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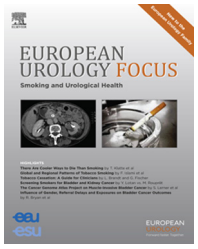

Prostate Cancer

Interrogating Metastatic Prostate Cancer Treatment Switch Decisions: A Multi-institutional Survey

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Abstract

Background: Evaluation of responses to treatment for metastatic castration-resistant prostate cancer (mCRPC) remains challenging. Consensus criteria based on prostate-specific antigen (PSA) and clinical and radiologic biomarkers are inconsistently utilized. Circulating tumor cell (CTC) counts can inform prognosis and response, but are not routinely used.
Objective: To evaluate the use of biomarkers and trends in clinical decision-making in current mCRPC treatment.
Design, setting, and participants: A 23-part online questionnaire was completed by physicians treating mCRPC.
Outcome measures and statistical analysis: Results are presented as the proportion (%) of physicians responding to each of the options. We used χ^2 and Fisher's tests to compare differences.
Results and limitations: A total of 118 physicians (22.1%) responded. Of these, 69.4% treated ≥50 mCRPC patients/year. More physicians administered four or fewer courses of cabazitaxel (27.9%) than for docetaxel (10.4%), with no significant difference in the number of courses between bone-only disease and Response Evaluation Criteria in Solid Tumours (RECIST)–evaluable disease. Some 74.5% of respondents considered current biomarkers useful for monitoring disease, but only 39.6% used the Prostate Cancer Working Group (PCWG2) criteria in clinical practice. PSA was considered an important biomarker by 55.7%, but only 41.4% discarded changes in PSA before 12 wk, and only 39.4% were able to identify bone-scan progression according to PCWG2. The vast majority of physicians (90.5%) considered clinical progression to be important for switching treatment. The proportion considering biomarkers important was 71.6% for RECIST, 47.4% for bone scans, 23.2% for CTCs, and 21.1% for PSA. Although 53.1% acknowledged that baseline CTC counts are prognostic, only 33.7% would use CTC changes alone to switch treatment in patients with bone-only disease. The main challenges in using CTC counts were access to CTC technology (84.7%), cost (74.5%), and uncertainty over utility as a response indicator (58.2%).

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Conclusions: A significant proportion of physicians discontinue treatment for mCRPC before 12 wk, raising concerns about inadequate response assessment. Many physicians find current biomarkers useful, but most rely on symptoms to drive treatment switch decisions, suggesting there is a need for more precise biomarkers.

Patient summary: In this report we analyse the results of a questionnaire evaluating tools for clinical decision-making completed by 118 prostate cancer specialists. We found that most physicians favour clinical progression over prostate-specific antigen or imaging, and that criteria established by the Prostate Cancer Working Group are not widely used.

1. Introduction

The past decade has seen an increase in the therapeutic armamentarium against metastatic prostate cancer, with agents proving survival benefit both in the castrate-resistant (mCRPC) [1–7] and castration-naïve stages [8,9] of the disease. This increased availability of treatment options necessitates improved biomarkers to determine treatment responses more rapidly and facilitate optimised decisions on therapeutic sequencing [10].

Prostate-specific antigen (PSA), bone scans, and Response Evaluation Criteria in Solid Tumours (RECIST) criteria are commonly utilized to evaluate responses and are recommended as outcome measures by the Prostate Cancer Working Group (PCWG2) for clinical trials [11]. However, these biomarkers have significant limitations. In particular, PSA and bone scans do not allow early response assessment, and none of the biomarkers provide patient-level surrogates of clinical benefit [12,13]. This challenge is compounded by the lack of RECIST-evaluable disease in a substantial proportion of patients [14]. For daily clinical practice, existing guidelines do not recommend specific treatment monitoring, an issue addressed by the Advanced Prostate Cancer Consensus conference [15].

The lack of adequate biomarkers may impact the dose intensity of chemotherapy and other anticancer (hormonal, radiopharmaceutical) agents administered in daily clinical practice. The fact that determining disease progression in the absence of clear clinical deterioration is impossible before 12 wk (owing to the possibility of an early PSA or bone scan "flare reaction") in patients with no RECIST-evaluable disease may contribute to both the administration of more chemotherapy cycles to patients with bone-only disease (overtreatment) and a higher reliance on PSA changes for early treatment discontinuation (undertreatment).

