World J Urol
DOI 10.1007/s00345-016-1803-9

INVITED REVIEW

Non-metastatic castrate-resistant prostate cancer: a call for improved guidance on clinical management

Francois Rozet[1] · Thierry Roumeguère[2] · Martin Spahn[3] · Dirk Beyersdorff[4] · Peter Hammerer[5]

Received: 16 October 2015 / Accepted: 5 March 2016

Abstract
Background Guidelines on the clinical management of non-metastatic castrate-resistant prostate cancer (nmCRPC) generally focus on the need to continue androgen deprivation therapy and enrol patients into clinical trials of investigational agents. This guidance reflects the lack of clinical trial data with established agents in the nmCRPC patient population and the need for trials of new agents.
Aim To review the evidence base and consider ways of improving the management of nmCRPC.
Conclusion Upon the development of castrate resistance, it is essential to rule out the presence of metastases or micrometastases by optimising the use of bone scans and possibly newer procedures and techniques. When nmCRPC is established, management decisions should be individualised according to risk, but risk stratification in this diverse population is poorly defined. Currently, prostate-specific antigen (PSA) levels and PSA doubling time remain the best method of assessing the risk of progression and response to treatment in nmCRPC. However, optimising imaging protocols can also help assess the changing metastatic burden in patients with CRPC. Clinical trials of novel agents in nmCRPC are limited and have problems with enrolment, and therefore, improved risk stratification and imaging may be crucial to the improved management. The statements presented in this paper, reflecting the views of the authors, provide a discussion of the most recent evidence in nmCRPC and provide some advice on how to ensure these patients receive the best management available. However, there is an urgent need for more data on the management of nmCRPC.

Keywords Non-metastatic castrate-resistant prostate cancer · Individualised management · Imaging · Management

✉ Francois Rozet
francois.rozet@imm.fr; rozetfrancois@gmail.com

Thierry Roumeguère
Thierry.Roumeguere@erasme.ulb.ac.be

Martin Spahn
Martin.Spahn@insel.ch

Dirk Beyersdorff
d.beyersdorff@uke.de

Peter Hammerer
hammerer11@mac.com

[1] Department of Urology, L'Institut Mutualiste Montsouris, 42 Boulevard Jourdan, 75014 Paris, France

[2] Department of Urology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

[3] Department of Urology, Bern University Hospital, Bern, Switzerland

[4] Clinic for Diagnostic and Interventional Radiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

[5] Department of Urology, Academic Hospital Braunschweig, Braunschweig, Germany

Introduction

In prostate cancer, changes in prostate-specific antigen (PSA) concentrations are still the most widely used and recommended method of monitoring disease progression and predicting outcomes [1, 2]. In many men with prostate cancer who are treated with curative intent (i.e. with radical prostatectomy or radiation therapy), PSA recurrence can develop. Although these men who have PSA recurrence are a heterogeneous group with a median metastasis-free

Published online: 17 March 2016

survival (MFS) >8 years and a median overall survival (OS) of >23 years [3–5], many patients and clinicians are reluctant to leave such PSA recurrence untreated. Disease staging is not always reliable for the detection of metastatic lesions, and therefore, many patients receive androgen deprivation therapy (ADT) when PSA levels increase but in the absence of metastasis. The evidence on immediate versus delayed initiation of ADT is inconclusive [6, 7], but as ADT is not curative, it is inevitable that a proportion of patients will develop non-metastatic castrate-resistant prostate cancer (nmCRPC).

There are challenges in the assessment, risk stratification and management of patients with nmCRPC [8], and improved predictive tools are needed to optimise individual treatment. In patients with nmCRPC, the endpoints differ from those of metastatic CRPC (mCRPC); namely, in nmCRPC the main aims are to delay the initiation of chemotherapy and delay the progression to metastasis (bone is the first site of metastasis in most patients) [9]. In nmCRPC, PSA kinetics remains the most important predictor of these endpoints [9]. Guidelines for mCRPC management (such as those from the National Comprehensive Cancer Network [NCCN] [10]) are clear and detailed. However, the equivalent guidance for nmCRPC management states that ADT should be maintained, and lists the enrolment into a clinical trial as the preferred option [10]. Recent recommendations from a consensus conference (held after our meeting) also highlight the lack of information on management options in nmCRPC, and some panellists did not recommend any intervention in this group [8]. The potential impact of continued ADT on the subsequent effectiveness of drugs targeting the androgen pathway (such as abiraterone and enzalutamide) when metastases do develop is not known. Furthermore, since most clinical trials recruiting patients with nmCRPC have produced negative outcomes, this recommendation is not ideal. Other alternative treatment options, such as anti-androgen addition or withdrawal, are also listed in these guidelines.

