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Original Research

Management of patients with advanced prostate cancer—metastatic and/or castration-resistant prostate cancer: report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022

Silke Gillessen [a,b,*], Alberto Bossi [c], Ian D. Davis [d], Johann de Bono [e,f], Karim Fizazi [g], Nicholas D. James [e], Nicolas Mottet [h], Neal Shore [i,j], Eric Small [k], Matthew Smith [l], Christopher J. Sweeney [m], Bertrand Tombal [n], Emmanuel S. Antonarakis [o], Ana M. Aparicio [p], Andrew J. Armstrong [q], Gerhardt Attard [r], Tomasz M. Beer [s], Himisha Beltran [t], Anders Bjartell [u], Pierre Blanchard [v], Alberto Briganti [w], Rob G. Bristow [x,y], Muhammad Bulbul [z], Orazio Caffo [aa], Daniel Castellano [ab], Elena Castro [ac], Heather H. Cheng [ad], Kim N. Chi [ae], Simon Chowdhury [af], Caroline S. Clarke [ag], Noel Clarke [ah], Gedske Daugaard [ai], Maria De Santis [aj,ak], Ignacio Duran [al], Ross Eeles [am], Eleni Efstathiou [an], Jason Efstathiou [ao], Onyeanunam Ngozi Ekeke [ap], Christopher P. Evans [aq], Stefano Fanti [ar], Felix Y. Feng [as], Valerie Fonteyne [at], Nicola Fossati [au], Mark Frydenberg [av], Dan George [aw], Martin Gleave [ax], Gwenaelle Gravis [ay], Susan Halabi [az], Daniel Heinrich [ba], Ken Herrmann [bb], Celestia Higano [bc], Michael S. Hofman [bd], Lisa G. Horvath [be,bf,bg], Maha Hussain [bh], Barbara A. Jereczek-Fossa [bi,bj], Rob Jones [bk], Ravindran Kanesvaran [bl], Pirkko-Liisa Kellokumpu-Lehtinen [bm,bn], Raja B. Khauli [bo], Laurence Klotz [bp], Gero Kramer [bq], Raja Leibowitz [br,bs], Christopher Logothetis [p,bt], Brandon Mahal [bu], Fernando Maluf [bv,bw], Joaquin Mateo [bx], David Matheson [by], Niven Mehra [bz], Axel Merseburger [cb], Alicia K. Morgans [t], Michael J. Morris [cc], Hind Mrabti [cd], Deborah Mukherji [ce], Declan G. Murphy [cf,cg],

* Correspondence to: Oncology Institute of Southern Switzerland, Bellinzona, Switzerland.
E-mail address: silke.gillessen@eoc.ch (S. Gillessen).

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Vedang Murthy [ch], Paul L. Nguyen [ci], William K. Oh [cj], Piet Ost [ck,cl], Joe M. O'Sullivan [cm], Anwar R. Padhani [cn], Carmel J. Pezaro [co], Darren M.C. Poon [cp,cq], Colin C. Pritchard [cr], Danny M. Rabah [cs,ct], Dana Rathkopf [cu], Robert E. Reiter [cv], Mark A. Rubin [cw], Charles J. Ryan [cx], Fred Saad [cy], Juan Pablo Sade [cz], Oliver Sartor [dc], Howard I. Scher [cu,dd], Nima Sharifi [de,df], Iwona Skoneczna [dg], Howard Soule [dh], Daniel E. Spratt [di], Sandy Srinivas [dj], Cora N. Sternberg [dk], Thomas Steuber [dl,dm], Hiroyoshi Suzuki [dn], Matthew R. Sydes [do], Mary-Ellen Taplin [dp], Derya Tilki [dq,dr,ds], Levent Türkeri [dt], Fabio Turco [a], Hiroji Uemura [du], Hirotsugu Uemura [dv], Yüksel Ürün [dw,dx], Claire L. Vale [dy], Inge van Oort [dz], Neha Vapiwala [ed], Jochen Walz [ee], Kosj Yamoah [ef], Dingwei Ye [eg,eh], Evan Y. Yu [ei], Almudena Zapatero [ej], Thomas Zilli [ek,el], Aurelius Omlin [em]

[a] *Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland*
[b] *Università della Svizzera Italiana, Lugano, Switzerland*
[c] *Genitourinary Oncology, Prostate Brachytherapy Unit, Gustave Roussy, Paris, France*
[d] *Monash University and Eastern Health, Victoria, Australia*
[e] *The Institute of Cancer Research, London, UK*
[f] *Royal Marsden Hospital, London, UK*
[g] *Institut Gustave Roussy, University of Paris Saclay, Villejuif, France*
[h] *University Jean Monnet, St Etienne, France*
[i] *Medical Director, Carolina Urologic Research Center, Myrtle Beach, SC, USA*
[j] *CMO, Urology/Surgical Oncology, GenesisCare, Myrtle Beach, SC, USA*
[k] *UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA*
[l] *Massachusetts General Hospital Cancer Center, Boston, MA, USA*
[m] *South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, SA, Australia*
[n] *Cliniques universitaires Saint Luc, Brussels, Belgium*
[o] *University of Minnesota Masonic Cancer Center, Minneapolis, MN, USA*
[p] *Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*
[q] *Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC, USA*
[r] *University College London Cancer Institute, London, UK*
[s] *Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA*
[t] *Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[u] *Department of Urology, Skåne University Hospital, Malmö, Sweden*
[v] *Gustave Roussy, Département de Radiothérapie, Université Paris-Saclay, Oncostat, Inserm U-1018, F-94805, Villejuif, France*
[w] *Unit of Urology/Division of Oncology, URI, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy*
[x] *Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK*
[y] *Christie NHS Trust and CRUK Manchester Institute and Cancer Centre, Manchester, UK*
[z] *Division of Urology, Department of Surgery, American University of Beirut Medical Center, Beirut, Lebanon*
[aa] *Department of Medical Oncology, Santa Chiara Hospital, 38122 Trento, Italy*
[ab] *Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain*
[ac] *Institute of Biomedical Research in Málaga (IBIMA), Málaga, Spain*
[ad] *University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA*
[ae] *BC Cancer, Vancouver Prostate Centre, University of British Columbia, Vancouver, British Columbia, Canada*
[af] *Guys and St Thomas's NHS Foundation Trust, London, United Kingdom*
[ag] *Research Department of Primary Care & Population Health, Royal Free Campus, University College London, London, UK*
[ah] *The Christie and Salford Royal Hospitals, Manchester, UK*
[ai] *Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*
[aj] *Department of Urology, Charité Universitätsmedizin, Berlin, Germany*
[ak] *Department of Urology, Medical University of Vienna, Austria*
[al] *Department of Medical Oncology, Hospital Universitario Marques de Valdecilla, IDIVAL, Santander, Cantabria, Spain*
[am] *The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK*
[an] *Houston Methodist Cancer Center, Houston, TX, USA*
[ao] *Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA*
[ap] *Department of Surgery, University of Port Harcourt Teaching Hospital, Alakahia, Port Harcourt, Nigeria*
[aq] *University of California Davis School of Medicine, Sacramento, CA, USA*
[ar] *IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*

[as] University of California, San Francisco, San Francisco, CA, USA
[at] Department of Radiation-Oncology, Ghent University Hospital, Ghent, Belgium
[au] Department of Urology, Ospedale Regionale di Lugano, Civico USI – Università della Svizzera Italiana, Lugano, Switzerland
[av] Department of Surgery, Prostate Cancer Research Program, Department of Anatomy & Developmental Biology, Faculty Nursing, Medicine & Health Sciences, Monash University, Melbourne, Australia
[aw] Departments of Medicine and Surgery, Duke Cancer Institute, Duke University, Durham, NC, USA
[ax] Urological Sciences, Vancouver Prostate Centre, University of British Columbia, Vancouver, Canada
[ay] Department of Medical Oncology, Institut Paoli Calmettes, Aix-Marseille Université, Marseille, France
[az] Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA
[ba] Department of Oncology and Radiotherapy, Innlandet Hospital Trust, Gjøvik, Norway
[bb] Department of Nuclear Medicine, University of Duisburg-Essen and German Cancer Consortium (DKTK)-University Hospital Essen, Essen, Germany
[bc] University of British Columbia, Vancouver, British Columbia, Canada
[bd] Prostate Cancer Theranostics and Imaging Centre of Excellence, Department of Molecular Imaging and Therapeutic Nuclear Medicine, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia
[be] Chris O'Brien Lifehouse, Camperdown, NSW, Australia
[bf] Garvan Institute of Medical Research, Darlinghurst, Sydney, NSW, Australia
[bg] The University of Sydney, Sydney, NSW, Australia
[bh] Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA
[bi] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[bj] Department of Radiotherapy, European Institute of Oncology (IEO) IRCCS, Milan, Italy
[bk] School of Cancer Sciences, University of Glasgow, United Kingdom
[bl] Division of Medical Oncology, National Cancer Centre, Singapore
[bm] Faculty of Medicine and Health Technology, Tampere University and Tampere Cancer Center, Tampere, Finland
[bn] Research, Development and Innovation Center, Tampere University Hospital, Tampere, Finland
[bo] Division of Urology and the Naef K. Basile Cancer Institute (NKBCI), American University of Beirut Medical Center, Beirut, Lebanon
[bp] Division of Urology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
[bq] Department of Urology, Medical University of Vienna, Vienna, Austria
[br] Oncology Institute, Shamir Medical Center, Be'er Ya'akov, Israel
[bs] Faculty of Medicine, Tel-Aviv University, Israel
[bt] University of Athens Alexandra Hospital, Athens, Greece
[bu] Department of Radiation Oncology, University of Miami Sylvester Cancer Center, Miami, FL, USA
[bv] Beneficiência Portuguesa de São Paulo, São Paulo, SP, Brasil
[bw] Departamento de Oncologia, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
[bx] Department of Medical Oncology and Prostate Cancer Translational Research Group. Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron University Hospital, Barcelona, Spain
[by] Faculty of Education, Health and Wellbeing, Walsall Campus, Walsall, UK
[bz] Department of Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[cb] Department of Urology, University Hospital Schleswig-Holstein, Luebeck, Germany
[cc] Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[cd] National Institute of Oncology, Mohamed V University, Rabat, Morocco
[ce] Clemenceau Medical Center Dubai, United Arab Emirates, Faculty of Medicine, American University of Beirut, Lebanon
[cf] Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia
[cg] Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Australia
[ch] Tata Memorial Centre, Mumbai, India
[ci] Department of Radiation Oncology, Brigham and Women's Hospital and Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
[cj] Chief, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, The Tisch Cancer Institute, New York, NY, USA
[ck] Department of Human Structure and Repair, Ghent University, Ghent, Belgium
[cl] Department of Radiation Oncology, Iridium Netwerk, Antwerp, Belgium, Ghent University, Ghent, Belgium
[cm] Patrick G. Johnston Centre for Cancer Research, Queen's University Belfast, Northern Ireland Cancer Centre, Belfast City Hospital, Belfast, Northern Ireland
[cn] Mount Vernon Cancer Centre and Institute of Cancer Research, London, UK
[co] Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[cp] Comprehensive Oncology Centre, Hong Kong Sanatorium & Hospital, Hong Kong
[cq] The Chinese University of Hong Kong, Shatin, Hong Kong
[cr] Department of Laboratory Medicine and Pathology, University of Washington, Seattle, USA
[cs] Cancer Research Chair and Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[ct] Department of Urology, KFSHRC Riyadh, Saudi Arabia
[cu] Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[cv] University of California Los Angeles, Los Angeles, CA, USA
[cw] Bern Center for Precision Medicine and Department for Biomedical Research, Bern, Switzerland
[cx] Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA
[cy] Centre Hospitalier de Université de Montréal, Montreal, Canada
[cz] Instituto Alexander Fleming, Buenos Aires, Argentina

[dc] Tulane Cancer Center, New Orleans, LA, USA
[dd] Department of Medicine, Weill Cornell Medical College, New York, NY, USA
[de] Department of Hematology and Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA
[df] Department of Cancer Biology, GU Malignancies Research Center, Cleveland Clinic Lerner Research Institute, Cleveland, OH, USA
[dg] Rafal Masztak Grochowski Hospital, Maria Sklodowska Curie National Research Institute of Oncology, Warsaw, Poland
[dh] Prostate Cancer Foundation, Santa Monica, CA, USA
[di] University Hospitals Seidman Cancer Center, Cleveland, OH, USA
[dj] Division of Medical Oncology, Stanford University Medical Center, Stanford, CA, USA
[dk] Englander Institute for Precision Medicine, Weill Cornell Medicine, Division of Hematology and Oncology, Meyer Cancer Center, New York Presbyterian Hospital, New York, NY, USA
[dl] Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[dm] Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[dn] Toho University Sakura Medical Center, Chiba, Japan
[do] MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London, UK
[dp] Department of Medical Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[dq] Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[dr] Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany
[ds] Department of Urology, Koc University Hospital, Istanbul, Turkey
[dt] Department of Urology, M.A. Aydınlar Acıbadem University, Altunizade Hospital, Istanbul, Turkey
[du] Yokohama City University Medical Center, Yokohama, Japan
[dv] Department of Urology, Kindai University Faculty of Medicine, Osaka, Japan
[dw] Department of Medical Oncology, Ankara University School of Medicine, Ankara, Turkey
[dx] Ankara University Cancer Research Institute, Ankara, Turkey
[dy] University College London, MRC Clinical Trials Unit at UCL, London, UK
[dz] Department of Urology, Radboud University Medical Center, Nijmegen, the Netherlands
[ed] Department of Radiation Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA
[ee] Department of Urology, Institut Paoli-Calmettes Cancer Centre, Marseille, France
[ef] Department of Radiation Oncology & Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, FL, USA
[eg] Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, China
[eh] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
[ei] Department of Medicine, Division of Oncology, University of Washington and Fred Hutchinson Cancer Center, G4–830, Seattle, WA, USA
[ej] Department of Radiation Oncology, Hospital Universitario de La Princesa, Health Research Institute, Madrid, Spain
[ek] Radiation Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland
[el] Faculty of Medicine, University of Geneva, Geneva, Switzerland
[em] Onkozentrum Zurich, University of Zurich and Tumorzentrum Hirslanden Zurich, Switzerland

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Castration-resistant prostate cancer (mCRPC) and oligometastatic and oligoprogressive prostate cancer;
Hormonal treatment;
Systemic therapy;
Chemotherapy;
Androgen receptor

Abstract ***Background:*** Innovations in imaging and molecular characterisation together with novel treatment options have improved outcomes in advanced prostate cancer. However, we still lack high-level evidence in many areas relevant to making management decisions in daily clinical practise. The 2022 Advanced Prostate Cancer Consensus Conference (APCCC 2022) addressed some questions in these areas to supplement guidelines that mostly are based on level 1 evidence.

Objective: To present the voting results of the APCCC 2022.

Design, setting, and participants: The experts voted on controversial questions where high-level evidence is mostly lacking: locally advanced prostate cancer; biochemical recurrence after local treatment; metastatic hormone-sensitive, non-metastatic, and metastatic castration-resistant prostate cancer; oligometastatic prostate cancer; and managing side effects of hormonal therapy. A panel of 105 international prostate cancer experts voted on the consensus questions.

Outcome measurements and statistical analysis: The panel voted on 198 pre-defined questions, which were developed by 117 voting and non-voting panel members prior to the conference following a modified Delphi process. A total of 116 questions on metastatic and/or castration-resistant prostate cancer are discussed in this manuscript. In 2022, the voting was done by a web-based survey because of COVID-19 restrictions.

pathway inhibitors (ARPI);
Next-generation imaging;
PSMA PET-imaging;
Treatment monitoring

Results and limitations: The voting reflects the expert opinion of these 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 are reported in the supplementary material. We report here on topics in metastatic, hormone-sensitive prostate cancer (mHSPC), non-metastatic, castration-resistant prostate cancer (nmCRPC), castration-resistant prostate cancer (mCRPC), and oligometastatic and oligoprogressive prostate cancer.

Conclusions: These voting results in four specific areas from a panel of experts in advanced prostate cancer can help clinicians and patients navigate controversial areas of management for which high-level evidence is scant or conflicting and can help research funders and policy makers identify information gaps and consider what areas to explore further. However, diagnostic and treatment decisions always have to be individualised based on patient characteristics, including the extent and location of disease, prior treatment(s), co-morbidities, patient preferences, and treatment recommendations and should also incorporate current and emerging clinical evidence and logistic and economic factors. Enrolment in clinical trials is strongly encouraged. Importantly, APCCC 2022 once again identified important gaps where there is non-consensus and that merit evaluation in specifically designed trials.

Patient summary: The Advanced Prostate Cancer Consensus Conference (APCCC) provides a forum to discuss and debate current diagnostic and treatment options for patients with advanced prostate cancer. The conference aims to share the knowledge of international experts in prostate cancer with healthcare providers worldwide. At each APCCC, an expert panel votes on pre-defined questions that target the most clinically relevant areas of advanced prostate cancer treatment for which there are gaps in knowledge. The results of the voting provide a practical guide to help clinicians discuss therapeutic options with patients and their relatives as part of shared and multidisciplinary decision-making. This report focuses on the advanced setting, covering metastatic hormone-sensitive prostate cancer and both non-metastatic and metastatic castration-resistant prostate cancer.

Twitter summary: Report of the results of APCCC 2022 for the following topics: mHSPC, nmCRPC, mCRPC, and oligometastatic prostate cancer.

Take-home message: At APCCC 2022, clinically important questions in the management of advanced prostate cancer management were identified and discussed, and experts voted on pre-defined consensus questions. The report of the results for metastatic and/or castration-resistant prostate cancer is summarised here.

1. Introduction

The multidisciplinary panel for the 2022 Advanced Prostate Cancer Consensus Conference (APCCC 2022) consisted of 117 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.

Seven controversial areas related to the management of patients with advanced prostate cancer were prioritised for discussion in 2022:

1. Intermediate- and high-risk and locally advanced prostate cancer.
2. Prostate-specific antigen (PSA) persistence and biochemical recurrence after definitive treatment.
3. Management of side effects caused by hormonal therapy.
4. Management of newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC).
5. Management of non-metastatic castration-resistant prostate cancer (nmCRPC).
6. Management of metastatic CRPC.
7. Oligometastatic and oligoprogressive prostate cancer.

Topics 1–3 have been discussed and published separately [1].

The conference and the consensus development process followed procedures that have been used and described previously [2–4]. Using a modified Delphi process, panel members prepared 198 questions, of which 116 are discussed in this manuscript. The other questions focusing on earlier disease states will be published in European Urology. Similar to 2021, the panellists voted via a web-based survey rather than in person because of COVID-19 restrictions. 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 for prostate cancer was defined as PET-CT/MRI (subsequently referred to in this paper as PET/CT, unless stated otherwise) with prostate-specific membrane antigen (PSMA), choline,

or fluciclovine tracers and/or whole-body morphologic and diffusion-weighted MRI.

The results of the voting are intended to serve as a guide to help clinicians and patients participate in shared and multidisciplinary decision-making. For each of the three sections, an accompanying table (Tables 1–8) summarises questions for which consensus was reached. For additional definitions used during APCCC 2022, refer to supplement S1.

The panel consisted of 105 voting members and 12 non-voting members. Both voting and non-voting members helped define the questions. In all, 50% of voting members were medical oncologists, 29% were urologists, and 21% were clinical and radiation oncologists. A total of 43% practiced in Europe, 38% in North America, and 19% in other regions of the world. Non-voting members were experts in areas such as nuclear medicine, radiology, pathology, statistics, and health economics and are not directly involved in clinical decision-making. In addition, one non-voting 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 on 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

Table 1
APCCC 2022 questions concerning management of newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC).

