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Prostate Cancer – Editor's Choice

Management of Patients with Advanced Prostate Cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019

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Abstract

Background: Innovations in treatments, imaging, and molecular characterisation in advanced prostate cancer have improved outcomes, but there are still many aspects of management that lack high-level evidence to inform clinical practice. The Advanced Prostate Cancer Consensus Conference (APCCC) 2019 addressed some of these topics to supplement guidelines that are based on level 1 evidence.
Objective: To present the results from the APCCC 2019.
Design, setting, and participants: Similar to prior conferences, experts identified 10 important areas of controversy regarding the management of advanced prostate cancer: locally advanced disease, biochemical recurrence after local therapy, treating the primary tumour in the metastatic setting, metastatic hormone-sensitive/naïve prostate cancer, nonmetastatic castration-resistant prostate cancer, metastatic castration-resistant prostate cancer, bone health and bone metastases, molecular characterisation of tissue and blood, inter- and intrapatient heterogeneity, and adverse effects of hormonal therapy and their management. A panel of 72 international prostate cancer experts developed the programme and the consensus questions.
Outcome measurements and statistical analysis: The panel voted publicly but anonymously on 123 predefined questions, which were developed by both voting and nonvoting panel members prior to the conference following a modified Delphi process.
Results and limitations: Panellists voted based on their opinions rather than a standard literature review or formal meta-analysis. The answer options for the consensus questions had varying degrees of support by the panel, as reflected in this article and the detailed voting results reported in the Supplementary material.
Conclusions: These voting results from a panel of prostate cancer experts can help clinicians and patients navigate controversial areas of advanced prostate management for which high-level evidence is sparse. However, diagnostic and treatment decisions should always be individualised based on patient-specific factors, such as disease extent and location, prior lines of therapy, comorbidities, and treatment preferences, together with current and emerging clinical evidence and logistic and economic constraints. Clinical trial enrolment for men with advanced prostate cancer should be strongly encouraged. Importantly, APCCC 2019 once again identified important questions that merit assessment in specifically designed trials.
Patient summary: The Advanced Prostate Cancer Consensus Conference provides a forum to discuss and debate current diagnostic and treatment options for patients with advanced prostate cancer. The conference, which has been held three times since 2015, aims to share the knowledge of world experts in prostate cancer management with

health care providers worldwide. At the end of the conference, an expert panel discusses and votes on predefined consensus questions that target the most clinically relevant areas of advanced prostate cancer treatment. The results of the voting provide a practical guide to help clinicians discuss therapeutic options with patients as part of shared and multidisciplinary decision making.

1. Introduction

The multidisciplinary panel for the 2019 Advanced Prostate Cancer Consensus Conference (APCCC 2019) consisted of 72 cancer physicians and scientists selected based on their academic experience and involvement in clinical or translational research in the field of advanced prostate cancer (APC).

Ten controversial areas related to the management of men with APC were prioritised for discussion:

1 Locally advanced prostate cancer
2 Biochemical recurrence of prostate cancer after local therapy
3 Management of primary tumour in the metastatic setting
4 Management of newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC), including oligometastatic prostate cancer
5 Management of nonmetastatic (M0) castration-resistant prostate cancer (CRPC)
6 Management of metastatic CRPC (mCRPC)
7 Bone health and bone metastases
8 Molecular characterisation of tissue and blood
9 Interpatient heterogeneity
10 Side effects of hormonal treatments and their management

The conference and the consensus development process followed procedures that have been described previously [1,2]. For all questions, unless stated otherwise, responses were based on the hypothetical scenario that all diagnostic procedures and treatments (including expertise in interpretation and application) were readily available, that there were no contraindications to treatment, and that there was no option to enrol the patient in a clinical trial. Unless stated otherwise, the questions applied only to fit patients with prostatic adenocarcinoma who had no treatment-limiting comorbidities. Next-generation imaging for prostate cancer was defined as positron emission tomography computed tomography (PET-CT)/magnetic resonance imaging MRI); subsequently referred to as PET/CT unless stated otherwise with prostate-specific membrane antigen (PSMA), choline, or fluciclovine tracers and/or whole-body morphological and diffusion-weighted MRI. At APCCC 2019, panellists also selected their preferred next-generation imaging modalities for different clinical scenarios.

The results of the voting are intended to serve as a guide to help clinicians speak with patients as part of shared and multidisciplinary decision making. For additional definitions used during APCCC 2019, please refer to the Supplementary material.

The panel consisted of 61 voting members, of whom four were not present during the voting and 11 were nonvoting members. Both voting and nonvoting members helped define the questions. The voting members comprised 44% medical oncologists, 30% urologists, 14% clinical oncologists, and 12% radiation oncologists. Of them, 35% practiced in Europe, 42% in North America, and 23% in other regions of the world. Nonvoting members consisted of experts such as nuclear medicine specialists, radiologists, pathologists, and statisticians who are not directly involved in clinical decision making, as well as four clinical experts who were not present during voting and one patient advocate. In the rest of this article, voting members are referred to as "panellists". Panellists were instructed to abstain from voting if, for any reason, they felt unable to vote for a best choice or had prohibitive conflicts of interest. Denominators were based on the number of panellists who voted on a particular question, excluding those who voted "abstain".

The Supplementary material shows detailed voting results for each question. The level of consensus was defined as follows: answer options with $\geq$75% agreement were considered consensus, and answer options with $\geq$90% agreement were considered strong consensus. Table 1 summarizes areas of consensus for APCCC 2019.

All panellists contributed to designing the questions and editing the manuscript and approved the final document.

2. Locally advanced prostate cancer

2.1. Newly diagnosed clinical N1 (cN1, pelvic lymph nodes), M0 (nonmetastatic) prostate cancer

In 2019, discussions on node-positive prostate cancer distinguished between clinical N1 (cN1) and pathological N1 (pN1) M0 disease. Experts also discussed the role of next-generation imaging with PSMA PET/CT in defining cN1 disease, and its impact on clinical management.

There is no standard recommendation for the treatment of newly diagnosed node-positive prostate cancer. In the absence of large prospective clinical trials, current European Association of Urology (EAU) guidelines recommend local treatment as part of a multimodal approach [3]. Androgen-deprivation therapy (ADT) alone is recommended only if patients are ineligible for or refuse local treatment. In a small retrospective case series of pN1 patients undergoing radical

Table 1 – Areas of consensus (≥75% agreement) APCCC 2019.

Question	Topic and result
Locally advanced prostate cancer	
Q1	Preferred treatment recommendation for the majority of patients with newly diagnosed cN1 (pelvic lymph nodes), M0 prostate cancer: strong consensus (98%) for radical locoregional treatment plus/minus systemic therapy
Q3	Systemic therapy for patients with M0 prostate cancer with cN1 disease who are receiving radical locoregional treatment with radiation therapy: no consensus for any given answer option, but a combined total of 98% voted for some form of systemic therapy
Q4	Duration of ADT for patients with cN1, cM0 prostate cancer who are receiving radiation therapy as radical locoregional treatment: no consensus for any given answer option, but no panellist voted for life-long ADT
Q7	Systemic therapy in combination with adjuvant RT in pN1 disease: no consensus for any given answer option, but a combined total of 98% voted for some form of systemic therapy
Q8	Duration of ADT in combination with adjuvant RT in pN1 disease: no consensus for any given answer option, but only 2% voted for life-long ADT
Biochemical recurrence after local therapy	
Q10	Imaging modality(ies) for patients with rising PSA after radical radiation therapy of the prostate: consensus (80%) for PSMA PET-CT
Q12	Imaging modality(ies) for patients with rising PSA after radical prostatectomy: consensus (87%) for PSMA PET-CT
Q15	In case systemic hormonal therapy was recommend in combination with salvage radiation therapy: strong consensus (91%) for LHRH agonist or antagonist
Q16	Duration of systemic hormonal treatment in combination with salvage radiation therapy for the majority of patients: consensus (79%) for short-term systemic therapy (4–12 mo) in combination with salvage radiation therapy
Q19	When to start long-term ADT in patients with nonmetastatic disease and confirmed rising PSA after local therapy (with or without salvage local radiation therapy): consensus (80%) for starting ADT only in selected patients
Management of the primary tumour in the metastatic setting	
Q20	Based on the current literature, local treatment of the primary tumour has an overall survival benefit in: strong consensus (98%) for an overall survival benefit from local treatment of the primary tumour in patients with low-volume/low-burden M1 disease
Q21	Extrapolation of the data from STAMPEDE (radiation therapy of the prostate) to radical surgery of the prostate: consensus (88%) for not extrapolating STAMPEDE data on radiation therapy to surgery of the prostate
Q22	Preferred local treatment of the prostate in patients with newly diagnosed low-volume/burden metastatic (M1) castration-sensitive/naïve prostate cancer: consensus (84%) for radiotherapy
Q23	In case of RT of the primary tumour in patients with newly diagnosed low-volume/burden metastatic (M1) castration-sensitive/naïve prostate cancer who also have clinical pelvic N1 disease, do you recommend that radiation treatment volume encompasses the pelvic lymph nodes? Consensus (75%) for radiation of the primary and pelvic nodes in patients with newly diagnosed cN1 disease
Oligometastatic prostate cancer	
Q47	Importance for treatment decisions in untreated de novo oligometastatic prostate cancer to distinguish lymph node–only disease (including distant lymph node metastases) from disease that includes metastatic lesions at other sites: strong consensus (92%) for making the distinction
Q51	Is imaging by CT and bone scintigraphy sufficient to define the oligometastatic state for treatment planning: consensus (79%) that CT and bone scintigraphy are not sufficient to define an oligometastatic state for treatment planning
Q58	Recommended imaging modalities in patients with rising PSA after radical treatment to confirm a diagnosis of oligorecurrent (metachronous) oligometastatic prostate cancer if detected on CT and bone scintigraphy: consensus (75%) for PSMA PET-CT/MRI
Q59	Recommended treatment for the majority of patients with oligorecurrent (metachronous) oligometastatic prostate cancer: consensus (75%) for systemic therapy plus local treatment of all lesions
Newly diagnosed hormone-sensitive prostate cancer (HSPC)	
Q25	To describe metastatic prostate cancer in patients who are about to start ADT: no consensus for any given answer option, but a combined total of 77% voted for a term that did not include “castration” in this setting
Q26	Terminology that best describes patients with metastatic prostate cancer who are progressing in the context of suppressed testosterone testosterone level (<50 ng/ml): consensus (87%) for the term CRPC
Q27	Measurement of total testosterone level before starting first-line treatment with ADT: no consensus for any given answer option, but a combined total of 82% voted to measure total testosterone before starting first-line ADT, at least in selected patients
Q28	Histopathological confirmation of prostate cancer (either before or after initiation of ADT) in patients with high suspicion of metastatic prostate cancer (based on PSA and imaging): strong consensus (95%) for histopathological confirmation of prostate cancer in the majority of patients
Q29	Initiation of ADT before histopathological confirmation in symptomatic patients with high suspicion of metastatic prostate cancer (PSA and imaging): no consensus for any given answer option, but a combined total of 96% voted to initiate ADT prior to histopathological confirmation, at least in selected patients
Q34	Preferred treatment in addition to ADT in patients with de novo high-volume metastatic (M1) castration-sensitive/naïve prostate cancer without symptoms from the primary tumour: no consensus for any given answer option, but no panellist voted for ADT alone
Q35	Preferred treatment in addition to ADT in patients with newly diagnosed high-volume metastatic (M1) castration-sensitive/naïve prostate cancer relapsing after local treatment of the primary tumour: no consensus for any answer option, but a combined total of 94% voted for some form of additional treatment together with ADT
Q36	Preferred treatment in addition to ADT in patients with de novo low-volume metastatic (M1) castration-sensitive/naïve prostate cancer without symptoms from the primary tumour: no consensus for any given answer option, but a combined total of 85% voted for some form of additional treatment together with ADT, and a combined total of 80% voted for treatment of the primary tumour
Q37	Preferred treatment in addition to ADT in patients with newly diagnosed low-volume metastatic (M1) castration-sensitive/naïve prostate cancer relapsing after local treatment of the primary tumour: no consensus for any given answer option, but a combined total of 93% voted for some form of additional treatment together with ADT
Q38	In case of combined treatment of docetaxel plus an AR pathway inhibitor (abiraterone or apalutamide or enzalutamide) in addition to ADT in a patient with newly diagnosed metastatic (M1) castration-sensitive/naïve prostate cancer, the panel voted on the preferred strategy: consensus (81%) for not using the combination of docetaxel plus an AR pathway inhibitor with ADT
Q39	Preferred treatment option in addition to ADT in a patient with de novo high-volume and/or high-risk metastatic (M1) castration-sensitive/naïve prostate cancer, Gleason score ≥9, multiple liver metastases and/or lytic bone metastases, and a low PSA value (<20), but no histopathological evidence of small cell carcinoma: consensus (75%) to add docetaxel to ADT in this setting
Q43	Recommended additional imaging modalities for the majority of patients with newly diagnosed high-volume metastatic (M1) castration-sensitive/naïve prostate cancer based on CT and bone scintigraphy: consensus (78%) for no additional imaging

Table 1 (*Continued*)

Question	Topic and result
Management of M0 CRPC (nmCRPC)	
Q66	Preferred choice of treatment in addition to ADT in the majority of nmCRPC (M0 CRPC) patients who have PSA ≥ 2 ng/ml and PSA doubling time ≤10 mo: no consensus for any given answer option, but a combined total of 86% voted for an AR antagonist (apalutamide, darolutamide or enzalutamide)
Q67	Is it appropriate to extrapolate data from ARAMIS, PROSPER, and SPARTAN to patients with nmCRPC (M0 CRPC) who have PSA doubling time >10 mo? Consensus (86%) for not extrapolating ARAMIS, PROSPER, and SPARTAN data to patients with PSA doubling time >10 mo
Management of mCRPC	
Q76	Recommended strategy regarding steroid therapy when discontinuing abiraterone or chemotherapy: consensus (86%) for tapering steroids over a course of some weeks
Q77	The panel was asked whether they recommended AR-V7 testing to select candidates for abiraterone after enzalutamide (or vice versa): consensus (85%) against the use of AR-V7 testing to identify candidates for treatment with abiraterone or enzalutamide
Q78	The panel voted on the recommended glucocorticoid regimen when starting abiraterone in patients with mCRPC: consensus (75%) for using prednisone/prednisolone 5 mg twice daily when starting abiraterone in patients with mCRPC
Q79	The panel voted on the question whether it was appropriate to prescribe a lower dose of abiraterone (250 mg) given with food for patients with metastatic prostate cancer in the context of limited resources (patient or system): consensus (89%) for a lower dose of abiraterone with food in the context of limited resources
Q95	The panel voted on the question: Do you recommend that the majority of patients with mCRPC receive cabazitaxel sometime during their disease course? Consensus (75%) for use of cabazitaxel sometime during the disease course
Bone health and bone metastases	
Q85	Routine screening for osteoporosis risk factors (eg, current/history of smoking, corticosteroids, family history of hip fracture, personal history of fractures, rheumatoid arthritis, ≥3 alcohol units/d, and BMI) in patients with prostate cancer starting on long-term ADT: consensus (77%) for routine screening for osteoporosis risk factors
Q91	Recommendation for osteoclast-targeted therapy at the higher dose and more frequent schedule used for reducing the risk of SRE when treatment with radium-223 is planned in patients with mCRPC: consensus (86%) for osteoclast-targeted therapy in the majority of patients planed for radium-223 therapy for mCRPC
Q96	Do you recommend that the majority of symptomatic patients with mCRPC and predominant bone metastases (without visceral disease and bulky lymph node disease) receive radium-223 sometime during their disease course? Consensus (87%) for the use of radium-223 sometime during the course of bone-predominant mCRPC in patients without visceral or bulky lymph node disease
Molecular characterisation of tissue and blood	
Q100	Should the majority of metastatic prostate cancer patients get their tumours tested for BRCA1/2 aberrations? No consensus for any given answer option, although a combined total of 90% voted for BRCA1/2 tumour testing at some point during the disease course
Q101	Should the majority of metastatic prostate cancer patients get their tumours tested for mismatch repair defects (MSI high)? No consensus for any given answer option, but a combined total of 94% voted for testing mismatch repair defects at some stage of disease, most frequently in the mCRPC setting
Q102	Recommend anti-PD1 therapy for patients with metastatic prostate cancer and a mismatch repair defect (MSI high) outside of a clinical trial: no consensus for any given answer option, but a combined total of 96% voted for anti-PD1 therapy sometime during the treatment sequence for patients with MSI-high metastatic prostate cancer
Q104	Recommendation that the majority of metastatic prostate cancer patients with a deleterious germline BRCA1/2 mutation receive a PARP inhibitor or platinum therapy during their disease course outside of a clinical trial if none is available: strong consensus (93%) for PARP inhibitor or platinum therapy at some point during the disease course in patients with a deleterious germline BRCA1/2 mutation
Q109	Recommended schedule for carboplatin therapy (monotherapy or combination): consensus (84%) for using carboplatin AUC 4–5 in a 3-weekly schedule
Q110	Collection of a detailed family history of cancer for all patients with newly diagnosed metastatic (M1) castration-sensitive/naïve prostate cancer: strong consensus (98%) for collecting a detailed family history for all patients with newly diagnosed M1 HSPC
Q111	Genetic counselling and/or germline DNA testing for patients with newly diagnosed metastatic (M1) castration-sensitive/naïve prostate cancer: consensus (84%) for genetic counselling and/or germline DNA testing for the majority of patients with newly diagnosed metastatic prostate cancer
Q112	Recommendation for germline DNA testing, in patients with prostate cancer: consensus (85%) for extended panel testing
Heterogeneity of prostate cancer	
Q115	Can mCRPC clinical trial data regarding efficacy can be extrapolated to the treatment of patients who are older than the majority of patients enrolled in these trials? Consensus (76%) for extrapolation of efficacy data to patients older than the majority of patients enrolled in a trial
Side effects of hormonal treatments and their management	
Q122	Preferred first management option to reduce fatigue in patients receiving systemic therapy for prostate cancer (apart from therapy dose reduction if possible): strong consensus (94%) for resistance and aerobic exercise to reduce fatigue

ADT = androgen-deprivation therapy; APCCC = Advanced Prostate Cancer Consensus Conference; AR = androgen receptor; AR-V7 = AR splice variant 7; AUC = area under the curve; BMI = body mass index; CRPC = castration-resistant prostate cancer; CT = computed tomography; HSPC = hormone-sensitive prostate cancer; LHRH = luteinising hormone-releasing hormone; mCRPC = metastatic CRPC; MRI = magnetic resonance imaging; MSI = microsatellite instability; nmCRPC = nonmetastatic CRPC; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RT = radiation therapy; SRE = skeletal-related event.

prostatectomy, treatment outcomes among patients with preoperative cN1 status did not differ from those with cN0 disease [4]. Nonrandomised data from 721 patients in the control arm of the STAMPEDE trial favoured the planned use of radiotherapy in addition to ADT for the management of either node-negative or node-positive M0 prostate cancer [5]. A retrospective study of almost 3000 patients with cN1 prostate cancer from the National Cancer Database also identified a strong overall survival (OS) benefit from local treatment [6], but such analyses are subject to selection bias and should be interpreted with caution. A benefit for local treatment also was demonstrated by a recent systematic review of >4500 patients with cN1 prostate cancer [7]. Although PSMA PET/CT has superior sensitivity for detecting nodal disease [8], its potential impact on clinical management remains under evaluation [9].