There are also challenges in the management of nmCRPC in routine clinical practice. The definition of CRPC requires the maintenance of castrate levels of testosterone <50 ng/dl, and it may be that many patients are classified as having CRPC based on rising PSA levels alone, without testosterone levels being measured [11, 12]. In addition, many patients classified as having nmCRPC may, on closer investigation, have mCRPC; or even when metastases are not detected, patients may have micrometastases below the level of detection.

Therefore, to consider ways of improving the management of nmCRPC, a group of experts (the authors of this paper) met at the end of 2014 [the meeting was financially supported by Ipsen (Paris, France)]. The aims of the meeting were to consider how nmCRPC can be more clearly identified and defined, and to propose the most appropriate medical management of nmCRPC based on published evidence and personal clinical experience.

Data analysis

Before the meeting, participants conducted PUBMED searches on specific topics. Each participant presented their findings on these topics during the meeting for discussion by the group, and all specialists then developed the recommendations and contents of this paper based on these discussions. As such, the contents of this paper represent the conclusions of the authors only. References in the text have been assessed according to their level of scientific evidence (Table 1), and recommendations have been graded according to the Oxford Centre for Evidence-based Medicine Levels of Evidence as used in the European Association of Urology (EAU) guidelines (Table 1) [13, 14].

Epidemiology of nmCRPC

Epidemiological data on nmCRPC are lacking. The exact proportion of nmCRPC versus mCRPC is not known because most cases of CRPC are declared on the basis of an isolated PSA increase [1], and therefore, metastasis may be present but not immediately detected in some cases. The discrimination between nmCRPC and mCRPC depends strongly on the sensitivity of the diagnostic tools used.

Table 1 Level of evidence and grades of recommendations

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities
Grade	**Nature of recommendations**
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

A systematic review of CRPC cases showed that in two studies (involving 351 patients) using bone scans to detect metastasis, ≥84 % of patients had metastasis at diagnosis. The same review concluded that the 2-year risk of bone metastases in the nmCRPC population was 33 % (based upon a single study only) [15]. However, this nmCRPC population is heterogeneous and time to bone metastasis varies greatly among patients—indeed, studies assessing MFS after radical prostatectomy suggest slower disease progression after PSA recurrence [3–5] and patient selection will alter these estimates of progression considerably.

The natural course of nmCRPC (level 1b)

Analysis of control/placebo arms in clinical trials provides some information on the natural history of the nmCRPC population. The study by Smith et al. [16] (which assessed zoledronic acid versus placebo in patients with nmCRPC) possibly gives the most useful insight—median MFS was 30 months in the placebo arm with 33 % of patients with nmCRPC progressing to metastasis and 21 % to death at 2 years. In this analysis, a PSA level >10 ng/ml and a PSA doubling time (PSADT) <6–8 months were associated with poorer OS and MFS than a lower PSA and longer PSADT. In a study of atrasentan versus placebo in patients with nmCRPC, the median OS was 46 months in the placebo arm [17]. A PSA level ≥13.1 ng/ml was used in a multivariate analysis of these trial data, and PSA levels above this cut-off were associated with reduced OS and MFS in the placebo arm of the study [18]. In the other useful study, which assessed denosumab versus placebo, 48 % of nmCRPC patients in the placebo arm had metastases at 2 years [19]. There was a suggestion from this study that a PSADT of approximately <6 months was associated with a considerably increased risk of progression to bone metastasis [20]. But the impact of a short PSADT on OS is not clear. Furthermore, it is not clear how valid a single PSADT cut-off is in such a heterogeneous population.

Recent trials recruiting patients with nmCRPC have struggled with high levels of screening failures, and this has been a result of the detection of small metastases that were not detected on initial routine assessment (implicated in 71 % of screening failures) [21, 22]. This outlines the importance of thorough assessment with optimum imaging techniques of all patients with CRPC even when symptoms are mild or absent, which in turn will ensure patients receive the optimum treatment.

Predicting outcomes in nmCRPC (level 1b)

From the few clinical trials recruiting men with nmCRPC, poorer outcomes are predicted by a PSA level of ≥13.1 ng/ml and a PSADT <6 months [18, 19]. Such measurements are useful to reassure patients and may help inform the scheduling of imaging [8]. However, although PSA kinetics remain the best option for predicting and measuring outcome in CRPC [17–19], there is little precision on the predictive value of PSA levels, there is no consensus on the magnitude or duration of PSA decline that can be used to define response, and PSA kinetics have little value in guiding management decisions. In practice, patients' awareness of their PSA levels and pressure to act upon any changes in PSA level may influence management decisions when PSA levels rise, irrespective of radiographic or other findings [23].

