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Review

Lack of consensus identifies important areas for future clinical research: Advanced Prostate Cancer Consensus Conference (APCCC) 2019 findings

Ursula M. Vogl [a], Tomasz M. Beer [b], Ian D. Davis [c], Neal D. Shore [d], Christopher J. Sweeney [e,aa], Piet Ost [f], Gerhardt Attard [g], Alberto Bossi [h], Johann de Bono [i], Charles G. Drake [j], Eleni Efstathiou [k], Stefano Fanti [l], Karim Fizazi [m], Susan Halabi [n], Nicolas James [o], Nicolas Mottet [p], Anwar R. Padhani [q], Mack Roach [r], Mark Rubin [s,ab], Oliver Sartor [t], Eric Small [r], Matthew R. Smith [u], Howard Soule [v], Matthew R. Sydes [w], Bertrand Tombal [x], Aurelius Omlin [ac,l], Silke Gillessen [a,y,z,ad,l,*] on behalf of the APCCC 2019 expert panel[2]

[a] *Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland*
[b] *Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA*
[c] *Monash University and Eastern Health, Victoria, Australia*
[d] *Carolina Urologic Research Center, Myrtle Beach, SC, USA*
[e] *Dana-Farber Cancer Institute, Boston, MA, USA*
[f] *Radiation Oncology, Ghent University Hospital, Ghent, Belgium*
[g] *University College London Cancer Institute, London, UK*
[h] *Genito Urinary Oncology, Prostate Brachytherapy Unit, Goustave Roussy, Paris, France*
[i] *The Institute of Cancer Research/Royal Marsden NHS Foundation Trust, Surrey, UK*
[j] *Division of Haematology/Oncology, Columbia University Medical Center, New York, NY, USA*
[k] *University of Texas MD Anderson Cancer Center, Houston, TX, USA*
[l] *Policlinico S.Orsola, Universitàdi Bologna, Italy*
[m] *Institut Gustave Roussy, University of Paris Sud, Villejuif, France*
[n] *Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA*
[o] *The Institute of Cancer Research, London, UK*

* *Corresponding author:* Oncology Institute of Southern Switzerland, Via Gallino 12, 6500, Bellinzona, Switzerland.
E-mail address: silke.gillessen@eoc.ch (S. Gillessen).

[1] These authors contributed equally to this article. [2] APCCC 2019 expert panel: Silke Gillessen, Gerhardt Attard, Tomasz M. Beer, Himisha Beltran, Anders Bjartell, Alberto Bossi, Alberto Briganti, Rob G. Bristow, Kim N. Chi, Noel Clarke, Ian D. Davis, Johann de Bono, Charles G. Drake, Ignacio Duran, Ros Eeles, Eleni Efstathiou, Christopher P. Evans, Stefano Fanti, Felix Y. Feng, Karim Fizazi, Mark Frydenberg, Martin Gleave, Susan Halabi, Axel Heidenreich, Daniel Heinrich, Celestia (Tia) S. Higano, Michael S. Hofman, Maha Hussain, Nicolas James, Ravindran Kanesvaran, Philip Kantoff, Raja B. Khauli, Raya Leibowitz, Chris Logothetis, Fernando Maluf, Robin Millman, Alicia K. Morgans, Michael J. Morris, Nicolas Mottet, Hind Mrabti, Declan G. Murphy, Vedang Murthy, William K. Oh, Piet Ost, Joe M. O'Sullivan, Anwar R. Padhani, Chris Parker, Darren M.C. Poon, Colin C. Pritchard, Robert E. Reiter, Mack Roach, Mark Rubin, Charles J. Ryan, Fred Saad, Juan Pablo Sade, Oliver Sartor, Howard I. Scher, Neal Shore, Eric Small, Matthew Smith, Howard Soule, Cora N. Sternberg, Thomas Steuber, Hiroyoshi Suzuki, Christopher Sweeney, Matthew R. Sydes, Mary-Ellen Taplin, Bertrand Tombal, Levent Türkeri, Inge van Oort, Almudena Zapatero, Aurelius Omlin