Circulating tumour cell (CTC) counts are prognostic and are associated with treatment response in mCRPC patients, with recent studies indicating value as a patient-level surrogate of survival [16,17]. Increasing evidence suggests that CTCs could be utilised to monitor disease progression in mCRPC [18]. However, CTC use is largely limited to academic centres in the setting of clinical trials.

We conducted an online survey of physicians treating mCRPC. The survey focused on how physicians make treatment switch decisions, opinion on response indicators, utilisation of PCWG2 criteria in routine practice, and the value of CTC counts to guide treatment switch decisions. The results will help to inform the design of an international trial and health economic evaluation to improve treatment switch decisions for mCRPC patients to improve outcomes, decrease overtreatment, and maximise resource utilisation.

2. Materials and methods

A 23-part online questionnaire, divided in four sections as outlined below, was compiled by the authors (Supplementary Fig. 1):

1. General questions on clinical practice.
2. Familiarity with progression criteria for currently established biomarkers.
3. CTCs and their assessment in patients with advanced prostate cancer.
4. Clinical decision-making using response indicators.

E-mails inviting participation in the survey were sent to 485 UK investigators participating in urologic cancer clinical trials, 29 physician members of the GU Group of the Swiss Group for Clinical Cancer Research, and 20 practising prostate cancer physicians in Australia and New Zealand. A link to the web-based survey (created with SurveyMonkey) was included.

2.1. Statistical analyses

Descriptive statistics were used; the proportion (%) of physicians responding to each option is presented. Physicians were classified according to the number of patients they treated ($\geq$50 vs $<$50 patients/year) or recruited to clinical trials ($\geq$25% vs $<$25%), and the number of cycles of docetaxel/cabazitaxel prescribed ($\leq$4, 5–6, $\geq$7 cycles). No pre-existing evidence was used in choosing classification cutoff values. Proportions were compared using a χ^2 test or Fisher's exact test (for cell frequencies $\leq$5). A p value of 0.05 was set as the limit for statistical significance. No adjustment for multiple testing was performed. SPSS version 21 (IBM IBM, Armonk, NY, USA) was used.

3. Results

3.1. Participant characteristics and their clinical practice

Between November 21, 2014 and December 18, 2014, 118 practising prostate cancer physicians (22.1%) replied. Sections 1, 2, 3, and 4 were completed by, 111, 106, 98, and 89 physicians, respectively. Most respondents (77.1%) practised in the UK. Nearly 70% treated $\geq$50 mCRPC patients/year (Table 1). Most reported prescribing 7–10 courses of docetaxel and 5–6 cycles of cabazitaxel (Fig. 1); there was no difference in the number of courses of either docetaxel ($p(\chi^2_2) = 0.519$) or cabazitaxel ($p(\chi^2_2) = 0.814$) administered to patients with RECIST-evaluable disease compared to patients with bone-only disease. Physicians

Table 1 – Participant characteristics

Question (number of responses)	*n* (%)
Q1: Specialty (*n* = 118)	
Oncologist	100 (84.7)
Urologist	17 (14.4)
Other	1 (0.8)
Q2: Practice location (*n* = 118)	
UK	91 (77.1)
Europe (non-UK)	16 (13.6
Australia/New Zealand	11 (9.3)
Q3: Number of mCRPC patients treated per year (*n* = 111)	
<10	3 (2.7)
10–49	31 (27.9)
50–99	48 (43.2)
≥100	29 (26.1)
Q4: Percentage of mCRPC patients entered into clinical trials (*n* = 111)	
None	6 (5.4)
<25%	53 (47.7)
25–49%	38 (34.2)
50–74%	12 (10.8)
≥75%	2 (1.8)

mCRPC = metastatic castration-resistant prostate cancer.

reported giving more courses of docetaxel than cabazitaxel in patients with both RECIST-evaluable and bone-only disease ($p(\chi^2_2) < 0.001$). Physicians with larger patient practices prescribed more courses of chemotherapy (Supplementary Table 1).

3.2. *Evaluation of currently available response biomarkers*

Current guidelines provide little instruction on the evaluation of response to treatment in mCRPC; this is particularly challenging in patients with only bone metastases and no other measurable disease [15,19]. PCWG2 progression criteria (Supplementary Table 2) are mainly used among patients treated within clinical trials. We evaluated the opinion of physicians on currently available biomarkers (PSA, bone scan, and CTCs) for monitoring response. Some 79 respondents (74.5%) rated these as useful (71.7%) or very useful (2.8%). Only 39.6% reported using PCWG2 criteria most or all of the time, and 27.3% reported rarely or never using the criteria (Table 2). Physicians recruiting more patients to trials were more likely to use PCWG2 frequently (56% vs 25%; $p(\chi^2_2) = 0.001$) = 0.001; Supplementary Table 3).