Question	Answers	Voting results (%/N)
72. What is your general treatment recommendation for the majority of patients with mHSPC?	**1) Combination therapy (ADT plus additional systemic therapy and/or local radiotherapy)**	**97% (101) strong consensus**
	2) ADT alone	3% (3)
	3) Abstain/unqualified to answer	1
73. What is your general treatment recommendation for the majority of patients with synchronous high-volume (on conventional imaging or unequivocal on NGI) mHSPC?	**1) Combination therapy (ADT plus additional systemic therapy)**	**96% (101) strong consensus**
	2) ADT alone	4% (4)
	3) Abstain/unqualified to answer	0
74. What is your general treatment recommendation for the majority of patients with synchronous low-volume (on conventional imaging or unequivocal on NGI) mHSPC?	**1) Combination therapy (ADT plus additional systemic therapy and/or local radiotherapy)**	**99% (103) strong consensus**
	2) ADT alone	1% (1)
	3) Abstain/unqualified to answer	1
75. What is your general treatment recommendation for the majority of patients with metachronous high-volume (on conventional imaging or unequivocal on NGI) mHSPC?	**1) Combination therapy (ADT plus additional systemic therapy)**	**93% (97) strong consensus**
	2) ADT alone	7% (7)
	3) Abstain/unqualified to answer	1
81. In the majority patients with synchronous low-volume mHSPC, where you have decided for triplet systemic therapy (ADT plus docetaxel plus AR pathway inhibitor) do you recommend radiation therapy of the primary tumour in addition?	**1) Yes**	**80% (45) consensus**
	2) No	20% (11)
	3) Abstain/unqualified to answer (including I do not use triplet systemic therapy)	Of note, a total of 49 panel members abstained
83. If you recommend triplet therapy (ADT plus docetaxel plus an AR pathway inhibitor) in patients with mHSPC, what is your preferred strategy?	1) Sequential administration (docetaxel completed first, as for TITAN, ARCHES)	18% (14)
	2) Concurrent administration (as for ARASENS, PEACE-1, ENZAMET)	**82% (62) consensus**
	3) Abstain/unqualified to answer (including I do not use triplet systemic therapy)	Of note, a total of 29 panel members abstained
88. In daily clinical practice and outside of clinical trials, do you perform (not only recommend) geriatric assessments by validated instruments (e.g. G8/miniCOG/CGA) in the majority of patients with mHSPC who are 75 years?	1) Yes	23% (23)
	2) No	**77% (76)**
	3) Abstain/unqualified to answer	6
99. Outside a clinical trial, would the information on tumour genomic profiling (primary tumour or biopsy of metastatic lesion) influence your decision for first-line treatment of mHSPC in the majority of patients if available without restrictions?	1) Yes	25% (25)
	2) No	**75% (76) consensus**
	3) Abstain/unqualified to answer	4
101. In the majority of patients with high-volume mHSPC and presence of ≥2 of the pathogenic alterations in RB1, TP53, and/or PTEN loss, what is your recommended systemic therapy?	1) ADT plus AR pathway inhibitor	15% (14)
	2) ADT plus docetaxel	10% (9)
	3) ADT plus AR pathway inhibitor plus docetaxel	**75% (68) consensus**
	Abstain/unqualified to answer	13
107. In the context of limited resources available for healthcare (country with limited resources or patients not fully covered by insurance), what do you recommend as ADT in the majority of patients with mHSPC?	1) LHRH agonist	24% (22)
	2) Orchiectomy	**76% (71) consensus**
	3) First generation AR antagonist (e.g. bicalutamide) as single agent	0% (0)
	4) Abstain/unqualified to answer	11

ADT, androgen deprivation therapy.

Table 2
APCCC 2022 questions concerning oligometastatic and oligoprogressive prostate cancer.

Question	Answers	Voting results (%/N)
169. If you voted for systemic therapy plus local treatment for the majority of patients with low-volume/oligometastatic synchronous mHSPC e.g. 1–3 bone lesions on next-generation imaging what is your treatment recommendation?	**1) ADT plus AR pathway inhibitor (Abi/Apa/Enza)**	**89% (85) consensus**
	2) ADT plus Docetaxel	2% (2)
	3) ADT plus Docetaxel plus an AR pathway inhibitor (Abi/Apa/Daro/Enza)	2% (2)
	4) ADT alone	7% (7)
	5) Abstain/unqualified to answer (including I don't recommend the combination of systemic plus local therapy in this situation)	8
170. If you voted for systemic therapy alone for the majority of patients with low-volume/oligometastatic synchronous mHSPC e.g. 1–3 bone lesions on next-generation imaging what is your treatment recommendation?	**1) ADT plus AR pathway inhibitor (Abi/Apa/Enza)**	**90% (27) strong consensus**
	2) ADT plus Docetaxel	0% (0)
	3) ADT plus Docetaxel plus an AR pathway inhibitor (Abi/Apa/Daro/Enza)	7% (2)
	4) ADT alone	3% (1)
	5) Abstain/unqualified to answer (including I don't recommend systemic therapy alone in this situation)	Of note, a total of 74 panel members abstained
171. For the majority of patients with low-volume/ oligometastatic synchronous mHSPC e.g. 1–3 bone lesions on next-generation imaging what is your treatment recommendation regarding the primary tumour?	**1) Radiation therapy**	**95% (97) strong consensus**
	2) Surgery	5% (5)
	3) Abstain/unqualified to answer	2
173. If you voted for MDT of the retroperitoneal lymph nodes what is your local treatment recommendation in the majority of patients?	**1) Radiation therapy**	**90% (57) strong consensus**
	2) Surgery	10% (6)
	3) Abstain/unqualified to answer (including I do not recommend MDT in this situation)	Of note, a total of 41 panel members abstained
174. If your recommend systemic therapy in patients with low-volume/oligometastatic synchronous mHSPC and retroperitoneal lymph nodes on PSMA PET what is your treatment recommendation?	**1) ADT plus AR pathway inhibitor (Abi/Apa/Enza)**	**92% (89) strong consensus**
	2) ADT plus Docetaxel	2% (2)
	3) ADT plus Docetaxel plus an AR pathway inhibitor (Abi/Apa/Daro/Enza)	1% (1)
	4) ADT alone	5% (5)
	5) Abstain/unqualified to answer (including I don't recommend systemic therapy in this situation)	7
176. If your recommend systemic therapy in the majority of patients with low-volume/oligometastatic metachronous mHSPC (e.g. 3 bone lesions on next-generation imaging) what is your treatment recommendation?	**1) ADT plus AR pathway inhibitor (Abi/Apa/Enza)**	**90% (79) strong consensus**
	2) ADT plus Docetaxel	1% (1)
	3) ADT plus Docetaxel plus an AR pathway inhibitor (Abi/Apa/Daro/Enza)	1% (1)
	4) ADT alone	8% (7)
	5) Abstain/unqualified to answer (including I don't recommend systemic therapy in this situation)	16

MDT, metastases-directed therapy.

number of panellists who voted on a particular question, excluding those who voted 'abstain.'

Supplement S1 shows detailed voting results for each question. The level of consensus was defined as follows: Answer options with ≥75% agreement were considered consensus, and answer options with ≥90% agreement were considered strong consensus based on the prior APCCC publications [2–4].

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

Table 3
APCCC 2022 questions concerning management of non-metastatic castration-resistant prostate cancer (nmCRPC).

Question	Answers	Voting results (%/N)
120. If you treat a patient with an AR pathway inhibitor (Apa, Daro, Enza) for nmCRPC (M0 CRPC), when do you recommend changing treatment (excluding treatment changes for toxicity)?	1) PSA rise (as per PCWG3 criteria) alone	17% (17)
	2) Occurrence of metastases and/or symptomatic progression	**83% (82) consensus**
	3) Abstain/unqualified to answer (including I do not give these treatments in this situation)	5

PSA, prostate-specific antigen.

Table 4
PARP inhibition plus androgen receptor pathway inhibitor (ARPI) in castration-resistant prostate cancer (mCRPC).

mCRPC patients about to start first-line ARPI	Recommend combination with PARP inhibitor	Do not recommend combination with PARP inhibitor	Comment
With known pathogenic BRCA1/2 alteration	52%	48%	No consensus
With known pathogenic DNA repair gene alteration (NOT BRCA1/2)	22%	**78%**	**Consensus** against combination with PARP inhibitor
No known DNA repair gene alteration	3%	**97%**	**Strong consensus** against combination with PARP inhibitor

2. Metastatic, hormone-sensitive prostate cancer (mHSPC)

2.1. General treatment considerations

The management of mHSPC was previously discussed in depth at APCCC 2021 [4], but the results of the ARASENS trial were subsequently presented and published [5]. Interestingly, studies of practice patterns presented at large conferences suggest that a relevant proportion of patients with mHSPC are still treated with androgen deprivation therapy (ADT) alone or with ADT plus bicalutamide [6]. The APCCC 2022 panel therefore voted on four very general questions related to the management of patients with mHSPC:

Q72. As a general treatment recommendation for patients with mHSPC, 97% of panellists voted for combination therapy (ADT plus additional systemic therapy and/or local radiotherapy) and 3% voted for ADT alone. There was one abstention. (Strong consensus for combination therapy)

Q73. As a general treatment recommendation for patients with synchronous high-volume (on conventional imaging or unequivocal on next-generation imaging) mHSPC, 96% of panellists voted for combination therapy (ADT plus additional systemic therapy) and 4% voted for ADT alone. There were no abstentions. (Strong consensus for combination therapy)

Q74. As a general treatment recommendation for patients with synchronous low-volume (on conventional imaging or unequivocal on next-generation imaging) mHSPC, 99% of panellists voted for combination therapy (ADT plus additional systemic therapy and/or local radiotherapy) and 1% voted for ADT alone. There was one abstention. (Strong consensus for combination therapy)

Q75. As a general treatment recommendation for patients with metachronous high-volume (on conventional imaging or unequivocal on next-generation imaging) mHSPC, 93% of

Table 5
First-line castration-resistant prostate cancer (mCRPC) treatment options in patients without evidence of DDR gene alterations depending on prior metastatic, hormone-sensitive prostate cancer (mHSPC) therapy.

Clinical setting	Highest % vote	Second highest % vote	Other options	Comment
mCRPC, no DDR gene alteration, ADT only for mHSPC	93% ARPI	4% Docetaxel	3% ARPI + PARP	Consensus for ARPI
mCRPC, no DDR gene alteration, ADT only for mHSPC, progression to CRPC in ≤6 months	54% chemotherapy (taxane or platinum)	43% ARPI	3% ARPI + PARP	No consensus
mCRPC, no DDR gene alteration, ADT + ARPI for mHSPC	83% docetaxel	9% alternate ARPI	4% alternate ARPI plus PARP 4% radium-223	Consensus for docetaxel
mCRPC, no DDR gene alteration, ADT + ARPI for mHSPC, progression to CRPC in ≤6 months	95% chemotherapy (taxane or platinum)	3% alternate ARPI	1% alternate ARPI plus PARP 1% radium-223	Consensus for chemotherapy
mCRPC, no DDR gene alteration, ADT + docetaxel for mHSPC	93% ARPI	5% alternate ARPI	2% taxane chemotherapy	Consensus for ARPI
mCRPC, no DDR gene alteration, ADT + docetaxel for mHSPC, progression to CRPC in ≤6 months	75% ARPI	19% chemotherapy (cabazitaxel or platinum-based)	5% alternate ARPI plus PARP 1% radium-223	Consensus for ARPI
mCRPC, no DDR gene alteration, ADT + docetaxel + ARPI for mHSPC	56% ^{177}Lutetium-PSMA	27% taxane	9% radium-223 5% alternate ARPI 3% alternate ARPI plus PARP	No consensus
mCRPC, no DDR gene alteration, ADT + docetaxel + ARPI for mHSPC, progression to CRPC in ≤6 months	51% ^{177}Lutetium-PSMA	47% chemotherapy (cabazitaxel or platinum-based)	1% alternate ARPI 1% radium-223	No consensus

ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor.

Table 6
APCCC 2022 questions concerning management of metastatic CRPC.

Question	Answers	Voting results (%/N)
139. In the majority of patients with symptomatic mCRPC meeting criteria for both treatment with Radium-223 and 177Lu-PSMA, which treatment do you recommend?	1) Radium-223	21% (20)
	2) 177Lu-PSMA	**79% (76) consensus**
	3) Abstain/unqualified to answer	8
141. Do you recommend docetaxel re-challenge anytime in the treatment sequence in the majority of patients who have received docetaxel in the mHSPC setting and progress to mCRPC within 12 months?	1) Yes	14% (13)
	2) No	**86% (79) consensus**
	3) Abstain/unqualified to answer	12
142. Do you recommend docetaxel re-challenge anytime in the treatment sequence in the majority of patients who have received docetaxel in the mHSPC setting and progress to mCRPC > 36 months?	**1) Yes**	**76% (70) consensus**
	2) No	24% (22)
	3) Abstain/unqualified to answer	12
143. Do you recommend a direct switch to another AR pathway inhibitor therapy (Abi/Apa/Daro/Enza) in the majority of patients who have received one line of AR pathway inhibitor (Abi/Apa/Daro/Enza) and then progressed?	1) Yes	15% (15)
	2) No	**85% (82) consensus**
	3) Abstain/unqualified to answer	7
	5) Abstain/unqualified to answer	8
	5) Abstain/unqualified to answer	8
152. In the majority of patients with a pathogenic BRCA1/2 alteration (germline and/or somatic) who have received ADT and an AR pathway inhibitor, what is your next systemic treatment recommendation?	1) Alternate AR pathway inhibitor	0% (0)
	2) Alternate AR pathway inhibitor plus PARP inhibitor	12% (11)
	3) PARP inhibitor	**75% (71) consensus**
	4) Docetaxel	13% (12)
	5) Radium-223 (if relevant treatment criteria are met)	0% (0)
	6) Abstain/unqualified to answer	10
153. In the majority of patients with a pathogenic BRCA1/2 alteration (germline and/or somatic) who have received ADT, docetaxel and an AR pathway inhibitor, what is your next systemic treatment recommendation?	1) Alternate AR pathway inhibitor	0% (0)
	2) Alternate AR pathway inhibitor plus PARP inhibitor	11% (10)
	3) PARP inhibitor	**82% (77) consensus**
	4) Cabazitaxel	4% (4)
	5) Radium-223 (if relevant treatment criteria are met)	0% (0)
	6) 177Lutetium-PSMA	3% (3)
	7) Abstain/unqualified to answer	10
156. In the majority of patients with dMMR/MSI-high do you recommend treatment with an immune checkpoint inhibitor in the course of the disease?	**1) Yes**	**96% (82) strong consensus**
	2) No	4% (3)
	3) Abstain/unqualified to answer	19
157. In the majority of patients with high tumour mutational burden (TMB ≥ 10 mutations/megabase) do you recommend treatment with an immune checkpoint inhibitor in the course of the disease?	**1) Yes**	**79% (66) consensus**
	2) No	21% (18)
	3) Abstain/unqualified to answer	20
158. If the approval does not require a PSMA PET for selection of treatment with 177Lu-PSMA therapy do you still recommend a baseline PSMA PET in the majority of patients?	**1) Yes**	**92% (87) strong consensus**
	2) No	8% (8)
	3) Abstain/unqualified to answer	9
164. For the majority of patients with mCRPC on taxane chemotherapy what ongoing monitoring by imaging do you recommend (if they do not develop new symptoms)?	1) No imaging until PSA progression	20% (19)
	2) Regular imaging regardless of PSA	**80% (78) consensus**
	3) Abstain/unqualified to answer	7

ADT, androgen deprivation therapy; TMB, tumour mutational burden; PSA, prostate-specific antigen (PSA).

Table 7
Definition of 'unfit' for docetaxel.

	As sole factor	In combination with other factors	No	Comment
Severe liver impairment	**92%**	**7%**	**1%**	**Strong consensus**
PS 3 (ECOG)	**81%**	**18%**	**1%**	**Consensus**
Sensory neuropathy grade ≥2	**74%**	**20%**	**6%**	**Close to consensus as sole factor**
Platelets < 50 G/l and /or neutrophils < 1.0 G/l	**73%**	**16%**	**11%**	**Close to consensus as sole factor**
Frailty	**40%**	**60%**	**0%**	**No consensus (40% as sole factor, 60% in combination)**
Moderate liver impairment	**36%**	**45%**	**19%**	**No consensus (36% as sole factor, 45% in combination)**
PS 2 (ECOG)	**12%**	**83%**	**5%**	**No consensus (12% as sole factor, 83% in combination)**

Table 8
Definition of poor prognosis prostate cancer.

	Yes, this factor alone is sufficient for this definition	This factor in combination with other unfavourable factors	No	Comment
Lack of expression of both AR activity (AR and/or PSA) and neuroendocrine markers on biopsy (double negative prostate cancer)	**71%**	**26%**	**3%**	No consensus, but a combined 97% voted for this factor at least in combination with other unfavourable factors
Partially neuro-endocrine differentiation with high proliferation index on tumour biopsy and/or low or absent AR expression	**69%**	**30%**	**1%**	No consensus, but a combined 99% voted for this factor at least in combination with other unfavourable factors
Rapid unequivocal progression (clinical and/or on imaging) that does not correlate with PSA kinetics	**69%**	**29%**	**2%**	No consensus, but a combined 98% voted for this factor at least in combination with other unfavourable factors
Multiple liver metastases	**67%**	**29%**	**4%**	No consensus, but a combined 96% voted for this factor at least in combination with other unfavourable factors
Short response (≤6 months) to ADT plus ARPI and/or docetaxel in mHSPC	**64%**	**32%**	**4%**	No consensus, but a combined 96% voted for this factor at least in combination with other unfavourable factors
Exclusively visceral metastases (excluding lung)	**63%**	**32%**	**5%**	No consensus, but a combined 95% voted for this factor at least in combination with other unfavourable factors
Low PSA (≤10 ng/mL) at initial presentation (before ADT) or at the time of symptomatic progression of castration-resistant disease plus high volume (≥20) bone metastases	**52%**	**42%**	**6%**	No consensus, but a combined 94% voted for this factor at least in combination with other unfavourable factors
Evidence of pathogenic alterations: any combination of two of the following genes: RB1, TP53, PTEN	**40%**	**52%**	**8%**	No consensus, but a combined 92% voted for this factor at least in combination with other unfavourable factors
Low PSA level relative to tumour burden	**32%**	**64%**	**4%**	No consensus, but a combined 96% voted for this factor at least in combination with other unfavourable factors
Lytic bone metastases	**23%**	**72%**	**5%**	No consensus, but a combined 95% voted for this factor at least in combination with other unfavourable factors
Bulky lymphadenopathy (≥5 cm) or bulky high-grade mass(es) (≥5 cm, Gleason ≥8) in the prostate or pelvis	**18%**	**60%**	**22%**	No consensus, but a combined 78% voted for this factor at least in combination with other unfavourable factors
Serum CEA and/or LDH twice the upper limit of normal	**15%**	**61%**	**24%**	No consensus, but a combined 76% voted for this factor at least in combination with other unfavourable factors

PSA, prostate-specific antigen; ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; mHSPC, metastatic, hormone-sensitive prostate cancer.

panellists voted for treatment with combination therapy (ADT plus additional systemic therapy) and 7% voted for ADT alone. There was one abstention. (Strong consensus for combination therapy)

2.2. Management of synchronous and metachronous mHSPC

Since APCCC 2021, primary results from the ARASENS and the PEACE-1 trials have been published, and therefore, some questions that were previously discussed in 2021 were discussed again [5,7]. In particular, panellists at APCCC 2022 discussed the question of triplet therapy given that there is now evidence from two large phase III trials (PEACE-1: only synchronous (*de novo*) mHSPC, and ARASENS: mostly synchronous but also a minority of patients with metachronous (=recurrent) mHSPC) showing an overall survival (OS) benefit for triplet therapy with ADT plus docetaxel plus abiraterone or darolutamide as compared with ADT plus docetaxel [5,7]. Only the ARASENS trial was designed such that docetaxel therapy was planned for all patients [5]. Scientifically, the question of the added value of docetaxel in combination with ADT and an androgen receptor pathway inhibitor (ARPI) remains unexamined. APCCC 2022 included specific questions to address the question of fitness for docetaxel, as well as the management of patients who are not fit to receive docetaxel.

