Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial

Abdel-Rahmène Azzouzi, Sébastien Vincendeau, Eric Barret, Antony Cicco, François Kleinclauss, Henk G van der Poel, Christian G Stief, Jens Rassweiler, Georg Salomon, Eduardo Solsona, Antonio Alcaraz, Teuvo T Tammela, Derek J Rosario, Francisco Gomez-Veiga, Göran Ahlgren, Fawzi Benzaghou, Bertrand Gaillac, Billy Amzal, Frans M J Debruyne, Gaëlle Fromont, Christian Gratzke, Mark Emberton, on behalf of the PCM301 Study Group

Summary

Background Vascular-targeted photodynamic therapy, a novel tissue-preserving treatment for low-risk prostate cancer, has shown favourable safety and efficacy results in single-arm phase 1 and 2 studies. We compared this treatment with the standard of care, active surveillance, in men with low-risk prostate cancer in a phase 3 trial.

Methods This randomised controlled trial was done in 47 European university centres and community hospitals. Men with low-risk, localised prostate cancer (Gleason pattern 3) who had received no previous treatment were randomly assigned (1:1) to vascular-targeted photodynamic therapy (4 mg/kg padeliporfin intravenously over 10 min and optical fibres inserted into the prostate to cover the desired treatment zone and subsequent activation by laser light 753 nm with a fixed power of 150 mW/cm for 22 min 15 s) or active surveillance. Randomisation was done by a web-based allocation system stratified by centre with balanced blocks of two or four patients. Best practice for active surveillance at the time of study design was followed (ie, biopsy at 12-month intervals and prostate-specific antigen measurement and digital rectal examination at 3-month intervals). The co-primary endpoints were treatment failure (histological progression of cancer from low to moderate or high risk or death during 24 months' follow-up) and absence of definite cancer (absence of any histology result definitely positive for cancer at month 24). Analysis was by intention to treat. Treatment was open-label, but investigators assessing primary efficacy outcomes were masked to treatment allocation. This trial is registered with ClinicalTrials.gov, number NCT01310894.

Findings Between March 8, 2011, and April 30, 2013, we randomly assigned 206 patients to vascular-targeted photodynamic therapy and 207 patients to active surveillance. Median follow-up was 24 months (IQR 24–25). The proportion of participants who had disease progression at month 24 was 58 (28%) of 206 in the vascular-targeted photodynamic therapy group compared with 120 (58%) of 207 in the active surveillance group (adjusted hazard ratio 0·34, 95% CI 0·24–0·46; p<0·0001). 101 (49%) men in the vascular-targeted photodynamic therapy group had a negative prostate biopsy result at 24 months post treatment compared with 28 (14%) men in the active surveillance group (adjusted risk ratio 3·67, 95% CI 2·53–5·33; p<0·0001). Vascular-targeted photodynamic therapy was well tolerated. The most common grade 3–4 adverse events were prostatitis (three [2%] in the vascular-targeted photodynamic therapy group *vs* one [<1%] in the active surveillance group), acute urinary retention (three [2%] *vs* one [<1%]) and erectile dysfunction (two [1%] *vs* three [1%]). The most common serious adverse event in the vascular-targeted photodynamic therapy group was retention of urine (15 patients; severe in three); this event resolved within 2 months in all patients. The most common serious adverse event in the active surveillance group was myocardial infarction (three patients).

Interpretation Padeliporfin vascular-targeted photodynamic therapy is a safe, effective treatment for low-risk, localised prostate cancer. This treatment might allow more men to consider a tissue-preserving approach and defer or avoid radical therapy.

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Department of Urology, Angers University Hospital, Angers, France (Prof A-R Azzouzi MD); **Department of Urology, CIC-INSERM 1414, Rennes University Hospital, Rennes, France** (Prof S Vincendeau MD); **Department of Urology, Institut Montsouris, Université Paris Descartes, Paris, France** (Prof E Barret MD); **Department of Urology, Centre Catalan Urologie Andrologie, Cabestany, France** (Prof A Cicco MD); **Department of Urology, Besançon University Hospital, Besançon, France** (F Kleinclauss MD); **Department of Urology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands** (H G van der Poel MD); **Department of Urology, LMU-Klinikum der Universität München, Munich, Germany** (Prof C G Stief MD, Prof C Gratzke MD); **Department of Urology, SLK Kliniken, Heilbronn, Germany** (Prof J Rassweiler MD); **Martini-Clinic Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany** (G Salomon MD); **Department of Urology, Fundación Instituto Valenciano de Oncología, Valencia, Spain** (Prof E Solsona MD); **Department of Urology, Hospital Clinic, Barcelona, Spain** (Prof A Alcaraz MD); **Department of Urology, Tampere University Hospital**

Introduction

Active surveillance, a policy of delayed selective intervention, is an appropriate therapeutic option for low-risk prostate cancer that helps to mitigate the consequences of overtreatment.[1] Most studies—although admittedly single-centre and non-comparative—have demonstrated favourable outcomes with active surveillance, but this approach has been associated with fairly high intervention rates, especially in cohorts with less stringent eligibility criteria.[2] Intervention, or crossover to radical treatment (surgery or radiotherapy) or systemic therapy (androgen suppression), tends to be driven by—

and School of Medicine, Tampere, Finland (Prof T T Tammela MD); Academic Department of Urology, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK (D J Rosario MD); Department of Urology, Salamanca University Hospital GITUR-IBSAL, Salamanca, Spain (F Gomez-Veiga MD); Department of Urology, University Hospital Complex, La Coruna, Spain (F Gomez-Veiga MD); Department of Urology, Skäne University Hospital, Malmö, Sweden (G Ahlgren MD); Medical Department, Steba Biotech, Paris, France (F Benzaghou MD, B Gaillac MD); LA-SER Analytica, London, UK (B Amzal PhD); Andros Men's Health Institute, Arnhem, Netherlands (F M J Debruyne MD); Department of Pathology, Tours University Hospital, Tours, France (G Fromont MD); and Division of Surgery and Interventional Science, University College London, London, UK (Prof M Emberton FMedSci)

Correspondence to: Prof Mark Emberton, UCL Faculty of Medical Sciences, London W1T 7NF, UK
m.emberton@ucl.ac.uk

Research in context

Evidence before this study

We searched Medline (through PubMed), Embase, Web of Science, and Cochrane Review databases from inception to Oct 31, 2012. During the past decade, several proof-of-concept studies of focal therapy for prostate cancer have been published, but they have typically been single-centre, small, and of low quality. However, results of these studies showed the feasibility of more targeted treatment for prostate cancer and, more importantly, suggested high levels of patient acceptability because of excellent functional outcomes. More recently, registered prospective development studies and formal phase 1 and phase 2 studies have demonstrated both safety and early (short-term) oncological efficacy of focal therapy in the management of localised prostate cancer. These studies were summarised in a systematic review by Valerio and colleagues, who identified the need for comparative studies.

