European Journal of Cancer (2014) xxx, xxx–xxx

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel ☆

John M. Fitzpatrick [a,*], Joaquim Bellmunt [b], Karim Fizazi [c], Axel Heidenreich [d], Cora N. Sternberg [e], Bertrand Tombal [f], Antonio Alcaraz [g], Amit Bahl [h], Sergio Bracarda [i], Giuseppe Di Lorenzo [j], Eleni Efstathiou [k], Stephen P. Finn [l], Sophie Fosså [m], Silke Gillessen [n], Pirkko-Liisa Kellokumpu-Lehtinen [o], Frédéric E. Lecouvet [f], Stephane Oudard [p], Theo M. de Reijke [q], Craig N. Robson [r], Maria De Santis [s], Bostjan Seruga [t], Ronald de Wit [u]

[a] *Irish Cancer Society and University College, Dublin, Ireland*
[b] *University Hospital del Mar, Barcelona, Spain*
[c] *Institut Gustave Roussy, University of Paris Sud, Villejuif, France*
[d] *University Hospital Aachen, Aachen, Germany*
[e] *San Camillo and Forlanini Hospital, Rome, Italy*
[f] *Centre du Cancer et Institut de Recherche Expérimental et Clinique (IREC), Cliniques Universitaires Saint Luc, Brussels, Belgium*
[g] *Hospital Clinic de Barcelona, Barcelona, Spain*
[h] *University Hospitals Bristol, Bristol, United Kingdom*
[i] *Ospedale San Donato, Istituto Toscano Tumori (ITT), Arezzo, Italy*
[j] *University Federico II, Napoli, Italy*
[k] *University of Texas, M.D. Anderson Cancer Center, Houston, TX, United States*
[l] *St. James's Hospital and Trinity College, Dublin, Ireland*
[m] *Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway*
[n] *Kantonsspital St. Gallen, St. Gallen, Switzerland*
[o] *Tampere University Hospital, Tampere, Finland*
[p] *Georges Pompidou European Hospital, Paris, France*
[q] *Department of Urology, Academic Medical Center, Amsterdam, The Netherlands*
[r] *Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom*
[s] *Ludwig Boltzmann Institute for Applied Cancer Research, Kaiser Franz Josef-Spital, Vienna, Austria*
[t] *Department of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia*
[u] *Erasmus University Medical Center, Rotterdam, The Netherlands*

Received 3 March 2014; accepted 9 March 2014

Financial support was provided by an educational grant from Sanofi Oncology.

* *Corresponding author:* Address: Irish Cancer Society, 43/45 Northumberland Road, Dublin 4, Ireland. Tel.: +353 1 2310 544; fax: +353 1 2310 555.
E-mail address: jfitzpatrick@irishcancer.ie (J.M. Fitzpatrick).

http://dx.doi.org/10.1016/j.ejca.2014.03.010

KEYWORDS
Metastatic castration-resistant prostate cancer
Consensus
Radium 223 dichloride
Abiraterone
Enzalutamide
Docetaxel
Circulating tumour cells
Sipuleucel-T
Cabazitaxel
Denosumab

Abstract The exponential growth of novel therapies for the treatment of metastatic castration-resistant prostate cancer (mCRPC) over the last decade has created an acute need for education and guidance of clinicians regarding optimal strategies for patient management. A multidisciplinary panel of 21 European experts in mCRPC assembled for comprehensive discussion and consensus development, seeking to move the field forward and provide guidance and perspectives on optimal selection and sequencing of therapeutic agents and monitoring of response to treatment and disease progression. A total of 110 clinically-relevant questions were addressed and a modified Delphi method was utilised to obtain a consensus. The panel reached a consensus on several important issues, providing recommendations on appropriate phase III clinical trial end-points and optimal strategies for imaging and monitoring of bone metastases. Guidance regarding selection and sequencing of therapy in patients with newly diagnosed or progressive mCRPC is emphasised, including the use of novel bone-targeted agents, chemotherapy, androgen receptor pathway-targeted agents and immunotherapy. The impact of drug resistance and prostate-specific antigen flare on treatment decisions was also addressed. Ultimately, individualised therapy for patients with mCRPC is dependent on continued refinement of clinical decision-making based on patient and disease characteristics. This consensus statement offers clinicians expert guidance on the implementation of recent advances to improve patient outcome, focusing on the future of prostate cancer care.

1. Introduction

Despite continued advances, prostate cancer claims the lives of over 70,000 men in the European Union (EU) each year [1]. Although docetaxel has been established as the standard of care for progressing patients with metastatic castration-resistant prostate cancer (mCRPC) who are able to tolerate this agent, it is now clear that this agent could not be universally used [2–4]. Intense research and a better understanding of the pathophysiology of the disease have resulted in the development of new drugs that are now making their way into the clinic.

Since 2004, we have learned that the androgen receptor (AR) could be further manipulated by novel hormone therapy (i.e. abiraterone acetate and enzalutamide), that the patient immune system could be enlisted to fight the cancer (sipuleucel-T), that novel chemotherapy active against docetaxel-resistant cells could be used (cabazitaxel), and that the bone microenvironment could more effectively be targeted to delay skeletal complications (i.e. denosumab) or even increase overall survival (OS) ($^{223}RaCl_2$ — radium 223 dichloride [Ra223]) [5–13]. Clinical trials have compared these new drugs either to placebo or outdated comparators and there is no head-to-head comparison between these agents. As a result, the need for individualised therapy is widely recognised and treating physicians are left with difficult choices and few available solid determinants.