3.2.1. *PSA*

A total of 59 respondents (55.7%) reported that PSA was a useful/very useful biomarker for monitoring response to treatment (Table 2). We asked participants to identify PSA progression in graphical examples showing consecutive PSA values to evaluate their ability to utilize PCWG2 criteria. Only 41.4% of physicians correctly recognised that at least 12 wk are required to define PSA progression (Fig. 2A). Most physicians (84.8%) correctly identified that a 25% increase from the nadir value (confirmed by a second value at least 3 wk later) constituted progression (Fig. 2B). Some 90.9% failed to recognise that PSA progression holds even if the confirmatory second value is lower than the first, providing both values show a 25% increase from the nadir (Fig. 2C). Only two physicians (2.0%) answered all three questions correctly.

3.2.2. *Bone scintigraphy*

PCWG2 criteria define bone scan progression as a minimum of two new lesions, with new lesions observed at the first 12-wk reassessment requiring a confirmatory scan (Supplementary Table 2). When respondents were asked to choose from a number of definitions of bone scan progression (selecting more than one was permitted), only 39.4% answered the correct option (as per PCWG2) and discarded the incorrect options, indicating diversity in bone scan interpretation.

3.2.3. *CTCs*

Some 98% of respondents were familiar with the concept of CTCs, but only 53.1% recognised that baseline CTCs have

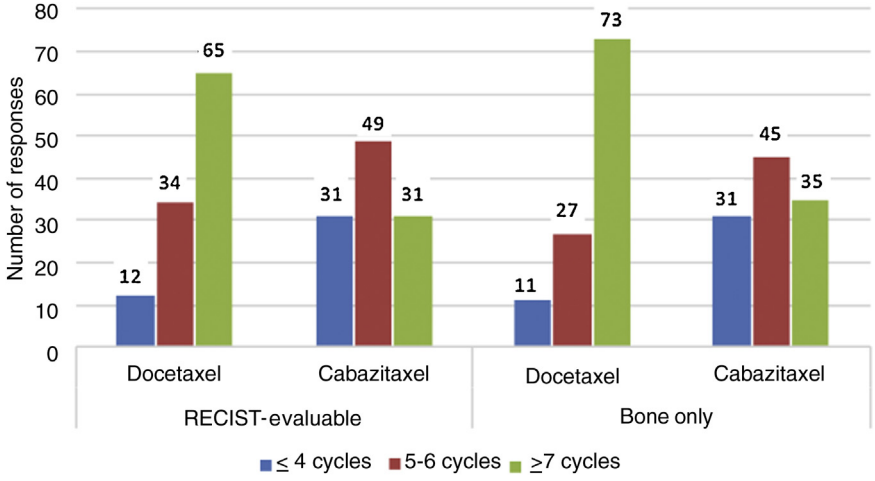

Fig. 1 – Number of cycles of chemotherapy administered to patients with Response Evaluation Criteria in Solid Tumours (RECIST)–evaluable disease and bone-only metastatic castration-resistant prostate cancer (mCRPC). The figure summarises replies for Questions 5–8 ("How many cycles of docetaxel/cabazitaxel do you prescribe, on average, to mCRPC patients with RECIST-evaluable/bone only disease?").

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Table 2 – Evaluation of currently available biomarkers, CTCs and use of Prostate Cancer Working Group (PCWG2) criteria in mCRPC

