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Prostate Cancer

Management of Patients with Advanced Prostate Cancer: Report from the Advanced Prostate Cancer Consensus Conference 2021

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Abstract

Background: Innovations in treatments, imaging, and molecular characterisation in advanced prostate cancer have improved outcomes, but various areas of management still lack high-level evidence to inform clinical practice. The 2021 Advanced Prostate Cancer Consensus Conference (APCCC) addressed some of these questions to supplement guidelines that are based on level 1 evidence.

Objective: To present the voting results from APCCC 2021.

Design, setting, and participants: The experts identified three major areas of controversy related to management of advanced prostate cancer: newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC), the use of prostate-specific membrane antigen ligands in diagnostics and therapy, and molecular characterisation of tissue and blood. A panel of 86 international prostate cancer experts developed the programme and the consensus questions.

Outcome measurements and statistical analysis: The panel voted publicly but anonymously on 107 pre-defined questions, which were developed by both voting and non-voting panel members prior to the conference following a modified Delphi process.

Results and limitations: The voting reflected the opinions of panellists and did not incorporate a standard literature review or formal meta-analysis. The answer options for the consensus questions received varying degrees of support from panellists, as reflected in this article and the detailed voting results reported in the Supplementary material.

Conclusions: These voting results from a panel of experts in advanced prostate cancer can help clinicians and patients to navigate controversial areas of management for which high-level evidence is scant. However, diagnostic and treatment decisions should always be individualised according to patient characteristics, such as the extent and location of disease, prior treatment(s), comorbidities, patient preferences, and treatment recommendations, and should also incorporate current and emerging clinical evidence and logistic and economic constraints. Enrolment in clinical trials should be strongly encouraged. Importantly, APCCC 2021 once again identified salient questions that merit evaluation in specifically designed trials.

Patient summary: The Advanced Prostate Cancer Consensus Conference is a forum for discussing current diagnosis and treatment options for patients with advanced prostate cancer. An expert panel votes on predefined questions focused on the most clinically relevant areas for treatment of advanced prostate cancer for which there are gaps in knowledge. The voting results provide a practical guide to help clinicians in discussing treatment options with patients as part of shared decision-making.

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1. Introduction

The multidisciplinary panel for the 2021 Advanced Prostate Cancer Consensus Conference (APCCC 2021) consisted of 86 cancer physicians and scientists who were selected based on their academic experience and involvement in clinical or translational research in the field of advanced prostate cancer.

Three controversial areas related to the management of patients with advanced prostate cancer were prioritised for discussion in 2021:

1. Management of newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC);
2. Prostate-specific membrane antigen (PSMA) ligands in diagnostics and therapy; and
3. Molecular characterisation of tissue and blood.

The conference and the consensus development process followed procedures that have previously been described [1–3]. Using a modified Delphi process, panel members prepared 123 questions, of which three were excluded from the final analysis because of incomplete answer options, and 13 on the management of patients during the COVID-19 pandemic were reported separately. The remaining 107 questions were voted on at APCCC 2021, which was held virtually for the first time because of the COVID pandemic. For this reason, panellists voted via a web-based survey rather than in person. 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 consensus questions applied only to fit patients with prostatic adenocarcinoma who had no treatment-limiting comorbidities. Next-generation imaging (NGI) for prostate cancer was defined as positron emission tomography (PET)-computed tomography (CT)/magnetic resonance imaging (MRI)—subsequently referred to as PET/CT, unless stated otherwise—with choline, or fluciclovine tracers and/or whole-body morphological and diffusion-weighted MRI.

The results of the voting are intended to serve as a guide to help clinicians and patients to participate in shared and multidisciplinary decision-making. For each of the three sections, an accompanying table (Tables 1–3) summarises questions for which consensus was reached. Additional definitions used during APCCC 2021 are provided in the Supplementary material.

The panel consisted of 73 voting members and 13 nonvoting members. Both voting and nonvoting members helped to define the questions. In all, 48% of voting members were medical oncologists, 31% were urologists, and 21% were clinical and radiation oncologists. A total of 35% practiced in Europe, 41% in North America, and 24% in other regions of the world. Nonvoting members were experts in areas such as nuclear medicine, radiology, pathology, statistics, and health economics who are not directly involved in clinical decision-making. In addition, one nonvoting member was a patient advocate. Throughout the rest of this article, voting members are referred to as "panellists". Panellists were instructed to vote "abstain" if they perceived that they lacked expertise for a specific question, if they felt that they were unable to vote for a best answer option for some other reason, or if they 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 as consensus, and answer options with $\geq$90% agreement were considered as strong consensus.

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

2. Management of newly diagnosed mHSPC

In recent years, multiple studies have confirmed that addition of docetaxel or an androgen receptor pathway inhibitor (ARPI; abiraterone, enzalutamide, or apalutamide) to androgen deprivation therapy (ADT) significantly prolongs survival [4–9]. As a result, these doublet regimens have become standard treatments for mHSPC. Combining ADT with radiation of the primary tumour has become another standard option for patients with mHSPC who have synchronous disease and a low metastatic burden [10,11].

Thus far, data on triplet regimens in mHSPC have been more mixed. In 2021, the randomised phase 3 PEACE-1 trial, which only included patients with synchronous mHSPC, demonstrated a significant overall survival (OS) advantage with abiraterone, ADT, and docetaxel when compared to standard ADT-docetaxel doublet therapy [12]. However, in the randomised phase III ENZAMET trial, adding

Table 1 – Areas of consensus (≥75% agreement) at the Advanced Prostate Cancer Consensus Conference 2021: mHSPC

Question	Topic and result
Q2	When deciding how to treat low-volume mHSPC, 84% of panellists voted that it is important to distinguish synchronous (de novo) metastatic (M1) HSPC from metachronous (relapsing) metastatic prostate cancer (recurring after radical local therapy given with curative intent in the M0 setting), irrespective of the imaging used, while 16% voted that this is unimportant. **Consensus (84%)** that it is important to distinguish synchronous from metachronous HSPC.
Q4	When deciding whether to recommend local treatment of the primary tumour in mHSPC, 99% of panellists voted that it is important to distinguish low-volume from high-volume disease on the basis of conventional imaging results, while 1% voted that this is unimportant. **Strong consensus (99%)** to use conventional imaging to distinguish low-volume from high-volume mHSPC.
Q9	Some 99% of panellists voted that it is **not** important to distinguish low-volume from high-volume mHSPC via conventional imaging for the use of ARPIs; the remaining 1% voted that they restrict their use of ARPIs in mHSPC mainly to patients with low-volume mHSPC. **Strong consensus (99%)** for ARPIs independent of volume.
Q15	For asymptomatic, synchronous, low-volume mHSPC, 14% of panellists voted to add local treatment of the primary tumour (with or without MDT) to ADT, 8% voted to add additional systemic therapy to ADT, 77% voted to add both radical local treatment of the primary tumour and additional systemic therapy (with or without MDT), and 1% voted for no additional treatment (ADT alone). **Consensus (77%)** for radical local treatment of the primary tumour plus ADT and additional systemic therapy with or without MDT.
Q17	For synchronous, low-volume mHSPC without symptoms from the primary tumour, 93% of panellists voted to treat the primary tumour with radiation therapy, 6% voted to treat it with surgery, and 1% voted against local treatment. **Strong consensus (93%)** for radiation therapy.
Q18	For synchronous, low-volume mHSPC in cases for which radical local treatment of the primary tumour is recommended with our without MDT, 84% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 1% voted to add docetaxel to ADT, 3% voted to add docetaxel plus an ARPI, and 12% voted against adding systemic treatment(s) to ADT. **Consensus (84%)** for local treatment of the primary tumour plus ADT and an ARPI.
Q19	For synchronous, low-volume mHSPC in cases for which **no** radical local treatment of the primary tumour is recommended, 91% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 5% voted to add docetaxel plus an ARPI to ADT, and 4% voted for no additional treatment (ADT alone). **Strong consensus (91%)** for ADT plus an ARPI among the panellists who did not vote for radical local treatment of the primary.
Q22	For metachronous mHSPC that is low volume according to conventional imaging, among those panellists who voted for systemic therapy alone, 100% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), while 0% voted for ADT alone, ADT plus docetaxel, or triple-combination therapy. **Strong consensus (100%)** for ADT plus an ARPI among the panellists who voted for systemic therapy.
Q23	For metachronous mHSPC that is low volume according to NGI and nonmetastatic according to conventional imaging, among those panellists who voted for systemic treatment alone, 90% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), while 10% voted for ADT alone. **Strong consensus (90%)** for ADT plus an ARPI among the panellists who voted for systemic therapy.
Q27	Among panellists who voted for systemic treatment plus MDT for metachronous, low-volume mHSPC, 78% voted for intermittent (temporary) systemic therapy and 22% voted for continuous/lifelong systemic therapy. **Consensus (78%)** for intermittent systemic therapy among the panellists who voted for systemic therapy.
Questions for which no single answer option received ≥75% agreement but combining answer options led to ≥75% agreement	
Q12	For systemic treatment of synchronous, high-volume mHSPC (defined via conventional imaging or unequivocal NGI), 49% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 11% voted to add docetaxel to ADT, and 40% voted to add both an ARPI and docetaxel to ADT. No consensus for any answer option; **0% of panellists voted for ADT alone.**
Q13	For systemic treatment of metachronous, high-volume mHSPC (defined via conventional imaging or unequivocal NGI), 71% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 7% voted to add docetaxel to ADT, 21% voted to add both drugs, and 1% voted for no additional treatment (ADT alone). No consensus for any answer option; **only 1% of panellists voted for ADT alone.**
Q20	For treatment of metachronous, low-volume mHSPC (defined via conventional imaging), 64% of panellists voted for MDT plus systemic therapy, 26% voted for systemic therapy alone (including ADT), and 10% voted for MDT alone (without systemic therapy). No consensus for any answer option, but a **combined 90% of panellists** voted that MDT alone is not sufficient.
Q35	For high-volume mHSPC (defined via conventional imaging or unequivocal NGI) in patients with low baseline PSA (eg, <5 ng/ml) and no neuroendocrine component on biopsy, 46% of panellists voted for ADT plus docetaxel and an ARPI (abiraterone, apalutamide, or enzalutamide), 29% voted for ADT plus docetaxel, 18% voted for ADT plus an ARPI, and 7% voted for ADT plus platinum-based combination therapy. No consensus for any answer option, but a **combined 82% of panellists** voted for chemotherapy.
Q36	When asked how soon they usually start docetaxel or an ARPI in relation to ADT, 23% of panellists voted that they start immediately (within ~2 wk of starting ADT), 71% voted that they start within 3 mo of starting ADT, and 6% voted that they start within 6 mo of starting ADT. No consensus for any answer option, but a **combined 94% of panellists** voted for starting within 3 mo.

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; HSPC = hormone-sensitive prostate cancer; mHSPC = metastatic HSPC; MDT = metastases-directed therapy; NGI = next-generation imaging; PSA = prostate-specific antigen.

enzalutamide to ADT did not significantly improve OS among the 45% of study participants who received early docetaxel [5]. Note that ENZAMET included a mix of patients (synchronous and metachronous), and a difference in OS might emerge with longer follow-up. Data from the ARASENS trial comparing ADT plus docetaxel with or without darolutamide were not available at the time of APCCC 2021 [13].

Currently, a number of questions remain open. One pertains to the role of disease volume in treatment selection, particularly since the use of NGI modalities such as PSMA PET (including PSMA PET/CT or PET/MRI) for staging can result in upstaging and treatment intensification with either radiation of the prostate or docetaxel. Another question is whether it is clinically relevant to distinguish synchronous from metachronous mHSPC [14].

Panellists first voted on their preferred terminology for mHSPC.

> **Q1.** Regarding their preferred terminology for mHSPC, 66% of panellists voted for "de novo and relapsed mHSPC", 24% voted for "synchronous and metachronous mHSPC", and 10% voted for "de novo and metachronous mHSPC". There were no abstentions. (No consensus for any answer option.)

Panellists next considered whether it is important to distinguish synchronous from metachronous mHSPC when making treatment decisions in low-volume and high-volume mHSPC.

Table 2 – Areas of consensus (≥75% agreement) at the Advanced Prostate Cancer Consensus Conference: PSMA in diagnostics and therapy

