Prostate Cancer and Prostatic Diseases (2017) 20, 352–360

www.nature.com/pcan

ORIGINAL ARTICLE

Lutetium-177-labelled anti-prostate-specific membrane antigen antibody and ligands for the treatment of metastatic castrate-resistant prostate cancer: a systematic review and meta-analysis

RJS Calopedos[1], V Chalasani[2], R Asher[1,3], L Emmett[4] and HH Woo[1,2]

BACKGROUND: Promising therapeutic results of the prostate-specific membrane antigen (PSMA) ligand have been shown when labelling with lutetium-177 (^{177}Lu). We performed a systematic review and meta-analysis to assess the therapeutic response of ^{177}Lu-PSMA in the treatment of metastatic castration-resistant prostate cancer (mCRPC).
METHODS: A systematic review was conducted using electronic databases up to December 2016. Two reviewers independently extracted data and assessed methodological quality. The main outcome of interest was antitumour biochemical response of ^{177}Lu-PSMA, analysing two measures: 'any PSA decline' and '>50% decline' from baseline. A random-effects meta-analysis was used to calculate the pooled proportion across studies. The I^2 statistic was calculated in each case to investigate the extent of heterogeneity across the studies. A sensitivity analysis was conducted removing two studies, which were presented as abstracts and proportions were summarised by chemical type (^{177}Lu-J591/DKZ/I&T). All analyses were conducted using Stata v14.
RESULTS: A total of 10 studies were included in the analysis giving a total sample size of 369, 220 (of 334 analysable) experienced any PSA decline. The pooled proportion of patients with any PSA decline was 68% (95% confidence interval (CI): 61–74). The I^2 statistic was 39.1% ($P = 0.11$) suggesting minor heterogeneity between results. The pooled proportion of patients with >50% PSA decline was 37% (95% CI: 22–52). The I^2 statistic was 91.0% ($P < 0.001$) suggesting substantial heterogeneity between results. On subgroup analysis, a higher proportion of patients in the ^{177}Lu-DKZ/I&T subgroup had a PSA decline >50%, however, it can be seen that the ^{177}Lu-DKZ/I&T subgroup had a substantial amount of heterogeneity across studies.
CONCLUSIONS: This review suggests promising early results for the treatment of mCRPC, especially from patients treated with the more recently developed radioligands. Overall, our meta-analysis showed that approximately two-thirds of patients had a biochemical response. Randomised-controlled trials would be necessary to verify its effectiveness against current systemic therapies and create an ideal treatment protocol.

Prostate Cancer and Prostatic Diseases (2017) **20,** 352–360; doi:10.1038/pcan.2017.23; published online 25 April 2017

INTRODUCTION

Most cases of prostate cancer (PCa) are curable if diagnosed at an early stage; although a number of patients will still progress from organ-confined disease to metastatic PCa or metastatic castration-resistant PCa (mCRPC). Despite the effectiveness of hormone therapy in the treatment of metastatic PCa, our patients who live long enough will ultimately succumb to mCRPC. Castration-resistant PCa is defined as any disease progression, whether biochemical or radiological, with the presence of castrate-level testosterone values.[1] While palliative chemotherapy and supportive care were the only options available for men with mCRPC in the early 2000s, the therapeutic landscape for mCRPC has changed significantly over the past decade.

The discovery of tumour-associated and tumour-specific target antigens has given rise to the use of radioimmunotherapy (RIT) in the treatment of mCRPC. The most promising target for RIT of PCa to date is glutamate carboxypeptidase II, otherwise known as prostate-specific membrane antigen (PSMA). PSMA is a non-secreted type II transmembrane protein produced almost exclusively by prostatic tissue and on tumour-associated neovasculature.[2] Unlike other biomarkers, such as PSA, which may decrease with increasing neoplastic de-differentiation, the level of PSMA has been shown to be upregulated on high-grade, de-differentitated PCa.[3]

Antibodies that bind to the extracellular domain of PSMA were then developed[4,5] to create a high affinity for mCRPC tissue. Despite the disadvantages of radiolabelled 7E11 monoclonal antibody, it has been Food and Drug Administration approved and validated the use of PSMA for *in vivo* imaging and therapy. This approval has lead the way for a generation of other promising anti-PSMA antibodies.[6] Among these, humanised IgG monoclonal antibody 'J591' was initially identified as the most appropriate anti-PSMA antibody for further trials.[7] ^{177}Lu is a radio-isotope produced in reactors by neutron-capture on natural Lu or enriched ^{176}Lu. The radioisotope is then bound to the anti-PSMA antibody to form therapeutic antibodies, such as ^{177}Lu-J591, which are

[1]Department of Uro-Oncology, Chris O'Brien Lifehouse, University of Sydney, Sydney, NSW, Australia; [2]Northern Clinical School, University of Sydney, Sydney, NSW, Australia; [3]NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia and [4]Nuclear Medicine Department, St Vincent's Hospital, Sydney, NSW, Australia. Correspondence: Professor HH Woo, Department of Uro-Oncology, Chris O'Brien Lifehouse Missendon Road, Camperdown, Sydney, NSW 2006, Australia.
E-mail: hwoo@urologist.net.au
Received 15 February 2017; revised 4 March 2017; accepted 16 March 2017; published online 25 April 2017

administered intravenously. The antibody then binds with the PSMA molecule and is rapidly internalised by malignant cells for the delivery of antibody-conjugated isotopes. Other more recent anti-PSMA ligands showing promising results are the DKFZ-PSMA-617 ligand and the peptide-linker unit DOTAGA-(l-y)fk (Sub-KuE), termed PSMA-I&T.[8–12] The resultant ligand, in its various forms, has been labelled with lutetium-177 (^{177}Lu) for therapeutic purposes in the treatment of mCRPC.

Despite its infancy, numerous individual single-arm trials have shown promising results. In this study, we performed a systematic review and meta-analysis of all trials assessing the *in vivo* therapeutic response of ^{177}Lu-PSMA in the treatment of mCRPC.

MATERIALS AND METHODS

The conduct and reporting of this systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis with predefined search terms, inclusion/exclusion criteria, data collection and analyses.