Question (number of responses)	*n* (%)
Q9: Suitability of currently available biomarkers (PSA, bone scans, CTCs) in monitoring disease in mCRPC (*n* = 106)	
Very useful	3 (2.8)
Useful	76 (71.7)
Not very useful	25 (23.6)
Poor	2 (1.9)
Q11: Suitability of PSA as a chemotherapy response marker in mCRPC (*n* = 106)	
Very useful	3 (2.8)
Useful	56 (52.8)
Not very useful	44 (41.5)
Poor	3 (2.8
Q10: Use of PCWG2 criteria for decision-making when treating patients with mCRPC (*n* = 106)	
Always	3 (2.8)
Mostly	39 (36.8)
Sometimes	35 (33)
Rarely	12 (11.3)
Never	17 (16)
Q14: Familiar with the concept of CTCs (*n* = 98)	
Yes	96 (98)
No	2 (2)
Q15: Baseline number of CTCs at start of chemotherapy is prognostic for overall survival in mCRPC (*n* = 98)	
Yes	52 (53.1)
No	0 (0)
Unsure	46 (46.9)
Q16–17: Change in number of CTCs is associated with response in mCRPC during (*n* = 98): Chemotherapy	
Yes	53 (54.1)
No	0 (0)
Unsure	45 (45.9)
Abiraterone	
Yes	49 (50)
No	0 (0)
Unsure	49 (50)
Q18: Challenges associated with use of CTCs in prostate cancer (*n* = 98)	
Cost	73 (74.5)
Lack of/uncertainty about prognostic significance	43 (43.9)
Lack of/uncertainty about predictive information on treatment response	57 (58.2)
Difficulty in interpreting changes in CTC number	41 (41.8)
Poor access to CTC enumeration technology	83 (84.7)
Other	4 (4.1)
Q20: Likelihood of switching or stopping chemotherapy in an asymptomatic mCRPC patient with PSA increase at 12 wk and no radiologic progression (*n* = 95)	
Definitely	0 (0)
Likely	16 (16.8)
Unlikely	70 (73.7)
Definitely not	9 (9.5)
Q21: Likelihood of switching or stopping abiraterone or enzalutamide in an asymptomatic mCRPC patient with PSA increase at 12 wk and no radiologic progression (*n* = 95)	
Definitely	0 (0)
Likely	9 (9.5)
Unlikely	68 (71.6)
Definitely not	18 (18.9)
Q23: Likelihood of using CTC changes alone, independently of PSA or bone scan findings, in guiding decision-making to switch or stop therapy in an mCRPC patient with bone-only disease (*n* = 89)	
Definitely	1 (1.1)
Likely	29 (32.6)
Unlikely	55 (61.8)
Definitely not	4 (4.5)

CTC = circulating tumour cell; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.

prognostic value. Similarly, only 50.0% and 54.1% respondents were aware that a post-treatment change in CTCs was associated with outcome in patients treated with abiraterone and chemotherapy, respectively (Table 2).

Major challenges identified by respondents as currently limiting the use of CTCs in prostate cancer were assay cost (74.5%), poor access to CTC enumeration tests (84.7%), and uncertainty over their clinical utility in response assessment (58.2%; Table 2).

3.3. *Clinical decision-making in CRPC*

According to PCWG2, clinical progression is defined as worsening pain and analgesic use, deteriorating quality of life, urinary or bowel compromise, or a need for new anticancer therapy. Of these, only worsening pain is associated with outcome in prospective clinical trials [20]. Almost all physicians (90.5%) considered clinical progression to be important for driving treatment switches.

