

## End points of clinical trials in metastatic castration-resistant prostate cancer: A systematic review

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### Abstract

**AIM:** To review the definition and performance of the commonly used end points in trials of systemic therapies in metastatic castration-resistant prostate cancer patients.

**METHODS:** A literature search was undertaken on PubMed database to identify studies meeting established criteria, with the aim of selecting randomized clinical trials and study definition and performance of their end points. The end points were grouped into three categories: overall survival (OS), time-to-event end points, and response end points. A special analysis was performed for secondary end points of the studies which documented a benefit in OS in the experimental arm. Finally, publishes analyses for surrogacy of the included end points were also reported.

**RESULTS:** OS, time-to-event and response end points in 31 selected trials were analyzed. OS was the primary end point in 14 trials, and the secondary end point in 17. A time-to-event end point was the primary

end point in 8 studies, and the secondary end point in 22; the most reported time-to-event end points were composite end points, and the events changed among trials. A response end point was the primary end point in 9 studies, in 3 it was prostate-specific antigen (PSA)-related, in 3 pain-related and in 3 mixed. A response end point was the secondary end point in 19 studies: PSA response and radiologic response were the most frequently used secondary end points in 19 and 11 trials, respectively, while pain response was used in 5 studies.

**CONCLUSION:** A homogeneous definition of progression in future trials is mandatory. Among response end points, pain-response and PSA-response appear to be the most reliable.

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**Key words:** Metastatic castration-resistant prostate cancer; End points; Progression-free survival; Prostate-specific antigen; Chemotherapy; Palliative response

**Core tip:** The approval in the last decade of new drugs that have increased survival of patients with metastatic castration-resistant prostate cancer (mCRPC) has weakened the role of overall survival (OS) as end point. The prevailing bone-only spread of mCRPC severely limits disease evaluation using the standard criteria of conventional radiology. On the other hand, recent retrospective analyses of prostate-specific antigen response after chemotherapy did not support this measure as a surrogate end point of OS. This lack of reliable surrogate end points is a problem for the conduction of phase II studies which test the activity of new drugs.

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## INTRODUCTION

Prostate cancer (PC) is the most common malignancy in elderly men and the second leading cause of cancer death in Europe<sup>[1]</sup>. Death due to PC occurs in the later stages of the disease course in metastatic hormone-sensitive and mainly in metastatic castration-resistant prostate cancer (mCRPC)<sup>[2]</sup>. The median time from diagnosis of metastasis to death is 5 years<sup>[3]</sup>.

Since 1996 a role for systemic antineoplastic treatment has been recognized, when a clinical trial, for the first time, reported a reduction in disease-related pain in patients undergoing cytotoxic chemotherapy with mitoxantrone and prednisone<sup>[4]</sup>. Subsequent studies have documented a benefit in overall survival (OS) for patients receiving systemic therapy with docetaxel<sup>[5,6]</sup>, cabazitaxel<sup>[7]</sup>, abiraterone<sup>[8]</sup>, enzalutamide<sup>[9]</sup> and radium-223<sup>[10]</sup>.

Due to the prevalent bone dissemination of mCRPC, metastatic disease is difficult to measure and to evaluate using the response evaluation criteria in solid tumors (RECIST)<sup>[11]</sup>. Therefore, the study of surrogate endpoints (SEs) of OS and the development of combined criteria for disease assessment were strongly supported by the prostate specific antigen working group (PSAWG)<sup>[12]</sup>. However, the prostate specific antigen (PSA)-response after first-line chemotherapy has not received validation as a SE of OS<sup>[13]</sup>. It lacks prospective validation<sup>[14,15]</sup>, and the analysis of data from the TAX327 study reported wide confidence intervals around the estimate of PSA decline > 30%<sup>[14]</sup>. Similarly, PSA-response failed to be a SE of OS even after second-line chemotherapy<sup>[16]</sup>.

As a result, the time-to-event measures have attracted the attention of researchers as possible SEs of OS, as they were reported by the Prostate Cancer Working Group 2 (PCWG2) in 2008, and are summarized in Table 1<sup>[17]</sup>. However, none of these measures, to date, has been validated as a SE of OS. Parallel to the increase in the number of effective drugs for mCRPC and the increase in median OS of patients, in the last decade there has been a rapid evolution of possible end points related to the disease and the patient.