Q76. For patients with synchronous mHSPC who are chemotherapy fit, 70% of panellists voted to recommend triplet therapy with ADT plus docetaxel plus an ARPI only if patients have high-volume disease, 26% voted that they do not usually recommend this triplet combination, and 4% voted that they recommend it in the majority of patients, independent of disease volume. There were four abstentions. (No consensus for any given answer option)

Q77. For patients with metachronous mHSPC who are chemotherapy fit, 58% of panellists voted to recommend triplet therapy with ADT plus docetaxel plus an ARPI only for patients with high-volume disease, 37% voted that they do not usually recommend this triplet combination, and 5% voted that they recommend this triplet combination in the majority of patients in this setting, independent of disease volume. There were five abstentions. (No consensus for any given answer option)

Q78. When asked about their preferred systemic treatment in addition to ADT for patients with synchronous high-volume mHSPC (on conventional imaging or unequivocal on next-generation imaging, with corresponding sclerotic lesions on CT if the patient was evaluated with PSMA PET), 61% of panellists voted for docetaxel plus an ARPI, 33% voted for an ARPI as sole additional therapy, and 6% voted for docetaxel as sole additional therapy. There were five abstentions. (No consensus for any given answer option)

With the increasing use of PSMA PET for staging and re-staging, the APCCC 2022 panel addressed the question of how to manage patients presenting with mHSPC that is low-volume on conventional imaging but high-volume on next-generating imaging. It is important to recognise that none of the trials of mHSPC in which patients were treated with docetaxel, ARPI or the combination have used next-generation imaging. Thus, the available evidence is based on the presence and number of metastases on conventional imaging.

Q79. Regarding the recommended treatment strategy for patients whose mHSPC is low volume on conventional imaging but high volume on next-generation imaging, 53% of panellists voted to treat as per low volume and 47% voted to treat as per high volume. There were three abstentions. (No consensus for any given answer option)

The management of patients with synchronous low-volume mHSPC is challenging because of the number of available treatment options (ADT, additional systemic therapy, local treatment of the primary tumour, metastases-directed therapy (MDT). In the PEACE-1 trial, about 35% of patients who received docetaxel had low-volume synchronous mHSPC [7]. In the ARASENS trial, data on disease volume had not yet been reported as of this writing [7]. At APCCC 2022, panellists addressed the question of in which patients to recommend systemic triplet therapy in low-volume synchronous mHSPC, and whether to also recommend radiation therapy of the primary tumour. This was one of the regimens in the 2×2 randomised PEACE-1 trial, but results on radiation therapy were pending at the time of APCCC 2022.

Q80. For patients with synchronous low-volume mHSPC on conventional imaging, 68% of panellists voted not to recommend triplet systemic therapy with ADT plus docetaxel plus an ARPI, irrespective of a decision about local radiation therapy; 30% voted to recommend the triplet combination only in patients with low-volume mHSPC who have 'borderline' high-risk features (e.g. at least one of the following: Gleason score 8–10, 3–4 bone metastases, extensive lymph node involvement, or disease that cannot be covered by SBRT); and 2% voted to recommend the triplet combination in the majority of patients. There were four abstentions. (No consensus for any given answer option)

Q81. When recommending triplet therapy with ADT plus docetaxel plus an ARPI for patients with synchronous low-volume mHSPC, 80% of panellists voted to also add radiation therapy of the primary tumour and 20% voted against adding local radiation therapy. There were 49 abstentions (including panellists who voted that they do not use systemic triplet therapy in this setting). (Consensus to add radiation therapy of the primary tumour among the panellists voting for triplet therapy)

When voting on questions, the APCCC panel assumes that all treatment options are available without restrictions. Triplet systemic therapy is a hot topic at the moment, but there has been no direct head-to-head comparison between different ARPIs combined with

ADT versus the combination of ADT plus an ARPI and docetaxel. Also, there has been no direct comparison between concomitant versus sequential ARPI therapy. By far the strongest evidence has been generated for concomitant administration (ENZAMET, PEACE-1, ARASENS) [4,6,7], but there are also some data on small subgroups of patients who received an ARPI after completing six cycles of docetaxel (ARCHES, TITAN) [9,10]. Data from PEACE-1 and ARASENS have generated level 1 evidence for the safety of the combination of abiraterone or darolutamide with docetaxel [5,7].

Q82. When recommending triplet therapy with ADT and docetaxel plus an ARPI for patients with synchronous mHSPC, 49% of panellists voted for abiraterone, 46% voted for darolutamide, and 5% voted for apalutamide. There were 31 abstentions (including panellists who voted that they do not use systemic triplet therapy in this setting). (No consensus for any given answer option, no one voted for enzalutamide)

Q83. When recommending triplet therapy with ADT and docetaxel plus an ARPI for patients with mHSPC, 82% of panellists voted in favour of concurrent administration (as in the ARASENS, PEACE-1, and ENZAMET trials)

and 18% voted for sequential administration (with docetaxel completed first, as in the TITAN and ARCHES trials). There were 29 abstentions (including panellists who voted that they do not use systemic triplet therapy in this setting). (Consensus for concurrent administration among the panellists voting for triplet therapy)

For patients with mHSPC, the role of docetaxel as a sole additional therapy in combination with ADT was established by three trials, each of which completed recruitment to the docetaxel question before data on ARPIs were available (GETUG-15, CHAARTED, STAMPEDE) [11–13]. Subsequent evidence showed that adding an ARPI to ADT was of clinical benefit and had a favourable safety profile. In addition, as mentioned previously, the phase 3 PEACE-1 and ARASENS trials have shown the benefit of adding an ARPI to ADT and docetaxel [5,7]. The APCCC 2022 panel addressed the question of whether to add docetaxel alone to ADT in mHSPC.

Q84. For patients with low-volume mHSPC, 74% of panellists voted that they do not recommend adding docetaxel alone to ADT (assuming that ARPIs are available), 24% voted that they recommend it for a minority of selected patients, and 2% voted that they recommend it for the majority of patients. There were two abstentions. (No consensus for any given answer option)

Q85. For patients with high-volume mHSPC, 49% of panellists voted against adding docetaxel alone to ADT (assuming that ARPIs are available), 40% voted for it for a minority of selected patients, and 11% voted for it for the majority of patients. There were three abstentions. (No consensus for any given answer option)

2.3. Metastatic hormone-sensitive prostate cancer: management of frail patients

The International Society for Geriatric Oncology (SIOG) recommends that patients with prostate cancer who are older than 75 years receive a health status assessment [14]. This practice is also supported by the EAU guidelines, although these guidelines generally recommend a health status assessment from the age of 70 onward and incorporating individual life expectancy, health status, and co-morbidity/ies into prostate cancer management [15]. Generally, age alone should not drive management decisions. At previous APCCC conferences, panellists voted on whether to perform health status assessments in patients with advanced prostate cancer. At APCCC 2022, panellists voted on whether to perform assessments specifically in patients with mHSPC, given the wealth of treatment options that are now available for these patients.

Q86. For patients with mHSPC who are ≥75 years old, 56% of panellists voted to recommend geriatric assessment (assuming it is readily available) before selecting treatment only if red flag issues are raised during consultation (e.g. frailty, cognitive issues, heart disease, or a significant other co-morbidity); 25% voted to recommend a geriatric assessment in the majority of patients; and 19% voted against a geriatric assessment in this setting. There were three abstentions. (No consensus for any given answer option, a combined 81% voted for a health status assessment at least in selected patients)

Q87. Among the panellists who voted for a geriatric assessment in Q86, 70% voted to perform a Geriatric 8 (G8)/Mini-COG/Comprehensive Geriatric Assessment (CGA), or a similar evaluation, in addition to a clinical assessment, while 30% voted to perform a clinical assessment only. There were 26 abstentions (including panellists who did not vote for geriatric assessment). (No consensus for any given answer option)

Q88. Panellists were asked whether, for patients with mHSPC aged ≥75 years seen in daily clinical practice outside the setting of clinical trials, they not only recommend but also perform geriatric assessments by using validated instruments (e.g. G8/Mini-COG/CGA). In all, 77% voted 'no,' and 23% voted 'yes.' There were six abstentions.

The APCCC panel voted on treatment recommendations for patients with mHSPC aged 75 years and older who are frail, as defined, for example, by the updated international society of geriatric oncology (SIOG) guidelines: > 2 abnormal activities of daily living [ADLs] and/or > 10% weight loss and/or Cumulative Illness Rating Scale-Geriatric [CIRS-G] grade 3–4 [14]. Patients ≥75 years of age who are screened and found to be vulnerable (e.g. 1–2 ADLs, 5–10% weight loss, CIRS-G grade 1–2) are candidates for geriatric interventions, which may make it appropriate for them to receive standard prostate cancer treatment [14]. Questions 89–96 distinguish between asymptomatic and symptomatic disease because this may influence treatment

decisions, particularly in patients with low-volume mHSPC. Currently, there is no evidence for primary dose reduction of ARPI in patients with mHSPC, even if frailty is present. There also are currently no data to support the use of darolutamide in combination with ADT alone in patients with mHSPC.

Q89. For patients with low-volume mHSPC who are ≥75 years old, frail (e.g. >2 abnormal activities of daily living [ADLs], >10% weight loss, Cumulative Illness Rating Scale-Geriatric [CIRS-G] grade 3–4) and whose life expectancy is >12 months the panel voted on the addition of radiation therapy to the primary tumour: 40% of panellists voted to add radiation therapy of the primary tumour to ADT in the majority of patients, 46% voted to add it only after a clinical re-assessment performed 3–6 months after the start of ADT, and 14% voted against this combination. There were two abstentions. (No consensus for any given answer option, a combined 86% voted for radiation of the primary tumour at least in selected patients)

For questions 90–96, the panel voted on systemic therapy in frail patients with mHSPC.

Q90. For patients with asymptomatic high-volume mHSPC who are ≥75 years old, frail (e.g. >2 abnormal ADLs, >10% weight loss, CIRS-G grade 3–4) and whose life expectancy is >12 months, 57% of panellists voted to treat with ADT plus an ARPI, 27% voted for ADT alone, 15% voted for ADT plus an ARPI at a reduced dose, and 1% voted for watchful waiting (deferring ADT until onset of symptoms). There were four abstentions. (No consensus for any given answer option)

Q91. For patients with symptomatic high-volume mHSPC who are ≥75 years old, frail (e.g. >2 abnormal ADLs, >10% weight loss, CIRS-G grade 3–4) and whose life expectancy is >12 months, 70% of panellists voted to treat with ADT plus an ARPI, 17% voted for ADT alone, and 13% voted for ADT plus an ARPI at a reduced dose. There were five abstentions. (No consensus for any given answer option, a combined 83% voted for ADT plus ARPI at the regular or a reduced dose)

Q92. For patients with asymptomatic low-volume mHSPC who are ≥75 years old, frail (e.g. >2 abnormal ADLs, >10% weight loss, CIRS-G grade 3–4) and whose life expectancy is >12 months, 40% of panellists voted to treat with ADT plus an ARPI, 39% voted for ADT alone, 12% voted for ADT plus an ARPI at a reduced dose, 8% voted for watchful waiting (deferring ADT until onset of symptoms), and 1% voted for an ARPI alone. There were four abstentions. (No consensus for any given answer option)

Q93. For patients with symptomatic low-volume mHSPC who are ≥75 years old, frail (e.g. >2 abnormal ADLs, >10% weight loss, CIRS-G grade 3–4) and whose life expectancy is >12 months, 60% of panellists voted to treat with ADT plus an ARPI, 27% voted for ADT alone, 12% voted for ADT plus an ARPI at a reduced dose, and 1% voted for supportive care only. There were four abstentions. (No consensus for any given answer option)

Q94. Among the panellists who voted for an ARPI for the majority of frail patients (e.g. >2 abnormal ADLs, >10% weight loss, CIRS-G grade 3–4) with mHSPC whose life expectancy is >12 months, 41% of panellists voted for abiraterone, 35% voted for darolutamide, 20% voted for apalutamide, and 4% voted for enzalutamide. There were 26 abstentions (including panellists who did not vote for administering an ARPI in this setting). (No consensus for any given answer option)

Q95. For patients with severe comorbidities independent of their age (e.g. CIRS-G grade 3–4, severe renal impairment, history of major cardiovascular events) and symptomatic high-volume mHSPC, 39% of panellists voted to recommend treatment with ADT plus an ARPI as systemic therapy, 31% voted for ADT alone, 26% voted for ADT plus an ARPI at a reduced dose, 3% voted for supportive care only (no ADT), and 1% voted for an ARPI alone. There were eight abstentions. (No consensus for any given answer option)

Q96. For patients with severe comorbidities independent of their age (e.g. CIRS-G grade 3–4, severe renal impairment, history of major cardiovascular events) and symptomatic low-volume mHSPC, 53% of panellists voted to recommend treatment with ADT alone, 28% voted for ADT plus an ARPI, 18% voted for ADT plus an ARPI at a reduced dose, and 1% voted for an ARPI alone. There were nine abstentions. (No consensus for any given answer option)

For older patients with prostate cancer, EAU guidelines recommend performing an individual estimation of life expectancy prior to making treatment decisions [15]. However, available calculators are not very accurate for these patients. When recommending combination therapy for patients with mHSPC, the EAU guidelines recommend that life expectancy be ≥1 year assuming that patients are willing to accept the increased risk of side effects with combination regimens [15].

Q97. For patients with low-volume synchronous mHSPC, 51% of panellists voted to recommend combination systemic therapy if minimum life expectancy is >3 years, 29% voted for >1 year, and 20% voted that they do not base their recommendation on estimated life expectancy. There were four abstentions. (No consensus for any given answer option, but a combined 80% of the panel recommend using some form of life expectancy estimation)

Q98. For patients with high-volume synchronous mHSPC, 47% of panellists voted to recommend combination systemic therapy if minimum life expectancy is >1 year, 32% voted for >3 years, and 21% voted that they do not base their recommendation on estimated life expectancy. There were four abstentions. (No consensus for any given answer option, but a combined 79% of the panel recommend using some form of life expectancy estimation)

2.4. Metastatic hormone-sensitive prostate cancer: genomic profiling

Advances in tumour molecular characterisation and the identification of potentially actionable genetic alterations in patients with advanced prostate cancer have

increased the use of tumour genomic profiling. NCCN guidelines now recommend tumour genomic profiling for all patients with mHSPC or more advanced prostate cancer and include a recommendation to test for the following alterations: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2 and CDK12 [16]. Similar recommendations are included in the ESMO and EAU guidelines [15,17]. In addition, for patients with mCRPC, the NCCN guidelines now recommend testing for defective mismatch repair (dMMR) and microsatellite instability and evaluating for high tumour mutational burden (TMB-high). This recommendation is based on the tumour-agnostic approval of pembrolizumab for treating patients with such alterations [16].

A current question in daily practice is whether tumour genomic profiling should influence treatment decisions in patients with mHSPC, given that there is no approved targeted therapy in this setting.

Q99. A total of 75% of panellists voted that their decision regarding the first-line treatment of the majority of patients with mHSPC would not be affected by the results of tumour genomic profiling (from a primary tumour, or a biopsy of a metastatic lesion) outside the setting of a clinical trial and assuming that genomic profiling was available without restrictions. The remaining 25% voted that tumour genomic profiling would influence their treatment decision in this setting. There were four abstentions. (Consensus that tumour genomic profiling results would not yet influence treatment choice)

Recent studies indicate that copy number loss or deleterious mutation(s) of one or more tumour suppressor genes (TP53, PTEN, and RB1) are associated with poor prognosis in mHSPC, while SPOP mutations appear to characterise a subset of patients with mHSPC that is more dependent on AR signalling, and germline inheritance of the adrenal-permissive *HSD3B1* confers clinical dependence on non-gonadal androgens [18–24].

A Prostate Cancer Foundation (PCF) workshop on HSPC has summarised available emerging biomarkers in this setting [25]. The authors concluded that a number of potential biomarkers should be prospectively assessed and validated for use in clinical practice. Although there was consensus tumour genomic profiling results do not alter treatment choice for most patients with mHSPC (see Q99), the panel voted on additional questions concerning how best to manage patients with mHSPC with specific genomic alterations.

Q100. For patients with low-volume mHSPC and ≥2 pathogenic alterations in RB1, TP53, and/or PTEN loss, 71% of panellists voted to recommend systemic therapy with ADT plus an ARPI, 16% voted for ADT plus docetaxel, and 13% voted for ADT plus an ARPI plus docetaxel. There were 14 abstentions. (No consensus for any given answer option)

Q101. For patients with high-volume mHSPC and ≥2 pathogenic alterations in RB1, TP53, and/or PTEN loss, 75% of panellists voted to recommend systemic therapy with ADT plus an ARPI plus docetaxel, 15% voted for ADT plus an ARPI, and 10% voted for ADT plus docetaxel. There were 13 abstentions. (Consensus for ADT plus an ARPI plus docetaxel, see also Q76)

Q102. For patients with high-volume mHSPC and a pathogenic germline BRCA1/2 alteration, 56% of panellists voted to recommend systemic therapy with ADT plus an ARPI plus docetaxel, 21% voted for ADT plus an ARPI, 20% voted for ADT an ARPI plus a PARP inhibitor, and 3% voted for ADT plus a PARP inhibitor. There were 12 abstentions. (No consensus for any given answer option, a combined 77% of the panel did not vote for a PARP inhibitor in this situation)

Q103. For patients with high-volume mHSPC and the presence of a pathogenic SPOP mutation, 50% of panellists voted to recommend systemic therapy with ADT plus an ARPI plus docetaxel, 47% voted for ADT plus an ARPI, and 3% voted for ADT plus docetaxel. There were 16 abstentions. (No consensus for any given answer option)

2.5. Metastatic hormone-sensitive prostate cancer: treatment monitoring

Current guidelines are vague about strategies for monitoring treatment response, but it is recommended that the plan for follow-up be individualised based on stage of disease, prior symptoms, prognostic factors, and treatment(s) given. Clinical trials in mHSPC have applied various treatment monitoring schedules, but required schedules for (protocol-mandated) imaging have generally been more intensive and frequent in industry-sponsored trials and somewhat less intensive and frequent in academic trials. More rigorous imaging schedules are mainly used in trials where radiographic progression-free survival (rPFS) is a primary or secondary endpoint.

There currently is insufficient evidence to support PSMA PET-based monitoring in lieu of conventional CT and bone scintigraphy. However, experience with the use of PSMA PET for monitoring is evolving and its use in this context is increasing. Clinical trials are increasingly incorporating PSMA PET as an imaging strategy, and thus the evidence base is likely to continue to evolve. A recent post-hoc analysis from the ARCHES trial reported frequent discordance between PCWG2-defined PSA progression and radiographic progression among patients receiving ADT plus enzalutamide [26].

