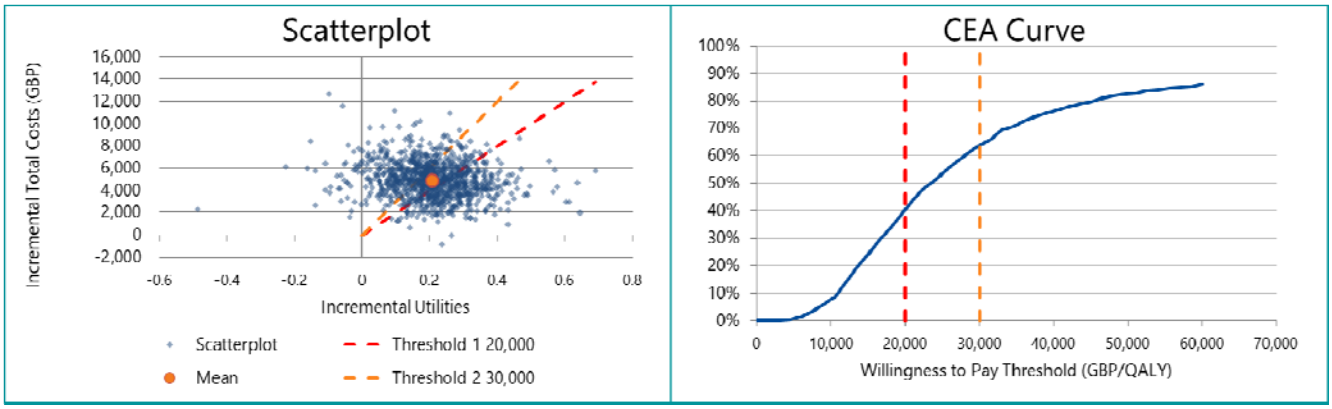
PSA was performed to get an accurate estimate of the central estimate and also translate the uncertainty in input variables into a measure of decision uncertainty in the cost-effectiveness model for the options being compared. The point estimates, standard errors/confidence intervals and distribution choices have been described for each parameter in Table 57, Section B.3.6 of the original submission (Form B) Uncertainties for survival distributions were tested by drawing random samplings from the multivariate-normal distribution derived from the variance-covariance matrix.

The mean probabilistic results for the revised base case are reported in Table 21 . The scatterplots and cost acceptability curves are provided from Figure 5 to Figure 7.

Table 21: Probabilistic sensitivity analysis results for revised base case

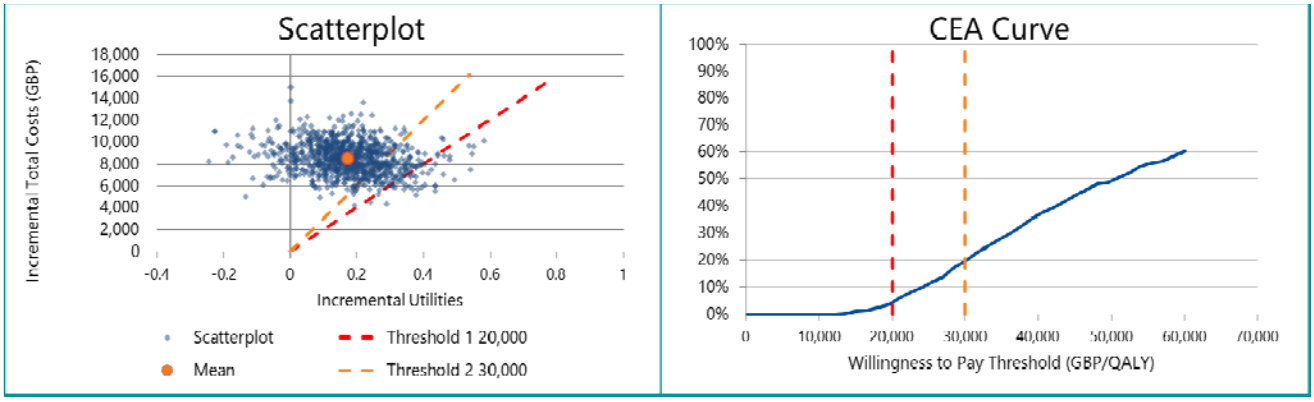
	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pair-wise Analysis (padeliporfin vs Radical prostatectomy)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	4,907	0.206	0.000	23,778
Pair-wise Analysis (padeliporfin vs EBRT)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	5,854	0.166	-0.002	35,258
Pair-wise Analysis (padeliporfin vs Brachytherapy)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
Brachytherapy	[redacted]	[redacted]	[redacted]	3,454	0.331	-0.002	10,423
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; EBRT, external beam radiotherapy.							

Figure 5: Scatterplot and cost-effectiveness acceptability curves of padeliporfin vs Radical prostatectomy



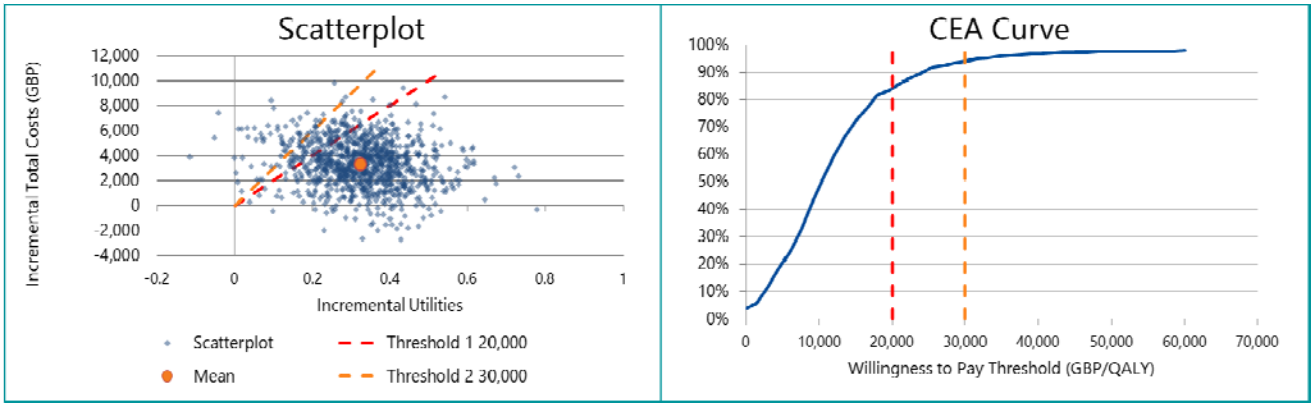
Abbreviation: CEA, cost-effectiveness acceptability.

Figure 6: Scatterplot and cost-effectiveness acceptability curves of padeliporfin vs EBRT



Abbreviation: CEA, cost-effectiveness acceptability.

Figure 7: Scatterplot and cost-effectiveness acceptability curves of padeliporfin vs Brachytherapy



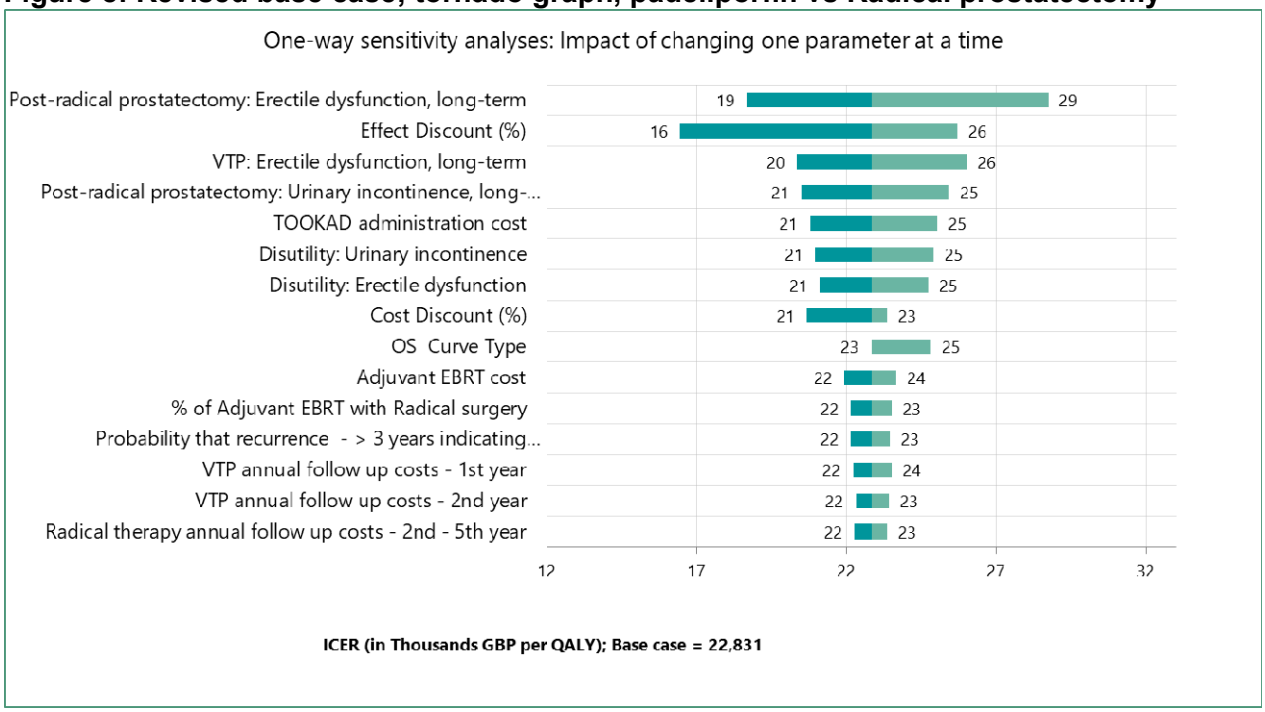
Abbreviation: CEA, cost-effectiveness acceptability.

Deterministic sensitivity analysis

An assessment of parameter uncertainty was also performed via deterministic sensitivity analysis. The model parameter values were individually varied to test the sensitivity of the model's results to specific parameters or sets of parameters. The inputs and the range tested are reported in Section B.3.6, Table 57 of the original submission (Form B).