The purpose of this systematic review is to examine the end points of randomized prospective studies of systemic treatments in mCRPC patients.

## MATERIALS AND METHODS

A literature search of randomized trials of systemic treatments in patients with mCRPC was undertaken in October 2013. This search was performed on the electronic database PubMed. The criteria used for the search were as follows: “prostate cancer” and (“castration resistant” or “hormone refractory” or “hormone resistant”) and (“chemotherapy” or “docetaxel” or “mitoxantrone” or

“cabazitaxel” or “estramustine” or “radium” or “abiraterone” or “enzalutamide” or “prednisone” or “hydrocortisone” or “zoledronate”).

The search was restricted to randomized prospective studies published from September 1993 to September 2013. Editorials, commentaries, letters, academic papers and abstracts were excluded, reviews were considered for references, but were not included in the final analysis, as well as other non-randomized studies. The participants were adult patients with a diagnosis of mCRPC who received systemic treatment, hormonal, cytotoxic or radiometabolic. A first selection of eligible studies from PubMed was performed independently by two authors (Colloca G and Governato I), who selected, by title and abstract, randomized studies that included patients with mCRPC and reported the analysis of one or more end points. Candidate articles were then selected for eventual inclusion in the review. Further literature was identified from the references lists of these articles. Differences of opinion were resolved by discussion or by the third review author (Venturino A).

This was followed by a further analysis of the selected articles, and only those that examined OS and at least one end point were included in the final analysis. The end points were grouped into three categories: overall survival, time-to-event end points, and response end points. Results of clinical trials and analyses for surrogacy of the included end points were discussed. A special analysis was performed for secondary end points in the 6 studies that documented a benefit in OS in the experimental arm. When the final report of a study did not supply adequate data on the secondary end points, further details were sought in the original protocol of the study, sometimes provided as an appendix on the journal's website, or from abstracts, comments and revisions, available at other websites.

## RESULTS

From 1819 reports in PubMed, and subsequent evaluation of the reference lists of selected papers, 69 candidate articles were identified.

Following analysis and selection of manuscripts, 41 eligible articles were identified, which referred to the results of 31 prospective randomized studies. These studies were included in the analysis.

### OS

OS was the primary end point in 14 trials, as summarized in Table 2. OS was reported as a secondary end point in 17 studies. OS was uniquely defined as the time from randomization to death from any cause. All six studies that changed the standard of care of mCRPC patients had OS as the primary end point.

### Time-to-event end points

A time-to-event end point was the primary end point in 8 studies, as shown in Table 3. Only two studies reported a

**Table 1** Prostate cancer working group-2 suggested outcome measures for metastatic castration-resistant prostate cancer trials

Variable	Outcome measure
Progression criteria	
PSA	A favorable effect on PSA may be delayed for 12 wk or more, even for a cytotoxic drug Decline from baseline. PSA increase $\geq 25\%$ and $\geq 2$ ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later No decline from baseline. PSA progression $\geq 25\%$ and $\geq 2$ ng/mL after 12 wk
Bone metastases	The appearance of $\geq 2$ new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan showing the changes
Soft tissue lesions	RECIST criteria, with the additional requirement that progression at first assessment is confirmed by a second scan 6 or more weeks later. For some treatments, a lesion may increase in size before it decreases
Symptoms	Consider independently of other outcome measures. Document pain/analgesia at entry and measure repeatedly at 3- to 4-wk intervals. Ignore early changes ( $\leq 12$ wk) in pain or HRQOL in the absence of compelling evidence of disease progression. Confirm progression of pain or HRQOL end points $\geq 3$ wk later
Response criteria	
PSA	Ignore early rises (prior to 12 wk) in determining PSA response Record the percent change from baseline at 12 wk, and the maximal change at any time using a waterfall plot
Bone metastases	Record outcome as new lesions or no new lesions. If at the first scheduled reassessment there are not new lesions, continue therapy; if there are new lesions, perform a confirmatory scan 6 or more weeks later and only where new lesions are present stop therapy due to progressive disease
Soft tissue lesions	RECIST criteria, with some caveats: only report changes in lymph nodes that were $\geq 2$ cm in diameter at baseline; record changes in nodal and visceral soft tissue sites separately; record complete elimination of disease at any site separately; confirm favorable change with second scan; record changes using a waterfall plot
Symptoms	Consider independently of other outcome measures. Document pain/analgesia at entry and measure repeatedly at 3- to 4-wk intervals. Ignore early changes ( $\leq 12$ wk) in pain or HRQOL in the absence of compelling evidence of disease progression Confirm response of pain or HRQOL end points $\geq 3$ wk later