Question	Topic and result
Q44	For staging purposes, 78% of panellists voted that data from ^{68}Ga-PSMA-11 PET imaging can be extrapolated to other PSMA tracers (eg, ^{18}F-DCFPyL, ^{18}F-PSMA-1007), while 22% voted against this extrapolation. **Consensus (78%)** that ^{68}Ga-PSMA PET imaging data can be extrapolated to other PSMA tracers.
Q45	Some 90% of panellists voted that data from PSMA PET imaging for staging **cannot** be extrapolated to choline PET imaging, while 10% voted for this extrapolation. **Strong consensus (90%)** that PSMA PET imaging data **cannot** be extrapolated to choline PET/CT.
Q46	A total of 87% of panellists voted that data from PSMA PET imaging for staging **cannot** be extrapolated to fluciclovine PET/CT imaging, while 13% voted for this extrapolation. There were nine abstentions. **Consensus (87%)** that PSMA PET imaging data **cannot** be extrapolated to fluciclovine PET/CT.
Q48	Among the panellists who voted for PSMA PET for staging of localised prostate cancer (Q47), 87% voted that mpMRI is still necessary for local tumour staging, while 13% voted that mpMRI is unnecessary. **Consensus (87%)** that mpMRI is still necessary among the panellists voting for PSMA PET for staging.
Q49	Among the panellists who voted for PSMA PET for staging of localised prostate cancer, 84% voted that bone scintigraphy is not necessary, while 16% voted that it is still necessary. **Consensus (84%)** that bone scintigraphy is **not** necessary among the panellists voting for PSMA PET for staging.
Q50	For patients with high-risk localised prostate cancer who plan to receive radical prostatectomy, if there is no PSMA PET evidence of metastatic disease (N0 M0), 17% of panellists voted to omit ePLND, 77% voted not to omit ePLND, and 6% voted that they generally did not recommend ePLND for high-risk localised prostate cancer. **Consensus (77%)** not to omit ePLND.
Q51	For patients with high-risk localised prostate cancer who plan to receive RT of the prostate, if they have no PSMA PET evidence of metastatic disease (N0 M0), 20% of panellists voted to omit RT of the pelvis, 76% voted not to omit it, and 4% generally did not recommend RT of the pelvis in this setting. **Consensus (76%)** not to omit RT of the pelvis.
Q54	Among the panellists who voted for adding systemic therapy to the original treatment plan (Q52 and Q53), 81% preferred abiraterone, 17% apalutamide or enzalutamide, and 2% abiraterone plus enzalutamide. There were 27 abstentions. **Consensus (81%)** to add abiraterone among the panellists voting for additional systemic therapy.
Q57	Among the panellists who voted for additional systemic therapy to long-term (2–3 yr) ADT (Q55 and Q56), 77% preferred abiraterone, 18% apalutamide or enzalutamide, 3% docetaxel, and 2% abiraterone plus enzalutamide. **Consensus (77%)** to add abiraterone among the panellists voting for additional systemic therapy.
Q59	Among those panellists who voted to continue with radical local treatment for Q58, 87% preferred definitive RT of the primary tumour (with or without the pelvis), and 13% preferred radical prostatectomy (with or without lymphadenectomy). **Consensus (87%)** for definitive RT of the primary tumour with or without pelvis
Q63	For chemotherapy-fit patients with PSMA-positive mCRPC who have received at least 1 line of ARPI therapy and 1 line of taxane-based chemotherapy, and who meet the relevant criteria for ^{177}Lu-PSMA therapy, 77% of panellists voted for ^{177}Lu-PSMA therapy, 13% for cabazitaxel, and 10% for radium-223 (assuming that the relevant treatment criteria are met). **Consensus (77%)** for ^{177}Lu-PSMA therapy
Q64	For chemotherapy-fit patients with PSMA-positive mCRPC who have received at least 1 line of ARPI therapy but not chemotherapy, and who meet the relevant criteria for ^{177}Lu-PSMA therapy, 85% of panellists voted for docetaxel, 14% for ^{177}Lu-PSMA, and 1% for radium-223 (assuming that the relevant treatment criteria are met). **Consensus (85%)** for docetaxel.
Q67	For chemotherapy-unfit patients with PSMA-positive mCRPC who are progressing after at least 1 line of ARPI therapy, meet the relevant criteria for ^{177}Lu-PSMA therapy, and cannot enrol in a clinical trial, 80% of panellists voted for ^{177}Lu-PSMA, 17% voted for ^{177}Lu-PSMA if patients did not meet the criteria for radium-223 therapy, and 3% voted against ^{177}Lu-PSMA. **Consensus (80%)** for ^{177}Lu-PSMA.
Q68	In all, 86% of panellists voted that it is inappropriate to recommend ^{177}Lu-PSMA therapy to patients with mHSPC outside the setting of a clinical trial, while 14% voted that this is appropriate. **Consensus (86%) not** to recommend ^{177}Lu-PSMA in mHSPC outside a clinical trial.
Q72	For selection of patients for treatment with ^{177}Lu-PSMA, 83% of panellists voted that data on ^{68}Ga-PSMA-11 PET from the VISION trial can be extrapolated to ^{18}F-PSMA-1007 PET/CT, while 17% voted against this. **Consensus (83%)** that VISION results can be extrapolated to ^{18}F-PSMA-1007 PET/CT
Q75	If patients respond (ie, demonstrate PSA and/or clinical or radiological improvement) to 4 cycles of ^{177}Lu-PSMA therapy, but their post-treatment PSMA PET (planar or SPECT) shows significant residual uptake as defined by the treating physician, 86% of panellists voted to administer two additional cycles of ^{177}Lu-PSMA therapy, while 14% voted not to do so. **Consensus (86%)** to administer two additional cycles of ^{177}Lu-PSMA if there is significant remaining uptake.
Q77	For patients with mCRPC who previously received an ARPI as well as chemotherapy, and who are now receiving ^{177}Lu-PSMA, 21% of panellists voted to add the alternate ARPI, while 79% voted against this. **Consensus (79%) not** to add the alternate ARPI to ^{177}Lu-PSMA in patients with mCRPC who are already post-ARPI and postchemotherapy.
Q80	For patients with mCRPC who have exhausted standard treatment options, previously showed a documented response to ^{177}Lu-PSMA therapy (eg, lasting ≥6 mo), and are now progressing again with cancer that continues to meet initial treatment criteria, 81% of panellists voted to rechallenge with ^{177}Lu-PSMA, while 19% voted against rechallenge. **Consensus (81%)** to rechallenge with ^{177}Lu-PSMA.
Q82	A total of 76% of panellists voted that it is safe, while 24% voted that it is unsafe, to recommend radium-223 to patients with mCRPC who have previously received ^{177}Lu-PSMA therapy (panellists were informed that in the VISION trial, ~2% of patients received radium-223 after ^{177}Lu-PSMA). **Consensus (76%)** that it is safe to use radium-223 after ^{177}Lu-PSMA.
Q83	For patients with mCRPC who have relevant impairment of bone marrow function, 85% of panellists voted that it is **not** safe to recommend treatment with ^{177}Lu-PSMA, while 15% voted that this is safe. For this question, impaired bone marrow function was defined according to exclusion criteria for the VISION trial (haemoglobin <9 g/dl and/or absolute neutrophil count < 1.5×10^9 cells/l and/or platelets < 100×10^9 cells/l). **Consensus (85%)** that it is **not** safe to recommend ^{177}Lu-PSMA to patients with mCRPC who have relevant impairment of bone marrow function.

(*continued on next page*)

Table 2 (*continued*)

Question	Topic and result
Questions for which no single answer had ≥75% agreement but combining answer options resulted in ≥75% agreement	
Q47	Regarding when to use PSMA PET imaging to stage localised prostate cancer, 50% of panellists voted for high-risk disease only, 23% voted for intermediate- and high-risk disease, 4% voted for the majority of patients independent of risk, and 23% voted against its use for staging of localised disease. No consensus for any answer option, **but a combined total of 77% of panellists** voted for PSMA PET in high-risk localised prostate cancer.
Q56	For patients with high-risk localised prostate cancer for whom definitive RT of the prostate plus ADT is planned, if they have N0, M0 status on conventional imaging but are found to have ≥4 PSMA-positive lymph node(s) limited to the pelvis (cN1, M0), 27% of panellists voted to continue treatment as planned, 72% voted to change treatment to RT of the prostate and pelvis, plus long-term ADT, plus another systemic therapy (an AR pathway inhibitor or docetaxel), and 1% voted to change treatment to radical prostatectomy plus ePLDN. No consensus for any answer option, but **a combined total of 99% of panellists** voted to proceed with RT plus systemic therapy.
Q58	For patients with high-risk localised prostate cancer for whom radical local treatment (prostatectomy or RT) of the primary tumour is planned, if they have N0, M0 status on conventional imaging but are found to have 1–3 PSMA-positive lesion(s) in bone (M1), 23% of panellists voted to also add a systemic therapy, 10% voted to add MDT instead of systemic therapy, 51% voted to add both MDT and systemic therapy, 12% voted to change treatment to standard mHSPC therapy, and 4% voted to continue with radical local treatment as planned and monitor the PSMA-positive lesions. No consensus for any answer option, but **a combined total of 96% of panellists** voted for a treatment change.
Q60	For patients with high-risk localised prostate cancer for whom radical local treatment (prostatectomy or RT) of the primary tumour is planned, if they have N0, M0 status on conventional imaging but are found to have ≥4 PSMA-positive lesions in bone (M1), 44% of panellists voted to intensify the original treatment plan by also adding systemic therapy, 3% voted to instead add MDT, 22% voted to add both systemic therapy and MDT, 29% voted to change treatment to standard mHSPC therapy, and 2% voted to continue with radical local treatment as planned while monitoring the PSMA-positive lesions. No consensus for any given option, but **a combined total of 98% of panellists** voted for a treatment change.
Q85	For patients with mCRPC who have impaired renal function (eg, GFR 30–49 ml/min), 30% of panellists voted that it is safe to recommend treatment with ^{177}Lu-PSMA, 51% voted for a reduced ^{177}Lu-PSMA dose, and 19% voted that it is unsafe to recommend ^{177}Lu-PSMA. No consensus for any answer option, but **a combined total of 81% of panellists** voted for ^{177}Lu-PSMA, mostly at a reduced dose.
Q84	For patients with mCRPC who have a malignant superscan (bone scintigraphy) and do not have relevant impairment of bone marrow function, provided that relevant PET criteria are met, 71% of panellists voted that it is safe to recommend treatment with ^{177}Lu-PSMA, 24% voted for a reduced dose of ^{177}Lu-PSMA, and 5% voted that it is unsafe to recommend ^{177}Lu-PSMA. No consensus for any answer option, but **a combined total of 95% of panellists** voted that ^{177}Lu-PSMA can be administered at a full or reduced dose.

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; ePLND = extended pelvic lymphadenectomy; GFR = glomerular filtration rate; HSPC = hormone-sensitive prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic HSPC; MDT = metastases-directed therapy; mpMRI = multiparametric magnetic resonance imaging; NGI = next-generation imaging; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RT = radiotherapy; SPECT = single-photon emission computed tomography.

Q2. When deciding how to treat **low-volume** mHSPC, 84% of panellists voted that it is important to distinguish synchronous (de novo) metastatic (M1) HSPC from metachronous (relapsing) metastatic prostate cancer (recurring after radical local therapy given with curative intent in the M0 setting), irrespective of the imaging used, while 16% voted that this is unimportant. There were no abstentions. (**Consensus** that it is important to distinguish synchronous from metachronous HSPC.)

Q3. When deciding how to treat **high-volume** mHSPC, 63% of panellists voted that it is important to distinguish synchronous (de novo) metastatic (M1) HSPC from metachronous (relapsing) metastatic prostate cancer (recurring after radical local therapy given with curative intent in the M0 setting), irrespective of the imaging used, while 37% voted that this is unimportant. There was one abstention. (No consensus for any answer option.)

The panel was also asked whether disease volume, as defined on conventional imaging, is important when deciding whether to recommend local treatment of the primary tumour [10,15].

Q4. When deciding whether to recommend local treatment of the primary tumour in mHSPC, 99% of panellists voted that it is important to distinguish low-volume from high-volume disease on the basis of conventional imaging, while 1% voted that this is unimportant. There were no abstentions. (**Strong consensus** that it is important to distinguish high- from low-volume mHSPC defined on conventional imaging.)

Q5. When deciding whether to recommend local treatment of the primary tumour in mHSPC, 55% of panellists voted that it is important to distinguish low-volume from high-volume disease on the basis of NGI, while 45% voted that this is unimportant. There were three abstentions. (No consensus for any answer option.)

In the STAMPEDE trial, an exploratory analysis of outcomes after prostate radiation therapy showed a continuous, inverse relationship between bone metastases on conventional imaging (CT and bone scintigraphy) and survival; among individuals with more than three bone metastases, the 95% confidence interval for OS crossed the line of equivalence regardless of whether patients had nonregional lymph node metastases [15]. At APCCC 2021, panellists voted on the best cutoff number of bone metastases for recommending local treatment of the primary tumour. For this topic, conventional imaging and NGI were addressed in two separate questions.

Q6. When deciding whether to recommend local treatment of the primary tumour in mHSPC where bone metastases were identified on conventional imaging, 64% of panellists voted for a cutoff of three or fewer bone metastases, 29% voted for five or fewer, 6% voted for no upper limit, and 1% voted against local treatment of the primary tumour in the metastatic setting. There was one abstention. (No consensus for any answer option.)

Q7. When deciding whether to recommend local treatment of the primary tumour in mHSPC where bone metastases were identified on NGI, 50% of panellists voted for a cutoff of five or fewer bone metastases, 29% voted for no upper limit, 19% voted for three or fewer, and 2% voted against local treatment of the primary tumour in the metastatic setting. There were 12 abstentions. (No consensus for any answer option.)

Table 3 – Areas of consensus (≥75% agreement) at the Advanced Prostate Cancer Consensus Conference 2021: genetic testing, tumour molecular characterisation, and targeted therapies

Question	Topic and result
Q86	In all, 87% of panellists voted for and 13% voted against recommending germline counselling and/or testing for most patients with metastatic prostate cancer, assuming that testing is available and local regulations permit. **Consensus (87%)** to recommend germline counselling and/or testing for most patients with metastatic prostate cancer.
Q87	A total of 80% of panellists voted that if local regulations allow, it is appropriate for a physician to order germline testing in the absence of genetic counselling if genetic counselling is unavailable. The remaining 20% of panellists voted that this is inappropriate. **Consensus (80%)** for physicians to order germline testing before counselling (provided local regulation allows it)
Q90	For patients with localised prostate cancer of any risk group who have a positive family history (eg, according to NCCN criteria), 77% of panellists voted to recommend genetic counselling/germline testing, while 23% voted against it. There was one abstention. **Consensus (77%)** to recommend genetic counselling/germline testing for patients with localised prostate cancer and a positive family history.
Q94	Among the panellists who voted for tumour (somatic) genomic testing only in the mCRPC setting, 76% voted to perform it after progression on an ARPI, 18% after progression on an ARPI and 1 line of taxane chemotherapy, 4% after all standard treatment options are exhausted, and 2% voted that they do not routinely recommend tumour somatic testing. **Consensus (76%)** to perform tumour (somatic) genomic testing after progression on an ARPI among the panellists voting for tumour genomic testing.
Q99	When testing for alterations in DDR genes in order to select PARPi therapy for patients with no identified germline variant, 88% of panellists voted for tissue-based testing, and 12% voted for liquid biopsy (ctDNA testing). **Consensus (88%)** for tissue-based testing.
Q100	When performing tumour tissue-based (somatic) testing for selection of PARPi therapy, 96% of panellists voted that they preferred to test recent biopsy tissue, but if unavailable, then archival tissue is sufficient, 3% voted that recent biopsy is mandatory, and 1% voted to test archival tissue. **Strong consensus (96%)** to test recent biopsy tissue, if available, and to otherwise test archival tissue.
Q102	For patients with a pathogenic, monoallelic, somatic (not germline) *BRCA1/2* alteration, 76% of panellists voted for PARPi therapy, 16% voted for it only if there is a positive HRD score, and 8% voted against PARPi therapy. **Consensus (76%)** for PARPi therapy.
Questions for which no single answer had ≥75% agreement but combining answer options resulted in ≥75% agreement	
Q92	For patients with prostate cancer without a significant family history, 14% of panellists voted that they test for *BRCA1* and *BRCA2* mutations only, 61% voted that they use a more extended panel (eg, *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *RAD51C*, *HOXB13*), and 25% voted that they use comprehensive genomic testing of all known cancer-associated germline mutations. No consensus for any answer option, but **a combined 86% of panellists voted** for a panel including more than just *BRCA1/2*.
Q93	A total of 48% of panellists voted for tumour genomic profiling (tissue or ctDNA) only in the mCRPC setting, 39% voted for it at the time of diagnosis of any mHSPC, 9% at diagnosis of synchronous mHSPC, and 4% voted that they do not routinely recommend tumour genetic profiling. For this question, panellists were asked to assume that tumour genomic profiling was readily available. No consensus for any answer option, **but a combined 96% of panellists voted** for tumour testing either in mHSPC or mCRPC.
Q96	Among the panellists who voted for tumour (somatic) genomic testing in metastatic prostate cancer, 20% voted that it is relevant, when testing for the purposes of treatment selection, to include *BRCA1/2* plus dMMR evaluation (MSI high/dMMR ± high TMB), 34% would also test for additional DDR gene alterations, and 46% would perform comprehensive panel testing (eg, *BRCA1/2*, dMMR evaluation, additional DDR genes, and *PTEN*, *PI3K*, *SPOP*, *RB1*, *TP53*, and *AR*). No consensus for any answer option, but a **combined 100% of panellists** voted for *BRCA1/2* and dMMR/MSI testing.
Q98	Regarding whether tumour (somatic) genomic testing should be performed at the same time as germline testing (eg, as part of a paired tumour-germline analysis), 56% of panellists voted to recommend this, 25% voted to recommend it if there is access to genetic counselling, and 19% did not recommend it. No consensus for any answer option, but a **combined 81% of panellists voted** for testing at the same time, provided that genetic counselling is available.
Q101	For patients with a pathogenic *BRCA1/2* aberration (germline/somatic or somatic alone), 55% of panellists voted to start PARPi therapy after 1 line of ARPI, 41% after 1 line of ARPI and 1 line of chemotherapy, and 4% after 1 line of ARPI, 1 line of chemotherapy, and lutetium-PSMA. No consensus for any answer option, but a **combined 100% of panellists voted** to use PARPi therapy in the disease course
Q109	For patients with a pathogenic *BRCA1/2* aberration (germline/somatic or somatic alone), if PARPi therapy is not accessible, 35% of panellists voted for platinum-based therapy, 61% voted for it only for patients who have already received at least 1 ARPI and 1 line of taxane chemotherapy, and 4% voted against it. No consensus for any answer option, **but a combined 96% of panellists voted** for platinum-based chemotherapy if PARPi therapy is not available, at least after 2 prior lines of therapy

