# Management of Patients with Advanced Prostate Cancer

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*Editorial by Megan E.V. Caram and David C. Miller on pp. 212–214 of this issue*

# Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017

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## Abstract

***Background:*** In advanced prostate cancer (APC), successful drug development as well as advances in imaging and molecular characterisation have resulted in multiple areas where there is lack of evidence or low level of evidence. The Advanced Prostate Cancer Consensus Conference (APCCC) 2017 addressed some of these topics.
***Objective:*** To present the report of APCCC 2017.
***Design, setting, and participants:*** Ten important areas of controversy in APC management were identified: high-risk localised and locally advanced prostate cancer; "oligometastatic" prostate cancer; castration-naïve and castration-resistant prostate cancer; the role of imaging in APC; osteoclast-targeted therapy; molecular characterisation of blood and tissue; genetic counselling/testing; side effects of systemic treatment(s); global access to prostate cancer drugs. A panel of 60 international prostate cancer experts developed the program and the consensus questions.
***Outcome measurements and statistical analysis:*** The panel voted publicly but anonymously on 150 predefined questions, which have been developed following a modified Delphi process.
***Results and limitations:*** Voting is based on panellist opinion, and thus is not based on a standard literature review or meta-analysis. The outcomes of the voting had varying degrees of support, as reflected in the wording of this article, as well as in the detailed voting results recorded in Supplementary data.
***Conclusions:*** The presented expert voting results can be used for support in areas of management of men with APC where there is no high-level evidence, but individualised treatment decisions should as always be based on all of the data available, including disease extent and location, prior therapies regardless of type, host factors including comorbidities, as well as patient preferences, current and emerging evidence, and logistical and economic constraints. Inclusion of men with APC in clinical trials should be strongly encouraged. Importantly, APCCC 2017 again identified important areas in need of trials specifically designed to address them.
***Patient summary:*** The second Advanced Prostate Cancer Consensus Conference APCCC 2017 did provide a forum for discussion and debates on current treatment options for men with advanced prostate cancer. The aim of the conference is to bring the expertise of world experts to care givers around the world who see less patients with prostate cancer. The conference concluded with a discussion and voting of the expert panel on predefined consensus questions, targeting areas of primary clinical relevance. The results of these expert opinion votes are embedded in the clinical context of current treatment of men with advanced prostate cancer and provide a practical guide to clinicians to assist in the discussions with men with prostate cancer as part of a shared and multidisciplinary decision-making process.

## 1. Introduction

The panel for the 2017 Advanced Prostate Cancer Consensus Conference (APCCC 2017) consisted of 61 multidisciplinary cancer physicians and scientists from 21 countries selected based on their academic track record and involvement in clinical or translational research in the field advanced prostate cancer (APC; Table 1).

For discussion, 10 controversial areas related to the management of men with APC that were judged to be most important for discussion were identified:

1. Management of high-risk localised and locally advanced prostate cancer
2. "Oligometastatic" prostate cancer
3. Management of castration-sensitive/naïve prostate cancer (CNCP)
4. Management of castration-resistant prostate cancer (CRPC)
5. Imaging in APC
6. Use of osteoclast-targeted therapy for skeletal related events (SRE)/symptomatic skeletal events (SSE) prevention for metastatic CRPC (mCRPC; not for osteoporosis/bone loss)
7. Molecular characterisation
8. Genetic counselling/testing
9. Side effects of systemic treatment: prevention, management, and supportive care
10. Global access to prostate cancer drugs and treatment in countries with limited resources

The consensus development process followed the procedures previously described (Supplementary data) [1]. The conference was organised around state-of-the-art lectures and presentations and debates by panellists who reviewed and discussed the evidence relevant to the above selected topics. On the last day of the conference, 150 previously agreed-upon questions were presented with options for answers in a multiple-choice format see Supplementary data. The questions were voted on publicly but anonymously.

For all questions, unless stated otherwise, responses were based on the idealised assumptions that all diagnostic procedures and treatments (including expertise in their interpretation and application) mentioned were readily available; there were no treatment contraindications and no option to include the patient in a clinical trial.

In addition, voting answers apply only to fit patients without limiting comorbidities and for patients with prostate adenocarcinoma (unless stated otherwise). When metastases were mentioned, they were detected by bone scintigraphy and/or cross-sectional imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI), if not stated otherwise. Importantly, in an effort to address questions from an evidence-based and clinical utility perspective, panellists were specifically instructed not to consider cost, reimbursement, and access as factors in their deliberations, unless otherwise stated, although clearly these are critical factors in the decision making for the physician and individual patient.

**Table 1 – Panel members by country and specialty**

| Name | First name | Speciality |
|---|---|---|
| Attard | Gert | Medical Oncology |
| Beer | Tomasz M. | Medical Oncology |
| Beltran | Himisha | Medical Oncology |
| Bossi | Alberto | Radiation Oncology, nonvoting (absence during voting) |
| Bristow | Rob | Radiation Oncology |
| Carver | Brett | Urology |
| Castellano | Daniel | Medical Oncology |
| Chung | Byung Ha | Urology |
| Clarke | Noel | Urology |
| Daugaard | Gedske | Medical Oncology |
| Davis | Ian D. | Medical Oncology |
| de Bono | Johann | Medical Oncology |
| Borges dos Reis | Rodolfo | Urology |
| Drake | Charles G. | Medical Oncology |
| Eeles | Ros | Clinical Oncology and Genetics |
| Efstathiou | Eleni | Medical Oncology |
| Evans | Christopher P. | Urology |
| Fanti | Stefano | Nuclear Medicine, nonvoting member |
| Feng | Felix | Radiation Oncology |
| Fizazi | Karim | Medical Oncology |
| Frydenberg | Mark | Urology |
| Gleave | Martin | Urology |
| Gillessen | Silke | Medical Oncology |
| Halabi | Susan | Clinical Trials and Statistics, nonvoting member |
| Heidenreich | Axel | Urology |
| Higano | Celestia S. | Medical Oncology |
| James | Nicolas | Clinical Oncology |
| Kantoff | Philip | Medical Oncology |
| Kellokumpu-Lehtinen | Pirkko-Liisa | Clinical Oncology |
| Khauli | Raja B. | Urology |
| Kramer | Gero | Urology |
| Logothetis | Chris | Medical Oncology |
| Maluf | Fernando | Medical Oncology |
| Morgans | Alicia K. | Medical Oncology and Epidemiology |
| Morris | Michael J. | Medical Oncology |
| Mottet | Nicolas | Urology |
| Murthy | Vedang | Radiation Oncology |
| Oh | William | Medical Oncology |
| Omlin | Aurelius | Medical Oncology, nonvoting member |
| Ost | Piet | Radiation Oncology |
| Padhani | Anwar R. | Radiology, nonvoting member |
| Parker | Chris | Clinical Oncology |
| Pritchard | Colin C. | Pathology, nonvoting member |
| Roach | Mack | Radiation Oncology |
| Rubin | Mark A. | Pathology, nonvoting member |
| Ryan | Charles | Medical Oncology |
| Saad | Fred | Urology |
| Sartor | Oliver | Medical Oncology |
| Scher | Howard | Medical Oncology |
| Sella | Avishay | Medical Oncology |
| Shore | Neal | Urology |
| Smith | Matthew | Medical Oncology |
| Soule | Howard | Prostate Cancer Foundation, nonvoting member |
| Sternberg | Cora N. | Medical Oncology |
| Suzuki | Hiroyoshi | Urology |
| Sweeney | Christopher | Medical Oncology |
| Sydes | Matthew R. | Clinical Trials and Statistics, nonvoting member |
| Tannock | Ian | Medical Oncology |
| Tombal | Bertrand | Urology |
| Valdagni | Riccardo | Radiation Oncology |
| Wiegel | Thomas | Radiation Oncology |

The results are intended to serve only as a guide to clinicians to assist in the discussions with patients as part of a shared and multidisciplinary decision-making process. For the definitions used for APCCC 2017 please refer to Supplementary data.

The panel consisted of voting (52) and nonvoting members (9). The nonvoting members were panellists, for example, radiologists, pathologists, and statisticians who are not involved in clinical management decision making, and one clinical expert who was not present during the voting. The option "unqualified to answer" (short form "unqualified") should have been chosen if a panellist lacked experience for a specific question; the "abstain" option should have been chosen if a panellist felt unable to vote for a best choice for any reason or had prohibitory conflicts of interest. The conference also included an explicit approach to management of conflicts of interest (Supplementary data).

Detailed voting records for each of the questions brought to the panel are provided in the Supplementary data. The denominator was based on the number of panel members who voted on the particular question, excluding those who voted "unqualified to answer." In case of questions related to a topic of a previous question where only a subset of the panellists had voted for a specific answer option the votes of panel members who voted "abstain" and "unqualified to answer" were excluded.

Consensus was declared if ≥75% of the panellists who did not vote for "unqualified" or "abstain" chose the same option [2]. Throughout, the percentage of voting panellists who gave a particular response are reported, the number of voters, and the number of panellists for each answer are provided in the Supplementary data. All panellists have contributed to the designing of the questions, editing the manuscript, and have approved the final document.

Importantly, this process was uniquely able to highlight areas of disagreement and identified priorities for future clinical research, meaning areas where additional data acquisition is warranted.

## 2. High-risk localised and locally advanced prostate cancer

The panellists noted that there is lack of precision in the use of the term "high risk" in localised prostate cancer that is in part influenced by a discipline specific perspective. The commonly used definitions of high-risk localised patients by various societies plus the definitions used in the STAMPEDE trial are summarised in Supplementary data. High-risk localised patients have relatively good long-term outcomes [3,4]. For the APCCC 2017 conference, the European Association of Urology (EAU) guideline definition was used [5].

### 2.1. Pathology in locally advanced prostate cancer

Pathology reporting for radical prostatectomies (RP) should adhere to the recently published American Joint Committee on Cancer eighth edition cancer staging manual [6]. The new guidelines include the adoption of Prognostic Gleason Groups along with Gleason scores, the collapsing of pT2 to one single group, and the use of elevated prostate-specific antigen (PSA) to increase clinical staging. RP reports should comment on tumour Gleason scores using the International Society of Urological Pathology guidelines [7,8].

In men with positive lymph nodes, the total number of nodes with metastases, the tumour volume within the lymph node, and extracapsular nodal extension are poor prognostic factors [9].

In tissue from patients who have previously been treated with androgen deprivation therapy (ADT) and/or other systemic treatment or radiation therapy (RT) no Gleason score should be reported.

*The panel unanimously agreed (100%) that apart from morphology and tumour stage, the following factors should be reported from a RP sample: (1) seminal vesicle involvement, (2) extraprostatic extension, (3) positive surgical margins (number, length and location, grade at margin), (4) Gleason score, and (5) grade group. There was also consensus that the following factors should be reported: (1) extent of prostatic involvement (96%), (2) number and anatomic region of resected lymph nodes and number and location of involved lymph nodes (94%), (3) tertiary Gleason grade (94%), and (4) micrometastases versus macrometastases in involved lymph nodes (81%), extranodal extension (81%), and metastatic deposits in perinodal fat tissue (79%; Table 2).*

Current guidelines (EAU, National Comprehensive Cancer Network [NCCN]) recommend performing extended pelvic lymph node dissection for men with high-risk and locally APC treated by RP particularly if the risk for lymph node metastases based on available nomograms is estimated to be ≥5% despite the fact that there are no data from randomised prospective trials supporting an improvement in outcome with lymph node dissection [10–12]. The impact of minimal template versus extended lymph node dissection is not known and the pathological processing and reporting of the dissected material is not well defined.

*There was a consensus (84%) that a lymph node dissection should be performed in the majority of men with cN0 cM0 high-risk prostate cancer undergoing RP whereas 9% voted for a lymph node dissection in a minority of selected patients and 5% did not vote for a lymph node dissection.*

*Regarding the minimum number of lymph nodes to constitute an adequate dissection in the majority of men with cN0 cM0 high-risk prostate cancer 76% of the panellists voted for a minimum of ≥11 lymph nodes (49% for 11–19 lymph nodes and 27% for ≥20 lymph nodes); 15% of the panellists voted for five to 10 lymph nodes, 9% abstained.*

*Regarding the template of lymph node dissection in men with high-risk and locally advanced prostate cancer, there was a consensus that the obturator region (98%), internal iliac region (90%), and external iliac region (85%) should be dissected. Regarding the presacral lymph nodes, 51% of the panellists voted against and 46% in favour of dissection, similarly for common iliac lymph nodes 52% of the panellists voted against and 45% in favour of dissection. There was a consensus (95%) **against** routine dissection of para-aortic lymph nodes (Table 3).*

**Table 2 – Prostatectomy pathology reporting (as clinicians, which factors do you want to be reported from a prostatectomy specimen in men with locally-advanced prostate cancer apart from morphology and tumour stage?)**

| Factor | Yes, useful test for majority of patients (influences your management decision; %) | Only for minority of selected patients (%) | No (%) | Abstain (%) |
|---|---|---|---|---|
| Seminal vesicle invasion | 100 | 0 | 0 | 0 |
| Extraprostatic extension | 100 | 0 | 0 | 0 |
| Positive surgical margins: number, length and location as well as grade at margin | 100 | 0 | 0 | 0 |
| Gleason score and grade group | 100 | 0 | 0 | 0 |
| Extent of prostatic involvement | 96 | 2 | 2 | 0 |
| If lymphadenectomy is performed: number and anatomic region of resected lymph nodes and number and location of involved lymph nodes | 94 | 6 | 0 | 0 |
| Tertiary Gleason score | 94 | 4 | 2 | 0 |
| In any involved lymph nodes: micro- vs macrometastases | 81 | 9 | 10 | 0 |
| In any involved lymph nodes: extranodal extension | 81 | 9 | 10 | 0 |
| In any involved lymph nodes: metastatic deposits in perinodal fat tissue | 79 | 15 | 6 | 0 |
| Cribriform growth pattern and intraductal tumour spread | 73 | 14 | 13 | 0 |
| Lymphovascular invasion | 68 | 18 | 14 | 0 |
| Intraductal carcinoma | 67 | 21 | 12 | 0 |
| Markers of inflammation (eg, inflammation within prostate cancer tissue, tumour infiltrating lymphocytes) | 23 | 24 | 53 | 0 |

### 2.2. *Adjuvant radiation therapy after RP*

Adjuvant radiation therapy (ART) is largely considered as the administration of external beam RT in the postoperative phase in absence of objective evidence that disease has recurred or persisted. In the case of prostate cancer this would mean delivering RT when the PSA is "undetectable." Interestingly, the definition of "undetectable" has varied over the past 25 yr by nearly 100 fold from <0.3 ng/ml into the pg/ml range more recently [13].

Three randomised controlled trials have demonstrated that ART in case of unfavourable pathological features (eg, pT3b, R1) after RP delays PSA recurrence free survival; in one of these trials metastases-free survival and overall survival (OS) were also improved. Interpretation of those results is generally biased by the inclusion of men with persistent disease evidenced by low but detectable PSA levels [14–16]. Thus, in fact many of these patients treated on the ART arm should be described as receiving early salvage radiation therapy (SRT) [17,18].

Because several retrospective studies have shown that SRT, offered at PSA recurrence, may be efficient and since this approach may save some men the application of ART, many physicians defer treatment until there is evidence of recurrent disease. Unfortunately there is no prospective randomised trial comparing "pure" ART at undetectable PSA levels as currently defined versus SRT at "appropriately" low PSA levels.