PSA: Prostate-specific antigen; RECIST: Response evaluation criteria in solid tumors; HRQOL: Health-related quality of life.

significant benefit in the experimental arm, documenting the effect of treatment with mitoxantrone or vinorelbine in patients with mCRPC: the USOR study documented a time-to-treatment failure (TTTF) of 8.1 mo *vs* 4.1 mo for the mitoxantrone and prednisone arm *vs* prednisone alone<sup>[28]</sup>; another study reported a significantly higher progression-free survival (PFS) of 3.7 mo *vs* 2.8 mo for the combination of vinorelbine plus hydrocortisone *vs* the hydrocortisone arm<sup>[29]</sup>.

Time-to-progression (TTP) was the primary end point in 3 studies, PFS in 2, TTTF in 2, and time-to-subjective-progression in another trial. The definition of events related to progression varied between trials. In the EORTC trial, TTP was evaluated relative to the best condition, observed at the start of treatment or obtained during treatment; this occurred if patients had an increase in pain score by at least one level, increase in the daily analgesic dose by at least 25%, the need for additional pain treatment, and WHO performance status deterioration by at least one level<sup>[27]</sup>. In the Sipuleucel-T study, TTP was defined as progressive disease on serial radiographic imaging tests, new cancer-related pain associated with a radiographic anatomic correlation, or other clinic events consistent with progression (spinal cord compression, nerve root compression, pathologic fracture)<sup>[30]</sup>. In the Atrasentan trial, TTP was determined according to radiographic (different criteria to define progression of bone lesions and soft-tissue lesions) and clinical measures (metastatic pain, skeletal-related events, requirement of a new intervention)<sup>[31]</sup>. PFS was also a composite end point

in the vinorelbine trial, in which it was defined as the time from randomization until progression or death, last news or initiation of a new therapy; the event of progression was the first among radiologic, serologic or pain-related events<sup>[29]</sup>. PFS in the PROSTVAC trial was related to radiologic progression by RECIST criteria or to the appearance of at least two new lesions on a bone scan, even if patients who developed clinical signs or symptoms of progression, but who did not meet the radiologic criteria were also considered to have progressed at the discretion of the investigator<sup>[32]</sup>. TTTF was the primary end point in two positive trials: in the USOR trial it was an aggregate end point, defined as the interval between the start of treatment and occurrence of progressive disease, removal from study or initiation of other antitumor therapy; in this study, progressive disease was radiologic only, by RECIST criteria<sup>[28]</sup>; the PROSTY study used a different definition of TTTF, calculated from randomization to first disease progression (PSA or measurable), unacceptable toxic effects, death or discontinuation of therapy for any reason<sup>[33]</sup>.

Time-to-event end points were reported as secondary end points in 22 studies. In Table 4 these studies are grouped according to the event that defined the measure. The events most often used to define the end point were radiologic progression and PSA progression, in 7 and 6 studies, respectively, although 9 studies used a composite end point of progression. A "subjective" progression was the primary end point in the DAPROCA 9002 study<sup>[26]</sup>, and was defined as an increase in a score including can-

**Table 2** Characteristics of randomized clinical trials including overall survival as the primary end point after first-line and/or second-line medical treatment of metastatic castration-resistant prostate cancer