This highlights the need to have more accurate assessment of nmCRPC severity and the risk of progression. With improved imaging, the ability to detect metastatic progression will improve, and following the recommendations of the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group for optimal imaging in nmCRPC appears logical [24]. However, imaging procedures and protocols can also be improved.

Improving diagnosis and assessment through imaging (level 3)

There are no specific guidelines on imaging requirements for nmCRPC patients. As such, clinical practice will vary at individual centres, and more defined imaging protocols are needed in prostate cancer [25]. In patients with CRPC, it is important to be able to detect the presence of metastasis early and have a reliable technique to monitor response to treatment of both the primary tumour and metastases.

Bone metastases

Conventional bone scintigraphy scans with ^{99m}TC bisphosphonate are widely used [26], but bone scans may not be as sensitive as magnetic resonance imaging (MRI) for detecting bone metastases [27]. However, the impact this improved detection may have on management is unclear—for example, detecting metastases 3 months earlier with MRI than with conventional bone scans may have minimal impact if the centre's practice is to assess patients with imaging modalities every 6 or 12 months (cost implications may also limit the usefulness of this technique and the frequency of assessment). Furthermore, for now, most centres and most clinical trial protocols use bone scans (combined with CT for detection of visceral metastasis).

Other experimental techniques such as ^{11}C-choline PET/CT or ^{68}Ga-labelled prostate-specific membrane antigen (PSMA) may detect metastatic lesions in bone that cannot be detected with conventional modalities [28, 29]. PSMA

PET/CT has shown some promise in advanced disease [30]. Eiber et al. [31], showed that in a group of 248 patients with biochemical recurrence after radical prostatectomy ^{68}Ga-PSMA PET/CT was able to detect areas suspicious for recurrent prostate cancer in 89.5 % of patients. The detection was dependent on the PSA level. In patients with PSA levels of ≥2 ng/ml, the detection rate was 96.8 %, whereas in patients with PSA levels of 0.2 to <0.5 ng/ml the detection rate was only 57.9 %. In 81 patients, PSMA/PET was able to find relevant additional findings compared to contrast enhanced CT alone. In this study, the detection rate of suspicious areas by ^{68}Ga-PSMA PET/CT had no correlation with previous anti-androgen therapy [31].

Other procedures that are largely experimental but may be useful include the calculation of the bone scan index (BSI) for quantitative analysis [32], guided biopsy using MR biopsy or fusion biopsy, and using iron superparamagnetic nanoparticles to aid lymph node staging [33]. However, evidence is needed to recommend these techniques more widely for monitoring bone metastases.

Visceral metastases

For detecting suspected distant metastases not involving bone, CT scans must be used (approximately 5–10 % of patients with prostate cancer develop distant visceral metastases). Upon development of castrate resistance, an initial CT scan is recommended to check for the absence of visceral metastasis. The regularity of CT scans should be assessed on a case-by-case basis and may be driven by PSA kinetics and indicative symptoms. The frequency may mirror the frequency of bone scans. As newer treatments lead to extended OS in patients with prostate cancer, the incidence of visceral metastases may increase. The early detection of visceral metastases is important to allow optimum intervention, but detection methods will need to be specific in order to avoid over-treatment, and there may therefore be an increasing need to define CT scan protocols in patients with advanced prostate cancer. Whole-body MRI with diffusion-weighted MRI may be a useful technique for screening of nodal disease and visceral metastases, but more evidence and greater access may be needed before this technique is more widely used.

Optimising imaging

New imaging techniques may help with some of the barriers in the management of nmCRPC, but they may also create new challenges. The poor evidence base means that any guidance on detecting bone metastases in patients with CRPC is largely based on clinical experience, and an individualised approach is recommended for all management decisions. Upon progress to CRPC, a bone scan with ^{99m}TC bisphosphonate should be performed, and then at regular intervals every 3–12 months, depending on PSA kinetics. The BSI may be a useful tool during follow-up to assess the impact of treatment on metastatic burden because it is simple and low cost. Although choline PET scans are increasingly used in place of bone scans to detect micrometastases, the resolution of this technique may in fact be insufficient (e.g. it may be unable to detect lesions <4 mm in diameter).

A whole-body MRI may become a useful option for assessing visceral metastases and bone metastases using a single technique [34, 35], but currently bone scans and CT scans together may remain the routine techniques. More sensitive techniques for detecting bone and/or visceral metastases, combined with the future introduction of newer agents for non-metastatic prostate cancer, would bring additional issues such as over-treatment. Therefore, when optimising imaging techniques, it will become increasingly important to interpret the findings to provide individualised imaging schedules and management strategies.