Eligibility criteria

We included studies that reported original quantitative data on the therapeutic response and side-effect profile of ^{177}Lu-PSMA therapy in the treatment of mCRPC. We included studies without restrictions of sample size, country of origin or age of sample population. The review focused on the antitumour biochemical response of ^{177}Lu-PSMA in men with mCRPC. Studies with incomplete data or purely reporting on the radiological effect or therapeutic side effects of treatment were ineligible (Supplementary Table 1). All studies using ^{177}Lu for the treatment of mCRPC, despite the specific anti-PSMA ligand or antibody used, were included in the analysis. If multiple papers originated from one data set, we included the one with the longest follow-up period.

Search strategy and study selection

A systematic review using electronic databases up to December 2016 was conducted via a search of MEDLINE, Cochrane Library and EmBase. Search terms used in both isolation and combination included 'Lutetium-labeled anti-PSMA, Lutetium-labeled PSMA, Lutetium, PSMA, prostate cancer, radioimmunotherapy, radioligand therapy' and their relevant synonyms. We also hand-searched key journals in the field and abstracts presented at international urological conferences. Reference lists were also searched for potentially eligible publications and previous literature reviews of the use of ^{177}Lu-PSMA in mCRPC. Two reviewers (HW and RC) independently screened all the titles and abstracts, and the resulting reference list was compiled by a third reviewer (VC). Full-text screening, data extraction and assessment of methodological quality were completed independently by all three aforementioned reviewers. Any disagreements were resolved by consensus.

Statistical analysis

The main outcome of interest was the proportion of patients with PSA decline. Two measures of PSA decline were analysed; any PSA decline and >50% decline from baseline. A random-effects meta-analysis was used to calculate the pooled proportion across studies. A random-effects model was chosen instead of a fixed-effects model due to the uncertainty in the 'true' effect; the random-effect component allows the estimate to vary across studies. The I^2 statistic was calculated in each case to investigate the extent of heterogeneity across the studies. A sensitivity analysis was conducted removing two studies, which were presented as abstracts. Proportions were summarised by chemical type.

Before analysis, sample sizes were adjusted where study populations overlapped to ensure that patients were not double-counted. Half of the overlapping patients were deducted from the total of each of the overlapping studies. To adjust the number of 'successes' (that is, patients with any or >50% PSA decline), the number removed from the total number of successes in each study was determined according to the study's estimated 'success' proportion.

All analyses were conducted using Stata v14 (College Station, TX, USA).

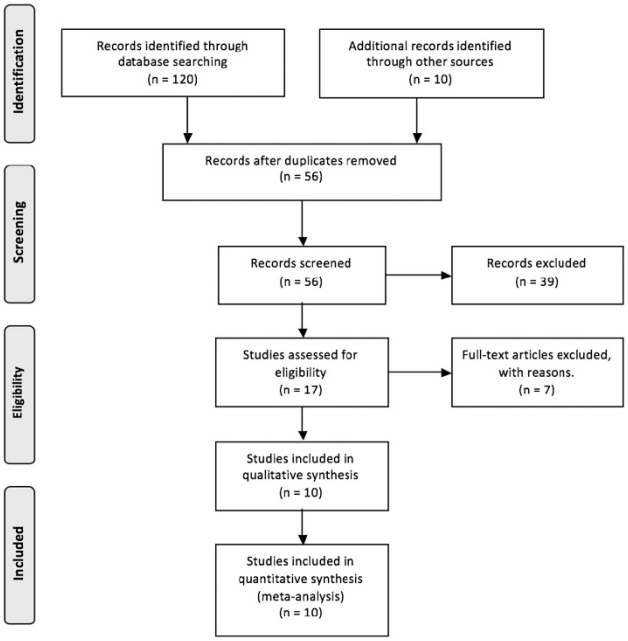

Figure 1. Study selection (in accordance with 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow-diagram).

RESULTS

Our search strategy retrieved 56 non-duplicate records with 10 ultimately selected for the study (Figures 1 and 2; refs 13–21). A total of 10 studies were included in the analysis giving a total sample size of 369 men, 220 (out of 334 analysable) experienced any PSA decline. There were 9 retrospective clinical trials and one multicentre retrospective analysis. Studies came from the United States ($n=3$), Germany ($n=5$) and India ($n=2$). Three studies used the radiolabelled anti-PSMA monoclonal antibody ^{177}Lu-J591, and 7 studies used the molecularly smaller radioligands ^{177}Lu-DKZ and ^{177}Lu-PSMA-I&T. Study characteristics have been summarised in Table 1.

Overlapping studies

A total of 10 studies were included in this analysis; two of which overlapped with the multicentre retrospective analysis.[18] To avoid 'double-counting' those patients who were included in both studies, the sample sizes were adjusted accordingly. A summary of the adjusted sample sizes is tabulated in Table 2.

Any PSA decline. In all, 9 of the 10 studies presented data on any PSA decline; 1 was excluded due to the results being unclear.[13] Combined, the 9 studies had a total of 334 patients of which 220 experienced any PSA decline. The pooled proportion of patients with any PSA decline was 68% (95% confidence interval (CI): 61–74). The I^2 statistic was 39.1% ($P=0.11$) suggesting minor heterogeneity between results (Figure 2).

More than 50% PSA decline. All studies presented results for PSA decline >50% and when combined, contributed a total of 369 patients of which 131 experienced >50% PSA decline. The pooled proportion was 37% (95% CI: 22–52). The I^2 statistic was 90.9% ($P<0.001$) suggesting substantial heterogeneity between results. This heterogeneity can be seen clearly in Figure 3 where there is poor overlap of the CIs across studies.