Added value of this study

To our knowledge, our study is the first prospective comparative trial of the efficacy and safety of focal therapy and the first assessment of active surveillance for prostate cancer in a comparative setting. Our results show that men with localised, low-risk prostate cancer can be treated in a way that not only preserves their genitourinary function but also results in a lower progression rate, a greater chance of being declared disease-free, and a reduction in need for whole-gland radical therapy in the form of surgery or radiotherapy compared with active surveillance.

Implications of all the available evidence

Our study adds substantial weight to the argument that we need a more risk-stratified approach to care. Between the extremes of active surveillance for men at very low risk and radical therapy and multimodality treatments for men at high risk (for whom the consequences of treatment are matched by benefit) is the option of vascular-targeted photodynamic therapy, an intervention that preserves prostate tissue when it is both possible and practical to do so. In view of the precision of current risk stratification, future research will need to explore patient preferences and the upper threshold of risk (as defined by tumour grade, volume, location, multiplicity) that determines the transition point at which tissue preservation is likely to confer diminishing returns and should be supplanted by whole-gland radical therapy.

in descending order of frequency—pathological upgrading on repeat biopsy, biochemical progression, and patient choice.[3]

Focal therapy and active surveillance are both tissue-preserving strategies. They share the goal of preserving prostate tissue and consequently function by delaying or avoiding radical whole-gland treatment in men in whom it is safe to do so.[4] However, focal therapy differs from active surveillance in that it treats disease—by the process of selective tissue ablation—above a certain risk threshold and monitors disease below that threshold, because the latter is deemed to be clinically insignificant. A risk-stratified clinical pathway that offers men focal therapy in a manner complementary to active surveillance might result in two potential benefits: a reduction in the probability of progression or crossover to radical therapy and an increase in the proportion of men eligible and willing to undergo a tissue-preserving treatment.

Focal therapy and active surveillance have not previously been compared in a prospective efficacy study. Both approaches have been assessed in single-centre series,[2,5,6] in which the outcomes were dependent on the population studied, the diagnostic precision at baseline, the intensity and manner of the reclassification tests, and the study duration. These limitations challenge informed decision making by patients because the attributes that are most likely to influence treatment selection are the failure rates and toxicity profiles of the two approaches and the likelihood of avoiding radical therapy.

We compared the efficacy and safety of focal therapy versus the standard of care, active surveillance, in men with low-risk, localised prostate cancer. The selective ablation in our focal therapy group was achieved by vascular-targeted photodynamic therapy with padeliporfin (WST 11), an agent that achieves its tissue effects non-thermally and had previously been assessed in both preclinical and clinical settings.[7,8]

Methods

Study design and participants

This study (CLIN1001 PCM301) was a randomised, controlled, clinical trial done in 47 university centres and community hospitals in ten European countries (Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the UK). Men aged 18 years or older with low-risk, localised prostate cancer diagnosed by transrectal ultrasound (TRUS)-guided biopsy who had received no previous treatment were enrolled, provided they were eligible to be exposed to a photosensitising agent and had no contraindications to undergoing MRI. Participants were required to have low-risk, but not very low-risk, prostate cancer. Men were eligible if one core of cancer that was free of Gleason patterns 4 or 5 was present, provided that the cancer core length was between 3 mm and 5 mm. In other words, if only one core was positive, only Gleason pattern 3 was permitted, but the cancer core length had to be greater than or equal to 3 mm and less than or equal to 5 mm. Men with two or three positive cores were also included, but cancer core length could not exceed 5 mm, and Gleason patterns 4 or 5 were excluded. Clinical stage was limited to up to T2a (pathological or radiological up

to T2c disease permitted), prostate-specific antigen (PSA) concentration less than or equal to 10 ng/mL, and prostate volume greater than or equal to 25 cm³ and less than 70 cm³. These criteria were based on prediction determinants in active surveillance subsequently reported by Welty and colleagues.[9] Patients' performance status was not a criterion for study inclusion. Instead, two overarching requirements had to be satisfied: men had to have a predicted life expectancy of 10 years or more and also had to be free of any medical conditions that were deemed to be a contraindication to general anaesthesia. We excluded men with a contraindication to MRI (eg, cardiac pacemaker), factors excluding accurate reading of pelvic MRI (eg, bilateral hip replacements), or any disorder or history of illness or surgery that might have posed an additional risk to men undergoing the vascular-targeted photodynamic therapy procedure. Criteria for study discontinuation were occurrence of a serious adverse event (and if recommended by the investigator), participant withdrawal, or a major protocol violation. A protocol amendment (Oct 23, 2012) excluded men with a history of surgery for benign prostatic hypertrophy (including transurethral prostatectomy) for safety reasons.

The study was done in compliance with Good Clinical Practice and according to a written protocol approved by each centre's ethics committee. All participants provided written informed consent. The trial was completed in accordance with the protocol.

Randomisation and masking

Investigators enrolled participants and allocated them to the vascular-targeted photodynamic therapy or active surveillance groups in a 1:1 ratio by use of a web-based randomisation system generated by the sponsor and stratified by centre with balanced blocks of variable size (two or four men). Treatment was open-label (participants and investigational site staff were not masked to study treatment), but investigators assessing primary efficacy outcomes were masked to treatment allocation.

Procedures

Active surveillance was done according to best practice at the time of study design,[10,11] and consisted of a protocol-directed biopsy at 12-month intervals and PSA measurement coupled with a digital rectal examination at 3-month intervals.

Men randomly assigned to vascular-targeted photodynamic therapy underwent pretreatment multiparametric MRI, which was centrally reviewed with the biopsy results by a committee composed of radiologists and urologists who made detailed recommendations on the number, length, and position of interstitial optical fibres using treatment guidance software.[8,12] The treatment guidance software was used to generate a light-density index (a measure of the energy exposure per unit volume of target tissue) of more than 1, which had been associated with a high probability of ablation in a single zone in earlier studies.[8] However, the urologist in charge of the treatment was allowed to adapt the treatment recommendations to the actual volume and shape of the prostate observed on the TRUS images at the time of the procedure. Once the fibres were accurately positioned in the prostate to cover the desired treatment zone, 4 mg/kg padeliporfin (Aptuit Glasgow, Glasgow, UK) was administered intravenously over 10 min. The drug was activated in the treatment zone by laser light at 753 nm with a fixed power of 150 mW/cm over 22 min 15 s, corresponding to an energy dose of 200 J/cm.[13] Patients with bilateral cancer received a second procedure for contralateral tissue treatment. Retreatment of tissue positive for prostate cancer at the 12-month biopsy was permitted. The vascular-targeted photodynamic therapy procedure was done under a general anaesthetic during a 2-h operating theatre allocation with a planned overnight stay. The urethral catheter was removed the morning after the procedure.