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[p] University Hospital Nord, St Etienne, France
[q] Mount Vernon Cancer Centre and Institute of Cancer Research, London, UK
[r] UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA
[s] Bern Center for Precision Medicine, Bern, Switzerland
[t] Tulane Cancer Center, New Orleans, LA, USA
[u] Massachusetts General Hospital Cancer Center, Boston, MA, USA
[v] Prostate Cancer Foundation, Santa Monica, CA, USA
[w] MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London, UK
[x] Cliniques Universitaires Saint Luc, Brussels, Belgium
[y] University of Bern, Bern, Switzerland
[z] Università della Svizzera Italiana, Lugano, Switzerland
[aa] Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[ab] Department for Biomedical Research, University of Bern, Bern, Switzerland
[ac] Department of Medical Oncology and Haematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland
[ad] Division of Cancer Science, University of Manchester, Manchester, UK

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Abstract ***Background:*** Innovations in treatments, imaging and molecular characterisation have improved outcomes for people with advanced prostate cancer; however, many aspects of clinical management are devoid of high-level evidence. At the Advanced Prostate Cancer Consensus Conference (APCCC) 2019, many of these topics were addressed, and consensus was not always reached. The results from clinical trials will most reliably plus the gaps.
Methods: An invited panel of 57 experts voted on 123 multiple-choice questions on clinical management at APCCC 2019. No consensus was reached on 88 (71.5%) questions defined as <75% of panellists voting for the same answer option. We reviewed clinicaltrials.gov to identify relevant ongoing phase III trials in these areas of non-consensus.
Results: A number of ongoing phase III trials were identified that are relevant to these non-consensus issues. However, many non-consensus issues appear not to be addressed by current clinical trials. Of note, no phase III but only phase II trials were identified, investigating side effects of hormonal treatments and their management.
Conclusions: Lack of consensus almost invariable indicates gaps in existing evidence. The high percentage of questions lacking consensus at APCCC 2019 highlights the complexity of advanced prostate cancer care and the need for robust, clinically relevant trials that can fill current gaps with high-level evidence. Our review of these areas of non-consensus and ongoing trials provides a useful summary, indicating areas in which future consensus may soon be reached. This review may facilitate academic investigators to identify and prioritise topics for future research.

The Advanced Prostate Cancer Consensus Conference (APCCC) provides a forum to discuss and debate pressing questions on the clinical management of men with advanced prostate cancer, with a special focus on areas of controversy. Expert opinion is the lowest level of evidence but still can be valuable where higher level evidence is lacking. Although areas of agreement have been published as part of a consensus document, APCCC also uncovered significant areas where consensus could not be reached, nominating areas for impactful future clinical research [1,2]. This article outlines and summarises the major themes of APCCC 2019 where consensus was not reached.

1. Locally advanced prostate cancer (cN1 and pN1)

1.1. Clinically node-positive (cN1) prostate cancer

A multimodality therapy approach is generally recommended as standard of care for clinically node-positive prostate cancer.

1.1.1. Areas of non-consensus

Although there was consensus for performing local treatment, there was no consensus regarding the type of preferred local treatment for cN1 prostate cancer and

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Table 1
Summary of unanswered clinical questions in the areas discussed at APCCC 2019.