The recent consensus guidelines simply stated that newer imaging methods were not associated with patient benefit in nmCRPC [8]. However, while the impact newer techniques have on management of CRPC is unknown, they may have an impact on our understanding of the incidence and natural history of nmCRPC. We do not know if, for example, detecting metastasis 6 months earlier will benefit the patient—earlier introduction of modern drugs that are indicated for mCRPC may, or may not, have benefits in the longer term. Therefore, PSA kinetics will remain central to our assessment of risk of disease progression in patients with nmCRPC.

Management of nmCRPC (level 4)

The conflicting data on the impact of early initiation of ADT (on progression to metastasis, castrate resistance or death) in non-metastatic prostate cancer [6, 7] highlight both the need to identify patients at higher risk of progression who are most likely to benefit from treatment and the complexity of managing patients with non-metastatic prostate cancer. Firstly, a deferred ADT policy is not suitable for patients with rapidly progressing disease, but a definition of this at-risk group is not validated. The trials mentioned above rely on either retrospective classification (death within 3–5 years) or measurements taken over a prolonged period (PSADT ≤ 12 months), neither of which help in initial management decisions. Secondly, while early initiation of ADT could expose patients to possible and unnecessary side effects without altering the risk of death from prostate cancer, compared with deferred ADT, it also delays the time to progression and the potential associated symptoms.

Thirdly, the choice of initiating or delaying treatment has to be balanced with the anxiety felt by a patient when he is diagnosed with prostate cancer or when rising PSA levels are measured.

The key issue therefore is not whether ADT should be started early or as soon as PSA levels increase, but how to identify patients most at risk of progression who will benefit most from early ADT, and how to distinguish these from patients who do not need to be exposed to the potential side effects of early treatment.

As discussed above, this issue is hindered by the reliance on PSA measurements. In 'real life,' ADT is frequently started early and this seems to be driven partly by the evidence that some patients benefit from this, by the fact that it is a reversible treatment (as opposed to surgery), and as a result of patient anxiety over rising PSA levels [23]. In future, genetic characterisation of patients and prostate cancer may guide such decisions.

In nmCRPC, when patients have progressed while receiving ADT, the disease can have a relatively indolent natural history, and therefore, what is the evidence for benefits of continued ADT? Guidelines recommend continued ADT based upon clinical data and upon the fact that tumours remain sensitive to secondary hormonal manipulations [13, 36, 37]. However, there are limited data from prospective trials recruiting patients with nmCRPC and focussing on the important endpoint of time to progression or time to chemotherapy. Published studies in nmCRPC have recently been summarised [38]. Many trials have been of bone-targeted agents. For example, clodronate had no effect on MFS or OS, a trial of zoledronic acid was terminated before completion of patient accrual, atrasentan increased PSADT but did not delay time to disease progression, zibotentan did not improve OS or PFS, and denosumab increased MFS [38]. In the trial of denosumab, which showed an increased MFS of >6 months in the treatment arm, OS was not improved and troublesome adverse events such as osteonecrosis of the jaw were observed [20].

These data are not sufficiently robust to allow a recommendation for the use of bone-targeted agents in nmCRPC, and while radium-223 has been widely licensed for treatment of mCRPC, there is no evidence of its use in nmCRPC. Likewise, there is no evidence to support the use of other hormonal agents that have been licensed for use in metastatic prostate cancer in recent years (such as abiraterone and enzalutamide) in the nmCRPC setting. As data emerge, these agents may have a role in some patients with nmCRPC, but as discussed above, an individualised approach will be needed to target those who are most likely to benefit from such intervention.

Other trials with experimental agents for CRPC have generally failed to reach their predefined endpoints: somatostatin analogues in prostate cancer with neuroendocrine involvement have not been shown to be effective [39], and the epidermal growth factor receptor (EGFR) inhibitor erlotinib showed some moderate activity in CRPC that may warrant investigation as an agent in combination with conventional agents [40]. Recently, a phase II study of orteronel (TAK-700) reported reductions in PSA levels of 30 %, but this single-arm study did not report any survival data [41].

This lack of data means that patients with nmCRPC are often managed with conventional secondary hormonal manipulations including [8]:

- Maximal androgen blockade (MAB) by adding an anti-androgen to the existing ADT regimen, but this has only a limited impact on OS and increases side effects [42].
- Switching to a different GnRH analogue may increase the time to PSA progression, but the clinical importance of this is not known [43, 44].
- Anti-androgen withdrawal provides a modest PSA response, and a prolonged period of prior MAB is mandatory for any observable effect [45].
- Preliminary data with GnRH antagonists suggest they may delay the time to progression, but these data require confirmation [46–48].