**Table 3 – Lymph node (LN) dissection in localised prostate cancer (which LN regions should be sampled [minimal requirement] in men with cN0 cM0 high-risk prostate cancer?)**

| LN region | Yes (%) | No (%) | Abstain (%) |
|---|---|---|---|
| Obturator | 98 | 2 | 0 |
| Internal iliac | 90 | 10 | 0 |
| External iliac | 85 | 15 | 0 |
| Presacral | 46 | 51 | 3 |
| Common iliac | 45 | 52 | 3 |
| Para-aortic | 5 | 95 | 0 |

#### 2.2.1. *ART for high risk localised prostate cancer pN0*

The topic of ART was addressed in men post-RP without lymph node involvement on surgical pathology (pN0), with undetectable postoperative PSA, and who have recovered urinary continence.

*There was no consensus on ART in high-risk localised prostate cancer patients. Forty-eight percent of the panellists voted for ART for any positive surgical margins, whilst 27% of the panel voted for ART only in case of multifocal or extensive margins. Twenty-one percent of the panel did not vote for ART in this setting.*

*In the presence of seminal vesicle involvement alone 38% of the panel voted for ART in the majority of patients, 32% of the panel voted for ART only if combined with positive surgical margins. Twenty-six percent of the panel did not vote for ART at all in this setting.*

*Fifty-five percent of panellists did* ***not*** *vote for ART in the case of Gleason 8–10 (Gleason Grade Group 4 or 5) as the only adverse factor, 20% of the panel voted for ART in case of Gleason 8–10 (Gleason Grade Group 4 or 5) alone for the majority of patients, and 23% in a minority of selected patients.*

*Regarding radiation field, 51% of the subset of panellists who voted for ART voted for treatment of the whole pelvis and prostatic bed, while 41% voted for treating only the prostatic bed.*

*Thirty-six percent of the subset of panellists who voted for ART voted for adding ADT in the majority of patients, 32% in a minority of selected patients, and 32% did not vote for the addition of ADT at all. From the subset of panellists who voted for addition of ADT to ART, 69% voted for this combined treatment in men with either pT stage ≥3b and/or Gleason score ≥8 (Grade group 4–5); 28% voted for combined treatment in men with pT stage ≥3b alone independent of Gleason score;*

*and 3% voted for combined treatment in men with Gleason 8–10 (Gleason Grade Group 4 or 5) alone. Regarding the form of ADT 61% of the subset of panellists voted for a luteinizing hormone-releasing hormone (LHRH) agonist/antagonist, 24% for combined ADT, and 15% for an androgen receptor antagonist monotherapy. Regarding duration of ADT, 39% of the subset of panellists voted for 3–6 mo, 43% for 6–12 mo, and 18% for 18–36 mo of ADT.*

#### 2.2.2. ART for pN1 prostate cancer

For men with prostate cancer and lymph node involvement, cancer mortality rises significantly when >2 positive lymph nodes are present [19].

The question of ART in men with pN1 disease (assuming adequate lymph node sampling, section 2.1) and no local adverse factors (no pT3b, no R1) and undetectable postoperative PSA and who have recovered urinary continence was addressed by the consensus panel.

*There was no consensus on ART in pN1 disease. Twenty-six percent of the panel voted for ART in men with pN1 disease in a majority of patients, 29% voted for ART in a minority of selected patients, while 43% of the panel did not vote for ART in this setting.*

*Regarding radiation field, 97% of the subset of panellists who voted for ART voted for the whole pelvis plus prostatic bed as radiation field.*

*The subset of panellists who voted for ART also voted on factors that influenced their decision to recommend ART: 62% voted for taking both the number and location of positive lymph nodes into consideration when recommending ART, 33% based their decision only on the number of involved lymph nodes, and 5% only on the location of involved lymph nodes. Fifty percent of this subset of panellists voted for ART in men with one or two positive lymph nodes in the presence of intermediate- or high-grade, nonorgan-confined disease and in those with three to four lymph nodes irrespective of grade and T-stage, 17% voted for ART in all patients, 15% voted for ART in patients with ≤2 positive lymph nodes independent of grade and T-stage, and 15% in patients with ≤4 positive lymph nodes independent of grade and T-stage.*

*Of the panellists who voted for ART for pN1 disease, 100% voted for adding ADT to ART. Regarding the duration of ADT in this situation, 18–36 mo was voted for by 57% of these panellists, 6–12 mo by 30%; 11% voted for 3–6 mo, while 2% voted for life-long ADT.*

### 2.3. Salvage radiation therapy after RP

While RP generally yields excellent results in patients with localised prostate cancer, the recurrence rates after RP for high-risk prostate cancer may rise as high as 50–80% [15]. In the case of recurrence, SRT is a treatment option [20].

The appropriate PSA level at which to initiate SRT is still unclear. European guidelines recommend initiating SRT before the post-RP PSA level exceeds 0.5 ng/ml, whilst NCCN guidelines recommend SRT in patients with confirmed increasing PSA [21,22].

Two multi-institutional retrospective studies showed an improved freedom from biochemical progression and distant metastases following very early SRT at a PSA <0.2 ng/ml as opposed to patients in which SRT was initiated at a PSA level of 0.2–0.5 ng/ml versus higher PSA values [23,24]. Such analyses are confounded by lead-time and length-time bias and the topic remains an area of uncertainty.

According to the current EAU guidelines, the SRT dose should be at least 66 Gy but the optimal dose may be higher; the optimal dose and fractionation is unclear and is being addressed in several ongoing trials.

Combining SRT with ADT may be an option, particularly in men with high-risk disease. In the GETUG-AFU 16 trial, the 5-yr freedom from biochemical progression was 80% with SRT plus 6 mo of ADT versus 62% with SRT alone [25]. In the RTOG 9601 trial, OS was improved with SRT plus 2 yr of high-dose bicalutamide (150 mg daily) compared with SRT plus placebo but a significant proportion of included men had PSA levels ≥0.7 ng/ml [26].

*Regarding the confirmed PSA level at which to initiate SRT, 44% of the panel voted for 0.2 ng/ml, whilst 38% voted for 0.1 ng/ml, 10% voted for 0.5 ng/ml, and 4% for <0.1 ng/ml.*

*The panel reached no consensus regarding a level of PSA above which SRT would not be recommended. Twenty-five percent of the panellists considered 2 ng/ml the maximum value, 19% considered 1 ng/ml the maximum value, 11% chose 0.5 ng/ml as a maximum value, and 19% of the panel voted that there should be no maximal upper limit of PSA.*

*The subset of panellists who voted for SRT also voted on the addition of ADT. Sixty-one percent voted for ADT in the majority of men, 29% in a minority of selected patients, for example, based on PSA level and PSA doubling-time, and 10% of these panellists did not vote for the addition of ADT. Regarding the duration of ADT in combination with SRT, 34% of these panellists who opted for the addition of ADT voted for 3–6 mo, 41% for 6–12 mo, and 25% for 18–36 mo of ADT.*

### 2.4. Discussion of high-risk localised and locally advanced prostate cancer

The consensus questions focused on men undergoing RP and the topics of ART and SRT. The choice of primary treatment of high-risk and locally advanced prostate cancer is also an area of controversy, but was not addressed at this conference.

The votes of the panel showed a consensus on the required information for pathology reporting in men undergoing a RP.

There was a lack of consensus regarding the role of ART and SRT reflecting the many uncertainties and multiple unanswered questions in both topics. One of the reasons for uncertainty is that the ART trials did not have an early SRT arm as a comparator and as such are not comparable to current practice. Another weakness of these trials is the relatively high PSA at which "adjuvant" RT was started, again not comparable to current practice.

As with any adjuvant treatment, ART bears the risk of overtreatment and can result in acute side effects as well as deleterious effects on long-term functional outcome

(eg, potency, continence) but such potential risks must be balanced against the potential benefits, namely improved oncological outcomes [18,27,28].

The quest to define "unnecessary" RT and how to select which patients really require ART and for which patients SRT is appropriate is currently ongoing. Several well-powered phase 3 trials (RADICALS, RAVES, and GETUG-17) will provide evidence on which to base updated discussions.

In the meantime, regarding SRT, recent retrospective studies suggest that initiating SRT at lower PSA values (< 0.2 ng/ml) improves biochemical progression free survival as compared with using the traditional recommended confirmed value of 0.2 ng/ml and rising for definition of biochemical relapse (BCR) [23,24]. These data were reflected by the votes of the panel wherein a significant proportion of panellists would initiate SRT below the PSA threshold recommended by current guidelines.

The addition of ADT to RT as primary treatment of the prostate is a well-established concept [29–33]. But the addition, timing, and duration of ADT, specifically for ART but also for SRT, are less well examined [26]. Accordingly, there was no consensus regarding the role of adding ADT to ART and SRT.

Prospectively validated prognostic and predictive molecular biomarkers are required that will improve the performance of clinical and pathological features but this can only be determined in the context of large phase 3 randomised trials with adequate long-term follow-up. Additionally, the increasing use of next-generation imaging methods in combination with more sensitive PSA assays may also alter treatment approaches in the future.

## 3. Oligometastatic prostate cancer

### 3.1. Definition of oligometastatic prostate cancer

Hellman and Weichselbaum [34] proposed the term "oligometastases" in 1995 for defining a disease stage with a limited number of clinically detectable metastases.

The biological definition of oligometastatic prostate cancer is open to interpretation as is the entire concept that this is a prognostic and therapeutically distinct subset of patients that falls somewhere in-between localised and metastatic disease. No formal cut-off for "oligo" has been defined in the literature [35]. Some definitions incorporate both the site of metastases in addition to the number of lesions to define the oligometastatic state [35,36]. Variables to include in the description of men with oligometastatic disease include: the distinction of synchronous versus metachronous metastases, the number and site of lesions, and whether the patient is castration-naïve or castration-resistant [36]. Of importance is also the imaging method used to define oligometastatic disease. Newer imaging techniques will detect more metastases in many patients classified as "oligometastatic" by conventional imaging (CT and bone scintigraphy). Many patients considered as M0 on conventional imaging may turn out to have oligometastatic disease especially when imaging is performed at lower PSA levels than in the past.

*The panel did not reach consensus on what constituted the definition of oligometastatic disease. Sixty-one percent of the panellists voted for a limited number of bone and/or lymph nodes as a clinically meaningful definition of oligometastatic prostate cancer that influences treatment decisions (local ablative treatment of all lesions ± systemic therapy), 10% of the panellists voted for an oligometastatic definition which includes only patients with a limited number of lymph node metastases, 13% voted for patients with a limited number of metastases at any location (including visceral disease), and 10% of the panellists did not believe that oligometastatic prostate cancer exists as a clinically meaningful entity.*

*The subset of panellists who believed in the concept of oligometastatic prostate cancer voted on the number of lesions. Regarding the cut-off for the number of metastases to consider a prostate cancer patient as oligometastatic 14% voted for ≤2 metastases, 66% for ≤3 metastases, and 20% of these panellists voted for ≤5 metastases as a cut-off. Of the panellists believing in the oligometastatic concept, 52% voted for a biopsy (if feasible) of an oligometastatic lesion for diagnostic purposes in a minority of selected patients, while 34% voted for biopsy in the majority of patients and 14% of these panellists did not vote for a biopsy.*

### 3.2. Synchronous "oligometastatic" castration-naive prostate cancer

This section addresses patients diagnosed with de novo apparent oligometastatic disease in the castration-naïve state, that is, they present with synchronous oligometastases and an untreated primary. In such patients, no prospective randomised data are available to show a benefit for ablative treatment of all lesions including the primary—either with or without systemic therapy.

*For men who present with de novo oligometastatic disease, a total of 25% of the panellists voted for lifelong ADT ± six cycles of docetaxel without local ablative treatment. Eight percent of panellists voted for local ablative treatment of all lesions including the primary (surgery or RT) without any systemic treatment, 22% of panellists voted for local ablative treatment with a short course (6–12 mo) of ADT ± docetaxel, 31% of panellists voted for local ablative treatment and an intermediate long course (24–36 mo) of ADT ± docetaxel, 8% of panellists voted for local ablative treatment and life-long ADT ± docetaxel.*

*Among the panellists who voted for local ablative treatment plus ADT in men with de-novo oligometastatic prostate cancer and an untreated primary, 28% voted for the addition of docetaxel in the majority of patients, 39% voted for the addition of docetaxel in a minority of selected patients; 33% of these panellists did not vote for the addition of docetaxel in this situation. If they voted for treatment of the primary tumour in this situation, 45% voted for RT, 22% voted for surgery, and 31% voted for either RT or surgery.*

### 3.3. Metachronous oligometastatic castration-naïve prostate cancer

This section addresses men who present with recurrent apparent oligometastatic prostate cancer in the castration-

naïve state; that is, they present with metachronous metastases after local treatment of the primary. No prospective randomised data are available to show a benefit for radical ablative treatment of all lesions with or without systemic therapy as compared with standard of care (ADT ± docetaxel) [37]. A meta-analysis of 20 small studies of local lymph node only recurrence after primary treatment suggested that, despite a lack of high-level evidence, ablative node-directed therapy may yield in good short-term oncologic outcomes and may defer the need for systemic treatment [38].

*There was no consensus on treatment options. For treatment of men with asymptomatic oligometastatic recurrent CNPC 32% of the panel voted for systemic therapy with lifelong ADT ± docetaxel without local ablative therapy of the metastases. Twelve percent voted for local ablative therapy of the metastases without additional systemic therapy, while 30% voted for local ablative therapy with a short course (6–12 mo) of ADT ± docetaxel, 18% for local ablative therapy with a longer course (24–36 mo) of ADT ± docetaxel, and 4% voted for local ablative therapy and lifelong ADT ± docetaxel.*

*Among the panellists who voted for local ablative treatment in men with oligometastatic recurrent CNPC limited to lymph node metastases in the pelvis, 23% voted for salvage lymph node dissection, 19% for salvage lymph node dissection plus RT to the pelvis (if no prior whole-pelvis RT), 16% of these panellists voted for focal RT, and 42% for whole pelvis RT (if no prior whole-pelvis RT) ± a boost to the suspicious nodes.*

### 3.4. Rising PSA on ADT (mCRPC) and oligometastatic disease

This section addresses patients diagnosed with oligometastatic disease progression in the castration resistant state. No prospective randomised data are available demonstrating a benefit for local radical treatment of all lesions in addition to ADT, compared with standard of care, that is, the addition of a new systemic treatment to ADT.

*Among the panellists who believed that oligometastatic mCRPC is a meaningful entity there was no consensus on treatment options. Forty-four percent of these panellists voted for continuation of ADT and adding additional systemic therapy, 29% for local ablative treatment of all lesions in combination with ongoing ADT and addition of systemic treatment, 25% for local ablative treatment of all lesions while continuing ADT without addition of systemic treatment and 2% voted for local ablative treatment of all lesions and the cessation of ADT.*

### 3.5. Discussion of oligometastatic prostate cancer

In addition to prostate cancer, the oligometastatic state is of interest in a growing number of other cancer types, for example, breast, renal cell, colorectal, gastric, and non-small cell lung cancer. Like in prostate cancer, in these diseases the majority of data are retrospective in nature and therefore difficult to interpret. In some cases, treatment of local disease appears to be associated with long-term survival. Prospective trials are ongoing in several of these entities.