Against the backdrop of these novel therapeutic developments, a panel of European experts convened with the following objectives:

1. To examine appropriate end-points for current and future clinical trials in mCRPC.
2. To assess the role of imaging in diagnosing metastases and monitoring response to therapy.
3. To discuss the importance of patient phenotype in therapeutic decision-making.
4. To review the role of novel bone-targeted radiopharmaceuticals, chemotherapy, immunotherapy and AR pathway-targeted agents.
5. To evaluate current opinion regarding the most appropriate sequencing of available therapies for mCRPC.

2. Methodology

The European Consensus Panel was held on 7th September 2013 in Nice, France, and consisted of 21 experts with extensive experience in the field of prostate cancer (Appendix A). The format of the consensus conference was modelled after that of the very successful St. Gallen Early Breast Cancer Consensus Conference organised biannually by Professors H.-J. Senn and A. Goldhirsch [14]. A modified Delphi method was used to obtain a consensus and a consensus threshold of 70% was agreed upon. Participants considered a series of 110 questions, completing a baseline questionnaire prior to any discussion. The experts then shared their assessment of topics by answering specific questions during the conference. Guided by the moderator, the panel debated any conflicting viewpoints, followed by another opportunity to vote on the same question. The process continued until

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

the consensus threshold was met, or until it became apparent that a consensus was lacking (Table 1). Not all questions resulted in a consensus and some experts chose to abstain due to perceived lack of information or expertise regarding the topic. To better quantify the results of this conference, we have used the following nomenclature throughout this manuscript: strong consensus ($\geqslant$80% agreement on a choice, with $\leqslant$5% abstaining), consensus ($\geqslant$70% agreement on a choice, with $\leqslant$20% abstaining) and no consensus (<70% agreement or >20% abstaining).

3. Consensus development and panel discussion

3.1. Clinical trial end-points

Clinical trials and appropriate primary end-points are critical for moving the field of prostate cancer forward. The panel consensus was that OS and radiologic progression-free survival (rPFS) were appropriate primary end-points for phase III clinical trials investigating cancer-specific therapeutic agents for mCRPC. In contrast, the panel felt that clinical PFS (based on physical exam and/or pain and/or deterioration of performance status [PS]), prostate specific antigen (PSA) progression, occurrence of symptomatic skeletal-related events (SREs), occurrence of pain and quality of life were not appropriate primary end-points for phase III trials, but could serve as important secondary end-points. Panelists emphasised that primary end-points will most likely evolve with the continued emergence of novel therapeutic agents. For bone-targeted therapies, OS is not required, but the occurrence of SREs may be a sufficient end-point in clinical trials.

Circulating tumour cell (CTC) count is a predictor of OS in patients with CRPC receiving either chemotherapy or abiraterone [15–17]. However, the technology for detection of CTCs requires further fine-tuning to ensure accuracy [15]. Furthermore, preclinical data suggest that the interaction of CTCs with platelets may promote evasion of immune surveillance and current CTC detection methods, suggesting CTC enumeration may not reflect a patient's true risk for metastatic disease [18]. Based on currently available data, 86% of the panel agreed that CTCs are not ready for use as a surrogate OS marker in clinical trials of CRPC. They also emphasised that there are currently no other reliable surrogates for OS in prostate cancer, including PFS.

3.2. Monitoring progression and response

Despite advances in mCRPC, disease diagnosis and monitoring of progression and response in bone still rely on ^{99m}Tc-polyphosphonate bone scintigraphy and standard x-rays or computed tomography (CT), even with a proven poor sensitivity and specificity. The limitations of bone scanning were reiterated by the panel, emphasising that a negative bone scan is not sufficient to exclude the presence of bone metastases, particularly in patients with bone pain or rapidly rising PSA levels.

The use of advanced imaging modalities, such as positron emission tomography (PET)/CT and magnetic resonance imaging (MRI), has important implications in treatment decision-making [19]. For patients with bone pain and equivocal or negative bone scans, the panel strongly agreed that axial skeleton MRI was a reasonable and appropriate diagnostic imaging study [20]. Despite initial disagreement regarding the role of plain x-rays, discussion led to a consensus that x-rays also have diagnostic value in patients with bone pain and an equivocal or negative bone scan. Consensus was reached that [^{18}F]-fluorodeoxyglucose (FDG)–PET/CT and whole-body MRI are not appropriate in this clinical setting. The panel identified axial skeleton MRI as the most useful imaging tool for assessing response of bone metastases to therapy over bone scan, whole body MRI and FDG–PET/CT [21]. The panel stressed that advanced imaging modalities are not readily accessible in all areas of the world [19]. Future efforts should focus on validating newer imaging technologies and making them affordable and available to all patients.

The panel was initially divided on whether early imaging was appropriate to detect primary resistance to novel agents targeting the AR pathway. While early response assessment gives the opportunity to discontinue ineffective therapies, accuracy is highly dependent on the sensitivity of the imaging method utilised. Following discussion, 81% of the panel members agreed that early imaging should be performed during therapy for mCRPC to detect resistance to novel agents targeting the AR pathway and 3 months was recommended as the appropriate minimum time point based on the imaging modalities currently available. Imaging prior to 3 months may detect bone flare and should be avoided.

3.3. Therapeutic implications of patient phenotype

The panel agreed unanimously that prostate cancer demonstrates significant heterogeneity between individuals and even within the same patient. In order to better understand prostate cancer heterogeneity and move the field forward with regard to personalised treatment decisions, the panel reached a consensus that, when possible, biopsy of metastatic lesions should be considered. Biopsy of accessible metastatic lesions provides the opportunity to reassess differentiation and proliferation characteristics, confirm that the histology is consistent with the primary tumour and assess potential tumour heterogeneity. Discussion amongst the panelists emphasised that re-biopsy of metastatic sites is important, provided that the results can influence treatment

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

Table 1
European Consensus Panel voting results. Bolded values indicate the consensus.