Although more individualised treatment in nmCRPC is the goal, currently ADT remains a critical part of management of aggressive and advanced prostate cancer. In less aggressive disease, ADT may be over-used. The relative importance of ADT use in mCRPC versus nmCRPC is simply not known, and better assessment of patients may help individualise treatment in the future.

Emerging evidence from clinical trials in nmCRPC

New data have become available on the use of newer agents to treat chemotherapy-naïve metastatic CRPC. The COU-302 trial tested the use of abiraterone acetate plus prednisone versus placebo plus prednisone, in 1088 asymptomatic or mildly symptomatic patients. Abiraterone improved OS (HR 0.79; 95 % CI 0.66–0.95) [49]. Enzalutamide has also been compared to placebo in the PREVAIL trial and shown to improve OS (HR 0.71; 95 % CI 0.60–0.84) [50]. However these drugs should not be used in the setting of nmCRPC.

Ongoing trials recruiting nmCRPC patients include:

- The PROSPER trial of enzalutamide versus placebo started in December 2013 with an estimated enrolment of 1560 men. The primary endpoint is MFS, and ADT is maintained in both treatment arms. The study completion date is in 2017.

- The SPARTAN trial of the novel androgen receptor antagonist ARN-509 versus placebo will enrol 1200 men and also has MFS as the primary endpoint. The estimated primary completion date of this trial is December 2016 with full study completion in August 2019.
- And the ARAMIS trial of the androgen receptor inhibitor ODM-201 versus placebo, with a primary endpoint of MFS and an estimated completion date of December 2020.

Recruitment is slow in these trials. Many patients classified as having nmCRPC are found on closer investigation to have small metastases which exclude them from recruitment into these studies [21, 22]. In future, and if the sensitivity of imaging techniques for the detection of metastases improves, many more patients with micrometastases below the current levels of detection may be classified as having mCRPC, and recruiting patients for such trials may become even more problematic.

It may be difficult to demonstrate positive outcomes in ongoing trials in nmCRPC due to the relatively 'benign' nature of the disease. Even if MFS results are positive, the usual practice of switching patients in the placebo arm to abiraterone or enzalutamide upon progression will probably result in similar OS in both arms of such studies. Such data may not convince payers and insurance companies that novel treatments should be reimbursed for this indication.

The design of future trials of drugs for nmCRPC could potentially be standardised as shown in Fig. 1. An immediate versus delayed trial design as shown in Fig. 1 may be more useful for measuring clinical benefit and may allow the use of more established endpoints such as OS and time to symptomatic progression.

Conclusion and panel recommendations (level 4)

- A lack of data from well-designed studies means that all recommendations on the monitoring and management of nmCRPC are largely based on clinical practice experience.
- In nmCRPC, the key management issue is not whether ADT should be maintained, but how we identify patients most at risk of progression who will benefit most from additional treatments.
- Until techniques improve to allow better assessment of the risk of progression to metastasis in nmCRPC, we need to rely on careful observation of PSA kinetics (a PSADT of around <6 months could be an important sign that there is a high risk of progression and alter the schedule of imaging [8]) [recommendation grade B]. Likewise, lymph node metastasis at the time of nmCRPC and a PSA concentration >10 ng/ml may indicate higher risk of progression to bone or visceral metastasis [recommendation grade C].
- However, PSA kinetics are not ideal, and two patients with similar PSA kinetics do not necessarily have disease that progresses at the same rate. Until more sensitive biomarkers are found, improved assessment with imaging is needed to resolve this issue of risk assessment.
- The optimal use of imaging may include:
  - Bone scans with ^{99m}TC bisphosphonate performed upon PSA change and at regular intervals every 3–12 months, depending on PSA kinetics, remain the optimal method of detecting bone metastasis. Include BSI to quantify bone metastatic burden at baseline and follow-up [recommendation grade C].