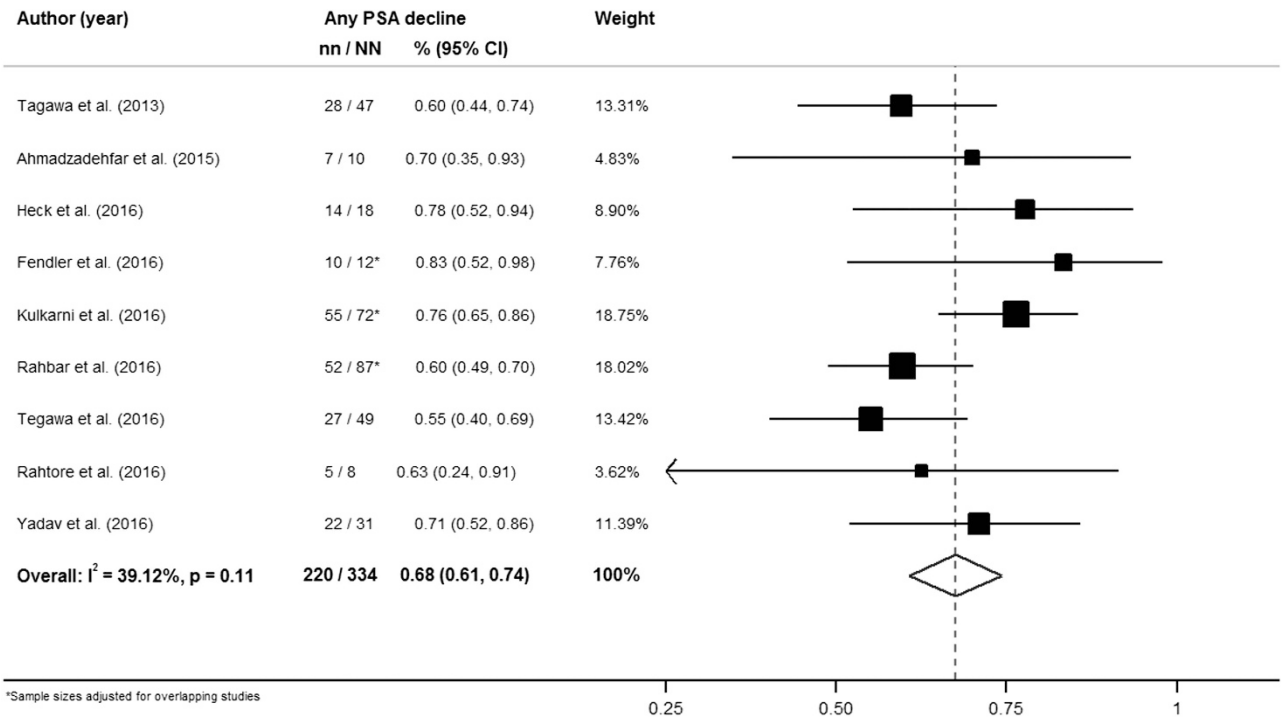

Figure 2. Forest plot for meta-analysis results of the proportion of patients with any PSA decline.

Sensitivity analysis. A sensitivity analysis was conducted removing two studies presented as abstracts (Tagawa *et al.*[19] and Rathore *et al.*[20]) from the meta-analysis. The pooled proportions for any PSA decline and >50% PSA decline were comparable to the initial estimates (70% [95% CI: 62–77] and 41% [95% CI: 24–59], respectively).

Subgroup analysis. Three studies used ^{177}Lu-J591, giving a combined sample of 131 men; 55 (of 96 analysable) had any PSA decline. The remaining studies used ^{177}Lu-DKZ/I&T with a combined sample of 238 men; 165 having any PSA decline.

The ^{177}Lu-DKZ studies had a higher proportion of patients with any PSA decline compared to those in the Lu-J591 studies (71% vs 67%; Figure 4) and a higher proportion of patients with a PSA decline >50% (51% vs 13%; Figure 5). However, there is a significant heterogeneity seen across the ^{177}Lu-DKZ/I&T studies, which could affect the comparability of the pooled estimates.

DISCUSSION

Despite our best efforts in localised cancer control, then medical or surgical castration, mCRPC develops in ~10–20% of men with PCa.[22] Chemotherapeutic agents such as docetaxel (first line) and cabazitaxel (second line) have an important role in this population, however are often toxic and prolong life by only a few months.[23] Abiraterone acetate and enzalutamide can also be used as post-chemotherapy androgen deprivation therapy (ADT), but again, prolongation in overall survival averages only 3.9 and 4.8 months, respectively, compared to placebo.[24,25] Despite these innovations in systemic treatment, it is estimated that 250 000 men internationally die from mCRPC each year.[26] Fortunately, recent theragnostic advances utilising our innate antibody–antigen interactivity has provided promising developments in the treatment of mCRPC.

PSMA-targeted RIT is a novel and promising concept, which provides a highly targeted systemic therapy for mCRPC, especially after exhaustion of the above conventional treatments.[2] This new therapy involves the selective binding of a radioligand/antibody to PSMA, a readily expressed surface enzyme on mCRPC tissue, to increase tumour dose and spare normal tissue.[3] Extra-prostatic expression is limited to small bowel, proximal renal tubules and salivary glands but expression in these tissues is significantly (100–1000×) less than PCa cells. The mechanism of internalisation of these radiolabelled molecules by tumour cells is essential to the cell-killing effect in this form of 'endoradiotherapy'.[10] Once intracellular, internalised radioligands accumulate in the peri-nuclear location allowing direct DNA damage.[27] In this study, we analysed 10 trials evaluating safety and efficacy of ^{177}Lu in the treatment of this subgroup of patients. To our knowledge, this study represents the largest systematic review and meta-analysis of the utility of ^{177}Lu-PSMA in treating mCRPC.