ARPI = androgen receptor pathway inhibitor; ctDNA = circulating tumour DNA; DDR = DNA damage repair; dMMR = deficient mismatch repair; HRD = homologous recombination deficiency; mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; MSI = microsatellite instability; NCCN = National Comprehensive Cancer Network; PARPi = PARP inhibitor; PSMA = prostate-specific membrane antigen; TMB = tumour mutational burden.

Some patients in the CHAARTED, GETUG-15, and STAMPEDE trials had low-volume mHSPC. In the CHAARTED trial, in which patients were randomised 1:1 to receive ADT or ADT plus docetaxel, patients were stratified according to whether they had predefined low-volume (n = 277; 143 ADT alone, 134 ADT plus docetaxel) or high-volume (n = 513, 250 ADT alone, 263 ADT plus docetaxel) disease [16]. The subgroup of patients with low-volume disease (of whom 55% had synchronous and 45% metachronous disease) showed no OS benefit from receiving docetaxel in addition to ADT. However, a test of heterogeneity revealed a significantly different (heterogeneous) treatment effect for docetaxel plus ADT when patients had high- versus low-volume disease (p = 0.033) [16]. As noted in the discussion section of that paper, there also was a suggestion of possible benefit in the subgroup with de novo low-volume disease, with a hazard ratio (HR) of 0.86 (95% confidence interval [CI] 0.52–1.42), but there was no evidence of benefit in the subgroup of patients with more indolent metachronous low-volume disease (HR 1.25, 95% CI 0.60–2.60).

To assess for reproducibility and increase the sample size, these findings were explored and confirmed by combining CHAARTED data with data from the GETUG15 study, in which 100% of retrospective scan data were available and approximately 30% of patients had metachronous disease [17]. This combination resulted in a total of 341 patients with high-volume disease and 245 patients with low-volume disease who received ADT alone, and 355 patients

with high-volume disease and 245 with low-volume disease who received ADT plus docetaxel.

The STAMPEDE trial also retrospectively compared subgroups of patients who were stratified on the basis of low- versus high-volume disease [18]. Among 1086 patients initially eligible for this comparison, 24% were excluded because of missing imaging data. Given the 2:1 randomisation design of the study, 238 patients with low-volume disease and 320 patients with high-volume disease received ADT only, while 124 patients with low-volume disease and 148 patients with high-volume disease received ADT plus docetaxel. Among patients with low-volume disease (of whom 95% had synchronous and 5% metachronous disease), the effect of docetaxel was not significant (HR 0.76, 95% CI 0.54–1.07), which resembles the findings from the CHAARTED trial. In contrast to CHAARTED, however, there was no evidence of heterogeneity of the treatment effect on survival by disease volume (interaction $p = 0.827$) [18]. On the basis of these findings, the authors concluded that docetaxel is a valid treatment option for fit patients with mHSPC, irrespective of metastatic disease volume.

The discrepant findings from CHAARTED and STAMPEDE might result from the markedly different proportions of patients with metachronous versus synchronous low-volume mHSPC. The latter might represent a mix of individuals with more diverse underlying biology, which could result in a greater proportion of patients with de novo low-volume disease deriving some benefit from docetaxel when compared to patients with metachronous low-volume disease. The results for the de novo low-volume subgroup also need to be considered from the perspective of the relative OS benefit versus the treatment burden from radiation to the prostate or abiraterone, enzalutamide, or apalutamide therapy, and this may be reflected in the voting results. We note that in an initial analysis of data from the PEACE-1 trial, triplet therapy was associated with a more pronounced OS benefit in the subgroup of patients with synchronous high-volume mHSPC (HR 0.72, 95% CI 0.55–0.95), and while the point estimate for the HR for OS was less pronounced for the subgroup of patients with low-volume mHSPC (HR 0.83, 95% CI 0.5–1.38), there was no evidence of heterogeneity of the treatment effect between these two subgroups after median follow-up of 3.8 yr, the cutoff for the first report of study results [12]. Of note, none of the previously mentioned trials were prospectively powered to specifically assess for differences between subgroups of patients with low- versus high-volume disease.

Q8. In all, 67% of panellists voted that they mainly restrict their use of docetaxel in mHSPC to high-volume disease; the other 33% voted that their use of docetaxel in mHSPC is independent of disease volume. There were no abstentions. (No consensus for any answer option.)

For patients with mHSPC, multiple studies now have shown that adding an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT produces an OS benefit, irrespective of disease volume [4–6,9,19,20].

Q9. Some 99% of panellists voted that it is **not** important to distinguish **low-volume from high-volume mHSPC** via conventional imaging for the use of ARPIs. The remaining 1% voted that they restrict their use of ARPIs in mHSPC mainly to patients with low-volume mHSPC. There were no abstentions. (**Strong consensus** for ARPIs independent of disease volume.)

As mentioned above, patients with mHSPC may only have been staged with NGI, especially with PSMA PET/CT. The panel voted on whether patients with between four and ten bone lesions visualised on PSMA PET/CT should also undergo bone scintigraphy to help guide the selection of local and systemic treatment.

Q10. For mHSPC in which PSMA PET/CT shows between four and ten bone metastases, 47% of panellists voted against performing bone scintigraphy, stating that PSMA PET/CT alone is sufficient to select local and/or systemic treatment; 32% voted for bone scintigraphy to define disease volume and obtain a baseline for future monitoring; 14% voted for bone scintigraphy only to define disease volume; and 7% voted for bone scintigraphy only to obtain a baseline. There was one abstention. (No consensus for any answer option.)

All patients in the LATITUDE trial had synchronous mHSPC, as did the vast majority (95%) of participants in the STAMPEDE trial [4,19]. Consequently, only limited data are available on abiraterone in metachronous mHSPC, which raises the question of whether to extrapolate data from trials of other ARPIs.

Q11. For managing metachronous mHSPC, 63% of panellists voted that it is appropriate to extrapolate data from the phase 3 TITAN, ARCHES, and ENZAMET trials of apalutamide and enzalutamide to abiraterone/prednisone, while 37% voted that this is inappropriate. There were two abstentions. (No consensus for any answer option.)

The APCCC 2021 panel voted on the preferred systemic treatment for synchronous (Q12) and metachronous (Q13) high-volume mHSPC.

Q12. For systemic treatment of synchronous, high-volume mHSPC (as defined via conventional imaging or unequivocal NGI), 49% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 11% voted to add docetaxel to ADT, and 40% voted to add both an ARPI and docetaxel to ADT. There were no abstentions. (No consensus for any answer option; none voted for ADT alone.)

Q13. For systemic treatment of metachronous, high-volume mHSPC (as defined via conventional imaging or unequivocal NGI), 71% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 7% voted to add docetaxel to ADT, 21% voted to add both drugs, and 1% voted for no additional treatment (ADT alone). There were no abstentions. (No consensus for any answer option; only 1% voted for ADT alone.)

In the risk classification system introduced by the LATITUDE trial, patients with high-risk disease met at least two of the following three criteria: at least three bone metastases; Gleason score 8–10; and visceral metastases. However, clinical data were exclusively from patients with high-risk disease; moreover, in the abiraterone arm of the STAMPEDE trial, 50% of patients had high-risk features, as assessed in a retrospective analysis [4,20].

Q14. For patients with low-risk mHSPC, 69% of panellists voted that it is appropriate to extrapolate results from the phase 3 TITAN, ARCHES, and ENZAMET trials of apalutamide and enzalutamide to abiraterone/prednisone, while 31% voted that this extrapolation is inappropriate. There were three abstentions. (No consensus for any answer option.)

For patients with low-volume mHSPC, there is sparse evidence on the effect of combining local radiation therapy of the primary tumour with ADT plus another systemic therapy. Only 18% of patients in the STAMPEDE trial received docetaxel in addition to ADT and radiation therapy, and data on radiation therapy from the PEACE-1 trial have not yet been analysed [10,19]. For patients with synchronous low-volume mHSPC, there also is little evidence regarding any benefit of treating all detectable metastases [21].

Q15. For asymptomatic, synchronous, low-volume mHSPC, 14% of panellists voted to add local treatment of the primary tumour (with or without metastasis-directed therapy [MDT]) to ADT, 8% voted to add additional systemic therapy to ADT, 77% voted to add both radical local treatment of the primary tumour and additional systemic therapy (with or without MDT), and 1% voted for no additional treatment (ADT alone). There were no abstentions. (**Consensus** for radical local treatment of the primary tumour plus ADT and additional systemic therapy.)

Q16. For management of metastatic lesions in asymptomatic, synchronous, low-volume mHSPC, 60% of panellists voted for MDT plus systemic therapy, 4% for MDT without systemic therapy, and 36% for no MDT (systemic therapy only). There was one abstention. (No consensus for any answer option.)

Q17. For synchronous, low-volume mHSPC without symptoms from the primary tumour, 93% of panellists voted to treat the primary tumour with radiation therapy, 6% voted to treat it with surgery, and 1% voted against local treatment. There were no abstentions. (**Strong consensus** for radiation therapy.)

Q18. For synchronous, low-volume mHSPC in cases for which radical local treatment of the primary tumour is recommended, 84% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 1% voted to add docetaxel to ADT, 3% voted to add docetaxel plus an ARPI, and 12% voted against adding systemic treatment(s) to ADT. There were no abstentions. (**Consensus** for local treatment of the primary tumour plus ADT and an ARPI.)

Q19. For synchronous, low-volume mHSPC in cases for which **no** radical local treatment of the primary tumour is recommended, 91% of panellists voted to add an ARPI (abiraterone, apalutamide, or enzalutamide) to ADT, 5% voted to add docetaxel plus an ARPI to ADT, and 4% voted for no additional treatment (ADT alone). There were 28 abstentions. (**Strong consensus** for ADT plus an ARPI, no one voted for ADT plus docetaxel among the panellists who did not vote for radical local treatment of the primary tumour.)

Questions 20–27 belong together and queried the APCCC 2021 panel about their preferred strategies for treating metachronous low-volume mHSPC. There is no level 1 evidence related to MDT in this setting; available data have been generated mostly from small to medium-sized clinical trials, including some randomised phase 2 trials [21–24].

Q20. For treatment of metachronous, low-volume mHSPC (as defined via conventional imaging), 64% of panellists voted for MDT plus systemic therapy, 26% for systemic therapy alone (including ADT), and 10% for MDT alone (without systemic therapy). There was one abstention. (No consensus for any option, but a combined 90% voted that MDT alone is not sufficient.)

Q21. For metachronous mHSPC that is low volume on NGI and nonmetastatic on conventional imaging, 57% of panellists voted for MDT plus systemic therapy, 22% for MDT only (without systemic therapy), and 21% for systemic therapy alone (including ADT). There were three abstentions. (No consensus for any answer option.)

Q22. For metachronous mHSPC that is low volume on conventional imaging, **among those panellists who voted for systemic therapy alone**, 100% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), while 0% voted for ADT alone, ADT plus docetaxel, or triple-combination therapy. There were 43 abstentions. (**Strong consensus** for ADT plus an ARPI among the panellists voting for systemic therapy.)

Q23. For metachronous mHSPC that is low volume on NGI and nonmetastatic on conventional imaging, **among those panellists who voted for systemic treatment alone**, 90% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), while 10% voted for ADT alone, there were 49 abstentions (**Strong consensus** for ADT plus an ARPI among the panellists voting for systemic therapy.)

Q24. For metachronous mHSPC that is low volume on conventional imaging, **among those panellists who voted for systemic treatment plus MDT**, 73% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), 25% voted for ADT alone, and 2% voted for ADT plus docetaxel. There were 25 abstentions. (No consensus for any answer option.)

Q25. For metachronous mHSPC that is low volume on NGI and nonmetastatic on conventional imaging, **among those panellists who voted for systemic treatment plus MDT**, 68% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), 27% voted for ADT alone, and 5% voted for ADT plus docetaxel plus an ARPI. There were 29 abstentions. (No consensus for any answer option.)

Q26. Among panellists who voted for systemic treatment without MDT for metachronous, low-volume mHSPC, 72% voted for continuous/lifelong therapy and 28% voted for intermittent (temporary) systemic therapy. There were 41 abstentions. (No consensus for any answer option.)