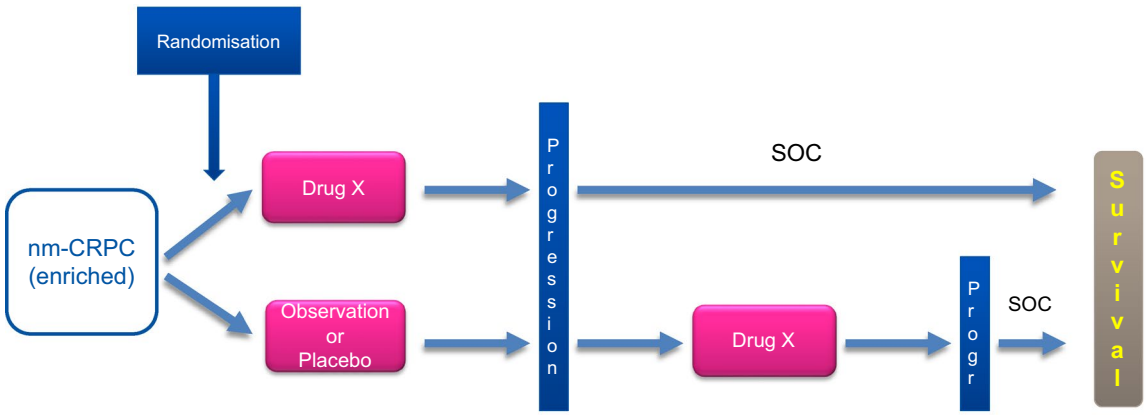

Fig. 1 Proposed trial design for novel agents in nmCRPC

  - And an initial CT scan of the whole abdomen is also recommended. CT scan should be repeated regularly in follow-up [recommendation grade C].
  - An initial mpMRI, and possibly whole-body MRI, when PSA rises are first observed, may gain prominence when these techniques are more routinely available [recommendation grade C].
  - Assessment of new imaging technology or protocols should be conducted within the framework of a clinical trial [recommendation grade C].
- Ongoing trials of, for example, enzalutamide, could provide positive MFS data. However, until further data are available to assess the efficacy of newer agents (such as enzalutamide and abiraterone) in nmCRPC, their use cannot be recommended except within the context of a clinical trial:
  - Clinical trials recruiting enriched populations of nmCRPC patients and using a standardised design (Fig. 1) with survival as the primary endpoint instead of MFS (which is not a good surrogate marker of survival) will provide more useful information on the efficacy of newer agents.

Authors' contributions F. Rozet, T. Roumeguère, M. Spahn, D. Beyersdorff and P. Hammerer were involved in project development, data collection, data analysis, manuscript writing/editing, and other (approval of final draft for submission).

Compliance with ethical standards

Conflict of interest Francois Rozet, Thierry Roumeguère, Martin Spahn and Dirk Beyersdorff have no conflict of interest to declare. Peter Hammerer has been an advisor for Janssen, Takeda and Ipsen.

Ethical standards This manuscript was funded by Ipsen. The authors take full responsibility for the content of the paper. Martin Gilmour of ESP Bioscience, Crowthorne, UK (supported by Ipsen) provided editorial assistance in the preparation of the manuscript.

References

1. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M, Prostate Cancer Clinical Trials Working G (2008) Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26(7):1148–1159
2. Hussain M, Goldman B, Tangen C, Higano CS, Petrylak DP, Wilding G, Akdas AM, Small EJ, Donnelly BJ, Sundram SK, Burch PA, Dipaola RS, Crawford ED (2009) Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. J Clin Oncol 27(15):2450–2456
3. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC (1999) Natural history of progression after PSA elevation following radical prostatectomy. JAMA 281(17):1591–1597
4. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, Partin AW (2005) Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 294(4):433–439
5. Antonarakis ES, Feng Z, Trock BJ, Humphreys EB, Carducci MA, Partin AW, Walsh PC, Eisenberger MA (2012) The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int 109(1):32–39
6. Moul JW, Wu H, Sun L, McLeod DG, Amling C, Donahue T, Kusuda L, Sexton W, O'Reilly K, Hernandez J, Chung A, Soderdahl D (2004) Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. J Urol 171(3):1141–1147
7. Studer UE, Whelan P, Wimpissinger F, Casselman J, de Reijke TM, Knonagel H, Loidl W, Isorna S, Sundaram SK, Collette L, Group EGC (2014) Differences in time to disease progression do not predict for cancer-specific survival in patients receiving immediate or deferred androgen-deprivation therapy for prostate cancer: final results of EORTC randomized trial 30891 with 12 years of follow-up. Eur Urol 66(5):829–838
8. Gillessen S, Omlin A, Attard G, de Bono JS, Efstathiou E, Fizazi K, Halabi S, Nelson PS, Sartor O, Smith MR, Soule HR, Akaza H, Beer TM, Beltran H, Chinnaiyan AM, Daugaard G, Davis ID, De Santis M, Drake CG, Eeles RA, Fanti S, Gleave ME, Heidenreich A, Hussain M, James ND, Lecouvet FE, Logothetis CJ, Mastris K, Nilsson S, Oh WK, Olmos D, Padhani AR, Parker C, Rubin MA, Schalken JA, Scher HI, Sella A, Shore ND, Small EJ, Sternberg CN, Suzuki H, Sweeney CJ, Tannock IF, Tombal B (2015) Management of patients with advanced prostate cancer: recommendations of the St. Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol 26(8):1589–1604
9. Tombal B (2012) Non-metastatic CRPC and asymptomatic metastatic CRPC: which treatment for which patient? Ann Oncol 23(Suppl 10):x251–x258
10. NCCN (2014) NCCN clinical practice guidelines in oncology. Prostate cancer. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
11. Schulman CC, Irani J, Morote J, Schalken JA, Montorsi F, Chlosta PL, Heidenreich A (2010) Testosterone measurement in patients with prostate cancer. Eur Urol 58(1):65–74
12. Zlotta A, Debruyne FMJ (2005) Expert opinion on optimal testosterone control in prostate cancer. Eur Urol Suppl 4(8):37–41
13. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N (2014) EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 65(2):467–479
14. Philips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M (2009) Oxford centre for evidence-based medicine levels of evidence. http://www.cebm.net/
15. Kirby M, Hirst C, Crawford ED (2011) Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract 65(11):1180–1192
16. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL, Wynne C, Murray R, Zinner NR, Schulman C, Linnartz R, Zheng M, Goessl C, Hei YJ, Small EJ, Cook R, Higano CS (2005) Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 23(13):2918–2925
17. Nelson JB, Love W, Chin JL, Saad F, Schulman CC, Sleep DJ, Qian J, Steinberg J, Carducci M, Atrasentan Phase 3 Study G (2008) Phase 3, randomized, controlled trial of atrasentan in