The concept of oligometastases implies that a local therapy directed at the primary cancer and/or metastases might improve survival though there is no strong evidence to support this. There was no consensus on treatment options, but from the voting it seems that the enthusiasm for the topic exceeds the evidence reported to date. The available data are not prospective, are subject to selection bias, and thus require validation in prospective randomised controlled trials. Such trials should focus on OS as an endpoint, since earlier endpoints such as progression-free survival (PFS) or time to systemic therapy are not well defined and their clinical importance is less clear. Distinguishing between synchronous and metachronous lesions, and separating pelvic nodal relapse from M1 disease is also likely to be important. Studies of patients with oligometastatic disease are of increasing importance, since more sensitive imaging techniques are anticipated to increase the proportion of men with radiographically detected lesions. At the very least, until randomised clinical trial data are available, large collaborative national and international registries of men treated for oligometastatic prostate cancer should be initiated to prospectively collect data on consecutively treated patients.

## 4. Castration-naive prostate cancer

There was inconsistent use in discussions of the terms castration-naïve or castration-sensitive, to designate prostate cancer either not previously treated with ADT, or cancers demonstrating ongoing sensitivity to ADT. The term castration-naïve is used in this manuscript for simplicity to cover both clinical scenarios.

### 4.1. When to start ADT (post-RP ± RT or post RT)

The optimal timing of initiation of ADT, duration, specific ADT modality, and the indications for initiating ADT are not well defined. For patients presenting with metastases with impending complications and especially if symptomatic, an initial short course of AR antagonist treatment to prevent the unwanted clinical consequences of testosterone surge is recommended when LHRH agonists are initiated.

For patients with BCR, the decision to initiate ADT will likely depend upon several parameters including life expectancy, time to PSA relapse after local therapy, PSA kinetics, absolute PSA level, age, sexual function, baseline fatigue, cardiovascular risk, and neurologic and cognitive status. For patients with BCR without overt metastatic disease, the decision to proceed with intermittent ADT versus continuous ADT should also be considered.

*In men with nonmetastatic disease and confirmed rising PSA (postlocal therapy ± SRT), 65% of the panellists voted for the initiation of ADT only in a minority of selected men, for example, in case of a PSA ≥4 ng/ml and rising with doubling time less than 6 mo or a PSA ≥20 ng/ml (STAMPEDE inclusion criteria). Twenty-one percent voted for starting ADT in the majority of men irrespective of these factors and 12% voted for starting ADT only after detection of metastases.*

#### 4.1.1. Monitoring of testosterone

Current data do not provide clarity regarding the optimal level of testosterone suppression to be achieved in men

with advanced prostate cancer on ADT. The regulatory-approved level of less than 50 ng/dl, per Food and Drug Administration and European Medicines Agency, was based upon the initial leuprolide registration trial and 50 ng/dl was the lowest limit of detection of the radioimmunoassay used at that time [39]. Ensuing trials have suggested that reaching a testosterone level of ≤20 ng/dl may achieve a delay in time toward the development of castration resistance; however, this threshold, as well as the interval at which to measure serum testosterone levels remains uncertain [40].

*In men with prostate cancer responding to ADT, 44% of the panel voted for regular monitoring of testosterone levels (apart from measuring testosterone at biochemical progression) and 34% of the panellists voted for measuring testosterone in a minority of selected patients (eg, failure to achieve PSA nadir < 0.2 ng/ml), 22% of the panel did not vote for regular testosterone measurement in responding patients.*

*Fifty-four percent of the panel voted for a testosterone level <50 ng/dl (< 1.73 nmol/l) as appropriate for men on ADT, 36% voted for a testosterone level <20 ng/dl (< 0.69 nmol/l), while 10% abstained.*

*There was no consensus on the therapeutic approach to men with rising PSA on a LHRH agonist whose testosterone level is confirmed as being noncastrate (apart from ruling out application errors and/or poor compliance). Despite the lack of evidence, 36% of the panel voted for a change to a LHRH antagonist, 26% for addition of a first-generation AR antagonist, 20% for a change to an alternative LHRH agonist, and 14% voted for orchiectomy.*

### 4.2. Chemotherapy in castration-naïve nonmetastatic prostate cancer

There is some evidence to support combination treatment as an upfront alternative to single-modality therapy for men who present with high-risk localised prostate cancer. Such approaches generally combine ADT with RT and docetaxel-based chemotherapy. A total of three randomised trials in such patients have been reported. The GETUG-12 trial showed an improvement in failure-free survival (FFS) with four cycles of docetaxel and estramustine plus ADT as compared with ADT alone [41,42]. The second trial, RTOG 0521, so far only presented as an abstract, examined the combination of six cycles of adjuvant docetaxel postradical RT with ADT for 24 mo (NCT00288080). The STAMPEDE trial allowed inclusion of high-risk localised as well as biochemical recurrent and metastatic patients. The number of events for definitive interpretation of survival of M0 patients in the docetaxel arm of STAMPEDE is too low and no conclusions regarding the effect of addition of docetaxel on OS in this trial can be drawn [43].

A meta-analysis reported a consistent effect on FFS for chemo-hormonal therapy in the M0 subgroup as opposed to ADT alone [44]. Data for OS are not yet mature.

*For men with N1 M0 CNPC, 71% of the panel did not vote for the addition of docetaxel to ADT, 25% voted for the addition in a minority of minority of selected patients, and 4% for the majority of patients.*

*For men with biochemical relapse only, there was a consensus (90%) for not adding docetaxel to ADT.*

### 4.3. Castration-naive prostate cancer M1 (metastatic)

Testosterone suppression alone has long been the standard treatment for patients with metastatic prostate cancer commencing systemic treatment [45]. Although the majority of men with mCNPC experience a PSA decline with ADT, the median FFS in a cohort of newly diagnosed mCNPC was approximately approximately 1 yr, with a wide range [46]. Subgroup analyses from recent clinical trials showed that higher volume of metastases and presentation with de novo metastatic disease are risk factors associated with a shorter OS with ADT alone. Other purported poor prognostic clinical factors include higher Gleason score, pain, and elevated alkaline phosphatase [45,47,48].

Docetaxel given at the start of ADT was the first drug shown to improve the OS of men with mCNPC in two large trials [43,49]. The first phase 3 study of docetaxel in mCNPC, GETUG 15, showed an improvement in PFS but not OS [47].

There is ongoing discussion on the definition of "high-volume" disease and whether there is a definition that is prognostically relevant or predictive of treatment benefit.

*For a definition of high-volume disease, 74% of the panellists voted for the definition, as used in CHAARTED (visceral [lung or liver] and/or ≥ 4 bone metastases, at least one beyond pelvis and vertebral column), either with standard imaging (59%) or with any imaging (15%), 6% voted for the high-volume definition developed by SWOG (visceral [lung or liver] and/or any appendicular skeletal involvement) and 6% voted for a simplified version of high-volume of visceral and/or ≥4 bone lesions regardless of distribution and imaging used. Fourteen percent of the panellists had the opinion that high-volume disease is not a clinically meaningful entity.*

*For men with high-volume mCNPC, 68% of the panellists voted for continuous ADT using a LHRH agonist (plus a short course of first-generation AR antagonist to prevent testosterone surge) as their preferred hormone therapy, another 10% for starting with an LHRH antagonist (no flare-up prevention needed) and switching to an LHRH agonist in the course of treatment. Continuous LHRH antagonist treatment was voted for by 6%, orchiectomy by 2%, and continuous combined ADT by 14% of the panellists. None of the panellists voted for any form of intermittent ADT or AR-antagonist monotherapy in the high-volume M1 setting.*

Not all men are suitable for chemotherapy with docetaxel and the criteria rendering a patient "unsuitable" for docetaxel are not well defined.

The panel voted on factors they would consider rendering a man "unfit" for docetaxel.

*There was a consensus for severe hepatic impairment (96%), neuropathy grade ≥2 (82%), and platelets <50 × $10^9$/l and/or neutrophils <1.0 × $10^9$/l (81%). For the other proposed factors alone there was no consensus (Table 4).*

In the original publication of the CHAARTED trial, the subgroup of men with high-volume disease showed a clinically significant survival benefit and the point estimate for the low volume patients was the same in that

**Table 4 – Definition "unfit" for docetaxel**

| What are meaningful definitions "not being suitable for docetaxel", apart from allergy to the substance ("docetaxel ineligible")? | Yes (%) | Only in combination with other factors (%) | No (%) | Abstain (%) |
|---|---|---|---|---|
| Severe hepatic impairment (eg, ALT/AST > 5 × ULN and/or bilirubin > 3 × ULN) | 96 | 2 | 2 | 0 |
| Neuropathy grade ≥2 | 82 | 18 | 0 | 0 |
| Platelets $<50 \times 10^9$/l and/or neutrophils $<1.0 \times 10^9$/l | 81 | 15 | 4 | 0 |
| Frailty assessed by geriatric or other health status evaluation | 69 | 29 | 2 | 0 |
| Performance status ≥2 for reasons other than cancer | 62 | 32 | 4 | 2 |
| Moderate hepatic impairment (eg, ALT/AST > 3–5 × ULN and/or bilirubin > 1.5–3 × ULN) | 52 | 48 | 0 | 0 |

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

publication, albeit with much wider confidence intervals [49]. No OS benefit has yet been demonstrated for early docetaxel use with longer-term follow-up in subgroup analyses performed in both the low-volume mCNPC cohorts of the GETUG 15 (posthoc) or CHAARTED (prespecified) trials [49,50]. Further subgroup analyses for men with de novo metastatic prostate cancer (majority of included patients) versus men with relapse after local treatment were presented but have not yet been published (European Society for Medical Oncology 2016 and GU-ASCO 2017).

The large STAMPEDE trial included both M0 and M1 patients and no heterogeneity of treatment effect was observed.

*For men who are suitable for chemotherapy and have de novo mCNPC and high-volume disease as defined by CHAARTED, there was a consensus (96%) for addition of docetaxel to ADT in the majority of patients, 4% voted for docetaxel in a minority of these men. For the other subgroups of mCNPC there was no consensus (Table 5). There was consensus that men with biochemical relapse (N0M0) should not receive docetaxel in addition to ADT.*

*If chemo-hormonal treatment is used in men with mCNPC there was consensus (78%) that docetaxel should be started within 3 mo of starting ADT and 20% of these panellists voted for starting even within 2–4 wk. Within 4 mo was considered sufficient for another 18% of the panellists.*

*In the subset of panellists who voted for chemo-hormonal therapy there was also consensus (96% of the panel) for the 3-weekly regimen of docetaxel with 75 mg/m$^2$. Only 4% of the panel voted for the use of the 2-weekly regimen with 50 mg/m$^2$.*

Docetaxel in the 3-weekly regimen does not bear a high risk (>20%) of febrile neutropenia; however, according to existing guidelines (NCCN, ESMO, ASCO), primary granulocyte-colony stimulating factor prophylaxis should be considered in men with risk factors namely prior chemo- or RT, bone marrow involvement by tumour, renal dysfunction (creatinine clearance < 50 ml/min), or age >65 yr, and receiving full chemotherapy dose and intensity. It is not uncommon that such risk factors are present in men with APC. Of note, there is preclinical data suggesting that myeloid-derived suppressor cells, which may play a role in

**Table 5 – Chemo-hormonal therapy with docetaxel**

| Do you recommend docetaxel in addition to ADT: | Yes, in the majority of patients (%) | In a minority of selected patients (%) | No (%) | Abstain (%) | Unqualified to answer (%) |
|---|---|---|---|---|---|
| In men with de novo metastatic castration-naive prostate cancer and high-volume disease as defined by CHAARTED (visceral metastases and/or ≥ 4 bone lesions with ≥ 1 beyond vertebral bodies and pelvis)? | 96 | 4 | 0 | 0 | 0 |
| In men with de novo metastatic castration-naive and low-volume disease as per CHAARTED? | 29 | 65 | 9 | 0 | 0 |
| In men with metastatic castration-sensitive/naive disease relapsing after prior treatment for localised prostate cancer and with high-volume disease as per CHAARTED? | 74 | 24 | 2 | 0 | 0 |
| In men with metastatic castration-sensitive/naive disease relapsing after prior treatment for localised prostate cancer with low-volume bone metastases as per CHAARTED criteria? | 19 | 54 | 25 | 2 | 0 |
| In men with castration-sensitive/naive N1 M0 prostate cancer? | 4 | 25 | 71 | 0 | 0 |
| In men with castration-sensitive/naive N0 M0 (nonmetastatic) prostate cancer with biochemical relapse? | 0 | 10 | 90 | 0 | 0 |

ADT = androgen deprivation therapy.

cancer progression can be influenced by granulocyte-colony stimulating factor [51–53].

*In the subset of panellists who voted for chemo-hormonal therapy, 6% voted for white blood cell (WBC) growth factors from start of therapy in the majority of patients, 50% for a minority of selected patients. Forty-four percent of these panellists did not vote for WBC growth factors from start of therapy*.

Regarding concomitant steroid dosing the CHAARTED and GETUG-15 trials did not require daily steroids, whereas STAMPEDE required prednisone (10 mg) daily.

*In the subset of panellists who voted for chemo-hormonal therapy, 58% voted for prescribing the 3-weekly docetaxel regimen with no daily steroid in the chemo-hormonal setting and 38% with 10 mg prednisone daily*.

#### 4.4. Local therapy in men with mCNPC

The current standard of care for patients presenting with de novo metastatic prostate cancer is ADT with or without docetaxel (section 4.3). Transurethral resection of the prostate may be used to palliate local symptoms. The rationale for potentially using a local ablative treatment (external beam RT or RP) in these patients is based on several considerations. Significant morbidity related to local symptoms including pain, obstructive urinary symptoms, and haematuria can occur in these men, either when the cancer is diagnosed or when it progresses later in the disease course [54]. A local ablative treatment used upfront may prevent these adverse events, as suggested in a retrospective analysis [55]. Local treatment, however, can add considerable toxicity.

In men with mCNPC, there is no randomised prospective data to support local ablative treatment of the primary. Retrospective studies based on registries, while biased by design, suggest a survival benefit when a local treatment is applied upfront [56–58]. Similar findings were reported in men with nodal disease treated locally with either RT or RP [38,59,60]. These results have to be interpreted with caution and treatment of the primary for this specific disease state should only be done in the context of a clinical trial.

*Fifty-two percent of the panel was* ***against*** *treating the primary tumour in addition to systemic therapy in men with de novo high-volume mCNPC who are not symptomatic from their primary, 38% voted for treating the primary in a minority of patients, 10% in the majority of patients in this situation.*

*In the subset of panellists who voted for treatment of the primary in this situation, 71% voted for RT, 26% voted for a RP; 3% voted for other treatments.*

#### 4.5. Discussion of CNPC

In summary, although docetaxel-based CNPC studies have provided evidence that some patients benefit from early docetaxel, the field is rapidly evolving and a number of unanswered questions have emerged [44]. Less than a third of the panel recommended addition of docetaxel to ADT in the majority of patients with low-volume metastatic disease despite the fact that use of data from subgroups has limitations and is considered hypothesis generating. Importantly, there is probably significant overlap between patients called "low-volume" metastatic and "oligometastatic." The panel seemed more conservative in relation to addition of docetaxel than in relation to local ablative treatment.

Additional studies are needed to focus on identifying more accurate biomarkers and better understanding of the underlying mechanisms of resistance to ADT to define a more precise therapeutic strategy for a given biological driver for a given cancer and therefore the biological basis for the benefit of AR targeting and cytotoxic treatment of their prostate cancer [61–63]. Moreover, since the studies of ADT plus abiraterone in the mCNPC setting have shown an overall survival benefit, further work will be required to determine the role of docetaxel either with ADT alone or with ADT plus abiraterone [64,65]. Further studies with other AR targeted agents including the combination with chemotherapy are ongoing in the same setting.