Q27. Among panellists who voted for systemic treatment plus MDT for metachronous, low-volume mHSPC, 78% voted for intermittent (temporary) systemic therapy, and 22% voted for continuous/lifelong systemic therapy. There were 24 abstentions. (**Consensus** for intermittent systemic therapy among the panellists voting for systemic therapy.)

As we have noted, some patients may be classified as having low-volume mHSPC according to conventional imaging but high-volume mHSPC according to NGI. This can lead to either undertreatment or overtreatment, as a recent editorial discussed [14].

Q28. For patients whose mHSPC is low volume on conventional imaging but high volume on NGI, 47% of panellists voted to treat as for high-volume disease and 53% voted to treat as for low-volume disease. There were no abstentions. (No consensus for any answer option.)

The PEACE-1 trial only enrolled patients with synchronous mHSPC, and data on local radiation therapy had not been analysed as of the time of writing [12]. Data on triplet therapy with abiraterone, ADT, and docetaxel were presented in 2021 at the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) congresses.

Q29. For chemotherapy-fit patients with synchronous mHSPC, 55% of panellists voted to recommend triplet therapy with ADT-docetaxel-abiraterone only in high-volume disease, 4% voted to recommend this for the majority of patients regardless of disease volume, and 41% voted that they usually do not recommend this combination. There was one abstention. (No consensus for any answer option.)

Q30. In all, 68% of panellists voted that it is **inappropriate** to extrapolate data from the PEACE-1 trial to patients with metachronous mHSPC, while 32% voted that this is appropriate. There were four abstentions. (No consensus for any answer option.)

Approximately 45% of patients in the ENZAMET trial received triplet therapy with ADT plus docetaxel and concurrent enzalutamide, and small proportions of patients in the ARCHES and TITAN trials received ADT plus docetaxel, followed sequentially by either enzalutamide or apalutamide after completion of chemotherapy.

Q31. For chemotherapy-fit patients with mHSPC, regarding whether to recommend the triplet of ADT, docetaxel, and enzalutamide or apalutamide, 21% of panellists voted for this combination only in patients with high-volume diseases and 19% only in patients with synchronous, high-volume disease, while 60% voted that they usually do not recommend this combination. There were three abstentions. (No consensus for any answer option.)

APCCC 2021 panellists voted on their preferred strategy (concurrent vs sequential) for administering triplet therapy in mHSPC.

Q32. For patients with mHSPC, 43% of panellists voted to administer the triplet therapy of ADT and docetaxel plus an ARPI concurrently (as in ENZAMET and PEACE-1), 26% voted for sequential administration (as in the small subgroups in the TITAN and ARCHES trials), and 31% voted against these combinations. There were three abstentions. (No consensus for any answer option.)

For the special situation of patients with newly diagnosed mHSPC and liver metastases, the panel voted on whether to request a liver biopsy (Q33) and on their preferred treatment to add to ADT (Q34).

Q33. For patients with synchronous mHSPC, liver metastases, and elevated prostate-specific antigen (PSA; >200 ng/ml) who have a prostate biopsy showing adenocarcinoma, 48% of panellists voted for liver biopsy to assess neuroendocrine or small-cell differentiation, perform tumour genomic profiling, and rule out secondary malignancy, while 52% of panellists voted against liver biopsy. There were no abstentions. (No consensus for any answer option.)

Q34. For patients with mHSPC and liver metastases, 48% of panellists voted for ARPI therapy (abiraterone, apalutamide, or enzalutamide) plus docetaxel and ADT, 31% voted for docetaxel plus ADT, 18% voted for an ARPI plus ADT, and 3% voted for platinum-based combination therapy plus ADT. There were two abstentions. (No consensus for any answer option.)

The panel also voted on the preferred treatment strategy for patients with mHSPC who have a low PSA level relative to their disease burden.

Q35. For high-volume mHSPC (defined via conventional imaging or unequivocal NGI) in patients with a low baseline PSA level (eg, <5 ng/ml) and no neuroendocrine component on biopsy, 46% of panellists voted for ADT plus docetaxel and an ARPI (abiraterone, apalutamide, or enzalutamide), 29% voted for ADT plus docetaxel, 18% voted for ADT plus an ARPI, and 7% voted for ADT plus platinum-based combination therapy. There was one abstention. (No consensus for any answer option, but a combined 82% voted for chemotherapy.)

In large phase 3 studies demonstrating the efficacy of docetaxel or ARPIs in mHSPC, patients were generally started on these additional treatments within 3–4 mo after initiating ADT [4–6,8,9,12,25]. In the TITAN and ARCHES trials, patients who initially received ADT plus docetaxel started on ARPIs no later than 6 mo after starting ADT.

Q36. When asked how soon they usually start docetaxel or an ARPI in relation to ADT, 23% of panellists voted that they start immediately (within ~2 wk of starting ADT), 71% voted that they start within 3 mo of starting ADT, and 6% voted that they start within 6 mo of starting ADT. There were three abstentions. (No consensus for any answer option, but a combined 94% voted for **not** starting later than within 3 mo.)

For patients with metastatic castration-resistant prostate cancer (mCRPC), docetaxel has been studied in combination with a twice-daily 5-mg dose of oral prednisone/prednisolone. For patients with mHSPC, the CHAARTED and GETUG-15 trials did not include prednisone, while the STAMPEDE trial evaluated docetaxel in combination with a standard prednisone dose of 10 mg/d. Thus, it remains unclear if prednisone is necessary for patients with mHSPC receiving docetaxel [8,25,26].

Q37. In all, 52% of panellists voted against concurrent prednisone for most patients receiving docetaxel for mHSPC, 26% voted for a 5-mg daily dose, and 22% voted for a 10-mg daily dose. There were 11 abstentions. (No consensus for any answer option.)

The panel voted on the preferred management strategy for patients with mHSPC whose PSA response to ADT plus docetaxel is unfavourable.

Q38. For patients with mHSPC who responded inadequately to ADT and docetaxel (PSA >4 ng/ml after 6 cycles), 59% of panellists voted to add an ARPI without waiting for the development of CRPC, while 41% voted against this approach. There were two abstentions. (No consensus for any answer option.)

In clinical trials, patients with mHSPC have always remained on ARPIs until disease progression, unacceptable toxicity, or death. In daily practice, however, clinicians

increasingly see patients who have had deep, long-lasting PSA responses to ARPI-based combination regimens. For such patients, it is unclear whether systemic therapies or at least the ARPI can be stopped (pending PSA relapse) without hastening metastatic progression.

Q39. For patients with mHSPC who have deep, durable remissions to systemic treatment (eg, undetectable PSA [≤0.2 ng/ml] at 2–3 yr), 61% of panellists voted to discuss stopping all systemic therapy, while 39% voted against this approach. There were two abstentions. (No consensus for any answer option.)

Q40. For patients with mHSPC who have deep, durable remissions to systemic treatment, 50% of panellists voted to discuss stopping only the ARPI while continuing ADT, while 50% voted against this approach. There was one abstention. (No consensus for any answer option.)

It has been suggested that gonadotropin-releasing hormone (GnRH) antagonists such as degarelix and relugolix are associated with a lower risk of cardiovascular complications in comparison to GnRH agonists. Recently, the randomised phase 3 PRONOUNCE study found no significant difference in 1-yr rates of major adverse cardiovascular events among patients with advanced prostate cancer who received degarelix versus the GnRH agonist leuprolide; however, the trial was terminated early owing to slow accrual, and the investigators concluded that it was not sufficiently powered to conclusively address the relative cardiovascular safety of these drugs [27-29].

Q42. For patients with mHSPC, 22% of panellists voted to start ADT with a luteinising hormone–releasing hormone (LHRH) antagonist (instead of an LHRH agonist plus flare protection) in the majority of patients, 48% voted to do so only if patient had a recent (<2 yr) history of a severe cardiovascular event or a risk of harm from disease flare (eg, risk of spinal cord compression), 14% voted to do so only if there was a risk of harm from disease flare, 5% voted to do so only if there was a recent history of a severe cardiovascular event, and 11% voted that they do not routinely recommend LHRH antagonist therapy. There were no abstentions. (No consensus for any answer option.)

In lieu of using the older androgen receptor (AR) antagonist bicalutamide, patients with mHSPC could be started directly on an LHRH agonist in combination with an ARPI.

Q43. For patients with mHSPC for whom initiation of LHRH agonist therapy in combination with a novel AR antagonist (enzalutamide or apalutamide) is planned, 49% of panellists voted to start the AR antagonist immediately instead of first using, for example, bicalutamide to help protect against flare, while 51% voted against this approach. There were four abstentions. (No consensus for any answer option.)

2.1. Discussion of mHSPC

New treatment options for mHSPC have emerged since 2019. In some countries, the increasing use of NGI, particularly PSMA PET/CT, is identifying metastatic disease in some patients who would have been classified as having high-risk localised prostate cancer on conventional imaging. These trends raise new questions about mHSPC management. More granular data and studies are needed, particularly because responses to combination therapy for mHSPC can vary significantly among individuals [30]. In addition, it may be worth studying why many clinicians still use ADT monotherapy for patients with mHSPC despite strong level 1 evidence for the superiority of combination treatment.

At APCCC 2021, panellists reached consensus (Table 1) that for patients with low-volume mHSPC it is important to distinguish synchronous from metachronous disease to help guide treatment decisions. However, there was no consensus about the importance of this distinction in high-volume mHSPC or about how to handle discordant findings in patients with mHSPC who are evaluated with both NGI and conventional imaging. Thus far, all phase 3 trials in mHSPC have used conventional imaging exclusively, and it remains unclear how to apply conclusions from these trials to patients who are staged with NGI. There is a need for studies to address this question.

For some scenarios, panellists appear to have become more aligned regarding treatment decisions. At APCCC 2021, there was strong consensus, despite a lack of high-level supporting evidence, that for patients with low-volume mHSPC who are receiving radiation therapy of the primary tumour, it is preferable to add an ARPI to ADT. Although consensus was not reached regarding whether to combine MDT with systemic therapy in low-volume mHSPC, almost two-thirds of panellists voted for this option despite a lack of data from phase 3 trials. Regarding the management of metachronous low-volume mHSPC, there was no consensus, but an even larger proportion of panellists voted for MDT, either in combination with systemic therapy (64%) or alone (10%); a slightly larger proportion (22%) voted for MDT alone if lesions are detected only on NGI. It is important to note that these votes were cast in the absence of any phase 3 clinical trials showing that MDT, either alone or with systemic therapy, improves survival in patients with synchronous or metachronous mHSPC. The panel was divided on how to treat patients with low-volume disease on conventional imaging but high-volume disease on NGI, which highlights the uncertainties that have evolved around the new diagnostic modalities. Thus far, the best evidence on managing mHSPC is from studies that only utilised conventional imaging.

Interestingly, despite the absence of any data from randomised clinical trials, there was consensus to only administer short-term systemic therapy to patients with metachronous mHSPC (diagnosed on conventional imaging, or unequivocal on NGI) who are receiving MDT.

The results from the PEACE-1 trial of ADT, docetaxel, and abiraterone provide a new option for treating synchronous mHSPC. However, there was no consensus regarding the use of this triplet regimen, which might in part be because the PEACE-1 study results were presented only weeks before the APCCC 2021 meeting. More data on triplets are expected, including an updated survival analysis from the ENZAMET trial and primary results from the ARASENS trial, in which patients received ADT, docetaxel, and darolutamide. The data from the ARASENS trial were not available at the time of APCCC 2021 [13]. These trials all added an ARPI to docetaxel, and there is no study evaluating the flip side of this question of whether docetaxel should be added

to an ARPI. For patients who receive ADT plus docetaxel but respond inadequately (PSA >4 ng/ml after completing the docetaxel regimen) the panel discussed whether to switch them directly to an ARPI or wait for additional therapy until the onset of castration resistance. Little is known about outcomes among patients with an inadequate PSA response to ADT plus docetaxel, but on the basis of data from studies of intermittent ADT, it may be speculated that these patients have poor prognosis. Whether early additional systemic therapy can improve this prognosis remains unclear and merits further study [31].

There was also no consensus on the treatment of patients with mHSPC who have possible features of aggressive variant prostate cancer (liver metastases; low PSA in relation to disease burden). However, the majority of panellists favoured either docetaxel or a docetaxel-ARPI combination in addition to ADT.

Finally, there was no consensus regarding de-escalation of treatment in patients with a favourable response to combined systemic therapy; further research in this area may be of interest.

3. PSMA ligands in diagnostics and therapy

PSMA PET/CT is becoming more widely available and can be used in all prostate cancer disease states from clinically localised disease to mCRPC. However, there is a dearth of knowledge regarding how to use PSMA PET/CT images to guide therapy and improve patient outcomes. In this section, we present voting results related to the use of PSMA PET/CT in localised prostate cancer, mCRPC, and biochemically recurrent disease, as well as the use of ^{177}Lu-labelled PSMA-ligand theranostics in mCRPC.

At the previous APCCC in 2019, most panellists selected PSMA PET/CT as their preferred imaging modality for patients with biochemical (PSA) recurrence of prostate cancer after prior local treatment. In the prospective two-arm proPSMA trial, which enrolled patients with high-risk localised prostate cancer, PSMA PET/CT–based staging was associated with superior accuracy, fewer equivocal findings, and lower radiation doses when compared to conventional imaging based on CT and technetium bone scintigraphy [32]. While the impact of imaging findings on treatment decisions was significantly higher in the PSMA PET/CT arm of this trial, the study did not evaluate long-term clinical outcomes. Patients in this study remain under follow-up, with longer-term outcomes to be reported in the future [32,33].

Data from this and other trials have led to US Food and Drug Administration (FDA) approval of two PSMA PET tracers, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (piflufolastat), for detection of PSMA-positive lesions. Other tracers, such as ^{18}F-PSMA-1007, are increasingly being used because they are more accessible in some regions; not only do they entail fewer intellectual property issues but ^{18}F production is also relatively more efficient because it is made using cyclotrons. The future availability of medical radioisotopes in the context of rising demand also needs to be taken into account.

Current recommendations for prostate cancer treatment are based on data from large prospective clinical trials in which staging was performed with conventional imaging. It is controversial whether additional evidence is needed before PSMA PET/CT imaging can replace conventional imaging, and it remains unclear if treatment decisions should be based on staging with conventional imaging or NGI. Some experts are concerned that the use of PSMA PET/CT might lead to overtreatment or undertreatment in certain patient populations or settings [34]. Another question is whether various tracers are clinically and radiologically equivalent. A recent review identified 25 different PSMA tracers for which published data are available [35], but evidence on their comparability is limited, and thus far no formal validation studies have compared these tracers with ^{68}Ga-PSMA-11. In addition, panellists have emphasised that PSMA-based PET imaging is not available in many countries and regions, and in some countries choline-based or fluciclovine-based PET imaging still is used if PET is performed at all.