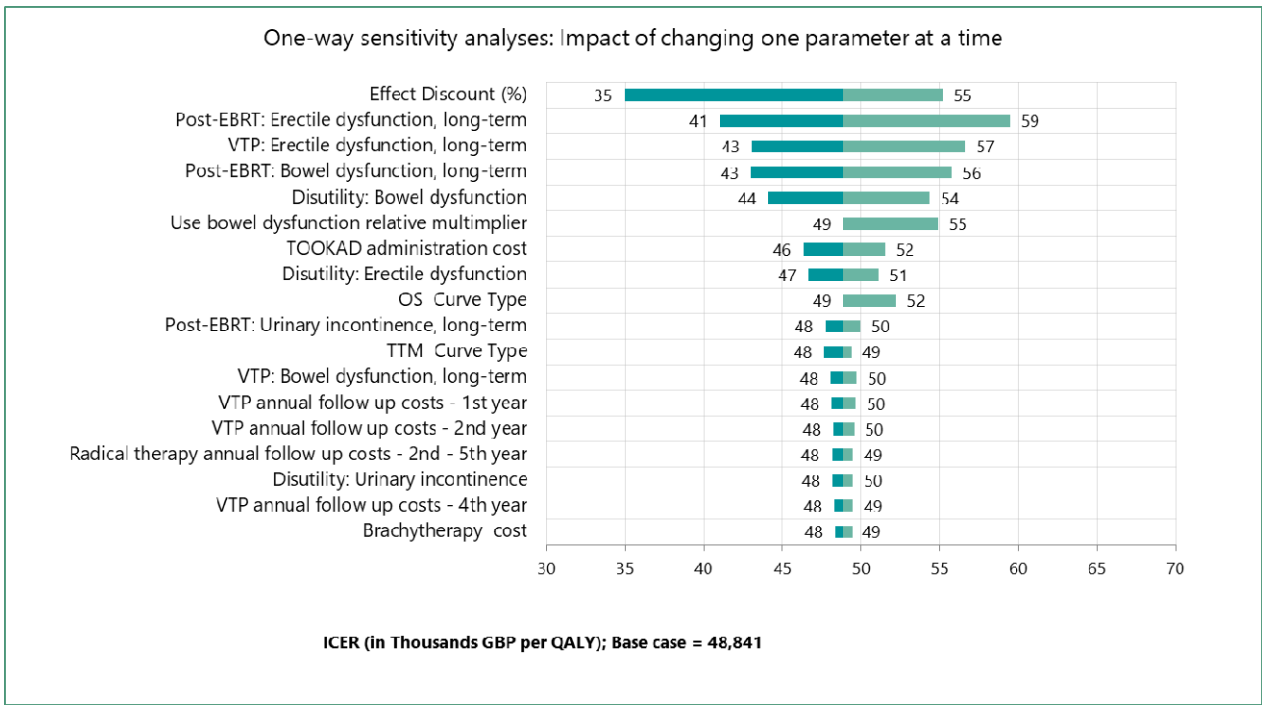
Figure 8 - Figure 10 show tornado diagrams depicting those variables that increase or decrease the ICERs by more than £1,000 per QALY. Results are robust to isolated parameter changes to the vast majority of variables in the model.

Figure 8: Revised base case; tornado graph, padeliporfin vs Radical prostatectomy



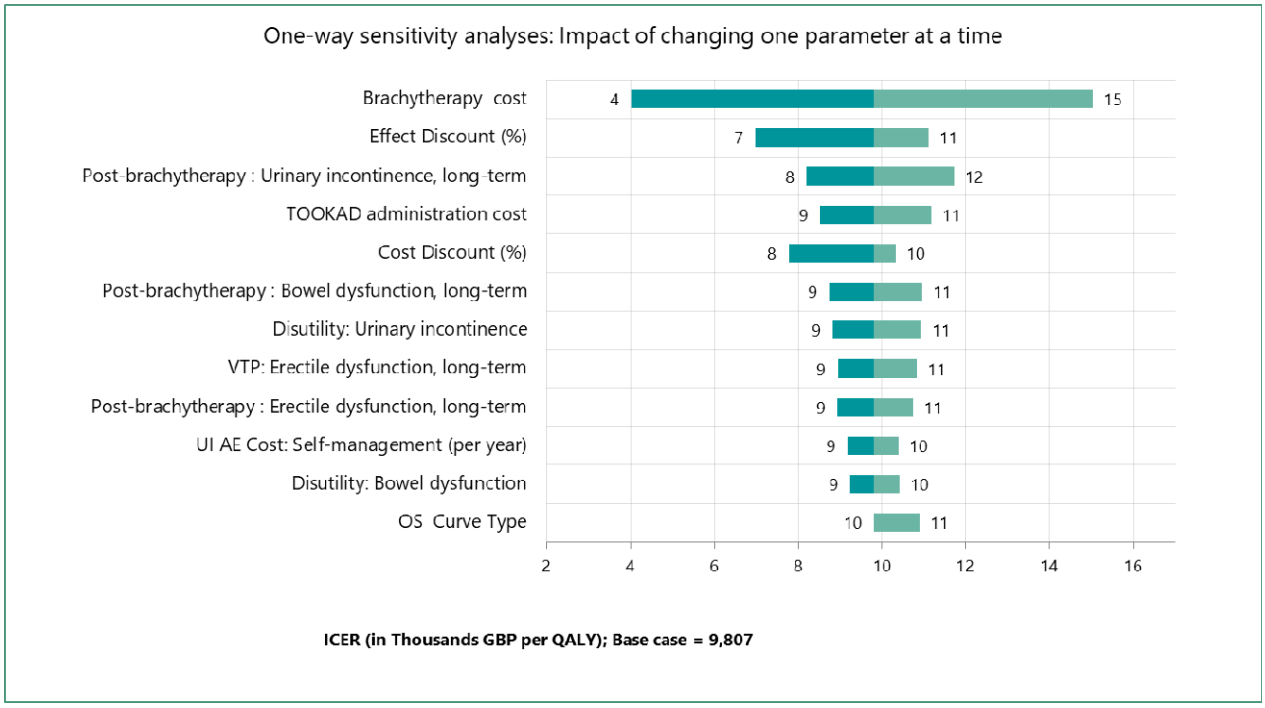
Abbreviation: VTP, padeliporfin vascular-targeted photodynamic therapy; OS, overall survival; EBRT, external beam radiotherapy.

Figure 9: Revised base case; tornado graph, padeliporfin vs EBRT



Abbreviation: VTP, padeliporfin vascular-targeted photodynamic therapy; OS, overall survival; EBRT, external beam radiotherapy.

Figure 10: Revised base case; tornado graph, padeliporfin vs Brachytherapy



Abbreviation: VTP, padeliporfin vascular-targeted photodynamic therapy; OS, overall survival**.**

Scenario analysis (SA)
The scenarios tested are shown from Table 22 to Table 24

Table 22: Revised deterministic scenario analysis padeliporfin vs RP

Scenario		Total cost		Total QALY		ICER
		Padeli-porfin	RP	Padeli-porfin	RP	
Base case (time horizon=40 years, cycle length=6 months)		[redacted]	[redacted]	[redacted]	[redacted]	22,831
Time horizon	20 years	[redacted]	[redacted]	[redacted]	[redacted]	26,035
	30 years	[redacted]	[redacted]	[redacted]	[redacted]	23,030
Cycle length	3 months	[redacted]	[redacted]	[redacted]	[redacted]	23,079
OS curve	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	22,877
Localised prostate cancer without AEs utility value	0.96	[redacted]	[redacted]	[redacted]	[redacted]	22,831
AE disutility value	UI: -0.14	[redacted]	[redacted]	[redacted]	[redacted]	11,722
	ED: -0.10	[redacted]	[redacted]	[redacted]	[redacted]	13,271
	UI: -0.14 ED: -0.10	[redacted]	[redacted]	[redacted]	[redacted]	8,557
Radical therapy distribution after padeliporfin	RP: 83% EBRT: 9% BT: 9%	[redacted]	[redacted]	[redacted]	[redacted]	23,152

Abbreviation: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; RP, radical prostatectomy; OS, overall survival; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; EBRT, external beam radiotherapy; BT, brachytherapy.

Table 23: Revised deterministic scenario analysis padeliporfin vs EBRT

Scenario		Total cost		Total QALY		ICER
		Padeli-porfin	EBRT	Padeli-porfin	EBRT	
Base case (time horizon=40 years, cycle length=6 months)		[redacted]	[redacted]	[redacted]	[redacted]	48,841
Time horizon	20 years	[redacted]	[redacted]	[redacted]	[redacted]	54,468
	30 years	[redacted]	[redacted]	[redacted]	[redacted]	49,189
Cycle length	3 months	[redacted]	[redacted]	[redacted]	[redacted]	47,189
OS curve	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	48,869
Localised prostate cancer without AEs utility value	0.96	[redacted]	[redacted]	[redacted]	[redacted]	48,841
AE disutility value	UI: -0.14	[redacted]	[redacted]	[redacted]	[redacted]	42,388
	ED: -0.10	[redacted]	[redacted]	[redacted]	[redacted]	34,398
	UI: -0.14 ED: -0.10	[redacted]	[redacted]	[redacted]	[redacted]	31,067
Radical therapy distribution after padeliporfin	RP: 83% EBRT: 9% BT: 9%	[redacted]	[redacted]	[redacted]	[redacted]	49,216

Abbreviation: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; BT, brachytherapy; OS, overall survival; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; RP, radical prostatectomy.

Table 24: Revised deterministic scenario analysis padeliporfin vs brachytherapy

Scenario		Total cost		Total QALY		ICER
		Padeli-porfin	BT	Padeli-porfin	BT	
Base case (time horizon=40 years, cycle length=6 months)		[redacted]	[redacted]	[redacted]	[redacted]	9,807
Time horizon	20 years	[redacted]	[redacted]	[redacted]	[redacted]	11,582
	30 years	[redacted]	[redacted]	[redacted]	[redacted]	9,917
Cycle length	3 months	[redacted]	[redacted]	[redacted]	[redacted]	9,983
OS curve	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	9,833
Localised prostate cancer without AEs utility value	0.96	[redacted]	[redacted]	[redacted]	[redacted]	9,807
AE disutility value	UI: -0.14	[redacted]	[redacted]	[redacted]	[redacted]	4,519
	ED: -0.10	[redacted]	[redacted]	[redacted]	[redacted]	10,027
	UI: -0.14 ED: -0.10	[redacted]	[redacted]	[redacted]	[redacted]	4,565
Radical therapy distribution after padeliporfin	RP: 83% EBRT: 9% BT: 9%	[redacted]	[redacted]	[redacted]	[redacted]	10,014

Abbreviation: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; BT, brachytherapy; OS, overall survival; AE, adverse event; UI, urinary incontinence; ED, erectile dysfunction; RP, radical prostatectomy; EBRT, external beam radiotherapy.