	Yes	No	Abstain	Consensus level
Definition of CRPC				
In patients with castrate serum testosterone levels, CRPC can be defined as				
Confirmed PSA progression	**81%**	19%	0%	Strong consensus
Confirmed PSA progression having received combined androgen blockade and after anti-androgen withdrawal for ⩾4 weeks	57%	38%	5%	No consensus
Confirmed PSA progression after ⩾2 prior hormonal therapies	10%	**81%**	10%	Consensus
End-points for Phase III Clinical Trials				
Appropriate primary end-points for phase III clinical trials				
OS	**100%**	0%	0%	Strong consensus
Radiographic progression-free survival	**71%**	10%	19%	Consensus
Clinical progression-free survival	29%	**71%**	0%	Consensus
PSA progression	11%	**89%**	0%	Strong consensus
Skeletal-related events	29%	**71%**	0%	Consensus
Pain/pain deterioration	10%	**90%**	0%	Strong consensus
Quality of life deterioration	14%	**81%**	5%	Strong consensus
Should phase III trial end-points differ depending on the line of therapy?	**71%**	29%	0%	Consensus
Are coprimary end-points appropriate for phase III clinical trials in mCRPC?	**76%**	24%	0%	Consensus
Can CTC count serve as a surrogate for OS in phase III clinical trials of systemic therapy for mCRPC?	10%	**86%**	5%	Strong consensus
Are there other reliable surrogates for OS?	10%	**81%**	10%	Consensus
Imaging				
In the absence of bone pain, is an unequivocally positive or negative bone scan adequate to assess presence or absence of bone metastases?	38%	62%	0%	No consensus
If bone scan is equivocal or negative despite bone pain, which of the following is reasonable and appropriate for diagnostic imaging?				
Plain x-rays of areas of concern	**70%**	30%	0%	Consensus
Axial skeleton MRI scan	**85%**	10%	5%	Strong consensus
Whole body MRI scan	29%	**71%**	0%	Consensus
FDG-PET/CT	5%	**86%**	10%	Consensus
Fluoride PET/CT	53%	47%	0%	No consensus
Choline PET/CT	60%	40%	0%	No consensus
Which of the following imaging studies is most useful for assessment of response of bone metastases to therapy?				
Tc-99 bone scan	29%	**71%**	0%	Consensus
Whole body MRI	24%	**71%**	5%	Consensus
Axial skeleton MRI	**75%**	25%	0%	Consensus
PET/CT	21%	68%	11%	No consensus
Should early imaging be performed to detect primary resistance to novel agents targeting the AR pathway?	**81%**	19%	0%	Strong consensus
Therapeutic Implications of Patient Phenotype				
Prostate cancer exhibits histological/genomic heterogeneity				
Within the same patient	**100%**	0%	0%	Strong consensus
Between patients	**100%**	0%	0%	Strong consensus
Should biopsy of a metastatic site be performed for selected patients with CRPC and accessible lesions?	**71%**	19%	10%	Consensus
Which of the following are reasons for rebiopsy?				
To confirm that histology is consistent with prostatic origin	**71%**	29%	0%	Consensus
To reassess differentiation or proliferation	**71%**	29%	0%	Consensus
To assess potential tumour heterogeneity	**84%**	11%	5%	Strong consensus

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

Table 1 (*continued*)

	Yes	No	Abstain	Consensus level
How would you define primary resistance to AR pathway-targeted agents?				
Lack of PSA decrease of ⩾50% during therapy	5%	**84%**	11%	Consensus
Lack of PSA decrease of ⩾30% during therapy	5%	**90%**	5%	Strong consensus
PSA progression within 3 months of therapy initiation	19%	**76%**	5%	Consensus
Radiological progression within 3 months of therapy initiation	**76%**	14%	10%	Consensus
<1 year duration of response to first hormonal therapy	5%	**90%**	5%	Strong consensus
Indicators of increased risk for primary resistance to AR pathway-targeted agents include				
High Gleason score grade of primary tumour	53%	42%	5%	No consensus
Short duration of response to first-line ADT	**86%**	14%	0%	Strong consensus
Presence of visceral metastases	10%	**90%**	0%	Strong consensus
Rapid PSA doubling time	15%	**80%**	5%	Strong consensus
Testosterone level	0%	**100%**	0%	Strong consensus
Anaemia	0%	**95%**	5%	Strong consensus
High LDH	10%	**90%**	0%	Strong consensus
Alkaline phosphatase	0%	**100%**	0%	Strong consensus
Degree of bone pain	5%	**95%**	0%	Strong consensus
Decreased performance status	5%	**95%**	0%	Strong consensus
Preferred first-line therapy for a patient with an increased risk for primary resistance to AR-targeted therapy				
Taxane	**70%**	15%	15%	Consensus
AR-targeted therapy prior to chemotherapy	10%	**81%**	10%	Consensus
Bone-targeted Therapy				
Should every patient with mCRPC and bone metastases (and no contraindications) receive bone-modifying agents?	24%	**76%**	0%	Consensus
When might radium-223 be used for mCRPC with symptomatic bone metastases?				
Postdocetaxel as monotherapy	**75%**	20%	5%	Consensus
Predocetaxel as monotherapy	**80%**	20%	5%	Strong consensus
Concomitantly with other pre- or post-docetaxel therapies	33%	48%	19%	No consensus
Is there a role for radium-223 in asymptomatic mCRPC?	52%	33%	14%	No consensus
Assuming EMA approval of radium-223, is there a role for continued use of beta-emitting radiopharmaceuticals?	48%	38%	14%	No consensus
Cross-resistance Between AR Pathway Inhibitors				
Is there cross-resistance between approved AR-targeted agents?	**90%**	5%	5%	Strong consensus
For a patient with disease progression on abiraterone, when could enzalutamide be considered?				
If any clinical and/or biochemical response to abiraterone has occurred	29%	67%	5%	No consensus
Only if a 'durable' response to abiraterone has occurred	24%	**76%**	0%	Consensus
Independent of response to abiraterone	40%	60%	0%	No consensus
Should not be considered due to cross-resistance	10%	**85%**	5%	Strong consensus
For a patient with disease progression on enzalutamide, when could abiraterone be considered?				
If any clinical and/or biochemical response to enzalutamide has occurred	24%	**76%**	0%	Consensus
Only if a 'durable' response to enzalutamide has occurred	24%	**76%**	0%	Consensus
Independent of response to enzalutamide	48%	52%	0%	No consensus
Should not be considered due to cross-resistance	10%	**86%**	5%	Strong consensus