From subgroup analyses, we can observe the technological progression in RIT in the treatment of mCRPC, from the use of radiolabelled antibodies targeting its extracellular structure to very small radioligands targeting its catalytic site. This is most evident in Figure 5, which suggests a superior PSA response in patients treated in the latter group. J591 was the first humanised monoclonal antibody targeting the extracellular domain of PSMA.[7] ^{177}Lu-J591 went on to demonstrate antitumour activity and acceptable tolerability in a phase 1 clinical trial,[13] represented by the earliest study in the present meta-analysis (Table 1). Tagawa *et al.*[14,19,28,29] continued the work by Bander *et al.*[13] with ^{177}Lu-J591. However, both Bander's and Tagawa's work report significant toxicity and inferior PSA response compared to the subsequent studies outlined in this meta-analysis. In the phase 2 clinical trial of ^{177}Lu-J591, 46.8% of the patients suffered grade 4 thrombocytopaenia and a 25.5% of them grade 4 neutropoenia.[13] This ^{177}Lu-J591-associated haematotoxicity could be explained by the fact that whole antibodies are large molecules that penetrate less effectively into tumours and for the same reasons, have decreased glomerular clearance leading to a relatively longer circulatory half-life and greater radiation exposure to bone marrow.[16] On the other hand, multicenter analysis on smaller

Table 1. Summary of study characteristics

Study details				*Study population*				*Study outcomes*		
Reference	*Study arm*	*Study type*	n	*Age, median (range)*	*Clinical stage*	*Metastases*	*Baseline PSA, median (range)*	*Follow-up*	*Primary*	*Secondary*
Bander *et al.*[13]	^{177}Lu-J591	Phase I dose escalation	35	69 (47–85)	mCRPC; 97% prior hormonal therapy, 37% prior chemotherapy, 29% prior radiotherapy to bone mets	Bone: 60% Soft tissue: 17% Both: 9% None: 14%	29.6 (2.3–2746)	12 weeks minimum	MTD	Toxicity, response, pharmacokinetics
Tagawa *et al.*[14]	^{177}Lu-J591	Phase II trial	47	73.9 (49–90)	mCRPC; 100% prior hormonal therapy, 55.3% prior chemotherapy, 53% radiotherapy	Bone: 98% LN: 60% Lung: 23% Liver: 8% Other: 6%	74.4 (3.3–2185)	Every 3 months until progression	Response rate (PSA decline and measureable disease)	Disease response Survival
Ahmadzadehfar *et al.*[15]	^{177}Lu-DKFZ-PSMA-617	Retrospective study	10	Mean: 73.5 (62—81)	mCRPC; hormone and/or chemotherapy refractory	Bone: 80% LN: 90% 3 with local recurrence	298.5 (5–853)	8 weeks	Side effects, response rate	
Heck *et al.*[16]	^{177}Lu-PSMA-I&T	Clinical trial	18	71 (46–77)	mCPRC; all patients received prior systemic treatment	Bone: 95% LN: 82% Liver: 18% Lung: 14%	349 (0–2905)	8 weeks	Safety profile	Antitumour activity
Fendler *et al.*[17]	^{177}Lu-DKFZ-PSMA-617	Clinical trial	15	73 (54–81)	mCRPC; 66% prior chemotherapy, 93% prior abiraterone/enzalutamide	Bone: 93% LN: 80% Liver: 20% Lung: 7% Other: 13%	388 (3.2–10 661)		Dosimetry	Safety, efficacy
Kulkarni *et al.* [a2]	^{177}Lu-DKFZ-PSMA-617 and ^{177}Lu-PSMA-I&T	Retrospective review	80	71 s.d.: 7	mCRPC; patients who had not responded to ADT, systemic chemotherapy, newer hormonal therapies (abiraterone/enzalutamide), or taxan-based chemotherapy, or medically unfit for chemotherapy	Bone: 81% LN: 71% Visceral: 26%	NA	NA	NA	NA
Rahbar *et al.* [b18]	^{177}Lu-DKFZ-PSMA-617	Multicentre retrospective study	99	73 (43–88)	mCRPC; disease progression despite abiraterone or enzalutamide, first- or second-line chemotherapy (docetaxel and cabazitaxel), or were not eligible for chemotherapy	Bone: 87% LN: 77% Liver: 20% Lung: 14% Other: 2%	214 (0.4–5436)	Median: 16 weeks	Optimal dose and number of therapy cycles	Predictors of response
Tagawa *et al.*[19]	^{177}Lu-J591	Phase I dose escalation	49	74.1 (55–95)	mCRPC; unspecified	Bone: 84% LN: 61% Visceral: 41%	44.9 (1.9–767)	Unknown	Change in PSA	Overall survival

Table 1. (Continued)

Study details				Study population				Study outcomes		
Reference	*Study arm*	*Study type*	n	*Age, median (range)*	*Clinical stage*	*Metastases*	*Baseline PSA, median (range)*	*Follow-up*	*Primary*	*Secondary*
Rathore *et al.*[20]	^{177}Lu-DKFZ-PSMA-617	Initial experience of Lu-PSMA	8		mCRPC; refractory to conventional treatment including hormonal, chemo- and radiotherapy	Unspecified	Unspecified	6 weeks	PSA decline	Side effects
Yadav *et al.*[21]	^{177}Lu-DKFZ-PSMA-617	Clinical trial	31	65.9 (38–81)	mCRPC; all patients had progressive disease despite ADT and/or systemic chemotherapy	Skeletal: 42% Skeletal and LN: 55% Skeletal, LN and liver: 3%	275 (21–2493)	3 months	Biochemical, metabolic and clinical response	Survival analysis

Abbreviations: ADT, androgen deprivation therapy; LN, lymph node; Lu, lutetium; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; NA, not available; PSMA, prostate-specific membrane antigen. [a]Study included 119 patients, 80 of which had information on PSA. Summaries are based on 119 patients. [b]Study included 145 patients, 99 of which had information on PSA. Summaries are based on 145 patients.

ligand therapy by Rahbar *et al.*[18] yielded a grade 3–4 haemotoxicity in 12% of patients.