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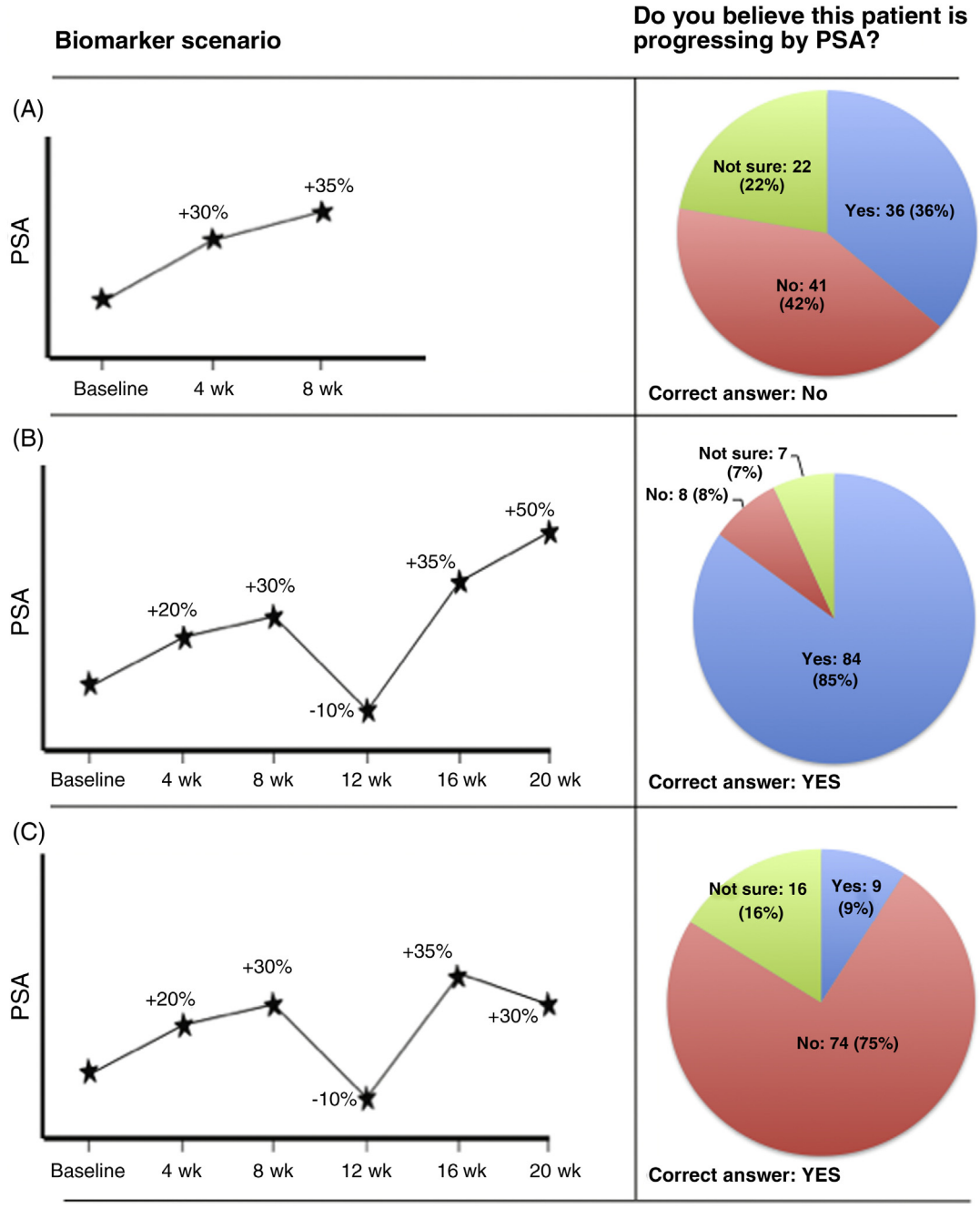

Fig. 2 – Evaluation of prostate-specific antigen (PSA) progression criteria. The figure summarises replies for Question 12. Participants were shown three different PSA biomarker scenarios for patients with bone-only disease. The percentage of participants who believed the scenario corresponded to PSA progression is shown in the pie charts. Correct response: (A) No; (B) Yes; (C) Yes.

Some 71.6% and 47.7% felt RECIST and bone scan progression to be important, and only 23.2% and 21.1% felt CTC and PSA progression to be important, respectively.

Overall, 55.7% considered PSA useful/very useful in guiding therapy, but only 21.1% considered it important for decision-making (Fig. 3). Physicians who considered PSA and bone scans important/very important for decision-making did not have a better understanding of response criteria (Supplementary Table 4). Only 30% of physicians who considered PSA important/very important in guiding treatment switches acknowledged that at least 12 wk is needed to define PSA progression (Supplementary Table 4).

In the case of an asymptomatic mCRPC patient with a rising PSA at 12 wk but no evidence of radiologic progression, most physicians were unlikely to switch/stop chemotherapy (83.2%) or abiraterone/enzalutamide (90.5%). Only 33.7% of respondents were ready to use CTC changes alone, independently of PSA or bone scans, to guide switching/stopping therapy in patients with bone-only disease; among those who acknowledged the value of