Section 2.2: Wastage explanation

Wastage was already taken into the account in the original submitted model. The recommended dosage of padeliporfin is 3.66 mg/kg. As a vial of padeliporfin contains 183 mg, each vial is suitable for 50 kg. For patients weighing >50 kg and ≤100 kg, two vials of padeliporfin are required. For patients weighing >100 kg and ≤150 kg, three vials of padeliporfin are required. In addition, each vial is for single use only. In PCM301, of the 158 patients in the indication population, 152 patients weighed >50 kg and ≤100 kg and the remaining six patients weighted >100 kg and ≤150 kg. Based on this distribution, each VTP procedure requires approximately 2.04 vials of padeliporfin, which was applied in the model.

Reference

1 European Medicines Agency. Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500201945.pdf. (Accessed 22 May 2018).

2 Merino T, San Francisco IF, Rojas PA, Bettoli P, Zuniga A, Besa P. Intensity-modulated radiotherapy versus radical prostatectomy in patients with localized prostate cancer: long-term follow-up. BMC Cancer 2013;13:530

3 Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med 2016;375(15):1425-37.

4 Greenberg DC, Lophatananon A, Wright KA, Muir KR, Gnanapragasam VJ. Trends and outcome from radical therapy for primary non-metastatic prostate cancer in a UK population. PLoS One 2015;10(3):e0119494

5 Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, et al. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur Urol 2016;70(6):954-60.

6 Bul M, Zhu X, Valdagni R, Pickles T, Kakehi Y, Rannikko A, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol 2013;63(4):597-603.

7 Ramsay CR, Adewuyi TE, Gray J, Hislop J, Shirley MD, Jayakody S, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess 2015;19(49):1-490.

8 Post-hoc analysis of PCM301 trial data. 2017.

9 Hummel S, Simpson EL, Hemingway P, Stevenson MD, Rees A. Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation. Health Technol Assess 2010;14(47):1-iv

10 Godtman RA, Holmberg E, Khatami A, Pihl CG, Stranne J, Hugosson J. Long-term results of active surveillance in the Goteborg randomized, population-based prostate cancer screening trial. Eur Urol 2016;70(5):760-6.

Appendices

Appendix 1: Detailed calculation for revised AE rates

Table 25: Number of patients with one or more pads per day in past 4 weeks from ProtecT study

	AS (No RT)	RP	EBRT
Baseline	0.0%	1.6%	0.0%
Month 6	0.0%	45.6%	5.0%
Month 12	0.0%	26.2%	3.6%
Month 24	0.5%	20.1%	4.1%
Month 36	0.4%	19.6%	3.0%
Month 48	1.6%	17.1%	3.5%
Month 60	1.5%	16.8%	3.2%
Month 72	1.9%	17.4%	3.5%
Long-term (average of Month 6-72)	1.0%	19.5%	3.5%
Change in % 6 months	**0.0%**	**44.0%**	**5.0%**
Change in % long-term	**1.0%**	**17.9%**	**3.5%**

Abbreviation: AS, active surveillance; RT, radical therapy; RP, radical prostatectomy; EBRT, external beam radiotherapy.
Source: ProtecT study (Donovan 2016)[3]

Table 26: Number of patients with issue of erection from ProtecT study

	Erection firm enough for intercourse			Erection not firm enough for intercourse		
	AS (No RT)	RP	EBRT	AS (No RT)	RP	EBRT
Baseline	64.8%	65.7%	68.4%	35.2%	34.3%	31.6%
Month 6	57.0%	12.0%	22.2%	43.0%	88.0%	77.8%
Month 12	53.3%	14.6%	37.6%	46.7%	85.4%	62.4%
Month 24	51.0%	18.9%	34.0%	49.0%	81.1%	66.0%
Month 36	50.6%	20.8%	34.0%	49.4%	79.2%	66.0%
Month 48	47.3%	20.1%	31.8%	52.7%	79.9%	68.2%
Month 60	44.7%	20.3%	27.1%	55.3%	79.7%	72.9%
Month 72	37.6%	16.5%	27.4%	62.4%	83.5%	72.6%
Long-term (average of Month 6-72)	-	-	-	52.6%	81.47	68.02
Change in % 6 months	-	-	-	**7.8%**	**53.7%**	**46.2%**
Change in % long-term	-	-	-	**17.4%**	**47.2%**	**36.4%**

Abbreviation: AS, active surveillance; RT, radical therapy; RP, radical prostatectomy; EBRT, external beam radiotherapy.
Source: ProtecT study (Donovan 2016)[3]

Table 27: Number of patients with bowel dysfunction from ProtecT study

	Fecal incontinence		Loose stools		Bloody stools		Sum	
	AS (No RT)	EBRT	AS (No RT)	EBRT	AS (No RT)	EBRT	AS (No RT)	EBRT
Baseline	2.0%	0.4%	17.3%	15.6%	2.0%	1.6%	-	-
Month 6	1.7%	5.2%	19.5%	25.1%	2.0%	3.8%	-	-
Month 12	1.1%	3.9%	16.0%	21.5%	1.4%	3.9%	-	-
Month 24	2.5%	4.3%	14.1%	19.6%	0.8%	7.4%	-	-
Month 36	2.3%	2.5%	14.9%	15.7%	1.6%	7.4%	-	-
Month 48	2.6%	2.4%	14.8%	15.9%	2.2%	7.4%	-	-
Month 60	2.4%	2.3%	14.2%	17.9%	2.2%	8.4%	-	-
Month 72	2.6%	4.1%	13.1%	15.5%	1.3%	5.6%	-	-
Long-term (average of Month 6-72)	2.3%	3.3%	14.5%	17.7%	1.6%	6.7%	-	-
Change in % 6 months	0.0%*	4.8%	0.0%*	9.5%	0.0%*	2.2%	**0.0%**	**16.5%**
Change in % long-term	0.0%*	2.9%	0.0%*	2.1%	0.0%*	5.1%	**0.0%**	**10.0%**

Abbreviation: AS, active surveillance; RT, radical therapy; RP, radical prostatectomy; EBRT, external beam radiotherapy.
Note: *these numbers were assumed to be zero, the same approach as taken by ERG.
Source: ProtecT study (Donovan 2016)[3]

Table 28: Adjustment of padeliporfin AE data based on the data from ProtecT study and PCM 301 trial

Intervention	Duration	Urinary incontinence	Erectile dysfunction	Bowel dysfunction
Padeliporfin (PCM301)	Short-term	0.013	0.175	0.050
	Long-term	0.000	0.100	0.013
Active surveillance (PCM301)	Short-term	0.013	0.013	0.000
	Long-term	0.000	0.013	0.000
Difference (padeliporfin-AS)	**Short-term**	**0.000**	**0.162**	**0.050**
	Long-term	**0.000**	**0.087**	**0.013**
Active surveillance (ProtecT)	Short-term	0.000	0.078	0.000
	Long-term	0.010	0.174	0.000
Padeliporfin (derived)	**Short-term**	**0.000**	**0.240**	**0.050**
	Long-term	**0.010**	**0.261**	**0.013**

Abbreviation: AE, adverse event; AS, active surveillance.
Source: ProtecT study (Donovan 2016)[3]; PCM301 trial[8]

Appendix 2: Parameters and statistical fits for the new 'time radical therapy' curves

Table 29: Parameters for the new TTRT curves (defining any death as the events)

Treatment	Model	Parameter	Estimate	StdErr	LowerCL	UpperCL	Intercept	Scale	Shape	Rate
AS	Exponential	Intercept	[redacted]							
AS	Exponential	Scale								
AS	Weibull	Intercept								
AS	Weibull	Scale								
AS	Lognormal	Intercept								
AS	Lognormal	Scale								
AS	LogLogistic	Intercept								
AS	LogLogistic	Scale								
AS	Gamma	Intercept								
AS	Gamma	Scale								
AS	Gamma	Shape								
AS	Gompertz	Shape								
AS	Gompertz	Rate								
Padeliporfin	Exponential	Intercept								
Padeliporfin	Exponential	Scale								
Padeliporfin	Weibull	Intercept								
Padeliporfin	Weibull	Scale								
Padeliporfin	Lognormal	Intercept								
Padeliporfin	Lognormal	Scale								
Padeliporfin	LogLogistic	Intercept								
Padeliporfin	LogLogistic	Scale								
Padeliporfin	Gamma	Intercept								
Padeliporfin	Gamma	Scale								
Padeliporfin	Gamma	Shape								
Padeliporfin	Gompertz	Shape								
Padeliporfin	Gompertz	Rate								

Abbreviation: AS, active surveillance; StdErr; standard error; LowerCL, lower confidence interval; UpperCL, upper confidence interval.

Appendix 3: Detailed information for active surveillance TTRT curve in ProtecT study

The 'time to radical therapy' curve for padeliporfin relative to the one for active surveillance was estimated with the following steps:

- With the fitted curve to 'time to radical therapy' from PCM 301, the probabilities of receiving radical therapies at each cycle were derived for padeliporfin and active surveillance, see the formula below.

$$Probability\ of\ receiving\ radical\ therapies\ at\ Cycle\ N\ = 1 - \frac{Number\ of\ patients\ not\ receiving\ radical\ therapies\ at\ Cycle\ N}{Number\ of\ patients\ not\ receiving\ radical\ therapies\ at\ Cycle\ N-1}$$

$$Probability\ of\ receiving\ radical\ therapies\ at\ Cycle\ N\ = 1 - \frac{Number\ of\ patients\ not\ receiving\ radical\ therapies\ at\ Cycle\ N}{Number\ of\ patients\ not\ receiving\ radical\ therapies\ at\ Cycle\ N-1}$$

- Relative relation between padeliporfin and active surveillance was derived with the probabilities obtained from the last step.