(*continued on next page*)

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

Table 1 (*continued*)

	Yes	No	Abstain	Consensus level
Immunotherapy				
Is sipuleucel-T a reasonable option for asymptomatic or minimally symptomatic mCRPC?	**71%**	29%	0%	Consensus
How should sipuleucel-T be positioned relative to other approved therapies?				
Before docetaxel	**81%**	5%	14%	Consensus
After docetaxel	10%	65%	25%	No consensus
Before abiraterone and/or enzalutamide	**70%**	10%	20%	Consensus
After abiraterone and/or enzalutamide, regardless of whether docetaxel is given	10%	67%	24%	No consensus
Managing Disease Progression and Sequencing Therapy				
mCRPC disease progression can be defined as				
Confirmed PSA progression	**80%**	20%	0%	Strong consensus
Radiologic progression	**90%**	10%	0%	Strong consensus
Clinical progression	**71%**	29%	0%	Consensus
Pain progression only	10%	**90%**	0%	Strong consensus
Decreased quality of life	15%	**85%**	0%	Strong consensus
Which of the following warrants a switch in therapy?				
Confirmed PSA progression	14%	**81%**	5%	Strong consensus
Radiologic progression	**81%**	14%	5%	Strong consensus
Clinical progression	**75%**	20%	5%	Consensus
Does the sequence of taxane versus AR pathway-targeted therapy first change the efficacy of subsequent therapy?	62%	10%	29%	No consensus
Which of the following should be used following disease progression during docetaxel therapy?				
AR pathway-targeted agent only	0%	**100%**	0%	Strong consensus
Cabazitaxel only	10%	**90%**	0%	Strong consensus
Both an AR pathway-targeted agent and cabazitaxel are reasonable	**86%**	10%	5%	Strong consensus
Some other approach	5%	35%	60%	No consensus
Is there a clinically relevant difference between primary and acquired resistance to docetaxel?	**76%**	19%	5%	Consensus
For a patient with a partial response to docetaxel and disease progression $\leqslant$6 months following docetaxel discontinuation, the next line of therapy should be				
An AR pathway-targeted agent	**95%**	5%	0%	Strong consensus
Rechallenge with docetaxel	33%	62%	5%	No consensus
Cabazitaxel	**100%**	0%	0%	Strong consensus
All three options are reasonable	52%	48%	0%	No consensus
Some other approach	**75%**	20%	5%	Consensus
For a patient with a partial response to docetaxel and disease progression >6 months following docetaxel discontinuation, the next line of therapy should be				
An AR pathway-targeted agent	**100%**	0%	0%	Strong consensus
Rechallenge with docetaxel	**76%**	24%	0%	Consensus
Cabazitaxel	**100%**	0%	0%	Strong consensus
All three options are reasonable	**90%**	10%	0%	Strong consensus
Some other approach	**86%**	10%	5%	Strong consensus
When prescribing an AR pathway-targeted agent, which one would you use first?				
Abiraterone first	10%	**85%**	5%	Strong consensus
Enzalutamide first	29%	65%	6%	No consensus
It does not matter	**71%**	19%	10%	Consensus

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

Table 1 (*continued*)

	Yes	No	Abstain	Consensus level
Should ongoing LHRH agonist or antagonist therapy be continued when a patient is starting on abiraterone or enzalutamide?	**95%**	0%	5%	Strong consensus
In a patient receiving LHRH agonist or antagonist at the time of disease progression on either abiraterone or enzalutamide, should abiraterone or enzalutamide be discontinued?	**85%**	0%	15%	Strong consensus
Do you agree that initial PSA rise during docetaxel or cabazitaxel therapy should be ignored?	**95%**	5%	0%	Strong consensus
Is the occurrence of PSA flare during taxane therapy associated with a similar response compared to primary responders?	71%	0%	29%	No consensus
Is the occurrence of bone flare associated with an inferior response to therapy compared to a primary responder without a flare?	0%	76%	24%	No consensus

Abbreviations: ADT, androgen deprivation therapy; AR, androgen receptor; CRPC, castration-resistant prostate cancer; CTC, circulating tumour cell; EMA, European Medicines Agency; LDH, lactate dehydrogenase; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic CRPC; MRI, magnetic resonance imaging; OS, overall survival; PET/CT, positron emission tomography/computed tomography; PSA, prostate specific antigen.

decisions. At this point in time, however, it is not standard of care since this will require predictive biomarkers to allow individualised treatment selection [15].