Q104. Regarding ongoing monitoring by imaging for patients with mHSPC who are on systemic therapy (assuming they develop no new symptoms), 50% of panellists voted to perform imaging every 6–12 months regardless of PSA level, 30% voted to perform imaging at about 6–12 months and then not again until confirmed PSA progression, and 20% voted that imaging should not begin until PSA progression. There were four abstentions. (No consensus for any given answer option, but 80% voted for performing at least an imaging in the initial 6–12 months after commencing therapy)

Q105. When asked to select a preferred imaging modality for treatment monitoring in patients with mHSPC, 66% of panellists voted for conventional imaging, 30% voted for PET/CT with various tracers, and 4% voted for whole-body/diffusion-weight MRI. There were 12 abstentions. (No consensus for any given answer option)

Little is known about the efficacy of systemic treatments for epidural manifestations of prostate cancer. In the mHSPC setting, it seems not unreasonable to assume that systemic therapy, especially a combined approach, may be effective. In mCRPC, researchers recently reported results from the PROMPTS trial, in which patients with mCRPC and asymptomatic spinal cord metastasis were randomly assigned to observation only or to receive screening spinal MRI, with pre-emptive treatment (physician's choice of radiotherapy or surgical decompression) if radiographic spinal cord compression (SCC) was detected [27]. The primary endpoint was time to and incidence of confirmed clinical SCC. Rates of clinical SCC were low in both groups (6.7% in the control group and 4.3% in the intervention group), and the researchers concluded that screening and pre-emptive treatment are not generally warranted in patients with asymptomatic spinal metastasis, but that particular vigilance is merited for these patients, with a low threshold for recommending spinal MRI if patients develop new back pain.

Q106. For patients with mHSPC with asymptomatic epidural disease (not qualifying for spinal cord compression; not leptomeningeal), 34% of panellists voted to recommend standard systemic treatment plus treatment of the epidural disease with surgery and/or radiation therapy, while 66% of panellists voted for standard systemic treatment alone, with the addition of surgery and/or radiation to manage the epidural disease only if required. There were five abstentions. (No consensus for any given answer option)

2.6. Metastatic hormone-sensitive prostate cancer: treatment of mHSPC in the context of limited resources

Similar to APCCC 2017, panellists voted on appropriate treatment options in settings where healthcare resources are limited. While voting on these questions, the panel referred to the World Health Organisation (WHO) essential medicines list and/or to treatment options that can be sourced at an affordable price from a generic manufacturer.

*Q107. For the majority of patients with mHSPC treated in the context of limited healthcare resources (*i.e. *in a country with limited resources, or when patients are not fully covered by insurance), 76% of panellists voted to recommend ADT by means of orchiectomy, while 24% voted for LHRH agonist therapy. There were 11 abstentions. (Consensus for orchiectomy)*

*Q108. For the majority of patients with high-volume mHSPC treated in the context of limited healthcare resources (*i.e. *in a country with limited resources, or when patients are not fully covered by insurance), 51% of panellists voted for ADT plus docetaxel, 19% voted for ADT plus docetaxel plus abiraterone, 19% voted for ADT plus a reduced dose of abiraterone with food, and 11% voted for ADT plus abiraterone. There were 15 abstentions. (No consensus for any given answer option, no one voted for ADT alone)*

*Q109. For the majority of patients with low-volume mHSPC treated in the context of limited healthcare resources (*i.e. *in a country with limited resources, or when patients are not fully covered by insurance), 33% of panellists voted for ADT plus a reduced dose of abiraterone with food, 29% voted for ADT alone, 27% voted for ADT plus abiraterone, and 11% voted for ADT plus docetaxel. There were 15 abstentions. (No consensus for any given answer option)*

Among one of the best documented gaps in care globally is the lack of access to radiotherapy [28,29]. In mHSPC, radiation therapy of the primary tumour is associated with an improvement in OS at 3 years in patients with low-volume disease [30]. At APCCC 2022, panellists voted on whether they would recommend radiation therapy in the context of limited resources, recognising that radiation therapy may be reserved for patients with curable diseases (which are not limited to prostate cancer).

Q110. For the majority of patients with synchronous low-volume mHSPC treated in the context of limited access to radiation therapy (e.g. in a country where the availability of radiation treatment units is limited), 52% of panellists voted that they would recommend radiation therapy of the primary tumour, while 48% voted that they would not. There were 18 abstentions. (No consensus for any given answer option)

2.6.1. Discussion of mHSPC

For mHSPC, APCCC 2022 addressed a significant number of questions that complement topics which were discussed and voted on at APCCC 2021 [4] (Table 1 and supplement 1 for details). There was consensus that the majority of fit patients with mHSPC should receive a combination of systemic therapies, rather than ADT alone. There was no consensus on which patients with mHSPC should receive triplet therapy, but 70% of panellists voted for triplet therapy in patients with high-volume synchronous mHSPC, with a split vote between abiraterone and darolutamide as the preferred ARPI to include in the triplet regimen.

The role of docetaxel as a sole additional therapy in mHSPC is declining; there was near consensus (74% of panellists) not to recommend the addition of docetaxel alone to ADT in low-volume mHSPC, and only 11% of panellists voted to add docetaxel alone for the majority of patients with high-volume mHSPC. It seems hard to justify adding docetaxel alone to ADT if an ARPI is available, and only a few panellists voted for this option. Of note, data from the ARASENS trial showed a clear benefit from adding darolutamide in a design in which all patients received docetaxel plus ADT. Similarly, PEACE-1 showed a benefit from adding abiraterone to ADT in the subgroup of patients who had also received docetaxel.

For some patients with mHSPC, conventional and next-generation imaging results are discordant. When asked how to manage these patients, the panel was split, with half voting to primarily base treatment on conventional imaging and the other half voting to primarily base treatment on next-generation imaging. This discrepancy highlights the ongoing uncertainty about how to best use next-generation imaging in practice and the need to perform trials including questions about this topic.

A significant proportion of patients with mHSPC seen in daily clinical practice are older than 75 years, but this is not the case in clinical trials. At APCCC 2022, a notable discrepancy was that a combined 81% of panellists voted for performing a health status assessment or geriatric screening in at least some older ($\geq$75 years) patients with mHSPC, while only 25% of panellists reported performing such assessments themselves in practise; 75% declared candidly that they do not perform such standardised assessments but probably rely instead on personal experience. Sixty percent of patients are aged 65 years and older at diagnosis, and this proportion will increase to about 70% by 2040, while the median age at prostate cancer-related death is approximately 80 years [14]. Geriatric screening with the G8 and mini-COG can be performed by trained nurses and typically takes no more than 5 min [14]. Such screening can identify patients who might benefit from a more comprehensive geriatric or neurocognitive assessment.

With regards to the minimal estimated life expectancy at which to recommend combination therapy, 20% of panellists voted that they do not base treatment decisions on such estimations, whereas the rest were split between 1 and 3 years. A practical issue here is the lack of well-defined and validated tables for evaluating life expectancy at an individual level.

Regarding treatment recommendations for frail patients with mHSPC, there was consensus for radiation therapy of the primary tumour in low-volume disease. For asymptomatic patients with low-volume disease, a considerable proportion of panellists also voted for ADT alone or even for watchful waiting. For frail patients with symptomatic, synchronous, high-volume mHSPC, a total of about 80% of panellists voted for ADT plus an ARPI (some voted for ARPI at an ARPI at a reduced dose). Regarding the preferred ARPI to recommend for frail patients with mHSPC (provided that all drugs are available), the panel was again split between abiraterone and darolutamide, despite the fact there are that no reported data on ADT plus darolutamide from a large phase III trial. The results of the PEACE-6 trial will address this open question.

There was consensus that the results of tumour genomic profiling currently should not directly influence treatment decisions for the majority of patients with mHSPC. However, when asked about specific genomic alterations in patients with high-volume mHSPC with unfavourable genomic profiling (two or more alterations in RB1, TP53, and/or PTEN), there was consensus for triplet therapy. This voting result is very similar to that for patients with synchronous mHSPC for whom there is no information on specific genomic alterations available. For patients with high-volume mHSPC and a pathogenic SPOP mutation, only 50% of panellists voted for triplet therapy, and 47% voted for ARPI therapy, demonstrating that panellists are influenced to a certain extent by molecular profiles (when known).

Concerning strategies for treatment monitoring in mHSPC, there was again no consensus but only 20% of panellists voted for a purely PSA-based approach, while the rest voted to incorporate imaging at least 6–12 months after start of treatment (even in the context of a falling or stable PSA); with 66% voted to use conventional imaging as the monitoring tool.

The SIOG guidelines note that in developing countries, prostate cancer tends to be diagnosed at an advanced stage, treatment resources and access are often limited, and outcomes are generally poor [31–33]. This is particularly notable because the number of older patients with prostate cancer in these countries is expected to rapidly increase [14]. Nonetheless, limited healthcare resources and insufficient access to care are not only a problem in developing countries. Many patients with cancer in other countries also face financial toxicity because they have no or limited healthcare insurance coverage, and healthcare systems globally have finite resources in terms of both funds and staff time. In the context of mHSPC, the APCCC 2022 panel reached consensus for orchiectomy as the preferred form of ADT when resources are limited. There was no consensus on additional systemic therapy, but relatively more panel members voted for docetaxel for patients with high-volume mHSPC. For patients with low-volume mHSPC, one third of panellists voted for a reduced dose of abiraterone taken with food, even though data from a meta-analysis suggest that adding docetaxel to ADT is of similar benefit in synchronous low-volume mHSPC as in high-volume mHSPC [34]. For patients with low-volume mHSPC, there was no consensus regarding whether to recommend radiation therapy of the primary tumour in settings where access to radiation therapy is limited. This is in contrast to the voting results for Q81, where 80% of panellists voted to add radiation therapy of the primary tumour when recommending systemic triplet therapy in synchronous low-volume mHSPC. The lack of consensus on radiation therapy of the primary tumour in resource-limited settings probably reflects the use of radiation therapy with a curative intent in many cancer types; in the context of limited resources, these patients should be prioritised. However, the STAMPEDE trial included a very pragmatic once-weekly radiation schedule. A limitation of these questions is that we lacked information on the cost-effectiveness of these interventions in the setting of limited resources or in specific countries. Also,

only a minority of APCCC panellists are from low and middle-income countries.

3. Oligometastatic prostate cancer

3.1. Synchronous oligometastatic prostate cancer

At APCCC 2022, the panel focused mostly on synchronous, hormone-sensitive oligometastatic prostate cancer (Table 2 and supplement 2 for details). Systemic treatment options for mHSPC have evolved rapidly in recent years, and a parallel expansion in the use of next-generation imaging, particularly PSMA PET, for staging newly diagnosed prostate cancer has increased the proportion of patients diagnosed with synchronous low-volume disease. In daily practice clinicians face the increasingly challenging question of which treatment(s) to recommend for such patients. In synchronous oligometastatic HSPC, available treatment options include ADT, additional systemic therapy, local treatment of the primary tumour, MDT, and any combination of these options.

It may be worth stating that there is no randomised trial evidence specifically in synchronous oligometastatic HSPC suggesting a benefit from MDT of all documented lesions, nor is there any formal and generally accepted definition of this oligometastatic stage. Available evidence comes from several case series in which a combined approach to therapy (systemic, local and MDT) was investigated. In a series of 20 patients with synchronous oligometastatic HSPC, the primary endpoint of undetectable PSA after testosterone recovery was achieved in 20% of patients who received multimodal treatment with ADT, radical prostatectomy plus pelvic lymphadenectomy (in the presence of clinically positive retroperitoneal nodes), and stereotactic body radiation therapy (SBRT) to osseous disease or the primary site [35]. In another case series, 12 patients received neoadjuvant chemo-hormonal therapy followed by radical prostatectomy, adjuvant radiation to the prostate bed/pelvis, SBRT to oligometastases, and adjuvant hormonal therapy [36]. When possible, a PSMA-targeted 18F-DCFPyL PET/CT scan was obtained, and abiraterone was added to neoadjuvant ADT. An undetectable PSA after testosterone recovery was reported in 67% of patients. In a study of 52 patients with oligometastatic HSPC (maximum of 5 metastatic lesions on conventional imaging), patients with synchronous disease received ADT and docetaxel (with concurrent abiraterone added in a protocol amendment), followed by prostatectomy, adjuvant radiation (if positive margins, T3/4, or detectable PSA), and MDT. For patients with metachronous oligometastatic HSPC, the study protocol assigned the same therapies but omitted prostatectomy. Overall, the primary endpoint of undetectable PSA in the context of testosterone recovery was achieved in 80% of patients [36]. In a series of 39 patients with synchronous oligometastatic HSPC (maximum of 2 bone lesions on conventional imaging), 4-year biochemical relapse-free survival was 53% with the same treatment approach [38].

Considering the increasing availability of next-generation imaging in many localities, the panel voted on whether it is still appropriate to base treatment decisions on conventional imaging alone in patients with low-volume mHSPC.

Q167. In all, 53% of panellists voted that it is appropriate to base treatment recommendations for low-volume/oligometastatic synchronous mHSPC on conventional imaging only, without next-generation imaging even if it is readily available. The remaining 47% of panellists voted that this is not appropriate. There was one abstention. (No consensus for any given answer option)

For Q168, panellists voted on their general treatment approach in low-volume mHSPC.

Q168. For the majority of patients with low-volume/oligometastatic synchronous mHSPC and 1–3 bone lesions on next-generation imaging, 61% of panellists voted for systemic therapy plus local treatment of the primary tumour and metastases-directed therapy, 33% voted for systemic therapy plus local treatment of the primary tumour, 4% voted for local treatment of the primary tumour and metastases-directed therapy without systemic therapy, and 2% voted for systemic therapy alone. There was one abstention. (No consensus for any given answer option, a combined total of 96% voted for systemic therapy)

Panellists who voted for maximal treatment with systemic therapy plus local treatment (of the primary tumour ± metastases) in Q168 were asked a follow-up question related to the recommended systemic therapy:

Q169. Among the panellists who voted for systemic therapy plus local treatment of the primary tumour in the majority of patients in Q168, 89% voted to recommend that systemic therapy consist of ADT plus an ARPI (abiraterone, apalutamide or enzalutamide), 7% voted for ADT alone, 2% voted for ADT plus docetaxel, and 2% voted for the triplet ADT plus docetaxel plus an ARPI (abi, apa, daro, enza). There were eight abstentions (including panellists who did not vote to recommend the combination of systemic plus local therapy in this setting). (Consensus for ADT plus an ARPI among the panellists voting for systemic therapy plus local treatment)

For Q170, panellists voted on their recommendation for systemic therapy without local treatment.

Q170. Among the panellists who voted for systemic therapy alone in the majority of patients in Q168, 90% voted to recommend that treatment consist of ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), 7% voted for triplet therapy ADT plus docetaxel plus an ARPI (abi, apa, daro, enza), and 3% voted for ADT alone. There were 74 abstentions (including panellists who did not vote for systemic therapy alone). (Strong consensus for a doublet of ADT plus an ARPI among the panellists voting for systemic therapy alone)

With regards to local treatment of the primary tumour, a combined analysis of data from the HORRAD

and STAMPEDE clinical trials (a STOPCAP meta-analysis) reported a 7% improvement in 3-year OS among patients with prostate cancer who had up to four bone metastases [39]. Prospective randomised clinical trial data on surgery in this setting are pending. A recently published randomised phase II trial enroled 200 patients with synchronous oligometastatic HSPC (defined as five or fewer bone or extrapelvic lymph node metastases and no visceral metastases), who were randomly assigned to receive either ADT or ADT plus radical local treatment of the primary tumour. Both rPFS and OS were significantly improved in the arm in which patients received radical local treatment of the primary tumour in addition to ADT [40].

Q171. For the majority of patients with low-volume/oligometastatic synchronous mHSPC (e.g. 1–3 bone lesions on next-generation imaging) 95% of panellists voted to recommend that treatment of the primary tumour consist of radiation, while 5% voted for surgery. There were two abstentions. (Strong consensus for radiation therapy)

Questions 172–174 relate to a very specific subset of patients with synchronous mHSPC who have evidence of retroperitoneal lymph node disease (M1a) on PSMA PET imaging.

Q172. For the majority of patients with low-volume/oligometastatic synchronous mHSPC and PSMA PET-positive retroperitoneal lymph nodes, 57% of panellists voted to recommend that treatment consist of systemic therapy plus local treatment of the primary tumour and metastases-directed therapy, 35% voted for systemic therapy plus local treatment of the primary tumour, 2% voted for local treatment of the primary tumour and metastases-directed therapy without systemic therapy, and 6% voted for systemic therapy alone. There was one abstention. (No consensus for any given answer option, a combined 92% voted for systemic therapy plus local treatment of the primary)

Q173. Among the panellists who voted for metastases-directed therapy of the retroperitoneal lymph nodes in Q172, 90% voted that this consist of radiation therapy and 5% voted for surgery. There were 41 abstentions (including panellists who voted that they do not recommend metastases-directed therapy in this setting) (Strong consensus for radiation therapy among the panellists voting for MDT)

Q174. Among the panellists who voted to recommend that treatment include systemic therapy in Q172, 92% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), 5% voted for ADT alone, 2% voted for ADT plus docetaxel, and 1% voted for the triplet ADT plus docetaxel plus an ARPI (abi, apa, daro, enza. There were seven abstentions. (Strong consensus for ADT plus an ARPI among the panellists voting for systemic therapy).

3.2. Metachronous oligometastatic prostate cancer

In metachronous oligometastatic HSPC, some prospective clinical trial data are available, albeit from relatively small studies that were not randomised phase III trials (STOMP, ORIOLE, SABR-COMET, POPSTAR) [41–45]. In SABR-COMET, only 16% of patients had prostate cancer. An important point when interpreting results from these trials is that STOMP used choline PET for screening, while ORIOLE used 18F-DCFPyL PSMA PET imaging only for the subset of patients who were randomly assigned to receive stereotactic ablative radiation therapy (SABR). STOMP demonstrated an improvement in ADT-free survival among patients who received MDT compared with those who underwent surveillance only, and ORIOLE showed an improvement in 6-month PSA-progression-free survival with MDT compared with observation. In ORIOLE, the treatment plan was based on conventional imaging. Among 36 patients who had an additional baseline PSMA PET and were treated with SABR, 16 had a baseline PET showing positive lesions that were not included in the radiation field. The proportion of patients with no untreated lesions with progression at 6 months was 5%, compared with 38% among patients who had one or more untreated lesions [41,42]. The SABR-COMET trial reported improved OS with MDT compared with standard of care, but the study population was heterogeneous, making it difficult to draw any definitive conclusions from these data.

Q175. For the majority of patients with low-volume/oligometastatic metachronous mHSPC (e.g. 3 bone lesions on next-generation imaging), 67% of panellists voted to recommend systemic therapy plus metastases-directed therapy, 18% voted for systemic therapy alone, and 15% voted for metastases-directed therapy without systemic therapy. There were two abstentions. (No consensus for any given answer option)

Q176. Among the panellists who voted for systemic therapy in Q175, 90% voted for ADT plus an ARPI (abiraterone, apalutamide, or enzalutamide), 8% voted for ADT alone, 1% voted for ADT plus docetaxel, and 1% voted for triplet therapy ADT plus docetaxel plus an ARPI (abi, apa, daro, enza). There were 16 abstentions (including panellists who voted that they do not recommend systemic therapy in this setting) (Strong consensus for ADT plus an ARPI among the panellists voting for systemic therapy)

3.2.1. Discussion of oligometastatic prostate cancer

Oligometastatic prostate cancer has been a topic at the APCCC since the first conference in 2015. Since then, systemic therapy options in hormone-sensitive prostate cancer have rapidly increased, and next-generation imaging, particularly PSMA PET, has become a new and frequently used diagnostic procedure. While the evidence for systemic treatment in patients with synchronous or metachronous oligometastatic HSPC is now strong and backed by data from multiple phase III trials, the evidence for MDT remains weak. Thus, it is not surprising that the panel was split on the question of whether it still is appropriate to base treatment decisions

on conventional imaging in low-volume mHSPC or whether next-generation is necessary (Table 2).