Despite the lack of prospective data from randomised trials, a rather high percentage of the panel would consider treatment of the primary tumour in some men with metastatic disease. Applying such a local ablative treatment to men with metastases in a nonresearch setting could be "excessive" in terms of treatment burden and is unproven but some panellists have voted for this approach, not only in the oligometastatic setting, but also in the general metastatic setting, and this seems to be done in clinical practice all over the world.

This "try it because you believe it" approach is well-intentioned but may result in adverse consequences for patients, in some cases on a large scale, as in the gross overtreatment of low-risk localised prostate cancer. In the era of evidence-based medicine, this approach is disappointing and we, as a scientific community, should do everything we can to avoid having this happen again. It is worth remembering that in other malignancies, for example, in metastatic breast cancer, retrospective data and even a meta-analysis had similarly suggested an OS benefit with locoregional treatment in metastatic disease that was not confirmed in a randomised prospective study [66]. Despite a large percentage of the panel considering treatment of the primary in the metastatic setting, there is still an overwhelming recommendation that this question for prostate cancer has to be answered in prospective randomized trials before being widely adopted in clinical practice. Several such trials are currently testing whether a local definitive treatment directed to the prostate primary cancer can improve patient outcome in men with mCNPC (eg, NCT00268476, NCT01957436, NCT02454543; ISRCTN06890529).

## 5. Castration-resistant prostate cancer

#### 5.1. Sequencing and combinations in mCRPC

The field of prostate cancer drug development has seen remarkable progress in the past 10 yr. However, this

progress is largely based on registration studies conducted by a "one size fits all" approach in a regulatory framework that focused on prior therapy with ADT and docetaxel exposure rather than one defined by individual patient biology. With current knowledge about heterogeneity in prostate cancer, future registration trials will need to have more specific eligibility criteria related to the mechanism of action of the drug being studied.

Because the registration trials for each of these agents were conducted contemporaneously, the question of sequencing of the available treatment options is still relevant. The earlier inclusion of docetaxel as part of a chemo-hormonal therapy regimen in CNPC (section 4.2 and 4.3) may have implications on subsequent treatment choices. None of the registration trials for agents in the CRPC setting included such patients.

#### 5.1.1. First-line treatment for men with mCRPC

Several prospective randomised phase 3 trials showed an OS benefit for first-line treatment in men with mCRPC. None of the control arms used in these trials is currently considered standard of care. Abiraterone, enzalutamide, and sipuleucel-T were evaluated as first-line agents in asymptomatic patients, docetaxel in both symptomatic and asymptomatic patients, and radium-223 dichloride (radium-223) in symptomatic patients with bone metastases [67–72]. Sipuleucel-T is only available in the USA.

Another first-line trial testing cabazitaxel in two different doses versus docetaxel has been reported and failed to show superiority of cabazitaxel, but has not yet been published (NCT01308567, ASCO 2016).

*There was consensus that asymptomatic men with mCRPC should receive abiraterone or enzalutamide as first-line treatment. This recommendation was independent of whether they had received ADT alone (86%) or ADT plus docetaxel (90%) in the castration-naïve setting.*

*In case of progression within 6 mo after completion of docetaxel in the castration-naïve setting in an asymptomatic man, 77% of the panellists voted for abiraterone or enzalutamide as first-line mCRPC treatment, 17% voted for cabazitaxel, and 2% each docetaxel or platinum-based chemotherapy (Table 6).*

#### 5.1.2. Second-line treatment for men with mCRPC

There are only prospective randomised data for second-line treatment in men who have received docetaxel as first-line treatment for mCRPC. In this setting, abiraterone, cabazitaxel, enzalutamide, and radium-223 (about half of the patients included were pretreated with docetaxel) have shown an OS benefit [72–75]. Currently, most patients are treated with abiraterone or enzalutamide in the first-line setting and there is not a lot of prospective data on second- or further-line treatment in these men.

*In symptomatic men who had primary resistance to first-line treatment with abiraterone or enzalutamide there was a consensus (96% of the panel) for treatment with a taxane.*

*In symptomatic men who had acquired resistance to first-line abiraterone or enzalutamide there was a consensus (90% of the panellists) for a taxane, 8% voted for radium-223, and 2% had no preferred option.*

**Table 6 – Sequencing of metastatic castration-resistant prostate cancer (mCRPC) first-line options**

| What is your preferred first-line mCRPC treatment option: | Abiraterone or enzalutamide (%) | Cabazitaxel (%) | Docetaxel (%) | Platinum-based chemotherapy (%) | Radium-223 (%) | Sipuleucel-T (%) | No preferred option (%) | Abstain (%) | Unqualified to answer (%) |
|---|---|---|---|---|---|---|---|---|---|
| In the majority of asymptomatic men who did not receive docetaxel in the castration-naive setting? | 86 | 0 | 6 | 0 | 0 | 8 | 0 | 0 | 0 |
| In the majority of symptomatic men who did not receive docetaxel in the castration-naive setting? | 52 | 0 | 46 | 0 | 0 | 0 | 2 | 0 | 0 |
| In the majority of asymptomatic men who did receive docetaxel in the castration-naive setting? | 90 | 2 | 2 | 0 | 0 | 6 | 0 | 0 | 0 |
| In the majority of symptomatic men who did receive docetaxel in the castration-naive setting? | 73 | 19 | 6 | 0 | 2 | 0 | 0 | 0 | 0 |
| In the majority of asymptomatic men who received chemo-hormonal therapy and who progressed within ≤6 mo after completion of docetaxel in the castration-naive setting? | 77 | 17 | 2 | 2 | 0 | 0 | 2 | 0 | 0 |
| In the majority of symptomatic men who received chemo-hormonal therapy and who progressed within ≤6 mo after completion of docetaxel in the castration-naive setting? | 57 | 27 | 0 | 4 | 8 | 2 | 2 | 0 | 0 |

*In asymptomatic men with disease progression on or after first-line docetaxel for mCRPC, there was a consensus (92%) for abiraterone or enzalutamide as second-line treatment. Only 6% of the panellists voted for treatment with cabazitaxel and 2% for radium-223.*

*In symptomatic men with disease progression on or after first-line docetaxel for mCRPC there was consensus (76%) for treatment with abiraterone or enzalutamide, 18% voted for cabazitaxel and 6% voted for radium-223 (Table 7).*

#### 5.1.3. Third-line treatment for men with mCRPC

There are no randomised prospective data for third-line treatment in mCRPC.

*In a man who has received abiraterone or enzalutamide as first-line treatment, and docetaxel as second-line treatment, 61% of the panellists voted for treatment with cabazitaxel, 15% for radium-223, 8% voted for abiraterone or enzalutamide (depending on which has already been used), 8% had no preferred choice, and 6% voted for a platinum-based chemotherapy.*

Platinum compounds have been studied in a variety of monotherapy schedules and in different combinations and clinical disease stages in men with APC [76]. In unselected patients the response rates to platinum compounds are not convincing and derived from mostly small clinical trials.

*In men with mCRPC who have exhausted approved treatments and if no clinical trial was available a total of 96% of the panellists voted for a carboplatin-based chemotherapy in certain situations: 33% in the majority of patients, 2% only in patients with DNA repair defects, 14% only in patients with neuroendocrine differentiation or clinical evidence suggestive of neuroendocrine differentiation (eg, atypical pattern/distribution of metastases, rapid progression without correlation with PSA kinetics; sudden onset of rapid growth of visceral metastases or multiple lytic bone metastases; presence of paraneoplastic syndromes), and 47% in patients with DNA repair defects and/or neuroendocrine differentiation or suggestion thereof.*

### 5.2. Treatments and schedules for mCRPC

Newer androgen-receptor pathway targeted therapies such as enzalutamide or abiraterone carry risks of class-specific adverse events. Abiraterone adverse events include those related to mineralocorticoid excess, hypertension, cardiac and liver dysfunction, and fluid retention. Enzalutamide can be associated with fatigue, hypertension, cognitive and mood impairment, falls, and fractures. Both drugs carry the risk of pharmacokinetic drug-drug interactions that can increase the risk of toxicity particularly in older men treated with multiple other drugs.

Abiraterone and enzalutamide have been developed almost simultaneously and there are no published randomised prospective trials available that compare these two agents against each other.

*Asked about their preferred choice between abiraterone and enzalutamide for first-line treatment of men with mCRPC and no contraindication to either drug, 35% of the panellists voted*

**Table 7 – Sequencing of metastatic castration-resistant prostate cancer (mCRPC) second-line options**

| What is your preferred second-line mCRPC treatment option: | Abiraterone or enzalutamide (depending which has already been used; %) | Taxane (%) | Radium-223 (%) | Sipuleucel-T (%) | No preferred option (%) | Abstain (including other treatment option) (%) | Unqualified to answer (%) |
|---|---|---|---|---|---|---|---|
| In the majority of men with asymptomatic mCRPC who had progressive disease as best response to first-line abiraterone or enzalutamide? | 14 | 70 | 4 | 6 | 6 | 0 | 0 |
| In the majority of men with symptomatic mCRPC who had progressive disease as best response to first-line abiraterone or enzalutamide? | 0 | 96 | 4 | 0 | 0 | 0 | 0 |
| In the majority of men with asymptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression) after use of first-line abiraterone or enzalutamide? | 27 | 57 | 10 | 4 | 2 | 0 | 0 |
| In the majority of men with symptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression) after use of first-line abiraterone or enzalutamide? | 0 | 90 | 8 | 0 | 2 | 0 | 0 |
| In the majority of asymptomatic men, progressing on or after docetaxel for mCRPC (without prior abiraterone or enzalutamide)? | 92 | 6 | 2 | 0 | 0 | 0 | 0 |
| In the majority of symptomatic men with mCRPC, progressing on or after docetaxel for mCRPC (without prior abiraterone or enzalutamide)? | 76 | 18 | 6 | 0 | 0 | 0 | 0 |

*for abiraterone, 24% for enzalutamide, and 37% had no preferred choice.*

The panellists were also asked to vote for their preferred choice between abiraterone and enzalutamide in patients with special situations (mainly comorbidities; Table 8).

*There was a consensus for abiraterone over enzalutamide in men with a history of falls (94%), significant baseline fatigue (88%), and significant neurocognitive impairment (84%). There was consensus for enzalutamide over abiraterone in men with diabetes mellitus requiring prescription drug therapy (84%; Table 8).*

*The preferred glucocorticoid regimen when starting abiraterone was prednisone 10 mg daily for 67% of panellists and 5 mg daily for 27% of the panellists. Six percent voted for dexamethasone.*

There is a retrospective analysis of patients on abiraterone plus prednisone who had PSA progression with or without progression by imaging but in the absence of clinical progression. In these patients abiraterone was continued and prednisone was switched to 0.5–1 mg dexamethasone/d. There were responses demonstrated by PSA as well as by imaging [77,78]. The level of evidence for this intervention is low.

*In men with mCRPC who are asymptomatic and have a rising PSA on abiraterone plus prednisone, 37% of the panellists voted for a steroid switch to dexamethasone in the majority of patients, 35% in a minority of selected patients, and 26% did not vote for a steroid switch.*

The pivotal trial which led to the registration and approval of docetaxel in men with mCRPC included two regimens: docetaxel 75 mg/m$^2$ every 3 wk and a weekly docetaxel schedule of 30 mg/m$^2$ (d 1, d 8, d 15, d 22, and d 29 of a 6-wk cycle) both with prednisone 10 mg daily. In contrast to the 3-weekly regimen there was no survival benefit of the weekly schedule regimen compared with mitoxantrone and the side effect profile for the weekly compared to the 3-weekly schedule was not favourable apart from a lower incidence of neutropenia [70]. A smaller phase 3 trial randomised men with mCRPC to docetaxel 3-weekly versus a 2-weekly schedule (50 mg/m$^2$ d 1 and d 15, every 28 d). There was a small benefit for the 2-weekly schedule for the primary endpoint (time to treatment failure) as well as an improvement in OS and there was a lower rate of haematological toxicity for the 2-weekly schedule [79].

*Regarding docetaxel chemotherapy for men with mCRPC there was a consensus (86%) that the 3-weekly regimen (75 mg/m$^2$) should be used, 10% voted for the 2-weekly (50 mg/m$^2$) schedule and 4% for a weekly schedule.*

The FIRSTANA trial compared cabazitaxel 25 mg/m$^2$ to cabazitaxel 20 mg/m$^2$ and to docetaxel 75 mg/m$^2$ as first-line chemotherapy in men with mCRPC. The data were presented (ASCO 2016; NCT01308567) but are not published and did not show a significant difference in OS. The PROSELICA trial was also presented at ASCO 2016 and showed noninferiority for the primary endpoint of OS for cabazitaxel 20 mg/m$^2$ compared with cabazitaxel 25 mg/m$^2$ in men with mCRPC progressing on or after docetaxel (NCT01308580).

*For cabazitaxel there was a consensus (79%) to start with the 20 mg/m$^2$ dose in the majority of patients, 59% of panellists use this dose (with dose reductions in subsequent cycles if indicated), 20% voted for starting with this dose and to escalate to 25 mg/m$^2$ in the absence of relevant side effects. Seventeen percent of the panellists voted for starting with a dose of 25 mg/m$^2$ in the majority of men.*

*In the subset of panellists who voted for cabazitaxel 25 mg/m$^2$, 57% of the panellists voted for the use of prophylactic WBC growth factors from start of therapy in the majority of patients, 26% voted for the use in a minority of selected patients, 8% voted for use of these growth factors only for marrow toxicity occurring beyond start of therapy, and 9% do not use them at all.*

*In the subset of panellists who voted for cabazitaxel 20 mg/m$^2$, 30% voted for prophylactic WBC growth factors from start of therapy in the majority of patients, 32% in a minority of selected patients, 27% only for marrow toxicity, and 11% did not vote for the use of growth factors.*

**Table 8 – What is your preferred choice between abiraterone and enzalutamide at any time in the treatment sequence in men with metastatic castration-resistant prostate cancer (mCRPC) if all options are available in case of the following medical situations?**

| What is your preferred choice between abiraterone and enzalutamide at any time in the treatment sequence in men with mCRPC if all options are available in case of the following medical situations? | Abiraterone (%) | Enzalutamide (%) | Either (%) | Neither: alternative treatment option preferred (%) | Abstain (%) |
|---|---|---|---|---|---|
| History of falls | 94 | 2 | 4 | 0 | 0 |
| Baseline significant fatigue | 88 | 6 | 6 | 0 | 0 |
| Baseline significant neurocognitive impairment | 84 | 4 | 10 | 2 | 0 |
| Stable brain metastases | 73 | 6 | 10 | 11 | 0 |
| Long QTc-syndrome or men on not replaceable drugs with potential QT prolongation | 27 | 31 | 24 | 12 | 6 |
| Asymptomatic men with a duration of response to ADT (no chemo-hormonal therapy) <12 mo | 6 | 11 | 56 | 27 | 0 |
| Cardiac ejection fraction below 45–50 | 6 | 63 | 27 | 2 | 2 |
| Active liver dysfunction | 8 | 66 | 14 | 12 | 0 |
| Diabetes mellitus requiring prescription drug therapy | 6 | 84 | 10 | 0 | 0 |

ADT = androgen deprivation therapy.