Q1: For the majority of patients with newly diagnosed cN1 (pelvic lymph nodes), M0 prostate cancer, 98% of panellists voted for radical locoregional treatment with or without systemic therapy, and 2% voted for systemic therapy alone. There were no abstentions. (Strong consensus for locoregional treatment)
Q2: For radical locoregional treatment of cN1 (pelvic lymph nodes), M0 prostate cancer, 39% of panellists voted for radiation therapy, 12% voted for surgery, and 49% had no preference. There were no abstentions. (No consensus for any given answer option)

If radiation therapy is used in patients with cN1 prostate cancer, then guidelines from the National Comprehensive Cancer Network (NCCN) and EAU recommend combining it with ADT based on the results of a subgroup analysis of the Radiation Therapy Oncology Group (RTOG) 85-31 trial in which a statistically significant improvement in progression-free survival (PFS) was reported for radiation therapy plus long-term ADT compared with radiation therapy alone [10]. There are also retrospective studies supporting radiotherapy for node-positive disease [7]. The optimal duration of ADT remains unclear; although lifelong ADT has been used in studies of locally advanced (cN0) disease, the risks of long-term ADT should be balanced against any potential benefit [10,11]. Patients with cN1 disease were included in the EORTC trials of 6 mo versus 3 yr of ADT, and ADT plus radiation therapy versus ADT alone for the treatment of high-risk localised prostate cancer [12,13]. The standard duration of ADT in patients with high-risk localised prostate cancer is 2–3 yr.

The STAMPEDE trial also compared ADT plus external beam radiation therapy (standard of care) with standard of care plus either docetaxel or abiraterone acetate in patients with M0 but locally advanced or cN1 prostate cancer [14,15]. Of note, abiraterone was administered for up to 2 yr. After a median follow-up time of 40 mo, adding either docetaxel or abiraterone to ADT was associated with a statistically significant improvement in failure-free survival (FFS), but no OS benefit has been reported [14,15].

Q3: For patients with newly diagnosed cN1 M0 prostate cancer who are fit (ie, have no contraindications) for additional treatment with docetaxel and/or abiraterone (without regulatory limitations), 52% of panellists voted for ADT plus abiraterone, 39% voted for ADT alone, 7% voted for ADT plus docetaxel, and 2% voted for no systemic therapy. There were no abstentions. (No consensus for any given answer option, but a combined total of 98% voted for some form of systemic therapy)
Q4: Regarding the duration of ADT in newly diagnosed cN1 M0 patients who are receiving radical locoregional treatment with radiation therapy, 55% of panellists voted for >24–36 mo of ADT (long term), 41% voted for >12–24 mo of ADT (medium term), 4% voted for 4–12 mo of ADT (short term), and none voted for life-long ADT. There were no abstentions. (No consensus for any given answer option, but no panellist voted for life-long ADT)

The question of adjuvant radiation therapy for patients with pN1 postprostatectomy prostate cancer was also discussed in detail at APCCC 2017 [2]. For patients with prostate cancer and lymph node involvement, cancer mortality seems to rise significantly when three or more positive lymph nodes are present [16–18].

When considering adjuvant radiation therapy for patients with confirmed regional lymph node metastases (pN1) who have undetectable prostate-specific antigen (PSA) after radical surgery, a number of factors can be considered, including pT status, pathological margin involvement, International Society of Urological Pathology (ISUP) grade groups, and pathology of resected lymph nodes (number, density, size, and whether there is extranodal extension) [2]. In a retrospective study of 1338 patients with pN1 disease after radical prostatectomy, a statistically significant increase in OS was reported for adjuvant radiation therapy plus ADT compared with observation or ADT alone [19]. The duration of ADT in this series was highly variable, but approximately 90% of patients were treated for at least 1 yr. In addition, a series of >8000 patients from the National Cancer Database found a statistically significant increase in OS with adjuvant radiation therapy plus ADT, especially in patients with adverse pathological features (≥pT3b disease, Gleason score ≥9, three or more positive nodes, or positive surgical margins) [20]. In another series of 5498 patients with pN1 prostate cancer, the increase in OS with adjuvant radiation therapy plus ADT was limited to patients with either (1) one to two positive nodes, pathological Gleason score 7–10, and pT3b/4 disease or positive surgical margins, or (2) three to four positive nodes, regardless of local tumour characteristics [21].

Based on this newly available evidence, panellists considered management options for patients with newly diagnosed nonmetastatic (M0) prostate cancer with confirmed regional lymph node metastases (pN1) who, after undergoing radical surgery, have an undetectable PSA level and have recovered urinary continence.

Q5: For patients with pN1 disease of two or fewer lymph nodes with negative margins, no pT4 disease, and undetectable postoperative PSA, most panellists voted for adjuvant radiation therapy either in a minority of selected patients (53%) or in the majority of patients (18%), while 29% voted against adjuvant radiation therapy. There was one abstention. (No consensus for any given answer option)
Q6: For patients with pN1 disease of three or more lymph nodes who have negative margins, no pT4 disease, and undetectable postoperative PSA, most panellists voted for adjuvant radiation therapy in a minority of selected patients (41%) or in the majority of patients (44%), while 15% voted against adjuvant radiation therapy. There were no abstentions. (No consensus for any given answer option)
Q7: For patients receiving adjuvant radiation therapy for pN1 M0 disease who are fit for additional treatment with docetaxel and/or abiraterone and live in areas with no regulatory limitations, 65% of panellists voted for

systemic therapy with ADT alone, 31% voted for ADT plus abiraterone, 2% voted for ADT plus docetaxel, and 2% voted against systemic treatment in these patients. There were five abstentions. (No consensus for any given answer option, but a combined total of 98% voted for some form of systemic therapy)

Q8: Regarding the duration of ADT for these patients, 46% of panellists voted for >12–24 mo (medium term), 31% voted for >24–36 mo (long term), 21% voted for 4–12 mo (short term), and 2% voted for life-long ADT. There were eight abstentions. (No consensus for any given answer option, but only 2% voted for life-long ADT)

2.2. Discussion of locally advanced prostate cancer

Several situations in locally advanced prostate cancer lack randomised level 1 evidence to guide management decisions. Physicians face the challenge of advising patients regarding treatment decisions when they cannot currently distinguish patients whose best option is aggressive locoregional therapy plus systemic therapy with curative intent from patients who should receive intensified systemic therapy plus local treatment to control local disease and delay time to distant metastasis.

Despite a lack of data from large prospective randomised phase 3 clinical trials, there was a strong consensus at APCCC 2019 that patients with newly diagnosed, locally advanced, and clinically positive regional lymph node (cN1) prostate cancer should receive radical locoregional therapy combined with systemic therapy. There was no consensus on the type of local therapy (radiation vs surgery) or the type of systemic therapy. In addition, almost no panellists voted for lifelong ADT in this setting.

The value of adjuvant therapy for patients with positive pathological regional lymph nodes was a subject of debate at both APCCC 2017 and APCCC 2019. For patients with pN1 disease of two or fewer lymph nodes with negative margins, no pT4 disease, and undetectable PSA, the majority (53%) of APCCC 2019 panellists voted for adjuvant radiation therapy in selected patients, while 18% voted for treating the majority of patients. For patients with pN1 disease of three or more lymph nodes, negative margins, no pT4 disease, and undetectable PSA, 44% of panellists voted for adjuvant radiation therapy in the majority of patients and 41% voted for treating selected patients. Clearly, additional clinical and pathological factors need to be evaluated when considering adjuvant radiation therapy in this setting. In addition, while nearly all (98%) panellists voted for a limited duration of ADT for pN1 M0 patients, there was no consensus regarding whether these patients should receive ADT alone (65%) or in combination with abiraterone (31%). In addition, the optimal duration of adjuvant systemic therapy needs to be clarified.

Finally, there is an on-going need for clinical trials that specifically evaluate treatment strategies for both de novo cN1 disease and pN1 disease in the era of more sensitive imaging modalities. Both these stages are likely to become more prevalent in some countries with the increased use of both more sensitive imaging and surgery with lymph node dissection in patients with high-risk prostate cancer. It is worth noting that patients with cN1 disease on conventional imaging are probably different from those whose N1 disease is detected only by molecular imaging (smaller-volume disease burden). The ENZARAD (ANZUP 1303) and ATLAS trials also enrolled patients with cN1 disease, and STAMPEDE will continue to randomise patients with locally advanced and cN1 disease to its various arms. The results of these trials will help elucidate some of the remaining questions concerning the management of these patients.

3. Biochemical recurrence after local therapy

The management of biochemical recurrence after local therapy with curative intent for prostate cancer is changing with the introduction of more sensitive PSA tests and novel imaging methods, particularly PSMA PET/CT-based imaging [8]. In a recently published systematic review of 20406 patients with biochemical recurrence, factors associated with worse survival after prostatectomy included short PSA doubling time and a higher Gleason score, while factors associated with worse OS after radical prostate radiation therapy included a high Gleason score and short time to biochemical failure after radiation therapy [22]. The 2019 EAU guidelines recommend integrating these risk factors to stratify patients with biochemical recurrence into low- and high-risk categories [3]. Low-risk biochemical recurrence after radical prostatectomy is defined as PSA doubling time of >12 mo and pathological ISUP grade <4, while low-risk biochemical recurrence after radical radiation therapy is defined as a >18-mo interval from radiation therapy or from the last luteinising hormone-releasing hormone (LHRH) analogue injection to biochemical failure and biopsy ISUP grade <4. These criteria were validated recently by the results of an independent retrospective cohort study of 1125 patients with biochemical recurrence following radical prostatectomy [23].

3.1. PSA recurrence after radical radiation therapy

The RTOG and the American Society for Therapeutic Radiology and Oncology (ASTRO) define biochemical recurrence after external beam radiation therapy of the primary tumour as a ≥2 ng/ml increase above the nadir PSA, with or without hormonal therapy [24]. For high-risk cases, the authors recommend not to wait for a ≥2 ng/ml increase above nadir if patients are fit for salvage therapy and if relapse is confirmed by positive biopsy. The biochemical recurrence risk categories proposed by the EAU guidelines may influence patient management in the sense that patients classified to be at low risk as per EAU definition may be offered observation and possibly delayed salvage radiotherapy [3]. Data on salvage therapies for local recurrence after radiation therapy are limited and are primarily retrospective, but these approaches may be considered in fit patients if there is potential for cure [25,26].

Q9: For asymptomatic patients with rising PSA after radical (definitive) radiation therapy, 29% of panellists

would perform imaging if the confirmed PSA level was rising but was <2 ng/ml above nadir, 39% would perform imaging if PSA was ≥2 ng/ml above nadir (Phoenix criteria), 3% would perform imaging if PSA was ≥2 ng/ml above nadir with a PSA doubling time of <12 mo, and 29% would not perform imaging based on PSA value or PSA kinetics alone, but instead would consider a combination of PSA kinetics and ISUP grade. There were no abstentions. (No consensus for any given answer option)

3.2. PSA recurrence after radical prostatectomy

The EAU and ASTRO/American Urological Association guidelines have defined biochemical recurrence after prostatectomy as a confirmed serum PSA value of ≥0.2 ng/ml [27,28]. Time from prostatectomy until biochemical recurrence, PSA kinetics (namely PSA doubling time), pathological ISUP grade, and local disease characteristics (surgical margin, pT status, and pN status) are important prognostic factors [29,30]. Current EAU guidelines no longer include a specific PSA threshold when defining biochemical recurrence [3]. Instead, they suggest evaluating specific risk factors and considering whether the results of further investigations will influence subsequent treatment decisions.

Q11: For patients with rising PSA after radical prostatectomy, 4% of panellists would perform imaging if the confirmed PSA level was <0.2 ng/ml, 56% would perform imaging if PSA was >0.2–0.5 ng/ml, 16% would perform imaging if PSA was >0.5–1.0 ng/ml, 11% would perform imaging if PSA was >1 ng/ml, and 13% would not perform imaging based on PSA value or PSA kinetics alone, but instead would consider a combination of PSA kinetics and ISUP grade. There were no abstentions. (No consensus for any given answer option)

At APCCC 2017, 38% of panellists voted for starting salvage radiation therapy at a confirmed PSA level of >0.1 ng/ml, while 44% voted for a threshold of >0.2 ng/ml [2]. Rather than setting a specific threshold, current EAU guidelines recommend treating patients whose PSA rises from the undetectable range (especially if patients meet high-risk criteria, as discussed above) and potentially postponing salvage external beam radiation therapy if patients are at low risk [3].

Q13: For the majority of postprostatectomy patients with isolated rising PSA, if salvage radiation therapy is planned, 4% of panellists would start before PSA reached 0.1 ng/ml, 33% before PSA reached 0.2 ng/ml, 46% before PSA reached 0.5 ng/ml, and 6% before PSA reached 1.0 ng/ml, and 11% would not perform salvage radiation therapy based on PSA level alone, but instead would consider a combination of PSA kinetics and ISUP grade. There were three abstentions. (No consensus regarding at which PSA level to start salvage radiation therapy)

Imaging in patients with biochemical recurrence plays a role in either localising recurrent disease in the prostate bed, or detecting regional or distant metastases. The current literature suggests that PSMA PET/CT-based imaging has the highest sensitivity for detecting recurrent prostate cancer. However, it is unknown whether the results of PSMA PET/CT lead to management changes that alter clinically relevant outcomes, as opposed to those of standard early salvage prostate bed radiotherapy.

Q10: For imaging of patients with rising PSA after radical radiation therapy of the prostate, 80% of panellists voted for PSMA PET/CT (plus/minus pelvic MRI), 9% voted for CT and/or bone scintigraphy (plus/minus pelvic MRI), 7% voted for fluciclovine or choline PET/CT (plus/minus pelvic MRI), and 4% voted for whole-body MRI alone (plus/minus pelvic MRI). There were no abstentions. (Consensus for PSMA PET/CT)

Q12: For imaging of patients with rising PSA after radical prostatectomy, 87% of panellists voted for PSMA PET/CT (plus/minus pelvic MRI), 7% voted for CT and/or bone scintigraphy (plus/minus pelvic MRI), 4% voted for fluciclovine or choline PET/CT (plus/minus pelvic MRI), and 2% voted for whole-body MRI alone (plus/minus pelvic MRI). There were no abstentions. (Consensus for PSMA PET/CT)

In the phase 3 RTOG 9601 trial, the addition of 2 yr of bicalutamide therapy (150 mg daily) to radiation therapy was associated with a statistically significant improvement in OS compared with radiation therapy alone among patients with a detectable PSA level (0.2–4.0 ng/ml) after radical prostatectomy. Of note, the study included patients with PSA persistence as well as PSA recurrence [31]. The phase 3 GETUG-16 trial, which enrolled only patients with postprostatectomy PSA recurrence, identified a statistically significant improvement in PFS with 6 mo of gonadotropin-releasing hormone (GnRH) analogues plus salvage radiation therapy as compared with radiation therapy alone [32]. In a recent update of this trial, an increase in the secondary endpoint of 120-mo metastasis-free survival (MFS) was reported, but this was a post hoc analysis [33]; furthermore, these results were reported after APCCC 2019. The phase 3 RTOG 0534 trial also demonstrated an increase in FFS with the addition of 4–6 mo of GnRH analogues to salvage radiation therapy [34], but to date, these results have been published only in abstract form.

A recent systematic review of hormone therapy in the setting of salvage radiation therapy identified important risk factors (including PSA prior to salvage radiation therapy, Gleason score, and margin status) that may identify which patients undergoing radiation therapy are most likely to benefit from the addition of hormone therapy [35]. As the authors emphasised, the optimal type and duration of hormone therapy in the setting of salvage radiation therapy remain unknown; these questions are currently the subject of large phase 3 clinical trials (RADICALS, completed, NCT00541047; and GETUG-AFU 17, NCT00667069).

Q14: For patients with PSA recurrence after radical prostatectomy, 61% of panellists voted for systemic

hormonal therapy in combination with salvage radiation therapy for the majority of patients, while 39% voted for this combination only in a minority of selected patients based on factors such as PSA level, PSA kinetics, and primary tumour characteristics. There was one abstention. (No consensus for any given answer option)

Q15: For patients for whom systemic hormonal therapy is recommended in combination with salvage radiation therapy, 91% of panellists voted for LHRH agonist or antagonist therapy, 7% voted for bicalutamide 150 mg daily, 2% voted for bicalutamide 50 mg daily, and none voted for another hormonal therapy. There were no abstentions. (Strong consensus for LHRH agonist or antagonist as systemic therapy in combination with salvage radiation therapy)

Q16: Regarding the recommended duration of systemic hormonal treatment in combination with salvage radiation therapy for the majority of patients, 79% of panellists voted for short-term (4–12 mo) hormonal treatment and 21% voted for >12–24 mo of hormonal treatment. No panellists voted for long-term or lifelong hormonal treatment for the majority of patients. There were no abstentions. (Consensus for short-term systemic therapy in combination with salvage radiation therapy)

3.3. PSA persistence

Detectable PSA (PSA persistence) after radical prostatectomy, which may be associated with poorer oncological outcomes [36], has a prevalence of approximately 5–20% based on contemporary sensitive assays and cancer stage at surgery [37,38]. Higher preoperative PSA, more advanced pathological tumour stage, pathological ISUP grade groups 3–5, positive surgical margins, and pN1 status all have been associated with an increased risk of PSA persistence [36]. The EAU guidelines define PSA persistence as a detectable PSA level of >0.1 ng/ml within 4–8 wk after surgery, while NCCN guidelines define PSA persistence as a failure of PSA to fall to undetectable levels [3].

Accurate imaging for staging is critical to identify disease outside the planned surgery or radiotherapy field that will inevitably lead to PSA persistence. More accurate imaging with PSMA PET/CT may enable more rational selection of optimal therapy. The results of a large randomised controlled trial, the ProPSMA study, will help establish whether PSMA PET/CT should replace conventional staging with CT and bone scanning [9].

With the availability of more sensitive imaging, the question also arises as to whether imaging should be repeated soon after surgery in patients with PSA persistence. Factors such as pT stage, resection margins, and ISUP grade should be taken into consideration, and while PSMA PET/CT-based imaging may help identify residual regional or distant tumour, pelvic MRI may also merit inclusion to rule out significant residual tumour or retained prostatic tissue.