For synchronous oligometastatic HSPC, it is surprising that a combined 65% of panellists voted for MDT (mostly with systemic therapy) even though we lack strong evidence supporting this approach. It is most important that this conviction not hamper accrual to ongoing and planned randomised studies of MDT. When it comes to systemic treatment, there was a consensus for adding an ARPI, not docetaxel or a triplet regimen (i.e. docetaxel plus an ARPI). Also, there was strong consensus for radiation therapy and not surgery if local treatment of the primary is recommended, and there was consensus that systemic therapy should be part of the treatment strategy. The same applies to patients with low-volume M1a prostate cancer on PSMA PET imaging.

For metachronous oligometastatic HSPC, only 15% of panellists voted for MDT alone without systemic therapy, while 67% voted for systemic therapy in combination with MDT. In terms of systemic therapy, 90% voted to add an additional ARPI.

Although there seems to be considerable enthusiasm for MDT in oligometastatic prostate cancer, it may be wise to keep in mind that a recent trial of MDT in breast cancer (N = 129) failed to show any improvement in PFS or OS [45]. There is hope that ongoing phase III trials (e.g. PEACE-6 Oligo [PRESTO; STAMPEDE protocol 2, METRO, START-MET and SPARKLE) will add substantial evidence on this very important clinical question. These trials generally include patients with both synchronous and metachronous mHSPC.

4. Non-metastatic, castration-resistant prostate cancer (nmCRPC)

Non-metastatic CRPC, also known as M0 CRPC, is defined as PSA progression in the setting of castrate levels of testosterone and no evidence of metastases on conventional imaging. Three pivotal phase 3 trials (ARAMIS, PROSPER, and SPARTAN) have demonstrated statistically significant improvements in the primary endpoint of MFS and subsequently in OS among patients who received darolutamide, apalutamide, or enzalutamide, respectively [46–48]. The APCCC 2022 panel discussed specific questions related to nmCRPC (Table 3 and supplement 3 for details).

Some patients with nmCRPC have an untreated primary tumour or a local relapse that can be visualised only by MRI and/or PET-based imaging. In the three pivotal randomised phase III trials in nmCRPC, only about 50% of patients had previously received radical local treatment (radiation therapy or prostatectomy) [50]. Not much is known about whether such patients might benefit from local treatment of the primary tumour, if feasible, either alone or in combination with systemic treatment; to our knowledge, this subgroup of patients has not been studied separately. The panel voted on this question twice: once for patients with a rapid PSA-doubling time (as required for enrolment in these trials) and the second time for patients with slower PSA kinetics.

Q111. For the majority of patients with asymptomatic nmCRPC (on ADT) and a PSA doubling time ≤10 months and a confirmed local progression in the prostate, and no prior history of radical local treatment, 61% of panellists voted in favour of local therapy of the prostate plus additional systemic therapy (ARPI), 20% voted for additional systemic therapy (an ARPI) alone, and 19% voted for local therapy of the prostate. There were three abstentions. (No consensus for any given answer option)

Q112. For the majority of asymptomatic patients with nmCRPC (on ADT) and a PSA doubling time > 10 months and confirmed local progression in the prostate, and no prior history of radical local treatment, 69% of panellists voted in favour of local therapy of the prostate, 7% voted for additional systemic therapy (an ARPI) alone, 19% voted for local therapy of the prostate plus additional systemic therapy (ARPI), and 5% voted for surveillance. There were two abstentions. (No consensus for any given answer option, a combined 88% voted for local treatment with or without additional systemic therapy)

It has been demonstrated that many patients in the nmCRPC trials would have had low-volume metastatic disease detected had they undergone next-generation imaging. For example, in a retrospective study of 200 patients with prostate cancer who were at high risk for metastatic disease (PSA doubling time ≤10 months and/or Gleason score ≥8) with no evidence of metastatic disease on conventional imaging, 44% had PSMA-positive pelvic nodal disease, and 55% had distant metastases [51]. Based on such data, a current question is whether patients with rising PSA who are on ADT, have been staged by conventional imaging, and were found to have non-metastatic disease also should have a PSMA PET scan.

*Q113. For the majority of patients with nmCRPC on conventional imaging whose PSA doubling time is ≤10 months, 28% of panellists voted to recommend performing PSMA PET prior to starting apalutamide, darolutamide, or enzalutamide; 42% voted to recommend this only if patients are candidates for radiation therapy (*i.e. *have local relapse and/or oligometastatic disease); and 30% voted against the use of PSMA PET in this setting. There were four abstentions. (No consensus for any given answer option)*

*Q114. For the majority of patients with nmCRPC on conventional imaging whose PSA doubling time is > 10 months, 21% of panellists voted to recommend performing PSMA PET prior to starting apalutamide, darolutamide, or enzalutamide; 49% voted to recommend this only if patients are candidates for radiation therapy (*i.e. *have local relapse and/or oligometastatic disease), and 30% voted against the use of PSMA PET in this setting. There were three abstentions. (No consensus for any given answer option)*

Considering the increasingly wide availability of PSMA PET for staging, patients with prostate cancer often undergo PSMA PET imaging without prior conventional imaging (i.e. CT and bone scintigraphy). Because apalutamide and darolutamide are only approved for treating nmCRPC, rather than overtly metastatic mCRPC, the question can arise as to whether to recommend conventional imaging (bone scintigraphy, CT only if PET was not already combined with diagnostic CT) to confirm that disease is non-metastatic by conventional imaging. This question is particularly salient if small lesions have been identified on PSMA PET.

Q115. For the majority of patients with PSA doubling time ≤10 months who's initial PSMA PET shows 1–3 lesions, 62% of panellists voted that they would not go back and perform conventional imaging (CT plus bone scintigraphy) to determine if the disease state was nmCRPC by conventional imaging, 32% voted that they would do so only in order to access standard-option apalutamide, darolutamide, or enzalutamide, and 6% voted that they would do so for the majority of patients. There were five abstentions. (No consensus for any given answer option)

The panel additionally voted on a series of questions related to patients diagnosed with nmCRPC on conventional imaging who also had 1–3 lesions identified on PSMA PET. For these questions, is important to reiterate that the assumption was that conventional imaging had shown no evidence of metastatic disease; lesions had been detected only on PSMA PET. In addition, patients were categorised based on PSA doubling time (≤10 months [Q116 and Q11] versus >10 months [Q118 and Q119] and lesion location (lesions in distant [not pelvic] lymph nodes versus in both lymph nodes and bone).

Q116. For the majority of patients with nmCRPC on conventional imaging and PSA doubling time ≤10 months, if PSMA PET shows 1–3 lesions in distant (not pelvic) lymph nodes, 39% of panellists voted to recommend MDT plus systemic therapy (either for nmCRPC or mCRPC), 35% voted to treat as nmCRPC with standard-option apalutamide, darolutamide, or enzalutamide, 15% voted to treat as mCRPC with standard-option therapy, and 11% voted for MDT alone. There were seven abstentions. (No consensus for any given answer option, but a combined 89% voted for systemic therapy plus/minus MDT)

Q117. For the majority of patients with nmCRPC on conventional imaging and PSA doubling time ≤10 months, if PSMA PET shows 1–3 lesions in lymph nodes and bone, 45% of panellists voted to recommend MDT plus systemic therapy (either for nmCRPC or mCRPC), 28% voted to treat as nmCRPC with standard-option apalutamide, darolutamide, or enzalutamide, 18% voted to treat as mCRPC with standard-option therapy, and 9% voted for MDT alone. There were five abstentions. (No consensus for any given answer option)

Q118. For the majority of patients with nmCRPC on conventional imaging and PSA doubling time >10 months, if PSMA PET shows 1–3 lesions in distant (not pelvic) lymph nodes, 41% of panellists voted to recommend treatment with MDT alone, 28% voted for additional systemic treatment (ARPI) plus MDT, 19% voted for additional systemic treatment (ARPI) alone, and 12% voted for ongoing active monitoring without a change in management. There were nine abstentions. (No consensus for any given answer option)

Q119. For the majority of patients with nmCRPC on conventional imaging and PSA doubling time >10 months, if PSMA PET shows 1–3 lesions in lymph nodes and bone, 37% of panellists voted to recommend treatment with MDT alone, 30% voted for additional systemic treatment (ARPI) plus MDT, 28% voted for additional systemic treatment (ARPI) alone, and 5% voted for ongoing active monitoring with a change in management. There were nine abstentions. (No consensus for any given answer option)

As per PCWG3 recommendations, patients in the SPARTAN, PROSPER, and ARAMIS trials were monitored by conventional imaging (every 16 weeks) and PSA (every 4–16 weeks) [47–49]. Treatment was stopped in cases of radiographic progression as per PCWG3 criteria, and investigators were discouraged from changing treatment based solely on rising PSA. In a population-based, patterns-of-care study in nmCRPC, investigators reported that PSA testing and imaging studies were underutilized in real-world settings [52]. The APCCC 2022 panel voted on questions related to how best to use imaging for treatment monitoring in patients with nmCRPC, and when to change treatment.

Q120. When asked about ongoing monitoring by imaging for patients undergoing treatment for nmCRPC, 40% of panellists voted to recommend imaging at regular intervals regardless of PSA level, 31% voted for imaging at about 6–12 months and then not again until PSA and/or symptomatic progression, and 29% voted not to perform imaging until the time of PSA and/or symptomatic progression. There were six abstentions. (No consensus for any given answer option)

Q121. For patients with nmCRPC (M0 CRPC) who are receiving an ARPI (apalutamide, darolutamide, or enzalutamide), 83% of panellists voted to change treatment if metastases and/or symptomatic progression occur(s), while 17% voted to change treatment at the time of PSA rise (as per PCWG3 criteria) alone. There were five abstentions. (Consensus to change ARPI at onset of metastases or symptomatic progression)

4.1. Discussion of nmCRPC

The recent approval of potent ARPIs is specifically linked to the nmCRPC disease state, and these drugs have been shown to improve OS in patients with high-risk nmCRPC. Thus, decisions on their use remain relevant in daily practice, even if nmCRPC is defined differently in the future as next-generation imaging becomes more common. It was recently reported that a relevant proportion of patients in the ARAMIS trial had an untreated primary tumour [47]. These patients were generally older than those who had received prior

radical local treatment (median 76 versus 72 years), and they had a worse performance status at enrolment (PS of 1: 36% versus 26% of patients, respectively). For patients with nmCRPC who have an untreated primary tumour, APCCC panellists seemed to find PSA doubling time relevant when considering whether to recommend local treatment alone: 69% of panellists recommended this approach when PSA-DT was > 10 months, while 19% recommended it when PSA-DT was ≤10 months (Table 3). It is surprising that according to the voting, ADT monotherapy without local treatment of the primary tumour seems to be used in a relevant proportion of patients.

There was no consensus on the question of whether to use PSMA PET imaging in patients with nmCRPC on conventional imaging. From the nuclear medicine perspective, the 2021 Society of Nuclear Medicine Appropriate Use Criteria (AUC) panel supported the use of PSMA PET as appropriate in this setting but acknowledged that it is unclear how to use PSMA PET findings to guide management decisions [53]. While 30% of panellists would generally not use PSMA PET in these patients, the majority of experts recommended PSMA PET for either all patients or selected patients.

As noted at previous APCCC conferences, a significant proportion (about 50%) of panellists are very proactive about recommending MDT in patients who have nmCRPC based on conventional imaging but metastatic disease on PSMA PET. In patients whose PSA doubling time is ≤10 months, most panellists voted for MTD in combination with systemic therapy, even though there is no strong evidence supporting such an approach. For patients with PSA doubling time > 10 months, even more (about 67%) panellists recommended MDT, mostly without additional systemic therapy. The available evidence for MDT in nmCRPC is scarce and is limited to small trials or retrospective case series [54–58]. In patient with high-risk features (based on both total PSA and PSA kinetics), the evidence is again best for systemic therapy (showing improvements in both MFS and OS), and any additional benefit of MDT is unproven.

When it comes to treatment monitoring in nmCRPC, almost 70% of panellists voted to include some form of imaging, while about 30% voted to only follow patients by PSA. There was consensus not to change treatment based on a rising PSA alone but rather only to alter treatment if patients show radiographic and/or symptomatic progression.

5. Management of patients with mCRPC

5.1. Best use of PARP inhibition

PARP inhibitors are now considered a standard of care for patients with mCRPC who have relevant genomic alterations in homologous recombination repair (HRR) genes [59,60]. In Europe, the PARP inhibitor olaparib is approved for patients with prostate cancer who have germline and/or somatic alterations in BRCA1 or BRCA2 genes, while the US approval also includes additional DNA repair gene alterations, based on the results of the PROFOUND trial [59]. In the United States, the PARP inhibitor rucaparib also is approved for the treatment of patients with prostate cancer who have deleterious germline or somatic BRCA1/2 alterations [60].

At ASCO GU 2022, researchers presented findings from two phase III trials of combination therapy with PARP inhibitors plus abiraterone/prednisone in patients with prostate cancer [61,62]. Given that these trials generated partially divergent results, the APCCC 2022 panel discussed several questions on whether first-line treatment of mCRPC with a PARP inhibitor plus abiraterone/prednisone is appropriate in unselected patients or only in biomarker-selected patients.

The PROPEL trial randomly assigned 796 patients with mCRPC to receive first-line treatment with abiraterone plus olaparib or abiraterone plus placebo [61]. DNA repair gene defects were assessed retrospectively by FoundationOne and/or FoundationOne Liquid testing. The primary endpoint of rPFS favoured the combination in the overall study population (24.8 versus 16.6 months, HR 0.66, 95% CI 0.54–0.81). However, the largest rPFS benefit was seen in the 28% of patients who were classified as biomarker positive (NR versus 13.9 m, HR 0.5, 95% CI 0.34–0.73). A less pronounced benefit was observed in the biomarker-negative subgroup (24.1 versus 19 m, HR 0.76, 95% CI 0.6–0.97). Recent data from this study presented at ESMO 2022 showed a continued rPFS benefit with longer follow-up in all subgroups, which mainly was driven by patients with BRCA1/2 alterations [63]. Data on OS remain immature, but no significant OS benefit was identified at data cut-off (HR 0.86, 95% CI 0.66–1.12). The side effect profile in the combination group was as expected: Compared with the abiraterone-placebo group, higher rates of anaemia, nausea, and fatigue were observed, and there were more dose reductions and treatment discontinuations.

The MAGNITUDE trial planned to enrol 1000 patients with mCRPC and group them into one of two cohorts depending on whether they showed pathogenic alterations in HR genes on the FoundationOne or Resolution Bioscience assays. Within each cohort, patients were randomly assigned to receive first-line niraparib plus abiraterone/prednisone or placebo plus abiraterone/prednisone [62]. After 200 patients were enroled into the biomarker-negative cohort, the independent data monitoring committee recommend closing it due to futility. Ultimately, 433 patients were enroled into the biomarker-positive cohort, in which patients underwent prospective liquid biopsy testing with the FoundationOne or Resolution Bioscience assays; only patients with evidence of pathogenic alterations were enroled into the final biomarker-positive cohort. The primary endpoint of rPFS was significantly improved with the combination of PARP inhibition plus

abiraterone treatment (19 versus 13.9 m, HR 0.64, 95% CI 0.49–0.86). Combination treatment showed greater rPFS benefit in 52% of patients with evidence of a BRCA1/2 alteration (either alone or as co-mutation) (19.3 vs 12.4 m, HR 0.5, 95% CI 0.33–0.75); compared with the rest of the biomarker (ATM, PRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2) positive patients (14.8 versus 16.4 m, HR 0.99, 95% CI 0.68–1.45). Similar to the PROPEL trial, more side effects (mainly haematological) were observed in the combination-therapy arm, as well as more dose reductions and treatment discontinuations.

APCCC 2022 addressed the topic of two trials generating conflicting results and asked the question of choice of first-line mCRPC therapy in different molecularly defined subgroups (see Table 6 and supplement 4 for details).

Q133. For the majority of patients with mCRPC with a pathogenic BRCA1/2 alteration who are about to start an ARPI, 48% voted against combination treatment with a PARP inhibitor as first-line therapy, while 52% voted in favour of the combination. There were 12 abstentions. (No consensus for any given answer option)

Q134. For the majority of patients with mCRPC with a pathogenic DNA repair gene alteration (NOT BRCA1/2) who are about to start an ARPI, 78% voted against combination treatment with a PARP inhibitor as first-line therapy, while 22% voted in favour of the combination. There were 14 abstentions. (Consensus not to recommend combination treatment with a PARP inhibitor)

Q135. For the majority of patients with mCRPC without a known DNA repair gene alteration who are about to start an ARPI, 97% of panellists voted against combining it with a PARP inhibitor as first-line therapy, while 3% voted for the combination. There were nine abstentions. (Strong consensus not to recommend combination treatment with a PARP inhibitor)

Both PROPEL and MAGNITUDE included patients with little exposure to therapies other than ADT (in both trials, docetaxel for mHSPC was allowed and was given to about 20% of patients; MAGNITUDE permitted up to four months of abiraterone before enrolment, and 23% of patients had received it). The reality is, however, that many patients now receive an ARPI in the mHSPC setting. Hence, the APCCC 2022 panel addressed the selection of first-line treatment for mCRPC in patients whose disease is progressing on ADT plus an ARPI that was started for mHSPC.

Q136. For the majority of patients with mCRPC with pathogenic BRCA1/2 alteration who are progressing on treatment with an ARPI that was started for mHSPC (with or without docetaxel for mHSPC), 64% of panellists voted to treat with a PARP inhibitor alone, 19% voted for continuing the ARPI and adding a PARP inhibitor, 11% voted for chemotherapy, and 6% voted to switch to an alternate ARPI and add a PARP inhibitor. There were 10 abstentions. (No consensus for any given answer option, a combined 89% voted for a PARP inhibitor)

Q137. For the majority of patients with mCRPC with pathogenic DNA repair gene alterations (germline and/or somatic) other than BRCA1/2 who are progressing on treatment with an ARPI that was started for mHSPC (with or without docetaxel for mHSPC), 56% of panellists voted to recommend chemotherapy, 28% voted for a PARP inhibitor alone, 12% voted to continue the ARPI and add a PARP inhibitor, and 4% voted to switch to an alternate ARPI and add a PARP inhibitor. There were 15 abstentions. (No consensus for any given answer option)

Q138. For the majority of patients with mCRPC with no known DNA repair gene alterations who are progressing on treatment with an ARPI that was started for mHSPC (with or without docetaxel for mHSPC), 96% of panellists voted to recommend chemotherapy, 3% voted to switch to an alternate ARPI and add a PARP inhibitor, and 1% voted to continue the ARPI and add a PARP inhibitor. There were 14 abstentions. (Strong consensus for chemotherapy)

5.2. General principles of treatment sequencing

At APCCC 2021, there was consensus for treatment with Lutetium-177 (^{177}Lu)-PSMA in patients with mCRPC progressing after at least one line of ARPI and one line of chemotherapy [4]. In many patients with symptomatic bone metastases and no relevant soft tissue disease, treatment with radium-223 may also be useful and conserves ^{177}Lu-PSMA for later-line treatment.