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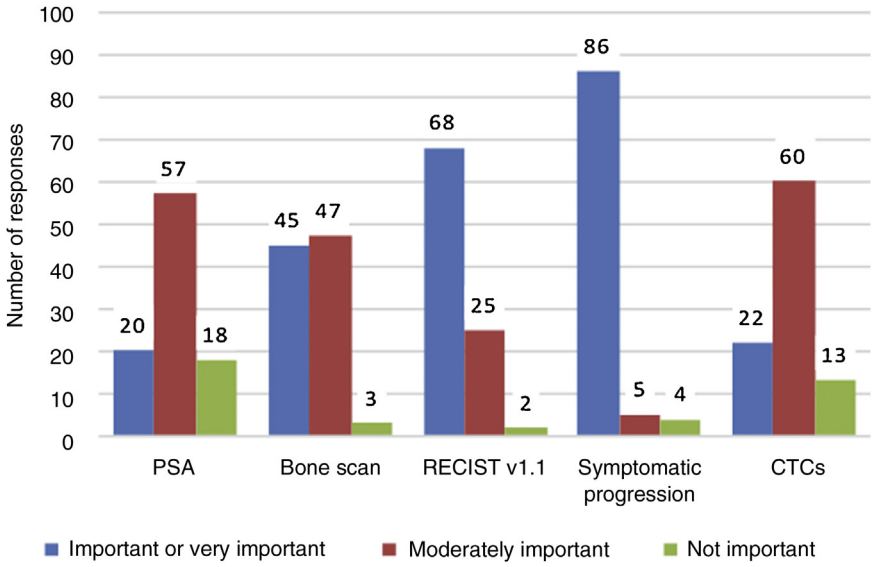

Fig. 3 – Importance of different biomarkers in clinical decision-making (stopping therapy) in metastatic castration-resistant prostate cancer. The figure summarises replies for Question 19. Participants were asked to rank each of the different types of disease progression listed from 1 (extremely important) to 6 (not at all important) in their clinical decisions to switch or stop therapy. RECIST = Response Evaluation Criteria in Solid Tumours; PSA = prostate-specific antigen; CTCs = circulating tumour cells.

CTCs as a response-biomarker, the proportion was 43.5%. Of those who were likely/very likely to switch on CTC changes alone independently of PSA or bone scans, a larger proportion were physicians who felt that currently available biomarkers are not very useful/poor in monitoring disease ($p = 0.03$; Supplementary Table 5). Among those who were unlikely/unwilling to switch on CTC changes alone, 57.6% cited uncertainty over predictive information on treatment response as a challenge in use of CTCs, with 52.5% and 42.4% citing uncertainty over prognostic significance and difficulty in interpreting CTC changes, respectively.

3.4. *Treatment switches in mCRPC*

The final part of the questionnaire asked respondents to consider scenarios involving clinically stable mCRPC patients with bone-only disease. For a >25% PSA rise but a CTC decline to <5 cells/7.5 ml (“favourable” CTC conversion) and a stable bone scan at 12 wk, 92.1% of respondents would not switch/stop therapy (Fig. 4A). The proportion fell to 68.5% if the bone scan showed increased tracer uptake but no new lesions (Fig. 4B). For a 50% fall in PSA but a CTC rise to ≥5 cells/7.5 ml (“unfavourable” CTC conversion) at 12 wk and stable disease according to a bone scan, only 11.2% would switch/stop therapy (Fig. 4C). For a 50% PSA decline and CTC conversion from “unfavourable” to “favourable” count at 12 wk, but two new lesions on a bone scan, most respondents (70.8%) reported they would not switch/stop therapy (Fig. 4D).

Respondents who believed that post-treatment CTC changes were associated with treatment response were more likely to switch/stop therapy on CTC progression as in Figure 4C ($p = 0.023$), and were more likely to continue treatment with CTC response as in Figure 4B ($p = 0.003$) and Figure 4D ($p = 0.005$; Supplementary Table 3).

4. Discussion

It is imperative that more precise response biomarkers that can guide more rapid identification of drug resistance and treatment termination are developed to minimise the overtreatment of patients with ineffective therapies, decrease the toxicity of ineffective treatment, and maximize the utilisation of resources. We conducted this survey to evaluate current practice in clinical decision-making by physicians specialised in the treatment of CRPC. Our results highlight difficulties in the application of current biomarkers in the treatment of advanced prostate cancer in daily clinical practice.

Are physicians giving too much chemotherapy, or too little? The optimum number of chemotherapy courses is unclear. In the TROPIC trial, although a maximum number of ten cycles of chemotherapy was allowed, a median of six courses was reported, and 28% of patients completed ten courses [7]. This is similar to numbers reported in expanded-access programmes [21,22]. In TAX-327, in which the number of cycles of docetaxel was not limited to ten, the median number of cycles in the three-weekly docetaxel arm was 9.5 [23]. Our survey, however, indicates that a significant number of physicians discontinue treatment before four courses (12 wk) of treatment; this is especially true for cabazitaxel. According to our survey, early discontinuation does not appear to be related to radiologic disease progression, since no difference in the number of chemotherapy courses between RECIST-evaluable and bone-only disease was reported.