For men in both groups, PSA was measured and digital rectal examination done every 3 months. TRUS-guided, 12-core biopsy was done at months 12 and 24. Thus, the sampling density (number of cores per unit volume of tissue) in men who received vascular-targeted photodynamic therapy was greater than in men in the active surveillance group, particularly for photodynamic therapy-treated tissue with reduced volume associated with post-treatment fibrosis. Biopsy samples were read centrally by an independent pathologist masked to treatment assignment and also by a local pathologist. An independent, blinded outcomes review panel reviewed all PSA data and TRUS-guided biopsy reports to assess these results and determined the number and location of positive cores. In the case of discrepancy between the local and central biopsy readings, the panel's pathologist adjudicated. Any additional radical prostate cancer treatments, metastases, evidence of T3 disease, and severe prostate cancer-related events were recorded at months 12 and 24. Any participant who underwent radical prostate cancer treatment without histological progression (because of patient or physician preference) continued in the study until the end (month 24) and subsequently returned to standard care.

The International Prostate Symptom Score (IPSS) and the 15-question International Index of Erectile Function (IIEF-15) questionnaires were administered every 3 months until month 12 and at month 24 (and at 7 days post procedure for men who received vascular-targeted photodynamic therapy). Validity and sensitivity of these questionnaires to detect change in genitourinary function have been established.[14,15] The EuroQol-5D (EQ-5D) questionnaire was administered at month 12 and month 24 to assess quality of life. All adverse events were recorded from signing of the consent form until the end of the study (including any occurring after the initiation of additional prostate cancer treatment). At each study

For the **protocol synopsis of this study** see http://www.stebabiotech.com/protocole301.pdf

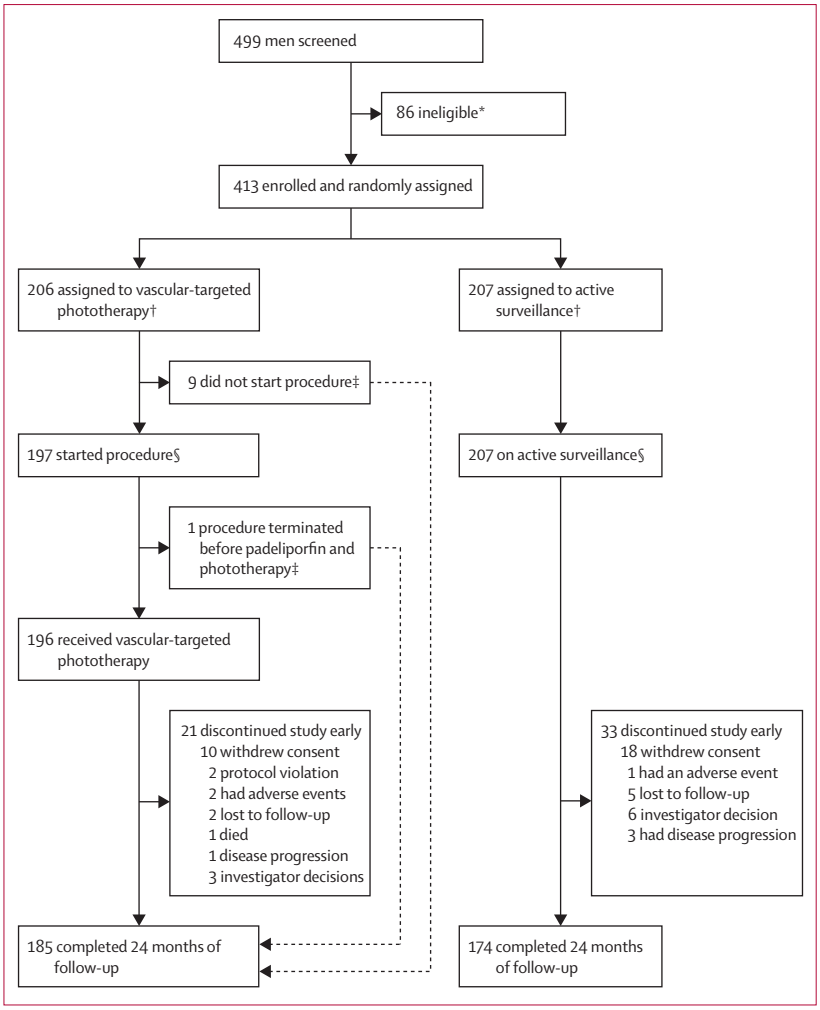


Figure 1: **Trial profile**
*Reasons for ineligibility are included in the appendix. †All randomised participants were included in the efficacy analyses (intention-to-treat population). ‡Three withdrew consent, three withdrawn because of exclusion criteria (bladder cancer discovered on pretreatment MRI, Gleason 3 + 4 score, history of transurethral prostate resection), one withdrawn by the investigator because of non-compliance, one had a myocardial infarction, and one was claustrophobic so unable to undergo the pretreatment MRI. §All men randomly assigned to vascular-targeted photodynamic therapy who received any padeliporfin or initiated any study treatment-related procedure and all men randomly assigned to active surveillance were included in the safety analyses.

visit, the investigator asked the participant about adverse events and intercurrent illnesses since his last visit. The questions were general, and the presence or absence of specific adverse events was not solicited from participants. Severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The investigator assessed the relation of each adverse event to the study drug (padeliporfin), device, and procedure. Adverse events were coded and categorised according to the Medical Dictionary for Regulatory Activities version 18.0. Laboratory assessments (haematology, coagulation studies, serum chemistry, and urinalysis) were assessed every 3 months. Troponin was measured before discharge and quantitative D-Dimer tests were given before anaesthesia, before discharge, and at 7 days post treatment in men who received vascular-targeted photodynamic therapy. Vital signs assessments, electrocardiogram, and physical examination were done before and after the procedure in men who received vascular-targeted photodynamic therapy. An independent data safety monitoring board (consisting of two urologists, a laser surgery expert, and a statistician) reviewed safety data and serious adverse events reports throughout the study and advised the sponsor on matters of participant safety.