Resistance to treatment is unfortunately common in mCRPC. The panel consensus was that primary resistance to AR pathway-targeted agents can be defined as radiologic progression within 3 months following therapy initiation. Panel members agreed that primary resistance cannot be sufficiently defined by a lack of PSA decrease or PSA progression within 3 months of therapy initiation. While short response to initial hormonal therapy seems to be associated with poor response to subsequent hormonal therapies, this is not always an indicator of absolute androgen independence and does not exclude potential benefit from novel AR-targeting strategies, such as abiraterone or enzalutamide.

The panel agreed that short duration of response (<1 year) to first-line androgen deprivation therapy (ADT) could potentially be used to identify patients with an increased risk for primary resistance to AR pathway-targeted agents [22]. The panel felt there is not sufficient evidence to use high Gleason score, the presence of visceral metastases, rapid PSA doubling time, testosterone level, anaemia, high lactate dehydrogenase, alkaline phosphatase, degree of bone pain and decreased PS as indicators of resistance. While all of these factors may influence resistance, none alone would be sufficient to select first-line chemotherapy over AR-targeted therapy. Data from the post-docetaxel era are currently limited regarding the benefit of abiraterone or enzalutamide in patients with a high risk for primary resistance. Thus, clinicians should consider all patient and disease characteristics when choosing between chemotherapy and AR-targeted therapies. Given these caveats, the panel agreed that the preferred first-line therapy for patients with mCRPC and a *well-defined* risk of primary resistance to AR-targeted therapies would be a taxane rather than an AR-targeted agent.

3.4. Bone-targeted therapies

Denosumab and zoledronic acid are commonly used to delay and prevent SREs in patients with CRPC and bone metastases. Despite the significant published data supporting the value of these agents, the panel felt that the use of bone-targeted therapy should remain an individualised treatment decision based on evaluation of the benefit/risk ratio [11,12,23]. When asked if *every* patient with mCRPC and bone metastases should be treated with a bone-modifying agent, the panel consensus was 'no'.

There is renewed interest in bone-targeted radiopharmaceuticals for mCRPC based on recent data demonstrating an OS advantage for the alpha-emitting agent Ra223 over placebo in patients with mCRPC and bone metastases [13]. Consistent with the patient population from this trial, the panel agreed that Ra223 can be considered as pre-docetaxel or post-docetaxel therapy in patients with mCRPC and symptomatic bone metastases. The panel did not feel there was sufficient data to support its use in patients with asymptomatic bone metastases. Given the excellent safety profile of Ra223, there is interest in combination regimens with therapies such as abiraterone and enzalutamide. However, further studies are needed before these combinations can be routinely recommended in clinical practice.

3.5. Cross-resistance between AR pathway inhibitors

Regulatory approval of both abiraterone and enzalutamide raises questions regarding potential cross-resistance and optimal sequencing of AR-targeted therapy [24]. The panel strongly agreed that at least partial cross-resistance does exist between approved AR-targeted agents. Small retrospective studies evaluating patients with progressive CRPC following docetaxel and enzalutamide demonstrated that subsequent abiraterone produced few responses of brief duration [25,26]. Similarly, two retrospective analyses of patients

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

who received enzalutamide for CRPC progressing after docetaxel and abiraterone showed a modest response rate and evidence of cross-resistance [27,28].

However, cross-resistance was not inevitable and responses to secondary AR-targeted therapy were observed [25–28]. Abiraterone and enzalutamide inhibit persistent AR signalling through different mechanisms, suggesting that patients with resistance to one agent may still benefit from the other agent. Based on insufficient data to exclude the possibility of crossover responses, the panel agreed that abiraterone or enzalutamide could be considered for patients who experienced disease progression while receiving the other AR-targeted agent. However, no consensus was reached regarding precisely which patients should receive a second AR-targeted therapy following progression. Until conclusive data are available, clinicians need to carefully consider both patient and disease characteristics when sequencing these therapies.

3.6. Immunotherapy

Based on current phase III data demonstrating good tolerability and an OS benefit for sipuleucel-T [9], the panel agreed it is a reasonable option for patients with asymptomatic or minimally symptomatic mCRPC. Importantly, they felt that sipuleucel-T should be considered prior to docetaxel, abiraterone and enzalutamide, not following these agents. This is in agreement with the recent EU regulatory approval, which specified eligibility only in patients for whom chemotherapy was not yet clinically indicated [29]. Sipuleucel-T provides a new treatment option during the time period between development of castration-resistant disease and becoming a candidate for chemotherapy. Further studies will be necessary to determine the efficacy, safety and cost-effectiveness of sipuleucel-T in patients who have already received abiraterone and/or enzalutamide.

3.7. Managing disease progression and sequencing therapy

Clear guidelines regarding when to switch therapy and how to sequence therapy for mCRPC are currently lacking. It is important to avoid premature treatment discontinuation and allow adequate time for systemic therapies to be effective [30]. The panel agreed that radiologic progression and clinical progression would warrant a switch in therapy. Importantly, 81% agreed that it was inappropriate to switch therapy based solely on confirmed PSA progression. Careful assessment of all response parameters must be weighed against the specific agent's mode of action in order to determine whether treatment should be continued or switched [30].

Sequencing therapy is complicated by the potential for cross-resistance between AR pathway-targeted agents and taxanes [24]. Preclinical studies suggest that the mechanisms of action for AR-targeted agents and taxanes overlap regarding interference with AR nuclear translocation, raising concerns that the action of one of these agents on AR signalling as first-line therapy may impair the ability of a second-line agent to subsequently inhibit this pathway [31,32]. This is supported by a retrospective analysis of 35 patients with abiraterone-pretreated CRPC who subsequently received docetaxel at progression [33]. Only four patients achieved a partial radiologic response and the median OS was 12.5 months, compared to a median OS of 18.9 months for docetaxel administered in a different setting but using the same schedule in patients without prior abiraterone in the phase III TAX327 trial [2,33]. In a similar retrospective study of cabazitaxel in patients with progressive mCRPC following abiraterone and docetaxel, 56% of patients had a PSA decline of $\geqslant$50% and 15% had a partial response (PR) [34].