Area	Relevant clinical questions that need to be answered	Addressed in phase III clinical trial(s)
1. Locally advanced PCa	1.a **cN1 PCa**	
	The type of local treatment to apply and the benefit of added systemic therapies (type and duration)	Yes, partly
	1.b **pN1 PCa**	
	Which patients to select for adjuvant treatment and which for early salvage radiotherapy	No
	In case that adjuvant treatment is applied, the benefit of added systemic therapies (type and duration)	Yes, partly
2. Biochemical recurrence of PCa after local therapy	Should PSMA or Axumin PET be used to guide radiation?	Yes
	At which PSA level to start salvage RT	No
	Systemic therapy in combination with salvage RT	Yes
	Which systemic therapy, duration of systemic therapy	Yes, partly
3. Management of primary tumour in the metastatic setting	What is the role of surgery (RP) in the mHSPC disease setting?	Yes
	What is the added value of RT of pelvic lymph nodes in addition to RT of the primary tumour?	Yes, partly
	What is the role AR pathway inhibitor in addition to ADT and in combination with RT of the primary tumour?	Yes
4. Management of newly diagnosed metastatic hormone-sensitive PCa (mHSPC)	How to select patients for combined therapy in the mHSPC setting?	Yes, partly
	How to monitor patients on ADT plus an additional therapy in order to recognise cancer progression early and prevent complications?	Yes, but not with novel imaging
	How to identify the development of aggressive variant PCa and how to treat such aggressive variant disease?	No
5. Oligometastatic PCageneral	5.a **Synchronous low-volume metastatic (M1) hormone-sensitive PCa (mHSPC)**	
	Imaging for patient selection and monitoring of treatment response	Yes
	Local treatment primary	Yes
	Local treatment metastases	Yes
	Systemic therapy (type and duration)	Yes, partly
	5.b **Metachronous low-volume metastatic (M1) hormone-sensitive PCa (mHSPC)**	
	Imaging for patient selection and monitoring of treatment response	Yes
	Local treatment metastases	Yes
	Systemic therapy (type and duration)	Yes, partly
	5.c **Oligoprogressive PCa**	
	Imaging for patient selection and monitoring of treatment response	No
	Local treatment	No
	Systemic therapy (type and duration)	No
6. Management of non-metastatic (M0) castration-resistant PCa (CRPC)	The use of novel imaging and consequently oligometastatic disease management	No
	Local treatment in case of untreated primary or in case of suspected local recurrence after RP/RT	No
	Monitoring of patients on novel potent AR antagonists in the nmCRPC situation	No
7. Management of metastatic CRPC (mCRPC)	Switching treatment on PSA only progression without available imaging and equivocal progression on next-generation imaging without PSA or clinical progression?	No
	The role of sequential novel hormonal agents in the treatment of mCRPC including darolutamide, apalutamide	Yes, partly
	Role of ^{177}Lu-PSMA in mCRPC	Yes
	How to select mCRPC patients for treatment with ^{177}Lu-PSMA	No
	How to monitor patients with mCRPC on treatment with ^{177}Lu-PSMA	No
8. Bone health and bone metastases	For HSPC:	No

(*continued on next page*)

Table 1 (*continued*)

Area	Relevant clinical questions that need to be answered	Addressed in phase III clinical trial(s)
	• Optimal timing and type of osteoclast-targeted therapy to use to reduce the risk for CTIBL in advanced PCa	
	For mCRPC: • Frequency of administration, schedule and overall duration of osteoclast-targeted therapy	Yes
9. Molecular characterisation of tissue and blood	When to use tumour genomic profiling and which tests to use	Yes
	Use of checkpoint inhibitors in patients with MSI-high and/or biallelic CDK12 loss	Yes
	Us of PARP inhibitors: • In patients with a strong family history but not detection of somatic or germline pathogenic alteration • In patients with mono-allelic loss only • In patients previously treated with a platinum-based therapy	No
	Platinum-based therapy after PARP inhibition	No
10. Interpatient heterogeneity	What is the additional value of geriatric screening in patients ≥70 of age with advanced PCa?	Yes
	Which health status assessments to use for geriatric screening	Yes
11. Side effects of hormonal treatments and their management	Hot flashes • How to reduce bothersome hot flashes and improve quality of life with interventions/drugs of attractive side effect profile	Yes, partly (not phase III)
	Management of fatigue in patients on enzalutamide/ apalutamide therapy	Yes, not phase III

PCa = prostate cancer; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; PSA = prostate-specific antigen; RT = radiotherapy; RP = radical prostatectomy; mHSPC = metastatic hormone-sensitive prostate cancer; AR = androgen receptor; CRPC = castration-resistant prostate cancer; nmCRPC = non-metastatic castration-resistant prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; ^{177}Lu-PSMA = Lutetium prostate -specific membrane antigen; CTIBL = cancer treatment induced bone loss; MSI = microsatellite instability; CDK12 = cyclin-dependent kinase-12; PARP = poly(ADP-ribose)-polymerase.

the preferred type and duration of systemic treatment (Table 1).

1.1.2. What is being done

Overall, 15–20% of men randomised in the STAMPEDE trial have cN1 disease [3]. Approximately 300 participants starting long-term androgen deprivation therapy (ADT) were randomised in the trial's 'docetaxel comparison' and 800 in its 'abiraterone comparisons' (with or without enzalutamide). As these men have had fewer events than the M1 patients, the benefit of systemic therapy requires longer follow-up. In this trial, cN1 patients who were planned for radiotherapy to the prostate and pelvic nodes (~85%) received fixed duration abiraterone for 2 years compared with treatment until progression for patients with metastatic disease outside of the pelvis [4]. Further analyses of these cohorts will be carried out in 2021.