3.1. *Staging of localised prostate cancer*

The APCCC 2021 panel voted on whether data on ^{68}Ga-PSMA-11 PET imaging can be extrapolated to other PSMA-specific tracers used for prostate cancer staging.

Q44. For staging purposes, 78% of panellists voted that that data on ^{68}Ga-PSMA-11 PET-based imaging can be extrapolated to other PSMA tracers (eg, ^{18}F-DCFPyL, ^{18}F-PSMA-1007), while 22% voted against this extrapolation. There were seven abstentions. (**Consensus** that ^{68}Ga-PSMA PET-based imaging data can be extrapolated to other PSMA tracers.)

Q45. In all, 90% of panellists voted that data from PSMA PET–based imaging for staging **cannot** be extrapolated to choline PET imaging, while 10% voted for this extrapolation. There were two abstentions. (**Strong consensus** that PSMA PET–based imaging data **cannot** be extrapolated to choline PET/CT.)

Q46. A total of 87% of panellists voted that data from PSMA PET–based imaging for staging **cannot** be extrapolated to fluciclovine PET/CT imaging, while 13% voted for this extrapolation. There were nine abstentions. (**Consensus** that PSMA PET–based imaging data **cannot** be extrapolated to fluciclovine PET/CT.)

The proPSMA trial only enrolled patients with localised prostate cancer who had high-risk features: PSA $\geq$20 μg/l, International Society of Urological Pathology grade group 3–5, or clinical stage $\geq$T3. The APCCC 2021 panel voted on questions related to the use of imaging to stage localised prostate cancer of all risk categories.

Q47. Regarding when to use PSMA PET imaging to stage localised prostate cancer, 50% of panellists voted for high-risk disease only, 23% voted for intermediate- and high-risk disease, 4% voted for the majority of patients independent of risk, and 23% voted against its use for staging localised disease. There were two abstentions. (No consensus for any answer option; a combined 77% of panellists voted for using PSMA PET to stage high-risk localised prostate cancer.)

Q48. Among the panellists who voted for PSMA PET for staging localised prostate cancer (Q47), 87% voted that

multiparametric MRI (mpMRI) is still necessary for local tumour staging, while 13% voted that mpMRI was unnecessary. There were 16 abstentions. (**Consensus** that mpMRI is still necessary in the presence of PSMA PET among the panellists voting for PSMA PET for staging.)

Q49. Among the panellists who voted for PSMA PET for staging localised prostate cancer, 84% voted that bone scintigraphy is not necessary, while 16% voted that it is still necessary. There were 16 abstentions. (**Consensus** that bone scintigraphy is **not** necessary in the presence of a PSMA PET among the panellists voting for PSMA PET for staging.)

3.2. Implications of PSMA PET/CT findings for treatment decision-making in localised prostate cancer

The sensitivity reported for PSMA PET for nodal staging ranges widely but is realistically only approximately 60% [36]. Thus, it remains unclear whether and how PSMA PET–based staging of localised prostate cancer should influence decisions about treating the pelvic lymph nodes of patients undergoing radical prostatectomy or radiation therapy of the prostate.

Q50. For patients with high-risk localised prostate cancer for whom radical prostatectomy is planned, if there is no PSMA PET evidence of metastatic disease (N0 M0), 17% of panellists voted to omit extended pelvic lymphadenectomy (ePLND), 77% voted not to omit ePLND, and 6% voted that they generally did not recommend ePLND for high-risk localised prostate cancer. There were seven abstentions. (**Consensus** to perform ePLND.)

Q51. For patients with high-risk localised prostate cancer for whom radiation therapy of the prostate is planned, if they have no PSMA PET evidence of metastatic disease (N0 M0), 20% of panellists voted to omit radiation therapy of the pelvis, 76% voted not to omit it, and 4% generally did not recommend radiation therapy of the pelvis in this setting. There were six abstentions. (**Consensus** to perform radiation therapy of the pelvis.)

In the proPSMA trial, PSMA PET–based staging of patients with high-risk localised prostate cancer led to changes in treatment plans: 14% were switched from a curative to a palliative treatment approach, and 14% had a change in surgical approach or radiation therapy technique [32]. The panel voted on whether and how to alter planned treatment of high-risk localised prostate cancer in which PSMA PET has revealed lesions that were not evident on conventional imaging.

Q52. For patients with high-risk localised prostate cancer for whom radical prostatectomy is planned, if their status is N0, M0 on conventional imaging but they are found to have up to three PSMA PET–positive lymph node(s) limited to the pelvis (cN1, M0), 53% of panellists voted to continue treatment as planned, 15% voted to change treatment to radiotherapy of the prostate and pelvis plus long-term ADT, and 32% voted to change treatment to radiotherapy of the prostate and pelvis, plus long-term ADT, plus an additional systemic therapy (docetaxel or an ARPI). There were four abstentions. (No consensus for any answer option.)

Q53. For patients with high-risk localised prostate cancer for whom definitive radiotherapy of the prostate plus ADT is planned, if their status N0, M0 on conventional imaging but they are found to have up to three PSMA PET–positive lymph node(s) limited to the pelvis (cN1, M0), 43% of panellists voted to continue treatment as planned, 54% voted to add another systemic therapy (docetaxel or an ARPI) to the existing treatment plan, and 3% voted to change treatment to radical prostatectomy plus ePLND. There were three abstentions. (No consensus for any answer option.)

At ESMO 2021, researchers reported that in the STAMPEDE trial, patients with very high-risk localised or node-positive prostate cancer who received limited-duration (2 yr) abiraterone in addition to ADT had statistically significant and clinically relevant improvements in metastasis-free survival and OS as compared to patients who received ADT alone [37]. The STAMPEDE trial used conventional imaging, but if PSMA PET had been used, a significant proportion of these patients would probably have had small PSMA-expressing metastatic lesions extending beyond the pelvic lymph nodes.

Q54. Among the panellists who voted for adding systemic therapy to the original treatment plan (Q52 and Q53), 81% preferred abiraterone, 17% apalutamide or enzalutamide, and 2% abiraterone plus enzalutamide. There were 27 abstentions. (**Consensus** to add abiraterone among the panellists voting for additional systemic therapy.)

The same questions were asked for high-risk localised prostate cancer with more extensive pelvic nodal involvement ($\geq$4 PSMA PET–positive lymph nodes in the pelvis).

Q55. For patients with high-risk localised prostate cancer for whom radical prostatectomy and ePLND are planned, if their status is N0, M0 on conventional imaging but they are found to have four or more PSMA PET–positive lymph nodes limited to the pelvis (cN1, M0), 27% of panellists voted to continue treatment as planned, 18% voted to change treatment to radiotherapy of the prostate and pelvis plus long-term ADT, and 55% voted to change treatment to radiotherapy of the prostate and pelvis, plus long-term ADT, plus another systemic therapy (an ARPI or docetaxel). There were three abstentions. (No consensus for any answer option.)

Q56. For patients with high-risk localised prostate cancer for whom definitive radiotherapy of the prostate plus ADT is planned, if their status is N0, M0 on conventional imaging but they are found to have four or more PSMA PET–positive lymph nodes limited to the pelvis (cN1, M0), 27% of panellists voted to continue treatment as planned, 72% voted to change treatment to radiotherapy of the prostate and pelvis, plus long-term ADT, plus another systemic therapy (an ARPI or docetaxel), and 1% voted to change radical prostatectomy plus ePLND There were two abstentions. (No consensus for any answer option, but a combined total of 99% of panellists voted to proceed with RT plus systemic therapy.)

Q57. Among the panellists who voted for additional systemic therapy to long-term (2–3 yr) ADT (Q55 and Q56), 77% preferred abiraterone, 18% apalutamide or enzalutamide, 3% docetaxel, and 2% abiraterone plus enzalutamide. There were 14 abstentions. (**Consensus** to add abiraterone among the panellists voting for additional systemic therapy.)

When staging high-risk localised prostate cancer, the identification of PSMA-positive bone lesions may lead some clinicians to switch their treatment plan from therapy with a curative intent to therapy with a palliative intent. This has important clinical implications, particularly if PSMA PET/CT

findings are falsely positive [14]. For this reason, the sensitivity and specificity of PSMA PET tracers are highly relevant. In the proPSMA trial, ^{68}Ga-PSMA-11 staging identified bone metastases in 10% of patients, and the false positive rate for distant metastases was lower than that observed with bone scan with single-photon emission computed tomography (SPECT)/CT. However, because nonspecific bone uptake is seen with ^{18}F-PSMA-1007 PET/CT, the results from the proPSMA trial should be extrapolated with caution. In a retrospective matched-pair comparison study of 102 patients with biochemically recurrent prostate cancer, ^{18}F-PSMA-1007 identified fivefold more lesions that were attributed to a benign origin when compared to ^{68}Ga-PSMA-11 PET (245 vs 52 lesions) [38]. In a similar comparative study of 50 patients, ^{18}F-PSMA-1007 detected a higher number of equivocal lesions when compared to ^{68}Ga-PSMA-11, and the maximum standardised uptake value for equivocal lesions was significantly higher with ^{18}F-PSMA-1007 than with ^{68}Ga-PSMA-11 (6.2 vs 2.4; p = 0.028) [39].

Q58. For patients with high-risk localised prostate cancer for whom radical local treatment (prostatectomy or radiotherapy) of the primary tumour is planned, if patients are staged as N0, M0 on conventional imaging but are found to have one to three PSMA PET–positive lesion(s) in bone (M1), 23% of panellists voted to also add a systemic therapy, 10% voted to add MDT instead of systemic therapy, 51% voted to add both MDT and systemic therapy, 12% voted to change treatment to standard mHSPC therapy, and 4% voted to continue with radical local treatment as planned and monitor the PSMA PET–positive lesions. There were no abstentions. (No consensus for any answer option, but a combined total of 96% of panellists voted for a treatment change.)

Q59. Among those panellists who voted to continue with radical local treatment for Q58, 87% preferred definitive radiation therapy of the primary tumour (with or without the pelvis) and 13% preferred radical prostatectomy (with or without lymphadenectomy). There were seven abstentions. (**Consensus** for definitive radiation therapy of the primary tumour.)

Q60. For patients with high-risk localised prostate cancer for whom radical local treatment (prostatectomy or radiotherapy) of the primary tumour is planned, if they are staged as N0, M0 on conventional imaging but are found to have four or more PSMA PET–positive lesions in bone (M1), 44% of panellists voted to intensify the original treatment plan by also adding systemic therapy, 3% voted to instead add MDT, 22% voted to add both systemic therapy and MDT, 29% voted to change treatment to standard mHSPC therapy, and 2% voted to continue with radical local treatment as planned while monitoring the PSMA PET–positive lesions. There was one abstention. (No consensus for any answer option, but a combined total of 98% of panellists voted for a treatment change.)

3.3. PSMA PET/CT in mCRPC

Because all the phase 3 trials of standard mCRPC therapies have been performed with conventional imaging, the question arises in daily practice as to whether patients with PSMA PET–staged mCRPC should also undergo baseline conventional imaging. Conversely, as PSMA PET becomes more available, experts have debated whether and under what circumstances patients with evidence of mCRPC on conventional imaging should also be staged via PSMA PET.

Q61. For patients with mCRPC who have evidence of disease on PSMA PET, 55% of panellists voted **not** to perform conventional imaging with CT and bone scintigraphy before starting a new treatment, while 45% voted that this was necessary. There was one abstention. (No consensus for any answer option.)

Q62. For patients with mCRPC who have evidence of disease on CT and bone scintigraphy, 15% of panellists voted to perform PSMA PET imaging before starting a new treatment, 55% voted to perform this only if the current treatment plan included PSMA-targeted therapy, and 30% voted against PSMA PET imaging. There were no abstentions. (No consensus for any answer option.)

3.4. Treatment with ^{177}Lu-PSM)

In the phase 3 VISION trial, results from which were reported at the 2021 ASCO Annual Scientific Meeting, third- or later-line ^{177}Lu-PSMA-617 therapy significantly prolonged the co-primary endpoints of radiographic progression-free survival (PFS) and OS when added to standard treatment in patients with advanced mCRPC who had positive ^{68}Ga-PSMA-11 PET imaging scans [40]. However, several questions about ^{177}Lu-PSMA-617 therapy for mCRPC remain unresolved. Because approximately 13% of patients were excluded from enrolment in VISION on the basis of their imaging results, the study findings might not be generalisable to the general population of patients with advanced mCRPC. In addition, in the intervention arm, ^{177}Lu-PSMA-617 was combined with protocol-permitted standard of care (primarily treatment with steroids or ARPIs), which might complicate interpretation of the study results.

In the randomised TheraP trial, ^{177}Lu-PSMA-617 led to a higher PSA response rate and fewer grade 3–4 adverse events when compared to cabazitaxel in patients with mCRPC who had previously received docetaxel and enzalutamide or abiraterone [41]. Although this was a phase 2 trial, it provides complementary information.

Panellists voted on several questions related to ^{177}Lu-PSMA-617 therapy. For questions 63–67, panellists were asked to assume that all listed treatments were readily available and that patients had no molecular alteration(s) for which there is an approved therapy.

Q63. For chemotherapy-fit patients with PSMA imaging–positive mCRPC who have received at least one line of ARPI therapy and one line of taxane-based chemotherapy and who meet the relevant criteria for ^{177}Lu-PSMA therapy, 77% of panellists voted for ^{177}Lu-PSMA therapy, 13% for cabazitaxel, and 10% for radium-223 (assuming that the relevant treatment criteria are met). There were four abstentions. (**Consensus** for ^{177}Lu-PSMA therapy.)

All patients in the VISION study had previously received at least one ARPI and one or two lines of chemotherapy, while all participants in the TheraP trial had received docetaxel, and 91% had also received enzalutamide or abiraterone. Less is known about the relationship between

earlier-line ^{177}Lu-PSMA-617 therapy and the safety and efficacy of subsequent treatments, particularly chemotherapy. Currently, two phase 3 studies are comparing ^{177}Lu-PSMA with ARPI therapy in patients with chemotherapy-naïve mCRPC. The phase 3 PSMAfore trial (NCT04689828) is evaluating ^{177}Lu-PSMA-617, while the phase 3 SPLASH trial (NCT04647526) is evaluating ^{177}Lu-PSMA-PNT2002 (^{177}Lu-PSMA-I&T).