While this suggests prior AR pathway-targeted therapy could compromise the efficacy of subsequent taxane therapy, it is unclear whether the reverse is true. Overall survival data from the phase III COU-AA-301 and AFFIRM trials demonstrated sensitivity to abiraterone and enzalutamide in docetaxel-pretreated mCRPC [6,8]. However, retrospective studies have shown poor response to abiraterone and enzalutamide in patients with disease progression following docetaxel therapy [22–25,35]. Given the lack of prospective data, the panel failed to reach a consensus regarding whether the sequence in which agents are administered changes the efficacy of subsequent taxane or AR pathway-targeted therapy, although a majority did feel that drug sequence may affect response to subsequent therapies.

The panelists also agreed that there is a clinically relevant difference between primary and acquired resistance to docetaxel. The panel reached a strong consensus that both AR pathway-targeted agents and cabazitaxel are reasonable second-line options for patients experiencing disease progression during docetaxel therapy and for those with a PR to docetaxel who progress $\leqslant$6 months after discontinuing therapy. There was no consensus on the role for docetaxel rechallenge in patients who progressed within 6 months following completion of initial docetaxel. Conversely, for patients with disease progression >6 months following a PR to docetaxel, 90% of the panel felt that all three options (AR pathway-targeted agents, cabazitaxel and docetaxel rechallenge) were reasonable. Panel commentary emphasised that while approximately 50% of patients will respond to docetaxel rechallenge, there are currently no data to support an OS benefit [36,37]. This should be taken into consideration given the OS advantage associated with abiraterone, enzalutamide and cabazitaxel in patients with docetaxel-pretreated mCRPC [6,8,10]. The panel also agreed that regardless

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

of the duration of response to docetaxel, other approaches such as Ra223 or enrolment on a clinical trial could be considered following docetaxel.

When considering an AR pathway-targeted agent for a patient with disease progression following docetaxel, the panel agreed that either abiraterone or enzalutamide could be given first as they have not been compared head-to-head in a clinical trial. There was also a strong consensus that patients with mCRPC receiving either a luteinising hormone-releasing hormone (LHRH) agonist or antagonist should continue on these agents, or have orchidectomy, when initiating abiraterone or enzalutamide. This is consistent with the current EAU and European Society for Medical Oncology (ESMO) treatment guidelines [38–40]. Interestingly, 85% of the panel agreed that patients receiving LHRH agonists or antagonists with either abiraterone or enzalutamide should discontinue abiraterone or enzalutamide at the time of disease progression. It was felt that current clinical data are not sufficient to support continuation of these AR pathway-targeted therapies beyond disease progression, although ongoing clinical trials will address this issue.

Patients receiving taxanes can exhibit an immediate, transient rise in PSA levels at therapy initiation [41,42]. This flare phenomenon precedes actual response to treatment and can be misinterpreted as therapeutic failure, leading to premature discontinuation of potentially effective agents. While treatment discontinuation should be considered for patients with clear signs of rapid disease progression, 95% of the panel agreed that initial PSA rise during the first 12 weeks of taxane therapy should be ignored. Current data also suggest that PSA flare has no impact on disease outcome and survival for patients receiving docetaxel or cabazitaxel [41]. While the majority of panelists (71%) agreed that a PSA flare during taxane therapy is associated with similar response compared to patients who respond with no PSA flare, 29% abstained, preventing a consensus.

4. Conclusions

This consensus statement provides valuable guidance for clinicians regarding the optimal management of mCRPC given the current lack of definitive data and seeks to move the field forward towards more personalised patient care. The treatment of mCRPC is not only complicated by the sheer number of available therapies, but the prevalence of resistance to these agents and the lack of validated predictive markers. The panel identified considerations for diagnosing and monitoring metastatic disease, risk factors for drug resistance, indicators that warrant a switch in therapy and strategies for treatment selection and sequencing to maximise the potential for response. Importantly, there was a clear consensus that novel bone-targeted agents, immunotherapy, chemotherapy and AR pathway-targeted agents all play an important role across the mCRPC disease continuum. The difficulty lies in selecting the right therapy, at the right time and for the right patient. While this consensus statement provides guidance for making these difficult treatment decisions, evaluation of all the factors that contribute to treatment selection is critical in providing truly personalised care.