Several other ongoing phase III trials also including cN1 patients merit mention (Table 2a). The EORTC 1414 PEGASUS study evaluates radiation therapy in combination with a GnRH agonist or antagonist, and the ENZARAD trial combines radiation therapy with ADT and either 2 years of enzalutamide, or 6 months of non-steroidal AR antagonist. The ATLAS trial, enriched for high-risk patients, uses a similar concept as the ENZARAD trial while investigating the addition of apalutamide. Another large trial (DASL-HiCaP) evaluates external beam radiation therapy (EBRT) plus ADT with or without darolutamide, whereas in the PROTEUS trial, patients receive ADT for 6 months with apalutamide or placebo, followed by prostatectomy, after which they receive another 6 months of ADT, with apalutamide or placebo. The NRG-GU009 trial study uses the genomic classifier Decipher (GenomeDx Biosciences, Vancouver, British Columbia, Canada) to determine whether men with National Comprehensive Cancer Network (NCCN) high-risk prostate cancer who are in the upper 1/3 of Decipher genomic risk (>0.85) or have node-positive disease by conventional imaging (magnetic resonance imaging [MRI] or computed tomography [CT] scan) will have a superior metastasis-free survival (MFS) through treatment intensification with apalutamide added to the standard of RT plus 24 months of ADT. None of these trials includes cN1 patients exclusively, so any results for this population will be derived from subgroups. None of the open phase III trials is focused on comparison of local treatment options.

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1.2. Pathological node-positive (pN1) prostate cancer

Multiple options are available for patients with node-positive (pN1) prostate cancer following radical prostatectomy and lymphadenectomy, ranging from adjuvant ADT with or without radiation therapy to surveillance with prostate-specific antigen (PSA) monitoring and early salvage therapy in case of PSA rise.

1.2.1. Areas of non-consensus

There was no consensus on which patients should receive systemic therapy, for how it should be given, or whether to add adjuvant radiation therapy.

1.2.2. What is being done

A prior small trial with less than 100 patients suggested that immediate ADT in patients with pN1 prostate cancer improved survival compared with deferred ADT [5]. Several studies, some of which also included pN1 patients, have been published since APCCC 2019 relevant to the question of adjuvant therapy versus early salvage therapy. A meta-analysis of these trials suggested that compared with early salvage radiation therapy, adjuvant radiation therapy does not improve PSA-driven event-free survival in patients with high risk of recurrence; importantly, this was largely observed in patients with pNX or pN0 disease [6]. In an ongoing randomised trial (PROPER), patients with pN1 disease (one to four positive lymph nodes on extended lymphadenectomy) are receiving 2 years of ADT plus either pelvic radiotherapy or radiotherapy that is limited to the prostate bed (Table 2b). The NRG 008 phase III trial will randomise 586 patients with pN1 disease after radical prostatectomy with detectable PSA with a primary objective to compare MFS of salvage RT and GnRH agonist/antagonist versus RT/GnRH agonist/antagonist with apalutamide.

The role of adjuvant docetaxel to prevent clinical relapses is debated in men with high-risk localised prostate cancer: long-term GETUG-12 data suggest that among them, men with node-positive prostate cancer may benefit more [7]. The GETUG-AFU-23 trial (PEACE-2) evaluates the role of neoadjuvant cabazitaxel and that of pelvic radiotherapy in men treated with radiotherapy and ADT and patients with pelvic lymphadenectomy and pN0 and pN1 disease are eligible.

1.2.3. Outstanding gaps in knowledge

Two current clinical trials specifically aimed towards patients with pN1 prostate cancer, the PROPER and the NRG 008 studies (see Table 2b for details). A step towards more individualised, risk-adapted treatment decisions in node-positive prostate cancer using biomarkers such as genomic classifiers and molecular imaging is needed. There are also no large trials specifically for pN1 patients that use patient selection by either molecular imaging or genomic classifiers.

2. Biochemical recurrence after radical local therapy

Current best management for patients with biochemical recurrence (BCR) after radical prostatectomy consists of imaging by prostate-specific membrane antigen (PSMA) PET/CT and potential salvage radiation therapy often combined with short-term ADT. Unfortunately, this 'recommended procedure' remains more theoretical than real, given the limited availability of PSMA-PET in many countries. For patients with low-risk BCR according to the EAU definition, monitoring with PSA can be recommended because of a lack of established survival benefit and potential for harm with excessive ADT.

For patients with BCR after definitive radiation therapy to the prostate, there are several salvage therapy options available with similar outcomes in a recent meta-analysis of 150 trials. However, prospective studies of local salvage options are warranted [8].