Trial	Arms	No. pts	Publication year	Main conclusion	Median OS
LSG Trial <sup>[18]</sup>	LIA	160	1998	After adjustment for baseline prognostic factors, HR for OS favored the first arm	10.3 mo
	CPA	161			10.3 mo
CALGB 9182 <sup>[19]</sup>	MXN + HDC	119	1999	Better PSA-RR and PFS in the first arm	12.3 mo
	HDC	123			12.6 mo
HOG/FNC Trial <sup>[20]</sup>	VBL + ESM	95	1999	Better PSA-RR and PFS in the first arm	11.9 mo
	VBL	98			9.2 mo
SWOG 9916 <sup>[6]</sup>	DOC + ESM	338	2004	Longer OS in the first arm	17.5 <sup>1</sup> mo
	MXN + PDN	336			15.6 mo
TAX327 <sup>[5]</sup>	MXN + PDN	337	2004	DOC-based chemotherapy is the new standard first-line treatment of mCRPC	16.5 mo
	DOC + PDN	335			18.9 <sup>1</sup> mo
	wDOC + PDN	334			17.4 mo
<sup>3</sup> SPARC <sup>[21]</sup>	SPT + PDN	635	2009	Better PSA-RR in the first arm	61.3 wk
	Placebo + PDN	315			61.4 wk
<sup>2</sup> TROPIC <sup>[7]</sup>	CBZ + PDN	378	2010	CBZ-based therapy is effective in mCRPC progressing to DOC	15.1 <sup>1</sup> mo
	MXN + PDN	377			12.7 mo
IMPACT <sup>[22]</sup>	SIP-T	341	2010	Similar results	25.8 <sup>1</sup> mo
	Placebo	171			21.7 mo
<sup>2</sup> COU-AA-301 <sup>[8]</sup>	ABI + PDN	797	2011	ABI hormonal therapy is effective in mCRPC progressing to DOC	14.8 <sup>1</sup> mo
	Placebo + PDN	398			10.9 mo
ASCENT-2 <sup>[23]</sup>	DOC + DN101	477	2011	DN101 is inferior to PDN	17.8 mo
	DOC + PDN	476			20.2 <sup>1</sup> mo
CALGB 90401 <sup>[24]</sup>	DOC + PDN + BEV	524	2012	Better PSA-RR and PFS in the first arm	22.6 mo
	DOC + PDN + Placebo	526			21.5 mo
<sup>2</sup> AFFIRM <sup>[9]</sup>	ENZ	800	2012	ENZ hormonal therapy is effective in mCRPC progressing to DOC	18.4 <sup>1</sup> mo
	Placebo	399			13.6 mo
ENTHUSE M1C <sup>[25]</sup>	DOC + ZBT	524	2013	Similar results	20.0 mo
	DOC + Placebo	528			19.2 mo
<sup>3</sup> ALSYMPCA <sup>[10]</sup>	Radium-223	614	2013	Radium-223 effective in mCRPC with painful bone metastases	14.9 <sup>1</sup> mo
	Placebo	307			11.3 mo

<sup>1</sup>Statistically significant difference; <sup>2</sup>Trial of second-line medical treatment; <sup>3</sup>Trial of first or second-line medical treatment. ABI: Abiraterone; BEV: Bevacizumab; CBZ: Cabazitaxel; CPA: Cyproterone acetate; DN101: High-dose calcitriol; DOC: Docetaxel; ENZ: Enzalutamide; ESM: Estramustine; HDC: Hydrocortisone; HR: Hazard ratio; LIA: Liarozole; mCRPC: Metastatic castration-resistant prostate cancer; MXN: Mitoxantrone; OS: Overall survival; PDN: Prednisone; PFS: Progression-free survival; PSA-RR: Prostate-specific antigen response rate; SIP-T: Sipuleucel-T; SPT: Satraplatin; VBL: Vinblastine; wDOC: Weekly-docetaxel; ZBT: Zibotentan.

cer-related weight loss of more than 10%, cancer related decrease in hemoglobin of at least 25%, or the need for at least 2 units of blood a month. A similar composite end point of clinical progression was present in the ECOG 3882 study<sup>[34]</sup>.

Disease progression has had a very variable definition in studies of mCRPC. In the SWOG 99-16, progression was defined as the occurrence of a 50% increase or an increase of 10 cm<sup>2</sup> in the sum of measurements of metastatic lesions over the sum at baseline, reappearance of any lesion that had disappeared, appearance of any new lesion or death<sup>[6]</sup>. A more recent study, the SPARC study, calculated PFS as the time from randomization to the first occurrence of tumor progression, skeletal-related events, symptomatic progression, or death from any cause<sup>[21]</sup>, while the definition in the TROPIC study also included PSA progression<sup>[7]</sup>. Finally, progression has very often been defined by mixed criteria, either as a radiographic event according to RECIST criteria or scintigraphic progression, often the appearance of two or more new lesions on a bone scan, or as clinical progression or serological progression, and the first of these events is considered as the decisive event to define the date of progression.