### 5.3. Combination therapy for mCRPC

In mCRPC there are currently no combination treatment strategies for survival prolonging agents that have shown an OS benefit as compared with monotherapy. A number of large randomised phase 3 clinical trials combining abiraterone with enzalutamide or other novel endocrine agents and abiraterone or enzalutamide with radium-223 dichloride are currently ongoing (eg, NCT02194842M; NCT02043678; NCT01949337). The question of combination strategies is especially relevant for radium-223, because of the lack of antitumour activity outside the bone since soft tissue and visceral metastases are not uncommon in men with APC [80].

*In men with symptomatic mCRPC and bone metastases, 18% of the panellists voted for the combination of radium-223 with either abiraterone or enzalutamide from the beginning as a first-line treatment for mCRPC for the majority of patients, 38% in a minority of selected patients, and 42% of the panellists did not vote for this combination.*

*In men with mCRPC being treated with abiraterone or enzalutamide for bone and soft tissue metastases and who are progressing only in the bone, 43% of the panellists voted for the addition of radium-223 to the majority of such patients, 39% in a minority of selected patients, and 18% did not vote for adding radium-223 in this situation.*

*In men with mCRPC treated with radium-223 and progressing outside of the bone 52% of the panellists voted for completing treatment with radium-223 plus adding abiraterone or enzalutamide (if they have not received either drug before) in the majority of patients, 20% in a minority of selected patients, and 26% did not vote for this approach.*

### 5.4. Poor prognosis, aggressive variant mCRPC

While the majority of APCs remain driven by AR signalling, it has become increasingly recognized that a subset of mCRPC tumours may adapt during the course of therapy to become less dependent on the AR, and this is associated with loss of luminal prostate cancer markers (including PSA), the development of lineage plasticity, and the acquisition or expansion of small cell/neuroendocrine pathologic and molecular features [81,82]. Identification of mCRPC variants remains challenging but is often suspected in patients that develop rapidly progressive disease, unusual sites or pattern of metastases (eg, radiologically lytic bone or parenchymal brain metastases), and/or progression in the setting of a low and not or modestly rising PSA. Metastatic tumour biopsies in this setting may show small cell carcinoma, but are not always straightforward as mixed, atypical adenocarcinoma, and hybrid neuroendocrine phenotypes may also occur [82].

*The votes of the panellists concerning factors for definition of poor prognosis, aggressive variant mCRPC are reported in Table 9. There was no consensus regarding the definition of poor prognosis, aggressive variant mCRPC. Four percent of the panellists did not believe poor prognosis, aggressive variant mCRPC is a clinically meaningful entity.*

The publication of the olaparib data in heavily pretreated mCRPC patients with DNA repair defects in the absence of an approved poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor for mCRPC has revived the interest for the use of platinum-based chemotherapy regimens, especially in later lines. The combination of carboplatin and docetaxel has shown good antitumour activity in a nonrandomised phase 2 clinical trial with patients selected for poor prognosis features [83]. A randomised phase 2 trial of cabazitaxel plus carboplatin versus cabazitaxel alone has been presented but is not published and showed significantly improved antitumour activity with the combination treatment (NCT01505868, ASCO 2015).

*Regarding first-line treatment of the majority of men with poor prognosis, aggressive variant (putting aside pure small cell carcinoma) 58% of the panellists voted for standard mCRPC treatment, 36% voted for a platinum- and taxane-based combination therapy, 4% for a platinum- and etoposide-based combination therapy, and 2% for a platinum monotherapy.*

**Table 9 – Which of the following criteria would you use to define poor prognosis, aggressive variant metastatic castration-resistant prostate cancer (mCRPC) putting aside pure small cell prostate cancer?**

| Which of the following criteria would you use to define poor prognosis, aggressive variant mCRPC putting aside pure small cell prostate cancer: | Yes (%) | Only in combination with other unfavourable factors (%) | No (%) | I do not believe poor prognosis, aggressive variant mCRPC is a clinically meaningful entity (%) | Abstain (%) |
|---|---|---|---|---|---|
| Neuro-endocrine differentiation on a tumour biopsy and/or low or absent androgen receptor expression | 71 | 27 | 0 | 2 | 0 |
| Exclusive visceral metastases | 70 | 20 | 6 | 4 | 0 |
| Rapid progression without correlation with PSA kinetics | 63 | 31 | 4 | 2 | 0 |
| Low PSA levels relative to tumour burden | 45 | 47 | 6 | 2 | 0 |
| Predominantly lytic bone metastases | 45 | 39 | 14 | 2 | 0 |
| Short response to androgen deprivation therapy (≤12 mo) for metastatic prostate cancer | 34 | 60 | 4 | 2 | 0 |
| Bulky tumour masses | 21 | 65 | 12 | 2 | 0 |

PSA = prostate-specific antigen.

### 5.5. Monitoring in men with mCRPC treated with radium-223

The phase 3 radium-223 trial (ALSYMPCA) enrolled patients with symptomatic mCRPC [72]. Patients were randomised to six injections of radium-223 administered every 4 wk or to best standard of care alone. OS was improved in the intent to treat analysis for patients randomized to radium-223 [72]. Substantial declines in PSA and/or lactate dehydrogenase were uncommon in both arms. However, alkaline phosphatase (ALP) levels showed a decline in the radium treated patients with 87% of radium treated patients showing some decline in ALP at wk 12 [84].

*In the subset of panellists who use radium-223 in men with mCRPC 43% voted for testing of PSA every cycle, 43% for every 2–4 mo; 8% voted for PSA testing only if clinically indicated, and 6% for no PSA testing in this situation.*

*Regarding ALP testing these panellists voted for either every cycle (49%) or every 2–4 mo (37%). Eight percent voted for ALP testing only if clinically indicated and 6% voted for no ALP testing.*

Since the ALSYMPCA trial did not mandate any imaging for response monitoring, the role of imaging in men treated with radium-223 is not well documented. Symptomatic and PSA flares after radium-223 have been described and can be accompanied by bone scintigraphy flare [85]. Early changes in bone scintigraphy and CT assessments tend to be unreliable for bone response assessment and must thus be interpreted with caution. In a retrospective series of 130 men treated with radium-223 that had baseline imaging and monitoring by imaging after three and six cycles, the results showed a significant rate of progression outside of the bone detected by CT scanning [85].

*In the subset of panellists who use radium-223 in men with mCRPC there was consensus (75%) to use CT and bone scintigraphy for staging and monitoring of men on radium-223, while 23% of the panellists voted for one of the next-generation imaging methods. Regarding imaging frequency for men treated with radium-223, 41% of these panellists voted for every 3–4 mo, 27% voted for imaging after 6 mo (completion of radium-223) and every 3–4 mo thereafter, 24% voted for imaging after 6 mo (completion of radium-223) and follow-up imaging at progression, 4% voted for imaging only as clinically indicated.*

### 5.6. "Oligo-progressive" mCRPC

With the introduction of abiraterone and enzalutamide as first-line treatment for asymptomatic men with mCRPC, there are men in whom, for example, a single lymph node progresses in size with radiological stability of the other lesions. The term oligo-progressive is not well-defined in APC but in lung cancer patients on novel targeted agents such as anaplastic lymphoma kinase (ALK) inhibitors there is growing literature on definition and treatment strategies for oligo-progressive disease [86].

*There was no consensus as to the most meaningful definition of oligo-progressive prostate cancer (mCRPC). Forty percent of the panel voted that they did not believe in oligo-progressive disease as a meaningful clinical entity, 33% voted for the definition of only one progressing pre-existing lesion with otherwise stable/responding metastatic disease, 23% voted for $\leq$3 progressing pre-existing lesions with otherwise stable/responding metastatic disease.*

*The subset of the panel who believed in oligo-progressive mCRPC voted on biopsy of a progressing lesion (for diagnostic purposes). Twenty-nine percent of the panellists voted for a biopsy in the majority of patients, 52% for a biopsy in a minority of selected patients (eg, from visceral metastases), while 19% did not vote for a biopsy. These panellists also voted on the treatment for men with oligo-progressive mCRPC: 40% voted for a change or addition of systemic therapy without local treatment, 47% for local treatment of the progressing lesion(s) while continuing systemic therapy unchanged, and 13% for local treatment of the progressing lesion(s) plus adding or changing the systemic treatment.*

### 5.7. Discussion of CRPC

We have witnessed the successful development of agents including the novel androgen signalling inhibitors abiraterone and enzalutamide for earlier stage mCRPC. More recently, a significant survival advantage by introducing docetaxel treatment in the castration-naive state was confirmed. It thus appears that we are moving our therapies earlier in the disease, while the question of optimal sequencing of the treatment options is still unanswered. We know that a distinct subset of patients will not respond to treatment also depending on the sequence, or may experience unwarranted toxicity. Moreover, it is possible that with the appropriate sequencing we may augment the OS benefit of our patients.

Treatment sequencing in APC is governed by a number of parameters that unfortunately do not yet serve the ultimate goal of maximizing clinical outcome. Clinical decision-making is still largely dependent on local reimbursement policies and on a number of variables that are not truly objective. There are no validated clinical or molecular predictive markers for guiding our choice thus predetermining a more favourable cost/benefit ratio for our patients. Increased benefit is encompassing longer life with improved quality whereas minimising cost including components such as toxicity, financial burden, and uncertainty. Choices made in the clinic are in part based on objective data such as available level I evidence and access to agents. Yet, professional speciality and experience affect these choices. The presence or absence of symptoms clearly influenced treatment selection for the panellists.

We are also being challenged by the as-yet unproven hypothesis that combinatorial approaches may enhance outcome by potential synergistic activity or delay of resistance to treatment. We are anticipating results from several relevant phase 3 trials and should therefore avoid implementation of such approaches as long as they are unproven especially since concerns for toxicity arise.

Regarding the aggressive variant of CRPC, the majority of the panel recognises its existence and that it is important to recognise it since these patients may be less likely to respond to subsequent AR-directed therapies; however,

there was no consensus for the exact definition. With a more profound and eventually earlier suppression of AR pathways in the disease history, identifying and treating AR independent variants will become increasingly important [87]. The development of robust biomarkers is an area of active research. We may need a combination of clinical and molecular features to identify aggressive variants, encompassing but not limited to those with neuroendocrine carcinoma morphology detected on biopsy, as targeted treatment approaches based on a molecular subclassification of APC are developed. Understanding the role of DNA repair in contributing to the phenotype, mediating response to PARP inhibition, and also platinum sensitivity and potential immunotherapy treatment sensitivity is also important.

## 6. Imaging in APC

Reproducible and validated methods for detecting and quantifying metastatic disease are needed to manage patients with APC. Currently, recommended methods of metastatic imaging assessment, that is, with bone scintigraphy and CT scans, have significant limitations in detecting metastases as well as in monitoring response to treatment but remain the standard of care in most settings [1,21,88–91]. Due to limitations in systematically conducted prospective studies, the use of next-generation imaging has not been shown to impact on clinical outcome.

### 6.1. Nodal disease assessments in APC

Morphologic assessments for possible nodal disease using CT and MRI scans are based on the evaluation of detected nodes based largely on size criteria. Other morphologic criteria, such as the nodal shape, loss of nodal hilum fat, clustering, extranodal disease, and enhancement characteristics can serve as additional aids to diagnosis. Unfortunately, morphologic imaging is unable to identify micrometastases or to distinguish large hyperplastic benign from malignant nodes. Thus, the general test performance of morphologic imaging remains limited when histologic correlations using template lymphadenectomy are used as the standard of reference. A meta-analysis showed a CT scan sensitivity of 42% and specificity of 82%, while morphologic MRI had a sensitivity of 39% and a specificity of 82% [92]. While positron emission tomography (PET)/CT has improved sensitivity, it is important to keep in mind that the spatial resolution of PET/CT is approximately 4 mm.

### 6.2. Bone disease assessments in APC

For the sensitive detection of metastatic bone disease, the use of current recommendation of bone scintigraphy and CT scans has low sensitivity and specificity [93].

Systematic analyses, prospective clinical studies, and meta-analyses have shown comparative test performance of whole-body diffusion weighted MRI (WB-MRI) to NaF and choline PET/CT for the skeletal assessments in APC [94,95]. A recent meta-analysis underlined the usefulness of WB-MRI as a method that improves the MRI detection of bone metastases [96]. When evaluating the results of the above meta-analyses and indeed in all studies reporting test performance, the readers should note that there are intrinsic verification biases that are particularly prevalent at lesion level analyses, because it is not possible to obtain histopathology for every bone lesion detected. As a result, most studies are patient level analyses, using combinations of imaging methods and/or follow-up as the standards of reference [93,94].

PET/CT can detect a larger number of skeletal lesions than bone scintigraphy [97]. Regarding the PET/CT tracers comparative studies between prostate-specific membrane antigen (PSMA) and choline have demonstrated superiority of PSMA to identify bone lesions [98]. The PET tracer $^{18}$F-fluciclovine has recently been approved for use in North America; available data indicate good detection rates both for lymph nodes and for bone disease in biochemical recurrence of prostate cancer [99]. The diagnostic performance of fluciclovine PET was found to be superior to CT and to choline PET but there are no comparative data versus WB-MRI and PSMA PET [100].

Importantly, all our prognostic models and clinical trials in APC were developed using CT scan and bone scintigraphy and the essence of detection of disease at diagnosis is one of risk determination. Next generation imaging may have superior performance characteristics compared with older modalities, but clinical validation with regard to the question of impact on outcome has not yet been performed.

### 6.3. Imaging for locally advanced prostate cancer

In men presenting with high-risk or locally advanced prostate cancer and with biochemical recurrence after local therapy, imaging to document potential metastases may be important. At this state of the disease metastases are most commonly located within regional (N1) and nonregional lymph nodes as well as in bone (M1).

*There was no consensus regarding the imaging modality to "exclude" distant metastases in high-risk and locally advanced prostate cancer: 41% of the panel voted for a combination of CT and bone scintigraphy, while 47% of the panel voted for next-generation imaging methods (37% voted for a PET/CT with any of the tracers PSMA, choline, or fluciclovine and 10% voted for a WB-MRI).*

### 6.4. Imaging in the setting of BCR (PSA)

Clinical symptoms and PSA alone are not good indicators for absence of metastases, with 32% of clinical M0 CRPC patients being found to be metastatic when imaging was performed [101].

Regarding PET/CT in BCR, a meta-analysis including both C-11 and F-18 choline-based techniques reported detection rates greater than 50% for PSA values above 2 ng/ml, with rapid PSA kinetics and elevated Gleason score positively related to higher detection rates [102–105]. The main limitation of choline PET/CT is the low sensitivity when PSA values are $<$1 ng/ml. In BCR there are comparative studies

between Ga-PSMA and choline demonstrating the superiority of Ga-PSMA in terms of detection rates at any PSA level [106–108]. Guidelines (NCCN, EAU) have mentioned choline PET/CT in the situation of BCR [21,22].

The use of next-generation imaging modalities has led to identification of metastatic foci at lower PSA levels. Treating physicians may feel more comfortable offering ablation of limited metastases in these cases, but as of now there are no prospective data to show that earlier detection of metastatic disease with next-generation imaging results in a meaningful long-term clinical improvement.