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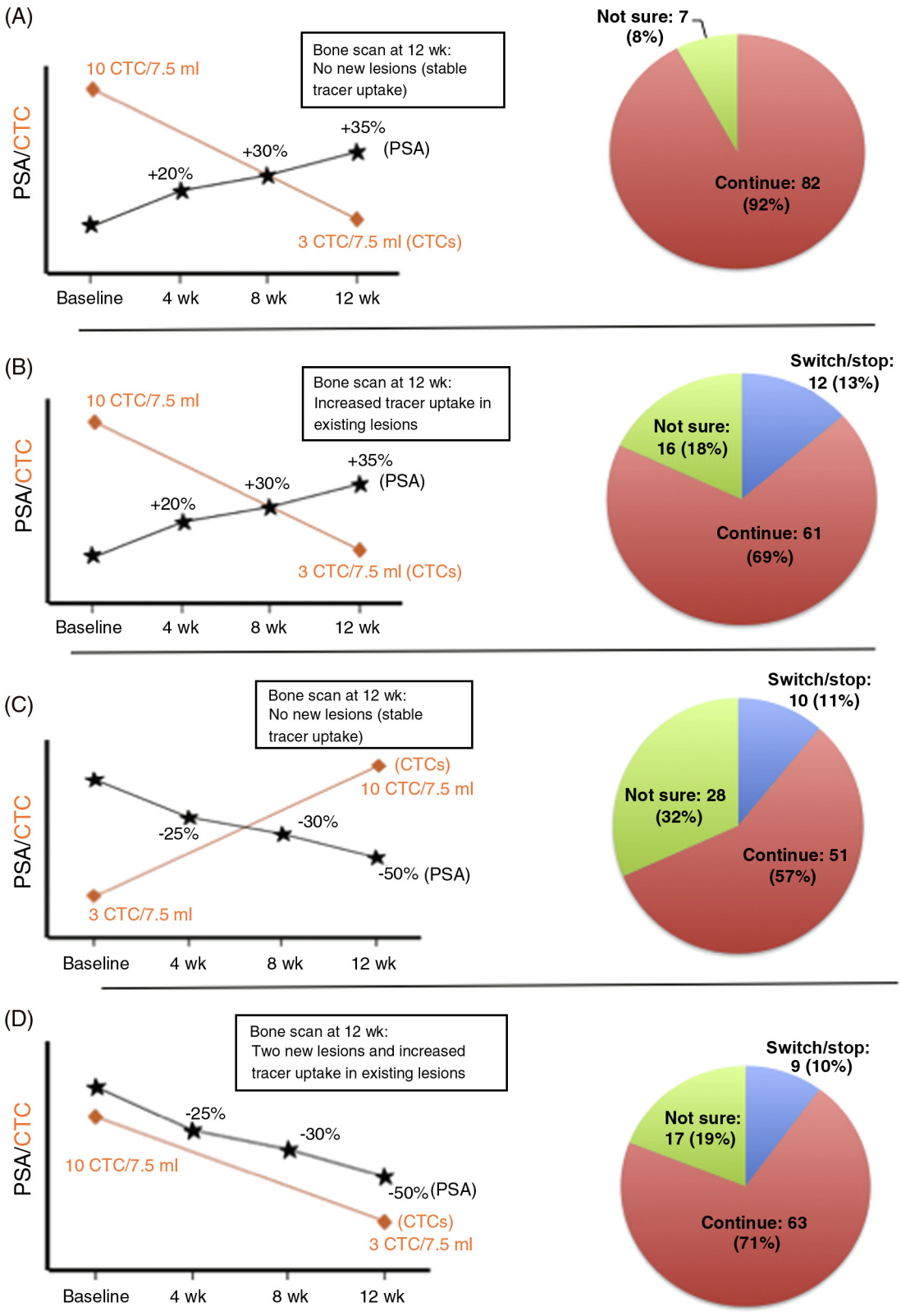

Fig. 4 – Decision-making for different biomarker scenarios. The figure summarises replies for Question 22. Participants were shown four different biomarker scenarios combining prostate-specific antigen (PSA), circulating tumor cells (CTCs), and bone scan findings for clinically stable patients. The proportion of participants who would switch or stop therapy at 12 wk is shown in the pie charts.