Outcomes

The prespecified co-primary efficacy endpoints were treatment failure (histological progression of cancer from low to moderate or high risk or death during 24 months' follow-up) and absence of definite cancer (absence of any histology result definitely positive for cancer at month 24). Moderate or high risk was defined as the observation of at least one of the following events: more than three cores definitely positive for cancer when considering all histological results available during follow-up in the study, any Gleason primary or secondary pattern of 4 or higher, at least one cancer core length more than 5 mm, PSA concentration more than 10 ng/mL in three consecutive measures, or any T3 prostate cancer, or metastasis. The prespecified secondary objectives were the total number of positive prostate core samples; the proportion of patients who underwent radical therapy; frequency of severe prostate cancer-related events (cancer progression to T3, metastasis, prostate cancer-related death); frequency of adverse events; proportion of patients with significant changes in scores of the IPSS questionnaire or the IIEF questionnaire and EQ-5D.

Statistical analysis

The sample size was based on an expected rate of progression from low to moderate or high risk over 2 years of 15% or more in the active surveillance group and 5% in the vascular-targeted photodynamic therapy group. On the basis of these assumptions, the sample size required was 400 men (200 per group), and at least 40 events (men with progression of cancer) needed to be observed for the final analysis to take place.

Statistical analyses were done with SAS version 9.3. All randomised participants were included in the efficacy analyses according to assigned treatment (intention-to-treat population). Missing data were not imputed. Treatment failure (progression) was analysed by survival analysis. Time to progression was compared between the two treatment groups by the log-rank test and quantified using a Cox proportional hazards regression model to derive hazard ratios at month 24, and treatment group and age, number of positive cores, prostate volume, and disease status at baseline were used as covariates. Absence of definite cancer (positive biopsy) was analysed as a dichotomous outcome. We compared proportions of

participants with observed success at month 24 by two-sided Pearson's χ^2 test, and calculated odds and risk ratios. Time to initiation of radical therapy was estimated by the Kaplan-Meier method, and the log-rank test was used for comparison. The mean number of positive cores and maximum cancer core length at months 12 and 24 were compared by Student's *t* test. Other efficacy data were summarised descriptively.

All men randomly assigned to vascular-targeted photodynamic therapy who received any padeliporfin or initiated any study treatment-related procedure and all men randomly assigned to active surveillance were included in the safety analyses according to treatment received. IIEF-15, IPSS, and EQ-5D results were analysed by analysis of covariance. Other safety data, including adverse events, were summarised descriptively. This trial is registered with ClinicalTrials.gov, number NCT01310894.

Role of the funding source

The study sponsor and funder, Steba Biotech, developed the protocol in consultation with the study investigators and the European Medicines Agency (EMA). ICON plc undertook data management on behalf of the sponsor. Statistical analysis was undertaken by Laser Analytica, on behalf of the sponsor. This manuscript was written and approved by all the authors with editorial assistance from a professional medical writer funded by Steba Biotech. AAz and ME had full access to all the data in the study and the corresponding author (ME) had the final responsibility for the decision to submit for publication.

	Vascular-targeted photodynamic therapy (n=206)	Active surveillance (n=207)
Age (years)	64·2 (6·7; 45–85)	62·9 (6·7; 44–79)
Race		
White	202 (98%)	206 (100%)
Other	4 (2%)	1 (<1%)
Body mass index (kg/m²)	26·5 (3·3; 18·8–38·6)	27·3 (4·0; 18·8–44·8)
Time since diagnosis (months)	6·3 (8·5; 0·2–54·2)	6·0 (7·9; 0·2–47·4)
TNM staging		
T1a	1 (<1%)	0
T1c	177 (86%)	180 (87%)
T2a	28 (14%)	27 (13%)
Prostate-specific antigen (ng/mL)	6·2 (2·1; 0·1–10·0)	5·9 (2·0; 0·5–10·0)
Estimated prostate volume (cm³), mean (SD)	42·5 (12·5)	42·5 (11·8)
Disease status		
Unilateral disease	157 (76%)	163 (79%)
Bilateral disease	49 (24%)	44 (21%)
Total number of pretreatment biopsy cores	13·6 (3·3; 10–25)	13·6 (3·6; 10–26)
Total number of pretreatment biopsy cores with cancer	2·1 (0·7; 1–3)	2·0 (0·7; 1–3)
Number of cores		
One core	39 (19%)	52 (25%)
Two cores	110 (53%)	100 (48%)
Three cores	57 (28%)	55 (27%)
Total cancer core length (mm)	4·3 (2·3; 0*–14)	3·8 (2·4; 0*–11)

Data are mean (SD; range) or n (%), unless otherwise stated. TNM=tumour, nodes, metastasis. *Some of the participants included on the basis of two biopsies at the beginning of the study had a negative result for one of the two biopsies.

Table 1: **Demographic and baseline characteristics**

Results

Participants were recruited from March 8, 2011, to April 30, 2013 (see appendix pp 1–3 for lists of investigational sites, principal investigators, and numbers of participants enrolled at each site and in each country). Median follow-up was 24 months (IQR 24–25) for the entire study population and 24 months (24–25) for the vascular-targeted photodynamic therapy group and 25 months (24–25) for the active surveillance group. The study was completed on June 25, 2015, and 413 men were enrolled and randomly assigned to the two treatment groups (206 to vascular-targeted photodynamic therapy and 207 to active surveillance; figure 1). More men in the active surveillance group (n=18) than in the vascular-targeted photodynamic therapy group (n=10) withdrew consent before study completion. Although unwillingness to accept randomisation to either group was an exclusion criterion, the sponsor anticipated that men randomised to active surveillance might withdraw because they had entered the study to receive active treatment; however, the number of such withdrawals was less than expected. Otherwise, the number of men who completed the study and reasons for withdrawal were similar between the two groups (figure 1).

Demographic and baseline disease characteristics were well balanced between the two groups and fit the profile of patients with low-risk prostate cancer (table 1). Of the 206 men randomly assigned to vascular-targeted photodynamic therapy, nine did not receive the procedure: three withdrew consent, three were excluded because of exclusion criteria (bladder cancer discovered on pretreatment MRI, Gleason 3+4 score on previous biopsy, history of transurethral prostate resection), one was withdrawn by the investigator because of non-compliance, one had a myocardial infarction, and one was claustrophobic so unable to undergo the pretreatment MRI.

See Online for appendix

Of the 197 men who started the vascular-targeted photodynamic therapy procedure, one had an anaesthesia reaction before receipt of any padeliporfin or laser treatment. Thus, 196 men received initial vascular-targeted photodynamic therapy (figure 1), of whom 62 received subsequent contralateral treatment, 11 received retreatment, and two received both contralateral treatment and retreatment. A light-density index of 1 or more was achieved in 252 (98%) of 258 initial treatments. Retreated tissue was less likely to achieve a light-density index of 1 or more, although it was exposed to the same energy of 200 J/cm (appendix).