*Imaging in men with rising PSA after RP before starting SRT was voted for by 44% of the panellists in the majority of patients independent of PSA level, by 29% of panellists in men with a PSA >0.5 ng/ml, by 12% of the panellists in men with a PSA >1 ng/ml and by 13% of the panellists in men with a PSA >2 ng/ml.*

*For imaging in men with oligometastatic recurrent disease after local treatment for prostate cancer with curative intent (± SRT), 78% of the subset of panellists who believed in the oligometastatic recurrent state voted for one of the next-generation imaging methods to detect metastatic disease: namely 47% voted for a PET/CT (PSMA, choline, or fluciclovine) alone, 2% voted for a WB-MRI alone, 25% of the panel members voted for a combination of a pelvic MRI and a PET/CT, 4% of the panellists voted for a combination of a pelvic MRI and a WB-MRI, and 22% of the panellists voted for imaging by CT and/or MRI and bone scintigraphy.*

*In men with de novo apparent oligometastatic disease, 72% of the subset panellists who believed in the oligometastatic state voted for one of the next-generation imaging methods to support this diagnosis (apart from local staging): namely 34% voted for a PET/CT (PSMA, choline, or fluciclovine), 4% voted for a WB-MRI, 34% voted for either a PET/CT or WB-MRI, and 26% of these panellists voted for imaging by CT and/or MRI and bone scintigraphy.*

*Asked about the recommended tracer in case of a PET/CT in men with apparent oligometastatic castration-naïve disease, there was a consensus (76%) amongst the panel members for PSMA as tracer, 10% voted for fluciclovine as a tracer, and 6% voted for choline; 4% of the panellists voted for any of the three tracers.*

*In men with rising PSA on ADT (CRPC) and potentially oligometastatic disease, 74% of the subset of panellists who believe in oligometastatic disease in mCRPC voted for one of the next-generation imaging methods to confirm this diagnosis: namely 48% voted for a PET/CT (PSMA, choline, or fluciclovine), 6% voted for a WB-MRI, 18% of the panel members voted for a combination of a pelvic MRI and a PET/CT, 2% of the panellists voted for a combination of a pelvic MRI and a WB-MRI, and 26% of the panellists voted for imaging by CT and/or MRI and bone scintigraphy.*

### 6.5. Staging and monitoring in mCNCP

In mCNPC, what is required is an imaging modality that confirms the presence of metastases and defines their location. This is important for assessing prognosis and for treatment decisions. Current guidelines (NCCN, EAU) do not comment on imaging methods for men with mCNPC because of lack of data.

*In mCNPC, 51% of the panel voted for baseline imaging and follow-up imaging at PSA nadir/completion of six cycles of docetaxel as part of chemo-hormonal therapy and again at progression (confirmed PSA rise and/or clinical progression), 31% of the panel voted for baseline imaging and regular monitoring by imaging every 3–6 mo, and 18% of the panel voted for baseline imaging only and monitoring by PSA alone with further imaging at progression.*

*Regarding the recommended imaging modality for staging and monitoring of men with mCNPC, 73% of the panel voted for CT and bone scintigraphy and 25% of the panellists voted for one of the next-generation imaging methods.*

### 6.6. Staging and monitoring in mCRPC

The early identification of treatment failure in men with mCRPC on systemic therapy would help in sparing some patients futile treatment and potential toxicity as well as in reducing the costs of ineffective treatments and decreasing the time to initiation of a next-line, potentially effective treatment [110]. Recent data indicate that there are a substantial number of patients who have radiographic progression without PSA progression, including some patients with aggressive variant prostate cancer [111]. Imaging before treatment initiation and on-therapy may be important in predicting both benefit and more importantly nonbenefit of treatments.

An ideal imaging method to monitor response to therapy should enable the evaluation of tumour cell viability, especially for bone disease. Techniques such as bone scintigraphy, CT scans, and NaF PET rely on tumour matrix interactions and are only indirect indicators of tumour cell viability. Imaging assessments should always be combined with clinical status and other factors as also recommended by the PCWG3 group [109].

*For monitoring by imaging in men with mCRPC on first-line therapy, 54% of the panel voted for baseline imaging and regular monitoring by imaging every 3–6 mo, 28% of the panellists voted for baseline imaging and follow-up imaging at PSA nadir and again at progression (confirmed PSA rise and/or clinical progression); 16% of the panel voted for baseline imaging only and monitoring by PSA alone with further imaging at progression.*

*Regarding imaging modality for staging and monitoring in men with mCRPC, 74% of the panel voted for CT and bone scintigraphy and 24% of the panellists voted for one of the next-generation imaging methods.*

*For monitoring of patients with a diagnosis of aggressive variant mCRPC, 62% of the panellists voted for standard imaging by CT and bone scintigraphy, 2% voted for CT alone, and 36% voted for next-generation imaging modalities.*

### 6.7. Discussion of imaging in APC

There are sufficient data indicating that next-generation imaging technologies have better accuracy for detecting metastases than CT and bone scintigraphy. However, their

current use is dependent on costs, local availability, and expertise of interpretation and the better accuracy has not been shown to correlate with improvement of clinical outcomes.

The performance of PET/CT with new tracers (PSMA and fluciclovine) as indicators of treatment efficacy and as predictors of patient outcome has yet to be assessed. PSMA PET/CT should be interpreted with caution since there are data suggesting correlation between PSMA expression and AR signalling [112–117]. Tumour foci not expressing PSMA (or lesions in organs with high PSMA expression, eg, liver) may not be assessable for response using PSMA PET/CT. Notably, other tumour types (eg, lung cancer, renal cell cancer) and nonmalignant processes like Paget's disease and haemangioma can express PSMA [118,119].

The use of these next-generation imaging modalities may be especially valuable in situations where the tumour burden assessments are needed for treatment decisions and/or when high sensitivity is a requirement. This may be particularly applicable when multimodality salvage therapy is being considered. However, the proof that their use leads to better treatment decisions and ultimately leads to improved outcomes is pending also in this situation.

For evaluation of response in men with mCRPC it is evident that next-generation imaging (MRI and PET) may prove to be more accurate for evaluating response to treatment [120]. However, it should be noted that the recently published PCWG3 do not recommend the routine use of next-generation imaging methods for men with APC treated on clinical trials mainly due to the lack of availability, outcome data, and standardisation across global sites [109]. The recently published guideline on reporting WB-MRI in men with APC is a step into the right direction but these recommendations need to be adopted, applied, and validated in clinical trials with primary endpoint of clinical outcome [88]. As an example, the systematic evaluation of FDG-PET studies in patients with Hodgkin's disease has resulted in a reduction in treatment intensity leading to reduction of toxicity [121]. Such trials with next-generation imaging are largely missing in men with APC [122].

The clinical introduction of potentially impactful imaging technologies has created an opportunity for progress by linking anatomy to underlying biology but there is also a risk of up-staging of many men in every disease state. The contribution of the next-generation imaging techniques to the welfare of patients depends on performance for the purpose they are being applied (''fit for use'') and their clinical utility (patient benefit). The early assessment of new technologies is therefore encouraged but their general acceptance before measures of performance and evidence of benefit are at least estimated should not be supported. Novel imaging techniques should be clinically deployed ideally in a trial setting but at least in registries with the goal of efficiently estimating performance and utility. Finally, it is important to recognise that the clinical trials that form the basis of the currently approved treatment options are based on evaluations with CT and bone scintigraphy.

## 7. Use of osteoclast-targeted therapy for SRE/SSE prevention for mCRPC (not for osteoporosis/bone loss)

In prostate cancer, two bone-directed agents, zoledronic acid and denosumab have been shown to prevent or delay the onset of SREs. Neither of the drugs influences OS or PFS significantly [123,124].

Of the bisphosphonates, zoledronic acid is the only one that has shown a protective effect against SRE in patients with mCRPC [124,125]. Denosumab is a fully human monoclonal antibody that specifically targets receptor activator of nuclear factor kappa-B ligand thus effectively inhibiting osteoclast function and bone resorption. In the setting of mCRPC, denosumab (120 mg subcutaneous every 4 wk) compared with zoledronic acid (4 mg intravenous every 4 wk) significantly improved the time to first SRE [123].

At the present time, these agents have proven relevant efficacy only in patients with bone mCRPC. There is no evidence to support their use in the nonmetastatic CRPC setting and there is evidence **not** to use it in the mCNPC setting apart from osteoporosis prevention, using a different regimen, and dosage for both drugs [43,126,127].

When looking at SSE, two prospective randomised studies in men with mCRPC demonstrated an advantage. The TRAPEZE study showed a significant delay in SSEs when docetaxel was combined with zoledronic acid as compared with docetaxel alone and that the combination was safe, but there was no improvement in OS [128]. Interestingly, the benefit in delaying SSEs was in the same range as what was seen in the pivotal zoledronic acid study when chemotherapy was not in use. Also, the recent analysis of the large pivotal denosumab trial confirmed a benefit in preventing SSEs [129]. Hypothesis-generating results have been presented from the ALSYMPCA trial where the subgroup of patients receiving a combination of radium-223 plus an osteoclast targeted therapy had a reduction in SSE compared with radium-223 alone [72,130].

In an era of life prolonging therapies for mCRPC that can also prevent or delay SREs, the added benefit of osteoclast-targeted therapy is difficult to estimate given the limited number of well designed, adequately powered studies with long term follow-up.

Regarding the frequency of administration of these bone-directed agents a recent randomised trial in different tumour types also including 689 men with prostate cancer showed no increased risk of skeletal events with zoledronic acid every 12 wk compared with every 4 wk [131]. However, the proportion of patients with CNPC versus CRPC is not reported and both were accrued to the trial. No firm conclusions can be made from this trial because of this variable.

*For reducing the risk of skeletal complications in men with mCRPC and bone metastases, 86% of the panel were in favour of some form of osteoclast-targeted therapy, 54% of the panel voted for denosumab, 8% voted for zoledronic acid, 24% of the panellists voted for either zoledronic acid or denosumab, and 10% did not vote for an osteoclast-targeted therapy at all.*

*Of those panellists who voted for an osteoclast-targeted therapy in men with mCRPC, 68% voted for a treatment*

*duration of about 2 yr and 32% voted for no limitation of treatment duration.*

The question of frequency and duration of osteoclast-targeted therapy in the absence of significant toxicity for asymptomatic men with mCRPC and bone metastases responding to first-line systemic mCRPC treatment is not resolved.

*In the subset of panellists who voted for osteoclast-targeted therapy in men responding to first-line mCRPC therapy, 17% of the panellists voted for every 4 wk without a defined maximum duration, 37% voted for every 4 wk for approximately 2 yr and then less frequently, 15% voted for every 3 mo, and 27% of the panel did not vote for an osteoclast-targeted therapy in this situation. In the same patient population, but when these men are no longer responding to first-line therapy, 27% of the panellists voted for osteoclast-targeted therapy every 4 wk without a defined maximum duration and 53% of the panel voted for every 4 wk for about 2 yr and then less frequently.*

Osteonecrosis of the jaw (ONJ) is a possible severe side effect of osteoclast-targeted therapy that increases with the duration of treatment [132,133]

*In men with mCRPC who develop ONJ while on osteoclast-targeted therapy, there was consensus (84%) to discontinue osteoclast-targeted therapy permanently while 16% of the panellists voted for discontinuation of the osteoclast-targeted therapy and restarting after complete wound healing.*

### 7.1. Discussion of the use of osteoclast-targeted therapy for SRE/SSE prevention for mCRPC

The optimal timing, schedule, and duration for osteoclast-targeted therapy and the overall balance of benefit and risk as well as efficacy in the era of novel mCRPC treatments are still a matter of debate as there is no Level I evidence to guide decision making.

Effective osteoclast inhibitors are commonly recommended as part of the overall therapeutic approach to mCRPC also in an era of multiple life prolonging agents. Their use in combination with approved life prolonging mCRPC treatments may enhance their utility in terms of reducing the risk for of skeletal complications and to maintain quality of life—but these data have been derived from posthoc and subgroup analyses and need to be addressed in prospective clinical trials. In daily clinical practice, the risk of side effects—especially ONJ—which increases with duration of therapy, by the early use of osteoclast-targeted therapy for men with mCRPC has to be weighed up against the potential benefit of reduction in risk of SRE/SSE [133].

## 8. Molecular characterisation

### 8.1. Tumour biopsy in APC

Since clinical heterogeneity is common, mCRPC tumour biopsies should be reviewed and interpreted in the appropriate clinical context. This is especially important for uncommon yet challenging cases with small cell or neuroendocrine differentiation or tumours that lack expression of classical prostate markers such as PSA or AR. Furthermore, not all patients with clinical features suggestive of androgen independence demonstrate small cell or neuroendocrine features on tumour biopsy although they may still benefit from platinum based chemotherapy. These data may potentially be explained by molecular overlap with neuroendocrine prostate cancer [81,134].

Moving forward, incorporating molecular biomarkers will likely improve the clinical diagnosis of non-AR driven mCRPC and may help in patient selection for current therapies and selection for biomarker stratified clinical trials [134–140]. Genomic alterations enriched in mCRPC with emerging prognostic and/or treatment implications include *AR* gene mutation and amplification, phosphoinositide 3-kinase/Akt/phosphatase and tensin homolog pathway alterations, DNA repair defects including loss of homologous recombination (eg, BRCA1/2, ATM), and mismatch repair (with microsatellite instability [MSI] and hyper-mutated phenotype), TP53 deletion/mutation, and RB1 loss [134,140–144]. Alterations involving RB1 and TP53 are universal in small cell cancers arising elsewhere in the body, such as lung cancer, and are enriched in prostate cancer patients with luminal to basal cell lineage switching and neuroendocrine biomarker expression and are mechanistically involved in the development of "androgen indifferent" resistance [136,139,140,143].

The panel voted on molecular factors that should be reported in a tumour biopsy in men with mCRPC apart from reporting tumour morphology (Table 10).

*There was a consensus (78%) that BRCA1, BRCA2, and ATM mutations should be reported because that knowledge will likely influence management decisions. For all other factors there was no consensus (Table 10).*

### 8.2. Androgen receptor splice variant-7 and AR amplification/mutation

Using liquid biopsies in mCRPC patients starting abiraterone or enzalutamide, statistically significant associations with worse outcome have been reported for detection of AR splice variants including the AR-V7 transcripts in circulating cells or in exosomes, AR-V7 protein in the circulating tumor cell nucleus, or by analysing plasma cell-free DNA *AR* gene copy number gain assessed via cell-free DNA or somatic point mutations similarly quantified [145–150]. All studies to date were single-arm trials, and statistically significant associations with response were noted—although the correlation with response has focused largely on rates of PSA declines. Moreover, evidence remains that some men with AR-V7 positive mCRPC may still respond to abiraterone/enzalutamide.

*There was a consensus (96%) not to use AR-V7 testing in daily routine clinical practice for the majority of men with mCRPC. Similarly, there was a consensus (92%) not to use cell-free DNA AR amplification and AR mutation testing in daily routine clinical practice for the majority of men with mCRPC.*

**Table 10 – As a clinician, which factors do you want to have reported back to you in men with metastatic castration-resistant prostate cancer who undergo a metastatic tumour biopsy apart from tumour morphology and differentiation? The question is only about management for a specific patient, not about familial implications, and based on knowledge in terms of test accuracy/validity and available treatments**

| Factor | Yes, useful test for majority of patients (influences your management decision; %) | Only for minority of selected patients (%) | No (%) | Abstain (%) |
|---|---|---|---|---|
| BRCA1, BRCA2, and ATM mutations | 78 | 20 | 2 | 0 |
| PSA IHC | 72 | 18 | 10 | 0 |
| Other DNA repair genes (eg, *CHEK2*, *PALB2*, and others) | 64 | 22 | 12 | 2 |
| MMR gene alterations (MSI, MMR protein IHC, or by direct sequencing) | 54 | 22 | 20 | 4 |
| Chromogranin, synaptophysin, CD56/NSE | 50 | 31 | 17 | 2 |
| Loss of PTEN | 44 | 26 | 26 | 4 |
| AR amplification and/or AR mutation | 43 | 18 | 37 | 2 |
| TP53 and RB1 | 34 | 22 | 40 | 4 |
| Nuclear AR | 34 | 18 | 46 | 2 |
| AR-V7 | 33 | 26 | 37 | 4 |
| PSMA | 32 | 22 | 44 | 2 |
| Ki67/MiB1 | 28 | 26 | 42 | 4 |
| Prostate acid phosphatase | 26 | 18 | 54 | 2 |
| PD-1/PD-L1 | 22 | 31 | 45 | 2 |
| NKX3.1 | 12 | 33 | 49 | 6 |
| ERG IHC | 12 | 30 | 56 | 2 |
| ERG FISH | 11 | 23 | 64 | 2 |

AR = androgen receptor; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry; MMR = mismatch repair; MSI = microsatellite instability; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; PTEN = phosphatase and tensin homolog.