Treatment failure has been reported as a composite outcome, which usually includes the first event in the progression of disease, the occurrence of unacceptable toxicity, patient refusal to continue therapy, removal from the study or the beginning of another antineoplastic treatment. Time to treatment failure was reported as the primary end point in 2 trials<sup>[31,33]</sup>.

### Response end points

A response end point was the primary end point in 9 studies, as summarized in Table 5 and 6. The end point was a palliative response in three studies, a PSA-response in 2, a double response (PSA and radiologic) in one, and a mixed response in the other 3 trials. Only two studies showed a positive result in the experimental arm: the ECOG 3882 study reported a higher mixed response rate, 63% *vs* 27% for diethylstilbestrol plus doxorubicin arm *vs* doxorubicin<sup>[34]</sup>, and the CALGB 9583 trial documented a higher mixed response rate after antiandrogen withdrawal in the ketoconazole plus hydrocortisone arm<sup>[41]</sup>. In more recent studies, the PSA response rate did not document significant differences when used as a primary end point<sup>[38,39]</sup>.

The CALGB 9181 study provided a mixed response



**Table 3** Characteristics of randomized clinical trials including time-to-event measures as the primary end point after first-line medical treatment of metastatic castration-resistant prostate cancer

Trial	Arms	No. pts	Publication year	End point	Result (mo)
DAPROCA 9002 <sup>[26]</sup>	ESM	61	1997	TTSP	2.2
	Placebo	68			5.0
EORTC <sup>[27]</sup>	FLT	100	2001	TTP	2.3
	PDN	101			3.4
USOR <sup>[28]</sup>	MXN + PDN	56	2002	TTTF	8.1 <sup>1</sup>
	PDN	63			4.1
Vinorelbine Trial <sup>[29]</sup>	VNR + HDC	206	2004	PFS	3.7 <sup>1</sup>
	HDC	208			2.8
UCSF <sup>[30]</sup>	SIP-T	82	2006	TTP	11.7
	Placebo	45			10.0
Atrasentan Trial <sup>[31]</sup>	ATR	408	2007	TTP	HR = 0.89
	Placebo	401			
PROSTVAC <sup>[32]</sup>	PROSTVAC	82	2010	PFS	3.8
	Placebo	40			3.7
PROSTY Trial <sup>[33]</sup>	DOC three-weekly	184	2013	TTTF	4.9
	DOC two-weekly	177			5.6 <sup>1</sup>

<sup>1</sup>Statistically significant difference. ATR: Atrasentan; DOC: Docetaxel; ESM: Estramustine; FLT: Flutamide; HDC: Hydrocortisone; HR: Hazard ratio; MXN: Mitoxantrone; PDN: Prednisone; PFS: Progression-free survival; PROSTVAC: Vaccinia-PSA-TRICOM and Fowlpoc-PSA-TRICOM; SIP-T: Sipuleucel-T; TTP: Time to progression; TTSP: Time to subjective progression; TTTF: Time to treatment failure; VNR: Vinorelbine.

**Table 4** Disease-progression-related events used to define secondary end points in randomized trials of metastatic castration-resistant prostate cancer

Progression event	Trial number	Ref.
Clinical	2	[26,34]
Pain	2	[25,35]
Skeletal-related events	4	[8-10,23]
Radiological	7	[6,8,9,22,24,25,36]
Prostate-specific antigen	6	[8-10,24,25,31]
Alkaline phosphatase	2	[10,31]
Mixed	9	[7,19,20,21,28,33,37-39]

end point, which included the classic radiological criteria, when applicable, PSA response and bone scan evaluation, but the latter was used only to define progression<sup>[40]</sup>. Two distinct response end points, radiologic response and PSA response, were the primary end points in the INT 0159 study<sup>[36]</sup>. In the ECOG 3882 trial, all patients were periodically evaluated by bone scan, serum acid phosphatase, and clinical status. There were reported internal criteria in the study to define the scintigraphic response and the serological response of acid phosphatase; a clinical response derived from the reduction of a point from baseline on the ECOG scale, an increase of 5% in weight, or an increase in hemoglobin of 2 g for at least 3 mo. In this study a scale of priorities was formalized to define progression: in patients with radiologically measurable disease, RECIST criteria were applied, and only in the case of radiologic stability a worsening of bone scintigraphy