Q17: For asymptomatic pN0 patients with negative preoperative imaging and PSA persistence 4–6 wk after radical prostatectomy (EAU guideline definition: confirmed ≥0.1 ng/ml) [3], 41% of panellists voted for repeat imaging, 22% voted for repeat imaging only given other adverse factors (eg, positive surgical margins), and 37% voted against repeat imaging. There was one abstention. (No consensus for any given answer option)

Few studies and no large prospective trials have evaluated the management of patients with PSA persistence after radical prostatectomy. Current treatment options include radiation therapy, which may be combined with hormonal therapy.

In a recent observational study of 925 patients who underwent radical prostatectomy followed by early salvage radiation therapy, early salvage radiation therapy provided a MFS benefit among patients with PSA persistence ($n = 224$) only when Gleason score was ≤7 [39].

Q18: For asymptomatic pN0 patients with negative preoperative imaging and PSA persistence (≥0.1 ng/ml) 4–8 wk after radical prostatectomy, assuming that repeat imaging (with physician's choice of imaging modality) shows no evidence of macroscopic disease, 66% of panellists voted for salvage radiation therapy plus systemic hormonal treatment, 28% voted for PSA surveillance without immediate active treatment, 4% voted for salvage radiation therapy alone, and 2% voted for systemic hormonal treatment alone. There were four abstentions. (No consensus for any given answer option)

3.4. Rising PSA in nonmetastatic disease

Limited data are available regarding the optimal timing, duration, and modality of ADT in patients whose prostate cancer fails local curative-intent treatment but who have no detectable metastases. Data from the TOAD trial suggest that initiating ADT immediately, when clinically feasible, rather than at least 2 yr later might improve 5-yr OS, although the study was probably underpowered [40]; moreover, a combined analysis of TOAD and ELAAT with additional follow-up did not demonstrate an OS benefit [41]. In recent years, the question of when to initiate ADT has become far more complex with the advent and evolution of novel imaging modalities, metastasis-directed therapy, and new options for treating newly diagnosed mHSPC and nonmetastatic CRPC (nmCRPC), as well as an improved understanding of the adverse effects of ADT.

Q19: For men with nonmetastatic disease and confirmed rising PSA after local therapy (with or without salvage local radiation therapy), 9% of panellists voted for starting long-term ADT for the majority of patients, 80% voted for starting long-term ADT for a minority of selected patients (eg, those with PSA ≥ 4 ng/ml and rising, PSA doubling time ≤6 mo, or PSA ≥ 20 ng/ml [STAMPEDE inclusion criteria]), and 11% voted for starting long-term ADT only after the detection of

metastatic disease. There was one abstention. (Consensus for starting ADT only in selected patients)

3.5. Discussion of biochemical recurrence after local therapy

In contrast to APCCC 2017, panellists at APCCC 2019 clearly voted for PSMA PET/CT as the imaging method of choice for patients with biochemical recurrence after either radical radiation therapy (80%) or radical prostatectomy (87%).

Panellists did not reach consensus regarding when to first image patients with rising PSA after radical prostate radiation therapy. Only 39% voted to postpone imaging until patients meet Phoenix criteria (PSA nadir +2 ng/ml), while nearly 60% voted for earlier imaging or voted to base this decision on additional factors besides PSA level, such as PSA kinetics and histological grade. It is important to acknowledge that the timing of imaging is affected both by individual patient characteristics and by the availability and accessibility of local salvage treatments.

There was no consensus regarding the specific post-prostatectomy PSA level at which to initiate salvage radiation therapy, but taken together, 83% of panellists voted for starting before PSA reaches 0.5 ng/ml. In all, 11% of panellists based this decision on PSA value, doubling time, and ISUP grade, as suggested by the most recent EAU guidelines [3]. Although there was a trend towards it, there was no consensus for adding short-term ADT to salvage radiation therapy. Of note, the update of the GETUG-16 study, which reported a increase in the secondary endpoint of MFS with the addition of short-term ADT [33], was published after APCCC 2019 took place.

For patients with PSA persistence after radical prostatectomy, 63% of panellists voted for performing immediate additional imaging, at least for selected patients with other adverse risk factors. In addition, 70% of panellists voted for immediate salvage radiation therapy, either alone (4%) or in combination with systemic hormonal therapy (66%).

As discussed at APCCC 2017, the decision to initiate ADT in patients with biochemical recurrence after local therapy usually depends on multiple parameters, including projected life expectancy, PSA value and kinetics, and comorbidities [2]. For patients with rising PSA and nonmetastatic disease (imaging modality unspecified), there was consensus that ADT should be initiated only if patients have high-risk features. It is important to note that if next-generation imaging is available, it will detect recurrent disease in a very high percentage of these patients, while CT and bone scintigraphy often will be negative for metastases. Clinicians should be aware, however, that PSMA is not detected in all prostate tumours and that PSMA PET/CT-based imaging, as a new modality, is subject to a variety of causes of false-positive and false-negative results [42,43]. Inclusion of nuclear medicine expertise in the multidisciplinary team is encouraged to optimise the use of next-generation imaging [44].

Overall, panellists' opinions reflected our current understanding that biochemical relapse after local therapy with curative intent is not, by itself, strongly or even moderately associated with worse OS. This is the rationale for deferring immediate treatment (and possibly not even recommending additional imaging) of these patients unless they have high-risk characteristics. There is a need for clinical trials to define the role of stereotactic body radiation therapy, systemic therapies, and withholding of salvage radiation therapy if pelvic disease is not detected.

4. Management of the primary tumour in the metastatic setting

Since APCCC 2017, new evidence has emerged regarding the management of the primary tumour in patients with *de novo* metastatic prostate cancer. Two trials were conducted to assess whether local radiotherapy of the primary tumour improves OS outcomes and prevents long-term local complications [45,46]. In the randomised HORRAD trial, 432 patients with newly diagnosed bone-metastatic prostate cancer and PSA > 20 ng/ml received the standard of care, with or without radiotherapy of the tumour (either 70 Gy in 35 fractions over 7 wk or 57.76 Gy in 19 fractions over 6 wk) [45]. The median follow-up time was 47 mo; neither radiotherapy regimen was found to improve OS when added to the standard of care.

The second source of evidence is from the "M1/RT comparison" of arms A and H of the STAMPEDE trial, in which 2061 patients with newly diagnosed metastatic prostate cancer were randomised to receive the standard-of-care treatment with or without radiotherapy of the primary tumour (either 55 Gy in 20 fractions over 4 wk or 36 Gy in six fractions over 6 wk) [46]. After a median follow-up time of 37 mo, the addition of radiation therapy did not improve OS in the overall cohort of unselected patients, but an OS benefit was reported in a prespecified subgroup analysis of patients with low-volume metastatic disease [46]. In addition, the STOPCAP meta-analysis of aggregate STAMPEDE and HORRAD data identified a 7% improvement in the 3-yr OS rate among men who had up to four bone metastases [47]. Results are pending from another large trial (PEACE-1; NCT01957436) that includes two arms in which patients with mHSPC received combination regimens that included radiotherapy.

To date, no randomised phase 3 trials have reported on the use of surgery for treating the primary tumour in the metastatic setting, although the phase 3 SWOG 1802 trial of standard systemic therapy with or without prostatectomy or radiation therapy is enrolling patients (NCT03678025).

Q20: Nearly all (98%) panellists agreed that based on the current literature, local treatment of the primary tumour has an OS benefit only in patients with newly diagnosed, low-volume/low-burden metastatic (M1) HSPC. The remaining 2% of panellists saw no clear OS benefit from local treatment of the primary tumour in any patient with newly diagnosed metastatic disease. There were no abstentions. (Strong consensus for an OS benefit from local treatment of the primary tumour in patients with low-volume/low-burden M1 disease)

Q21: For patients with newly diagnosed metastatic (M1) HSPC, 88% of panellists stated that it is not appropriate to extrapolate STAMPEDE data on prostate radiation therapy to radical surgery of the prostate, while 12% voted that it is appropriate to make this extrapolation. There was one abstention. (Consensus for not extrapolating STAMPEDE data on radiation therapy to surgery of the prostate)
Q22: For local treatment of the prostate in the majority of patients with newly diagnosed, low-volume/burden metastatic (M1) HSPC, 84% of panellists voted for radiation therapy to the prostate and 16% voted for prostatectomy. There was one abstention. (Consensus for radiotherapy)

In the STAMPEDE and HORRAD trials, only the prostate was included in the radiation therapy field [45,46]. In daily clinical practice, however, the question often arises as to whether to irradiate clinically enlarged pelvic lymph nodes (cN1) if the primary tumour is treated.

Q23: For patients with newly diagnosed, low-volume/burden metastatic (M1) HSPC who also have clinical pelvic N1 disease, 75% of panellists voted that the radiation treatment volume should encompass both the primary tumour and the pelvic lymph nodes, while 25% voted for radiation of the prostate only. There were three abstentions. (Consensus for radiation of the primary tumour and pelvic nodes in patients with newly diagnosed cN1 disease)

4.1. Discussion of management of the primary tumour in the metastatic setting

Thus far, only two trials have reported on local treatment of the primary tumour in newly diagnosed metastatic prostate cancer, and both were negative [45,46]. Nonetheless, panellists at APCCC 2019 reached a strong consensus for radiation therapy of the primary tumour for patients with M1 disease, provided that disease volume is low. Physicians seem to be convinced by the STAMPEDE subgroup analysis in which local treatment produced an OS benefit in patients with low-volume metastatic disease [46]. Of note, this subgroup analysis was preplanned and included a substantial number of patients.

The majority of panellists disagreed that the results from the STAMPEDE M1/RT comparison could be extrapolated to support radical prostatectomy in the setting of newly diagnosed M1 prostate cancer. Fortunately, several studies are underway, which may help clarify the value of this approach. The g-RAMPP study (NCT02454543) experienced slow accrual and closed prematurely after including 131 patients in the wake of the STAMPEDE results of the M1/RT arm, and the pilot TROMBONE trial (ISRCTN15704862) evaluated the safety of surgery in 51 patients with up to three metastases in bone or extrapelvic lymph nodes. A phase 2 trial has completed accrual (180 patients; NCT01751438), and a phase 3 trial (SWOG 1802, NCT03678025) plans to recruit 1200 patients who will receive systemic treatment with or without radical prostatectomy or radiation of the primary tumour.

Multidisciplinary tumour boards often discuss whether to include the pelvic lymph nodes in the radiation field when planning radiotherapy of metastatic cN1 prostate cancer. Although panellists at APCCC 2019 reached consensus that the radiation field for cN1 patients can include the pelvic lymph nodes, a word of caution is warranted that we lack data from large prospective trials supporting this approach. The HORRAD and STAMPEDE trials specifically limited the radiation field to the prostate [45,46], while in the fully accrued PEACE-1 trial (NCT01957436), additional radiation therapy of the pelvic nodes has been at the discretion of the investigators. Hence, this decision merits thoughtful, case-by-case consideration.

4.1.1. Oligometastatic prostate cancer

4.1.1.1. Defining oligometastatic prostate cancer. Despite a growing number of publications and even consensus statements [1,2,48–52], there is no consistent definition for oligometastatic prostate cancer. Patients may have either hormone-sensitive or castration-resistant disease; they may also differ with regard to the location and number of metastases, and whether these metastases are synchronous or metachronous relative to the initial diagnosis of prostate cancer. Although these differences may reflect different biological subtypes and the use of different imaging modalities, little is known about them or how they might affect treatment outcomes. Experts also continue to discuss how best to define clinically useful endpoints in clinical trials of oligometastatic prostate cancer.

Q45: Regarding which definition of oligometastatic prostate cancer is useful to guide treatment selection for local treatment of all lesions plus/minus systemic therapy, 46% of panellists voted for a limited number of synchronous or metachronous metastases in bone or lymph nodes, but not in visceral organs; 33% voted for a limited number of synchronous or metachronous metastases, including in visceral organs; 8% voted for a limited number of metachronous metastases in bone or lymph nodes, but not in visceral organs; 4% voted for a limited number of metachronous metastases, including in visceral organs; and 9% did not believe that oligometastatic prostate cancer exists as a clinically meaningful entity. There was one abstention. (No consensus for any given answer option)
Q46: In all, 68% of panellists considered it important to distinguish de novo treatment-naïve (synchronous) oligometastatic prostate cancer from oligometastatic prostate cancer recurring after local therapy (metachronous), while 32% viewed this distinction as unimportant. There was one abstention. (No consensus for any given answer option)
Q47: For patients with untreated de novo oligometastatic prostate cancer, 92% of panellists considered it important, when making treatment decisions, to distinguish

lymph node–only disease (including distant lymph node metastases) from disease that includes metastatic lesions at other sites, while 8% considered it unimportant. There were two abstentions. (Strong consensus for making the distinction)
Q48: Regarding treatment goals when recommending local treatment of all lesions instead of systemic therapy in oligometastatic prostate cancer, 18% of panellists voted for prolongation of PFS, 14% voted for prolongation of OS, 12% voted for delaying the start of ADT, 37% voted for all three reasons, 4% voted for disease cure, 2% voted for none of these answer options, and 13% voted against local treatment of all lesions in oligometastatic prostate cancer. There were no abstentions. (No consensus for any given answer option)
Q49: Regarding treatment goals when recommending local treatment of all lesions in addition to systemic therapy in oligometastatic prostate cancer, 69% of panellists voted for prolongation of both PFS and OS, 14% voted for prolongation of PFS only, 2% voted for prolongation of OS only, 4% voted for disease cure, and 11% voted against local treatment of all lesions in oligometastatic prostate cancer. There were no abstentions. (No consensus for any given answer option)
Q50: When considering prostate cancer to be oligometastatic, 48% of panellists voted for a cut-off of three or fewer metastases, 41% voted for a cut-off of five or fewer metastases, and 11% voted for any number of metastases that can be treated safely with ablative intent. There was one abstention. (No consensus for any given answer option)

The topic of next-generation imaging was thoroughly discussed at APCCC 2017 and in subsequent publications [2,53–56]. There is evidence that next-generation imaging is more sensitive and specific than CT or bone scintigraphy for detecting metastatic disease. However, the more important question remains unanswered, which is how the use of next-generation imaging affects relevant oncological outcomes. Although imaging with PSMA PET/CT is more sensitive, it remains unclear whether changes in management, particularly when identifying oligometastatic disease, are translating to better patient outcomes. At present, the reduction of false-positive results due to greater specificity and reporter agreement with PSMA PET/CT is an advantage that helps explain the rapid adoption of this imaging modality in jurisdictions where it is available and affordable [57].

Q51: In all, 79% of panellists voted that conventional imaging (CT and bone scintigraphy) was not sufficient to define the oligometastatic state for treatment planning, while 21% voted that conventional imaging was sufficient. There were no abstentions. (Consensus that CT and bone scintigraphy are not sufficient to define an oligometastatic state for treatment planning)
Q52: The panel voted on the question of whether low-volume disease defined by PET or MRI, but not evident on CT or bone scintigraphy, should be treated in the same way as low-volume disease by conventional definition (CT and bone scintigraphy). In all, 45% of panellists voted yes, and 55% voted no. There were two abstentions. (No consensus for any given answer option)
Q53: When planning local treatment of all lesions with or without systemic therapy in de novo oligometastatic prostate cancer, 30% of panellists voted to perform imaging in the majority of patients approximately 8–12 wk after initial diagnosis to confirm an oligometastatic state, 30% voted to perform this confirmatory imaging only in a minority of selected patients, and 40% voted against confirmatory imaging in these patients. There were three abstentions. (No consensus for any given answer option)

4.1.1.2. Synchronous "oligometastatic" prostate cancer. This section addresses the management of patients with de novo hormone-sensitive oligometastatic prostate cancer who, by definition, have an untreated primary tumour. No specific prospective randomised data are available showing a benefit of ablative treatment of all lesions, including the primary tumour. However, evidence from the STOPCAP meta-analysis and the STAMPEDE trial supports systemic therapy plus treatment of the primary tumour in patients with low-volume disease [47].

Q54: When performing confirmatory imaging (apart from local staging) for patients with de novo (synchronous) oligometastatic disease on CT and bone scintigraphy, 59% of panellists voted for PSMA PET/CT, 2% voted for fluciclovine or choline PET/CT, 3% voted for whole-body MRI without PET, 4% voted for a combination of two next-generation imaging methods, and 32% voted against additional imaging. There were no abstentions. (No consensus for any given answer option)
Q55: For the majority of patients with de novo (synchronous) oligometastatic prostate cancer based on conventional imaging who have an untreated primary tumour, 54% of panellists voted for systemic therapy plus treatment of the primary tumour and focal treatment of all lesions, 42% voted for systemic therapy plus treatment of the primary tumour, 2% voted for treatment of the primary tumour and focal treatment of all lesions without systemic therapy, and 2% voted for systemic therapy alone. There were no abstentions. (No consensus for any given answer option)
Q56: For patients with an untreated primary tumour and de novo (synchronous) oligometastatic prostate cancer detected by next-generation imaging but not by conventional imaging, 52% of panellists voted for systemic therapy plus treatment of the primary tumour and focal treatment of all lesions, 42% voted for systemic therapy plus treatment of the primary tumour, 4% voted for treatment of the primary tumour and focal treatment of all lesions without systemic therapy, and 2% voted for locoregional therapy only. There was one abstention. (No consensus for any given answer option)
Q57: For patients with de novo (synchronous) oligometastatic prostate cancer and an untreated primary

tumour who receive radical local treatment for the primary and all lesions, 56% of panellists voted to add an androgen receptor (AR) pathway inhibitor (abiraterone, apalutamide, or enzalutamide) to ADT, 8% voted to add docetaxel to ADT, 4% voted to add both docetaxel and an AR pathway inhibitor to ADT, and 32% would not add another systemic therapy to ADT. There were four abstentions. (No consensus for any given answer option)

4.1.1.3. Metachronous oligometastatic castration-naïve prostate cancer. This section addresses the management of castration-naïve patients who develop metachronous oligometastatic prostate cancer after receiving local curative-intent treatment for the primary tumour. Since APCCC 2017, one randomised trial has been published in this population, which showed longer ADT-free survival with local treatment of all lesions [58]. Another prospective trial, which was not randomised but consecutively enrolled patients with one to three lesions, found that about one-third remained ADT-free 2 yr after receiving stereotactic ablative body radiotherapy (SABR) [59]. Interestingly, SABR to metastatic lesions also showed an OS benefit in a randomised phase 2 trial of patients with various cancer types who had controlled primary tumours at baseline [60]. However, no randomised phase 3 trials with a primary endpoint of OS have yet been reported, and the overall clinical utility of SABR remains unknown.