### 8.3. Somatic mutations

Recent genomic studies of metastatic prostate cancer have identified new molecular targets in the AR signalling pathway, phosphoinositide 3-kinase pathway, WNT pathway, cell cycle pathways, and perhaps most importantly, in DNA repair pathways [135,141,151].

*Fifty-nine percent of the panellists did not vote for DNA sequencing of tumour biopsies in the majority of men with mCRPC in routine daily clinical practice, 37% of the panellists voted for a targeted/panel sequencing approach, and 4% voted for whole genome or exome sequencing.*

### 8.4. DNA repair testing in daily routine clinical practice

Recent studies have shown that men with APC commonly have somatic aberrations of genes that make up various elements of the DNA repair machinery with 20–30% of APCs having loss of function of proteins implicated in homologous recombination repair, including *BRCA2*, *BRCA1*, *ATM*, *PALB2*, and others [141]. These aberrations lead to homologous recombination deficiency (HRD) detectable by next-generation sequencing of these genes or of the genomic scars resulting from this repair defect estimated as an HRD score. A clinical trial (TOPARP) of the PARP inhibitor, olaparib, has shown antitumour activity against prostate cancers with HRD [142].

HRD defects have been previously reported to sensitise tumour cells to platinum-based chemotherapy [152]. Clinical data are now emerging that HRD defects in prostate cancers also sensitise to platinum-based chemotherapy [153] in keeping with previous reports that satraplatin has antitumour activity against this disease [76,154].

Somatic deleterious aberrations of mismatch repair genes (*MSH2*, *MSH6*, *MLH1*, *PMS2*) have been found in APC, and are possibly associated with ductal pathology, although their precise frequency remains uncertain and is in the range of 5% to 15% [144,155,156].

#### 8.4.1. DNA repair defects in CNPC

*The presence of DNA repair defects (germline or somatic) in men with newly diagnosed mCNPC does not change the standard treatment recommendation for 49% of the panel. Twenty-three percent of the panellists were more likely to give docetaxel in addition to ADT and 22% of the panel were more likely to include a platinum agent in the chemo-hormonal treatment regimen.*

#### 8.4.2. DNA repair defects in mCRPC

*When testing for DNA repair defects was considered for men with mCRPC, and no recent mCRPC tissue biopsy tissue was available, 70% of the subset of panellists who supported testing in this situation voted for a fresh mCRPC tumour biopsy, 16% of the panellists voted for testing in archival tissue, and 14% voted for testing in circulating cell-free DNA.*

*Sixty-five percent of the panel voted for treatment with olaparib, or another PARP inhibitor if available and approved, in men with mCRPC and the presence with DNA repair defects (germline or somatic) based on the phase 2 data with olaparib, 29% of the panel voted for such treatment in a minority of selected patients and 4% did not vote for it at all.*

*Some panel members voted that it was appropriate to extrapolate the phase 2 data from olaparib to platinum agents for men with mCRPC and presence of DNA repair defects (germline or somatic): 45% in the majority of patients and 14% in a minority of selected patients; however 35% of the panellists did not support this extrapolation.*

*Sixty-seven percent of the panel voted for standard first-line mCRPC therapy in men with mCRPC and presence of DNA repair defects (germline or somatic) progressing on ADT, 21% of the panellists voted for a platinum-based combination, and 10% for a PARP inhibitor.*

*In men with mCRPC and a presence of DNA repair defects in the second-line setting (after standard first-line therapy), 40% of the panellists voted for a platinum-based combination, 33% of the panel voted for standard second-line mCRPC treatment, 21% for treatment with a PARP-inhibitor, and 4% for a platinum monotherapy.*

### 8.5. Discussion of molecular characterisation

Given men with mCRPC are surviving longer, and with several treatment options available, biopsies of metastatic lesions are more commonly pursued to rule out small cell carcinoma, an aggressive variant, or a second malignancy. But the real place for metastases biopsy remains unclear in everyday practice. With a multitude of potential predictive and prognostic markers that can be tested in a mCRPC tumour biopsy, it is important to provide some guidance. As of March 2017, there was only consensus from the panel for testing of *BRCA1*, *BRCA2*, and *ATM* mutations in mCRPC tissue.

Several registration trials are now being conducted with different PARP inhibitors for men with APC and evidence of DNA repair defects (eg, NCT02952534, NCT02975934, NCT02854436, NCT03012321) and in the absence of approved PARP inhibitors for mCRPC, enrolment of men in clinical trials is strongly recommended.

Additionally, there are also prospective trials of platinum-based therapy ongoing in men with advanced molecularly selected prostate cancers, which may demonstrate that this is an important therapeutic strategy for this subgroup of patients (eg, NCT02598895, NCT02311764, NCT02955082).

Although true MSI is rare in prostate cancer, its presence is important because MSI+ cancers have a high rate of durable responses to immune checkpoint blockade using drugs that block the programmed cell death-1/programmed death-ligand 1 interaction [157]. Based on 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-center, single-arm clinical trials pembrolizumab has been approved by the FDA for use in MSI high and dMMR cancer patients regardless of histology. This approval is of clear interest to clinicians and to patients with prostate cancer and evidence of these alterations.

Although a proportion of the panel voted for using a PARP inhibitor or platinum-based chemotherapy in mCRPC, even in the first-line setting, there is no evidence that such a strategy is of advantage as compared with the standard approved mCRPC treatments to date. Therefore, in the absence of prospective randomised trials showing clinical benefit for a strategy using a PARP-inhibitor or a platinum-based chemotherapy, the use of these substances as first-line mCRPC treatment outside of clinical trials should not be generally recommended.

For the liquid biomarkers, namely AR-V7 and AR mutation or amplification, there was a consensus that currently none of these markers should be tested in routine practice for decision making. This consensus against testing is in part based upon the low detection levels of AR-V7 prior to first- and second-line therapies and the high probability that patients would receive abiraterone or enzalutamide in this situation. These tests need to be validated and further studies need to be performed to determine their impact on long-term outcomes.

## 9. Germline genetic counselling/testing

The aetiology of prostate cancer is not well understood, although epidemiological studies demonstrating a convergence of incidence rates in some populations migrating between areas with a low incidence to those with high incidence suggest environmental and lifestyle risk factors play a role [158]. Having a positive family history and/or a certain ethnic background such as Afro-Caribbean is a risk factor for prostate cancer development. Evidence from studies where monozygotic twins were compared with dizygotic twins suggest that 57% of the risk of prostate cancer prostate cancer is due to genetic factors [159]. Numerous studies of risks to relatives of prostate cancer cases show a higher relative risk of developing prostate cancer, which increases as the age of the proband decreases, and the number of affected relatives increases. First degree relatives of prostate cancer patients have twice the risk of developing the disease compared with the general population [160]. In men diagnosed under the age of 60 yr, the risk to their first degree relatives is more than fourfold that of those without a family history [161]. The variation in incidence according to ethnicity also suggests a genetic component; rates are higher in African American men compared with Asian-American men [162].

Studies of familial inheritance and segregation analyses have proposed various genetic models (autosomal dominant, recessive, and X-linked) [163]. It is now recognised that genetic predisposition to prostate cancer is composed of common (>5%) lower risk variants single nucleotide polymorphisms—most of which are not in coding regions and rare higher risk variants (coding mutations in genes). Over 100 single nucleotide polymorphisms associated with the development of prostate cancer have been identified thus far [164].

Rarer variants are those which have a minor allele frequency of <5%, and occur too infrequently to be detected on a genome-wide association study. Next-generation sequencing of targeted areas or whole genome/exome sequencing has enabled the detection of these rare variants. Results showed that men from families where females had developed breast and ovarian cancer caused by *BRCA* mutations have a five-fold relative risk of prostate cancer when they harbour a germline *BRCA2* mutation compared with men without a mutation. This relative risk increases to up to seven-fold if the men in the family develop prostate cancer below the age of 65 yr [165]. In a larger study, 2000 men with prostate cancer were screened. This showed

that just over 1% of men who developed prostate cancer below the age of 65 yr carried a deleterious *BRCA2* mutation and often they did not have a positive family history [166]. For men who are carriers of a *BRCA1* mutation, studies have shown that there is an approximately four-times relative risk of developing prostate cancer for men aged under 65 yr compared with those without the mutation [167]. It has been subsequently shown in men with a family history of at least three cases of prostate cancer that they have a germline mutation in DNA repair genes in 7.3% and that the disease was more likely to be aggressive [168].

Several groups have shown that *BRCA1* and *BRCA2* mutation carriers have a more aggressive form of prostate cancer and also have a worse prognosis [169,170]. Mutation carriers are also likely to present with a higher risk of local nodal involvement as well as with distant metastatic disease [171]. The optimal radical treatment option for these patients is yet to be determined, but RP may be the most suitable, although the numbers of patients studied are relatively small [172].

Remarkably, germline mutations have been found in about half of the men with tumour HR DNA repair gene defects and about one in five men with an mismatch repair DNA repair gene defect [141,173]. In a large multi-institutional study of almost 700 men with metastatic prostate cancer unselected for age or family history, 11.8% overall were found to have moderate or high penetrance germline mutations in one of 16 DNA repair genes, with 7.8% of mutations in *BRCA2*, *BRCA1*, and *ATM* [173]. Two large single-institution studies of metastatic prostate cancer found similar rates of germline *BRCA2*, *BRCA1*, and *ATM* mutations, with much lower rates in low risk indolent disease [174,175].

*Regarding genetic counselling and testing for men with newly diagnosed metastatic prostate cancer, 20% of the panel voted to do it in a majority of patients: 62% of the panel voted in favour of genetic counselling/testing in a minority of selected patients and 18% did not vote to do it at all.*

*The subset of panellists who had voted for genetic testing in a minority of selected patients supported genetic counselling and testing in men with a positive family history for prostate cancer (95%); also, 93% of these panellists supported counselling/testing in men with a positive family history for other cancer syndromes (eg, hereditary breast and ovarian cancer syndrome and/or pancreatic cancer or Lynch syndrome). Further, 74% of these panellists voted for genetic counselling and testing in men with prostate cancer diagnosed at ≤60 yr but 26% of these panellists did not vote for genetic counselling and testing based on an age cut-off alone.*

*Among the subset of panellists who recommended genetic testing, 61% voted for large panel testing including homologous recombination and mismatch DNA repair (eg, comprehensive cancer risk assessment panels), 15% voted for BRCA1 and BRCA2 testing only, 15% voted for BRCA1, BRCA2, and ATM testing, and 9% voted for large panel testing including homologous recombination DNA repair (eg, panels that are also used to assess breast cancer risk).*

*There was a consensus (92%) that in the presence of a germline BRCA1, BRCA2, or ATM mutation a prophylactic RP was* ***not*** *recommended.*

*The panel was asked whether the presence of a germline BRCA1, BRCA2, or ATM mutation would influence their treatment decision in men with low-risk localised prostate cancer. Forty-five percent voted against active surveillance in these patients, 35% voted for standard treatment options (including active surveillance), and 20% voted for another treatment option.*

*The panel was asked whether the presence of a germline BRCA1, BRCA2, or ATM mutation would influence their treatment decision in men with intermediate- or high-risk localised prostate cancer. Fifty-two percent of the panel voted for a RP over RT, 44% of the panel voted for standard recommendations, and 4% voted for RT over a RP.*

### 9.1. Discussion of germline genetic counselling/testing

The understanding of the role of genetics in prostate cancer development is evolving rapidly, which is reflected by the fact that 20% of the panellists recommended genetic counselling and testing in a majority of men with metastatic prostate cancer irrespective of family history. Age at diagnosis itself does not seem to be the best selection marker, but 74% of the panel who recommended genetic counselling and testing in selected patients would test in men aged ≤60 yr. The impact of a *BRCA2* germline mutation on the management in an otherwise healthy man is not clear and in the absence of any prospective data there was a consensus not to recommend prophylactic RP in such men.

Currently, for prostate cancer care providers ordering germline genetic cancer panel testing or ordering this testing in the near future, there are several important points to consider including which genes to test for. There are emerging prostate cancer practice recommendations only for *BRCA1*, *BRCA2*, and *ATM* mutations, yet most next-generation sequencing cancer panels include many more DNA repair genes for the same cost. There are currently no gene-specific data on treatment predication or prostate cancer risk for most DNA repair genes. Germline genetic testing should be ordered with adequate pretest and/or posttest genetic counselling. In particular, there is a need to counsel about the possibility of a variant of uncertain significance (VUS) being detected and/or a pathogenic mutation in a gene in which there are not adequate data to alter management for prostate cancer. Patients with VUS should be managed the same as patients with a negative test result, and there is a danger that in daily practice VUS may be misinterpreted as a positive result. The question of testing of family members is unanswered and screening recommendations if mutations are detected need to be generated. There are data suggesting earlier PSA screening in men with *BRCA2* and potentially also in men with *BRCA1* germline mutations [176]. More data are needed to appropriate counsel unaffected male family members about prostate cancer risk and make screening recommendations.

Large collaborative efforts are underway (eg, NCT00261456, PRACTICAL consortium) to address some of the open questions. However, in order to move the field forward more efforts are needed to collaborate—especially on prostate cancers with germline mutations that occur at a

low frequency. The panel recommends to be especially careful (not overinterpret) about treatment recommendations based on germline mutations in men with localised prostate cancer.

## 10. Side effects of systemic treatment: prevention, management, and supportive care

A substantial proportion of men with APC will die of a noncancer-related cause and must live with the acute and chronic side effects of treatment. Most men with localised prostate cancer do not die of their disease, but will spend the rest of their lives managing the effects of the treatment they have undergone. The wishes of our patients and their families are clear: they wish to be cured of their disease or to have their survival prolonged, but not necessarily at the cost of intolerable side effects of treatment. Sometimes it is easy to lose sight of this goal in the search for better oncological outcomes.