All 413 randomised participants were included in the efficacy analysis (figure 1). Median time to progression

from low-risk to moderate or high-risk prostate cancer was longer in the vascular-targeted photodynamic therapy group (28·3 months, 95% CI 26·0–30·6) than in the active surveillance group (14·1 months, 12·9–23·8; p<0·0001). The proportion of participants who had disease progression at month 24 was lower in the vascular-targeted photodynamic therapy group than in the active surveillance group (adjusted hazard ratio 0·34, 95% CI 0·24–0·46; p<0·0001; table 2). The distribution of predefined progression criteria showed that vascular-targeted photodynamic therapy was efficacious against the individual criteria for progression (table 2). The regression coefficients showed no effect of treatment group or baseline characteristics. The proportion of participants with a negative biopsy result at month 24 was higher in the vascular-targeted photodynamic therapy group than in the active surveillance group (adjusted risk ratio 3·67, 95% CI 2·53–5·33; p<0·0001; table 2). Eight men had a severe prostate cancer-related event within 24 months, only one of whom was in the vascular-targeted photodynamic therapy group (both T3 prostate cancer and metastasis). This participant was probably under-staged at study entry. His first protocol-required biopsy resulted in a Gleason upgrading that, for the purposes of the study, constituted his first—and therefore reported—progression event. Subsequent investigation revealed a locally advanced prostate cancer, and metastasis was detected on further staging investigation.

Compared with the active surveillance group, fewer men in the vascular-targeted photodynamic therapy group subsequently had radical therapy in the form of surgery or radiotherapy (12 [6%] of 206 men in the vascular-targeted photodynamic therapy group *vs* 60 [29%] of 207 men in the active surveillance group; p<0·0001). The time to initiation of radical therapy was also longer in the vascular-targeted photodynamic therapy group compared with the active surveillance group (p<0·0001; figure 2). For men whose prostate cancer did not progress during the study, vascular-targeted photodynamic therapy was associated with clinically and statistically significant decreases at month 24 in all mean tumour burden measurements compared with active surveillance—ie, total number of positive cores (0·9 [SD 1·32] in the vascular-targeted photodynamic therapy group *vs* 2·3 [1·98] in the active group; p<0·0001), total cancer core length (2·6 mm [5·26] *vs* 6·8 mm [9·26]; p<0·0001), and maximum cancer core length (1·6 mm [2·74] *vs* 3·4 mm [3·49]; p<0·0001). Moreover, PSA concentrations decreased by approximately 3·07 ng/mL (SD 2·91) relative to baseline over the course of the study in patients treated with vascular-targeted photodynamic therapy, with a change from baseline of –3·08 (SD 3·05). In the active surveillance group, mean 24 month PSA was 5·27 (SD 4·22), with a change from baseline of –0·68 (SD 4·10). Mean PSA was 6·19 (SD 2·11) in the vascular-targeted photodynamic therapy versus 5·91 (SD 2·05) in the active surveillance group.

Nine men who were randomly assigned to vascular-targeted photodynamic therapy but had no treatment-related procedure were excluded from the safety analysis (figure 1). In the vascular-targeted photodynamic therapy group, IIEF-15 and IPSS assessments showed transient deterioration in erectile and urinary function, but the result at month 24 was similar between the two groups (appendix). The mean EQ-5D questionnaire scores at baseline decrease slightly by month 24 in both the vascular-targeted photodynamic therapy and active surveillance groups with no difference between the two groups (p=0·64), suggesting no decrease in quality of life associated with vascular-targeted photodynamic therapy at month 24 (appendix).

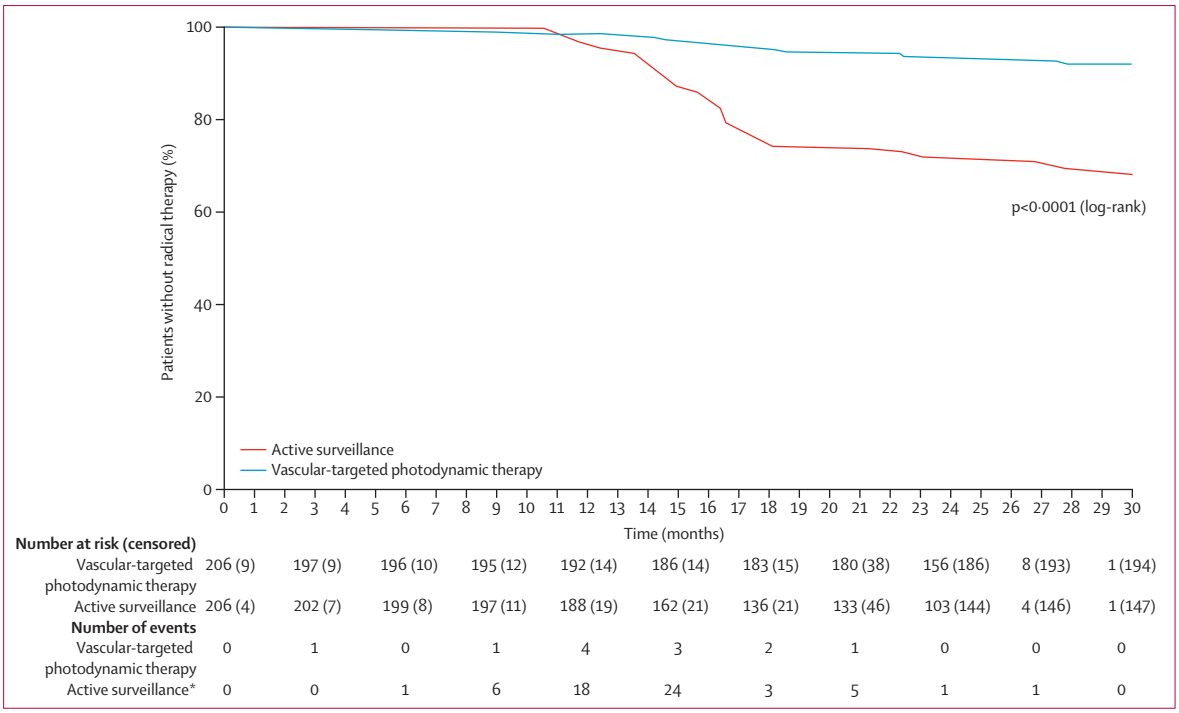
As expected, both the frequency and severity of adverse events and serious adverse events were higher in the vascular-targeted photodynamic therapy group than in the active surveillance group (table 3; appendix). Most men in the vascular-targeted photodynamic therapy group had an adverse event, most of which were mild or moderate in severity, occurred during the procedure or in the days immediately after the procedure, and resolved quickly without sequelae. The reporting of pain that was thought to be related to the procedure (caused by the transcutaneous needle placement or the swelling of the prostate, or both) was captured by the term perineal pain. This event was reported by 30 (15%) of 197 patients in the vascular-targeted photodynamic therapy group and one (<1%) man in the active surveillance group.