How familiar are physicians with consensus response criteria? In our survey, although most physicians considering currently available biomarkers (74.5%), and PSA in particular (55.6%), to be useful for monitoring disease, knowledge of the specific PCWG2 criteria is suboptimal. PCWG2 requires a confirmatory value at least 3 wk after a first progressing PSA, and recommends discarding any early (before 12 wk) PSA increase owing to the possibility of PSA "flare", reported in 16.7% of patients in TAX-327 [24]. In our survey, many physicians failed to acknowledge the possibility of a PSA flare in evaluating PSA progression.

Concerns regarding the interpretation of bone-scan imaging were also identified. Only around 40–60% of mCRPC patients are evaluable according to RECIST, with many patients having bone-only disease [14]. PCWG2 criteria indicate that bone scans can only be used for the assessment of progression and not response. New lesions at the first 12-wk assessment require a confirmatory scan, since early bone-scan "flare" is not uncommon [25]. Only 39.4% of respondents followed the PCWG2 definition of bone scan progression, despite recent studies indicating an association between radiographic progression-free survival (combining a bone scan and RECIST) and survival in the COU-302 phase 3 trial [26].

These findings suggest that decisions to switch treatment are challenging for physicians treating advanced prostate cancer. PCWG2 guidelines acknowledge difficulties in assessing progression according to clinical symptoms alone because of "subjectivity" [11]; however, this was overwhelmingly acknowledged as the most important determinant of disease progression in routine practice. RECIST criteria ranked second in importance, despite being useful for only some patients. Interestingly, only 39.6% commonly use PCWG2 criteria for clinical-decision making. When confronting physicians with clinical scenarios based on CTC, PSA and bone scan information no significant predominance of one biomarker was found. Physicians generally continued treatment in the face of "contradictory" biomarker information (ie, rising CTCs with falling PSA; falling CTCs with rising PSA; or falling CTCs and PSA with new lesions on bone scan), for which current European Association of Urology and European Society for Medical Oncology guidelines do not offer clear recommendations on optimal decision-making. Importantly, we observed no significant differences in the familiarity with PSA or bone scan progression criteria (questions 12 and 13), the importance of each of the biomarkers in the decision to switch or stop therapy (question 19), or the likelihood of switching or stopping in the face of the different proposed biomarker scenarios (question 20) between physicians treating in high-volume centres ($\geq$50 patients/yr) and those in low-volume centres ($<$50 patients/yr). These data suggest a need for more precise biomarkers to report on response and progression, since patients today appear to continue receiving treatment despite biomarkers indicating a lack of response.

CTC count holds promise as a response biomarker, with well-established prognostic utility that has been validated prospectively with chemotherapy [16,27], abiraterone [17], and enzalutamide [28]. A combination of lactate dehydrogenase and CTCs is a patient-level surrogate of survival [17], and post-treatment changes are robustly associated with outcome [29,30]. Moreover, CTC counts have greater sensitivity and specificity and inform on outcome earlier than changes in PSA do [30,31]. However, only half of the responding physicians were familiar with available CTC data, with very few prepared to stop abiraterone (9.5%) or chemotherapy (16.8%) on the basis of CTC progression. Nonetheless, physicians cognisant of available CTC data were more willing to guide treatment according to CTC changes. Cost was reported as a major caveat to the routine use of CTCs, although most of this could be easily recouped by earlier discontinuation of ineffective treatment.

We acknowledge a number of limitations to our study. The return rate was 22.1%, and not all physicians completed the entire survey. Reasons for not completing the survey are unknown, although this could be related to the lack of compensation offered. Furthermore, no distinction was made between academic and nonacademic centres, and no comparison was made between UK-based and non–UK-based physicians. To maximise the yield of information and study participants, the size of the questionnaire included only three questions on biomarker criteria, which may be insufficient to fully evaluate physician knowledge.

5. Conclusions

In conclusion, our data indicate that more precise response biomarkers and physician education are needed to interrogate outcome in daily clinical practice in mCRPC, and that it is likely that many patients are being over- and under-treated. Many physicians rely on the highly subjective reporting of symptoms for treatment switch decisions. Physician education on these challenges, and established working group criteria, are needed, as are prospective trials to clinically qualify biomarker utility, improve treatment switch decisions and patient outcome as well as change clinical practice.

Author contributions: David Lorente had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lorente, Ravi, de Bono.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euf.2016.09.005.

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