*One-hundred percent of the panel believed that there was at least moderate evidence that ADT increases the risk of bone loss and/or fractures; 87% believed this evidence was strong.*

*Baseline measurement of vitamin D for men with prostate cancer starting on ADT was voted for in the majority of patients by 43% of the panellists, in a minority of patients by 26% and 31% of the panellists did not vote for it.*

*Routine supplementation of calcium and vitamin D for men with prostate cancer starting on ADT was voted for by 73% of the panel, only of vitamin D by 13%, only calcium by 2%, and 12% of the panel did not vote for routine supplementation.*

*A baseline measurement of bone mineral density in men with prostate cancer starting on ADT was voted for by 62% of the panellists in the majority of patients, by 15% only in patients with nonmetastatic disease and 21% did not vote for it at all.*

*Drug therapy to prevent bone loss and/or fractures with denosumab or a bisphosphonate in the dose and schedule for osteoporosis prophylaxis in men with prostate cancer starting on ADT was voted for in the majority of patients by 16% of the panellists, by 70% of panellists only in patients with documented osteopenia or osteoporosis, and 12% did not vote for it.*

*Thirty-five percent of the panellists felt that there is strong evidence that ADT increases the risk of diabetes, 46% felt that there is moderate, and 17% that there is weak evidence for this correlation. Two percent believe that ADT does not change the risk of diabetes.*

*For cardiovascular disease, 12% of the panellists felt that there is strong evidence that ADT increases the risk, 39% felt that there is moderate, and 45% that there is weak evidence for this correlation. Four percent believe that ADT does not change the risk of cardiovascular disease.*

*A history of recent/severe cardiovascular disease influenced the choice of ADT in men with metastatic prostate cancer for 29% of the panellists in the majority of patients, for 41% of the panellists for a minority of selected patients, and for 28% of the panellists it did not influence their choice of ADT.*

*For the subset of panellists whose decisions was influenced by a history of recent/severe cardiovascular disease, 11% voted for using LHRH agonists, 52% for use of LHRH antagonists, 6% for orchiectomy, 20% for any form of intermittent ADT, and 11% voted for bicalutamide 150 mg/d in such a patient.*

*Eight percent of the panellists believed that there is strong evidence that ADT increases the risk of cognitive changes and/or dementia, 29% felt that there is moderate, and 50% that there is weak evidence for this correlation. Thirteen percent believe that ADT does not change the risk of cognitive changes and/or dementia.*

*For depression, 6% of the panellists believed that there is strong evidence that ADT increases the risk, 46% felt that there is moderate, and 44% that there is weak evidence for this correlation. Four percent believe that ADT does not change the risk of depression.*

A multidisciplinary management team can include the necessary expertise to deal with these issues [177]. Improved outcomes are apparent with involvement of prostate cancer nurses and care coordinators. Endocrinologists and andrologists can provide advice on the management of diabetes, metabolic syndrome, bone health, cardiovascular, and sexual health. Psychologists can provide support for the common problems of suicidal risk, distress, and long-term psychological and sexual morbidity [178–181]. The exercise physiologist can provide programs to counteract the effects of ADT, improve psychological symptoms, and improve overall and disease-specific survival [182–184]. The direct provider of care for men with APC can also learn such skills.

Comprehensive geriatric assessment has been shown to be associated with a higher probability of completing a treatment course, fewer modifications of treatment, and lower toxicity [185,186].

*Routine involvement of a multidisciplinary/multiprofessional team for prevention or management of ADT related adverse effects was voted for by 42% of the panellists for the majority of patients, by 39% in a minority of selected patients, and 17% did not vote for it.*

*Sixty-one percent of the panellists voted for early access to an expert in symptom palliation or a dedicated palliative care service and 39% of the panellists did not vote for it.*

*There was consensus (94% of the panellists) for access to opiate pain medication for men with metastatic prostate cancer and severe pain when lower level pain medication is not sufficient.*

*Thirty percent of the panellists voted for a health status assessment in men with APC $\geq$70 yr before treatment decision in the majority of patients, 42% voted for it in a minority of selected patients, and 24% did not vote for it.*

*The subset of panellists who voted for a health status assessment voted for comprehensive geriatric assessment in 26%, G8 and Mini-COG in 29%, G8 alone in 30%, and another tool in 15%.*

*There was consensus (98% of the panellists) for regular physical exercise in men with prostate cancer starting on ADT.*

### 10.1. Discussion of side effects of systemic treatment: prevention, management, and supportive care

The aging population of men with APC is now surviving longer, allowing longer-term complications of treatment to

become apparent and to affect function and symptoms. The evidence that ADT negatively impacts bone health and the attendant risk for fractures is considered strong by a majority of the panel. ADT has also been associated with an increased risk of metabolic syndrome, type 2 diabetes, and sarcopenia; however, evidence linking ADT directly as a cause of vascular disease is weak and there is no convincing evidence that ADT is linked causally to the development of dementia as reflected in the vote of the panellists [187–196]. Men should be informed about the acute but also the long-term side effects of ADT and importantly the possible preventive measures.

Interestingly, there was no consensus for the routine assessment of health status in men aged 70 yr, likely based on the fact that there are no large prospective clinical trials which have shown that using health status assessment in men with metastatic prostate cancer has a relevant impact on outcome, especially when compared with the judgement of experienced physicians. This recommendation could also reflect a lack of consensus on what would constitute such a "health status assessment." Finally, there is a need for clinical trials and registration studies specifically in this patient population.

## 11. Global access to prostate cancer drugs and treatment in countries with limited resources

The panel voted on a number of questions regarding treatment options in men with APC in lower and middle-income countries (LMIC) because the topic of global access to APC treatments was discussed at APCCC 2017.

*If living in a country with limited resources available for health care, 90% of the panellists voted for orchiectomy as ADT in the metastatic setting. The remaining 10% voted for an LHRH agonist.*

*As second-line endocrine manipulations in LMIC in men with mCRPC progressing on ADT, 44% of the panellists voted for a first generation AR antagonist, 24% for steroid monotherapy, 20% for ketoconazole, 8% for oestrogens, and 4% for estramustine.*

Each of the following drugs is on the World Health Organization (WHO) essential medicines list and/or they can be sourced at an affordable price from generic manufacturer. The panel voted on appropriate treatment options in the setting of limited health care resources in men with mCRPC who are progressing on or after docetaxel: *77% of the panellists voted for a platinum, 19% did not vote for it. Mitoxantrone was voted for by 69% of the panellists. Thirty-nine percent voted for the use of cyclophosphamide, 53% did not. There was a consensus not to use paclitaxel (78%) or doxorubicin (84%) in this situation.*

### 11.1. Discussion of global access to prostate cancer drugs and treatment in countries with limited resources

Prostate cancer generally is more common in higher income countries, but this is changing as men in LMIC live longer, due to better control of infectious disease and other causes of early mortality. Men in LMIC tend to present with more advanced disease and access to the survival prolonging agents for mCRPC is limited for many men in LMIC.

Although the panel recommended orchiectomy as first choice of ADT in men presenting with metastatic prostate cancer, the socio-cultural and psychological barriers to such an intervention must be taken into consideration in such treatment decisions.

As secondary hormonal treatment option for men with mCRPC, endocrine manipulations including glucocorticoids, oestrogens, first generation androgen receptor inhibitors, and ketoconazole are available and the panel considered especially first-generation AR inhibitors a valid treatment option in LMIC.

Abiraterone and enzalutamide are examples of high-cost drugs with limited access in LMIC. Both drugs were developed substantially through research in academic laboratories and cancer centres. In the USA, approved doses are marketed at ~US$ 7000/mo, while publicly funded health systems such as Britain and Canada have been able to negotiate a substantially lower price of ~$3000/mo. Generic abiraterone (but not enzalutamide) is available in India for about $450/mo, which is, however, still too expensive for many men with mCRPC in India.

The following drugs which have shown some antitumour activity but no OS benefit in men with mCRPC and are on the WHO essentials medicine list: carboplatin, paclitaxel, doxorubicin, and cyclophosphamide. Carboplatin was recommended by a majority of the panellists. Mitoxantrone is not on the WHO essentials medicine list but has shown a pain palliation benefit and could be sourced at a reasonable price. Many of these drugs are substantially cheaper than the approved and survival prolonging agents for mCRPC and they can be used sometimes as substitutes for newer agents in LMIC. While this is a reasonable strategy, it falls far short of the ideal of providing the most effective treatments to all men with APC.

A major goal of this consensus conference is to improve the management and outcomes of men with APC. However, it is a suboptimal clinical achievement to show that new treatments can improve the duration and quality of survival of men with APC, but to have such treatments unavailable to a large segment of the global population of men with APC. The availability of RT as a very effective bone pain palliation therapy is not given in many countries. We cannot easily change the way that drugs are developed and marketed for profit by academic, pharmaceutical, and biotechnology companies, and we certainly respect and collaborate within this system for the development of needed new treatments for men with APC. But men with APC are still unable to access optimal treatments, oftentimes not because they could not be made available, but because they are not made available at an affordable price. Hence, we encourage ongoing multidisciplinary and stakeholder dialogue to further address this global issue.

## 12. Conclusions

In the absence of Level I evidence and in areas where there are conflicting data or conflicting interpretation of available

**Areas of consensus (≥ 75% agreement) APCCC 2017**

Management of high-risk localised and locally advanced prostate cancer

- Lymph node dissection in men with cN0 cM0 high-risk prostate cancer undergoing prostatectomy: 84%
- Minimal requirement for lymph node sampling in men with cN0 cM0 high-risk prostate cancer
  - Obturator lymph nodes: 98%
  - External iliac lymph nodes: 85%
  - Internal iliac lymph nodes: 90%
  - Not to sample paraaortic lymph nodes: 95%
- For pathology reporting in case of lymphadenectomy:
  - Number and anatomic region of resected lymph nodes and no. and location of involved lymph nodes: 94%
  - Micro- vs macrometastases: 81%
  - Metastatic deposits in perinodal fat tissue: 79%
  - Extranodal extension of involved lymph nodes: 81%
- Reporting of prostatectomy specimen in locally advanced prostate cancer:
  - Seminal vesicle involvement: 100%
  - Extent of prostatic involvement: 96%
  - Gleason score or grade group, extraprostatic extension, positive surgical margins: number length, and location, as well as grade at margin: 100%
  - Tertiary Gleason score: 94%

"Oligometastatic" prostate cancer

- If positron emission tomography–computed tomography is considered in oligometastatic castration-naïve prostate cancer (CNPC) prostate-specific membrane antigen as a tracer: 76%

Management of castration-naive prostate cancer

- Factors rendering a patient as "not being suitable for docetaxel":
  - Severe hepatic impairment: 96%
  - Neuropathy grade ≥2: 82%
  - Platelets $<50 \times 10^9$/l and/or neutrophils $<1.0 \times 10^9$/l: 81%
- Docetaxel in addition to androgen deprivation (ADT) therapy in CNPC
  - De novo metastatic CNCP and high-volume disease: 96%
  - Not to add docetaxel in biochemical relapse (N0 M0): 90%
- 3-weekly docetaxel (75 mg/m$^2$) regimen in CNPC: 96%

Management of castration-resistant prostate cancer (CRPC)

- First-line CRPC
  - Abiraterone or enzalutamide for asymptomatic men without docetaxel for CNPC: 86%
  - Abiraterone or enzalutamide for asymptomatic men with docetaxel for CNPC: 90%
  - Abiraterone or enzalutamide for asymptomatic men with docetaxel for CNPC and progressed within ≤6 mo after completion of docetaxel in the CNPC setting: 77%
  - Not to combine radium-223 and docetaxel: 88%
- Second-line CRPC
  - Taxane in men with symptomatic mCRP C who had progressive disease as best response to first-line abiraterone or enzalutamide: 96%
  - Taxane in men with symptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression) after use of first-line abiraterone or enzalutamide: 90%
  - Abiraterone or enzalutamide for asymptomatic men with mCRPC progressing on or after docetaxel for mCRPC (without prior abiraterone or enzalutamide): 92%
  - Abiraterone or enzalutamide for symptomatic men with mCRPC progressing on or after docetaxel for mCRPC (without prior abiraterone or enzalutamide): 76%

**Fig. 1 – Areas of consensus Advanced Prostate Cancer Consensus Conference (APCCC) 2017.**

- Preferred choice between abiraterone and enzalutamide in special situations:
  - Abiraterone in case of a history of falls: 94%
  - Abiraterone in case of baseline significant fatigue: 88%
  - Abiraterone in case of baseline significant neurocognitive impairment: 84%
  - Enzalutamide in case of diabetes mellitus requiring prescription drug therapy: 84%
- 3-weekly docetaxel (75 mg/m$^2$) in the CRPC setting: 86%

Imaging

- Computed tomography and bone scintigraphy for staging and treatment monitoring in men with mCRPC on treatment with radium-223: 75%

Osteoclast-targeted therapies

- Discontinuation of osteoclast targeted treatment in men who develop osteonecrosis of the jaw while on osteoclast-targeted therapy for skeletal related events/symptomatic skeletal events prevention: 84%

Molecular characterisation

- Tumour biopsy reporting in mCRPC
  - *BRCA1, BRCA2, and ATM* status: 78%
- Liquid biomarkers in routine clinical practice
  - Not to do androgen receptor (AR)-variant 7 testing: 96%
  - Not to do cell-free DNA AR amplification and AR mutation: 92%

Genetic counselling/testing

- Not to do a prophylactic prostatectomy in t he presence of a germline *BRCA1, BRCA2, or ATM* mutation: 92%

Side effects of systemic treatment and supportive care

- Advise patients about strong evidence that ADT increasesrisk of bone loss and/or fractures: 87%
- Regular physical exercise in men with prostate cancer starting on ADT: 98%
- Access to opiate pain medication for men with metastatic prostate cancer and severe pain when their lower level pain medication is not sufficient: 94%

Global access to prostate cancer drugs and treatment in countries with limited resources

- Orchiectomy as ADT in the metastatic setting: 90%
- In men with mCRPC who are progressing on or after docetaxel:
  - Platinum (carboplatin/cisplatin): 77%
  - Not paclitaxel: 78%
  - Not doxorubicin: 84%

**Fig. 1. (*Continued*).**

data, weighted expert opinions can be helpful for treatment decisions in daily routine clinical practice. It is important to note that expert opinion is not equivalent to high-level evidence and that current expert consensus may be disproven by future clinical research.

There were several notable areas of consensus in APCC 2017 as summarised in Figure 1.

There were also several notable areas of panellist disagreement including but not limited to: (1) chemo-hormonal therapy in "low-volume" CNPC, (2) treatment of the primary tumour in metastatic disease, (3) radium-223 combination strategies, (4) use of platinum in mCRPC, (5) definition of aggressive variant prostate cancer, (6) use, schedule, and duration of osteoclast-targeted therapies especially in the context of newer survival prolonging mCRPC therapies; (7) use of next-generation imaging; (8) how to advise men with known *BRCA2*, *BRCA1*, or *ATM* mutations; (9) adjuvant RT; (10) when to initiate SRT; (11) definition and treatment for oligometastatic synchronous and metachronous prostate cancer; (12) health status assessment in patients aged $\geq$70 yr; and (13) pathology reporting of men undergoing a mCRPC biopsy.

The panel members recognise that the voting results may contribute to the adoption of unproven or controversial interventions and interfere with prospective clinical research to evaluate the efficacy and safety of those

interventions. A problem arising from the widespread initiation of unvalidated techniques and treatments is that they achieve a clinical momentum, which makes it very difficult to conduct effective comparative studies. The panel strongly recommends participation in clinical research to inform clinical management with high-level evidence. Important research areas are adjuvant and salvage treatment; diagnosis and treatment of oligometastatic disease; molecular characterisation; personalised therapy strategies; and supportive care including the impact of geriatric assessment and specific interventions.

We urgently need public and/or charity funding to carry out studies in areas such as surgery, RT, or imaging where financial support from industry is commonly not available.

Additional relevant questions remain that we were not able to address in detail in this meeting such as costs and cost-effectiveness of drugs, health economic issues, and patient-reported outcomes. APCCC 2019 plans to address these questions and the above-mentioned areas of controversy and new emerging topics.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2017.06.002.

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