A variety of small molecules that act as inhibitors to the enzymatic site on PSMA have been developed in the recent years.[30] These radioligands are very small compared to the much larger whole antibodies, such as J591. Competitive binding and internalisation experiments using the PSMA-positive LNCaP cell line have been carried out to develop these low-molecular-weight ligands for use in endoradiotherapeutics. PSMA-tracer affinity was first enhanced by increasing the lipophilic interaction of the peptidic linker unit DOTAGA-FFK(Sub-KuE); then higher internalisation capacity achieved with DOTAGA-[I-y]fk (Sub-KuE).[8–10] The resultant peptide PSMA-I&T (for imaging and therapy) was developed and evaluated in the studies included in this analysis (Table 1).[10] ^{177}Lu-DKFZ-617, also featured in this analysis, is a DOTA derivative of the Glu–urea–Lys motif, developed in the Department of Nuclear Medicine, University Hospital Heidelberg, Germany.[11] In its development, *in vitro* studies demonstrated highly efficient internalisation into LNCaP cells and small-animal positron emission tomography (PET) measures specific tumour uptake with rapid renal clearance.[12] In this meta-analysis, Kulkarni *et al.*[2] document their experience of both radioligands and conclude that ^{177}Lu-I&T and ^{177}Lu-DKZ did not significantly differ in response and toxicity profiles.[2]

Lutetium-PSMA is proving to have a promising therapeutic response for patients with mCRPC where other conventional treatments have failed. Most patients in the experimental studies making up this meta-analysis had docetaxel-refractory disease and failed post-chemotherapy ADT with abiraterone acetate and enzalutamide. This cohort of patients closely mimics those treated with cabazitaxel, a novel tubulin-binding taxane drug with antitumour activity in docetaxel-resistant cancers, in the TROPIC trial.[31] Inclusion criterion was documented disease progression despite ongoing castration by orchiectomy or luteinising hormone-releasing hormone agonists and cumulative docetaxel dose $>225\ mg\ m^{-2}$.[31] PSA response rate, defined by $>50\%$ reduction in PSA from baseline, was observed in 39.2% of men treated with cabazitaxel.[31] Overall, these results are comparable to those of the present meta-analysis, with the pooled proportion of those achieving a $>50\%$ PSA reduction occurring in 39% (95% CI: 24–54) of cases. However, on subgroup analysis of the smaller radioligands (Lu-DKZ/Lu-I&T), we observe possible superior therapeutic effect compared not only to Lu-J591 but also to equivalent systemic treatments such as Cabazitaxel (51%, 95% CI: 40–61 vs 39%, 95% CI: 24–54). While accurate comparisons of the treatments are not possible due to the heterogeneity of data, it provides an expansive and promising view of the future treatment of mCRPC.

Despite comparing similar patient groups, significant heterogeneity in follow-up and outcome measures still exist. The primary end point for efficacy in the present study was based on PSA reduction. While one can argue that PSA is the most objective and reliable marker of tumour response, compared to radiological follow-up, its clinical value in mCRPC remains controversial.[32] Further prospective randomised control trials comparing lutetium-PSMA with other systemic therapies are required to evaluate PSA response rate and survival data in an unbiased manner. In the near future, studies such as these may lead clinicians to consider systemic endoradiotherapy using ^{177}Lu-PSMA earlier in the line of management of men suffering from mCRPC.

Given the complexity and heterogeneity of PCa cells, researchers already speculate that multimodal systemic therapy may act synergistically to optimise therapeutic efficiency and increase life expectancy, without increasing toxicity levels to normal tissues.[33] Specifically, the use of ADT and lutetium-PSMA may be closer than expected. Without the opportunity to maximise this synergy, it has long been understood that PSMA is upregulated by ADT in patients with mCRPC, as PSMA genes are suppressed by

Table 2. Adjustment of sample sizes due to overlapping studies

Study	*Original totals*	*% of successes*	*Number overlapping*	*Number deducted*	*Adjusted totals*
Kulkami et al.					
Total	80		17	8	80–8 = 72
Any PSA decline	61	76			61–(8 × 0.76) = 55
>50% PSA decline	46	58			46–(8 × 0.58) = 41
Fendler et al.					
Total	15		6	3	15–3 = 12
Any PSA decline	12	80			12–(3 × 0.8) = 10
>50% decline	9	60			9–(3 × 0.6) = 7
Rahbar et al.					
Total	99		17+6	9+3	99–12 = 87
Any PSA decline	59	60			59–(12 × 0.60) = 52
>50% PSA decline	45	45			45–(12 × 0.45) = 40

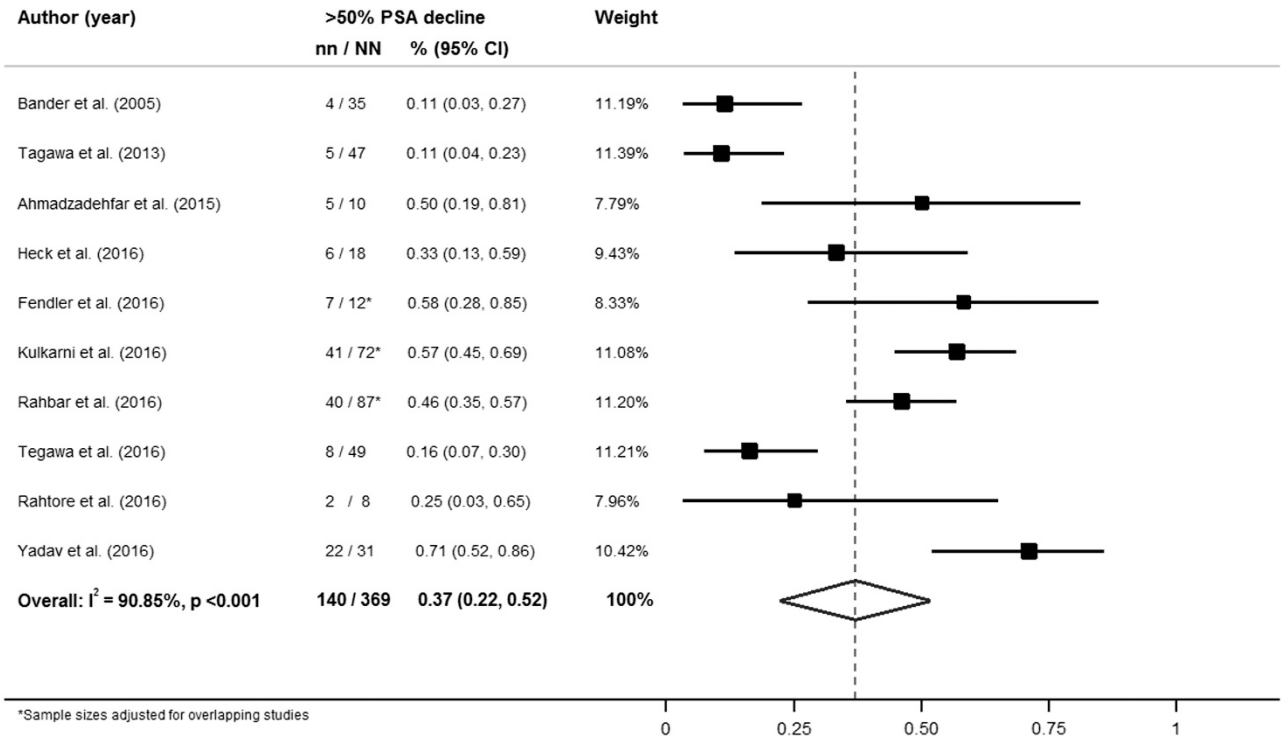

Figure 3. Forest plot for meta-analysis results of proportion of patients with >50% PSA decline.