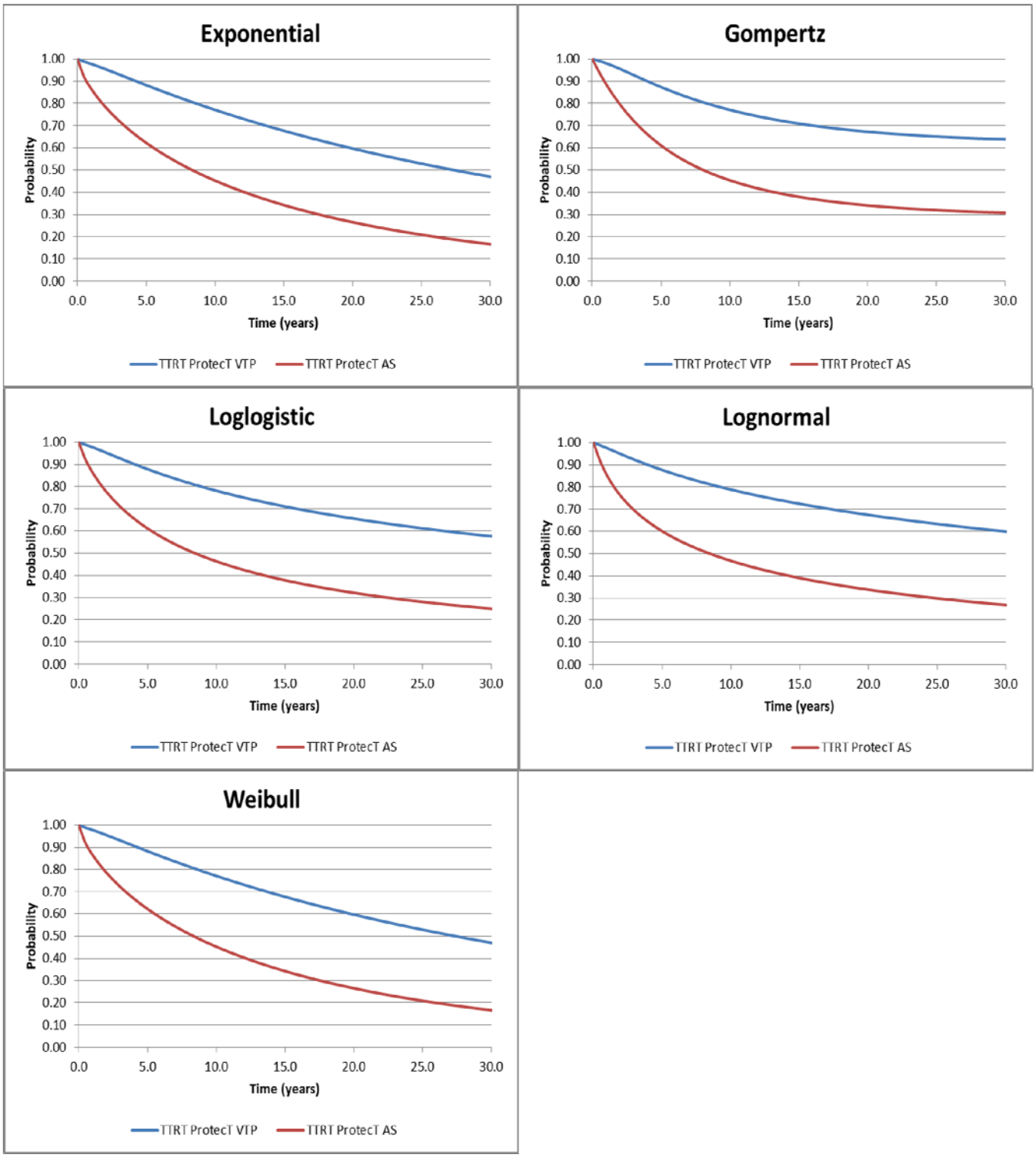
$$Relative\ relation\ between\ padeliporfin\ and\ active\ surveillance\ at\ Cycle\ N = \frac{Probability\ of\ receiving\ radical\ therapies\ at\ Cycle\ N\ (padiliporfin)}{Probability\ of\ receiving\ radical\ therapies\ at\ Cycle\ N\ (active\ surveillance)}$$

- The 'time to radical therapy' curve for padeliporfin was estimated by applying the relative relation on the curve for active surveillance from ProtecT study.

$$New\ probability\ of\ receiving\ radical\ therapies\ at\ Cycle\ N\ (padeliporfin) = Probability\ of\ receiving\ radical\ therapies\ at\ Cycle\ N\ (active\ surveillance\ from\ ProtecT) \times Relative\ relation\ between\ padeliporfin\ and\ active\ surveillance\ at\ Cycle\ N$$

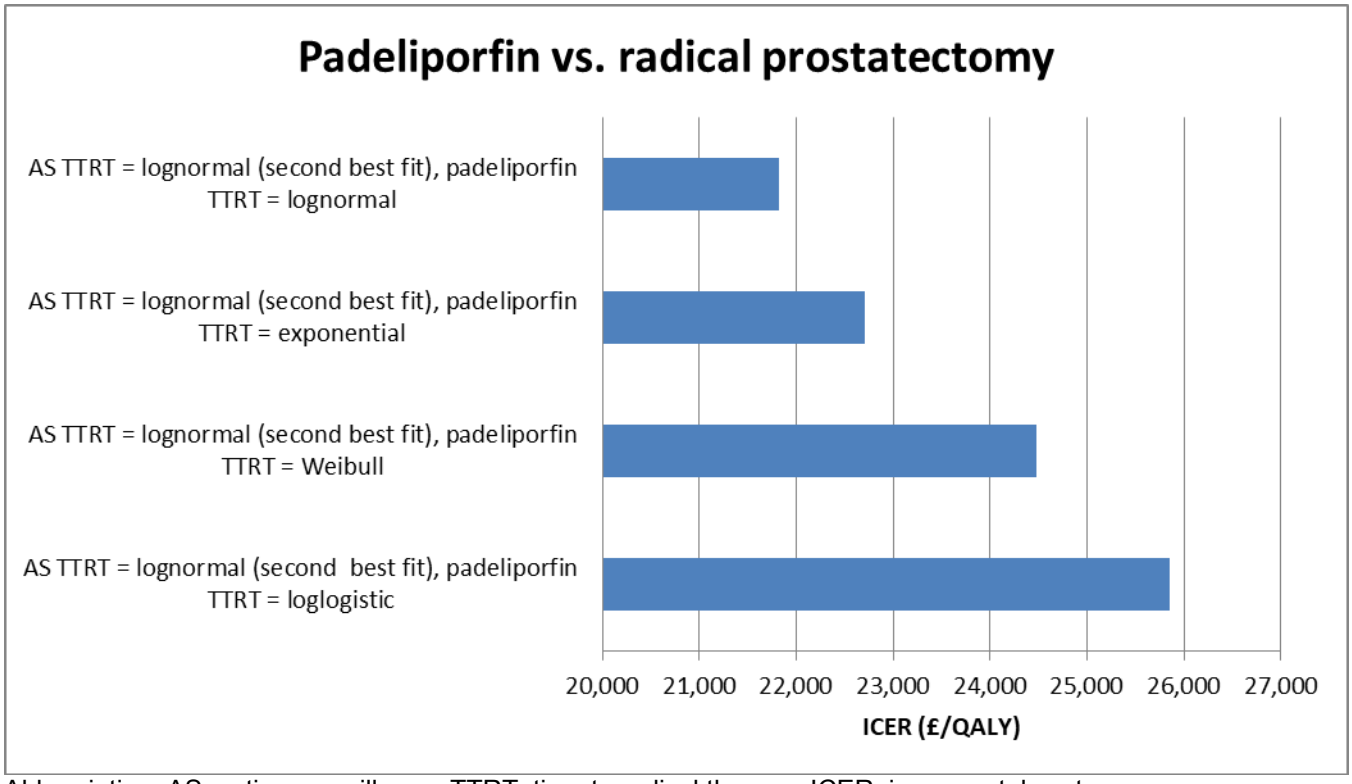
Figure 11 showed the 'time to radical therapy' curves for active surveillance and padeliporfin estimated relative to the active surveillance.

Figure 11: Comparison of fitted curves for ProtecT active surveillance arm (six distributions) and the derived VTP curves using the relative relation from PCM301 TTRT curves (lognormal)



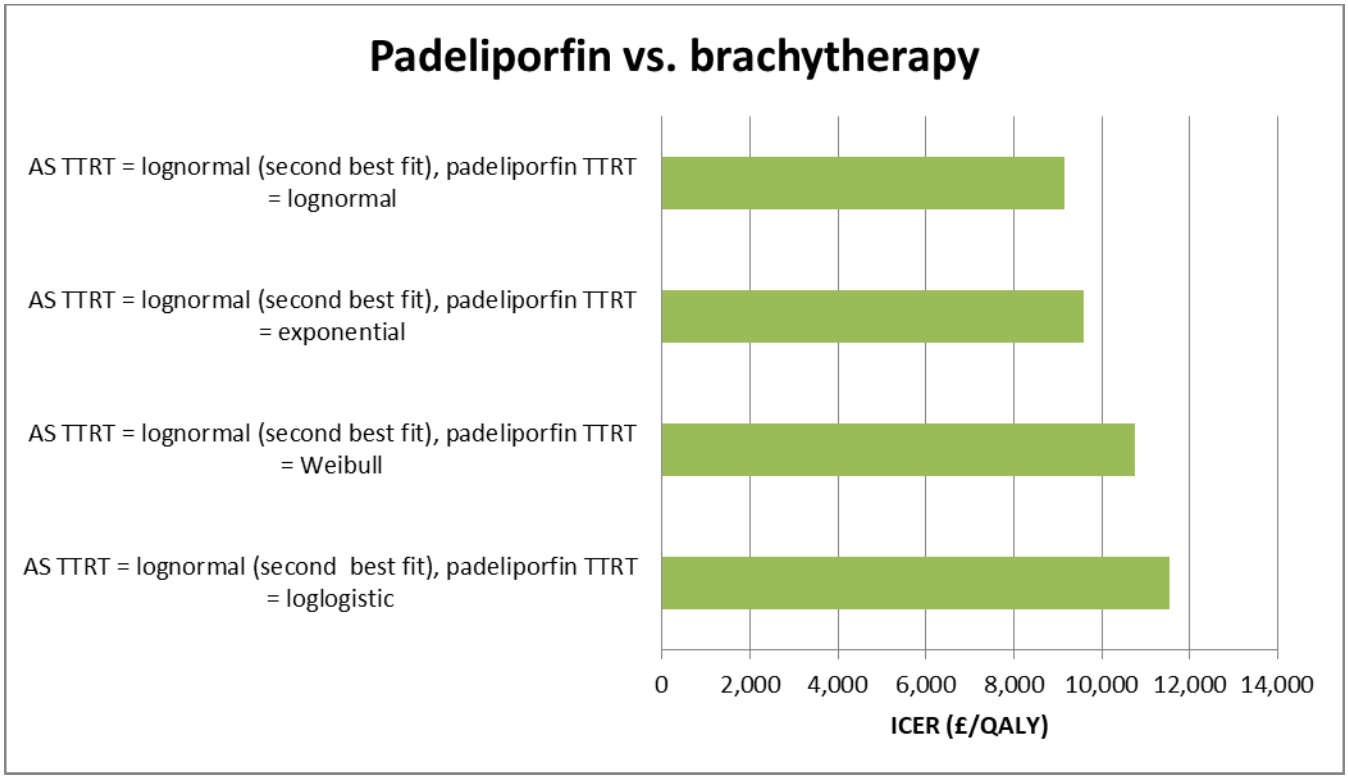
Appendix 4: Deterministic results for additional scenarios