patients with nonmetastatic, hormone-refractory prostate cancer. Cancer 113(9):2478–2487
18. Smith MR, Cook R, Lee KA, Nelson JB (2011) Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer 117(10):2077–2085
19. Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, Miller K, Sieber P, Karsh L, Damiao R, Tammela TL, Egerdie B, Van Poppel H, Chin J, Morote J, Gomez-Veiga F, Borkowski T, Ye Z, Kupic A, Dansey R, Goessl C (2012) Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 379(9810):39–46
20. Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, Tombal B, Damiao R, Marx G, Miller K, Van Veldhuizen P, Morote J, Ye Z, Dansey R, Goessl C (2013) Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 31(30):3800–3806
21. Miller K, Moul JW, Gleave M, Fizazi K, Nelson JB, Morris T, Nathan FE, McIntosh S, Pemberton K, Higano CS (2013) Phase III, randomized, placebo-controlled study of once-daily oral zibotentan (ZD4054) in patients with non-metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 16(2):187–192
22. Yu EY, Miller K, Nelson J, Gleave M, Fizazi K, Moul JW, Nathan FE, Higano CS (2012) Detection of previously unidentified metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic, castration resistant prostate cancer. J Urol 188(1):103–109
23. Dale W, Hemmerich J, Bylow K, Mohile S, Mullaney M, Stadler WM (2009) Patient anxiety about prostate cancer independently predicts early initiation of androgen deprivation therapy for biochemical cancer recurrence in older men: a prospective cohort study. J Clin Oncol 27(10):1557–1563
24. Crawford ED, Stone NN, Yu EY, Koo PJ, Freedland SJ, Slovin SF, Gomella LG, Berger ER, Keane TE, Sieber P, Shore ND, Petrylak DP, Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence G (2014) Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology 83(3):664–669
25. Sourbeer KN, Howard LE, Moreira DM, Amarasekara HS, Chow LD, Cockrell DC, Hanyok BT, Pratson CL, Kane CJ, Terris MK, Aronson WJ, Cooperberg MR, Amling CL, Hernandez RK, Freedland SJ (2015) Practice patterns and predictors of follow up imaging after a negative bone scan in men with castration resistant prostate cancer: results from the SEARCH database. J Urol 193(4):1232–1238
26. Van den Bergh L, Lerut E, Haustermans K, Deroose CM, Oyen R, Isebaert S, Budiharto T, Ameye F, Mottaghy FM, Bogaerts K, Van Poppel H, Joniau S (2015) Final analysis of a prospective trial on functional imaging for nodal staging in patients with prostate cancer at high risk for lymph node involvement. Urol Oncol 33(3):109e123–109e131
27. Tombal B, Lecouvet F (2012) Modern detection of prostate cancer's bone metastasis: is the bone scan era over? Adv Urol 2012:893193
28. Kitajima K, Murphy RC, Nathan MA, Froemming AT, Hagen CE, Takahashi N, Kawashima A (2014) Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. J Nucl Med 55(2):223–232
29. Afshar-Oromieh A, Haberkorn U, Schlemmer HP, Fenchel M, Eder M, Eisenhut M, Hadaschik BA, Kopp-Schneider A, Rothke M (2014) Comparison of PET/CT and PET/MRI hybrid systems using a 68 Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience. Eur J Nucl Med Mol Imaging 41(5):887–897
30. Kovar JL, Cheung LL, Simpson MA, Olive DM (2014) Pharmacokinetic and biodistribution assessment of a near infrared-labeled PSMA-specific small molecule in tumor-bearing mice. Prostate Cancer 2014:104248
31. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, Kubler H, Haberkorn U, Eisenhut M, Wester HJ, Gschwend JE, Schwaiger M (2015) Evaluation of hybrid 68 Ga-PSMA-ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 56(5):668–674
32. Erdi YE, Humm JL, Imbriaco M, Yeung H, Larson SM (1997) Quantitative bone metastases analysis based on image segmentation. J Nucl Med 38(9):1401–1406
33. Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, de la Rosette J, Weissleder R (2003) Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 348(25):2491–2499
34. Lecouvet FE, Simon M, Tombal B, Jamart J, Vande Berg BC, Simoni P (2010) Whole-body MRI (WB-MRI) versus axial skeleton MRI (AS-MRI) to detect and measure bone metastases in prostate cancer (PCa). Eur Radiol 20(12):2973–2982
35. Pasoglou V, Michoux N, Peeters F, Larbi A, Tombal B, Selleslagh T, Omoumi P, Vande Berg BC, Lecouvet FE (2015) Whole-body 3D T1-weighted MR Imaging in patients with prostate cancer: feasibility and evaluation in screening for metastatic disease. Radiol 275(1):155–166
36. Manni A, Bartholomew M, Caplan R, Boucher A, Santen R, Lipton A, Harvey H, Simmonds M, White-Hershey D, Gordon R et al (1988) Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. J Clin Oncol 6(9):1456–1466
37. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW (2009) Interval to testosterone recovery after hormonal therapy for prostate cancer and risk of death. Int J Radiat Oncol Biol Phys 75(1):10–15
38. Hong JH, Kim IY (2014) Nonmetastatic castration-resistant prostate cancer. Korean J Urol 55(3):153–160
39. Friedlander TW, Weinberg VK, Small EJ, Sharib J, Harzstark AL, Lin AM, Fong L, Ryan CJ (2012) Effect of the somatostatin analog octreotide acetate on circulating insulin-like growth factor-1 and related peptides in patients with non-metastatic castration-resistant prostate cancer: results of a phase II study. Urol Oncol 30(4):408–414
40. Nabhan C, Lestingi TM, Galvez A, Tolzien K, Kelby SK, Tsarwhas D, Newman S, Bitran JD (2009) Erlotinib has moderate single-agent activity in chemotherapy-naive castration-resistant prostate cancer: final results of a phase II trial. Urology 74(3):665–671
41. Hussain M, Corn PG, Michaelson MD, Hammers HJ, Alumkal JJ, Ryan CJ, Bruce JY, Moran S, Lee SY, Lin HM, George DJ, Prostate Cancer Clinical Trials Consortium apotDoDPCRP, the Prostate Cancer F (2014) Phase II study of single-agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. Clin Cancer Res 20(16):4218–4227
42. Prostate Cancer Trialists' Collaborative Group (2000) Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet 355(9214):1491–1498
43. Morote J, Orsola A, Planas J, Trilla E, Raventos CX, Cecchini L, Catalan R (2007) Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol 178(4 Pt 1):1290–1295
44. Lawrentschuk N, Fernandes K, Bell D, Barkin J, Fleshner N (2011) Efficacy of a second line luteinizing hormone-releasing

hormone agonist after advanced prostate cancer biochemical recurrence. J Urol 185(3):848–854
45. Sartor AO, Tangen CM, Hussain MH, Eisenberger MA, Parab M, Fontana JA, Chapman RA, Mills GM, Raghavan D, Crawford ED, Southwest Oncology G (2008) Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). Cancer 112(11):2393–2400
46. Scher HI, Morris MJ, Basch E, Heller G (2011) End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. J Clin Oncol 29(27):3695–3704
47. Schroder FH, Tombal B, Miller K, Boccon-Gibod L, Shore ND, Crawford ED, Moul J, Olesen TK, Persson BE (2010) Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: results from a 12-month, comparative, phase III study. BJU Int 106(2):182–187
48. Tombal B, Miller K, Boccon-Gibod L, Schroder F, Shore N, Crawford ED, Moul J, Jensen JK, Kold Olesen T, Persson BE (2010) Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol 57(5):836–842
49. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, Carles J, Flaig TW, Taplin ME, Higano CS, de Souza P, de Bono JS, Griffin TW, De Porre P, Yu MK, Park YC, Li J, Kheoh T, Naini V, Molina A, Rathkopf DE, Investigators C-A (2015) Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16(2):152–160
50. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B, the PI (2014) Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371(5):424–433