Q139. For the majority of patients with symptomatic mCRPC who meet criteria for treatment with radium-223 and criteria for treatment with ^{177}Lu-PSMA, 79% of panellists voted for choosing ^{177}Lu-PSMA therapy and 21% voted for radium-223. There were eight abstentions. (Consensus for ^{177}Lu-PSMA)

There is some evidence that ^{177}Lu-PSMA-617 can be given safely to patients who have received prior Radium-223-dichloride (Ra-223), but there is very little evidence for the reverse sequence [64].

Q140. In all, 56% of panellists voted in favour and 46% voted against treating symptomatic patients with mCRPC with radium-223 (if relevant treatment criteria are met) after they have received ^{177}Lu-PSMA. There were 20 abstentions. (No consensus for any given answer option)

For patients who have received docetaxel in the mHSPC setting, the question of docetaxel re-challenge in the mCRPC situation arises. Limited retrospective data on docetaxel re-challenge suggest limited anti-tumour activity [65].

Q141. For the majority of patients who receive docetaxel in the mHSPC setting and progress to mCRPC within 12 months, 86% of panellists voted against and 14% voted for docetaxel rechallenge. There were 12 abstentions. (Consensus against docetaxel rechallenge)

Q142. For the majority of patients who received docetaxel in the mHSPC setting and progressed to mCRPC after more than 36 months, 76% of panellists voted in favour of

docetaxel rechallenge and 24% voted against it. There were 12 abstentions. (Consensus for docetaxel rechallenge)

5.3. Sequencing of therapies in mCRPC

Previously, at APCCC 2019, panellists voted on the sequential administration of abiraterone after enzalutamide and the reverse sequence and expressed scepticism about the efficacy of serial AR signalling inhibition in the majority of patients with mCRPC [3].

Q143. For the majority of patients progressing after one line of ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide), 85% of panellists voted that they do not recommend switching directly to another ARPI and 15% voted in favour of a direct switch. There were seven abstentions. (Consensus against directly switching to another ARPI)

With the advent of various treatment options in mHSPC, the optimal sequencing of therapies in mCRPC has become more challenging, and even less evidence is present on which to base decisions. For Q144–Q153, APCCC 2022 panellists voted on their preferred next therapy option for patients with mCRPC who have received ADT alone, ADT plus an ARPI, ADT plus docetaxel, or triple therapy with ADT plus docetaxel plus an ARPI. It is important to note that drug approvals in mCRPC were based on studies of patients who had received ADT alone in the mHSPC setting. The management of patients whose disease progresses on ADT plus ARPI with or without docetaxel in the mHSPC setting is particularly challenging, because prospective trial data are lacking, and treatment options are generally limited. Another layer of complexity was introduced with data from PROPEL and MAGNITUDE (see our discussion above). To address the heterogeneity of prostate cancer outcomes in the mHSPC setting, the panel voted on questions about treatment sequencing in patients who rapidly develop castration resistance (within approximately 6 months). This is an especially challenging subgroup of patients to manage because of the aggressive nature of the disease.

Q144. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT only for mHSPC, 93% of panellists voted for an ARPI, 3% voted for an ARPI plus a PARP inhibitor, and 4% voted for docetaxel. There were eight abstentions. (Strong consensus for an ARPI)

Q145. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT only for mHSPC and progressed within 6 months, 54% of panellists voted for chemotherapy (e.g. docetaxel or a platinum-based regimen), 43% voted for an ARPI, and 3% voted for an ARPI plus a PARP inhibitor. There were nine abstentions. (No consensus for any given answer option)

Q146. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT plus an ARPI for mHSPC, 83% of panellists voted for docetaxel, 9% voted for an alternate ARPI, 4% voted for an alternate ARPI plus a PARP inhibitor, and 4% voted for radium-223 (if relevant treatment criteria are met). There were eight abstentions. (Consensus for docetaxel)

Q147. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT plus an ARPI for mHSPC and progressed within 6 months, 95% of panellists voted for chemotherapy (e.g. docetaxel or platinum-based regimen), 3% voted for an alternate ARPI, 1% voted for an alternate ARPI plus a PARP inhibitor, and 1% voted for radium-223 (if relevant treatment criteria are met). There were eight abstentions. (Strong consensus for chemotherapy)

Q148. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT plus docetaxel (without an ARPI) for mHSPC, 93% of panellists voted for an ARPI, 5% voted for an alternate ARPI plus a PARP inhibitor, and 2% voted for taxane chemotherapy. There were eight abstentions. (Strong consensus for ARPI)

Q149. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT plus docetaxel (without an ARPI) for mHSPC and progressed within 6 months, 75% of panellists voted for an ARPI, 19% voted for chemotherapy (e.g. cabazitaxel or a platinum-based regimen), 5% voted for an ARPI plus a PARP inhibitor, and 1% voted for radium-223 (if relevant treatment criteria are met). There were 10 abstentions. (Consensus for ARPI)

Q150. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT plus an ARPI plus docetaxel for mHSPC, 56% of panellists voted for ^{177}Lu-PSMA, 27% voted for taxane chemotherapy, 9% voted for radium-223 (if relevant treatment criteria are met), 5% voted for an alternate ARPI, and 3% voted for an alternate ARPI plus a PARP inhibitor. There were 11 abstentions. (No consensus for any given answer option)

Q151. When asked to select a first-line therapy for the majority of patients with mCRPC without DDR gene alterations who previously received ADT plus an ARPI plus docetaxel for mHSPC and progressed within 6 months, 51% of panellists voted for ^{177}Lu-PSMA, 47% voted for chemotherapy (e.g. cabazitaxel or a platinum-based regimen), 1% voted for radium-223 (if relevant treatment criteria are met), and 1% voted for an alternate ARPI. There were 12 abstentions. (No consensus for any given answer option)

Q152. When asked to select a first-line therapy for the majority of patients with mCRPC with a pathogenic BRCA1/2 alteration (germline and/or somatic) who have received ADT and an ARPI, 75% of panellists voted for a PARP inhibitor, 13% voted for docetaxel, and 12% voted for an alternate ARPI plus a PARP inhibitor. There were 10 abstentions. (Consensus for PARP inhibitor therapy)

Q153. When asked to select a first-line therapy for the majority of patients with mCRPC with a pathogenic BRCA1/2 alteration (germline and/or somatic) who have received ADT, docetaxel, and an ARPI, 82% of panellists voted for a PARP inhibitor, 11% voted for an alternate ARPI plus a PARP inhibitor, 4% voted for cabazitaxel, and 3% voted for ^{177}Lu-PSMA. There were 10 abstentions. (Consensus for PARP inhibitor therapy)

5.4. Treatment options in patients with specific genomic alterations

There is limited evidence for the potential activity of checkpoint inhibitors in patients who have CDK12 alterations based on an elevated neoantigen burden [66–69].

Q154. For the majority of patients with a pathogenic genomic *CDK12* aberration (germline/somatic or somatic alone), 21% of panellists voted to recommend treatment with a checkpoint inhibitor during the course of disease, 61% voted for checkpoint inhibitor therapy only in selected patients with high tumour mutational burden and/or biallelic activation and/or a tandem duplicator signature, and 18% voted against checkpoint inhibitor therapy. There were 22 abstentions. (No consensus for any given answer option, but 82% would use a checkpoint inhibitor in at least some selected patients)

About 3–5% of prostate cancer cases are found to have deficient mismatch repair (dMMR) or microsatellite instability (MSI) [16]. Assessment of dMMR/MSI is more challenging in prostate cancer compared to e.g. colorectal cancer. The widely used 5-marker MSI-PCR panel has inferior sensitivity when applied to prostate cancer and NGS testing with and expanded panel is recommended [70].

Q155. For evaluating mismatch repair deficiency (MSI high), 42% of panellists voted to recommend testing with next-generation sequencing (NGS), 12% voted for immunohistochemistry (IHC), and 46% voted to recommend using both NGS and IHC. There were 20 abstentions. (No consensus for any given answer option, a combined 88% voted for NGS testing alone or in combination with IHC)

Limited data currently are available on the activity of checkpoint inhibitors in patients with dMMR or MSI-high prostate cancer [71–74]. However, there are data on the activity of checkpoint inhibitors in patients with high tumour mutational burden (TMB-high) [75]. These questions are particularly relevant because of the tumour-agnostic approval of checkpoint inhibitors in the United States for patients whose tumours are dMMR/MSI-high or have a high-TMB. Results from a recent study suggest that patients with both MSI-high status and BRCA1/2 mutations should be treated with checkpoint inhibitors, rather than PARP inhibitors, due to the BRCA1/2 mutations likely being passenger events and not the primary driver of the disease [76].

Q156. For the majority of patients with dMMR/MSI-high, 96% of panellists voted for and 4% voted against recommending treatment with an immune checkpoint inhibitor during the course of disease. There were 19 abstentions. (Strong consensus for checkpoint inhibitor therapy)

Q157. For the majority of patients with high tumour mutational burden (TMB ≥10 mutations/megabase), 79% of panellists voted for and 21% voted against recommending treatment with an immune checkpoint inhibitor during the course of disease. There were 20 abstentions. (Consensus for checkpoint inhibitor therapy)

5.5. Treatment with ^{177}Lu-PSMA

Because of the relatively low rate of patients being excluded from the VISION trial based on their baseline ^{bp}Ga-PSMA PET, there was a discussion as to whether baseline PSMA PET was necessary at all [77]. Of note, the US Food and Drug Administration (FDA) approved 177Lu-PSMA-617 for use in patients with PSMA-positive mCRPC and also approved a diagnostic tracer (gallium Ga 68 gozetotide) for imaging. The Medicines and Healthcare products Regulatory Agency (MHRA) approved this treatment only in patients with PSMA PET-positive disease.

Q158. In all, 92% of panellists voted to recommend performing a baseline PSMA PET even if approval does not require a PSMA PET for selection of ^{177}Lu-PSMA therapy, while 8% voted against baseline PSMA PET. There were nine abstentions. (Strong consensus for baseline PSMA PET even if not required for ^{177}Lu-PSMA therapy)

The two randomised prospective trials in this setting (phase II: TheraP; phase III: VISION) have applied different approaches for patient selection [77,78]. In the TheraP trial, all patients were screened with both PSMA and FDG PET. In the VISION trial, baseline imaging consisted of PSMA PET accompanied by contrast-enhanced CT [77]. Of note, TheraP excluded about 28% of patients based on imaging, while VISION excluded about 13% based on the baseline PET CT [77,78].

Q159. For selecting treatment with ^{177}Lu-PSMA therapy, 74% of panellists voted to recommend that the threshold of uptake be based on VISION criteria (≥1 metastatic lesion with PSMA uptake greater than liver uptake), 24% voted to recommend that the threshold of uptake be based on TheraP criteria (≥1 metastatic lesion with PSMA uptake SUVmax > 20), and 2% voted that PMSA PET is not needed for treatment selection. There were 17 abstentions. (No consensus for any given answer option)

Q160. To identify PSMA-negative sites of disease as part of the workup for ^{177}Lu-PSMA therapy, 51% of panellists voted that they correlate PSMA PET/CT with contrast-enhanced CT (as in the VISION study), 29% voted that they correlate PSMA PET/CT with FDG PET/CT (as in the TheraP study), 17% voted that they use FDG PET/CT

selectively if the correlation with contrast-enhanced CT provides equivocal results, and 3% voted that it is not necessary to identify PSMA-negative lesions. There were 17 abstentions. (No consensus for any given answer option)

5.6. Oligoprogressive mCRPC

As discussed previously (in the nmCRPC section), the concept of oligoprogressive disease is not well defined in advanced prostate cancer, and available evidence for MDT is limited [54–57].

Q161. For patients with multiple metastases who have oligoprogressive mCRPC (a maximum of 3 progressing lesions), 10% of panellists voted to recommend performing a biopsy of a progressing lesion before making a treatment decision, 58% voted for biopsy only in selected patients (e.g. to rule out small cell component or to obtain tissue for NGS), and 32% voted against biopsy. There were five abstentions. (No consensus for any given answer option)

Q162. For the majority of patients with multiple metastases who have oligoprogressive mCRPC (a maximum of 3 progressing lesions, asymptomatic), 33% of panellists voted to recommend switching to another systemic therapy, 55% voted to recommend metastases-directed therapy of all progressing lesions and continue systemic therapy, and 12% voted to recommend a switch of systemic therapy and MDT of all progressing lesions. There were six abstentions. (No consensus for any given answer option)

5.7. Treatment monitoring in mCRPC

Similar to treatment monitoring in mHSPC, guidelines offer very little guidance on how to monitor patients with mCRPC who are receiving systemic therapy. Data from the PREVAIL trial suggest that radiographic progression can occur in up to a quarter of patients who did not fulfil PCWG criteria for PSA progression [79]. In addition, for patients with nmCRPC, a retrospective analysis of data from PROSPER showed that radiographic progression often occurred without PCWG2-defined PSA progression, suggesting that any increase in PSA may warrant closer monitoring [80]. Previously at APCCC, a risk-adapted approach to monitoring during first-line mCRPC treatment was discussed that involved less frequent imaging for patients with a relatively low burden of disease and a good response to systemic therapy (in particular ARPIs) and more frequent imaging for patients with more advanced disease and/or more lines of prior therapy. In addition to imaging, it is important that clinical factors are taken into consideration, as well as additional laboratory parameters, including, but not limited to, complete blood count, liver function, alkaline phosphatase, and lactate dehydrogenase [81].

Q163. For the majority of patients with mCRPC who are on an ARPI and have not developed new symptoms, 69% of panellists voted to recommend regular monitoring by imaging regardless of PSA level, and 31% voted not to perform imaging until PSA progression occurs. There were five abstentions. (No consensus for any given answer option)

Q164. For patients with mCRPC who are on taxane chemotherapy and have not developed new symptoms, 80% of panellists voted to recommend regular monitoring by imaging regardless of PSA level, and 20% voted not to perform imaging until PSA progression occurs. There were seven abstentions. (Consensus for regular imaging regardless of PSA)

So far, no large phase III trials in mCRPC have systematically used next-generation imaging for monitoring. For PSMA PET imaging, response criteria need to be defined because PSMA expression may increase with systemic therapy, in particular when starting ADT and/or ARPI therapy [82–85]. In 2016, the PCWG3 did not include next-generation imaging as a standard imaging modality for use in clinical trials, primarily due to the lack of criteria to define response/progression on systemic therapies [81].

Q165. When asked to identify their preferred imaging modality for treatment monitoring in the majority of patients with mCRPC, 72% of panellists voted for conventional imaging, 21% voted for PET-CT (with different tracers), 3% voted for whole-body diffusion-weighted MRI, and 4% voted that they do not use imaging for treatment monitoring in mCRPC unless patients are clinically progressing. There were seven abstentions. (No consensus for any given answer option, a combined total of 93% voted for at least a CT for monitoring)

In the mCRPC setting, researchers recently reported results from the PROMPTS trial, in which patients with mCRPC and asymptomatic spinal metastasis were randomly assigned to either observation only or screening MRI with pre-emptive treatment (radiotherapy or surgical decompression, as recommended by the treating physician) if screening detected radiographic spinal cord compression (SCC) [27]. The primary endpoint was time to and incidence of confirmed clinical SCC, with a primary timepoint of interest of one year after randomisation. Because rates of clinical SCC were low (6.7% control group vs 4.3% intervention group), and the investigators concluded that screening and pre-emptive treatment are not generally warranted.

Q166. For the majority of patients with mCRPC who have received an ARPI and one line of taxane chemotherapy and have asymptomatic epidural disease (not qualifying for spinal cord compression), 63% of panellists voted for and 37% voted against recommending treatment of the epidural disease. There were 11 abstentions. (No consensus for any given answer option)

5.7.1. Discussion of mCRPC

The therapeutic landscape of mCRPC is constantly evolving as new treatment options are introduced. The

most recent development in the mCRPC disease space was the presentation of findings from PROPEL and MAGNITUDE, two trials with results that are challenging to interpret. The voting at APCCC 2022 showed a clear trend that based on current knowledge and data presented through April 2022, combining PARP inhibition with abiraterone is only recommended for patients with a pathogenic germline and/or somatic BRCA1/2 alteration (Table 4). There was consensus not to recommend the combination for patients with other alterations in DNA repair genes or patients without a known DNA repair gene alteration. This view may change in the future with further follow-up of these two trials, including additional biomarker information and, in particular, updated OS data and also the results of other trials evaluating similar combination strategies (e.g. TALARPO-2, CASPAR).

For treatment sequencing in mCRPC, there was consensus in favour of first-line ARPI therapy if patients have received ADT alone or docetaxel alone in the mHSPC setting (Table 5). The more challenging question is how to treat patients who are progressing on combination treatment with ADT and an ARPI. Here there was consensus to recommend docetaxel as first-line mCRPC treatment. For patients who previously have received triplet therapy, the panel was split between recommending cabazitaxel versus ^{177}Lu-PSMA as first-line mCRPC treatment.

For the small proportion of patients with evidence of dMMR/MSI-high or high-TMB, there was consensus for the use of a checkpoint inhibitor. However, panellists did not vote on when to use immunotherapy in the treatment sequence in these patients. Generally, an ARPI should be used first, while immunotherapy may be an option for second or later-line treatment. This is based on the data reported so far in a limited number of cases of patients with dMMR/MSI-high or high-TMB where checkpoint inhibition was generally used later in the mCRPC treatment sequence.

There was consensus for using PSMA PET imaging to select patients for radioligand therapy, and there was near consensus (74% of votes) to use the same PSMA uptake threshold as in the VISION trial. In all, 29% of panellists voted to use combined PSMA/FDG-PET imaging to identify PSMA-negative disease in patients who are being considered for ^{177}Lu-PSMA radioligand therapy, but the majority of panellists (51%) voted to also correlate PSMA PET findings with the results of contrast-enhanced CT. In many countries, FDG PET is not approved for staging prostate cancer, and logistics also need to be considered–patients generally would need to come twice for separate PET imaging sessions. Better selection of patients for treatment with ^{177}Lu-PSMA is an area of unmet need. Data from the VISION trial presented at ASCO 2022 showed that whole-body mean SUV may be a biomarker for treatment selection, with a significant association between rPFS and OS among patients who were in the highest quartile for this measurement [86]. Similar findings were published from the TheraP trial [87]. Unfortunately, in daily practise, these measurements are mostly not reported.

Regarding treatment monitoring in mCRPC, there was consensus to perform imaging on a regular basis when patients are receiving docetaxel. In terms of which imaging modality to use for monitoring, 72% of panellists voted for conventional imaging (CT and bone scintigraphy), while the rest voted for next-generation imaging (Table 6).

6. Docetaxel fitness

Not all patients with prostate cancer are suitable for chemotherapy with docetaxel, and criteria rendering a patient 'unfit' for docetaxel are not well defined. At APCCC 2017, panellists voted on criteria for docetaxel fitness, reaching consensus that docetaxel ineligibility includes cases of severe hepatic impairment (96% of panellists), grade ≥2 neuropathy (82%), and platelets $< 50\times10^{i}$/l and/or neutrophils $< 1.0\times10^{i}$/l (81%) [2]. There was no consensus on the other proposed factors when considered individually. With the results of the PEACE-1 and ARASENS trials, the question of docetaxel fitness has become even more relevant (see Table 7 and supplement 5 for details).