Q64. For chemotherapy-fit patients with PSMA imaging–positive mCRPC who have received at least one line of ARPI therapy but not chemotherapy and who meet the relevant criteria for ^{177}Lu-PSMA therapy, 85% of panellists voted for docetaxel, 14% for ^{177}Lu-PSMA, and 1% for radium-223 (assuming that the relevant treatment criteria are met). There was one abstention. (**Consensus** for docetaxel.)

Because ^{177}Lu-PSMA undergoes renal clearance, VISION participants were required to have serum creatinine $\leq$1.5 times the upper limit of normal or creatinine clearance $\geq$50 ml/min. In the TheraP trial, creatinine clearance of $\geq$40 ml/min was required. The APCCC 2021 panel voted on the use of ^{177}Lu-PSMA in patients with impaired renal function.

Q65. For chemotherapy-fit patients with PSMA imaging–positive mCRPC who have received at least one line of ARPI therapy and one line of taxane-based chemotherapy and who have impaired renal function (glomerular filtration rate [GFR] 30–49 ml/min), and who meet the relevant criteria for ^{177}Lu-PSMA therapy, 55% of panellists voted for ^{177}Lu-PSMA, 32% for cabazitaxel, and 13% for radium-223 (assuming that the relevant treatment criteria are met). There were four abstentions. (No consensus for any answer option.)

Q85. For patients with mCRPC who have impaired renal function (eg, GFR 30–49 ml/min), 30% of panellists voted that it is safe to recommend treatment with ^{177}Lu-PSMA, 51% voted for a reduced dose of ^{177}Lu-PSMA, and 19% voted that it is unsafe to recommend ^{177}Lu-PSMA. There were 14 abstentions. (No consensus for any answer option.)

Liver metastases are a negative prognostic factor in mCRPC, and a recently published nomogram suggests that this association extends to the outcomes of ^{177}Lu-PSMA-617 therapy [42]. For patients with mCRPC and liver metastases who have progressed after one line of ARPI and one line of docetaxel, cabazitaxel is a standard treatment option, but it is unclear whether it should be used in lieu of ^{177}Lu-PSMA therapy.

Q66. For chemotherapy-fit patients with PSMA imaging–positive mCRPC who have liver metastases, are progressing after at least one line of ARPI therapy and one line of taxane-based chemotherapy, cannot enrol in a clinical trial, and meet the relevant criteria for ^{177}Lu-PSMA therapy, 60% of panellists voted for ^{177}Lu-PSMA and 40% for cabazitaxel. There were six abstentions. (No consensus for any answer option.)

Patients with mCRPC who progress on an ARPI and are unsuitable for chemotherapy have very few treatment options. In several recent trials, sequential treatment with another ARPI demonstrated only modest antitumour activity [43-45]. Radium-223 may be an option for treating bone-metastatic CRPC if patients do not have evidence of soft-tissue metastases.

Q67. For chemotherapy-unfit patients with PSMA imaging–positive mCRPC who are progressing after at least one line of ARPI therapy, meet the relevant criteria for ^{177}Lu-PSMA therapy, and cannot enrol in a clinical trial, 80% of panellists voted for ^{177}Lu-PSMA, 17% voted for ^{177}Lu-PSMA if patients did not meet the criteria for radium-223 therapy, and 3% voted against ^{177}Lu-PSMA. There were two abstentions. (**Consensus** for ^{177}Lu-PSMA.)

Prospective randomised clinical trials are evaluating ^{177}Lu-PSMA-617 in mHSPC. Relevant studies include UpFrontPSMA (NCT04343885), ENZA-p (NCT04419402), and PSMAaddition (NCT04720157) [46,47]. To date, study findings have not been reported.

Q68. In all, 86% of panellists voted that it is inappropriate to recommend ^{177}Lu-PSMA therapy to patients with mHSPC outside the setting of a clinical trial, while 14% voted that this is appropriate. There was one abstention. (**Consensus not** to recommend ^{177}Lu-PSMA in mHSPC outside a clinical trial.)

Participants in the VISION trial were required to have positive ^{68}Ga-PSMA-11 PET scans. The TheraP trial used stricter enrolment criteria, including imaging with FDG PET/CT [48], which led to exclusion of a higher proportion of patients (27% of those screened vs 13% of those screened in VISION).

Q69. When asked about additional imaging (FDG PET/CT or contrast-enhanced CT) to guide decisions about ^{177}Lu-PSMA therapy, 40% of panellists voted for this for select patients (eg, those with visceral metastases or suspected discordance), 34% voted for this in the majority of patients, and 26% voted against, preferring instead to rely on the absence of PMSA PET/CT–negative lesions. There were six abstentions. (No consensus for any answer option.)

Q70. Among the panellists who voted for additional imaging to guide decisions about ^{177}Lu-PSMA therapy, 69% voted for FDG PET/CT and 31% for contrast-enhanced CT. There were 22 abstentions. (No consensus for any answer option.)

Not all physicians are (or will be) able to access ^{68}Ga-PSMA-11 imaging to identify suitable candidates for ^{177}Lu-PSMA therapy. The APCCC 2021 panel addressed the use of other tracers for treatment selection.

Q72. For selection of patients for treatment with ^{177}Lu-PSMA, 83% of panellists voted that data on ^{68}Ga-PSMA-11 PET from the VISION trial can be extrapolated to ^{18}F-PSMA-1007 PET/CT, while 17% voted against this. There were seven abstentions. (**Consensus** that VISION results can be extrapolated to ^{18}F-PSMA-1007 PET/CT.)

Q73. For selection of patients for treatment with ^{177}Lu-PSMA, a total of 65% of panellists voted that VISION data on ^{68}Ga-PSMA-11 PET can be extrapolated to ^{18}F-DCFPyL PET/CT, while 35% voted against this. There were ten abstentions. (No consensus for any answer option.)

In the VISION trial, CT with contrast/MRI and bone scintigraphy were performed every 8 wk. In the TheraP trial, patients also underwent SPECT/CT after each cycle of therapy.

Q74. To monitor response to ^{177}Lu-PSMA therapy, 50% of panellists voted that it is sufficient to use PSMA-based imaging, (PET/CT, or post-therapy planar or SPECT), 21% voted for conventional imaging instead, and 29% voted for both

conventional imaging and PSMA-based imaging. There were eight abstentions. (No consensus for any answer option.)

In the VISION trial, patients who showed a radiological, PSA, and/or clinical response to four cycles of ^{177}Lu-PSMA-617 could receive two more cycles of treatment if they had tolerated therapy well and showed evidence of residual disease on CT with contrast/MRI or bone scintigraphy. In the TheraP trial, patients could receive up to six cycles of ^{177}Lu-PSMA-617 therapy; treatment was paused earlier in 7% of individuals with exceptional responses according to SPECT/CT.

Q75. If patients respond (ie, demonstrate PSA and/or clinical or radiological improvement) to four cycles of ^{177}Lu-PSMA therapy, but their post-treatment PSMA PET (planar or SPECT) shows significant residual uptake as defined by the treating physician, 86% of panellists voted to administer two additional cycles of ^{177}Lu-PSMA therapy, while 14% voted not to do so. There were 11 abstentions. (**Consensus** to administer two additional cycles of ^{177}Lu-PSMA if there is significant remaining uptake.)

Q76. If patients respond (ie, demonstrate PSA and/or clinical or radiological improvement) to four cycles of ^{177}Lu-PSMA therapy but their post-treatment PSMA PET (planar or SPECT) shows minimal residual uptake as defined by the treating physician, 42% of panellists voted to administer two additional cycles of ^{177}Lu-PSMA therapy, while 58% voted not to do so. There were ten abstentions. (No consensus for any answer option.)

All patients in the VISION trial received protocol-permitted standard-of-care therapy, most commonly with corticosteroids (64%) and/or ARPIs (57%). As we have noted, ARPIs exhibit only minimal to moderate antitumour activity if given sequentially. However, ARPIs may upregulate PSMA expression, thereby increasing the efficacy of ^{177}Lu-PSMA, raising the question of whether dual therapy is clinically advisable [49]. The randomised ENZA-p trial (NCT04419402) is comparing ^{177}Lu-PSMA-617 plus enzalutamide with ^{177}Lu-PSMA -617 alone in patients with mCRPC, but these patients are not permitted to have received chemotherapy for mCRPC or to have prior exposure to enzalutamide, apalutamide, or darolutamide (prior abiraterone is permitted). Moreover, primary results are not anticipated until late 2022. The APCCC 2021 panel considered whether patients should receive ^{177}Lu-PSMA as monotherapy or in combination with an ARPI or corticosteroids.

Q77. For patients with mCRPC who previously received an ARPI as well as chemotherapy and are now receiving ^{177}Lu-PSMA, 21% of panellists voted to add the alternate ARPI, while 79% voted against this. There were seven abstentions. (**Consensus not** to add the alternate ARPI pathway inhibitor to ^{177}Lu-PSMA in patients with mCRPC who are already post-ARPI and postchemotherapy.)

Q78. In all, 73% of panellists voted that it is possible to extrapolate data from the VISION trial (in which ^{177}Lu-PSMA was combined with standard protocol-permitted treatments, mostly steroids or ARPIs) to ^{177}Lu-PSMA therapy alone; 27% voted against making this extrapolation. There were six abstentions. (No consensus for any answer option.)

Other PSMA-based theranostics are being studied. The SPLASH phase 3 trial (NCT04647526) will evaluate ^{177}Lu-PSMA-I&T in patients with mCRPC that has progressed after one line of ARPI (patients are permitted to have received docetaxel for mHSPC).

Q79. Approximately two-thirds (66%) of panellists voted that data on ^{177}Lu-PSMA-617 from the VISION trial cannot be extrapolated to ^{177}Lu-PSMA-I&T (an alternate PSMA ligand), while 34% of panellists voted in favour of this extrapolation. There were 14 abstentions. (No consensus for any answer option.)

Only limited data on ^{177}Lu-PSMA re-challenge are available. In a first-in-kind prospective phase 2 trial, 15 of 50 patients (30%) who received ^{177}Lu-PSMA were rechallenged upon progression with PSMA-positive disease, of whom 11 (73%) experienced a PSA decline of 50% or greater [50]. This and other evidence suggests that retreatment is feasible, albeit with a lower probability of response or durability of response [51–53].

Q80. For patients with mCRPC who have exhausted standard treatment options, who previously showed a documented response to ^{177}Lu-PSMA therapy (eg, lasting $\geq$6 mo), and who are now progressing again with cancer that continues to meet the initial treatment criteria, 81% of panellists voted to rechallenge with ^{177}Lu-PSMA, while 19% voted against rechallenge. There were eight abstentions. (**Consensus** to rechallenge with ^{177}Lu-PSMA.)

Approximately 2.5% of patients in the VISION trial received radium-223 therapy after progressing on ^{177}Lu-PSMA-617 therapy.

Q82. A total of 76% of panellists voted that it is safe, and 24% voted that it is unsafe, to recommend radium-223 to patients with mCRPC who have previously received ^{177}Lu-PSMA therapy. There were 15 abstentions. (**Consensus** that it is safe to use radium-223 after ^{177}Lu-PSMA.)

For inclusion in the VISION trial, patients were required to have adequate bone marrow function, defined as a white blood cell count $\geq 2.5 \times 10^9$ cells/l or absolute neutrophil count $\geq 1.5 \times 10^9$ cells/l, platelets $\geq 100 \times 10^9$ cells/l, and haemoglobin $\geq$90 g/l. Limited data are available on ^{177}Lu-PSMA therapy for patients with impaired bone marrow function, although it has been reported that high tumour burden in the bone, grade 2 baseline cytopenia, and previous taxane-based chemotherapy are associated with a higher risk of haematological toxicity [54]. A retrospective multicentre series found that among heavily pretreated patients with diffuse marrow involvement, ^{177}Lu-PSMA had relevant antitumour activity and acceptable toxicity [55].

Q83. For patients with mCRPC who have relevant impairment of bone marrow function, 85% of panellists voted that it is **not** safe to recommend treatment with ^{177}Lu-PSMA, while 15% voted that this is safe. For this question, impaired bone marrow function was defined on the basis of exclusion criteria from the VISION trial (haemoglobin <9 g/dl and/or absolute neutrophil count $< 1.5 \times 10^9$ cells/l and/or platelets $< 100 \times 10^9$ cells/l). There were ten abstentions. (**Consensus**

that it is **not** safe to recommend ^{177}Lu-PSMA to patients with mCRPC who have relevant impairment of bone marrow function.)

Q84. For patients with mCRPC who have a malignant superscan (bone scintigraphy) and do not have relevant impairment of bone marrow function, provided that the relevant PET criteria are met, 71% of panellists voted that it is safe to recommend treatment with ^{177}Lu-PSMA, 24% voted for a reduced dose of ^{177}Lu-PSMA, and 5% voted that it is unsafe to recommend ^{177}Lu-PSMA. There were 16 abstentions. (No consensus for any answer option, but a combined total of 95% of panellists voted that ^{177}Lu-PSMA can be administered at a full or reduced dose.)

3.5. Discussion of PSMA-targeted agents in diagnostics and therapy

The PSMA tracers available differ in their biodistribution, stability, specificity, and sensitivity, which needs to be considered when interpreting the results from PSMA PET/CT imaging trials. For example, ^{18}F-PSMA-1007 exhibits nonspecific uptake in nonmetastatic (likely benign) bone lesions, typically in the ribs [38]. Nonetheless, panellists at APCCC 2021 reached consensus (Table 2) that data generated via ^{68}Ga-PSMA-11 PET/CT imaging for staging of prostate cancer can be extrapolated to other PSMA tracers (although not to choline or fluciclovine). This consensus suggests that even experienced clinicians may not fully appreciate the differences among PSMA tracers, which highlights the importance of consulting nuclear medicine physicians before making therapeutic decisions based on PSMA PET/CT scans [56]. In addition, standardised reporting guidelines such as the European Association of Nuclear Medicine E-PSMA guidelines may assist [57].

Most panellists voted to use PSMA PET/CT to stage localised prostate cancer, at least in high-risk patients, even though no data on long-term oncological outcomes are available. However, there was consensus not to omit lymphadenectomy or pelvic radiation therapy simply because a patient has a negative PSMA PET/CT scan. It is important to note that PSMA PET/CT is not very sensitive in detecting pelvic lymph node metastases. Thus, current standard approaches for treating localised prostate cancer should continue to be used until prospective clinical trials show that a treatment can be omitted if PSMA PET/CT imaging is negative [58–60]. Interestingly, in the POP-RT trial, in which estimated nodal risk exceeded 20% (according to the Roach formula) and 80% of patients had a negative staging PSMA PET/CT, 5-yr biochemical failure-free survival and disease-free survival were significantly higher with prophylactic pelvic lymph-node irradiation than with prostate-only radiation therapy [61].