Q58: Regarding which imaging modalities to use in patients with rising PSA after radical treatment to confirm a diagnosis of metachronous oligometastatic (oligorecurrent) prostate cancer if detected on CT and bone scintigraphy, 75% of panellists voted for PSMA PET/CT, 5% voted for whole-body MRI without PET, and 20% voted for no additional imaging. There was one abstention. (Consensus for PSMA PET/CT)
Q59: For the majority of patients with oligorecurrent prostate cancer, 75% of panellists voted for systemic therapy and local treatment of all lesions, while 25% voted for systemic therapy only. There were no abstentions. (Consensus for systemic therapy plus local treatment of all lesions)
Q60: For patients undergoing radical local treatment of all lesions for the management of oligorecurrent prostate cancer, 63% of panellists voted for adding a systemic AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide) to ADT, 4% voted for adding docetaxel to ADT, and 33% voted against adding another systemic therapy to ADT in these patients. There was one abstention. (No consensus for any given answer option)

4.1.1.4. Oligoprogressive disease. This section addresses the management of patients with limited metastatic progression of castration-resistant disease (ie, oligometastatic progression on ADT). No prospective randomised data have shown that local radical treatment of these few progressive lesions delays the need to initiate or switch to a new systemic treatment in addition to ADT.

Q61: Regarding the most useful definition of oligoprogressive prostate cancer, 60% of panellists voted for a limited number of progressing pre-existing or new lesion (s) in a patient with metastatic disease that is otherwise stable/treatment responsive, 13% voted for a single progressing pre-existing or new lesion in such a patient, and 27% did not believe that oligoprogressive prostate cancer is a meaningful clinical entity. There was one abstention. (No consensus for any given answer option)
Q62: For patients with oligoprogressive metastatic chemotherapy-naïve CRPC who experience further disease progression (without visceral metastases) on ADT plus an AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide), 46% of panellists voted for local treatment of all progressing lesions without switching to systemic therapy, 35% voted for switching from the current AR pathway inhibitor to another systemic therapy alone, and 19% voted for switching from the current AR pathway inhibitor to another systemic therapy and performing local treatment of all progressing lesions. There were four abstentions. (No consensus for any given answer option)

4.1.1.5. Discussion of oligometastatic prostate cancer. At APCCC 2019, the concept of oligometastatic prostate cancer seems to have emerged more clearly than in 2017 [2]. The majority of panellists considered the number of lesions and their synchronicity or metachronicity to be important prognostic variables; these factors, together with castration status, can help facilitate treatment planning [61–63]. In addition, lymph node–only oligometastatic disease should be differentiated from oligometastatic disease involving metastases at other sites, particularly visceral metastases.

When recommending local treatment of all lesions in lieu of systemic therapy, there was no specific consensus on treatment goals, with 81% of panellists voting that the goal of treatment was either to delay the initiation of ADT or to prolong PFS or OS. The lack of consensus on this question reflects the lack of evidence-based data supporting local treatment of all lesions without systemic therapy in these patients. There also was no specific consensus on local treatment of all lesions in addition to systemic therapy, although 69% of panellists voted for prolongation of both PFS and OS. Interestingly, for both questions, only 4% of panellists voted for cure as the treatment goal, reflecting the importance of the “metastatic state” in these patients. It is important to acknowledge the lack of definitive evidence that local treatment of all lesions significantly improves clinical endpoints for patients with oligometastatic prostate cancer.

The clear consensus that CT and bone scintigraphy are not sufficient to define the oligometastatic state reflects the increasing availability and familiarity in the use of next-generation imaging. Interestingly, 55% of panellists stated that low-volume disease should be treated differently

depending on whether it is detectable by conventional imaging (CT or bone scintigraphy) or only by PET/CT or MRI. This probably reflects the viewpoint that there is a clinical difference between a low-volume state based on conventional imaging and a low-volume state based on next-generation imaging.

For patients with synchronous oligometastatic prostate cancer, the voting reflected the results of the STAMPEDE [46] and HORRAD [45] trials (even if low volume did not always correlate with oligometastatic disease) and the STOPCAP meta-analysis [47], with a very strong majority (a composite 96%) of panellists recommending at least local treatment of the primary tumour in addition to systemic therapy. For this question, 54% of panellists voted to add focal treatment of all lesions, which lacks supporting evidence from the literature but will be assessed in forthcoming trials (new comparison in the STAMPEDE trial, NCT03298087, NCT03449719, NCT037847455, and NCT03436654). Regarding systemic therapy, a majority (68%) of panellists voted to intensify systemic treatment by adding a direct AR pathway inhibitor, docetaxel, or a combination of these therapies to ADT. Of note, currently there is no level 1 evidence supporting the addition of an AR pathway inhibitor to ADT for patients with synchronous oligometastatic prostate cancer who are receiving local treatment for the primary tumour.

For patients with metachronous oligometastatic prostate cancer, there was consensus for the use of PSMA PET/CT-based imaging to confirm this state and for systemic therapy plus local treatment of all lesions. Once again, there currently is no evidence for this treatment approach, and concerns have been raised about false-negative and false-positive results with this imaging modality. Individual patient factors, including time since local therapy, location and number of metastases, imaging modality, age, and comorbidities, should be taken into consideration during treatment planning. An increasing number of clinical trials are enrolling patients with oligometastatic prostate cancer [64], including several large phase 2/3 clinical trials (NCT03525288 [PSMA-PETgRT], NCT03678025, NCT02759783 [CORE; includes prostate but also other tumours], and an oligometastatic comparison in STAMPEDE).

The concept of oligoprogressive disease is even less well defined, which was reflected in the voting. However, with the increasing use of AR pathway inhibitors in patients with newly diagnosed HSPC (who have few other alternatives to chemotherapy), the early identification and possible local treatment of resistant clones/lesions may become increasingly important in the future and should be assessed in clinical trials.

4.1.2. Newly diagnosed HSPC

4.1.2.1. Nomenclature. The terms “hormone naïve”, “hormone sensitive”, “noncastrate”, “castration naïve”, and “castration sensitive” continue to be used interchangeably to refer to prostate cancer that either is previously untreated with ADT or demonstrates on-going ADT sensitivity. It is important to at least consider how to find a novel nomenclature that avoids using the term “castration”, which patients dislike [65,66]. In addition, as new AR-inhibitor therapies have emerged, it has become somewhat unclear what the term “ADT” refers to—testosterone suppression alone, AR inhibitor monotherapy, or testosterone suppression in combination with AR inhibition. For the sake of consistency, this paper uses the term “hormone-sensitive prostate cancer”.

> Q24: In all, 45% of panellists voted to avoid the term “castration” when discussing patients with APC, while 55% voted not to avoid the term. There were no abstentions. (No consensus for any given answer option)
> Q25: To describe metastatic prostate cancer in patients who are about to start ADT, 47% of panellists voted for the term hormone naïve, 23% voted for hormone sensitive, 18% voted for castration naïve, 7% voted for metastatic prostate cancer receiving a first-line (specific or given) systemic therapy, and 5% voted for castration sensitive. There were no abstentions. (No consensus for any given answer option, but a combined total of 77% voted for a term that did not include “castration” in this setting)
> Q26: To describe patients with metastatic prostate cancer who are progressing in the context of a suppressed testosterone (testosterone level $<$50 ng/ml), 87% of panellists voted for the term castration-resistant prostate cancer (CRPC), while 13% voted for metastatic prostate cancer progressing after (a specific or given) systemic therapy. There were no abstentions. (Consensus for the term CRPC)

Some men with prostate cancer may present with hypogonadal serum testosterone levels. Population data on this phenomenon are lacking, but one study identified hypogonadal levels of serum testosterone ($<$250 ng/dl) in 32.6% of 52 men with low-risk prostate cancer who had received local therapy only [67]. In most cases, their hypogonadal testosterone level was secondary to a low serum level of luteinising hormone (LH). There also is some evidence that the level of testosterone achieved on ADT correlates with the time of detection of castration resistance [68].

Importantly, most commercial assays cannot precisely or reliably quantify low serum testosterone levels in men receiving ADT. Both exogenous and endogenous factors impede the accuracy of these tests for detecting low serum testosterone levels in this population. Hence, liquid chromatography mass spectrometry remains the gold standard [69–73].

> Q27: In all, 70% of panellists voted for measuring total testosterone level in the majority of patients before starting first-line ADT, 12% voted for measuring total testosterone only in a minority of selected patients, and 18% did not support this practice. There was one abstention. (No consensus for any given answer option, but a combined total of 82% voted to measure total testosterone before starting first-line ADT, at least in selected patients)

Historically, many men who started on treatment for metastatic prostate cancer had a presumptive diagnosis

based on a characteristic clinical picture. At APCCC 2019, panellists discussed the need for tumour biopsy (from either the prostate or another easily accessible lesion) and whether to obtain histopathological confirmation before initiating ADT in symptomatic patients with high suspicion for metastatic prostate cancer based on PSA levels and imaging (eg, widespread and characteristic bone metastases on bone scintigraphy).

Q28: In all, 95% of panellists voted for histopathological confirmation of prostate cancer (either before or after initiation of ADT) in the majority of patients with high suspicion of metastatic prostate cancer (based on PSA and imaging), while 5% voted for histopathological confirmation only in a minority of selected patients. There were no abstentions. (Strong consensus for histopathological confirmation of prostate cancer in the majority of patients)
Q29: For symptomatic patients with high suspicion of metastatic prostate cancer (based on PSA and imaging), 54% of panellists voted for initiating ADT prior to histopathological confirmation in the majority of patients, 43% voted for doing so in a minority of selected patients, and 3% voted against doing so. There were no abstentions. (No consensus for any given answer option, but a combined total of 97% voted for initiating ADT prior to histopathological confirmation, at least in selected patients)

Initiation of a GnRH agonist causes an initial LH and testosterone surge before serum testosterone falls to castrate levels [74]. This surge can be associated with acute expansion of tumour deposits with associated symptom worsening. This phenomenon is specific to GnRH agonists and is not observed with either GnRH antagonist use or surgical castration [75].

Q30: For patients initiating GnRH agonist therapy for newly diagnosed metastatic (M1) HSPC, 68% of panellists voted for a short course of a first-generation nonsteroidal AR antagonist as flare protection in the majority of patients, 30% voted for this practice only if patients are at risk of harm from disease flare, and 2% voted against flare protection. There were two abstentions. (No consensus for any given answer option)

4.1.2.2. Metastatic (M1) HSPC. Testosterone suppression alone (monotherapy) has been the therapeutic standard for metastatic prostate cancer for nearly 70 yr [76]. Although the majority of men with mHSPC experience a PSA decline with ADT, the median FFS time is approximately 1 yr and ranges widely [77]. The first improvement in the existing standard of ADT alone came from two large studies in which the addition of docetaxel improved OS [15,78]. The GETUG-15 trial, which was the first published phase 3 study of docetaxel in mHSPC, showed an improvement in PFS but not in OS [79]. However, a subsequent meta-analysis of data from all relevant trials confirmed the OS benefit of adding docetaxel to ADT [80,81].

In recent years, additional large phase 3 trials have advanced the standard of care in patients with mHSPC by demonstrating that the addition of docetaxel, abiraterone, apalutamide, or enzalutamide to ADT is associated with a statistically significant improvement in PFS and/or OS compared with ADT alone [14,61,63,78,79,82–85]. However, experts continue to discuss how best to define "high-volume disease", "high-risk disease", and "burden of disease" for the purposes of treatment selection. Definitions that have been used in clinical trials are often applied in practice, even though they do not completely overlap. In the phase 3 CHAARTED trial, the benefit of adding docetaxel to ADT seemed to be limited to a prespecified subgroup of patients with high-volume disease [63], while a retrospective analysis of the 76% of M1 patients with available imaging in the larger phase 3 STAMPEDE trial found no evidence that the benefits of adding docetaxel varied to a statistically significant extent in low- versus high-volume disease as per CHAARTED criteria [86]. Of note, almost all M1 patients in STAMPEDE had de novo metastatic disease, whereas approximately a third of patients in CHAARTED and GETUG-15 had developed metastatic disease after receiving definite local treatment [61,63,86].

The phase 3 LATITUDE trial, which compared abiraterone-prednisone plus ADT with ADT alone, included only patients with at least two out of three high-risk features (Gleason score $\geq$8 or more, three or more bone lesions, and measurable visceral metastasis) [84]. Another comparison in the STAMPEDE protocol evaluated the same combination in M0 and unselected M1 patients, and also demonstrated a significant OS benefit for the M1 population. Additionally, a post hoc analysis of these STAMPEDE data indicated that patients derived a similar benefit from the addition of abiraterone-prednisolone to ADT, regardless of whether they were classified as high or low risk according to LATITUDE criteria [87]. In the TITAN and ENZAMET trials, which evaluated ADT with apalutamide and enzalutamide, respectively, there was no evidence of a differential effect based on disease volume [82,83].

Q31: To guide the treatment selection of docetaxel in addition to ADT in patients with HSPC, 46% of panellists voted for using the definition of high/low-volume disease, 9% voted for the definition of high/low-risk disease, 25% voted for either definition, and 20% voted for neither definition. There were no abstentions. (No consensus for any given answer option)
Q32: To guide the treatment selection of abiraterone in addition to ADT in patients with HSPC, 17% of panellists voted for using the definition of high/low-volume disease, 23% voted for the definition of high/low-risk disease, 26% voted for either definition, and 34% voted for neither definition. There were no abstentions. (No consensus for any given answer option)
Q33: To guide the treatment selection of enzalutamide or apalutamide in addition to ADT in patients with HSPC, 16% of panellists voted for using the definition of high/low-volume disease, 4% voted for the definition of high/low-risk disease, 25% voted for either definition, and 55%

voted for neither definition. There were no abstentions. (No consensus for any given answer option)

The results of an opportunistic comparison of randomised data from the abiraterone and docetaxel arms of STAMPEDE, which accrued simultaneously and are therefore contemporaneous, suggested that abiraterone was superior in terms of FFS and PFS but demonstrated no discernible advantage for either agent in terms of MFS, symptomatic skeletal events (SSEs), cause-specific survival, or OS [88]. However, the follow-up time for these analyses was rather short, and their results may have been affected by the short duration of docetaxel therapy (18 wk in STAMPEDE).

Initiation of enzalutamide or apalutamide together with ADT has also been found to improve radiological PFS and OS in men with either high- or low-volume prostate cancer [82,83,85]. However, triple therapy with an AR antagonist, concurrent docetaxel, and ADT increases the risk of toxicity and has not (thus far) been found to further prolong OS [83].

Questions 34–40 pertain to newly diagnosed mHSPC in patients who are fit for (ie, have no contraindications to) additional treatment with docetaxel, abiraterone, enzalutamide, or apalutamide in settings without regulatory limitations. Metastatic HSPC can be diagnosed either de novo or following relapse after local treatment. Experts continue to debate whether intensification of ADT by adding docetaxel, abiraterone, enzalutamide, or apalutamide produces similar effects in these two scenarios, so they were discussed separately at APCCC 2019.

Q34: Regarding which treatment to add to ADT in patients with de novo high-volume metastatic (M1) HSPC without symptoms from the primary tumour, 56% of panellists voted for either docetaxel or an AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide), 24% voted for an AR pathway inhibitor, 16% voted for docetaxel, 4% voted for docetaxel plus an AR pathway inhibitor, and none voted for ADT alone. There were no abstentions. (No consensus for any given answer option, but no panellist voted for ADT alone)
Q35: Regarding which treatment to add to ADT in patients with newly diagnosed high-volume metastatic (M1) HSPC relapsing after local treatment of the primary tumour, 58% of panellists voted for either docetaxel or an AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide), 26% voted for an AR pathway inhibitor, 8% voted for docetaxel, 2% voted for docetaxel plus an AR pathway inhibitor, and 6% voted for ADT alone (no additional treatment). There were no abstentions. (No consensus for any answer option, but a combined total of 94% voted for some form of additional treatment together with ADT)
Q36: Regarding which treatment(s) to add to ADT in patients with de novo low-volume metastatic (M1) HSPC without symptoms from the primary tumour, 54% of panellists voted for an AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide) plus local treatment of the primary tumour, 13% voted for docetaxel plus local treatment of the primary tumour, 11% voted for an AR pathway inhibitor as sole additional therapy, 2% voted for docetaxel as sole additional therapy, 5% voted for either docetaxel or an AR pathway inhibitor as sole additional therapy, 13% voted for treatment of the primary tumour alone, and 2% voted for ADT alone (no additional therapy). There were no abstentions. (No consensus for any given answer option, but a combined total of 85% voted for some form of additional treatment together with ADT, and a combined total of 80% voted for treatment of the primary tumour)
Q37: Regarding which treatment to add to ADT in patients with newly diagnosed low-volume metastatic (M1) HSPC relapsing after local treatment of the primary tumour, 59% of panellists voted for an AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide) as sole additional therapy, 4% voted for docetaxel as sole additional therapy, 30% voted for either docetaxel or an AR pathway inhibitor as sole additional therapy, and 7% voted for ADT alone (no additional therapy). There was one abstention. (No consensus for any given answer option, but a combined total of 93% voted for some form of additional treatment together with ADT)
Q38: Regarding the possibility of combining docetaxel and an AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide) in addition to ADT for the management of newly diagnosed metastatic (M1) HSPC, 11% of panellists voted for sequential administration (docetaxel first), 8% voted for concurrent administration, and 81% voted against the use of this combination. There were four abstentions. (Consensus for not using the combination of docetaxel plus an AR pathway inhibitor with ADT)
Q40: Regarding which AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide) to add to ADT for the majority of patients with newly diagnosed metastatic (M1) HSPC, 37% of panellists voted for abiraterone, 11% voted for either enzalutamide or apalutamide, and 52% had no preference. There was one abstention. (No consensus for any given answer option)

Some clinical scenarios may suggest variant histology, including small cell or neuroendocrine differentiation [2,89,90]. Examples include bulky metastatic disease in the context of low PSA and lytic bone metastases or liver metastases. Question 39 describes a patient with newly diagnosed metastatic prostate cancer who fits the criteria of “high-volume” and “high-risk” metastatic disease without histopathological evidence of small cell carcinoma.

Q39: For a patient with de novo high-volume and/or high-risk metastatic (M1) HSPC, Gleason score $\geq$9, multiple liver metastases and/or lytic bone metastases, and a low PSA value ($<$20 ng/ml) but no histopathological evidence of small cell carcinoma, 75% of panellists voted to add docetaxel to ADT, 16% voted to add platinum-based combination therapy, 9% voted to add an AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide), and none voted to add a PARP inhibitor to ADT or to administer ADT alone. There was one

abstention. (Consensus to add docetaxel to ADT in this setting)

When treating patients with CRPC using abiraterone, it is recommended to coadminister prednisone or prednisolone at a dose of 5 mg twice daily [91,92]. However, both the LATITUDE and STAMPEDE trials used abiraterone with only 5 mg prednisone once daily [14,84]. As the half-life of prednisone is <16 h, the lower dose—which arguably may be associated with fewer long-term side effects from glucocorticoid excess—may lead to inadequate blockage of the mineralocorticoid excess syndrome induced by abiraterone, thus resulting in higher rates of fluid retention, hypertension, and hypokalaemia [14,84]. Identification of the "best" steroid partner for abiraterone is important because of the potentially longer treatment durations in the HSPC setting, the risk of clinically important adverse events with lower doses of steroids, and the increasing awareness that steroid therapy can adversely affect bone health and can have other adverse effects with chronic use.