The APCCC 2022 panel voted on factors they would consider rendering a man 'unfit' (apart from allergy to the substance) for docetaxel at the standard dose of 75 mg/m^2.

Q177. In all, 83% of panellists voted that an ECOG performance status (ECOG PS) of 2 for reasons other than cancer is a meaningful definition only if other factors (e.g. frailty or some assessment of comorbidities) are also present, 12% voted that ECOG PS 2 is by itself a meaningful definition, and 5% voted that performance status is not a reason to exclude docetaxel. There were 20 abstentions. (Consensus that ECOG PS 2 is a meaningful definition of 'docetaxel unfit' only in combination with other factors)

Q178. In all, 81% of panellists voted that ECOG PS 3 for reasons other than cancer is by itself a meaningful definition of 'docetaxel unfit,' 12% voted that it is a meaningful definition only if other factors (e.g. frailty or some assessment of comorbidities) are also present, and 1% voted that performance status is not a reason to exclude docetaxel. There were 20 abstentions. (Consensus that an ECOG PS of 3 for reasons other than cancer is by itself a meaningful definition of 'docetaxel unfit')

Q179. A total of 40% of panellists voted that frailty (e.g. abnormal ADL > 2, weight loss > 10%, comorbidities CIRS-G grade 3–4) as assessed by a geriatric or other health status evaluation is by itself a meaningful definition of 'docetaxel unfit' while 60% voted that it is a meaningful definition only if other factors (e.g. poor performance status) are also present. There were 20 abstentions. (No consensus for any given answer option, no one voted that frailty is not a reason to exclude docetaxel at least in combination with other factors)

Q180. In all, 74% of panellists voted that neuropathy of grade 3 or worse is by itself a meaningful definition of 'docetaxel unfit,' 20% voted that it is a meaningful definition only if other factors (e.g. poor performance status) are also present, and 6% voted that neuropathy is not a reason to exclude docetaxel. There were 21 abstentions. (No consensus for any given answer option, a combined 94% voted that neuropathy is a reason for excluding docetaxel at least in combination with other factors)

Q181. A total of 36% of panellists voted that moderate hepatic impairment (i.e. ALT/AST > 3–5 times and/or bilirubin > 1.5–3 times the upper limit of normal, excluding patients with liver metastases) is by itself a meaningful definition of 'docetaxel unfit,' 45% voted that it is a meaningful definition only if other factors (e.g. poor performance status) are also present, and 19% voted that moderate hepatic impairment is not a reason to exclude docetaxel. There were 20 abstentions. (No consensus for any given answer option, a combined 81% voted that moderate hepatic impairment is a reason to exclude docetaxel at least in combination with other factors)

Q182. In all, 92% of panellists voted that severe hepatic impairment (e.g. ALT/AST > 5 times the upper limit of normal and/or bilirubin > 3 times the upper limit of normal), with or without liver metastases, is by itself a meaningful definition of 'docetaxel unfit,' 7% voted that severe hepatic impairment is a meaningful definition only if other factors (e.g. poor performance status) are also present, and 1% voted that severe hepatic impairment is not a reason to exclude docetaxel. There were 20 abstentions. (Strong consensus that severe hepatic impairment is by itself a meaningful definition of 'docetaxel unfit')

Q183. In all, 73% of panellists voted that platelets $< 50\times10^9$/L and/or neutrophils $< 1.0\times10^9$/L is by itself a meaningful definition of 'docetaxel unfit' 16% voted that it is a meaningful definition only if other factors (e.g. poor performance status) are also present, and 11% voted that platelets $< 50\times10^9$/L and/or neutrophils $< 1.0\times10^9$/L is not a reason to exclude docetaxel. There were 21 abstentions. (No consensus for any given answer option, a combined 89% voted that low platelets and/or neutrophils is a reason to exclude docetaxel at least in combination with other factors)

6.1. Discussion of docetaxel fitness

Similar to APCCC 2017 when panellists last discussed these criteria, it seems to be more challenging at least for patients with prostate cancer to define simple criteria for docetaxel fitness than it is to define criteria for fitness for therapies such as cisplatin. At APCCC 2022, the only consensus reached regarding docetaxel fitness was that patients are not fit to receive docetaxel if they have an ECOG performance status of 3 or severe hepatic impairment (Table 7). Almost a consensus was achieved for grade ≥3 sensory neuropathy, which was considered by 74% of panellists to be sufficient in itself to define docetaxel ineligibility. For some factors, some panel members voted that they would only consider them in combination with other factors. In the context of mHSPC, given the multitude of available alternatives to docetaxel, clinicians should carefully consider whether to recommend docetaxel in borderline-eligible patients. The voting results at APCCC 2022 make it clear that the role of docetaxel as sole additional therapy in mHSPC has decreased based on recent study results. Moreover, even for patients who are borderline docetaxel fit and for whom triplet therapy is being considered, the potential benefit of adding docetaxel should be weighed against potential side effects. Clinicians should bear in mind that docetaxel in combination with abiraterone/prednisone is associated with an increased rate of liver toxicity, and that we have no formal studies of the efficacy of adding docetaxel to an ARPI plus ADT.

7. Poor prognosis mCRPC/androgen-indifferent prostate cancer

While the majority of advanced prostate cancers remain driven by AR signalling throughout treatment, it has become increasingly recognised that a subset of advanced prostate cancer can adapt during the course of therapy to become less dependent on the AR, and that this adaptation is associated with loss of luminal prostate cancer markers (including PSA), the development of lineage plasticity, and the acquisition or expansion of pathologic and molecular small cell/neuroendocrine features [88]. The term 'poor prognosis prostate cancer' describes variants of androgen-indifferent prostate cancer (AIPC), in which tumour cells show attenuated or low AR expression. These AIPC variants include aggressive variant prostate cancer (AVPC, which is defined by clinical parameters), neuroendocrine prostate cancer (NEPC, in which tumour cells show loss of AR expression and the presence of neuroendocrine markers), and double-negative prostate cancer (DNPC, in which tumour cells show loss of AR expression and no expression of neuroendocrine markers) [89].

Defining and identifying poor prognosis prostate cancer remains challenging, but these variants are often suspected in patients who develop rapidly progressive disease, unusual sites or pattern of metastases (e.g. radiologically lytic bone or parenchymal brain metastases), and/or progression in the setting of a low PSA that is not rising or is rising modestly. At APCCC 2017, there was no consensus regarding how to define poor prognosis mCRPC. In the five years since, our understanding of these subtypes of prostate cancer has increased. For example, a molecular signature with loss of TP53 and RB1 and/or PTEN has been associated with androgen indifference [90,91]. Although relevant evidence is primarily limited to autopsy studies, the incidence of poor prognosis prostate cancer seems to have risen since the introduction of novel potent ARPIs [92].

At APCCC 2022 the panel voted on pragmatic, clinical features that may help to identify patients with poor prognosis mCRPC/androgen-indifferent prostate cancer excluding pure small cell prostate cancer.

Q184. In all, 63% of panellists voted that the presence of exclusively visceral metastases (excluding lung-only metastases) is sufficient, 32% voted that this is sufficient only if other unfavourable factors are also present, and 5% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were five abstentions. (No consensus for any given answer option, a combined 95% voted for this factor at least in combination with other unfavourable factors)

Q185. In all, 67% of panellists voted that the presence of multiple liver metastases is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 29% voted that is sufficient only in combination with other unfavourable factors, and 4% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were four abstentions. (No consensus for any given answer option, a combined 96% voted for this factor at least in combination with other unfavourable factors)

Q186. A total of 23% of panellists voted that the presence of lytic bone metastases is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 72% voted that is sufficient only if other unfavourable factors are also present, and 5% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were four abstentions. (No consensus for any given answer option, a combined 95% voted for this factor at least in combination with other unfavourable factors)

Q187. In all, 32% of panellists voted that low PSA level relative to tumour burden is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 64% voted that is sufficient only in combination with other unfavourable factors, and 4% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were four abstentions. (No consensus for any given answer option, a combined 96% voted for this factor at least in combination with other unfavourable factors)

Q188. In all, 18% of panellists voted that bulky lymphadenopathy (≥5 cm) or a bulky high-grade mass (≥5 cm, Gleason ≥8) in the prostate or pelvis is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 60% voted that is sufficient only in combination with other unfavourable factors, and 22% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were four abstentions. (No consensus for any given answer option, a combined 78% voted for this factor at least in combination with other unfavourable factors)

Q189. In all, 64% of panellists voted that a short response (≤6 months) to ADT plus an ARPI and/or docetaxel for mHSPC is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 32% voted that is sufficient only in combination with other unfavourable factors, and 4% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were four abstentions. (No consensus for any given answer option, a combined 96% voted for this factor at least in combination with other unfavourable factors)

Q190. In all, 52% of panellists voted that low PSA (≤10 ng/mL) at initial presentation (before ADT) or at the time of symptomatic progression of castrate-resistant disease plus high volume (≥20) bone metastases is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 42% voted that is sufficient only in combination with other unfavourable factors, and 6% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were six abstentions. (No consensus for any given answer option, a combined 94% voted for this factor at least in combination with other unfavourable factors)

Q191. In all, 15% of panellists voted that serum CEA and/or LDH twice the upper limit of normal is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 61% voted that is sufficient only in combination with other unfavourable factors, and 24% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were 12 abstentions. (No consensus for any given answer option, a combined 76% voted for this factor at least in combination with other unfavourable factors)

Q192. In all, 69% of panellists voted that rapid unequivocal progression (clinical and/or imaging) without correlation with PSA kinetics is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 29% voted that is sufficient only in combination with other unfavourable factors, and 2% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were four abstentions. (No consensus for any given answer option, a combined 98% voted for this factor at least in combination with other unfavourable factors)

Q193. In all, 69% of panellists voted that partly neuro-endocrine differentiation with high proliferation index on a tumour biopsy and/or low or absent androgen receptor (AR) expression is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 30% voted that is sufficient only in combination with other factors, and 1% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were seven abstentions. (No consensus for any given answer option, a combined 99% voted for this factor at least in combination with other unfavourable factors)

Q194. In all, 71% of panellists voted that lack of expression of both AR (AR and/or PSA) and neuroendocrine markers on biopsy (double-negative prostate cancer) is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 26% voted that is sufficient only in combination with other unfavourable factors, and 3% voted that it is not a criterion for

poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were 10 abstentions. (No consensus for any given answer option, a combined 97% voted for this factor at least in combination with other unfavourable factors)

Q195. In all, 40% of panellists voted that evidence of pathogenic alterations in any two of the following genes: RB1, TP53, and PTEN, is sufficient to define poor-prognosis mCRPC/androgen-indifferent prostate cancer (excluding pure small cell prostate cancer), 52% voted that is sufficient only in combination with other unfavourable factors, and 8% voted that it is not a criterion for poor-prognosis mCRPC/androgen-indifferent prostate cancer. There were 12 abstentions. (No consensus for any given answer option, a combined 92% voted for this factor at least in combination with other unfavourable factors)

The APCCC 2022 panel also voted on treatment recommendations for patients with poor prognosis prostate cancer (excluding pure small cell differentiated tumours, see Table 8 and supplement 5 for details). The NCCN guidelines discuss the option of the combination of carboplatin and cabazitaxel with granulocyte colony stimulating factor (GCSF) support for patients with mCRPC who show clinical evidence of poor prognosis prostate cancer or molecular alterations that are compatible with aggressive variant development (at least two of PTEN, TP53, and RB1). The inclusion of this regimen is based on the results of a phase I/II trial of patients with mCRPC in which the combination was associated with improved PFS, particularly in the subgroup of patients with characteristics of aggressive variant disease [93]. So far, there is no evidence to recommend using a platinum-based combination in newly diagnosed hormone-sensitive prostate cancer with aggressive disease features.

Q196. For the majority of patients with newly diagnosed poor prognosis/AR-indifferent prostate cancer, 58% of panellists voted that first-line treatment at diagnosis with ADT plus docetaxel with or without an ARPI, 32% voted for ADT plus a taxane-platinum-based combination treatment, 8% voted for ADT plus an ARPI, and 2% voted for chemotherapy without ADT. There were 13 abstentions. (No consensus for any given answer option, a combined 90% voted for chemotherapy)

Q197. For the majority of patients who develop poor prognosis/AR indifferent prostate cancer after receiving standard first-line therapy for mHSPC (ADT plus an ARPI), 58% of panellists voted to recommend that treatment at the time of progression to mCRPC should consist of platinum-based systemic treatment, and 42% voted for treatment as per mCRPC. There were 13 abstentions. (No consensus for any given answer option)

Q198. For the majority of patients who develop poor prognosis/AR indifferent prostate cancer after receiving standard first-line therapy for mHSPC (ADT plus docetaxel with or without an ARPI), 78% of panellists voted to recommend that treatment at the time of progression to mCRPC should consist of platinum-based systemic treatment, while 22% voted for treatment as per mCRPC. There were 13 abstentions. (Consensus for platinum-based systemic treatment)

7.1. Discussion of poor prognosis prostate cancer

It is important to recognise that clinical features alone are not enough to define poor prognosis prostate cancer. This is reflected by the voting at APCCC 2022: Panellists reached no consensus on any of questions 184–195, which asked if specific unfavourable clinical or pathologic features were sufficient in themselves for defining poor prognosis prostate cancer (Table 8). For each of these questions, substantial proportions of panellists only voted for the factor in combination with other clinical or pathological features.

There also is considerable uncertainty regarding the optimal treatment of patients with poor prognosis prostate cancer. For newly diagnosed prostate cancer with poor prognosis features, the panel did not reach consensus on any of the treatment options, but a combined 90% voted for a chemotherapy combination, including platinum-based chemotherapy (32% of votes). There also was consensus to recommend platinum-based combinations for patients who develop poor prognosis mCRPC after having received an ARPI and/or docetaxel for mHSPC. This is supported by current NCCN guidelines, which recommend the combination of carboplatin (AUC 4) plus cabazitaxel (20 mg/m^b) based on a randomised phase II trial showing an improvement in PFS (albeit at a cabazitaxel dose of 25 mg/m^b) in patients with mCRPC who had poor prognosis features [85].

7.2. General discussion and conclusions

Similar to the results of prior APCCC meetings, there was a high level of enthusiasm for MDT even though strong data to support this approach is lacking. We want to raise awareness that several randomised trials of MDT are now underway—eligible patients should be enroled in these trials, and clinicians should not assume that they know what is best for patients before these studies read out [94].

Interestingly, panellists required more evidence to embrace new treatments in some areas than others. Based on the voting results, considerably less evidence has been required to embrace MDT in oligometastatic disease and checkpoint inhibition in molecularly selected patients, whereas panellists seemed more conservative in recommending combination treatment with abiraterone/prednisone plus a PARP inhibitor. For this latter option, consensus was reached only in the first-line treatment of mCRPC in patients with pathogenic BRCA1/2 aberrations. Importantly, at the time of APCCC 2022, OS data from the PROPEL and MAGNITUDE trials were not mature and data were not published.

A potential weakness of our process is that we instruct our panellists to vote as though all diagnostic and therapeutic options are available, which is assuredly unrealistic from a global healthcare perspective. In real-world settings, healthcare budgets will not stretch to cover treatment for all patients with advanced prostate cancer, regardless of the results of evidence-based studies. Consequently, as healthcare providers, we routinely face dilemmas related to treatment access for our patients. Balancing limited resources means repeatedly determining how best to allocate available resources, which will affect access to care. A global healthcare perspective requires striking a balance so that the as many patients as possible can benefit as much as possible while minimising both waste of resources and differences among treatments offered (e.g. due to global disparities). Regulatory agencies attempt to address this dilemma by only approving treatments that have demonstrated a favourable cost-effectiveness profile so that clinicians can freely recommend whatever approved treatment is available and appropriate for an individual patient. If a treatment offers insufficient benefit to justify its cost, then it is evaluated as wasteful and thus is not made available. In that light, we as clinicians and clinical researchers should be vigilant and ensure that trials are performed correctly and with equipoise among standard-of-care control arms [95,96].

CRediT authorship contribution statement

Conceptualization: Scientific committee: Bossi Alberto, Davis Ian D, de Bono Johann, Fizazi Karim, Gillessen Silke, James Nicholas D, Mottet Nicolas, Omlin Aurelius, Shore Neal, Small Eric, Smith Matthew, Sweeney Christopher, Tombal Bertrand. **Methodology**: Scientific committee: Bossi Alberto, Davis Ian, de Bono Johann, Fizazi Karim, Gillessen Silke, James Nicholas D, Mottet Nicolas, Omlin Aurelius, Shore Neal, Small Eric, Smith Matthew, Sweeney Christopher, Tombal Bertrand. **Software**: Not applicable. **Validation**: Not applicable. **Formal analysis**: Not applicable. **Investigation:** All authors. **Resources**: All authors. **Data Curation**: Scientific committee: Bossi Alberto, Davis Ian, de Bono Johann, Fizazi Karim, Gillessen Silke, James Nicholas D, Mottet Nicolas, Omlin Aurelius, Shore Neal, Small Eric, Smith Matthew, Sweeney Christopher, Tombal Bertrand. **Writing - Original Draft**: Silke Gillessen and Aurelius Omlin. **Writing - Review & Editing**: All authors. **Visualisation**: Not applicable. **Supervision**: Silke Gillessen and Aurelius Omlin. **Project administration**: Scientific commitee: Bossi Alberto, Davis Ian, de Bono Johann, Fizazi Karim, Gillessen Silke, James Nicholas D, Mottet Nicolas, Omlin Aurelius, Shore Neal, Small Eric, Smith Matthew, Sweeney Christopher, Tombal Bertrand. **Funding acquisition**: Scientific commitee: Bossi Alberto, Davis Ian, de Bono Johann, Fizazi Karim, Gillessen Silke, James Nicholas D, Mottet Nicolas, Omlin Aurelius, Shore Neal, Small Eric, Smith Matthew, Sweeney Christopher, Tombal Bertrand.Uncited references
[8]; [37].