Figure 12: Overview of the deterministic results for scenarios for padeliporfin vs radical prostatectomy



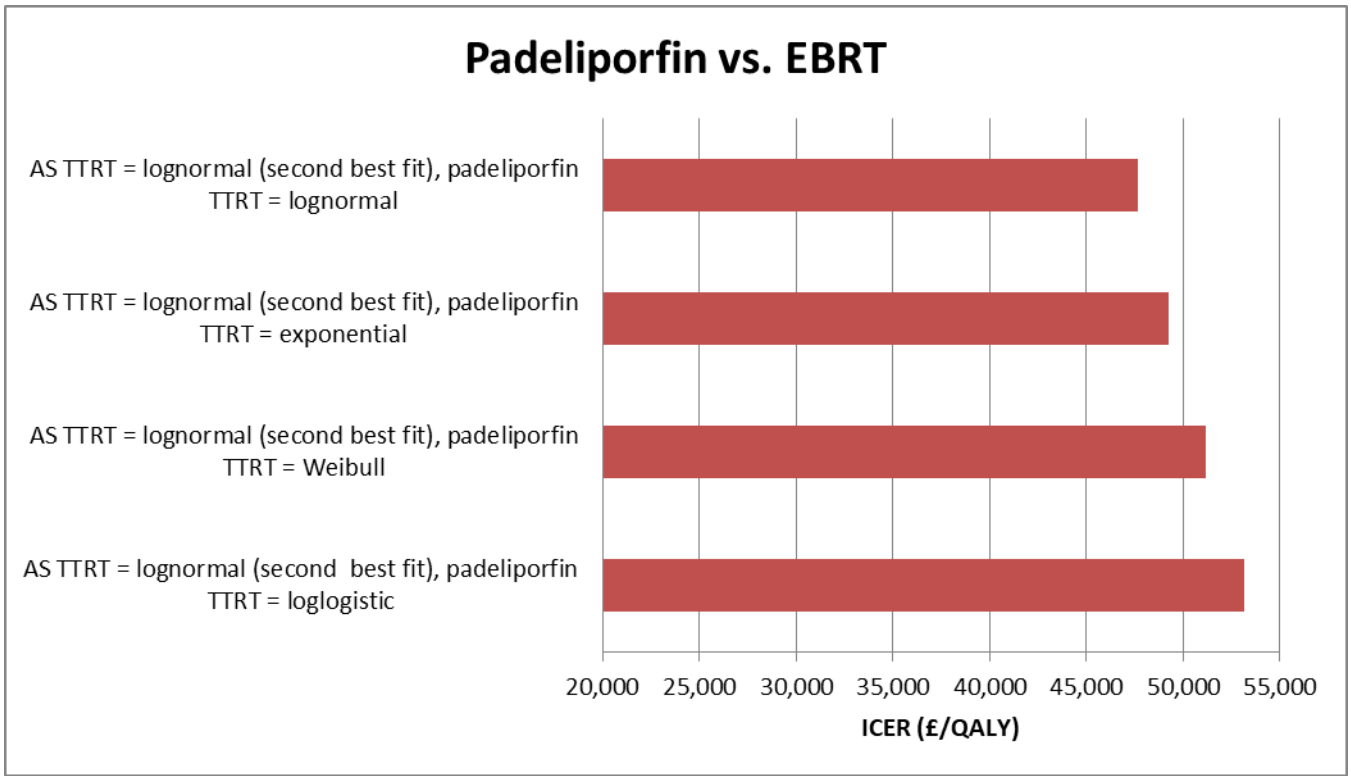
Abbreviation: AS, active surveillance; TTRT, time to radical therapy; ICER, incremental cost-effectiveness ratio.

Figure 13: Overview of the deterministic results for scenarios for padeliporfin vs brachytherapy



Abbreviation: AS, active surveillance; TTRT, time to radical therapy; ICER, incremental cost-effectiveness ratio.

Figure 14: Overview of the deterministic results for scenarios for padeliporfin vs EBRT



Abbreviation: EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy; ICER, incremental cost-effectiveness ratio.

Table 30: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = lognormal

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,650	0.213	0	21,821
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-4,650	-0.213	0	21,821
BT	[redacted]	[redacted]	[redacted]	-3,120	-0.340	0	9,166

Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.

Table 31: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = lognormal

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,263	-0.173	0	47,637
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 32: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = exponential

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,764	0.210	0	22,706
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-4,764	-0.210	0	22,706
BT	[redacted]	[redacted]	[redacted]	-3,233	-0.337	0	9,592
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 33: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = exponential

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,376	-0.170	0	49,230
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 34: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = Weibull

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	5,177	0.211	0	24,479
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-5,177	-0.211	0	24,479
BT	[redacted]	[redacted]	[redacted]	-3,647	-0.339	0	10,766
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 35: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = Weibull

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,790	-0.172	0	51,150
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 36: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = loglogistic

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	5,421	0.210	0	25,848
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-5,421	-0.210	0	25,848
BT	[redacted]	[redacted]	[redacted]	-3,890	-0.337	0	11,544
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table 37: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = lognormal (second best fit), padeliporfin TTRT = loglogistic

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-9,033	-0.170	0	53,119
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Padeliporfin for treating localised prostate cancer [ID866]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 23 July 2018 **email:** TACommB@nice.org.uk/NICE DOCS

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

Comment number	Comments Insert each comment in a new row.

Please return to: **TACommB@nice.org.uk** / NICE DOCS

Padeliporfin for treating localised prostate cancer [ID866]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments end of 23 July 2018 **email:** TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We 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. Our rationale for this is as follows: First, the radical treatment of low risk prostate cancer has been shown to have no cancer-specific or overall survival difference at 10 years in large randomised controlled trials in which the control has been watchful waiting or active monitoring. These studies, PIVOT and PROTECT, involved a lesser strategy of follow-up that did not involve the intense clinical and biopsy monitoring of active surveillance in the current era. Second, large prospective series have confirmed that active surveillance has extremely low mortality rates in the medium to long term. Third, whilst these series have shown transition to treatment of one-third to one-half of patients approximately, it is well accepted that this is on the whole due to mis-classification of disease risk at baseline transrectal systematic biopsy rather than progression. Therefore, the term progression to higher grade disease or higher volume of disease is on the whole due to such higher risk being missed at baseline biopsy and being found on subsequent repeat biopsy. It is therefore a correction of a miss-classification error rather than 'progression' in the manner in which we regard it. Fourth, as a result, the endpoint used in the RCT assessing padeliporfin compared to active surveillance is not a biological progression on the whole and therefore should be viewed with caution if the intervention reduces this endpoint which has no proven correlation to longer term survival. Fifth, the manner in which the many physicians tried to overcome the miss-classification error of transeptal systematic biopsies during the duration of this study was to include a confirmatory biopsy prior to active surveillance. In the NICE Clinical Guidance, there is also a pre-requisite to include multi-parametric MRI (mpMRI). 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. Sixth, over the last 5 years, the diagnostic pathway has changed. In the UK particularly, pre-biopsy mpMRI for all men with an elevated PSA as the initial diagnostic test followed by MRI-targeted biopsy means that the miss-classification error of the traditional transrectal systematic ('blind') biopsy is almost the norm in most units. NHS England have issued guidance to all regions and Trusts to bring in this diagnostic pathway. 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. In other words, as mpMRI before biopsy can identify 90% of significant cancers compared to approximately 50% by transrectal biopsy alone, men with low risk disease should have true low risk disease in 90% of the cases. In the current era of men diagnosed with a pre-biopsy mpMRI followed by targeted and systematic biopsies, 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. Lastly, there have been significant in-roads internationally with increasing proportions of men entering a programme of active surveillance rather than active treatment. This has been due to the recognition that any treatment in this group of men would confer some harm and no cancer control benefit. The mpMRI pathway will aid this further. The adage that only anxiety is being treated is correct when it comes to this group. 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 eligible for such a

Consultation on the appraisal consultation document – deadline for comments end of 23 July 2018 **email:** TACommB@nice.org.uk/NICE DOCS

	strategy. This would be an unacceptable regressive step in the field of prostate cancer. We would be happy to clarify any specific issues.

Insert extra rows as needed

Checklist for submitting comments

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

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

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

NHS England submission in July 2018 for the 2nd meeting on the NICE appraisal of padeliporfin for untreated and low risk prostate cancer

1. These comments have been drawn up by Professor Hashim Ahmed, chair of NHS England's Clinical Expert Group for prostate cancer.
2. Professor Ahmed states that the NHS England Clinical Expert Group and the NCRI Prostate CSG agree with the NICE ACD conclusion that padeliporfin for low risk prostate cancer should not be recommended.
3. Professor Ahmed was asked as to which focal therapies are used for localised prostate cancer. Currently under NICE Interventional Procedures Guidance IPG424 (high intensity focused ultrasound, HIFU) and IPG423 (cryoablation) and in certain centres which meet the requirements of the IPG guidelines , focal HIFU and cryotherapy are carried out. The UK Focal Therapy Users Group (Chair: Professor Hashim Ahmed) has issued guidance to its members and users that 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 (ie use of focal therapies is mainly in intermediate risk patients). This is 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. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, Bottomley D, Eggener S, Ehdaie B, Emberton M, Hindley R, Leslie T, Miners A, McCartan N, Moore CM, Pinto P, Polascik TJ, Simmons L, van der Meulen J, Villers A, Willis S, Ahmed HU. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol. 2015 Apr;67(4):771-7. doi: 10.1016/j.eururo.2014.09.018.
4. The majority (90%) of men treated with focal therapy historically in the UK are of intermediate and high risk. Of the 10% treated who are low risk, these cases are now uncommonly/rarely treated in the UK and are therefore mainly historical. There are occasionally exceptional cases in which some men with high volume Gleason 6 prostate cancer (>/=6mm of cancer on biopsy) are sometimes treated with focal therapy (these men generally would not be suitable for active surveillance either) or rarely in cases of strong patient refusal of active surveillance.
5. Professor Ahmed was also asked as to how people with low-risk prostate cancer with and without disease progression are treated in NHS clinical practice. 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 (NPCA). "*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 in this area of prostate cancer therapy.*" Quote from NPCA 2017 https://www.npca.org.uk/reports/npca-annual-report-2017/. This reassuring trend is as a result of: a) greater confidence in the attribution of a low risk status from MRI/targeted biopsies and transperineal saturation/mapping biopsies, b) long follow-up case series from Canada in which only transrectal systematic (inaccurate) biopsies were used and still show active surveillance has an extremely low risk of mortality (1.5% cancer-specific mortality and 2.8% metastases at median follow-up 6.4 years in 819 patients; Klotz

et al, 2015), and c) the recent data from the PIVOT and PROTECT RCTs showing no benefit in treating low risk prostate cancer at 10 years follow-up compared to radical radiotherapy or radical prostatectomy.