To address this knowledge gap, a recent open-label phase 2 clinical trial randomly assigned (1:1:1:1) 164 men with mCRPC receiving abiraterone to receive one of four glucocorticoid comedication regimens. The primary endpoint, the absence of mineralocorticoid excess (grade ≥1 hypokalaemia or grade ≥2 hypertension) in the first 24 wk, was met by regimens consisting of prednisone 5 mg twice daily or dexamethasone 0.5 mg once daily [93]. It is important to note that patients on abiraterone who are receiving lower steroid doses, such as prednisolone 5 mg once daily or 2.5 mg twice daily, are at increased risk for hypokalaemia or hypertension and therefore require careful monitoring.

Q41: Regarding which glucocorticoid regimen to use when starting abiraterone in patients with newly diagnosed metastatic (M1) HSPC, 52% of panellists voted for prednisone/prednisolone at 5 mg once daily, 39% voted for prednisone/prednisolone at 5 mg twice daily, 5% voted for prednisone/prednisolone at 10 mg once daily, and 4% voted for dexamethasone at 0.5–1 mg once daily. There was one abstention. (No consensus for any given answer option)

Owing to a lack of data, current guidelines provide very little guidance on the preferred modality and frequency of imaging or other strategies for monitoring patients with metastatic prostate cancer [3,94]. Despite the increasing use and availability of next-generation imaging, all trials discussed in this section have used conventional imaging (CT and bone scintigraphy) to categorise patients (eg, as high-risk or high-volume patients) and treatment response. Although PSMA PET/CT provides compelling imaging with striking tumour-to-background contrast, it remains unclear whether its use can improve outcomes among patients with newly diagnosed advanced metastatic disease compared with conventional imaging. Advantages of PSMA PET/CT may include the ability to assess response earlier and more reliably than anatomic imaging, and to differentiate a healing response from true progression on bone scanning. The incorporation of PSMA PET/CT into prospective trials is recommended to ascertain its additional utility and effectiveness in comparison with conventional imaging.

Q42: For the majority of patients with newly diagnosed metastatic (M1) HSPC, 56% of panellists voted for baseline imaging with follow-up imaging at 6–12 mo or best response followed by monitoring PSA alone with further imaging at progression, 27% voted for baseline imaging followed by monitoring PSA alone with further imaging at progression, and 17% voted for baseline imaging with follow-up imaging every 3–6 mo. There were two abstentions. (No consensus for any given answer option)

Q43: For the majority of patients with newly diagnosed high-volume metastatic (M1) HSPC based on CT and bone scintigraphy, 78% of panellists voted for no additional imaging (ie, CT and bone scintigraphy are sufficient), 18% voted for additional PSMA PET/CT, 2% voted for additional fluciclovine or choline PET/CT, and 2% voted for additional whole-body MRI. There were no abstentions. (Consensus for no additional imaging)

Q44: For the majority of patients with newly diagnosed low-volume metastatic (M1) HSPC based on CT and bone scintigraphy, 66% of panellists voted for no additional imaging (ie, CT and bone scintigraphy are sufficient), 32% voted for additional PSMA PET/CT, 2% voted for additional whole-body MRI, and none voted for additional fluciclovine or choline PET/CT. There were no abstentions. (No consensus for any given answer option)

4.1.2.3. Discussion of newly diagnosed HSPC. At APCCC 2017, only data on ADT plus docetaxel were available and discussed in detail. Since then, positive phase 3 trial data have also been published for abiraterone, enzalutamide, and apalutamide, and physicians and patients often must navigate increasingly complex decisions when evaluating the optimal therapy to add to ADT for patients with newly diagnosed mHSPC.

At APCCC 2019, there was clear consensus that histopathological confirmation of prostate cancer should be obtained for patients with newly diagnosed metastatic disease based on imaging and PSA. Histopathology may be important for risk classification (eg, high risk as per LATITUDE) and for tumour genomic profiling (see section 8). However, the majority of panellists would not delay initiation of ADT while awaiting biopsy results in symptomatic patients with high suspicion of metastatic disease. Furthermore (and especially in such patients), if a GnRH agonist is chosen for ADT, it should be initiated concomitantly with a short course of a first-generation nonsteroidal AR antagonist to protect against flare.

There was no consensus regarding the specific definition of mHSPC (high or low volume, or high or low risk) to use when evaluating whether to add docetaxel, abiraterone, enzalutamide, or apalutamide to ADT, although a combined total of 80% of panellists recommended using one or the

other definition to guide treatment selection. For docetaxel and abiraterone, the majority of panellists recommended using "high-volume disease", "high-risk disease", or either definition, while for enzalutamide and apalutamide, the majority of panellists did not recommend using either definition.

There was clear consensus to add either docetaxel or an AR pathway inhibitor to ADT in fit patients with either high-volume de novo mHSPC or high-volume mHSPC relapsing after local treatment. For de novo low-volume mHSPC, the majority of panellists would treat the primary tumour in the context of de novo low-volume mHSPC. The majority would also add an AR pathway inhibitor to ADT. As yet, there is no high-level evidence to support the triple combination of ADT, an AR pathway inhibitor, and treatment of the primary tumour. Only 10% of panellists recommended adding docetaxel to ADT, and there was clear consensus not to combine ADT with both an AR pathway inhibitor and docetaxel. This is in line with a prespecified subgroup analysis of the ENZAMET trial in which concomitant docetaxel was associated with prolonged PFS but not OS in men with mHSPC receiving enzalutamide plus ADT [83]. Longer follow-up is needed for triple combination therapies in various phase III mHSPC studies (ENZAMET; TITAN, and ARCHES), but for the moment, these regimens cannot be recommended. Of note, the on-going PEACE-1 study (NCT01957436) compares ADT plus docetaxel, with or without an AR pathway inhibitor (abiraterone), with or without local treatment of the primary tumour (radiotherapy), for the treatment of low-volume mHSPC. Another on-going trial, ARASENS (NCT02799602), compares ADT plus docetaxel, with or without darolutamide [95].

For patients with aggressive variant prostate cancer (lytic bone metastases, extensive liver metastases, and low PSA in relation to tumour volume), there was consensus to recommend addition of docetaxel rather than an AR pathway inhibitor to ADT, despite a lack of supporting data.

There was no consensus to treat mHSPC with a particular AR pathway inhibitor over others (assuming that all were available). While a combined total of 96% of panellists recommended the use of prednisone or prednisolone over dexamethasone when starting abiraterone therapy, only 52% recommended a prednisone/prednisolone dose of 5 mg once daily, which was the dose used in the STAMPEDE and LATITUDE trials [14,84]. Safety data from both trials support the use of 5 mg prednisone/prednisolone once daily for most patients. However, patients who receive this steroid dose and schedule should be monitored carefully for signs of secondary mineralocorticoid excess. If this occurs, a simple solution may be to increase the steroid dose by giving it twice daily. Prescribing information for abiraterone requires regular monitoring of potassium and liver function tests, which facilitates close surveillance of these patients, especially during the first few months of treatment.

Although there was no consensus for a specific imaging strategy in the mHSPC setting, only a minority of panellists recommended monitoring by PSA alone. Data on CRPC from the PREVAIL trial suggest that radiographic progression can occur in up to a quarter of patients with a nonrising PSA level defined as $\leq$1.05 times the PSA level from 3 mo earlier [96]. Previous APCCCs have also reached no consensus regarding monitoring by imaging [1,2]. The recommendations of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) [97], which are intended for the design of clinical trials, may support more consistent monitoring by imaging of patients with CRPC in daily clinical practice, and there are countries where next-generation imaging is readily accessible and frequently used for treatment monitoring. For patients with bone-only disease, serial whole-body MRI imaging may be valuable for assessing treatment response and detecting the development of resistance [53], although the real-world availability of this modality is limited. The superiority of next-generation imaging over CT and bone scintigraphy for treatment monitoring still needs to be demonstrated, as was discussed at APCCC 2017 [2]. This remains an unmet need that should be addressed by trials reflecting real-world patient populations and clinically relevant endpoints.

5. Management of M0 CRPC (nmCRPC)

Nonmetastatic CRPC, also known as M0 CRPC, has conventionally been defined as PSA progression in the setting of castrate levels of testosterone and no evidence of metastases on conventional imaging. Since 2015, when nmCRPC was last discussed, three new placebo-controlled phase 3 trials (SPARTAN, PROSPER, and ARAMIS) have demonstrated statistically significant improvements in the primary endpoint of MFS when patients with nmCRPC based on conventional imaging received second-generation AR antagonist therapy with apalutamide, enzalutamide, or darolutamide while continuing ADT [98–100]. All three trials enrolled only patients who were at high risk for metastatic disease (PSA doubling time $\leq$10 mo and PSA $\geq$ 2 ng/ml).

It is now clear that for many of the patients in these three trials, novel, more sensitive imaging modalities would have detected nodal or distant metastases. Imaging by PSMA PET/CT more accurately defines disease in patients with nmCRPC: In a retrospective study of 200 patients at high risk for metastatic disease (PSA doubling time $\leq$10 months and/or Gleason score $\geq$8), 44% had PSMA-positive pelvic nodal disease and 55% had M1 disease despite negative conventional imaging [101]. However, these data also contradict the frequent assumption that all patients with high-risk nmCRPC have occult distant metastases.

As time to metastasis is predicted by PSA doubling time, there is clinical interest in early intervention for men with shorter PSA doubling times [102]. Unless stated otherwise, the following questions pertain to patients with a total PSA level of $\geq$2 ng/ml and a PSA doubling time of $\leq$10 mo during continuous ADT. Finally, there are no randomised data on the use of abiraterone/prednisone in the setting of nmCRPC.

Q63: Regarding imaging, for the majority of patients with CRPC and rising PSA with no metastatic disease documented on past imaging, 58% of panellists voted for PSMA PET/CT, 39% voted for CT and/or bone

scintigraphy, and 3% voted for whole-body MRI without PET. There were no abstentions. (No consensus for any given answer option)

Q64: For asymptomatic patients with nmCRPC (M0 CRPC; no metastatic disease documented on past imaging) who are on ADT, have a rising PSA level, and have a PSA doubling time of ≤10 mo, 14% of panellists voted for performing imaging when PSA is <1 ng/ml, 26% voted for when PSA is ≥1 but ≤2 ng/ml, and 41% voted for when PSA is >2 but ≤10 ng/ml, and 19% would not use absolute PSA values to guide imaging. There were no abstentions. (No consensus for any given answer option)

Q65: In all, 60% of panellists stated that it is not appropriate to extrapolate data from SPARTAN, PROSPER, and ARAMIS to the use of abiraterone in nmCRPC (M0 CRPC), while 40% stated that this is appropriate. There were two abstentions. (No consensus for any given answer option)

Q66: For treating the majority of nmCRPC (M0 CRPC) patients whose PSA is ≥2 ng/ml and PSA doubling time is ≤10 mo, 4% of panellists voted for apalutamide, 16% voted for darolutamide, 4% voted for enzalutamide, 62% voted for any of these three AR antagonists, 5% voted for abiraterone, 2% voted for steroids, and 7% would not use additional therapy but would continue ADT alone. There were no abstentions. (No consensus for any given answer option, but a combined total of 86% voted for an AR antagonist [apalutamide, darolutamide, or enzalutamide])

Q67: In all, 86% of panellists stated that it is not appropriate to extrapolate data from ARAMIS, PROSPER, and SPARTAN to the treatment of patients with nmCRPC (M0 CRPC) and PSA doubling times >10 mo, while 14% stated that it is appropriate. There was one abstention. (Consensus for not extrapolating ARAMIS, PROSPER, and SPARTAN data to patients with PSA doubling time >10 mo)

Some patients with rising PSA and no metastases on conventional imaging have an untreated primary tumour or a local relapse that can be visualised only by MRI and/or PET-based imaging. Not much is known regarding whether these patients might benefit from systemic therapy or whether a local approach, if feasible, or a combination, would be of clinical benefit.

Q68: For patients with nmCRPC (M0 CRPC), an untreated primary tumour, confirmed local disease, and no evidence of disease outside the prostate, 46% of panellists voted for radical (definitive) local therapy over systemic therapy in the majority of patients, 42% voted for radical (definitive) local therapy over systemic therapy in a minority of selected patients, and 12% voted against radical (definitive) local therapy over systemic therapy. There was one abstention. (No consensus for any given answer option)

Q69: For patients with nmCRPC (M0 CRPC) who have a confirmed recurrence in the prostate bed and no evidence of disease outside the prostate bed, and who have received previous radical prostatectomy but not prior local radiation therapy, 54% of panellists voted for salvage radiation therapy over systemic therapy in the majority of patients, 32% voted for salvage radiation over systemic therapy in a minority of selected patients, and 14% voted against salvage radiation over systemic therapy. There were no abstentions. (No consensus for any given answer option)

Imaging was performed every 16 wk in the ARAMIS (darolutamide), PROSPER (enzalutamide), and SPARTAN (apalutamide) trials; PSA values were measured every 16 wk in PROSPER and ARAMIS, and every 4 wk in SPARTAN; and patients in all three trials were required to stop treatment in the event of radiographic progression [98–100]. Stopping treatment because of PSA progression was discouraged, and PSA values were not reported to the patients participating in these trials. In daily clinical practice, however, the optimal frequency of monitoring is unknown, and it is unclear when to stop treatment.

Q70: When treating patients with nmCRPC (M0 CRPC) with an AR pathway inhibitor (apalutamide, darolutamide, or enzalutamide), 49% of panellists voted to change treatment apart from ADT (excluding treatment changes for toxicity) when patients meet at least two of the following criteria: PSA rise (as per PCWG3 criteria), occurrence of metastases, and symptomatic progression. The remaining panellists voted to change treatment based on the occurrence of metastases alone (34%), rising PSA alone (7%), symptomatic progression alone (4%), or only if patients meet all the three criteria (6%). There were four abstentions. (No consensus for any given answer option)

Q71: For treatment monitoring for patients with nmCRPC who receive treatment with an AR pathway inhibitor (apalutamide, darolutamide, or enzalutamide), 35% of panellists voted for baseline imaging followed by monitoring of PSA alone with further imaging at progression, 35% voted for baseline imaging with follow-up imaging at 6–12 mo or best response followed by monitoring of PSA alone with further imaging at progression, and 30% voted for baseline imaging and follow-up imaging every 3–6 mo. There were two abstentions. (No consensus for any given answer option)

5.1. Discussion of management of M0 CRPC (nmCRPC)

Since the previous APCCC in 2017, the results of three large randomised phase 3 clinical trials (PROSPER, SPARTAN, and ARAMIS) have defined new treatment standards for patients with M0 CRPC/nmCRPC (based on CT and bone scintigraphy) and high-risk features (PSA doubling time ≤10 mo during continuous ADT and total PSA level ≥2 ng/ml) [98–100]. All three trials met their primary endpoint of MFS. In addition, quality-of-life data from all three trials demonstrated that baseline quality of life was usually maintained with the addition of enzalutamide, apalutamide, or darolutamide to on-going ADT [98,103,104]. A delay

in time to symptomatic progression also was observed in some of these trials, suggesting a clinical benefit [103,104].

It is important to emphasise that the results of these trials do not support treatment for all patients with M0 CRPC, but rather the consideration of treatment if patients show evidence of rapid disease progression (PSA doubling time ≤10 mo). It should also be recognised that the majority of patients in these trials who benefited from the addition of next-generation antiandrogen therapy would probably have had positive PSMA PET/CT imaging results. Although panellists at APCCC 2019 did not reach consensus regarding either the use of next-generation imaging in patients with high-risk nmCRPC or the specific PSA threshold at which to perform imaging, a majority recommended imaging before PSA reaches 10 ng/ml. In addition, many panellists voted for much earlier imaging with these more sensitive methods, despite the absence of data showing improvements in clinically relevant outcomes.

For abiraterone, a nonrandomised phase 2 clinical trial has demonstrated relevant antitumour activity in a similar high-risk M0 CRPC population [105]. Since generic abiraterone is available in some countries, it is important to discuss whether the results of PROSPER, SPARTAN, and ARAMIS can be extrapolated to abiraterone. Panellists did not reach consensus on this question, with 60% saying no. Panellists also did not prefer one of the three AR antagonists (enzalutamide, apalutamide, or darolutamide) over the others for the management of patients with high-risk M0 CRPC.

The US Food and Drug Administration (FDA) labels for enzalutamide, apalutamide, and darolutamide do not specify PSA doubling time, whereas the European Medicines Agency (EMA) labels specify the ≤10-mo PSA doubling time used in the trials. Of note, in all the three trials, the median PSA doubling time was <5 mo [98–100]. There was consensus among panellists that the data from PROSPER, SPARTAN, and ARAMIS cannot be extrapolated to patients with PSA doubling time >10 mo.

Interestingly, the reports of the ARAMIS, PROSPER and SPARTAN trials did not specify history of local treatment (radiation therapy or radical prostatectomy). The EMA filing reports data only from the PROSPER trial, which indicate that about 25% of patients had received radical prostatectomy and 40% had received prostatic radiation therapy. Hence, a significant proportion of men in this trial may have had a local recurrence or progression rather than systemic disease. Among patients with rising PSA on ADT and no evidence of metastases by conventional imaging, a local relapse or progression in the prostate or prostate bed cannot be excluded, because CT imaging is not sensitive enough to detect local recurrence. A combined total of 86% of panellists voted for consideration of salvage radiation therapy over systemic therapy in either most (54%) or selected (32%) patients with local recurrence, despite a lack of data supporting such an approach.

Similar to mHSPC, treatment monitoring is challenging in M0 CRPC. For patients receiving darolutamide, enzalutamide, or apalutamide, there was no consensus on when to switch treatment (eg, at first occurrence of metastatic disease, or only if there is evidence of new, clinically relevant sites of metastasis) or which imaging method or schedule was best. All of these topics merit investigation.

6. Management of mCRPC

Approved treatment options for mCRPC remain largely unchanged from APCCC 2017 [2]. However, the earlier use of combination treatments for HSPC, despite the absence of data on treatment sequencing, has clear implications for the castration-resistant treatment landscape. APCCC 2019 focused its discussion of the mCRPC treatment space on topics for which new data have been published since 2017.