**Table 5** Characteristics of randomized clinical trials including radiologic or serological response measures as the primary end point after first line medical treatment of metastatic castration-resistant prostate cancer

Trial	Arms	No. pts	Publication year	Response-related outcome	Response rate (%)
CALGB 9181 <sup>[40]</sup>	MA 160 mg/die	73	2000	MRR	3%
	MA 640 mg/die	76			3%
INT 0159 <sup>[36]</sup>	SUR 3,1	128	2002	PSA-RR/	24%/9%
	SUR 5,3	124		RRR	28%/7%
	SUR 7,6	120			34%/15%
ECOG 3882 <sup>[34]</sup>	DOXO + DES	74	2003	MRR	63% <sup>1</sup>
	DOXO	76			27%
CALGB 9583 <sup>[41]</sup>	AWD + KET + HDC	128	2004	MRR	27% <sup>1</sup>
	AWD	132			11%
Belgian Trial <sup>[38]</sup>	DOC + PDN + ESM	71	2008	PSA-RR	41%
	DOC + PDN	69			25%
NHS Trial <sup>[39]</sup>	DEX + ASP + DES	136	2011	PSA-RR	64%
	DEX + ASP	133			68%

<sup>1</sup>Statistically significant difference. ASP: Aspirin; AWD: Anti-androgen withdrawal; DES: Diethylstilbestrol; DEX: Dexamethasone; DOXO: Doxorubicin; ESM: Estramustine; HDC: Hydrocortisone; KET: Ketoconazole; MA: Medroxyprogesterone acetate; MRR: Mixed response rate; PDN: Prednisone; PSA-RR: Prostate-specific antigen response rate; RRR: Radiologic response rate; SUR: Suramine.

**Table 6** Characteristics of randomized clinical trials including clinical response measures as the primary end point after first line medical treatment of metastatic castration-resistant prostate cancer

Trial	Arms	No. pts	Publication year	PRO measure	Palliative response rate (%)
Canadian Trial <sup>[4]</sup>	MXN + PDN	80	1996	Palliative response (moore)	29 <sup>1</sup>
	PDN	81			12
SIG-1 Trial <sup>[37]</sup>	SUR + HDC	228	2000	Palliative response (BPI + analgesics)	43 <sup>1</sup>
	Placebo + HDC	230			28
NCIC PR06 <sup>[35]</sup>	MXN + PDN	104	2003	Palliative response (moore)	46
	+ CLD	105			39
	MXN + PDN + Placebo				

<sup>1</sup>Statistically significant difference. BPI: Brief pain inventory; CLD: Clodronate; HDC: Hydrocortisone; MXN: Mitoxantrone; PDN: Prednisone; PRO: Patient-reported outcome; SUR: Suramine.

or of clinical status were sufficient criteria for assigning progression<sup>[34]</sup>. In the CALGB 9583 study, patients with measurable disease were considered responsive only if they reported a reduction of at least 50% in the sum of the products of the target lesions, but this was associated with a reduction in baseline PSA of 75% and confirmed after 2 wk<sup>[41]</sup>.

Response end points were also used as secondary end points in 19 studies, as reported in Table 7. PSA response

**Table 7** Disease-control/response related events used to define secondary end points in randomized trials of metastatic castration-resistant prostate cancer

Progression event	Trial number	Ref.
Clinical	1	[27]
Pain	5	[7-9,18,21]
Radiological	11	[4,5,7,19,20,21,24,26,28,37,38]
Prostate-specific antigen	19	[4,5,7,8,19-22,24,25,27-29,33,35,37,38,40,41]
Alkaline phosphatase	1	[10]
Immunity	1	[32]

and radiologic response were the most commonly used secondary end points in 19 and 11 trials, respectively, while pain response was used in 5 studies.

Even though surrogacy has not been validated in prospective studies, more recent studies have continued to report the prostate-specific antigen response rate (PSA-RR) only as a primary end point, defining it as a reduction > 50%, as recommended by the previous PSAWG criteria<sup>[38,39,41]</sup>.