Prof Peter Clark

Chair NHS England Chemotherapy Clinical Reference Group and CDF National Clinical Lead for the Cancer Drug Fund

July 2018

Padeliporfin for treating localised prostate cancer

ERG critique of the new economic evidence submitted by the company in response to the ACD

Produced by: Aberdeen HTA Group

Authors: Graham Scotland[1,2]
Dwayne Boyers[1]

1. Health Economics Research Unit, University of Aberdeen
2. Health Services Research Unit, University of Aberdeen

Correspondence to: Graham Scotland
Health Economics Research Unit, University of Aberdeen
Polwarth Building,
Foresterhill, Aberdeen, AB25 2ZD
Email: g.scotland@abdn.ac.uk

Date completed: 30th July, 2018

Contains CiC

This report provides the ERG's brief commentary and critique of revised economic evidence submitted by the company (Steba Biotech S.A) on 24/07/2018 in response to the ACD and in advance of the second AC meeting for this appraisal.

This ERG commentary/critique should be read in conjunction with the company's submitted document: ID866 - padeliprofin - ACD Consultation Response - 2018Jul23 - final - 230718 [ACIC].

The company document focusses on clarifying the positioning of padeliporfin VTP in the treatment pathway for localised prostate cancer, and several revisions to the economic model addressing concerns raised by the committee as outlined in the Appraisal Consultation Document.

1. The positioning of padeliporfin VTP and its clinical benefit in localised prostate cancer

The first part of the company's submitted document focusses on: 1) how patients can be identified for treatment with padeliporfin VTP within the current clinical pathways; 2) clarifying the clinical benefits of the treatment in the context of low-risk prostate cancer; and 3) defining the subgroup of low-risk patients who would benefit from prostate cancer treatment.

The company's arguments are outlined on pages 5 to 9 of their submitted document. These arguments appear to be in line with those put forward by the clinical experts at the first appraisal meeting, and reflected in the committees preferences as outlined in the ACD.

In summary, the company clarify that "*padeliporfin VTP is indicated for as monotherapy for patients with unilateral low risk, but not very low risk disease, where:*

- *Low risk is defined as Gleason score ≤6 and PSA ≤10ng/mL and clinical stage T1 or T2a*
- *Very low risk is defined as low risk with the additional following criteria: maximum 2 positive cores and maximum 50% cancer involvement in any core and PSA density<0.15ng/ml/cm3*"

The company addressed the point raised in 3.1 of the ACD that the approach to diagnosis and risk stratification is currently evolving towards an approach based on MRI-targeted biopsy, which is more sensitive and more specific than the 12-core TRUS guided biopsy used to identify low risk patients for recruitment to the pivotal PCM301 trial. The company point out that clinical practice is still evolving, and they "*anticipate that patients eligible for treatment with padeliporfin will continue to be identified based on their 12-core TRUS biopsy results and their eligibility to padeliporfin will therefore be evaluated in the same way it was in the pivotal Phase III study (PCM301)*".

With respect to the clinical benefits required of new treatments in the area of low-risk localised prostate cancer, the company refer to the Appraisal Committee for Medicinal Products for Human Use (CHMP) guidelines on the evaluation of anticancer medicinal

products (EMA/CHMP/703715/2012 Rev. 2 – 17 Dec 2015)[1], which identifies the following three key benefits expected/required for new therapies in low-risk prostate cancer:

- Anti-tumour activity
- Reduction in the need for radical therapy
- Preservation of genitourinary function

The company go on to describe how padeliporfin meets these three criteria. The ERG would note that with respect to anti-tumour activity, padeliporfin has proven benefits over active surveillance, but not compared directly with available radical therapies or other focal therapies. With respect to the preservation of genitourinary function, there are demonstrable significant benefits compared with AS, from which it is reasonable to infer significant benefits against immediate radical therapy (although no direct randomised comparisons exit).

Finally, in clarifying the relevant comparators for padeliporfin VTP, the company agree with the appraisal committees judgment (outlined in section 3.4 of the ACD) that active surveillance is not a relevant comparator, and that it should be considered an alternative treatment option for those low-risk patients who:

- "*meet the indication criteria of padeliporfin (i.e. unilateral low risk but not very low risk, based on results of 12-core TRUS biopsy)*
- *have been offered active surveillance and want to proceed with an active treatment either at diagnosis or after an initial period on active surveillance*"

This argument appears to be centred around the fact that there is a significant proportion of patients with low-risk disease who opt for radical treatment at diagnosis or without clinical progression after a period on AS (see pages 8 and 9 of company submitted document). It is proposed that padeliporfin VTP should be offered as a treatment option for these patients who would otherwise receive radical therapy.

However, the Company also address a point highlighted by the Appraisal Committee (ACD, Section 3.69), that since padeliporfin VTP requires continued active surveillance following treatment, it is questionable whether this would be an acceptable solution for patients who decide to discontinue active surveillance due to surveillance fatigue. In response, the company note that "*several clinical experts they consulted believe that active surveillance after padeliporfin is not equivalent to active surveillance in the absence of any treatment for*

patients with low-risk prostate cancer". They further note that one obvious difference is "*that padeliporfin addresses the anxiety experienced by some patients in absence of any cancer control"*.

2. Revised cost-effectiveness model

The company provide details of the following changes to their cost-effectiveness model, addressing concerns raised by the appraisal committee:

1. Removal of active surveillance as a comparator
2. Incorporation of adverse event data from the ProtecT study
3. A revised analysis of 'time to radical therapy' from PCM 301, defining deaths as events rather than censoring events
4. Expressing TTRT on padeliporfin VTP relative to the baseline of TTRT observed for AS in the ProtecT study, rather than modelling directly from the PCM301 trial.
5. Revision of the bowel dysfunction utility decrement to -0.1, rather than -0.16
6. Application of the bowel dysfunction management cost from Hummel et al. once only.
7. Incorporation of multiparametric MRI costs for padeliporfin and radical therapies
8. Incorporation of the HRG costs for radical prostatectomy and EBRT
9. Application of a revised patient access scheme (PAS), in the form of a discount of [redacted] applied to both padeliporfin and the other consumables used with padeliporfin, including the optical fibre, catheter and rectal probe.

Most of these changes are self-explanatory and have been implemented in line with the appraisal committees' preferences as outlined in the ACD. However, the ERG believes changes two, three and four above warrant some further discussion. Point four in particular represents a substantial departure from the company's original base case, and significantly influences the ICER for padeliporfin VTP versus the radical therapies. These points are discussed in turn below.

2.1 Incorporation of adverse event data from the ProtecT study

The company describe on page 11 and 12, and appendix in 1, of their submitted document, how they have incorporated adverse event data from the ProtecT study.[2] This was done to address the committee's preference for adverse event rates based on ProtecT rather than Ramsay et al.[3] as applied in the company's original model (ACD section 3.14). The company describe how they have followed the approach of the ERG to estimate rates of urinary incontinence and erectile dysfunction following radical prostatectomy and external beam radiotherapy (EBRT). However, rather than using the difference in AE rates between AS and the radical therapies in ProtecT, to adjust the AE rates for the radical therapies relative to AS in PCM301, they have adjusted the padeliporfin rates relative to the active surveillance AE rates observed in ProtecT. The ERG believes this is an acceptable approach, which should result in adverse event rates that are more generalizable to the relevant UK clinical population. The company further describe how they have set the rate of bowel dysfunction following radical prostatectomy equal to the rate following Padeliporfin VTP in PCM301. Whilst the bowel dysfunction rate following RP was equal to that following AS in ProtecT, it was considered clinically implausible that the rate of bowel dysfunction following radical prostatectomy could be lower than the rate observed for padeliporfin in PCM301. The ERG agrees with this approach. The company's revised AE rates are provided in Table 2 of their submitted document. One further point to note is that the adverse event rates for brachytherapy remain unchanged from the company's original submission, since the ProtecT study did not include Brachytherapy as a comparator. This could potentially create bias in the comparisons with Brachytherapy. The ERG have therefore conducted a further exploratory analysis to assess the impact of adjusting the Brachytherapy AE rates to those observed for EBRT in ProtecT, using the difference in the rates for Brachytherapy and EBRT as estimated by Ramsay et al.

2.2 Revision of the 'time to radical therapy' analysis to include deaths as events

Section 3.16 of the ACD notes that the committee had a preference to include an adjustment of the TTRT curve for general population mortality. The ERG had conducted an exploratory analysis using the same approach that the company had used to adjust overall survival and time to metastasis in their original submission. However, in addressing this issue for TTRT the company have adopted a different approach. They have conducted a revised survival analysis of the individual patient data from PCM301, this time including deaths as events rather than censoring events. However, the ERG believes this analysis may be unreliable due to small numbers of deaths and short-term follow-up. The company notes that "*only one*

death in the active surveillance arm was changed from censoring to event, while there were no deaths in the padeliporfin arm". This approach therefore fails to capture the increasing mortality rate over time as the cohort ages, and it is also inconsistent with the approach used in the model to adjust OS and TTM for general population mortality. The ERG prefers the original approach of adjustment for general population mortality to be applied to all curves in the model.

2.3 Expressing time to radical therapy for padeliporfin VTP relative to TTRT for active surveillance in the ProtecT study

Section 3.17 of the ACD notes that that the company's original log-normal extrapolation of the TTRT curve for AS (from PBM301) predicted that most patients on AS would have radical therapy by 10 years, whilst only 55% on AS were observed to have radical therapy by 10 years in ProtecT. The ACD also notes that "*clinical experts explained that it was unlikely that such a high proportion of patients would have radical therapy within 10 years"*.