The results for PSMA PET/CT did influence the treatment recommendations of the panellists, particularly if PSMA PET/CT identified bone lesions. It is interesting to consider whether patients with M0 status on conventional imaging but positive bone lesions on PSMA PET can be classified as M1 or whether we need to add a new category to the TNM staging system to specify that metastases were only seen on PSMA PET and not on conventional imaging.

Panellists reached consensus that VISION data on ^{68}Ga-PSMA-11 PET/CT can be extrapolated to ^{18}F-PSMA-1007 PET/CT, but this consensus was not reached for ^{18}F-DCFPyL PET/CT. In fact, ^{68}Ga-PSMA-11 is more similar to ^{18}F-DCFPyL than to ^{18}F-PSMA-1007. The discrepancy in consensus is likely to reflect regional variations in availability and experience with these agents. Physiological liver uptake, used as a reference to define suitability for enrolment in the VISION trial, is of particular relevance here: DCFPyL has similar uptake to Ga-PSMA-11, whereas PSMA-1007 shows significantly greater uptake [62].

There was consensus that ^{177}Lu-PSMA therapy is the preferred third-line treatment option for patients with mCRPC progressing after one line of ARPI and one line of taxane therapy. For chemotherapy-fit patients with mCRPC who have received one line of ARPI but no taxane therapy, there was consensus to treat first with docetaxel rather than ^{177}Lu-PSMA or radium-223. For chemotherapy-unfit patients progressing after one line of ARPI, there was consensus to treat with ^{177}Lu-PSMA. Even though patients in the ^{177}Lu-PSMA arm of the VISION trial received protocol-permitted standard-of-care therapy, including ARPIs, there was consensus not to routinely recommend ^{177}Lu-PSMA in combination with an alternate ARPI. In addition, there was consensus not to recommend ^{177}Lu-PSMA therapy for patients with mHSPC outside the setting of a clinical trial.

Panellists were divided regarding how to monitor response to ^{177}Lu-PSMA therapy, with half of the panel voting for post-therapy planar/SPECT and the rest for conventional imaging, either alone or in combination with PSMA-based imaging. Clearly, the question of monitoring remains open, which may, in part, be related to regional differences in standards of nuclear medicine practice and reimbursement for scans.

Panellists reached consensus not to recommend ^{177}Lu-PSMA therapy for patients with relevant impairment of bone marrow function. For patients with impaired renal function, more than half of the panellists would treat only with a reduced ^{177}Lu-PSMA dose, and one-fifth would not use ^{177}Lu-PSMA at all. These questions were asked because many patients who are seen in daily practice would not have met the eligibility criteria for enrolment in the registrational ^{177}Lu-PSMA trial. However, most APCCC 2021 panellists acknowledge that in many of these situations, only limited clinical data are available. Thus, it is crucial to consider these voting results in clinical context, such as by considering all available evidence-supported treatment options and whether patients can enrol in clinical trials. The results provide a practical guide to assist clinicians in discussions with patients as part of a shared and multidisciplinary decision-making process, ideally with nuclear medicine specialists present in the multidisciplinary team meeting.

4. Genetic counselling and/or genetic testing

At APCCC 2019, panellists reached consensus that all patients with metastatic prostate cancer should receive genetic counselling and/or testing [3]. This consensus was based on data indicating that 10–15% of patients with

metastatic prostate cancer have a germline (inheritable) exome variant.

Some prostate cancer guidelines recommend genetic counselling and/or testing, but specifics and details vary substantially. The National Comprehensive Cancer Network (NCCN) provides highly comprehensive recommendations on genetic testing and counselling that are tailored according to whether patients have high-risk localised disease, histological tumour subtypes, metastatic disease, and/or a relevant family history of cancer [63]. The Philadelphia Prostate Cancer Consensus Conference 2019 also provides detailed recommendations on genetic counselling and testing [64]. Guidelines from the European Association of Urology (EAU) include a weak recommendation for genetic counselling and/or testing if patients have metastatic prostate cancer or a relevant family history [65]. The ESMO guidelines only address germline testing and genetic counselling related to pathogenic alterations in cancer risk genes [66].

Regulations concerning germline testing and genetic counselling also vary globally. In some countries, such as the USA, patients can legally receive germline testing without prior genetic counselling and usually receive genetic counselling only if their germline test is positive. By contrast, in many European countries, genetic counselling is required before patients can receive germline testing.

Q86. In all, 87% of panellists voted for and 13% voted against recommending germline counselling and/or testing for most patients with metastatic prostate cancer, assuming that testing is available and local regulations permit. There were no abstentions. (**Consensus** to recommend germline counselling and/or testing for most patients with metastatic prostate cancer.)

Q87. A total of 80% of panellists voted that if local regulations allow, it is appropriate for a physician to order germline testing in the absence of genetic counselling if genetic counselling is unavailable. The remaining 20% of panellists voted that this is inappropriate. There were two abstentions. (**Consensus** for physicians to order germline testing even if genetic counsellors are unavailable.)

Some experts have expressed concerns about relying on somatic (tumour) next-generation sequencing (NGS) to determine which patients should receive germline testing. For biological and technical reasons, somatic NGS does not reliably capture all germline alterations and is particularly likely to miss insertions, deletions, and copy number variants. In a recent cohort study of patients with various cancers, tumour sequencing failed to identify 8% of pathogenic germline variants [67]. It is therefore important to counsel patients and their relatives that a negative germline test does not exclude the possibility of carrying a relevant pathogenic variant or of developing prostate cancer.

Q88. In all, 68% of panellists voted to recommend additional germline testing for the majority of patients with a positive family history but no evidence on somatic (tumour) testing of DNA damage repair (DDR) alterations and/or mismatch repair (MMR) alterations. The remaining 32% of panellists voted against recommending additional germline testing in this setting. There were three abstentions. (No consensus for any answer option.)

At APCCC 2019 there was strong consensus (98%) to collect detailed family cancer histories from all patients with metastatic prostate cancer [3]. As mentioned previously, the NCCN guidelines have expanded their criteria for genetic testing to include patients with high-risk localised prostate cancer [63].

Q89. For patients with high-risk localised prostate cancer, 39% of panellists voted to recommend genetic counselling or germline testing regardless of histology, while 61% voted against this. There were no abstentions. (No consensus for any answer option.)

Current NCCN and EAU guidelines recommend germline testing and counselling on the basis of family history. The APCCC 2021 panel voted on this question.

Q90. For patients with localised prostate cancer of any risk group who have a positive family history (e.g., based on NCCN criteria), 77% of panellists voted to recommend genetic counselling/germline testing, while 23% voted against it. There was one abstention. (**Consensus** to recommend genetic counselling/germline testing for patients with localised prostate cancer and a positive family history.)

Histological variant prostate carcinomas, particularly intraductal and cribriform histologies, are associated with a poor prognosis [68]. Inherited defects in DNA repair mechanisms, including those involving DNA MMR, are more frequent in histological variants of prostate carcinoma than in pure acinar adenocarcinomas [69-71]. In a recent study, however, germline *BRCA2* alterations were not significantly associated with either intraductal or cribriform histology, while both of these histological variants were significantly associated with biallelic *BRCA2* loss, independent of other risk factors [72].

Q91. For patients with prostate cancer who have intraductal/cribriform histology components on histopathology, 54% of panellists voted to recommend genetic counselling/germline testing, while 46% voted against it. There were two abstentions. (No consensus for any answer option.)

The APCCC 2021 panel also voted on the extent of germline testing to perform in patients who lack a significant family history of prostate cancer.

Q92. For patients with prostate cancer without a significant family history, 14% of panellists voted that they test for *BRCA1* and *BRCA2* mutations only, 61% voted that they use a more extended panel (eg, *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *RAD51C*, *HOXB13*), and 25% voted that they use comprehensive genomic testing of all known cancer-associated germline mutations. There were two abstentions. (No consensus for any answer option; a combined 86% voted for a panel including more than just *BRCA1/2*.)

4.1. Tumour genomic profiling and targeted therapies

The field has evolved since 2019, and PARP inhibitors are now considered a standard of care for patients with mCRPC who have relevant genomic alterations [73,74]. The European Medicines Agency has approved the PARP inhibitor olaparib only for patients with germline and/or somatic

alterations in *BRCA1* or *BRCA2* genes [73]. By contrast, in 2020 the US FDA approved olaparib for treating mCRPC in patients with alterations in *BRCA1*, *BRCA2*, and/or a variety of other DDR genes represented in the registrational phase 3 PROfound trial (except for *PPP2R2A*, which the FDA excluded from the 14-gene companion diagnostic test owing to a lack of biological evidence linking it to DDR mechanisms, and because PROfound participants with *PPP2R2A* alterations did not benefit from olaparib therapy).

In addition to olaparib, in 2020 the FDA approved the PARP inhibitor rucaparib for treating mCRPC in patients with deleterious germline and/or somatic *BRCA1/2* alterations who have already received androgen-directed therapy and taxane-based chemotherapy. This approval was based on results from the single-arm TRITON2 trial, which evaluated rucaparib in patients with mCRPC who had DDR deficiencies. In this study, patients who lacked somatic *BRCA1* and *BRCA2* alterations showed only modest responses to rucaparib, particularly if they had somatic *ATM*, *CDK12*, or *CHEK2* alterations [75]. In this study, rucaparib did elicit a ≥50% PSA decrease in two of two study participants with *PALB2* alterations [74].

At APCCC 2019, 52% of panellists voted to perform tumour genomic profiling at the time of diagnosis of metastatic prostate cancer.

Q93. A total of 48% of panellists voted for tumour genomic profiling (tissue or ctDNA) only in the setting of mCRPC, 39% voted for it at the time of diagnosis of any mHSPC, 9% at diagnosis of synchronous mHSPC, and 4% voted that they do not routinely recommend tumour genetic profiling. There were no abstentions. For this question, panellists were asked to assume that tumour genomic profiling was readily available. (No consensus for any answer option, but a combined 96% of panellists voted for tumour testing either in mHSPC or mCRPC.)

Q94. Among the panellists who voted for tumour (somatic) genomic testing only in the setting of mCRPC, 76% voted to perform it after progression on an ARPI, 18% after progression on an ARPI and one line of taxane chemotherapy, 4% after all standard treatment options are exhausted, and 2% voted that they do not routinely recommend tumour somatic testing. There were 25 abstentions. (**Consensus** to perform tumour [somatic] genomic testing after progression on an ARPI among the panellists voting for tumour genomic testing.)

The APCCC 2021 panel also voted on the optimal specimen source and type of tumour genomic profiling to perform. In the PROfound trial, tumour tissue and circulating tumour DNA (ctDNA) showed high concordance for both *BRCA* and *ATM* alterations, although concordance was lower if samples were older or had either insufficient tissue or low plasma ctDNA. In this trial, the prevalence of DDR gene alterations was 28% overall and was similar for primary and metastatic tumour tissue specimens (27% vs 32%) [45].

Q95. When performing tumour (somatic) genomic evaluations, 57% of panellists voted to test the most recent available archival tumour tissue, 26% voted to obtain a new biopsy, 14% voted to test ctDNA, and 3% voted to test primary tumour archival tissue. There were three abstentions. (No consensus for any answer option.)

Q96. Among the panellists who voted for tumour (somatic) genomic testing in metastatic prostate cancer, 20% voted that it is relevant, when testing for the purposes of treatment selection, to include *BRCA1/2* plus MMR evaluation (microsatellite instability [MSI] high/deficient MMR [dMMR] ± high tumour mutational burden [TMB]), 34% would also test for additional DDR gene alterations, and 46% would perform comprehensive panel testing (eg, *BRCA1/2*, MMR evaluation, additional DDR genes, and *PTEN*, *PI3K*, *SPOP*, *RB1*, *TP53*, and *AR*). There were five abstentions. (No consensus for any answer option, but a combined 100% voted for at least *BRCA1/2* and dMMR/MSI testing.)

Q98. Regarding whether tumour (somatic) genomic testing should be performed at the same time as germline testing (eg, as part of a paired tumour + germline analysis), 56% of panellists voted to recommend this, 25% voted to recommend it only if there is access to genetic counselling, and 19% did not recommend it. There were four abstentions. (No consensus for any answer option, but a combined 81% voted for testing at the same time, provided that genetic counselling is available.)

The homologous recombination deficiency (HRD) score includes information on loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. In ovarian cancer, the HRD score may help to identify patients who are most likely to benefit from PARP inhibitor therapy [76]. However, in prostate cancer, the HRD score is neither established nor routinely used for treatment selection [77–79]. In a recent study of three cohorts of patients with prostate cancer, germline *BRCA2* alterations were associated with higher HRD scores than were *ATM* and *CHEK2* alterations [77].

Q97. In all, 17% panellists voted that tumour genomic profiling should include a HRD score, 36% voted that this should be included only if patients have known DDR gene alterations, and 47% voted against including a HRD score. There were 13 abstentions. (No consensus for any answer option.)

The panel voted on two questions specifically related to testing to select PARP inhibitor therapy.

Q99. When testing for alterations in DDR genes in order to select PARP inhibitor therapy for patients with no identified germline variant, 88% of panellists voted for tissue-based testing and 12% voted for liquid biopsy (ctDNA testing). There were four abstentions. (**Consensus** for tissue-based testing.)

Q100. When performing tumour tissue-based (somatic) testing for selection of PARP inhibitor therapy, 96% of panellists voted that they preferred to test recent biopsy tissue, but if unavailable, then archival tissue is sufficient, 3% voted that recent biopsy is mandatory, and 1% voted to test archival tissue. There were two abstentions. (**Strong consensus** to test recent biopsy tissue, if available, and to otherwise test archival tissue.)

Cohort A of the registrational PROfound trial included patients with at least one *BRCA1*, *BRCA2*, or *ATM* alteration. More than 60% of these patients had already received at least one line of chemotherapy (docetaxel, cabazitaxel, or both) and one or two lines of ARPI therapy [45]. Of note, patients in cohort A benefited similarly from olaparib regardless of whether their *BRCA* and/or *ATM* alterations

were detected in ctDNA or tumour tissue [80]. However, US and European regulatory agencies that approved olaparib for treatment of prostate cancer only required patients to have received one prior line of ARPI. This is probably because a subgroup analysis of cohort A (which excluded patients with *ATM* alterations) demonstrated better outcomes among taxane-naïve patients (HR 0.3, 95% CI 0.1–0.78) in comparison to taxane-experienced patients (HR 0.64, 95% CI 0.39–1.08) [73].