Next-generation imaging appears to be increasingly used for staging and monitoring mCRPC, despite a lack of large prospective randomised clinical trials showing any advantage for clinical outcome over conventional imaging (CT and bone scintigraphy). For clinical trial protocols, PCWG3 specifically recommends not switching treatment based on PSA progression alone in the absence of radiographic or clinical deterioration [97]. At APCCC 2015, there was consensus (82% of panellists) not to switch mCRPC therapy unless patients meet at least two of the following three criteria: PSA progression, radiographic progression, and clinical deterioration [1].

> Q72: For patients with mCRPC, 51% of panellists voted against switching treatment based on PSA progression alone (in the absence of other examinations), 46% voted for switching treatment based on PSA progression alone in a minority of selected patients, and 3% voted for switching treatment based on PSA progression alone in the majority of patients. There were no abstentions. (No consensus for any given answer option)
> Q73: For patients with mCRPC and no PSA or clinical progression but unequivocal progression on next-generation imaging (whole-body MRI, PET/CT with various tracers), 46% of panellists voted for switching treatment in the majority of patients, 39% voted for switching treatment in a minority of selected patients, and 15% voted against switching treatment. There was one abstention. (No consensus for any given answer option)

In the PLATO trial, patients with mCRPC and PSA progression on enzalutamide monotherapy experienced no clinically meaningful benefit from either adding or switching to abiraterone [106]. Of note, the analysis did not include the 17% of patients with a very prolonged response to enzalutamide. A multicentre, single-arm, open-label study of enzalutamide after abiraterone suggested that it produced some degree of antitumour activity in selected patients whose mCRPC had progressed after ≥24 wk on abiraterone [107]. In addition, in a randomised phase 3 trial, abiraterone plus enzalutamide was not significantly more efficacious for OS compared with enzalutamide alone and was associated with increased toxicities [108]. In the phase III CARD and PROFOUND trials [109,110], and in a recently published phase II trial [111], treatment with abiraterone or enzalutamide was associated with weak antitumour

activity among patients with prior exposure to the other agent; the findings of all three of these trials were reported or published after APCCC 2019.

Q74: For patients whose mCRPC is progressing on abiraterone, assuming that there are no regulatory limitations, 14% of panellists voted for switching to enzalutamide in the majority of patients, 63% voted for switching to enzalutamide in a minority of selected patients (eg, response ≥6 mo on treatment with abiraterone), and 23% voted against switching to enzalutamide. There were no abstentions. (No consensus for any given answer option)
Q75: For patients whose mCRPC is progressing on enzalutamide, assuming that there are no regulatory limitations, 6% of panellists voted for switching to abiraterone in the majority of patients, 49% voted for switching to abiraterone in a minority of selected patients, and 45% voted against switching to abiraterone. There was one abstention. (No consensus for any given answer option)

Since the initial report of the association between the detection of the AR splice variant AR-V7 in circulating mCRPC tumour cells and resistance to enzalutamide and abiraterone, a number of studies with different assays have been reported and have led to the inclusion of AR-V7 testing in the NCCN guidelines as a potentially useful biomarker [94,112–115]. Of note, not all AR-V7 tests are the same: These studies used different assays with varying degrees of analytical and/or clinical validation that importantly do not measure the same biomarker and therefore cannot be compared. Furthermore, the detection of circulating AR-V7 may be more prognostic than predictive. As AR-V7 can be present heterogeneously in tumour tissues, it is more likely to be detected at a higher tumour volume; in the absence of data from a randomised study, it may therefore be challenging to distinguish the test's prognostic versus predictive value [116]. Other factors, such as *AR* gene amplification and mutations, have also been associated with worse outcomes, and a composite AR assay may provide additional value [116,117]. Finally, the context of use for an approved AR-V7 test needs to be taken into consideration in the setting of a landscape with additional therapeutic options and a modest response rate from second-line AR signalling inhibitors.

Q77: In all, 15% of panellists voted for and 85% voted against the use of AR-V7 testing to select candidates for abiraterone after enzalutamide therapy (or vice versa). There was one abstention. (Consensus against the use of AR-V7 testing to identify candidates for treatment with abiraterone or enzalutamide)

The following questions on steroid dose were also asked in section 4B (HSPC).

Q78: When starting abiraterone in patients with mCRPC, 75% of panellists voted for a steroid regimen of prednisone/prednisolone 5 mg twice daily, 5% voted for prednisone/prednisolone 10 mg once daily, 16% voted for prednisone/prednisolone 5 mg once daily, and 4% voted for dexamethasone 0.5–1 mg once daily. There were no abstentions. (Consensus for using prednisone/prednisolone 5 mg twice daily when starting abiraterone in patients with mCRPC)
Q76: When discontinuing abiraterone or chemotherapy, 86% of panellists voted to taper steroids over a course of some weeks, 14% voted to stop steroids at the last administration of abiraterone or chemotherapy, and none voted to continue the same dose of steroids. There were no abstentions. (Consensus for tapering steroids over a course of some weeks)

Global access to prostate cancer drugs was identified as an important issue at APCCC 2017 [2]. Generic abiraterone is now available in many countries, but its cost may be prohibitive. Since APCCC 2017, a small phase 2 clinical trial that compared low-dose abiraterone administered with a low-fat meal with standard-dose abiraterone administered in the fasted state found no difference in the primary endpoint of change in PSA [118]. However, long-term efficacy data are lacking, and published studies did not assess time to progression. It also is unknown whether patients should receive standard-dose abiraterone at the time of progression.

Q79: In all, 89% of panellists considered it appropriate to prescribe a lower dose of abiraterone (250 mg) with food for patients with metastatic prostate cancer in the context of limited resources (patient or system), while 11% voted against this practice. There were no abstentions. (Consensus for a lower dose of abiraterone with food in the context of limited resources)

At APCCC 2015, 52% of panellists regarded bicalutamide and dexamethasone as inappropriate for treating mCRPC if abiraterone and enzalutamide are available [1]. In a subsequent double-blind, randomised, phase 2 trial of patients with asymptomatic or minimally symptomatic mCRPC, standard-dose enzalutamide significantly outperformed bicalutamide (50 mg once daily) based on both the primary PFS endpoint and several secondary endpoints [119].

Q80: Regarding the use of bicalutamide as sole additional therapy (with ADT) for the management of mCRPC, 49% of panellists voted for this practice only in the context of limited resources, 27% voted for it in a minority of selected patients, 20% voted against it, and 4% voted for it for the majority of patients. There were no abstentions. (No consensus for any given answer option)
Q81: Regarding the use of low-dose dexamethasone as sole additional therapy (with ADT) for the management of mCRPC, 44% of panellists voted for this practice only in the context of limited resources, 27% voted for it in a minority of selected patients, 20% voted against it, and 9%

voted for it in the majority of patients. There was one abstention. (No consensus for any given answer option)
Q95: The panel voted on the statement: "do you recommend that the majority of patients with mCRPC receive cabazitaxel sometime during their disease course?" In all, 75% of panellists voted yes and 25% voted no. There were no abstentions. (Consensus for use of cabazitaxel sometime during the disease course)

In response to the APCCC 2017 report [2], a letter was published noting that the conference did not address lutetium-177 (^{177}Lu)-PSMA therapy [120]. This was because at the time, only retrospective and single-arm case studies had been published [121]. Since then, a prospective phase 2 trial has shown relevant antitumour activity for ^{177}Lu-PSMA-617 radioligand therapy in patients with advanced and heavily pretreated mCRPC [122]. Results and long-term outcomes from an expanded 50-patient cohort of this trial have been published recently [123] and were discussed at APCCC 2019. In addition, a large randomised phase 3 trial (NCT03511664) is evaluating ^{177}Lu-PSMA-617 in patients with mCRPC who have progressed on enzalutamide or abiraterone and one to two lines of taxane chemotherapy [124], while a phase 2 trial (TheraP, NCT03392428) has randomised 200 patients to receive either ^{177}Lu-PSMA-617 or cabazitaxel [125]. These studies have completed recruitment, but results were not available at APCCC 2019. Both trials use gallium-68 (^{68}Ga) PSMA PET/CT to identify patients with high PSMA expression, who are suitable candidates for ^{177}Lu-PSMA-617 therapy, but they use different PET/CT imaging thresholds to define suitability; in addition, the TheraP trial has utilised fluorodeoxyglucose (FDG) PET/CT to assist in identifying sites of PSMA-negative disease that cannot be targeted with ^{177}Lu-PSMA. These patients have been shown to have a poor prognosis [126]. Importantly, studies indicate that both intra- and interpatient PSMA expression is highly heterogeneous, and that many APCs express little or no PSMA [43,126,127].

At APCCC 2019, panellists discussed the selection and monitoring of patients on PSMA radioligand therapy.

Q82: For patients with PSMA imaging-positive mCRPC who have exhausted approved treatments and cannot enrol in clinical trials, 43% of panellists voted for 177Lu-PSMA therapy in the majority of patients, 46% voted for it in a minority of selected patients, and 11% voted against it. There was one abstention. (No consensus for any given answer option)
Q83: For selecting patients for 177Lu-PSMA therapy, 64% of panellists voted for PSMA PET/CT plus FDG PET/CT with or without standard imaging, 21% voted for PSMA PET/CT plus standard imaging, and 15% voted for PSMA PET/CT alone. There were three abstentions. (No consensus for any given answer option)
Q84: For monitoring response to 177Lu-PSMA therapy, 33% of panellists voted for PSMA PET/CT plus FDG PET/CT with or without standard imaging, 37% voted for PSMA PET/CT alone, 24% voted for PSMA PET/CT plus standard imaging, and 6% voted for standard imaging alone. There were five abstentions. (No consensus for any given answer option)

6.1. *Discussion of management of patients with mCRPC*

Questions regarding when to switch treatments for mCRPC produced clear results, with only 4% of panellists recommending that the majority of patients switch treatment on the basis of rising PSA alone (in the absence of other examinations). The increasing use of next-generation imaging (whole-body MRI or PET/CT) also applies to the setting of mCRPC, as panellists agreed that treatment should be changed if one of these imaging methods reveals unequivocal progression.

With regard to sequencing, the majority of the panel members expressed scepticism about the efficacy of serial AR signalling inhibition in the majority of patients with mCRPC; only 14% of panellists recommended enzalutamide after abiraterone, and only 6% recommended abiraterone after enzalutamide. However, a substantial proportion of panellists voted for considering these treatment strategies in selected patients. Some data suggest that enzalutamide may be at least moderately active in patients who received abiraterone for $\geq$6 mo (and for a median of $>$12 mo) before progression [107], while data from the PLATO trial clearly demonstrated that the reverse strategy did not benefit most patients [106]. A recently published randomised phase II trial reported limited antitumour activity when enzalutamide was sequenced after abiraterone but very low activity with the reverse sequence [111]. Currently, it is unclear which subset(s) of patients may benefit from sequential AR pathway inhibitor therapy, especially if patients have already received enzalutamide. Panellists agreed that AR-V7 testing should not be used in daily clinical practice to sequence AR pathway inhibitors.

There also was consensus that patients receiving abiraterone for mCRPC should receive concomitant steroid therapy with prednisone/prednisolone 5 mg twice daily, and that steroids should be tapered for several weeks after stopping either abiraterone or chemotherapy. In the context of limited resources (whether related to the health care system or individual patient), there was consensus that a reduced dose of abiraterone taken together with food can be recommended.

The voting on the sequencing of cabazitaxel occurred before ESMO 2019, when investigators presented the results from the CARD trial, which compared third-line treatment with either cabazitaxel or alternative AR-targeted therapy (enzalutamide or abiraterone) in patients who had previously received docetaxel and whose mCRPC had progressed rapidly (within 12 mo) after starting their first AR-targeted therapy [109]. In the CARD trial, cabazitaxel therapy was associated with statistically significant improvements in the primary endpoint of radiographic PFS (rPFS), as well as OS and other clinical endpoints, including pain response [109]. Toxicity also appeared not to be worse for cabazitaxel versus the alternative AR-targeted therapy. Again, these

data were presented after APCCC 2019 and were not available to panellists during voting.

The growing interest in PSMA-targeted therapies, mainly with ^{177}Lu, has stimulated a number of questions. Most panellists would consider ^{177}Lu-PSMA therapy for patients who have exhausted approved treatment options, although 46% would do so only in a minority of selected patients. A majority of panellists recommended using a combination of PSMA and FDG PET/CT imaging to select patients for PSMA-targeted treatment, while only 15% of panellists would rely on PSMA PET/CT alone. For monitoring PSMA-targeted treatment response, most panellists recommended a combination of PET and standard imaging methods, 37% voted for PSMA PET/CT alone, and only 6% recommended standard imaging. There are concerns about using PSMA-based imaging alone to monitor therapeutic response, given that PSMA expression in tumour tissue has been found to change in response to treatment [128]. When deciding whether to continue PSMA-targeted therapy, the results of PSMA-based imaging should be considered together with RECIST measurements on conventional imaging, as well as other response parameters [129].

A number of questions regarding the use of PARP inhibitors, platinum-based chemotherapy, and immunotherapy were voted on, and these questions have been discussed in section 8.

7. Bone health and bone metastases

In 2017, APCCC panellists concluded that "the optimal timing, schedule, and duration for osteoclast-targeted therapies 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" [2]. Since then, the topic of cancer treatment–induced bone loss (CTIBL) has moved very much into focus with the publication of the ERA-223 trial, in which the addition of radium-223 therapy to abiraterone plus prednisone was associated with an increased rate of fractures compared with abiraterone-prednisone alone [130]. Although ERA-223 was performed in patients with chemotherapy-naïve mCRPC, the high rate of nonpathological fractures (fractures in an area of bone without evidence of metastases) in this trial has intensified discussions of bone health, particularly among patients with advanced HSPC who initiate long-term ADT—now often together with either docetaxel or abiraterone-prednisone (it is important to note that long-term use of corticosteroids is by itself a risk factor for osteoporosis).

Other factors besides cancer treatment often contribute to bone loss among patients with APC. Current or historical smoking, personal or family history of hip fracture, rheumatoid arthritis, regular consumption of more than 3 alcohol units per day, and high or low body mass index (BMI) all are well-established risk factors that warrant careful consideration when evaluating fracture risk [131,132]. Web-based tools, such as the Fracture Risk Assessment Tool (FRAX), can help clinicians evaluate risk factors for fracture and calculate individual fracture risk. When using this tool, it is important to insert ADT as a secondary risk factor within the context of hypogonadism.

In 2017, only 62% of APCCC panellists recommended measuring baseline bone mineral density (BMD) when initiating long-term ADT [2]. Panellists also debated whether bisphosphonate (oral or intravenous) or denosumab therapy was preferred for the prevention of CTIBL. It is important to distinguish this goal from that of reducing skeletal-related events (SREs) in mCRPC, which requires approximately 10-fold higher doses of osteoclast-targeted therapy.

Overall, many questions remain regarding the optimal management of bone health in APC, and these were revisited at APCCC 2019.

Q85: For patients with prostate cancer starting on long-term ADT, 77% of panellists reported that they routinely screen for osteoporosis risk factors (eg, current/historical smoking, corticosteroids, family history of hip fracture, personal history of fractures, rheumatoid arthritis, consumption of >3 alcohol units per day, and BMI), 21% do not screen these patients for osteoporosis risk factors, and 2% screen only patients with bone-metastatic disease. There were no abstentions. (Consensus for routine screening for osteoporosis risk factors)

Q86: For patients with prostate cancer starting on long-term ADT, 65% of panellists reported that they routinely measure BMD, 30% reported measuring BMD only in patients with risk factors for fracture, and 5% reported that they do not measure BMD in these patients. There were no abstentions. (No consensus for any given answer option)

Q87: To prevent CTIBL and fractures in patients starting on long-term ADT who do not have a BMD measurement, 17% of panellists voted that it is appropriate to routinely start osteoclast-targeted therapy at the dose and schedule used for osteoporosis, 60% voted that this is appropriate only if patients are at increased risk for fractures (eg, 10-yr FRAX risk of ≥3% for hip fractures and/or ≥20% for all major fractures), and 23% voted that this is not appropriate. There were no abstentions. (No consensus for any given answer option)

Q88: To prevent CTIBL and fractures in patients starting on long-term ADT whose BMD measurement does not indicate osteoporosis, 7% of panellists voted for routinely starting denosumab or a bisphosphonate at the dose and schedule used for osteoporosis, 50% voted for this only if patients are at increased risk for fracture (eg, 10-yr FRAX risk of ≥3% for hip fractures and/or ≥20% for all major fractures), and 43% voted against this practice. There were no abstentions. (No consensus for any given answer option)

Q89: To prevent CTIBL and fractures in patients with no documented osteoporosis who are initiating long-term ADT plus abiraterone and prednisone, 17% of panellists voted for routinely starting denosumab or a bisphosphonate at the dose and schedule used for osteoporosis, 60% voted for this only if patients are at increased risk for fracture (eg, 10-yr FRAX risk of ≥3% for hip fractures

and/or ≥20% for all major fractures), and 23% voted against this practice. There were no abstentions. (No consensus for any given answer option)

For patients with APC, experts continue to debate the optimal timing and type of osteoclast-targeted therapy to use to reduce the risk for CTIBL. Furthermore, for patients who are receiving denosumab or a bisphosphonate at the dose and schedule used for CTIBL, it remains unclear whether and when to switch to the higher dose and more frequent schedule used to reduce the risk of SREs. Panellists at APCCC 2017 often reached no consensus on these questions [2], which were revisited at APCCC 2019 in light of the increasing awareness of the importance of preserving or improving bone health when managing APC. The term "higher dose and frequency of osteoclast-targeted therapy" refers to the dose and schedule tested and approved in the mCRPC setting for denosumab (120 mg subcutaneously every 4 wk) or zoledronic acid (4 mg intravenously every 4 wk) [133–135].

Q90: For patients with mCRPC and bone metastases, 65% of panellists voted for the routine use of osteoclast-targeted therapy (zoledronic acid or denosumab) at the higher dose and more frequent schedule used to reduce the risk of SREs, 22% voted for this only for a minority of selected patients, and 13% voted that the lower dose and less frequent schedule used for osteoporosis are sufficient. There was one abstention. (No consensus for any given answer option)
Q92: For patients with mCRPC and bone metastases who are receiving osteoclast-targeted therapy at the higher dose and more frequent schedule used to reduce the risk of SREs, 61% of panellists voted to treat for approximately 2 yr and then stop, 4% voted to treat for approximately 5 yr and then stop, and 35% voted for indefinite treatment. There were eight abstentions. (No consensus for any given answer option)
Q93: For patients with mCRPC and bone metastases who are receiving osteoclast-targeted therapy at the higher dose and more frequent schedule used to reduce the risk of SREs, 46% of panellists voted for a treatment frequency of every 4 wk, 33% voted for every 12 wk, and 21% voted for every 4 wk for 2 yr followed by a lower treatment frequency. There were four abstentions. (No consensus for any given answer option)

In the ERA-223 trial, the addition of radium-223 to abiraterone-prednisone did not improve SSE-free survival and was associated with an increased risk of fractures compared with abiraterone-prednisone alone [130]. Based on these findings, regulatory bodies now recommend against the combination of abiraterone and radium-223; the EMA has additionally mandated that patients with mCRPC receive only radium-223 after they have progressed on two or more other lines of mCRPC therapy. There is concern, however, that the development of visceral metastases may preclude the later-line use of radium-223 in many of these patients [136]. Thus far, the EMA is the only regulatory agency to have restricted the use of radium-223 in this way.