In response to this comment, the company describe (pages 14-16 of their submitted document) how they have revised their base case to model TTRT for padeliporfin relative to the baseline TTRT observed for AS in ProtecT. This leads to a substantial reduction in the proportion of patients transitioning to radical therapies following padeliporfin compared to that observed in PCM301 (Figure 1). The company note that this "*is a more consistent approach than directly applying the 'time to radical therapy' curves from PCM 301 as the 'time to radical therapy' curve of active surveillance from ProtecT was the most reliable evidence to the UK population in a real-world setting and the model also used the data from the ProtecT study estimating the curve of 'time to metastasis', 'overall survival' and the AE rates"*. They also note that this approach was based on a scenario analysis which was originally requested by the ERG at the clarification stage.

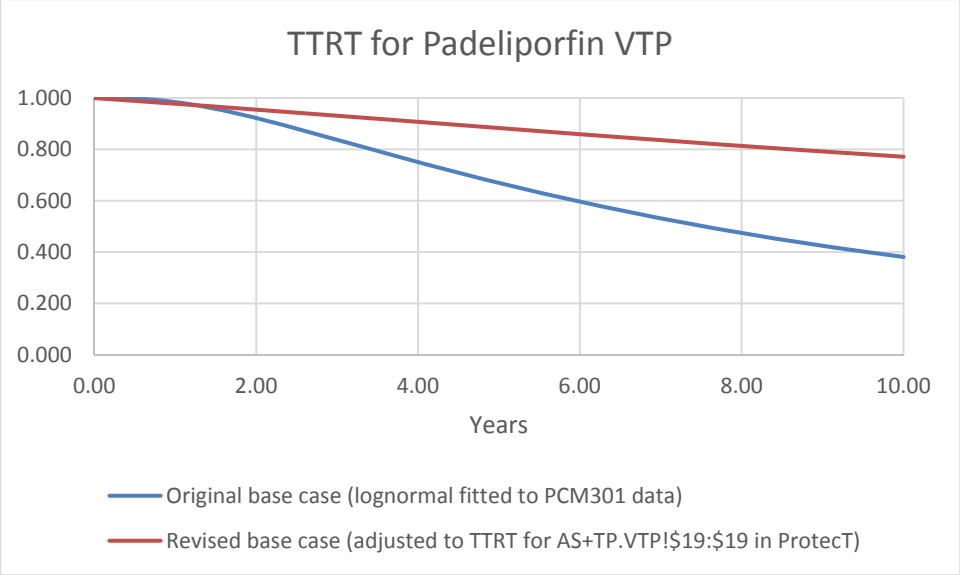


Figure 1: Comparison of modelling approaches for TTRT following treatment with Padeliporfin VTP

The ERG requested this analysis it in the context of the company's originally submitted model, which assumed that AS and padeliporfin would incur an increased risk of progression to metastasis compared to radical therapies, as observed for AS in the ProtecT trial. The company subsequently revised their base case to assume that all treatments would have equivalent time to metastasis. If the committee accept the revised approach to modelling TTRT for padeliporfin, they may also need to consider whether it is still reasonable to assume equivalence in progression to metastasis despite a much lower rate of initiation of radical therapy.

As highlighted by the company when they responded to the ERGs clarification letter, there are also key differences in the AS regimens and criteria for initiating radical therapy that were applied in ProtecT and PCM301. The AS regimen in ProtecT did not use any planned re-biopsies whilst patients in PCM301 had re-biopies at 12 and 24 months. Section 3.9 of the ACD notes that this is a likely explanation for the higher disease progression rate observed for AS in PCM301 compared to ProtecT. It is also a likely contributor to the higher rate of initiation of radical therapy observed for AS in PCM301 compared with ProtecT. Table 1 below outlines the key differences between PCM301 and ProtecT with respect to the surveillance schedules and criteria for initiating radical therapy applied - as provided by the company at clarification stage. A question for the committee, is which one is more likely to

reflect routine clinical practice for the company's selected population following treatment with Padeliporfin. The ERG would further note that the current NICE recommended active surveillance regimen includes a planned biopsy at 12 months, but not at 24 months.

Table 1 Criteria that affect the rate to radical therapy in PCM301 compared to ProtecT (Source: Table 25 of the Company's response to the clarification letter)

Criteria	PCM301	ProtecT	Conclusion
Monitoring schedule	In PCM301 RCT, PSA and DRE measured every 3 months. TRUS-guided biopsy at Month 12 and Month 24. In PCM301 FU5 observational study, PSA testing frequency was based on current practice, which would typically be every 3 to 12 months, depending on patient status and profile of PSA kinetics.	In the active monitoring group, PSA every 3 months in first year and twice yearly thereafter. Rise of at least 50% in PSA during previous 12 months triggered repeat testing within 6-9 weeks No scheduled re-biopsies, only ad-hoc.	While PCM301 and ProtecT have similar PSA schedules, PCM301 includes scheduled biopsies at M12 and M24, which are not included in ProtecT. These lead to earlier detection of disease upgrade and as a result earlier progression to radical therapy
Compliance with monitoring schedule	High compliance	No detailed data, but likely high compliance since ProtecT is an RCT.	Both PCM301 and ProtecT are RCTs with likely similar and high compliance with monitoring schedule. Hence, this parameter should not result in different rate of progression to radical therapy between the two studies.
Pre-planned criteria for consideration to initiate radical therapy	In PCM301, disease progression was defined through the composite co-primary endpoint that included any departure from the inclusion criteria. Specifically: • Any Gleason primary or secondary pattern of 4 or more • More than 3 cores definitively positive for cancer when considering all histological results available during follow-up in the study • At least 1 cancer core length > 5 mm • PSA > 10 ng/mL in 3 consecutive measures • Any T3 prostate cancer • Metastasis	In the AM group, an increase of at least 50% of PSA level during the previous 12 months triggered a review. Management options included continued monitoring or further tests and radical or palliative treatments as required.	Criteria to consider initiation of radical therapy in ProtecT seem to be based on looser guidelines compared to PCM301. It is not clear how frequently PSA increase was associated with re-biopsy and subsequently with treatment decision. Also, it is unclear how baseline disease (in particular Gleason Score 6 vs. greater than 6) impacted subsequent considerations of disease progression and treatment decisions. Therefore, it is likely that the tighter set of criteria in PCM301 led to more frequent detections of disease upgrade and progression to radical therapy than in ProtecT. Of note, initiation of radical

			therapy in PCM301 closely followed disease upgrade.
Baseline risk of progression in patient population	See Table **20** (of the Company's response to the clarification letter)	See **Table 20** (of the Company's response to the clarification letter)	The patient population in ProtecT is more heterogeneous, i.e. it includes very low risk and intermediate risk patients, compared to the patient population in the indication population of PCM301, which is all unilateral low risk, but not very low risk. As shown in Godtman 2016,[14] low risk and intermediate risk patients initially managed with active surveillance tend to have similar profiles of progression to radical therapy, while very low risk patients have a lower likelihood of progression to radical therapy. As a result, this parameter is likely to result in a lower rate of progression to radical therapy in the ProtecT trial compared to PCM301
PSA, prostate specific antigen; DRE, digital rectal exam; TRUS, transrectal ultrasound; AM, active monitoring; EBRT, external; beam radiation therapy; RP, radical prostatectomy; RCT, randomized clinical trial.			

3. Company revised results

The company provide the results from their revised base case analysis and several further sensitivity and scenario analyses in pages 18 to 34 of their submitted document. It can be noted that for each scenario, rather than providing a full incremental analysis which was stated in the ACD to be the preference of the committee, the company have provided an incremental analysis comparing padeliporfin VTP with radical prostatectomy and brachytherapy, and then provided a separate analysis comparing padeliporfin VTP with EBRT. No clear justification was offered for this approach, but it can be noted that EBRT would dominate both radical prostatectomy and brachytherapy in each of the scenarios presented in Tables 5 to 20 of the company's submitted response. Thus the relevant ICER for padeliporfin in a full incremental analysis would be the ICER versus EBRT.

Based on the company results presented, the ICER for padeliporfin compares more favourably to radical prostatectomy and brachytherapy than it does to EBRT. In fact, the ICER versus EBRT lies above £30,000 in the key scenarios presented in the tables 5 -20 of the company's submitted document.

A further point to note from the presented scenarios is the large impact that expressing the TTRT curve relative to the AS arm of ProtecT has had on the ICER. When the company apply a lognormal curve directly to their TTRT data from PCM301, the ICERs for padeliporfin increase from £22,805, £9,691 and 49,206, to £65,985, £17,765 and £113,214 versus radical prostatectomy, brachytherapy ad EBRT respectively. The results are less sensitivity to changes in the parametric curves fitted to PCM301 AS and padeliporfin TTRT data when the padeliporfin curve is estimated relative to ProtecT AS curve. This is because these fitted curves are only used to estimate relative multiplies which are then applied to the much shallower TTRT curve observed for AS in ProtecT.

Finally, the company have provided new probabilistic analyses for pairwise comparisons of padeliporfin versus each radical therapy (figures 5 to 7 of their submitted document). Compared with RP, the probability of cost-effectiveness ranges from ~40% to ~63% at willingness to pay per QALY thresholds of £20,000 and £30,000 per QALY respectively. The corresponding probabilities of cost-effectiveness compared with brachytherapy are ~85%

to ~94%. Compared with brachytherapy, the probability of cost-effectiveness remains below 20% across the £20,000 to £30,000 threshold range.

4. ERG further analysis

As noted above, the ERG has uncertainty about the following issues in the company's revised analysis:

- The comparability of the AE rates for brachytherapy, which are based on Ramsay et al.
- The approach used to incorporate mortality in the TTRT curve for padeliporfin
- The adjustment of the TTRT curve for padeliporfin relative to the TTRT curve observed for AS in ProtecT.

To further explore the uncertainty surrounding these issues, the ERG conduct the following scenario analyses.

1. Adjustment of adverse event rates for brachytherapy relative to the adverse event rates observed for EBRT in ProtecT, using the difference in the rates between EBRT and brachytherapy reported by Ramsay et al. In this analysis the brachytherapy rates are calculated by applying the following estimated rate increments to the EBRT prevalence rates from ProtecT - Short term UI: +0.29; short-term ED: +0.244; short-term BD +0.068; long-term UI: +0.287; long-term ED: +0.22; long-term BD: +0.035.
2. Application of the same approach to incorporate general population mortality in the TTRT curve for padeliporfin, as used to incorporate general population mortality into the overall survival and time to metastasis curves.
    a. For the companies revised TTRT curve which is expressed relative to TTRT for AS in ProtecT
    b. For the direct extrapolation of the TTRT curve from PCM301

These analyses are presented in Tables 2 and 3 below, with and without the revised PAS respectively.