Other response measures were derived from the assessment of disease-related symptoms, such as pain or fatigue, and other patient-related outcomes. Table 6 summarizes the three studies in which the primary end point was clinical and correlated with the response. Although these studies were published between 1996 and 2003, even recent studies have evaluated clinical outcomes, largely related to the patient, as secondary end points, better defining their thresholds of response. In the Canadian study<sup>[4]</sup>, the TAX 327<sup>[5]</sup>, SWOG 99-16<sup>[42]</sup>, SPARC<sup>[21]</sup>, TROPIC<sup>[7]</sup>, and NCIC PR06<sup>[35]</sup>, the palliative response was defined as a 2-point decrease in pain as assessed by a 6-point scale, patient-reported present pain intensity (PPI), without an increase in analgesic medication, and maintained for two consecutive evaluations at least 3 wk apart; pain progression required an increase in the weekly average PPI score of  $\geq 1$  point from baseline or  $\geq 2$  points from nadir for  $\geq 2$  consecutive wk or a more than 25% increase from baseline in the weekly average analgesic score for  $\geq 2$  consecutive weeks<sup>[43]</sup>. In the studies COU-AA-301<sup>[8]</sup>, AFFIRM<sup>[9]</sup>, and SIG-1<sup>[37]</sup> intended for pain palliation, a 30% decrease in the brief pain inventory-short form (BPI-SF) score in the absence of an increase in analgesic usage, while pain progression was an increase of > 30% in the worst pain in the past 24 h on the BFS observed on two consecutive evaluations 4 wk apart without a decrease in analgesic usage score, or an increase in analgesic usage score > 30% observed at 2 consecutive evaluations 4 wk apart; the timing of pain response assessment was reported at week 13 in the AFFIRM trial<sup>[9]</sup>. Other secondary end points were often protocol-dependent and included the Newling palliative response in the LSG trial<sup>[18]</sup>, with measures of pain and analgesic usage scales, the subjective response in the EORTC trial<sup>[27]</sup>, with pain and performance status scores, or the subjective response in the DAPROCA 9002 trial<sup>[26]</sup>, including pain, analgesics use, steroids, radiotherapy and

performance status, and finally the clinical response in the ECOG 3882 study, which collected performance status, pain, analgesic, hemoglobin and body weight scores<sup>[34]</sup>. Pain response was confirmed as highly predictive of outcome in patients with mCRPC<sup>[44]</sup>, but was weaker than the PSA decline > 30% as a possible SE of OS<sup>[14]</sup>.

Unlike PSA response and pain response, response using quality of life (QoL) scores did not correlate with OS in the TAX327 trial<sup>[45]</sup>. This study evaluated a QoL-response using the FACT-P questionnaire: a maximum score of 156 points indicated the highest level of QoL measured by FACT-P, and QoL improvement was defined by  $\geq 10\%$  (16 points) increase maintained for at least 3 wk; inversely, a decrease of 16 points was considered a deterioration in QoL. Among patients enrolled in the trial an impairment of QoL was detected in 92% of patients with pain and in 75% of those without pain, suggesting that disease-related symptoms other than pain contribute to QoL. The complexity of the clinical situation is underlined by the fact that patients with minimal symptoms at the beginning of chemotherapy in the weekly docetaxel arm most likely had an initial worsening of QoL scores. Therefore, it was not surprising that different from pain-response and PSA-response, QoL-response did not predict OS<sup>[45]</sup>.

Few studies have defined the role of other symptoms. Of these the most common is fatigue. In the COU-AA-301 trial, an analysis of a patient-reported questionnaire, the BFI, was performed. After a baseline assessment of the fatigue score distribution, some clinically significant changes in fatigue intensity and fatigue interference were defined. It appeared that in the abiraterone plus prednisone arm more patients experienced an improvement in fatigue intensity and fatigue interference and a delay in the progression of both<sup>[46]</sup>.

## DISCUSSION

PCWG2 recommended that, when possible, all assessments of the disease are carried out at the same time interval. In addition to PSA changes, it is important to confirm the post-treatment changes in the measurable target lesions, those of the radionuclide bone scan, and those of symptoms<sup>[17]</sup>. Following the results of studies on immunotherapy and targeted therapy in mCRPC the opportunity of an appropriate definition of different end points was discussed, and these were defined according to the different drugs and their mechanisms of action. It was proposed that the assessment of cytotoxic and non-cytotoxic therapies is performed in a different way, as cytotoxic chemotherapy and hormonal therapy produce a reduction in PSA and a regression of target lesions, while measures of early response to treatment would not show the effect of immunotherapy and some targeted therapies. In our opinion, although it is difficult to obtain evidence of a surrogate end point according to the criteria of Prentice<sup>[13]</sup>, it is nevertheless appropriate that the search for new SEs should avoid further fragmentation related to the different treatment options.