Conflict of interest statement

John M. Fitzpatrick has received consulting fees from Astellas, GlaxoSmithKline, Janssen, Millennium, Sanofi and Takeda. Joaquim Bellmunt has received consulting fees from Astellas, Janssen and Sanofi. Karim Fizazi has received consulting fees from Astellas, Bayer, Dendreon, Janssen and Sanofi. Axel Heidenreich has received consulting fees from Amgen, Astellas, Ferring, Ipsen, Sanofi and Takeda. He has performed contracted research for Astellas and Sanofi. Additionally, he has received fees for non-CME services (e.g. speakers' bureaus) from Amgen, Astellas, Bayer, Ferring, Ipsen, Sanofi and Takeda. Cora N. Sternberg has received consulting fees from Astellas, Bayer and Janssen. Bertrand Tombal has received consulting fees and fees for non-CME services (e.g. speakers' bureaus) from and performed contracted research for Amgen, Astellas, Bayer, Dendreon, Ferring, Medivation and Sanofi. Antonio Alcaraz has received consulting fees from GlaxoSmithKline and Janssen. Amit Bahl has received consulting fees from Amgen, Astellas, Janssen, Roche and Sanofi. Sergio Bracarda has received consulting fees from Bayer and Janssen. Giuseppe Di Lorenzo has no relevant relationships to report. Eleni Efstathiou has received consulting fees from Janssen and Sanofi. She has performed contracted research for Janssen, Millennium and Sanofi. Additionally, she has received fees for non-CME services (e.g. speakers' bureaus) from Astellas and Janssen. Stephen P. Finn has no relevant relationships to report. Sophie Fosså has no relevant relationships to report. Silke Gillessen has been a member of advisory boards for Astellas, Bayer, CellSearch, Curevac, Janssen Cilag, Millennium, Novartis, Pfizer, ProteomediX and Sanofi Aventis. Pirkko-Liisa Kellokumpu-Lehtinen has received consulting fees from Pfizer and Roche. She has performed contracted research for Pfizer, Roche and Sanofi. Frédéric E. Lecouvet has no relevant relationships to report. Stephane Oudard has received consulting fees from Astellas, Bayer, Janssen, Sanofi and Takeda. Theo M. de Reijke has received consulting fees from Amgen, Bayer, Ferring and Teva. Craig N. Robson has no relevant relationships to report. Maria De Santis has received consulting fees from Amgen, Astellas, Bayer, Dendreon, Genex, GlaxoSmithKline, Ipse, Janssen, Novartis, Pfizer, Sanofi. She has also performed contracted research for Pierre Fabre, Pfizer, Shionogi and Roche. Bostjan Seruga has received

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010

consulting fees from Janssen and Sanofi Aventis. Ronald de Wit has received consulting fees from and performed contracted research for Sanofi.

Acknowledgements

The authors would like to thank Julian Lee Lokey, MD, and Sanneke Koekkoek, BSN, for assistance with data collection; Tristin Abair, PhD, and Julian Lee Lokey, MD, for their assistance in drafting this manuscript; and Trudy Grenon Stoddert, ELS, for editorial assistance and assistance preparing the manuscript for submission. All were compensated by prIME Oncology. Financial support was provided by an educational grant from Sanofi Oncology.

Appendix A. European Consensus Panel Members

A.1. Panel chair

John M. Fitzpatrick, MD, Irish Cancer Society and University College, Dublin, Ireland.

A.2. Scientific committee

Joaquim Bellmunt, MD, PhD, University Hospital del Mar, Barcelona, Spain.
Karim Fizazi, MD, PhD, Institut Gustave Roussy, Villejuif, France.
Axel Heidenreich, MD, University Hospital Aachen, Aachen, Germany.
Cora N. Sternberg, MD, FACP, San Camillo and Forlanini Hospital, Rome, Italy.
Bertrand Tombal, MD, PhD, Centre du Cancer et Institut de Recherche Expérimental et Clinique (IREC); Cliniques Universitaires Saint Luc, Brussels, Belgium.

A.3. Panel members

Antonio Alcaraz, MD, PhD, Hospital Clinic de Barcelona, Barcelona, Spain.
Amit Bahl, MD, University Hospitals Bristol, Bristol, United Kingdom.
Sergio Bracarda, MD, Ospedale San Donato, Istituto Toscano Tumori (ITT), Arezzo, Italy.
Eleni Efstathiou, MD, PhD, University of Texas, M.D. Anderson Cancer Center, Houston, Texas, United States.
Stephen P. Finn, MB, PhD, St. James's Hospital and Trinity College, Dublin, Ireland.
Sophie Fosså, MD, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway.
Silke Gillessen, MD, Kantonsspital St. Gallen, St. Gallen, Switzerland.
Giuseppe Di Lorenzo, MD, PhD, University Federico II, Napoli, Italy.
Pirkko-Liisa Kellokumpu-Lehtinen, MD, PhD, Tampere University Hospital, Tampere, Finland.
Frédéric E. Lecouvet, MD, PhD, Centre du Cancer et Institut de Recherche Expérimental et Clinique (IREC); Cliniques Universitaires Saint Luc, Brussels, Belgium.
Stephane Oudard, MD, PhD, Georges Pompidou European Hospital, Paris, France.
Theo M. de Reijke, MD, PhD, Department of Urology, Academic Medical Center, Amsterdam, the Netherlands.
Craig N. Robson, PhD, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, United Kingdom.
Maria De Santis, MD, Ludwig Boltzmann Institute for Applied Cancer Research, Kaiser Franz Josef-Spital, Vienna, Austria.
Bostjan Seruga, MD, PhD, Department of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia.
Ronald de Wit, MD, PhD, Erasmus University Medical Center, Rotterdam, the Netherlands.

References

[1] Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2013. Ann Oncol 2013;24:792–800.
[2] Tannock IF, de Wit R, Berry WR, et alTAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[3] Italiano A, Ortholan C, Oudard S, et al. Docetaxel-based chemotherapy in elderly patients (age 75 and older) with castration-resistant prostate cancer. Eur Urol 2009;55:1368–75.
[4] Lissbrant IF, Garmo H, Widmark A, Stattin P. Population-based study on use of chemotherapy in men with castration resistant prostate cancer. Acta Oncol 2013;52:1593–601.
[5] de Bono JS, Logothetis CJ, Molina A, et alCOU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[6] Fizazi K, Scher HI, Molina A, et alCOU-AA-301 Investigators. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.
[7] Ryan CJ, Smith MR, de Bono JS, et alCOU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
[8] Scher HI, Fizazi K, Saad F, et alAFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[9] Kantoff PW, Higano CS, Shore ND, et alIMPAKT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.
[10] de Bono JS, Oudard S, Ozguroglu M, et alTROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic

castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[11] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813–22.
[12] Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2012;379:39–46.
[13] Parker C, Nilsson S, Heinrich D, et alALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.
[14] Goldhirsch A, Winer EP, Coates AS, et alInternational Breast Cancer Study Group Panel Members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013;24:2206–23.
[15] Armstrong AJ, Eisenberger MA, Halabi S, et al. Biomarkers in the management and treatment of men with metastatic castration-resistant prostate cancer. Eur Urol 2012;61:549–59.
[16] de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clin Cancer Res 2008;14:6302–9.
[17] Scher HI, Heller G, Molina A, et al. Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus low-dose prednisone (P) post docetaxel. J Clin Oncol 2011;29(Suppl.) [abstract LBA4517].
[18] Egan K, Crowley D, Smyth P, et al. Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signalling in ovarian cancer cells. PLoS One 2011;6:e26125.
[19] Sartor O, Eisenberger M, Kattan MW, Tombal B, Lecouvet F. Unmet needs in the prediction and detection of metastases in prostate cancer. Oncologist 2013;18:549–57.
[20] Lecouvet FE, Geukens D, Stainier A, et al. Magnetic resonance imaging of the axial skeleton for detecting bone metastases in patients with high-risk prostate cancer: diagnostic and cost-effectiveness and comparison with current detection strategies. J Clin Oncol 2007;25:3281–7.
[21] Tombal B, Rezazadeh A, Therasse P, et al. Magnetic resonance imaging of the axial skeleton enables objective measurement of tumor response on prostate cancer bone metastases. Prostate 2005;65:178–87.
[22] Loriot Y, Massard C, Albiges L, et al. Personalizing treatment in patients with castrate-resistant prostate cancer: a study of predictive factors for secondary endocrine therapies activity. J Clin Oncol 2012;30(Suppl. 5) [abstract 213].
[23] Saad F, Gleason DM, Murray R, et alZoledronic Acid Prostate Cancer Study Group. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004;96:879–82.
[24] Loriot Y, Fizazi K. Towards random sequencing or precision medicine in castration-resistant prostate cancer? Eur Urol 2013 [epub ahead of print].
[25] Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013;24:1802–7.
[26] Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013;24:1807–12.
[27] Schrader AJ, Boegemann M, Ohlmann CH, et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. Eur Urol 2013 [epub ahead of print].
[28] Bianchini D, Lorente D, Rodriguez-Vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer 2013 [epub ahead of print].
[29] Press release. *Dendreon announces marketing authorization for PROVENGE® in the European Union*. Available at: <http://files.shareholder.com/downloads/DNDN/2679987622x0x691078/965100e2-bcfd-4fb0-a8cb-1189bfa53b43/DNDN_News_2013_9_17_General.pdf> [accessed October 2, 2013].
[30] Merseburger AS, Bellmunt J, Jenkins C, Parker C, Fitzpatrick JM, European Treatment Practices Group. Perspectives on treatment of metastatic castration-resistant prostate cancer. Oncologist 2013;18:558–67.
[31] Van Soest RJ, van Royen ME, de Morrée ES, et al. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer. Eur J Cancer 2013;49:3821–30.
[32] Fitzpatrick JM, de Wit R. Taxane mechanisms of action: potential implications for treatment sequencing in metastatic castration-resistant prostate cancer. Eur Urol 2013 [epub ahead of print].
[33] Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Ann Oncol 2012;23:2943–7.
[34] Albiges L, Le Moulec S, Loriot Y, et al. Response to cabazitaxel in the postchemotherapy setting in CRPC patients previously treated with docetaxel and abiraterone acetate. Ann Oncol 2012;23(Suppl. 9) [abstract 3061].
[35] Mukherji D, Pezaro CJ, Bianchini D, Zivi A, De Bono JS. Response to abiraterone acetate in the postchemotherapy setting in patients with castration-resistant prostate cancer whose disease progresses early on docetaxel. J Clin Oncol 2012;30(Suppl. 5) [abstract 17].
[36] Oudard S, Kramer G, Creppy L, et al. Management of metastatic castration-resistant prostate cancer (mCRPC) after an initial good response to first-line docetaxel (D): a retrospective study on 270 patients (pts). Eur J Cancer 2011;47(Suppl. 1) [abstract 7049].
[37] Pfister DJ, Porres D, Piper C, Merseburger AS, Klotz T, Heidenreich A. Comparison of second-line treatments in patients with castration-resistant prostate cancer with PSA relapse after or during docetaxel chemotherapy. J Clin Oncol 2012;30(Suppl. 5) [abstract 243].
[38] Heidenreich A, Bastian PJ, Bellmunt J, et al. European Association of Urology: guidelines on prostate cancer 2013. Available at: <http://www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf> [accessed: October 2, 2013].
[39] Horwich A, Hugosson J, de Reijke T, Wiegel T, Fizazi K, Kataja V, Panel Members. Prostate cancer: ESMO Consensus Conference Guidelines 2012. Ann Oncol 2013;24:1141–62.
[40] Sternberg CN, Baskin-Bey ES, Watson M, Worsfold A, Rider A, Tombal B. Treatment patterns and characteristics of European patients with castration-resistant prostate cancer. BMC Urol 2013;13:58 [epub ahead of print].
[41] Thuret R, Massard C, Gross-Goupil M, et al. The postchemotherapy PSA surge syndrome. Ann Oncol 2008;19:1308–11.
[42] Angelergues A, Mercier F, Flechon A, et al. Retrospective registry evaluating the PSA flare phenomenon with cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2013;31(Suppl. 6) [abstract 122].

Please cite this article in press as: Fitzpatrick J.M. et al., Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel, *Eur J Cancer* (2014), http://dx.doi.org/10.1016/j.ejca.2014.03.010