Q94: The panel voted on the question, "Do you support the statement that mCRPC patients should receive radium-223 only after receiving two prior treatments for mCRPC or if they cannot receive other treatments?" In all, 34% of panellists voted yes and 66% voted no. There were no abstentions. (No consensus for any given answer option)
Q96: In all, 87% of panellists agreed that the majority of symptomatic patients with mCRPC and predominant bone metastases (without visceral disease or bulky lymph node disease) should receive radium-223 at some point during their disease course. The other 13% disagreed with this statement. There were two abstentions. (Consensus for the use of radium-223 sometime during the course of bone-predominant mCRPC in patients without visceral or bulky lymph node disease)

The PEACE-3 trial (NCT02194842) compares enzalutamide alone or with radium-223 for the treatment of mCRPC. In response to the ERA-223 results and higher-than-expected rates of fracture in the PEACE-3 trial, the independent data monitoring committee for PEACE-3 mandated bone health therapy for all participants. This change in protocol led to a significant reduction in fractures, according to the results of an interim analysis of PEACE-3 data presented at the 2019 American Society of Clinical Oncology (ASCO) meeting [137]. These results suggest that the use of osteoclast-targeted agents might reduce fractures in this population of men receiving first-line treatment for mCRPC.

Q91: When planning radium-223 therapy for mCRPC, 86% of panellists voted that the majority of patients receive osteoclast-targeted therapy at the higher dose and more frequent schedule used to reduce the risk of SREs, 2% voted for this only in a minority of selected patients, 8% voted for the less intensive dose and schedule used to treat osteoporosis, and 4% voted against osteoclast-targeted therapy in this setting. There were four abstentions. (Consensus for osteoclast-targeted therapy in the majority of patients planed for radium-223 therapy for mCRPC)

7.1. Discussion of bone health and bone metastases

It is essential that discussions of bone health in prostate cancer distinguish between the reduction of SREs associated with bone-metastatic disease and the prevention of CTIBL (ie, fragility fractures and osteoporosis) in the larger population of patients receiving long-term ADT, either alone or together with other systemic prostate cancer therapies. Results from large randomised prospective trials support the use of osteoclast-targeted therapy to reduce the risk of SREs in the mCRPC population, but these trials were conducted before novel antineoplastic agents joined the

mCRPC armamentarium in the past decade. In patients with mHSPC, the same dose and frequency of zoledronate (eg, 4 mg every 3–4 wk) did not reduce SRE risk and was associated with significant toxicity. Therefore, this more intensive dose and frequency of zoledronic acid therapy should not be used in the hormone-sensitive setting, as was reflected in the previous 2017 voting.

In 2015 and 2017, APCCC panellists debated the importance of measuring and supplementing vitamin D3 and calcium, and performing dental examinations before initiating bone-targeted therapies [1,2]. For patients starting long-term ADT, there was consensus for routine vitamin D3 supplementation but not for calcium supplementation. For patients with mCRPC, there was consensus for performing baseline examinations prior to initiating osteoclast-targeted therapy. At APCCC 2019, there was consensus to screen patients for risk factors for osteoporosis when starting long-term ADT.

Panellists supported measuring BMD at baseline when starting patients on long-term ADT, and many (65%) recommended doing so routinely, rather than only in patients with risk factors for fracture (of note, most patients starting on long-term ADT have such risk factors). For patients with bone-metastatic disease, it is important to keep in mind that BMD of the lumbar spine should be interpreted with caution, while BMD of the distal radius is more reliable [131].

For patients starting long-term ADT who do not have a BMD assessment and are at increased risk for fracture, 60% of panellists voted to start osteoclast-targeted therapy at the dose and schedule used for osteoporosis. To prevent CTIBL and fractures in patients starting on long-term ADT for prostate cancer, most panellists would not routinely start denosumab or a bisphosphonate at the dose and schedule used for osteoporosis, but a majority would do so if patients were at increased risk for fractures, and an even greater majority would do so if patients also were receiving abiraterone. For patients starting long-term ADT whose BMD measurement was not consistent with osteoporosis, only 7% of panellists voted for routinely starting osteoclast-targeted therapy, while 50% voted for doing so if these patients had risk factors for fracture.

In general, panellists seemed somewhat reluctant to initiate osteoclast-targeted therapy with the goal of reducing or preventing CTIBL. This was an unexpected finding, because treatment to prevent CTIBL in mCRPC requires a less intensive dose and schedule than treatment to prevent SREs and thus is associated with a lower risk of adverse effects. Of note, the National Institute for Health and Clinical Excellence (NICE) in the UK recommends oral bisphosphonates as an option for men with a 10-yr risk of fragility fracture of >1%, which includes all men starting on long-term ADT [138].

For patients with mCRPC and bone metastases, panellists voted for using zoledronic acid or denosumab therapy at the higher dose and frequency used to reduce the risk of SREs in the majority of patients (65%) or at least in selected patients (22%). Relevant considerations for patient selection may include overall prognosis, number of bone metastases, and dental health status. Similar to APCCC 2015 and 2017, there was no consensus on the duration and frequency of denosumab and zoledronic acid at the dose recommended to prevent SREs in the majority of patients with mCRPC.

There was consensus (86%) for the use of radium-223 sometime during the treatment course in patients with symptomatic mCRPC and bone-predominant metastases who have no visceral or bulky lymph node metastases. There also was consensus (87%) that osteoclast-targeted therapy should be initiated before starting radium-223 therapy. Two-thirds of panellists did not support the current EMA label limiting the use of radium-223 to patients who have received at least two prior approved lines of mCRPC therapy.

For most questions in this section, there was no consensus for a single answer option. However, combining voting results often revealed clear messages on bone health management. For instance, a combined total of 95% of panellists reported that they either “routinely measure bone mineral density” in patients starting on long-term ADT or that they “measure bone mineral density only in patients with risk factors” (which many men starting on ADT have). Thus, the vast majority of panellists consider measuring BMD in at least selected patients starting on long-term ADT. The same observation applies to a number of questions in this section. For example, a combined total of 87% of panellists voted that either the majority of patients with bone-metastatic CRPC or selected patients with risk factors should receive osteoclast-targeted therapy (zoledronic acid or denosumab) at the higher dose and more frequent schedule used to reduce the risk of SREs.

8. Molecular characterisation of tissue and blood

Advances in molecular characterisation and the identification of potentially actionable genetic alterations in patients with APC have increased the use of tumour genomic profiling [139]. The NCCN guidelines now recommend considering tumour genomic profiling for all patients with regional or metastatic disease [94]. These include tests for microsatellite instability (MSI)/defective mismatch repair (dMMR), and for variants involving other DNA repair genes, such as *BRCA1/2*, *ATM*, *CDK12*, and *PTEN*. Importantly, DNA repair gene alterations also can occur at the germline level, which may affect familial risk for certain cancers. The NCCN guidelines recommend considering germline testing for DNA repair genes (eg, *BRCA1* and *BRCA2*) in all patients with metastatic prostate cancer and for selected patients with localised disease [94].

A multitude of questions persist concerning tumour genomic profiling. Owing to absence of data, panellists at APCCC 2019 discussed concerns regarding the negative predictive value of these assays and their impact on therapeutic selection. They voted on the optimal time to test patients, which tests to perform, and the consequences of detecting a potentially actionable mutation.

Q97: Regarding when to first recommend tumour genomic testing, 52% of panellists voted for testing at

the first diagnosis of metastatic disease, 16% voted for testing at the first diagnosis of high-risk localised disease, 16% voted for testing after patients have received at least line of chemotherapy and at least one AR pathway inhibitor, 9% voted for testing after all standard treatment options are exhausted, and 7% voted against routine tumour genomic testing. There was one abstention. (No consensus for any given answer option) This question was voted on twice because some panellists did not realise when first voting that all diagnostic procedures were assumed to be readily available. These are the results of the second vote.

Q98: In terms of which tumour genomic tests are considered relevant in metastatic prostate cancer outside the setting of a clinical trial, 28% of panellists voted for DNA repair defects, including mismatch repair evaluation (MSI high), while 72% voted for prostate cancer-specific larger panel testing, including, for example, homologous recombination deficiency (*BRCA1*, *BRCA2*, *PALB2*, and *RAD51*), *PTEN*, *PI3K*, *SPOP*, *CDK12*, *ATM*, mismatch repair evaluation (MSI high), and tumour mutation burden. There were three abstentions. (No consensus for any given answer option)

True MSI in prostate cancer is detected with a frequency of at least 3% [140]. However, the presence of MSI can be therapeutically meaningful because it can predict more durable responses to immune checkpoint inhibition [140,141]. The checkpoint inhibitor pembrolizumab has received FDA approval for use in patients whose tumours are MSI high or dMMR.

Q101: When asked whether the majority of patients with metastatic prostate cancer should have their tumours tested for mismatch repair defects (MSI high), 34% of panellists voted yes, 60% voted yes, but only in the setting of mCRPC, and 6% voted no. There were four abstentions. (No consensus for any given answer option, but a combined total of 94% voted for testing mismatch repair defects at some stage of disease, most frequently in the mCRPC setting)

Immune checkpoint inhibitors have shown limited antitumour activity in unselected patients with APC [142,143]. In cases of documented mismatch repair defect (MSI high), the optimal timing of checkpoint inhibitor therapy remains unclear because of an absence of large datasets and prospective trials [140,142,144].

Q102: For patients with metastatic prostate cancer and a mismatch repair defect (MSI high), 10% of panellists voted for anti-PD1 therapy (outside the setting of a clinical trial) at the first diagnosis of metastatic disease (ie, at the start of ADT), 24% voted to use it after patients progress on ADT (first-line mCRPC), 31% voted to use it after at least one line of chemotherapy and at least one AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide), 31% voted to use it only after all standard treatment options have been exhausted, and 4% voted against its use in these patients. There were four abstentions. (No consensus for any given answer option, but a combined total of 96% voted for anti-PD1 therapy sometime during the treatment sequence for patients with MSI-high metastatic prostate cancer)

Patients with biallelic loss of *CDK12* have recently been found to have an elevated neoantigen burden, indicating that they may potentially benefit from immunotherapy [145,146]. These findings require validation in prospective clinical trials, but in the meantime, the increasing use of tumour genomic profiling means that biallelic *CDK12* loss will be detected, and affected patients may not be able to enrol in a clinical trial.

Q103: For patients with metastatic prostate cancer and biallelic *CDK12* loss, 2% of panellists voted for anti-PD1 therapy outside the setting of a clinical trial at the first diagnosis of metastatic disease (ie, at the start of ADT), 12% voted to use it after patients progress on ADT (first-line mCRPC), 31% voted to use it after at least one line of chemotherapy and at least one AR pathway inhibitor (abiraterone, apalutamide, or enzalutamide), 43% voted to use it after all standard treatment options have been exhausted, and 12% voted against its use in this setting. There were six abstentions. (No consensus for any given answer option)

Multiple studies have identified a 20–30% frequency of alterations in DNA repair machinery in patients with APC [147–150]. Evidence for the antitumour activity of PARP inhibitors in these patients is increasing and has recently been confirmed by a number of trials study [151–153]. The phase III PROFOUND study was presented after APCCC 2019 [110]. Although no regulatory body has approved PARP inhibitor therapy for prostate cancer, recent data, coupled with evidence that homologous recombination defects may sensitise tumours to platinum-based chemotherapies, have raised questions regarding whether patients with APC should routinely be tested at least for *BRCA1/2* mutations [154–158].

Q100: In all, 44% of panellists voted for *BRCA1/2* tumour testing for the majority of patients with metastatic prostate cancer, 46% voted for this only in patients with mCRPC, and 10% voted against it. There were four abstentions. (No consensus for any given answer option, although a combined total of 90% voted for *BRCA1/2* tumour testing at some point during the disease course)

Q104: For the majority of patients with metastatic prostate cancer and a confirmed deleterious germline *BRCA1/2* mutation, 93% of panellists voted for PARP inhibitor or platinum therapy at some point during the disease course outside the setting of a clinical trial if none is available. The remaining 7% voted for this only in a minority of selected patients. There were two abstentions. (Strong consensus for PARP inhibitor or platinum therapy at some point during the disease course in patients with a deleterious germline *BRCA1/2* mutation)

Even if patients have a strong family history of BRCA-associated cancers, genomic profiling may be unable to identify somatic or germline aberrations, or genomic profiling may not be available if access to health care resources is limited.

Q105: For patients with metastatic prostate cancer and a strong family history of BRCA-associated cancers but no documented somatic and germline aberrations, 61% of panellists voted against PARP inhibitor or platinum therapy, 24% voted for it in a minority of selected patients, and 15% voted for it in the majority of patients. There was one abstention. (No consensus for any given answer option)

Although a PARP inhibitor or platinum-induced synthetic lethality theoretically usually requires biallelic inactivation of *BRCA1/2*, often only one alteration is required for clinical trial enrolment, and the status of the second allele may not be reported [159].

Q106: For patients with metastatic prostate cancer and a somatic or germline *BRCA1/2* aberration, 62% of panellists voted for PARP inhibitor or platinum therapy only in cases of biallelic *BRCA1/2* loss, and 38% stated that monoallelic loss was sufficient. There were eight abstentions. (No consensus for any given answer option)

Known mechanisms of resistance to PARP inhibition include reversion mutations, upregulation of *ABCB1*, and alterations in PARP expression [160–164]. Studies of patients with ovarian and breast cancer indicate that PARP inhibition is active in patients who have received platinum-based combination therapy [165], but little is known about the optimal sequencing of PARP and platinum therapies for patients with APC.

Q107: In all, 56% of panellists voted for platinum-based therapy for a minority of selected patients with metastatic prostate cancer and deleterious somatic or germline *BRCA1/2* aberrations who have progressed on or after PARP inhibitor therapy, 39% voted for platinum-based therapy in the majority of these patients, and 5% voted against it. There were 12 abstentions. (No consensus for any given answer option)

Q108: In all, 47% of panellists voted for PARP inhibitor therapy for a minority of selected patients with metastatic prostate cancer and deleterious somatic or germline *BRCA1/2* aberrations who have progressed on or after platinum-based therapy, 44% voted for it for the majority of these patients and 9% voted against it. There were eight abstentions. (No consensus for any given answer option)

A multitude of platinum-based regimens have been tested in clinical trials and have produced no clear evidence as to the optimal dose and schedule [154,155].

Q109: Regarding the recommended schedule for carboplatin (as monotherapy or combination therapy), 84% of panellists voted for 3-weekly carboplatin, area under the curve (AUC) 4–5, and 16% voted for weekly carboplatin, AUC 2–3. There were 18 abstentions. (Consensus for using carboplatin AUC 4–5 in a 3-weekly schedule)

Patients with somatic BRCA1/2 alterations and localised intermediate- or high-risk prostate cancer seem to have worse outcomes [166]. In BRCA2-mutant prostate cancer, intraductal carcinoma of the prostate is frequently detected and is associated with worse outcomes [167].

Q99: When asked whether the presence of a tumour *BRCA1/2* aberration influenced their treatment of intermediate- or high-risk localised prostate cancer, 36% of panellists voted for radical prostatectomy over radiation therapy for these patients, 26% voted for making the standard treatment recommendation, and 38% voted for making the standard treatment recommendation but performing more intensive monitoring. None voted for radiation therapy over radical prostatectomy in this scenario. There were two abstentions. (No consensus for any given answer option)

8.1. *Genetic counselling—germline testing*

Germline testing and genetic counselling were discussed in detail at APCCC 2017 and in the subsequent manuscript [2]. Since then, a report of a recent consensus conference on genetic testing for inherited prostate cancer has been published [168]. At APCCC 2019, questions primarily focused on collecting a detailed family cancer history, although it is important to note that a substantial proportion of men with APC and germline DNA repair defects lack a family history of cancer [169].

Q110: A total of 98% of panellists voted for collecting a detailed family cancer history for all patients with newly diagnosed metastatic (M1) HSPC, while 2% of panellists voted against it. There were no abstentions. (Strong consensus for collecting a detailed family history for all patients with newly diagnosed M1 HSPC)

Current NCCN guidelines recommend both genetic risk evaluation, and *BRCA1* and *BRCA2* germline testing for any individual with a personal history of metastatic prostate cancer [94]. In many settings, however, clinicians still base this decision on whether patients have a strong family history of BRCA-associated cancers and on established criteria for germline testing in breast and ovarian cancer [94,170].

Q111: In all, 84% of panellists voted for genetic counselling and/or germline DNA testing for the majority of patients with newly diagnosed metastatic (M1) HSPC, 14% voted for it only in a minority of selected patients and 2% voted against it. There were no abstentions. (Consensus for genetic counselling and/or germline DNA testing for the majority of patients with newly diagnosed

metastatic prostate cancer) This question was voted on twice because some panellists did not realise that that all diagnostic procedures were assumed to be readily available. These are the results of the second vote.

At APCCC 2017, there was no consensus regarding the type of germline genetic testing to perform when such testing was recommended. Although 61% of panellists who supported genetic testing preferred the use of larger panels, these are more likely to identify alterations in intermediate-penetrant genes, for which there are no clear guidelines on risk management [94]. At the Philadelphia consensus meeting on genetic testing, genes with the highest consensus included *HOXB13*, *BRCA1/BRCA2*, and DNA mismatch repair (*MMR*) genes [168]. It should be noted that patients should always be referred for germline testing if their tumours test positive for mutations in *BRCA1/BRCA2*, *MMR* genes, *HOXB13*, or *ATM*.

Q112: When recommending germline DNA testing for patients with prostate cancer, 85% of panellists voted for extended panel testing, including for homologous recombination DNA damage repair mutations, while 15% voted for testing only for BRCA1 and *BRCA2* alterations. There were three abstentions. (Consensus for extended panel testing)

8.2. Discussion of molecular characterisation of tissue and blood

Significant advances have been achieved in the field of tumour genomic testing, and this was reflected by the voting results at APCCC 2019. In all, 77% of panellists voted for the molecular characterisation of tumours in patients with metastatic prostate cancer, with 16% voting for testing in the setting of high-risk localised disease. There was no consensus regarding the optimal disease stage at which to conduct these tests. The majority of panellists voted for *BRCA1/2* tumour testing and testing for mismatch repair defects (MSI high) at some point during the disease course. For tumour testing in general, 72% of panellists supported the use of a larger prostate cancer–specific panel.