Three men had events that required further intervention: two men with urethral stricture required

	Vascular-targeted photodynamic therapy (n=206)	Active surveillance (n=207)	Hazard ratio (95% CI)	p value
Progression	58 (28%)	120 (58%)	0·34 (0·24–0·46)†	<0·0001‡
Criteria for progression§				
>3 positive cores	23 (11%)	58 (28%)	NC	<0·0001¶
Gleason pattern ≥4	49 (24%)	91 (44%)	NC	<0·0001¶
Cancer core length >5 mm	25 (12%)	51 (25%)	NC	0·001¶
PSA >10 ng/mL in three consecutive measures	3 (1%)	14 (7%)	NC	0·007¶
Any T3 prostate cancer	0	4 (2%)	NC	NA
Metastasis	0	0	NC	NA
Prostate cancer-related death	0	0	NC	NA
Negative biopsy result at month 24	101 (49%)	28 (14%)	3·67 (2·53–5·33)‖	<0·0001¶

Data are n (%), unless otherwise stated. NA=not applicable. NC=not calculated. PSA=prostate-specific antigen. *The Hochberg procedure was used to adjust for multiplicity of the two co-primary endpoints. †Adjusted hazard ratio. Cox proportional hazards model with treatment as fixed effect and baseline age, number of positive cores, prostate volume, and disease status (unilateral/bilateral) as covariates. ‡From the log-rank test of equality of survival curves across treatment groups Cox proportional hazards model with treatment as fixed effect and baseline age, number of positive cores, prostate volume, and disease status (unilateral/bilateral) as covariates. §A participant might have met more than one criterion for progression. ¶From Pearson's χ^2 test for observed success. ‖Adjusted risk ratio. Logistic regression model with treatment as fixed effect and baseline age, number of positive cores, prostate volume, and disease status (unilateral/bilateral) as covariates.

Table 2: **Co-primary efficacy endpoints***



Number at risk (censored)											
Vascular-targeted photodynamic therapy	206 (9)	197 (9)	196 (10)	195 (12)	192 (14)	186 (14)	183 (15)	180 (38)	156 (186)	8 (193)	1 (194)
Active surveillance	206 (4)	202 (7)	199 (8)	197 (11)	188 (19)	162 (21)	136 (21)	133 (46)	103 (144)	4 (146)	1 (147)
Number of events											
Vascular-targeted photodynamic therapy	0	1	0	1	4	3	2	1	0	0	0
Active surveillance*	0	0	1	6	18	24	3	5	1	1	0

***Figure 2*: Time to initiation of radical therapy by treatment group**

*One patient who was noted as having had radical therapy had no procedure date and therefore cannot be attributed to any timepoint on the curve.

endoscopic dilatation and one man reported incontinence, which might in time require surgery to restore continence. Men with a history of surgery for benign prostatic hypertrophy (including transurethral prostatectomy) were subsequently excluded from the study (via protocol amendment Oct 23, 2012) to avoid this adverse event. All other reports of incontinence were self-limited, were usually urge-related, and occurred in the period after catheter withdrawal. Incontinence management was at the discretion of the investigator. The most common treatment-related serious adverse event in the vascular-targeted photodynamic therapy group was urinary retention. Typically, this event occurred on the first attempt to withdraw the urinary catheter (postoperative day 1) and was managed with immediate recatheterisation. The timing of a second attempt at removal of the urinary catheter was left to the discretion of the local investigator. All 15 cases of urinary retention resolved within 2 months. The most common serious adverse event in the active surveillance group was myocardial infarction (n=3).

No participants discontinued the vascular-targeted photodynamic therapy procedure because of an adverse event. Three participants discontinued the study because of adverse event: one man in the active surveillance group developed ureteric cancer; one man in the vascular-targeted photodynamic therapy group had an anaphylactic reaction to the anaesthesia given at the start of the procedure (he had received no padeliporfin or vascular-targeted photodynamic therapy); and one man in the vascular-targeted photodynamic therapy group died from myocardial infarction during mountain climbing roughly 8 months after the procedure (the investigator assessed the adverse event as unrelated to study drug, device, or procedure).

An independent data and safety monitoring board reviewed safety data roughly every 3 months throughout the study and advised the study sponsor on matters of participant safety. At all meetings, the members unanimously agreed that no safety issues had emerged in the study.

Discussion

Our findings suggest that compared with patients in the active surveillance group, men with low-risk prostate cancer treated with vascular-targeted photodynamic therapy had longer time to progression, a smaller proportion of patients had progression, and a higher proportion had negative prostate biopsy results at 24 months post treatment. Vascular-targeted photodynamic therapy was safe and well tolerated with only minor and transient deterioration in genitourinary function. Our study has shown that partial-gland ablation by vascular-targeted photodynamic therapy influences the course of prostate cancer in the short-to-medium term. First, the proportion of men with transition from a cancer status to a cancer-free status was increased in the vascular-targeted photodynamic therapy group compared

with the active surveillance group. Second, the proportion of men who progressed from a histologically defined low-risk status to a high risk status was diminished. As a result, fewer men in the vascular-targeted photodynamic therapy group chose to undergo radical therapy during the study period. Moreover, these benefits were achieved safely, efficiently, and without compromising genitourinary function when assessed at 12 and 24 months after the procedure.