Table 2: Further exploratory analysis undertaken by the ERG (with PAS)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) *	Pairwise ICER for VTP
Company post ACD revised base case (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	48,841
RP	[redacted]	[redacted]	[redacted]	3,613	-0.040	0	Dominated by EBRT	22,831
Brachytherapy	[redacted]	[redacted]	[redacted]	5,143	-0.167	0	Dominated by EBRT	9,807
VTP	[redacted]	[redacted]	[redacted]	8,483	0.174	0	48,841	-
1. Adjustment of brachytherapy AE rates to ProtecT (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	48,680
RP	[redacted]	[redacted]	[redacted]	3,613	-0.040	0	Dominated by EBRT	22,759
Brachytherapy	[redacted]	[redacted]	[redacted]	4,091	-0.001	0	Dominated by EBRT	25,057
VTP	[redacted]	[redacted]	[redacted]	8,479	0.174	0	48,680	-
2. ERG adjustment of TTRT for general population mortality – VTP curve adjusted to ProtecT AS data (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	54,826
RP	[redacted]	[redacted]	[redacted]	3,613	-0.040	0	Dominated by EBRT	25,600
Brachytherapy	[redacted]	[redacted]	[redacted]	5,143	-0.167	0	Dominated by EBRT	10,878
VTP	[redacted]	[redacted]	[redacted]	8,681	0.158	0	54,826	-
3. ERG adjustment of TTRT for general population mortality – VTP curve based directly on lognormal extrapolation of PCM301 data (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	130,307
RP	[redacted]	[redacted]	[redacted]	3,613	-0.040	0	Dominated by EBRT	63,065
Brachytherapy	[redacted]	[redacted]	[redacted]	5,143	-0.167	0	Dominated by EBRT	25,999
VTP	[redacted]	[redacted]	[redacted]	11,847	0.091	0	130,307	-

Notes: *ICER for full incremental analysis

Table 3: Further exploratory analysis undertaken by the ERG (without PAS)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY) *	Pairwise ICER for VTP
Company post ACD revised base case (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	[redacted]
RP	[redacted]	[redacted]	[redacted]	[redacted]	-0.040	0	[redacted]	[redacted]
Brachytherapy	[redacted]	[redacted]	[redacted]	[redacted]	-0.167	0	[redacted]	[redacted]
VTP	[redacted]	[redacted]	[redacted]	[redacted]	0.174	0	[redacted]	-
1. Adjustment of brachytherapy AE rates to ProtecT (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	[redacted]
RP	[redacted]	[redacted]	[redacted]	[redacted]	-0.040	0	[redacted]	[redacted]
Brachytherapy	[redacted]	[redacted]	[redacted]	[redacted]	-0.001	0	[redacted]	[redacted]
VTP	[redacted]	[redacted]	[redacted]	[redacted]	0.174	0	[redacted]	-
2. ERG adjustment of TTRT for general population mortality – VTP curve adjusted to ProtecT AS data (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	[redacted]
RP	[redacted]	[redacted]	[redacted]	[redacted]	-0.040	0	[redacted]	[redacted]
Brachytherapy	[redacted]	[redacted]	[redacted]	[redacted]	-0.167	0	[redacted]	[redacted]
VTP	[redacted]	[redacted]	[redacted]	[redacted]	0.158	0	[redacted]	-
3. ERG adjustment of TTRT for general population mortality – VTP curve based directly on lognormal extrapolation of PCM301 data (with PAS)								
EBRT	[redacted]	[redacted]	[redacted]	-	-	-	-	[redacted]
RP	[redacted]	[redacted]	[redacted]	[redacted]	-0.040	0	[redacted]	[redacted]
Brachytherapy	[redacted]	[redacted]	[redacted]	[redacted]	-0.167	0	[redacted]	[redacted]
VTP	[redacted]	[redacted]	[redacted]	[redacted]	0.091	0	[redacted]	-

Notes: *ICER for full incremental analysis

In addition to the above analyses, the ERG were unable to replicate a number of the Company's presented scenario analyses when applying the changes described. The ERG have therefore produced the results they have obtained for each of these scenarios for comparison with the company's results. These are provided in appendix 1, and show relatively minor differences.

3. Conclusions

In conclusion, the revised modelling submitted by the company is generally in line with the preferences of committee as outlined in the ACD. With the model revisions combined with the patient access scheme, the company base case ICER for padeliporfin VTP falls below £30,000 against radical prostatectomy and brachytherapy. However it remains above £30,000 against EBRT. It is also worth noting that that EBRT was omitted from the full incremental analysis in the company's submitted results, and EBRT in fact dominates the other radical therapies when applying the adverse event rates from ProtecT. It may be therefore be relevant, as the company suggest, to consider padeliporfin as an option for "*patients who refuse treatment with EBRT or are contraindicated for EBRT"*.

The company results appear robust to the majority of scenario analyses performed. However, they also illustrate the key impact of the approach to modelling TTRT for padeliporfin VTP. In their revised base case, the company have adjusted the TTRT curve for padeliporfin relative to the TTRT curve for AS observed in ProtecT. This substantially increases the proportion of patients remaining in the pre-RT state in comparison with the original approach of modelling TTRT based on extrapolation of the observed TTRT data from PCM301. When the original approach is applied in conjunction with the ProtecT adverse event data, the ICER for padeliporfin rises above £60,000 against radical prostatectomy, but remains below £20,000 against brachytherapy. It is important for the committee to consider whether this represents a valid approach in the context of current NHS practice. In particular, is it reasonable to continue to assume an equivalent risk of progression to metastasis for this population, in conjunction with this much lower rate of initiation of radical therapy? It is worth noting that the AS strategy applied in ProtecT (for the ProtecT population) was associated with an increased risk of metastasis compared with radical therapy. However, patients treated with padeliporfin will benefit from anti-tumour activity.

The substantially lower ICER for padeliporfin versus brachytherapy is due to the fact that the adverse event rates for brachytherapy in the company's revised model are much higher than the they are for radical prostatectomy and EBRT. This is because these rates remain based on the higher estimates from Ramsay et al. No data are available from ProtecT for this comparator. To address the impact of uncertainty surrounding the adverse event rates for brachytherapy, the ERG conducted a scenarios analysis where these rates were adjusted to the ProtecT EBRT rates - using the difference between the EBRT and brachytherapy rates estimated by Ramsay et al. This increased the ICER for padeliporfin versus brachytherapy from £9,807 to £25,057 (with PAS).

A further uncertainty relates to the approach the company have used to adjust the padeliporfin TTRT curve for general population mortality. Whilst in theory the company's approach is correct for the purpose of a partitioned survival analysis, the small sample combined with the short follow-up and lack of observed deaths, means that the TTRT curve for padeliporfin does not include deaths. This may fail to capture the increasing risk of death from the pre-radical therapy state as the cohort ages, and is inconsistent with the approach used to adjust the overall survival and time to metastasis (or death) curves used in the model. Therefore the ERG have assessed the impact of applying their previous approach to adjusting TTRT for mortality. This has a modest impact on the ICERs.

References

1. European Medicines Agency. Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500201945.pdf. (Accessed 39 July 2018)
2. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med 2016;375(15):1425-37.
3. Ramsay CR, Adewuyi TE, Gray J, Hislop J, Shirley MD, Jayakody S, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess 2015;19(49):1-490.

Appendix 1: ERG results for company presented scenarios which it cannot replicate exactly

Table A1: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = Weibull, padeliporfin TTRT = exponential (Table 7 from company's post-ACD submission)

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,649	0.207	0	22,420
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-4,649	-0.207	0	22,420
BT	[redacted]	[redacted]	[redacted]	-3,119	-0.335	0	9,321
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table A2: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = Weibull, padeliporfin TTRT = exponential (Table 8 from company's post-ACD submission)

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,262	-0.168	0	49,259
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Table A3: Revised scenario analysis for padeliporfin vs RP and BT; AS TTRT = Weibull, padeliporfin TTRT = loglogistic (Table 11 from company's post-ACD submission)

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Full Incremental analysis (versus baseline)							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	4,484	0.214	0	20,933
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-4,484	-0.214	0	20,933
BT	[redacted]	[redacted]	[redacted]	-2,954	-0.341	0	8,650
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AS, active surveillance; TTRT, time to radical therapy.							

Note the ERG can produce the results presented in Table 11 of the company's submitted document when loglogistic distributions are applied to both for AS and padeliporfin.

Table A4: Revised scenario analysis for padeliporfin vs EBRT; AS TTRT = Weibull, padeliporfin TTRT = loglogistic (Table 12 from company's post-ACD submission)

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise analysis (versus padeliporfin)							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-8,097	-0.175	0	46,384
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AS, active surveillance; TTRT, time to radical therapy.							

Note the ERG can produce the results presented in Table 12 of the company's submitted document when loglogistic distributions are applied to both for AS and padeliporfin

Table A5: Revised scenario analysis for padeliporfin vs RP and BT; ProtecT AE prevalence + TTRT from PCM 301 only (Table 19 from company's post-ACD submission)

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Incremental Analysis							
RP	[redacted]	[redacted]	[redacted]	-	-	-	-
BT	[redacted]	[redacted]	[redacted]	1,530	-0.127	0	Dominated by RP
Padeliporfin	[redacted]	[redacted]	[redacted]	8,336	0.146	0	57,094
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
RP	[redacted]	[redacted]	[redacted]	-8,336	-0.146	0	57,094
BT	[redacted]	[redacted]	[redacted]	-6,806	-0.273	0	24,904
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; RP, radical prostatectomy; BT, brachytherapy; AE, adverse event; TTRT, time to radical therapy.							

Note, the ERG believe the company made an error in their implementation of the above analysis in their submitted document as their RP total cost and QALY is different to the base case estimate, and the above scenario should only affect the VTP costs and QALYs.

Table A6: Revised scenario analysis for padeliporfin vs EBRT; ProtecT AE prevalence + TTRT from PCM 301 only (Table 20 from company's post-ACD submission)

Intervention	Total costs	Total QALYs	Total LYs	Incremental			ICER
				Costs	QALYs	LYs	(cost/QALY)
Pairwise Analysis							
Padeliporfin	[redacted]	[redacted]	[redacted]	-	-	-	-
EBRT	[redacted]	[redacted]	[redacted]	-11,949	-0.106	0	112,345
Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life years; QALYs, quality-adjusted life years; EBRT, external beam radiotherapy; AE, adverse events; TTRT, time to radical therapy.							

Note, the ERG believe the company made an error in their implementation of the above analysis in their submitted document as their EBRT total cost and QALY is different to the base case estimate, and the above scenario should only affect the VTP costs and QALYs.