With regard to treatment recommendations, the majority of panellists voted that patients with deleterious germline *BRCA1/2* mutations should receive a PARP inhibitor or platinum-based chemotherapy at some point during their disease course. This is supported by the results of the PROFOUND trial, which were presented at the 2019 ESMO conference after APCCC 2019. Results from this study demonstrated a statistically significant improvement in the primary endpoint of rPFS (7.39 vs 3.55 mo) with olaparib compared with AR pathway inhibitor therapy (abiraterone or enzalutamide) in patients with mCRPC and *BRCA1/2* or *ATM* mutations [110]. Panellists were less comfortable voting for PARP inhibitor or platinum-based chemotherapy for patients with a strong family history of cancer but no documented somatic or germline alterations. There have been anecdotal reports of exceptional responses to platinum-based chemotherapy among patients with APC, even in the absence of a known molecular alteration [158].

In all, 62% of panellists voted only for the use of a PARP inhibitor or platinum-based chemotherapy in the context of biallelic *BRCA1/2* loss. While this is biologically appropriate, it should be noted that on-going trials of PARP inhibitors have required evidence of monoallelic loss only and that biallelic loss is sometimes difficult for laboratories to confirm. For ethical and practical reasons, some clinicians may opt for these treatments in the setting of monoallelic *BRCA1/2* loss without confirmation of biallelic inactivation.

Regarding the optimal sequencing of PARP inhibitor therapy and platinum-based chemotherapy, the majority of panellists supported the use of either sequence, at least in molecularly selected patients. For fit patients with a deleterious somatic or germline *BRCA1/2* aberration and progression on either a PARP inhibitor or platinum-based chemotherapy, the other treatment option may be considered. However, limited data are available on the activity of PARP inhibitors after platinum chemotherapy and vice versa. There was consensus that if carboplatin chemotherapy is used, a 3-weekly application of AUC 4–5 is the preferred schedule.

A majority of panellists also supported anti-PD1 therapy for patients with evidence of dMMR or biallelic *CDK12* loss, but there was no consensus regarding at which stage of disease to initiate these treatments, and very limited data from clinical trials are currently available to guide patient care. Very few panellists voted to start anti-PD1 therapy when patients first present with metastatic disease, and many preferred to wait until after patients have received at least one AR pathway inhibitor and one line of chemotherapy, or even until after all standard treatment options had been exhausted.

Panellists almost unanimously recommended collecting a detailed family history for all patients with newly diagnosed metastatic prostate cancer, even though a relevant percentage of patients have no known family history for cancer. There was also consensus that these patients should be referred for genetic counselling and germline genetic testing, when appropriate. For germline testing, there was consensus for performing extended panel testing rather than testing only for *BRCA1/2* alterations. However, performing genetic counselling and germline testing in such a large group of patients is resource intensive and may not be feasible immediately in many settings. As tumour genomic testing becomes more common, physicians should know which alterations (such as *BRCA1, BRCA2,* and *MMR*) should trigger a prompt referral for counselling and possible germline testing.

Discussions also are needed on a number of other issues, such as how to manage or counsel patients with variants of unknown significance, and what cancer risk prevention strategies are warranted for patients with mutations in lower-penetrance genes, such as *NBN*, *CHEK2*, and *BRIP1*.

9. Heterogeneity of prostate cancer

Prostate cancer is strikingly heterogeneous with regard to its diagnosis, treatment response, and development of

resistance. In recent years, advances in molecular characterisation have led to key insights regarding intrapatient, intratumour, and interpatient heterogeneity [171–173]. Updated PCWG3 recommendations address disease heterogeneity and suggest designing clinical trials accordingly [97]. APCCC 2019 addressed a number of questions related to this topic. Genomic questions have been discussed in section 8 of this paper.

East Asian patients with mCRPC are known to experience increased toxicity at the standard dose of docetaxel (75 mg/m^2) and hence are often started at a lower dose [174–178]. In 2018, 20 experts who practice in the Asia-Pacific region met to discuss practical implications of the 2017 APCCC report [179]. Regarding the recommendation for upfront docetaxel in patients with mHSPC, they anecdotally confirmed an increased incidence of toxicity, especially febrile neutropenia, in East Asian patients. This issue was discussed again at APCCC 2019.

Q113: When initiating taxane chemotherapy for mCRPC in patients of East Asian ethnicity, 40% of panellists voted to start with the standard dose (75 mg/m2) and reduce the dose in subsequent cycles as indicated, 24% voted to start with a reduced dose (eg, 60 mg/m2) and reduce the dose in subsequent cycles as indicated, and 36% voted to start with a reduced dose and escalate the dose in the absence of relevant side effects. There were 15 abstentions. (No consensus for any given answer option)

Physicians also are sometimes uncertain about how to dose chemotherapy for prostate cancer in patients with obesity. For chemotherapy dosing, existing guidelines recommend the use of actual body weight to calculate body surface area (BSA) [180,181].

Q114: When administering chemotherapy for prostate cancer to patients who are highly obese, 26% of panellists voted to treat at the full dose according to actual BSA, 66% voted to cap the dose at an arbitrary BSA (eg, 2.0 m2) or at a cytotoxic dose, and 8% voted to calculate the dose based on actual BSA and then reduce that dose. There were 18 abstentions. (No consensus for any given answer option)

The International Society for Geriatric Oncology (SIOG) recommends health status assessments for patients with prostate cancer who are older than 70 yr [182,183]. This recommendation is supported by the recent finding that a comprehensive geriatric assessment is associated with significantly improved chemotherapy tolerance when its results are used to guide management of comorbidities and other coexisting issues (eg, poor appetite) in high-risk older patients [184]. However, there is a lack of robust prospective data on the safety of prostate cancer treatments in older patients in general. Preplanned subgroup analyses are often unavailable (in some cases because of insufficient power) or are not reported in detail.

Available safety and efficacy data on this topic are summarised as follows: For enzalutamide, a higher incidence of falls was observed among older patients enrolled in the PREVAIL [185] and TERRAIN [186] trials, and an increase in cardiac events was observed among older patients in TERRAIN. In contrast, a subgroup analysis of the COU-AA-302 trial demonstrated similar rates of adverse events and antitumour activity among elderly and younger recipients of abiraterone plus prednisone [187]. For radium-223, a small retrospective study reported increased haematological toxicity in elderly patients [188]. For docetaxel, another small retrospective study reported relevant antitumour activity but high rates of adverse events among very elderly men with mCRPC, with only 40% of patients completing the six planned cycles of chemotherapy [189]. An older case series from French centres also reported adequate antitumour activity, although 45% of patients received upfront dose-reduced docetaxel, usually because they were >80 yr old and had worse performance status [190]. For cabazitaxel, data from a compassionate use programme suggested a manageable toxicity profile for older patients, but the investigators recommended prophylactic granulocyte colony stimulating factor (G-CSF) to reduce the risk of febrile neutropenia [191]. All these analyses were retrospective, used variable definitions of "elderly", and focused only on mCRPC, which limits the generalisability and utility of their findings. In the important area of mHSPC, there is also a lack of data.

An increase in the number of octo- and nonagenarians with APC poses substantial treatment challenges in daily clinical practice [192]. These patients also are underrepresented in clinical studies, especially large phase 3 trials.

Q115: Regarding whether efficacy data from mCRPC clinical trials can be extrapolated to the treatment of patients who are older than the majority of patients enrolled, 76% of panellists voted yes and 24% voted no. There were two abstentions. (Consensus for extrapolation of efficacy data to patients older than the majority of patients enrolled in a trial)

Q116: Regarding whether toxicity data from mCRPC clinical trials can be extrapolated to the treatment of patients who are older than the majority of patients enrolled, 28% of panellists voted yes and 72% voted no. There was one abstention. (No consensus for any given answer option)

Q119: Regarding whether to recommend a health status assessment prior to treatment selection in patients with APC who are ≥70 yr old, 39% of panellists voted yes for the majority of patients, 52% voted yes for a minority of selected patients, and 9% voted no. There were no abstentions. (No consensus for any given answer option)

Q120: Among panellists who voted for a health status assessment, 39% voted for an extended assessment by the treating physician, 41% voted for referral to a geriatrician, and 20% voted for referral to other health care professional. There were eight abstentions. (No consensus for any given answer option)

There is a significant body of literature on disparity, prostate cancer risk, and outcomes in localised prostate

cancer, but there have been few corresponding studies of APC [193]. In an adjusted analysis of combined data from nine phase 3 clinical trials of docetaxel in mCRPC, there was a statistically significant decrease in hazard of death among black versus white men [194]. In a large multicohort study of data from the Surveillance, Epidemiology and End Results (SEER) programme, the US Veterans Affairs health system, and four pooled randomised phase 3 trials, black race was not associated with prostate cancer–specific mortality after adjusting for nonbiological differences, such as access to care [195]. In a separate large study of SEER data, black men with distant de novo metastatic prostate cancer had similar survival times as non-Hispanic white men, while Asian patients tended to survive longer [196]. This is in contrast to a recent meta-analysis of mCRPC (in print) [197]. In most individual clinical trials, race and ethnicity subgroups have been too small to draw conclusions. Recent studies with molecular profiling have revealed interesting molecular differences, including, for example, a loss of function in ERF, an ETS transcriptional repressor in black patients with prostate cancer [198–200].

Q117: Regarding whether efficacy data from mCRPC clinical trials can be extrapolated to the treatment of patients whose ethnicities differ from the majority of patients enrolled, 66% of panellists voted yes and 34% voted no. There were three abstentions. (No consensus for any given answer option)

Q118: Regarding whether toxicity data from mCRPC clinical trials can be extrapolated to the treatment of patients whose ethnicities differ from the majority of patients enrolled, 27% of panellists voted yes and 73% voted no. There were four abstentions. (No consensus for any given answer option)

9.1. Discussion on heterogeneity of prostate cancer

Although there was a range of opinions regarding the starting dose of chemotherapy in patients of East Asian ethnicity, 60% of panellists recommended starting chemotherapy at a reduced dose. This strategy is supported by the experience of physicians from the Asia-Pacific region and by limited studies. Although no large prospective clinical trials have compared dosing strategies (eg, a reduced dose vs a full dose with G-CSF support) in this population, the available literature suggests that antitumour activity is comparable, even if a reduced dose is used [174,175].

For morbidly obese patients, a majority of panellists (74%) voted to cap the dose of chemotherapy in some way, such as by using an arbitrary maximum BSA (eg, 2.0 or 2.2 m^2), a dose that is under the cytotoxic threshold, or a dose that is less than what is calculated based on the patient's actual BSA. Only 26% of panellists voted to use the full dose based on actual BSA. This is contrary to what current guidelines recommend, but in APC, the goal of treatment is palliation; moreover, the chemotherapy dose should be calculated with caution because the majority of these patients are older and have additional risk factors for febrile complications, such as prior radiation or impaired bone marrow reserve. For docetaxel, real-world experience has demonstrated a clear increase in toxicity when this chemotherapy agent is used outside the setting of clinical trials [201].

Older patients are significantly more likely to experience toxicities from anticancer therapies and also tend to be under-represented in clinical trials, including those of prostate cancer. Panellists' responses revealed a clear pattern of opinion that while it is generally acceptable to extrapolate efficacy data to the treatment of patients who are older than most of the participants in a study, it is not acceptable to generalise safety data in this manner. A similar pattern of responses was seen for ethnicity, highlighting the need to diversify clinical trial enrolment with regard to both these demographic variables.

Finally, despite the recommendations by the EAU and SIOG guidelines to perform a geriatric screening test (eg, by G8 and mini-COG screening tools) for patients older than 70 yr, only 39% of panellists recommended performing a health status assessment for all patients, and only 52% recommended such an assessment even for selected patients. For patients requiring a more detailed health status assessment, 61% of panellists voted for referral to another speciality doctor (eg, a palliative care specialist or geriatrician) and 39% voted for an extended assessment by the treating physician. Given the increased risk for adverse events (eg, falls, fractures, and cardiac events) especially in older patients receiving systemic life-prolonging treatments for prostate cancer, performing a baseline health status screening does not seem unreasonable, especially when considering treatment intensification with docetaxel or an AR pathway inhibitor in patients with mHSPC. Clearly, there is an urgent need for more clinical studies in these populations and more education for cancer experts on this topic.

10. Side effects of hormonal treatments and their management

Hormonal therapies for APC are frequently associated with toxicities that can adversely affect quality of life. Management of these toxicities is often inconsistent between and within health care systems. So far, only the EAU has published relevant guidelines [3].

Hot flushes, a particularly common side effect of hormonal therapies for APC, can be associated with significant distress and reduced quality of life [202, 204–207]. They are more pronounced in younger patients and in patients with lower BMI [208], and they can often be induced by thermogenic stimuli (eg, hot drinks, alcohol, radiant heaters, and thermal blankets). Counselling patients to avoid such stimuli may be helpful [209]. Patients can also be counselled to dress in layers and to cool the home environment when possible.

Hot flushes can be effectively controlled in some patients by means of low-dose oestrogens, cyproterone acetate, and medroxyprogesterone, although the potential cardiovascular toxicities of oestrogens such as diethylstilboestrol have raised concerns, and decreases in PSA following the

cessation of cyproterone acetate and medroxyprogesterone suggest that these drugs might contribute to prostate cancer progression [210–212]. Of note, there is a lack of well-designed controlled studies on the efficacy of acupuncture for reducing ADT-associated hot flushes [213,214].

Q121: Preferred first management options for patients on ADT with frequent or bothersome hot flushes were venlafaxine (28% of panellists), complementary approaches such as acupuncture (22%), cyproterone acetate (20%), medroxyprogesterone (11%), gabapentin (4%), and other options (15%). There was one abstention. (No consensus for any given answer option)

Fatigue is another common side effect of hormonal therapies, particularly ADT, abiraterone, and next-generation AR antagonists such as enzalutamide and apalutamide [82,83,92,99,215–217]. Managing fatigue is challenging because it often is multifactorial. Dose reduction may be an option for patients on AR antagonists, as was permitted in all the phase III protocols. Intermittent ADT may be considered if the patient is educated about the lack of noninferiority evidence supporting the efficacy of this approach in the metastatic setting [218,219]. Additionally, there is increased evidence that resistance exercise training can improve fatigue and other side effects from prostate cancer therapies [220–222].

Q122: Preferred first management options to reduce fatigue in patients receiving systemic therapy for prostate cancer (apart from dose reductions, if possible) were resistance and aerobic exercise (94% of panellists), caffeine (4%), and other management options (2%). There were no abstentions. (Strong consensus for resistance and aerobic exercise to reduce fatigue)

Both enzalutamide and apalutamide therapy are associated with cognitive impairment in a clinically significant proportion of patients [82,223,224]. Owing to this association, panellists at APCCC 2017 reached consensus that abiraterone is preferred for patients with prostate cancer who have significant baseline neurocognitive impairment. At APCCC 2019, panellists were asked how they would manage cognitive impairment that develops during treatment.

Q123: For patients who develop clinically significant cognitive impairment on enzalutamide or apalutamide, 66% of panellists voted to switch to abiraterone and 34% voted to first reduce the dose of enzalutamide or apalutamide. There were six abstentions. (No consensus for any given answer option)

10.1. Discussion of side effects of hormonal treatments and their management

Treatment side effects are of great importance to patients with APC, but their impact may be underestimated or downplayed in the context of opportunities to utilise new and potent life-prolonging therapies. For the management of hot flushes, there was no consensus on any treatment option. Interestingly, 63% of panellists voted for pharmacological treatments, while 22% voted for recommending complementary approaches first. Relevant data regarding the management of hot flushes in prostate cancer are limited [210] and are partly derived from the literature on women receiving systemic endocrine therapies for breast cancer. Even though panellists could not agree on the best choice, there was a clear message that several options are available, and should be discussed with and offered to patients.

In contrast, there was strong consensus regarding the management of fatigue, which is another very common adverse effect of systemic prostate cancer therapy. A striking 94% of panellists recommended resistance and aerobic training as their preferred first management option. Trials investigating exercise have been completed (EXCAP: NCT00815672) or are on-going (INTERVAL: NCT02730338), and will generate additional evidence in this area. Exercise is, of course, also recommended to improve bone health in men with prostate cancer. Exercise may also help reduce the frequency of bothersome hot flushes.

Concerns persist regarding the adverse cognitive effects of some hormonal drugs. Clinical experience suggests that these effects often abate when patients are switched to a different treatment. At APCCC 2019, two-thirds of panellists recommended switching to abiraterone if patients developed significant cognitive impairment on an AR antagonist (enzalutamide or apalutamide) [225]. However, various factors (availability, regulatory restrictions, and patient-specific characteristics) may preclude such a switch. In such cases, a dose reduction may be equally effective in reducing the intensity of the side effects, but patients should be clearly informed about the lack of noninferiority studies on the efficacy of full- versus reduced-dose treatment [218,219].

Novel systemic prostate cancer therapies with potentially fewer cognitive effects are emerging. This is an active area of investigation. We expect that patient-reported outcomes and management of side effects will receive more attention during the next APCCC, in 2021.

11. Conclusions

APCCC provides a structured mechanism to gather the opinions of recognised experts about vexing issues that are not fully addressed by the existing literature and guidelines on APC. APCCC also identifies areas where research should be concentrated to help answer critical open questions. The APCCC voting is based on a rigorous methodology in which questions are carefully designed by using a modified Delphi process. Such an approach has been used successfully in the field of early breast cancer treatment for >30 yr.

Importantly, APCCC is unlike guideline development processes because it imposes no rules of evidence on experts as they consider the questions. Hence, the methodology captures what the experts think and not

what the evidence indicates. This is a key distinction, because experts can be influenced not only by data, but also by their individual clinical experiences, the setting in which they practice, and the prevailing sentiments of their colleagues. The opinions of experts can represent the intuition of experienced, knowledgeable practitioners who correctly anticipate what the evidence would or will show, but they also can be wrong—and in the history of oncology, they have been proved wrong many times. Furthermore, in recent years, public discussion has been critical of expert opinions because of the potential for influence by financial conflicts of interest [226] and because investigators may possibly favour data from the trials they conducted, which may influence their perspectives.

With all this in mind, we note that some of the voting results from APCCC 2019 identified areas of consensus that lack supporting evidence from the current literature. As the questions asked at APCCC are highly relevant in daily clinical practice, we take particular care to note that merely because experts agree does not mean they are right. Although this report captures what experts in the field think today, it should be interpreted and integrated into clinical practice with the same scrutiny that any other major paper would receive, and with the knowledge that consensus does not constitute or substitute for evidence.

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Appendix A. Supplementary data

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