Potential biases in the present review could be due to the fact that we restricted the included studies to randomized clinical trials; these trials define the best level of evidence available, but this restriction could have excluded many other possible secondary end points. It is also possible that the population in the included studies was heterogeneous: this is because in some studies a second-line treatment was assessed, while in others patients with serologic progression only, with an early stage of mCRPC, were enrolled. Finally, the possibility of publication bias, *i.e.*, studies that did not find the treatment to be effective may not have been published.

To date, none of the end points studied in mCRPC has sufficient evidence to be considered a valid SE of OS. However, many end points have been well standardized and may allow us to better compare the results between studies. Following the recommendations of PCWG2, the time-to-event end points have received increasing attention compared to the response end points.

PFS is usually defined as the time from randomization to the first event in clinical, radiological or biochemical progression or death. PFS has been debated as a SE of OS in studies of mCRPC. The serological progression was the first event in disease progression in 60% of cases, bone progression in 18%, radiological progression in 7%, and death was the first event in 15%. Therefore, in phase-2 studies a PSA-related and time-to-event end point appears to be more practical than any other response end point, and may allow easier comparison of the results between studies with respect to the progression end points. Some preliminary information on PSA kinetics measures, as a growth rate constant, suggest that new measures related to PSA could better predict OS regardless of the type of medical therapy, and promises to overcome many of the limitations of PSA response/progression as defined by PCWG2<sup>[47]</sup>.

On the other hand, clinical research on patient-reported instruments is producing encouraging results and the use of patient-reported outcomes (PROs) in clinical trials is recommended<sup>[48]</sup>. PRO is any outcome based on data provided by patients or patient proxy, as opposed to data provided by other sources. Several types of measures have been included in PROs, such as QoL, functional status, symptoms, overall well-being, satisfaction with care, and treatment adherence. The predictive value of PROs-related end points in cancer patients has been reported in a comprehensive clinical review<sup>[49]</sup>: in 36/39 selected trials at least one PRO was significantly associated with survival after multivariate analysis. Pain-related outcomes have been well studied in patients with mCRPC and measured by two well-defined response end points, but their application is limited to patients with disease-related pain; they appear to be good candidate end points in trials of late stage mCRPC. Similar palliative fatigue-related end points could soon be developed. In addition to pain and fatigue, a rigorous evaluation of the general QoL and its domains may allow us to better capture the clinical benefit of new drugs and could address decision-making. FACT-P and EORTC-QLQ-PR25 are two questionnaires that have

been extensively studied in patients with prostate cancer. While the former seems more detailed<sup>[50]</sup>, it is always better to make a direct comparison with the aim of defining a unique tool for assessing QoL. A final standardization of this instrument could allow us to compare more information between studies.

In conclusion, given the failure of all end points to act as surrogates for OS in the mCRPC setting, defining new PSA-related and patient-related end points and standardizing them remain the most important goal of clinical research. To accomplish this, additional retrospective assessments of recent prospective studies with the aim to test new parameters related to PSA-kinetics and to extrapolate other scores from QoL questionnaires can help identify new end points as surrogates.

## COMMENTS

### Background

The prevalent bone-only dissemination of metastatic castration-resistant prostate cancer (mCRPC), limits the application of commonly used radiologic criteria of progression and response in the assessment of new drugs. Prostate-specific antigen (PSA)-related criteria of response/progression are not effective surrogate end points of overall survival and failed to predict the efficacy of immunotherapy and of some targeted therapies.

### Innovations and breakthroughs

In this review article the authors report how the end points of randomized trials of mCRPC change with the introduction of new drugs and with the improvement of disease-related symptoms and overall survival. They identify two future key areas in the field of end point research of mCRPC, PSA kinetics and patient-reported outcomes.

### Applications

To date, phase-2 trials of new anticancer drugs in mCRPC patients require a PSA-related and time-to-event end point. However, new end points should be tested prospectively.

### Peer review

This manuscript aims to systematically review the end points of 31 prospective clinical trials of medical therapies and/or radiometabolic treatments in hormonal-refractory prostate cancer.

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