Conflict of interest statement

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Name of commercial company: Astellas. • Funding for RADIO trial bladder cancer – Coordinating. PI – financial interest, Institutional. Name of commercial company: AstraZeneca. • Funding for STAMPEDE trial – Coordinating PI – No. financial interest, Institutional. Name of commercial company: Janssen; Receipt of honoraria or consultation fees: • Advisory Board – Advice around PARP inhibitors, Personal, < €5000. Name of commercial company: AstraZeneca dvisory Board – Prostate cancer therapies, Personal, < €5000. Name of commercial company: Clovis. Expert Testimony – Assisted with submissions. regarding licensing for abiraterone, Institutional > €100,001. Name of commercial company: Janssen. Advisory Board – Prostate cancer therapies, Personal, €5001–€10,000. Name of commercial company: Janssen. Advisory Board – Bladder cancer therapy, Personal, < €5000. Name of commercial company: Merck. Advisory Board – Prostate cancer therapies, Personal, < €5000. Name of commercial company: Novartis Expert Testimony – Providing STAMPEDE trial data to facilitate licence extensions internationally for docetaxel, Institutional, > €100,001. Name of commercial company: Sanofi. Advisory Board - Docetaxel, Personal, < €5000. Name of commercial company: Sanofi. Participation in a company sponsored speaker's bureau: Bayer, Novartis. **Nicolas MOTTET**: Receipt of grants/research supports: Astellas, Sanofi Pasteur, Pierre Fabre; Receipt of honoraria or consultation fees: Astellas, Jansen, BMS, Bayer, IPSEN, Ferring, Sanofi, Steba, Astra Zeneca, Carrik, Arquer. diagnostics, GE, Takeda. **Thomas ZILLI.** AFFILIATION: Geneva University Hospital, Geneva, Switzerland. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Varian Medical Systems International AG; Debiopharm. Receipt of honoraria or consultation fees: Janssen, Astellas, Debiopharm, Ferring, Varian Medical Systems International AG. Participation in a company sponsored speaker's bureau: Janssen, Astellas, Debiopharm. Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: Geneva 07.02.2022. **Christopher Logothetis.** AFFILIATION: MD Anderson Cancer Center. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Janssen, ORIC Pharmaceuticals, Novartis, Aragon Pharmaceuticals. Receipt of honoraria or consultation fees: Merck, Sharp & Dohme, Bayer, Amgen. Participation in a company sponsored speakers bureau: None. Stock shareholder: None. Spouse/partner: None. Other support (please specify): None. Signature: Date: February 7, 2022. **William Oh.** AFFILIATION: Chief Medical Officer at Sema4 and Clinical Professor of Medicine, Div. of Hematology/Medical Oncology at Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai. Type of affiliation /

financial interest Name of commercial company. Receipt of grants/research supports: Receipt of honoraria or consultation fees: GSK, Janssen, Merck, Pfizer. Participation in a company sponsored speakers bureau: Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: February 7, 2022. **Himisha Beltran**. AFFILIATION: Dana Farber Cancer Institute. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Janssen, AbbVie/Stemcentrx, Eli Lilly, Millennium Pharmaceuticals, Bristol Myers Squibb. Receipt of honoraria or consultation fees: Janssen, Astellas, Astra Zeneca, Merck, Pfizer, Foundation Medicine, Blue Earth Diagnostics, Amgen, Oncorus, LOXO. Participation in a company sponsored speaker's bureau: NONE. Stock shareholder: NONE. Spouse/partner: NONE. Other support (please specify): Signature: Date: Feb 7, 2022. **Pirkko-Liisa Kellokumpu-Lehtinen**. AFFILIATION: Tampere University and Tampere University Hospital, Tampere, Finland. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Only directly to my hospital; Lilly, Merck and Finnish Cancer Society. Receipt of honoraria or consultation fees: BMS, Merck. Participation in a company sponsored speaker's bureau: NONE. Stock shareholder: NONE. Spouse/partner: NONE. Other support (please specify):reimbursement of expenses to attend conference; Sanofi. Signature: Date: Feb 7, 2022. **Prof. Mark A. Rubin, MD**. AFFILIATION: University of Bern, Department for BioMedical Research (DBMR). Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Janssen, Roche, Novartis. Receipt of honoraria or consultation fees: NeoGenomics Labs. Participation in a company sponsored speaker's bureau: Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: Feb 8, 2022. **Prof. Dr. Thomas Steuber**. AFFILIATION: Martini-Klinik, Prostate Cancer Center, University Hospital Hamburg-Eppendorf. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: NONE. Receipt of honoraria or consultation fees: Astellas, Amgen, Bayer, Janssen, ProteoMedix, Sanofi, Merck, Astra Zeneca. Participation in a company sponsored speaker's bureau: Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: Feb 8, 2022. **Prof. Rob Bristow**. AFFILIATION: University of Manchester. I have no potential conflict of interest to report. **IGNACIO DURAN.** AFFILIATION: HOSPITAL UNIVERSITARIO MARQUES DE VALDECILLA. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Roche and Astra-Zeneca. Receipt of honoraria or consultation fees: Bristol Myers Squibb, MSD, Ipsen, Roche- Genentech, Janssen, Astellas Pharma, EUSA Pharma, Bayer, Novartis. Participation in a company sponsored speaker's bureau: Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: February 8th 2022. **FERNANDO MALUF.** AFFILIATION: ONCOLOGIST. I have no potential conflict of interest to report. Signature: Date: February 8th 2022. **Hiroyoshi Suzuki.** AFFILIATION: Department of Urology, Toho University Sakura Medical Center. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Takeda, AsahiKasei, Taiho, Ono, Chugai, Sanofi, Daiichi-Sankyo, Nihon, Nippon Shinyaku. Receipt of honoraria or consultation fees: Bayer, Janssen, AstraZeneca, Astellas, Chuga-Roche, MSD. Participation in a company sponsored speaker's bureau:Takeda, Bayer, Janssen, AstraZeneca, Astellas, Sanofi. Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: February 8th 2022. **Danny M. Rabah.** AFFILIATION: King Saud University and king Faisal specialist hospital and research centre. I have no potential conflict of interest to report. Signature: Date: February 8th 2022. **LEVENT TÜRKERİ.** AFFILIATION: ACIBADEM M.A. AYDINLAR UNIVERSITY, ISTANBUL, TURKEY. I have no potential conflict of interest to report. Signature: Date: February 8th 2022. **Mark Frydenberg.** AFFILIATION: ACIBADEM M.A. AYDINLAR UNIVERSITY, ISTANBUL, TURKEY. I have no potential conflict of interest to report. Signature: Date: February 8th 2022. **Anders Bjartell.** AFFILIATION: Dept. Of Urology, Skane University Hospital Malmö, Sweden. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Ferring, Bayer, Astellas. Receipt of honoraria or consultation fees: Astellas, AstraZeneca, Bayer, Janssen, Merck, Recordati, Sandoz. Participation in a company sponsored speaker's bureau:Astellas, Bayer, IPSEN, Janssen, Recordati, Sandoz. Stock shareholder: LIDDS Pharma, Glactone Pharma, WntResearch. Spouse/partner: NONE. Other support (please specify): Signature: Date: February 9th 2022. **Dingwei Ye.** AFFILIATION: Fudan University Shanghai Cancer Center. I have no potential conflict of interest to report. Signature: Date: February 9th 2022. **Ros Eeles**. AFFILIATION: ……. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: GU-ASCO, The Royal Marsden NHS Foundation Trust, University of Chicago, ESMO, AstraZeneca UK Limited. Receipt of honoraria or consultation fees: Honorarium as speaker. Participation in a company sponsored speaker's bureau: Stock shareholder: Spouse/partner: Other support (please specify): January 2016. Signature: Date: February 15th 2022. **Inge van Oort.** AFFILIATION: Urology, Radboudumc, Nijmegen, The Netherlands. Type of affiliation / financial interest Name of

commercial company. Receipt of grants/research supports: Astellas, Bayer, Janssen. Receipt of honoraria or consultation fees: Astellas, Bayer, MSD-Astra Zeneca, Janssen. Participation in a company sponsored speaker's bureau: Bayer, Astellas. Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: February 22nd 2022. **Ravindran Kanesvaran.** AFFILIATION: Urology, Radboudumc, Nijmegen, The Netherlands. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Sanofi, Eisai. Receipt of honoraria or consultation fees: MSD, BMS, AstraZeneca, Amgen, Astellas, Johnson&Johnson, Novartis, Merck, Pfizer. Participation in a company sponsored speaker's bureau:MSD, BMS, AstraZeneca, Amgen, Astellas, Johnson&Johnson, Novartis, Merck, Pfizer. Stock shareholder: Spouse/partner: Other support (please specify): Signature: Date: February 22nd 2022. Signature: Date: February 9th 2022. **Nicola Fossati.** AFFILIATION: Urology, Ente Ospedaliero Cantonale (EOC), Lugano, CH. I have no potential conflict of interest to report. Signature: Date: February 1st March 2022. **Hiroji Uemura.** AFFILIATION: Department of Urology and Renal Transplantation, Yokohama City University Medical Center. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: none. Receipt of honoraria or consultation fees: Bayer, Janssen, Sanofi, Takeda, Astellas, AstraZeneca, Amgen, Dai-ichi Sankyo, Pfizer, MSD, Chugai. Participation in a company sponsored speaker's bureau:none. Stock shareholder: none. Spouse/partner: none. Other support (please specify): none. Signature: Date: March 7th 2022. **Lisa Horvath.** AFFILIATION: Chris O′Brien Lifehouse. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: Astellas. Receipt of honoraria or consultation fees: Astellas, Janssen, Bayer, Imagion Biosystems. Participation in a company sponsored speaker's bureau:Astellas, Janssen, Bayer. Stock shareholder: Imagion Biosystems. Spouse/partner: Connected Medicine Solutions (Employee, stocks). Other support (please specify): none. Signature: Date: March 9th 2022. **Robert Reiter.** AFFILIATION: UCLA Urology. X I have no potential conflict of interest to report. Signature: Date: March 11th 2022. **Daniel Castellano.** AFFILIATION: MEDICAL ONCOLOGIST HEAD GU UNIT HOSPITAL UNIVERSITARIO 12 DE OCTUBRE. MADRID-UNIVERSIDAD COMPLUTENSE. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports: JANSSEN. Receipt of honoraria or consultation fees:ASTELLAS, ROCHE, MERCK, PFIZER, NOVARTIS, MSD, BMS, IPSEN, GILEAD, JANSSEN, BAYER. Participation in a company sponsored speaker's bureau:none. Stock shareholder: none. Spouse/partner: none. Other support (please specify): none. Signature: 28th March 2022. **Sandy Srinivas**. AFFILIATION: Stanford University, CA. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:. Receipt of honoraria or consultation fees:BAYER, JANSSEN, MERCK, NOVARTIS. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31ST March 2022. **Matthew Sydes**. AFFILIATION: MRC Clinical Trials Unit at UCL. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:ASTELLAS, CLOVIS ONCOLOGY, JANSSEN, NOVARTIS, PFIZER, SANOFI AVENTIS. Receipt of honoraria or consultation fees:ELI LILLY, JANSSEN. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 3Oth March 2022. **Ekeke, Onyanunam Ngozi.** AFFILIATION: DEPARTMENT OF SURGERY, UNIVERSITY OF PORT HARCOURT TEACHING HOSPITAL, PORT HARCOUT, NIGERIA. X I have no potential conflict of interest to report. Signature: Date: March 30 h 2022. **Susan Halabi, PhD.** AFFILIATION: Duke University. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:ASCO TAPUR, Astellas. Receipt of honoraria or consultation fees:Sanofi, Aveo Oncology. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 3Oth March 2022. **Cora N. Sternberg, MD, FACP.** AFFILIATION: Eeill Cornell Medicine, New York Presbyterian. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:. Receipt of honoraria or consultation fees:Astellas Pharma, Astrazeneca, Bayer, Genzyme, Gilead, Incyte, Medscape, Janssen, Bristol Myers Squibb, Merck, Msd, Pfizer, Roche, Impact Pharma, Sanofi-Genzyme, Urotoday, Cco Clinical, Nci. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 3Oth March 2022. **Hirotsugu Uemura.** AFFILIATION:. Kindai University Faculty of Medicine. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:AstraZeneca, Janssen, Takeda, Astellas, Sanofi, Taiho, Ono pharm, Kissei. Receipt of honoraria or consultation fees:Bayer, Sanofi, Janssen, MSD, Ono, BMS, Pfizer. Participation in a company sponsored speaker's bureau:Bayer, Sanofi, Janssen, MSD, Ono, BMS, Pfizer. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31st March 2022. **Orazio Caffo.** AFFILIATION: Santa Chiara Hospital – Trento (Italy). Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:none. Receipt of honoraria or

consultation fees:AAA, Astella, Bayer, Janssen, MSD, Pfizer. Participation in a company sponsored speaker's bureau:Astellas, Bayer, Janssen, Ipsen, MSD. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31st March 2022. **Valérie Fonteyne.** AFFILIATION:Ghent University Hospital. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Ipsen. Receipt of honoraria or consultation fees:Ipsen, Astellas, Janssen. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31st March 2022. **Muhammad Bulbul.** AFFILIATION: American University of Beirut. X I have no potential conflict of interest to report. Signature: Date: March 31st 2022. **Claire Vale.** AFFILIATION: MRC Clinical Trials Unit at UCL. X I have no potential conflict of interest to report. Signature: Date: March 31st 2022. **MRABTI Hind.** AFFILIATION: Institut National d'oncologie, Mohamed V University. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:. Receipt of honoraria or consultation fees:Astellas, Sanofi, Janssen, AstraZeneca, Ipsen, MSD, Pfizer, Amgen. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31st March 2022. **Deborah Mukherji**. AFFILIATION: American University of Beirut. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Astellas. Receipt of honoraria or consultation fees:Astellas, Janssen, MSD, Ipsen, BMS. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31st March 2022. Sloan Kettering Cancer Center. AIQ Pharma. Epic Sciences. Janssen. Menarini Silicon Biosystems. ThermoFisher. **Howard I. Scher, MD, FASCO.** AFFILIATION: Memorial Sloan Kettering Cancer Center. Howard I. Scher, MD, FASCO - Disclosure Form. March 31, 2022. Honoraria. Sidney Kimmel Cancer Center, Jefferson Health. Elsevier, LTD. Arsenal Capital. Consultancy/Advisory Board. Ambry Genetics Corporation, Konica Minolta,Inc. Amgen. Bayer. Janssen Research & Development, LLC. Pfizer Inc. Sun Pharmaceuticals Industries, Inc. WCG Oncology. Research Funding to Memorial Sloan Kettering Cancer Center. AIQ Pharma. Epic Sciences. Janssen. Menarini Silicon Biosystems. ThermoFisher. **Evan Y. Yu, M.D.** AFFILIATION: Fred Hutchinson Cancer Center and University of Washington. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Bayer, Blue Earth, Daiichi-Sankyo, Dendreon, Lantheus, Merck, Seagen. Receipt of honoraria or consultation fees:Abbvie, Advanced Accelerator Applications, Bayer, Clovis, Exelixis, Janssen, Merck, Sanofi. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31st March 2022. **Gedske Daugaard**. AFFILIATION: Rigshospitalet, Copenhagen. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:. Receipt of honoraria or consultation fees:Bayer, Sanofi, Astellas, MSD, Bristol Myers. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 30th March 2022. **Celestia S. Higano, MD, FACP**. AFFILIATION: University of Columbia. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:None last 24 months. Receipt of honoraria or consultation fees:AstraZeneca, Astellas, Genentech, Merck Sharp & Dohme, Myovant, Tolmar, Vaccitech, Verity. Participation in a company sponsored speaker's bureau:none. Stock shareholder: CTI Biopharma. Spouse/partner: none. Other support (please specify): Expert testimony, Ferring. Signature: 31st March 2022. **Dr. Vedang Murthy**. AFFILIATION: Radiotion Oncology. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Varian Medical Systems. Receipt of honoraria or consultation fees:. Participation in a company sponsored speaker's bureau: Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 1st April 2022. **Gero Kramer.** AFFILIATION: Department of Urology, Medical University of Vienna. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:None. Receipt of honoraria or consultation fees:Astellas, AstraZeneca, Bayer, BMS, Ipsen, Janssen, MSD, Novartis, Sanofi Genzyme, Takeda, Ferring. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 31st March 2022. **Niven Mehra**. AFFILIATION: Radboudumc. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Astellas, Astrazeneca, BMS. Receipt of honoraria or consultation fees:Astellas, Astrazeneca, Bayer, Janssen. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 1st April 2022. **Juan Pablo Sade.** AFFILIATION: Instituto Alexnder Fleming, Buenos Aires, Argentina. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Janssen, Astellas, AtraZeneca, MSD, BMS. Receipt of honoraria or consultation fees:Janssen, Bayer, Pfizer, Astellas. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 3rd April 2022. **Dr Maria De Santis.** AFFILIATION: Charité Universitätsmedizin Berlin, Department of Urology.

Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:. Receipt of honoraria or consultation fees:AAA, Amgen, Astellas, AstraZeneca, Basilea, Bayer, Bioclin, BMS, EISAI, Ferring, Immunomedics, Ipsen, Janssen, MSD, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, SeaGen. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 1st April 2022. **Iwona Skoneczna.** AFFILIATION: Maria Sklodowska-Curie National Research Institute of Oncology, Szpital Grochowski, Warsaw, Poland. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Astellas, Bayer, BMS, Janssen, Roche. Receipt of honoraria or consultation fees:Astellas, Bayer, Janssen. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 1st April 2022. **Laurence Klotz.** AFFILIATION: University of Toronto. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:miR Scientific, Exact Imaging. Receipt of honoraria or consultation fees:miR Scientific, Antev. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 30th March 2022. **Yüksel Ürün.** AFFILIATION: Ankara University School of Medicine. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:. Receipt of honoraria or consultation fees:Astellas, AtraZeneca, BMS, Janssen Oncology, MSD, Pfizer, Roche. Participation in a company sponsored speaker's bureau:Astellas, Amgen, AtraZeneca, BMS, Janssen Oncology, Pfizer, Roche. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 01st April 2022. **Howard R. Soule.** AFFILIATION: Prostate Cancer Foundation. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:. Receipt of honoraria or consultation fees:Compugen. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 4th April 2022. **Simon Chowdhury.** AFFILIATION:. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:Janssen Oncology, Beigene, Clovis Oncology, Pfizer,. Receipt of honoraria or consultation fees:. Participation in a company sponsored speaker's bureau:Janssen Oncology, AstraZeneca, Bayer, Pfizer, Sandoz. Stock shareholder:. Spouse/partner:. Other support (please specify): Janssen Oncology (Advisory board). Novartis (advisory board, consultancy). Bayer (Advisory board). Astellas (advisory board, consultancy). Athenex (advisory board). Beigene (advisory board). Clovis Oncology (Advisory board). Telix (advisory board, consultancy). Curve.Life (founder and stock). Huma (consulting fees and Stock). Remedy Bio: consulting fees, Stock. Signature: 4th April 2022. **Daniel Heinrich**. AFFILIATION: Innlandet Hospital, Department of Oncology and Radiotherapy, Gjøvik, Norway. X I have no potential conflict of interest to report. Signature: Date: 28th February 2022. **Raya Leibowitz.** AFFILIATION: Shamir Medical Center, Zerifin, Be'er Yaakov, Israel. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:none. Receipt of honoraria or consultation fees:MSD, BMS, Isotopia, Bayer, AstraZeneca, Astellas, Janssen, Pfizer. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Signature: 05th April 2022. **Raja Khauli.** AFFILIATION: American University of Beirut Medical Ctr Clinical. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:none. Receipt of honoraria or consultation fees:. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify): honoraria: Astellas, Janssen, Algorithm SAL. Signature: 06th April 2022. **Axel Merseburger.** AFFILIATION: Campus Lübeck, University Hospital Schleswig-Holstein. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:none. Receipt of honoraria or consultation fees:. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify):. Lectures/Speaker/Honoraria:. AstraZeneca, Bristol-Myers Squibb, Eisai, Ferring, Ipsen, MSD, Merck Serono, Janssen, Takeda, TEVA, Astellas, Novartis, Pfizer, Recordati and Roche. Consultant:. AstraZeneca, Astellas, Bristol-Myers Squibb, Ferring, Ipsen, Janssen, EUSAPharm, MSD, Merck Serono, Novartis, Takeda, Teva, Pfizer, Recordati and Roche. Research and clinical trials:. AstraZeneca, Astellas, Bristol-Myers Squibb, Ipsen, Janssen, EUSAPharm, MSD, Merck Serono, Novartis, Takeda, Teva, Pfizer und Roche. Signature: 06th April 2022. **Carmel Pezaro**. AFFILIATION: Sheffield Teaching Hospitals NHS Foundation Trust. Type of affiliation / financial interest Name of commercial company. Receipt of grants/research supports:none. Receipt of honoraria or consultation fees:Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, Janssen. Participation in a company sponsored speaker's bureau:. Stock shareholder:. Spouse/partner:. Other support (please specify): Bayer, Ipsen (travel support). Signature: 06th April 2022. All remaining authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.02.018.

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