androgens.[34] Furthermore, an understanding of why the addition of ADT to radiotherapy improves survival has remained elusive for decades.[35] A recent study is providing mechanistic insight into this benefit and providing hopeful evidence for the clinical benefits of combining ^{177}Lu-PSMA's endoradiotherapy with ADT. Androgen receptor (AR) pathway upregulation, as measured by a rise in serum levels of AR-regulated hK2 protein, was demonstrated in nearly 20% of patients after radiotherapy. These men were also three times more likely to experience biochemical failure. In fact, the degree of AR upregulation correlated with survival *in vitro* and time to tumour progression in animal models.[36] This evolving field demonstrates that radiotherapy may upregulate AR signalling post therapy and consequently negatively impact disease progression and survival. While this combination was not specifically measured in the included studies, future prospective studies analysing the benefits of ADT and ^{177}Lu-PSMA are warranted.

This meta-analysis is not without limitations. A major limitation of this meta-analysis is the fact that the majority of included data has come from small single-centre studies, and all studies were single arm. Nevertheless, despite the inherent bias of single-arm studies, the results from this meta-analysis indicate that larger trials are justified. While toxicity is an unmistakable consideration in this treatment, this analysis focuses on treatment efficacy, rather than toxicity, as there was significant heterogeneity in the documentation of toxicity in the included studies. Furthermore, despite taking appropriate steps to adjust for study population overlap between the multicentre study Rahbar *et al.*[18] and smaller single-institution studies, we are limited by the information presented and must acknowledge the possibility of persistent overlap, albeit small.

It is important to be cautious in extrapolating the present PSMA-based RIT efficacy data to the metastatic PCa in general. Results of this study are of course inherently curbed by the

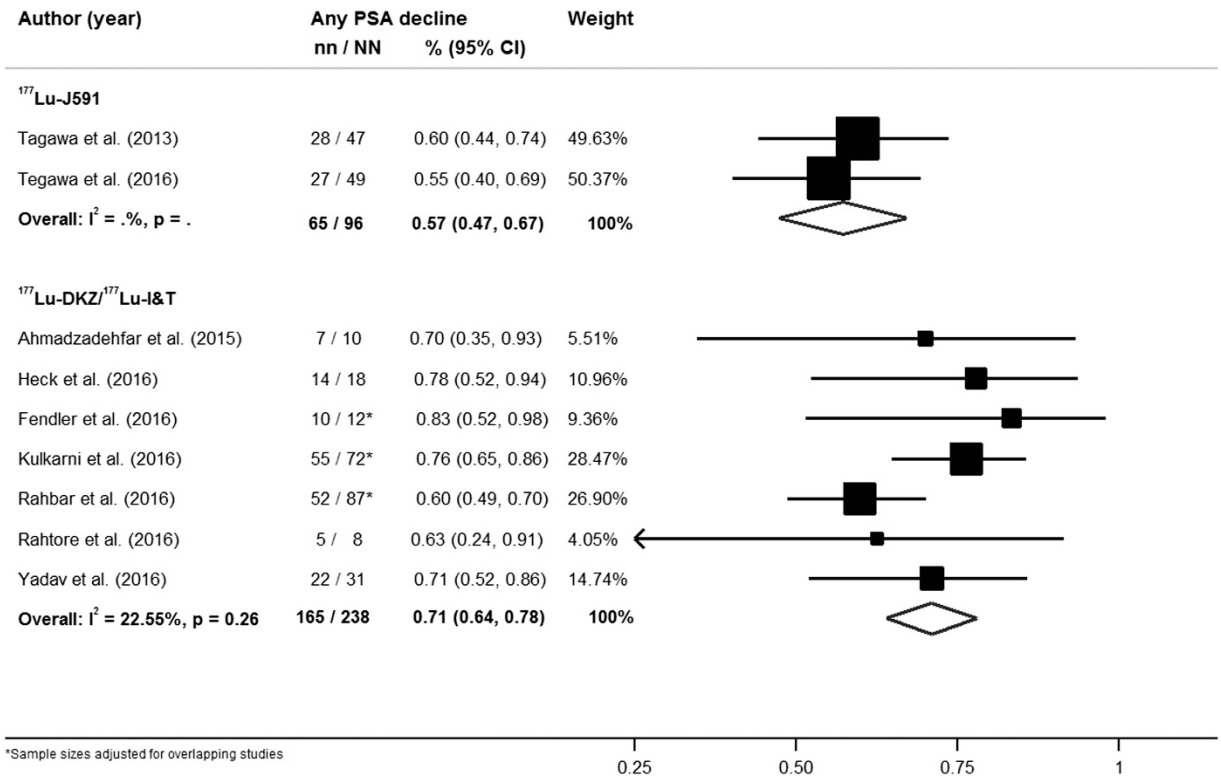

Figure 4. Forest plot for meta-analysis results of the proportion of patients with any PSA decline by chemical type.