Q101 For patients with a pathogenic *BRCA1/2* aberration (germline/somatic or somatic alone), 55% of panellists voted to start PARP inhibitor therapy after one line of ARPI, 41% after one line of ARPI and one line of chemotherapy, and 4% after one line of ARPI, one line of chemotherapy, and lutetium-PSMA. There were four abstentions. (No consensus for any answer option.)

Although PARP inhibitor–induced or platinum-induced synthetic lethality theoretically requires biallelic inactivation of *BRCA1/2*, patients often only need to have one alteration to enrol in a clinical trial, and the status of the second allele may not be reported. In the TRITON2 trial, the PSA response to rucaparib was higher among patients with biallelic versus monoallelic *BRCA1/2* alterations [75].

Q102. For patients with a pathogenic, monoallelic, somatic (not germline) *BRCA1/2* alteration, 76% of panellists voted for PARP inhibitor therapy, 16% voted for PARP inhibitor therapy only if there is a positive HRD score, and 8% voted against PARP inhibitor therapy. There were 11 abstentions. (**Consensus** for PARP inhibitor therapy.)

Little is known about how to optimally sequence PARP inhibitor and platinum therapies in patients with advanced prostate cancer [81,82]. At APCCC 2021, panellists considered pre-taxane and post-taxane patients progressing on PARP inhibitor therapy.

Q103. For patients with a pathogenic *BRCA1/2* aberration (germline/somatic or somatic alone) who have received one line of ARPI and are now progressing on or after second-line PARP inhibitor therapy, 53% of panellists voted for docetaxel, 25% for platinum-taxane combination therapy, 11% for platinum monotherapy, 6% for lutetium-PSMA therapy, 3% for radium-223 (if the relevant treatment criteria are met), and 2% for another ARPI. There were eight abstentions. (No consensus for any answer option.)

Q104. For patients with a pathogenic *BRCA1/2* aberration (germline/somatic or somatic alone) who have received one line of ARPI and docetaxel and are now progressing on or after third-line PARP inhibitor therapy, 48% of panellists voted for lutetium-PSMA therapy, 23% for cabazitaxel, 14% for platinum-taxane combination therapy, 8% for platinum monotherapy, 6% for radium-223 (if the relevant treatment criteria are met), and 1% for another ARPI. There were seven abstentions. (No consensus for any answer option.)

A relevant proportion (28%) of patients in the PROFOUND trial had *ATM* alterations. In this subgroup, olaparib was associated with similar OS (HR 0.93, 95% CI 0.53–1.75) as for enzalutamide or abiraterone, even after adjusting for treatment crossover (HR 0.84, 95% CI 0.19–3.75). Hypothesis-generating results did suggest that patients with *ATM* alterations had better OS with olaparib if they had previously received taxane therapy (HR 0.45, 95% CI 0.22–0.95) than if they were taxane-naïve (HR 2.82, 95% CI 0.96–12.03) [73].

In the TOPARP trial, 8% of evaluable patients with *ATM* alterations had objective responses to olaparib, and among the 19 patients with *ATM* alterations, 5% experienced at least a 50% PSA decline (one of several criteria for an objective response) [83]. *ATM* alterations identified via NGS do not necessarily indicate genomic instability, and immunohistochemistry analysis may better confirm true ATM loss [84]. Of note, clonal haematopoiesis of indeterminate potential (CHIP) can be an important confounder and can lead to "false positive" patients with *ATM* alterations. CHIP frequency increases with age and among individuals who smoke, and is more common among males. Limited data indicate that CHIP is both prevalent and relevant when using genomic profiling to select patients for PARP inhibitor therapy: in a recent study of 69 patients with advanced prostate cancer who underwent cell-free DNA testing, 19% had detectable CHIP and many CHIP variants affected DDR genes, most commonly *ATM* [85]. On the basis of these findings, the authors recommended that cell-free DNA testing should include a paired whole-blood control specimen to exclude CHIP variants and avoid misidentifications.

Q105. For patients with a pathogenic genomic *ATM* aberration (germline/somatic or somatic alone), 33% of panellists voted for PARP inhibitor therapy some time during the disease course, 29% voted for PARP inhibitor therapy if the HRD score is positive and/or immunohistochemistry confirms loss of protein function, and 38% voted against PARP inhibitor therapy. There were nine abstentions. (No consensus for any answer option.)

A total of 12% of patients in the PROfound trial had *CDK12* alterations [45]. In this small subgroup, olaparib demonstrated some degree of antitumour activity even after adjusting for treatment crossover (HR for OS 0.70, 95% CI 0.04–12.53). In a separate retrospective study in which 60 patients had detectable *CDK12* alterations (52% of which were biallelic), none of the 11 patients who received a PARP inhibitor demonstrated a PSA response [86]. In the TOPARP trial, there were likewise no objective responses to olaparib among 18 evaluable patients with *CDK12* alterations [83].

Q106. For patients with a pathogenic genomic *CDK12* aberration (germline/somatic or somatic alone), 19% of panellists voted for PARP inhibitor therapy some time during the disease course, 28% voted for PARP inhibitor therapy if the HRD score is positive, and 53% voted against PARP inhibitor therapy. There were ten abstentions. (No consensus for any answer option.)

Cohort B of the PROfound trial—in which patients had alterations in DDR genes other than *BRCA1*, *BRCA2*, or *ATM*—included only 12 patients with *CHEK2* alterations; hence, the antitumour activity of olaparib in such patients is unclear [45]. Patients with *CHEK2* alterations are also sparsely represented in other published trials of PARP inhibitors in prostate cancer [87]. Moreover, there are few data on the role of the HRD score in selecting therapies for these patients.

Q107. For patients with a pathogenic genomic *CHEK2* aberration (germline/somatic or somatic alone), 36% of panellists voted for PARP inhibitor therapy some time during the disease course, 27% voted for PARP inhibitor therapy if the HRD score is positive, and 37% voted against PARP inhibitor therapy. There were 11 abstentions. (No consensus for any answer option.)

The APCCC 2021 panel also voted on the use of PARP inhibitors for patients with other genomic alterations represented in the PROfound trial. This is particularly relevant because the FDA label for olaparib includes these alterations.

Q108. For patients with any other pathogenic DDR gene alteration(s) (germline/somatic, or somatic alone; eg, *BARD1*, *BRIP1*, *CHEK1*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*), 28% of panellists voted for PARP inhibitor therapy some time during the disease course, 32% voted for PARP inhibitor therapy if the HRD score is positive, and 40% voted against PARP inhibitor therapy. There were 11 abstentions. (No consensus for any answer option.)

Activity of platinum-based chemotherapies has been demonstrated in retrospective analyses of patients with DDR gene alterations [81,82,88].

Q109. For patients with a pathogenic *BRCA1/2* aberration (germline/somatic or somatic alone), if PARP inhibitor therapy is not accessible, 35% of panellists voted for platinum-based therapy, 61% voted for platinum-based therapy only for patients who have already received at least one ARPI and one line of taxane chemotherapy, and 4% voted against platinum-based therapy. There were five abstentions. (No consensus for any answer option; a combined 96% voted for platinum-based chemotherapy if PARP inhibitor therapy is not available, at least after 2 prior lines of therapy.)

PARP inhibitor maintenance therapy significantly prolongs PFS in patients with ovarian cancer [89]. However, data for prostate cancer are lacking.

Q110. For patients with a pathogenic BRCA1/2 aberration (germline/somatic or somatic alone), 70% of panellists voted for PARP inhibitor monotherapy, 19% voted to start with platinum-based chemotherapy and then use PARP inhibitor maintenance therapy or a PARP inhibitor at progression, and 11% voted to combine platinum-based chemotherapy with PARP inhibitor therapy. There were eight abstentions. (No consensus for any answer option.)

4.2. Discussion

At APCCC 2021, there was clear consensus (Table 3) that patients with advanced prostate cancer should receive germline testing and genetic counselling. Practically speaking, however, local regulations and resources in some areas may limit genetic counselling to patients in whom primary germline testing identifies a pathogenic alteration in a cancer predisposition gene.

A positive family history and Ashkenazi Jewish ancestry are key reasons to evaluate patients for cancer-related germline alterations. However, tumour genomic profiling can fail to detect nearly 10% of these alterations, making false negatives a real concern [90]. Perhaps for this reason, 68% of panellists voted to perform additional germline testing if patients with advanced prostate cancer have a negative tumour genetic profile but a positive family history. For patients with localised prostate cancer, the panel only reached consensus in favour of genetic counselling and testing if patients have a positive family history, not simply because they have high-risk localised disease or variant (intraductal or cribriform) histology.

For the general population of patients with advanced prostate cancer (ie, without a significant family history), only a minority of panellists voted to test only for *BRCA1/2* alterations, while the remainder favoured the use of more extended panels like those used in breast and ovarian cancer.

After considering various questions related to tumour genomic profiling, panellists reached consensus on the timing of tumour genomic testing in mCRPC (after one line of ARPI), the preference for upfront tissue-based testing (if sufficient tissue is available) as opposed to liquid biopsy (ctDNA), and the use of a recently obtained biopsy, if available, and otherwise archival tissue. The benefits of ctDNA testing include repeatability, ease of collection (particularly if tissue is not already available), and the possibility of capturing tumour evolution, while the downsides include low ctDNA fraction (if the tumour burden is low) and the possibility of interference or confounding by CHIP.

The recent regulatory approval of PARP inhibitors in the USA, Japan, and Europe, and of checkpoint inhibitors in the USA for molecularly selected patients (MSI high/dMMR ± TMB-high) with advanced cancers raises the question of how extensively to test tumours for relevant genomic alterations. Panellists did not reach consensus on this question, with 54% voting to evaluate for *BRCA1/2* and MMR alterations (MSI high/dMMR) with or without additional DDR genes, and the rest voting for broader panel testing for alterations in genes such as *RB1*, *PTEN*, *PI3K*, and *SPOP*. In addition, only half of the panellists voted to include the HRD score as part of tumour genomic profiling, either for the majority of patients or for those with DDR gene alterations.

Even as new data emerge on PARP inhibition in prostate cancer, clinicians are being called on to counsel patients and select patients for therapy in daily clinical practice. These patients typically have received prior lines of therapy in the metastatic setting, making sequencing questions both salient and complex. At APCCC 2021, panellists were split between sequencing a PARP inhibitor after one line of ARPI or after one line of ARPI and one line of chemotherapy. For chemotherapy-naïve patients progressing on or after a PARP inhibitor, the majority of panellists voted to administer third-line chemotherapy. For prior recipients of chemotherapy and an ARPI who were now progressing on a PARP inhibitor, there was no consensus as to which subsequent treatment to recommend, although almost half of the panellists voted for ^{177}Lu-PSMA therapy. For patients with mCRPC without access to PARP inhibitors, 96% of the panellists would use platinum-based chemotherapy at some point during the disease course.

Results from multiple clinical trials have confirmed the benefits of PARP inhibition in patients with a pathogenic *BRCA1/2* alteration (germline and/or somatic) [73,75,83,87]. However, data on *ATM*, *CDK12*, *CHEK2*, and

other DDR alterations are not as strong, in part because some of these alterations are rare. At APCCC 2021, the panellists did not reach consensus about the use of PARP inhibitors for patients with non-*BRCA* DDR alterations.

Our current understanding of PARP inhibitors in advanced prostate cancer is challenged by recently presented results from the PROPEL trial (NCT03732820), in which patients with mCRPC were randomly assigned to receive abiraterone in combination with either olaparib or placebo (patients were permitted to have received prior docetaxel when they had mHSPC). Other relevant trials in mCRPC are ongoing, some of which also combine PARP inhibitors with ARPIs. These studies include MAGNITUDE, in which patients receive abiraterone with or without niraparib; TRITON3, in which rucaparib is combined with either an ARPI or docetaxel; and TALAPRO2, in which enzalutamide is administered with or without talazoparib. Results from these studies were not available at the time of voting, but should generate a wealth of data related not only to these specific treatment combinations but also hopefully regarding the activity of PARP inhibitors in patients with relatively uncommon alterations in DDR genes.

5. Conclusions

The APCCC gathers expert opinions on a variety of topics that lack sufficient published data or for which there is conflicting interpretation of the data to guide treatment decisions in advanced prostate cancer. Votes are based on carefully phrased questions that have been circulated several times among all the experts to render them more useful and complete; corresponding answer options are created using a modified Delphi process.

Interestingly, panellists reached consensus on less than half of the questions at APCCC 2021, which clearly reveals persistent clinical uncertainty and gaps in knowledge about some areas of advanced prostate cancer management. In some cases, areas lacking consensus included hypothetical patients and scenarios that clinicians encounter on a daily basis; evaluation of these topics in prospective clinical trials is especially urgent (if such studies are not already under way). As others have noted, if pharmaceutical companies are not interested in exploring these high-priority topics, then academic clinical researchers need to step in and urgently seek funding for clinically relevant trials [91] such as studies of treatment de-escalation strategies.

For certain questions for which there was no consensus on a single answer option, there was substantial discussion regarding whether it was appropriate to combine voting results for several answer options with similar features for the purposes of discussion and interpretation. We decided to do this, but we have clearly indicated where this was the case in the tables and the text.

Some voting results were surprising and unsupported by published data. Readers should keep in mind that the method used in the consensus conference captures the opinions of experts who have extensive real-world clinical experience that informs their thinking about how best to manage patients in various situations, but they may not be real experts in all topics and may not always have chosen the option "abstain" for the voting as recommended.

In addition, although we asked panellists to assume that all diagnostic tools and treatments were readily available, it is probable that some experts voted for answer options that reflected their own realities, which are likely to differ regionally and internationally.

It is also important to keep in mind that the opinion of experts—even the large number of experts who voted at APCCC 2021—can sometimes be wrong. Physicians tend to always think that they do the good and right thing, but they may be mistaken. It is especially important to keep this in mind when considering some of the questions for which there was consensus despite a lack of robust supporting evidence. Sometimes, enthusiasm for new treatments and technologies is much stronger than the supporting evidence. Therefore, readers should remain critical when interpreting these voting results and integrating them into daily clinical practice. Expert voting results can never replace robust evidence from clinical trials, but they can help to inform clinical practice until such evidence is available.

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Supplementary data

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