	Vascular-targeted photodynamic therapy (n=197)*			Active surveillance (n=207)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Blood and lymphatic system disorders						
Thrombocytopenia	0	1 (<1%)	0	0	0	0
Cardiac disorders						
Angina unstable	0	0	1 (<1%)	0	0	0
Atrial fibrillation	0	1 (<1%)	0	1 (<1%)	0	0
Myocardial infarction	0	1 (<1%)	0	0	2 (<1%)	1 (<1%)
Endocrine disorders						
Hyperthyroidism	1 (<1%)	1 (<1%)	0	0	0	0
Eye disorders						
Cataract	0	2 (1%)	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	4 (2%)	1 (<1%)	0	1 (<1%)	0	0
Gastrointestinal haemorrhage	0	0	0	0	1 (<1%)	0
Inguinal hernia	4 (2%)	4 (2%)	0	1 (<1%)	0	0
Rectal haemorrhage	4 (2%)	4 (2%)	0	0	0	0
General disorders and administration site conditions						
Device failure	0	1 (<1%)	0	0	0	0
Pyrexia	4 (2%)	0	0	2 (<1%)	1 (<1%)	0
Immune system disorders						
Anaphylactic reaction	0	0	1 (<1%)	0	0	0
Drug hypersensitivity	1 (<1%)	2 (1%)	0	0	0	0
Infections and infestations						
Epididymitis	4 (2%)	1 (<1%)	0	0	0	0
Liver abscess	0	0	0	0	1 (<1%)	0
Otitis externa	0	0	0	0	1 (<1%)	0
Orchitis	6 (3%)	1 (<1%)	0	0	0	0
Staphylococcal infection	1 (<1%)	0	0	0	1 (<1%)	0
Urinary tract infection	19 (10%)	2 (1%)	0	7 (3%)	2 (<1%)	0
Injury, poisoning, and procedural complications						
Accident	0	1 (<1%)	0	0	0	0
Craniocerebral injury	0	1 (<1%)	0	0	0	0
Procedural pain	2 (1%)	0	0	2 (<1%)	1 (<1%)	0
Investigations						
Fibrin D-dimer increased	2 (1%)	2 (1%)	0	0	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	3 (2%)	2 (1%)	0	4 (2%)	0	0
Osteoarthritis	2 (1%)	2 (1%)	0	3 (1%)	1 (<1%)	0
Nervous system disorders						
Headache	3 (2%)	1 (<1%)	0	2 (<1%)	0	0
Neoplasms benign, malignant, and unspecified						
Ear neoplasm	0	0	0	0	1 (<1%)	0
Neuroendocrine carcinoma	0	1 (<1%)	0	0	0	0
Tongue cancer recurrent	0	0	0	0	1 (<1%)	0
Tonsillar neoplasm	0	1 (<1%)	0	0	0	0
Ureteric cancer metastatic	0	0	0	0	1 (<1%)	0
Ureteric cancer regional	0	0	0	0	1 (<1%)	0

(Table 3 continues on next page)

Since, to our knowledge, this trial is the first comparative efficacy study of vascular-targeted photodynamic therapy versus active surveillance in prostate cancer, it is important to consider the methodological considerations that were inherent in its design and conduct. Because vascular-targeted photodynamic therapy is an intervention involving both a drug (in this case, padeliporfin) and a device (laser light introduced into the prostate), it was subject to regulatory approval as a drug through the EMA. A pivotal comparative study was therefore necessary, but was challenging to design in a manner that would be acceptable to both patients and clinicians and in which the same primary outcome could be assessed for the intervention and the comparator. We had three options for the comparator: surgery, radiotherapy, or active surveillance. For the first two options, a primary outcome that could be applied to both the experimental group and the control group proved difficult to find. Surgery (radical prostatectomy) would not be suitable for a biopsy-based outcome because there would be no prostate from which to take a biopsy. Radiotherapy would be amenable to a protocol-required biopsy, but the histological outcome would be confounded by the necessary neoadjuvant and adjuvant androgen suppression that constitutes the standard of care. Therefore, active surveillance was the only comparator that could reasonably be used over the intended time frame of the study. In addition, by current standards, the population studied might be considered low risk. However, while the study was in development and being discussed with the EMA, neither active surveillance nor focal therapy were accepted as standard care. The EMA agreed that we could reasonably exclude very low-risk patients. Therefore, lower and upper thresholds of risk (defined by Gleason score and tumour burden) were set, below and above which men were excluded. This low-risk group was the only one that could have been studied at the time. Were the study designed today, in view of the changes to risk categorisation, it is likely that men with well characterised prostate cancer and low-volume secondary Gleason pattern 4 would be included.[16]

A second limitation relates to rapidly changing practice in risk stratification of patients with prostate cancer, most significantly the use of MRI in the diagnostic and re-evaluation phases of active surveillance and focal therapy.[17,18] When the study began, few centres offered MRI to patients on active surveillance or as part of the work-up for focal therapy. Now, it is difficult to imagine using either strategy without MRI. Although only men assigned to vascular-targeted photodynamic therapy had MRI in this study, images were used for treatment

planning only, not for detection or staging. The only way in which unilateral use of MRI could have biased participants' allocation was the detection of colorectal or bladder cancer, which would have triggered a study withdrawal. If the study were repeated today, MRI would have an important role in participant selection and risk stratification for both interventions.[19]

A third concern is discriminating true progression from reclassification. When a biopsy-based strategy is used to refine the risk stratification at given intervals in active surveillance, upgrading (transition from an exclusive Gleason pattern 3 status to one with elements of Gleason pattern 4 or 5) occurs. Determining whether the observed increase in the Gleason score is a correction of inherent diagnostic imprecision or the product of true disease progression has proved challenging. Although no universal definition of clinical significance exists, recently published MRI studies have used the presence of Gleason pattern 4 as the minimum definition of clinically significant prostate cancer.[17,18] Physicians have recommended treatment upon upgrading irrespective of its underlying cause. This strategy seems prudent given that recently published data from two mature series of active surveillance have identified higher risk groups (within the risk profile suitable for active surveillance) that are at greater risk of progression.[2,20,21]

The final issue relates to the efficacy endpoints assessed. If endpoints such as progression to metastases or death had been used, the natural history of low-risk prostate cancer would have required a very large study done over two decades. Some experts advocate prioritising shorter-term, relevant outcomes that are important to patients to support them and their physicians in clinical decision making.[22]

Results of this multicentre study have shown that padeliporfin vascular-targeted photodynamic therapy can be implemented widely and delivered effectively and safely. However, the issue of safety deserves some qualification. Exposure to vascular-targeted photodynamic therapy resulted in an increase in the frequency of serious adverse events from 1 in 10 men on active surveillance to 1 in 3 men who received vascular-targeted photodynamic therapy. Most of the events were expected, genitourinary in nature, and self-limited. The most important of these events was failure to void on catheter removal (urinary retention). This event was managed by replacement of the urethral catheter and extension of the period of dependent urinary drainage.

Notably, most study sites had no previous experience in delivering focal therapy, let alone vascular-targeted photodynamic therapy. Study recruitment was timely over a large geographical area, a scenario that contrasts with the many previous attempts to undertake randomised, comparative studies of treatment for early prostate cancer, which either failed to recruit completely or closed because of poor recruitment.[23] Feasibility is an important attribute for surgical interventions, and our results suggest that vascular-targeted photodynamic therapy can be taught, learned, and delivered by a range of health-care providers and systems; the incidence of permanent urinary toxicity (mainly incontinence), which only occurred in one participant, was also low in our study.