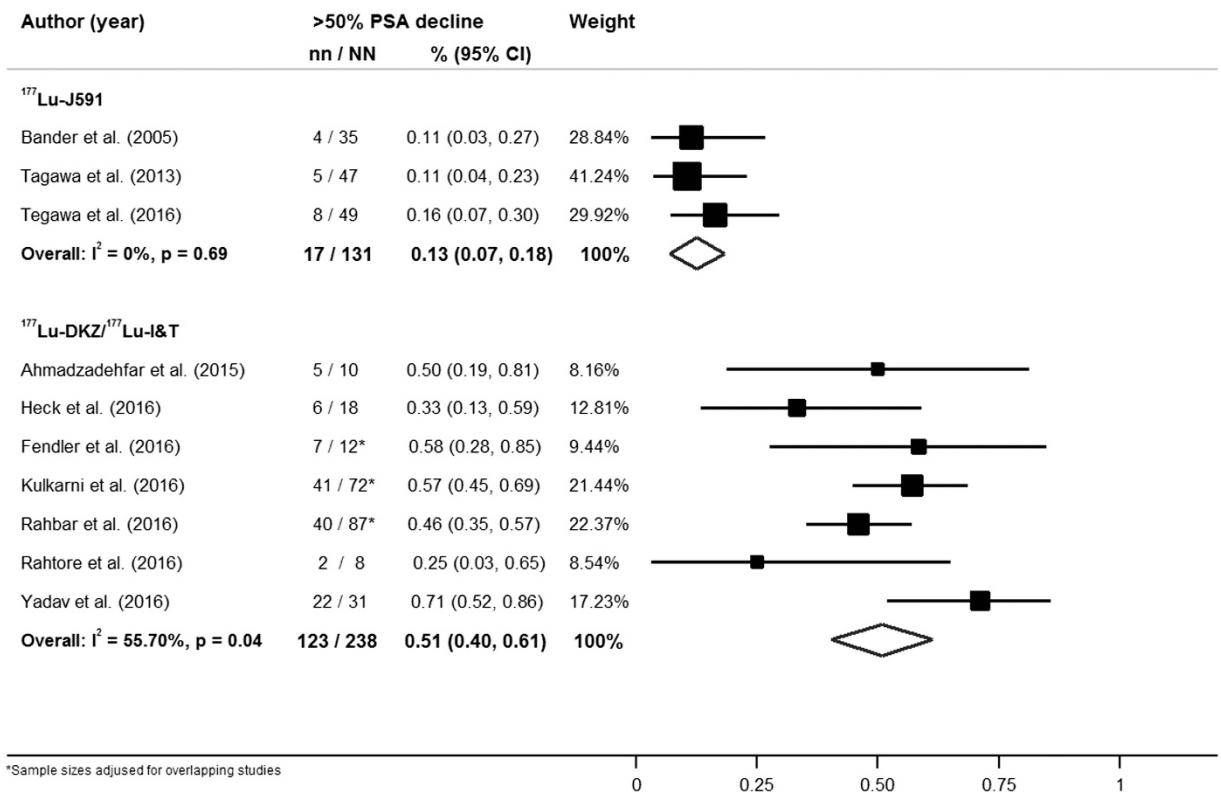

Figure 5. Forest plot for meta-analysis results of the proportion of patients with >50% PSA decline by chemical type.

limitation of PSMA expression itself and the increasing availability of PSMA-PET technology in the past decade. While PSMA has proved itself a very promising biomarker for de-differentiated mCRPC, there is recently emerging evidence that PSMA may in fact be downregulated in neuro-endocrine differentiation of PCa.[37] Given our evolving understanding of the heterogeneity of PCa, the apparent superiority of smaller molecular radioligands used in more recent studies needs to be considered in the context of increasing availability of PSMA-PET imaging. Unquestionably, recent studies have taken advantage of the recent availability of PSMA-PET imaging to select PSMA-positive (high) patients; whereas in earlier antibody-based studies, no such selection was attempted.

CONCLUSIONS

Despite significant heterogeneity in this meta-analysis, our review suggests promising early results of Lu-PSMA RIT for the treatment of mCRPC. While superior efficacy was observed in studies using the smaller radioligands Lu-DKZ and Lu-I&T, this needs to be considered in the context of the increasing availability of PSMA-PET and improved ability to select patients with metastatic PSMA-positive PCa. Overall, our meta-analysis produced PSA reductions comparable to current available systemic therapy for this cohort of patients. PSMA-targeted RIT, whether by ligand or antibody, co-validate PSMA as a viable target opportunity for personalised treatment of men with mCRPC and one worthy of further development and evaluation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Conford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T *et al.* EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic and castration-resistant prostate cancer. *Eur Urol* 2017; **71**: 630–642.
2 Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y *et al.* PSMA-based radioligand therapy for metastatic castration-resistant prostate cancer: the bad berka experience 2013. *J Nucl Med* 2016; **57**: 97S–104S.
3 Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wiessalla S *et al.* 177Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. *J Nucl Med* 2016; **57**: 1006–1013.
4 Liu H, Rajasekaran AK, Moy P, Xia Y, Kim S, Navarro V *et al.* Constitutive and antibody-induced internalization of prostate-specific membrane antigen. *Cancer Res* 1998; **58**: 4055–4060.
5 Liu H, Moy P, Kim S, Xia Y, Rajasekaran A, Navarro V *et al.* Monoclonal antibodies to the extracellular domain of prostate-specific membrane antigen also react with tumour vascular endothelium. *Cancer Res* 1997; **57**: 3629–3634.
6 Vallabhajosula S, Nikolopoulou A, Jhanwar YS, Kaur G, Tagawa ST, Nanus DM *et al.* Radioimmunotherapy of metastatic prostate cancer with 177Lu-DOTA-huJ591 anti-prostate specific membrane antigen specific monoclonal antibody. *Curr Radiopharm* 2016; **9**: 44–53.
7 Bander NH, Trabulsi EJ, Kostakoglu L, Yao D, Vallabhajosula S, Smith-Jones P *et al.* Targeting metastatic prostate cancer with radiolabeled monoclonal antibody J591 to the extracellular domain of prostate specific membrane antigen. *J Urol* 2003; **170**: 1717–1721.
8 Kularatne SA, Zhou Z, Yang J, Post CB, Low PS. Design, synthesis, and pre-clinical evaluation of prostate specific membrane antigen targeted 99mTc-radioimmaging agents. *Mol Pharm* 2009; **6**: 790–800.
9 Zhang AX, Murelli RP, Barinka C, Michel J, Cocleaza A, Jorgensen WL *et al.* A remote arene-bidning site on prostate specific membrane antigen revealed by antibody-recruiting small molecules. *J Am Chem Soc* 2010; **132**: 12711–12716.
10 Weineisen M, Schottelius M, Simecek J, Baum RP, Yildiz A, Beykan S *et al.* 68Ga- and 177Lu-labeled PSMA I&T: optimization of a PSMA targeted theranostic concept and first proof of concept human studies. *J Nucl Med* 2015; **56**: 1169–1176.
11 Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N *et al.* Pre-clinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. *Cancer Res* 2009; **69**: 6932–6940.
12 Benesova M, Schafer M, Bauder-Wust U, Afshar-Oromieh A, Kratochwil C, Mier W *et al.* Preclinical evaluation of tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med* 2015; **56**: 914–920.
13 Bander NH, Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ. Phase I trial of 177lutetium labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. *J Clin Oncol* 2005; **23**: 4591–4601.
14 Tagawa ST, Milowsky M, Morris M, Vallabhajosula S, Christos P, Akhtar NH *et al.* Phase II study of Lutetium-177-labelled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2013; **46**: 220–231.
15 Ahmadzadehfar H, Rahbar K, Kurpig S, Bogemann M, Claesener M, Eppard E *et al.* Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Res* 2015; **5**: 1–8.
16 Heck MM, Retz M, D'Alessandria C, Rauscher I, Scheidhauer K, Maurer T *et al.* Systemic radioligand therapy with 177Lu labeled prostate specific membrane for imaging and therapy in patients with metastatic castration-resistant prostate cancer. *J Urol* 2016; **196**: 382–391.
17 Fendler WP, Reinhardt S, Ilhan H, Delker A, Boning G, Gildehaus FJ *et al.* Preliminary experience with dosimetry, response and patient reported outcome after 177Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. *Oncotarget* 2016; **8**: 3581–3590.
18 Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schafers M, Essler M *et al.* German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. *J Nucl Med* 2017; **58**: 85–90.
19 Tagawa ST, Batra J, Vallabhajosula S, Jhanwar Y, Christos PJ, Emmerich L *et al.* Final results of 2-dose fractionation of 177Lu-J591 for progressive metastatic castration-resistant prostate cancer (mCRPC). Conference: 2016 Annual Meeting of the American Society of Clinical Oncology, ASCO. *J Clin Oncol* 2016; 34 (abstract 5022).
20 Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C *et al.* Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labeled prostate specific membrane antigen (177-Lu-DKFZ--617-PSMA) for metastatic castrate resistant prostate cancer (mCRPC): an initial experience in Jaslok. Conference: 29th Annual Congress of the European Association of Nuclear Medicine, EANM 2016, Spain. *Eur J Nucl Med Mol Imaging* 2016; **43**: S414.
21 Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A *et al.* 177Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging* 2017; **44**: 81–91.
22 Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract* 2011; **65**: 1180–1192.
23 Basch E, Loblaw DA, Oliver TK, Carducci M, Chen RC, Frame JN *et al.* Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care, Ontario clinical practice guideline. *J Clin Oncol* 2014; **32**: 3436–3448.
24 De Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L *et al.* Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; **364**: 1995–2005.
25 Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; **367**: 1187–1197.
26 Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O *et al.* International variation in prostate cancer incidence and mortality rates. *Eur Urol* 2012; **61**: 1079–1092.
27 Kiess A, Minn I, Chen Y, Hobbs R, Sgouros G, Mease RC *et al.* Auger radiopharmaceutical therapy targeting prostate-specific membrane antigen. *J Nucl Med* 2015; **56**: 1401–1407.
28 Tagawa ST, Akhtar NH, Nikolopoulou A, Vallabhajosula S, Osborne J, Beltran H *et al.* Phase I trial of fractionated-dose 177Lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (177Lu-J591) for metastatic castration-resistant prostate cancer (CRPC). Conference: European Cancer Congress, ECC 2013, Amsterdam, Netherlands. *Eur J Cancer* 2013; **49**: S701–S702.
29 Tagawa ST, Whang YE, Kaur G, Vallabhajosula S, Christos PJ, Nikolopoulou A *et al.* Phase I trial of docetaxel/prednisone plus fractionated dose radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody 177Lu-J591 in patients with metastatic, castration-resistant prostate cancer (mCRPC). Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO, Chicago, United States, 2014. *J Clin Oncol* 2014; **32** (Suppl 1): 15.

30 Lutje S, Heskamp S, Cornelissen AS, Poeppel TD, van den Broek SA, Rosenbaum-Krumme S *et al*. PSMA ligands for radionuclide imaging and therapy of prostate cancer: clinical status. *Theranostics* 2015; **5**: 1388–1401.
31 De Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; **376**: 1147–1154.
32 Scher HI, Morris MJ, Basch E, Heller G. End points and outcomes in castration resistant prostate cancer: from clinical trials to clinical practice. *J Clin Oncol* 2011; **29**: 3695–3704.
33 Evans-Axelsson S, Timmermand O, Bjartell A, Strand SE, Elgqvist J. Radio-immunotherapy for prostate cancer: current status and future possibilities. *Semin Nucl Med* 2016; **46**: 165–179.
34 Wright GL Jr, Grob BM, Haley C, Grossman K, Newhall K, Petrylak D *et al*. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. *Urology* 1996; **48**: 326–334.
35 Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G *et al*. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010; **11**: 1066–1073.
36 Spratt DE, Evans MJ, Davis BJ, Doran MG, Lee MX, Shah N *et al*. Androgen receptor upregulation mediates radioresistance after ionizing radiation. *Cancer Res* 2015; **75**: 4688–4696.
37 Tosoian JJ, Gorin MA, Rowe SP, Andreas D, Szabo Z, Pienta KJ *et al*. Correlation of PSMA-targeted 18F-DCFPyL PET/CT findings with immunohistochemical and genomic data in a patient with metastatic neuroendocrine prostate cancer. *Clin Genitourin Cancer* 2017; **15**: e65–e68.

Supplementary Information accompanies the paper on the Prostate Cancer and Prostatic Diseases website (http://www.nature.com/pcan)