Since our understanding and management of early prostate cancer have changed so much in the past few years, it is worth speculating on how vascular-targeted photodynamic therapy might be used with current diagnostics and risk stratification, which are unrecognisable from those at the time of study design. Adoption

	Vascular-targeted photodynamic therapy (n=197)*			Active surveillance (n=207)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Nervous system disorders						
Cerebrovascular accident	0	2 (1%)	0	0	0	0
Transient ischaemic attack	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0
Psychiatric disorders						
Depression	4 (2%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Renal and urinary disorders						
Dysuria	51 (26%)	0	0	5 (2%)	0	0
Haematuria	55 (28%)	1 (<1%)	0	6 (3%)	0	0
Micturition urgency	21 (11%)	0	0	2 (<1%)	0	0
Pollakiuria	20 (10%)	0	0	6 (3%)	0	0
Urinary incontinence	17 (9%)	2 (1%)	0	9 (4%)	1 (<1%)	0
Urinary retention	29 (15%)	3 (2%)	0	1 (<1%)	1 (<1%)	0
Reproductive system and breast disorders						
Ejaculation failure	14 (7%)	2 (1%)	0	1 (<1%)	0	0
Erectile dysfunction	72 (37%)	2 (1%)	0	21 (10%)	3 (1%)	0
Perineal pain	29 (15%)	1 (<1%)	0	1 (<1%)	0	0
Prostatic pain	5 (3%)	1 (<1%)	0	0	0	0
Prostatitis	7 (4%)	3 (2%)	0	9 (4%)	1 (<1%)	0
Urethral stenosis	1 (<1%)	1 (<1%)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders						
Bronchospasm	0	0	1 (<1%)	0	0	0
Skin and subcutaneous tissue disorders						
Purpura	0	1 (<1%)	0	0	0	0
Surgical and medical procedures						
Cataract operation	2 (1%)	1 (<1%)	0	1 (<1%)	0	0
Facial operation	0	1 (<1%)	0	0	0	0
Knee arthroplasty	0	1 (<1%)	0	0	0	0
Vascular disorders						
Phlebitis	0	0	0	2 (<1%)	1 (<1%)	0
Thrombosis	1 (<1%)	0	0	0	1 (<1%)	0

Data are n (%). Grade 1–2 (when the event occurred in ≥10% of the patients in at least one group) and all grade 3 and 4 treatment-emergent adverse events that occurred during the study period. The worst grade reported for each patient is listed. Events are listed by preferred terms (Medical Dictionary for Regulatory Activities version 18·0), and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). One patient in the vascular-targeted photodynamic therapy group died due to myocardial infarction during mountain climbing about 8 months after completing treatment; the death was assessed to be not related to treatment. *Nine men randomly assigned to vascular-targeted photodynamic therapy did not receive treatment and were excluded from the safety analysis.

***Table 3*: Treatment-emergent adverse effects**

of MRI and targeted biopsy into the clinical pathway has created more precise risk stratification, allowing a more nuanced approach to men with a new diagnosis of prostate cancer. It is likely that a care pathway based on MRI—because of its role as a triage test between a raised PSA concentration and biopsy—will result in a reduction in the number of men who have a biopsy taken and in the proportion of men receiving the diagnosis of clinically insignificant prostate cancer. By contrast, men with an MRI abnormality will undergo targeted biopsy (something that was not possible without MRI), resulting in a greater sensitivity for clinically significant disease. It is very likely that men with clinically significant isolated lesions will be the candidates for focal prostate therapy. Men who do not need treatment should not have it. Men who require whole-gland treatment because of bilateral clinically significant disease should be offered it. Men with locally advanced disease should be offered multimodality therapy. However, men who have low-risk, localised disease can now choose, on the basis of the evidence that our study has generated, how to approach tissue preservation.

More research is needed to address unanswered questions, the principal one being the long-term effect of tissue-preserving treatment on control rates of prostate cancer. One unknown element is the efficacy of padeliporfin vascular-targeted photodynamic therapy in eradicating cancers of different grades within the target volume. A study in men with Gleason pattern 4 (NCT01875393) has been submitted for publication. Another uncertainty relates to the stability of the tissue that lies beyond the treatment zone. This question requires long-term follow-up, which has been initiated in the participants in our study.

Contributors

Laser Analytica did the statistical analysis and interpretation on behalf of the sponsor. AAz, SV, EB, AC, FK, HGVP, CGS, JR, GS, ES, AAl, TTT, DJR, FG-V, GA, ME, and the PCM301 Study Group conducted the study and collected the data. Data management was undertaken by the ICON plc on behalf of the sponsor. FMJD chaired the data safety monitoring board, and GF and CG served on the outcomes review panel. ME prepared the first draft of the manuscript. All authors contributed to the final data interpretation and final draft of the report and approved submission for publication. FB was employed by Steba Biotech for the duration of the study and was responsible for quality control across the study sites. BG is an employee of Steba Biotech and was responsible for protocol development, data interpretation, and manuscript preparation.

Declaration of interests

A-RA, SV, EB, AC, FK, HGVP, CGS, JR, GS, ES, AA, TTT, DJR, FG-V, GA, and ME received payment from Steba as investigators on this study. A-RA and ME have also acted as consultants and proctors for Steba. FMJD, GF, and CG received payment from Steba for other roles on the study (data safety monitoring board, outcomes review panel). BA is a statistical consultant to Steba. FB and BG are employees of Steba. HGVP reports grants from Storz, Astellas, and Intuitive Surgical. FG-V reports receipt of funding for research from Astellas Pharma and acting as a paid proctor for Intuitive Surgical. AA reports payment for speaking engagements from several companies (Astellas Pharma, Janssen Pharmaceutica, Sanofi, Bayer, Steba Biotech, Olympus Corporation). TTT reports being an advisor for Astellas Pharma, Ferring Pharmaceuticals, Orion Corporation, and Bayer, and receiving institutional funding from Astellas Pharma, Ferring Pharmaceuticals, Medivation, Orion Corporation, Bayer, the Finnish Academy of Sciences, Finnish Cancer Foundation, Competitive State Research Financing, Lidds, and Camurus. ME reports acting as a principal/co-investigator in several prostate cancer studies supported by SonaCare Medical, Sophiris Bio, and TROD Medical, and as a consultant/advisor to GSK and Sanofi-Aventis, being a founding partner of London Urology Associates, and shareholdings in Nuada Medical.

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