2.1. Areas of non-consensus

There was no consensus on how to select salvage treatments for patients with BCR after local radical treatment, nor when to initiate additional diagnostics nor which systemic therapy to add in combination with salvage RT.

2.2. What is being done

Some retrospective studies support the need to detect PSA relapse early to allow for timely salvage therapy [9–13]. Localisation of disease remains a challenge. PSMA PET/CT is highly sensitive for detecting extraprostatic disease but is not available in many regions of the world, and not all prostate tumour tissue expresses PSMA. In addition, it has not been conclusively established that earlier detection and treatment of metastases improves overall survival in this setting. A recently published phase II/III trial randomised patients with BCR 1:1 to radiotherapy directed by conventional imaging alone or to conventional imaging plus 18F-fluciclovine-PET/CT and reported improved 3-year event-free survival (75.5% versus 63%) for the PET-imaging arm [14].

With regard to salvage radiotherapy (SRT), several studies are investigating the use of PET/CT or PET/MRI, with various radiotracers, to detect metastases and guide treatment (Table 3). Inclusion criteria in current trials are the Phoenix criteria for biochemical relapse after radiation therapy [15], the Memorial Sloan Kettering Cancer Center (MSKCC) calculator [16] and the American Urological Association definition for biochemical relapse after radical prostatectomy [17].

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Table 2
Ongoing phase III trials in locally advanced PCa (not reported at time of APCCC 2019).

Table 2a: Ongoing phase III trials in locally advanced PCa (cN1 ± pN1)

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Experimental treatment	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
STAMPEDE (NCT00268476)	n = 12,200 total Subgroup tany N + M0 (arms with no reported data)	Hormone-naïve or less <12 months prior ADT No other prior systemic treatment	Arm A: RT plus Abiraterone or docetaxel Arm J: ADT+ abiraterone + Enzalutamide Arm K: ADT + metformin Arm L: transdermal oestradiol	RT plus abiraterone RT plus docetaxel ADT plus abiraterone + enzalutamide ADT plus metformin Transdermal oestradiol	ADT Abiraterone Docetaxel Enzalutamide Metformin	OS	09/2024 (depending on arm)
PEGASUS (NCT02799706)	n = 885 PSA > 10 ng/ml and 2/4 criteria: PSA > 20 ng/ml Gleason sum ≥8 cN1 or pN1, M0 cT3–cT4	Hormone naïve	EBRT plus GnRH agonist EBRT plus GnRH antagonist	EBRT plus GnRH antagonist	GnRH agonist GnRH antagonist	PFS	06/2024
ENZARAD (NCT02446444)	n = 802 GS 8–10 or GS of 4 + 3 and clinical T2b-4 and PSA >20 ng/ml or N1 disease	Hormone naive	EBRT plus LHRHA for 24 months plus NSAA 6 months EBRT plus LHRHA for 24 months plus enzalutamide 24 months	EBRT plus LHRHA plus Enzalutamide 6 months	LHRHA Enzalutamide NSAA	MFS	12/2023
ATLAS (NCT02531516)	n = 1503 planned for primary RT cN1 allowed	Hormone naïve	RT plus GnRH agonist plus Bicalutamide RT plus GnRH agonist plus Apalutamide	Apalutamide for 30 months plus RT	GnRH agonist Apalutamide Bicalutamide	MFS at 84 months	12/2022
DASL-HiCaP (NCT04136353)	N = 1100 Planned for primary RT high risk of recurrence. Post RP with PSA persistence or rising PSA at high risk of recurrence (inclusive pelvic nodal LN)	Prior ADT allowed when commenced within 90 days of randomisation	EBRT + LHRHA EBRT + LHRHA plus darolutamide	Darolutamide for 96 weeks	LHRHA Darolutamide	MFS at 5 years	01/2028
PROTEUS (NCT03767244)	n = 1500 High-risk disease Candidate for RP and 1-year ADT cN1 allowed	Hormone naive	ADT 6 cycles pre- and post-RP + RPLND ADT plus apalutamide pre- and post-RP + RPLND	ADT + apalutamide	GnRH agonist or antagonist Apalutamide total 1 year	pCR MFS	04/2024
GETUG-AFU-23/	n = 1048	ADT up to 6 weeks	ADT + pelvic RT	ADT + pelvic RT	Cabazitaxel 25 mg/	PFS	10/2025

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PEACE-2 (NCT01952223)	Any T stage High risk pN + allowed	prior allowed	ADT + prostate RT + cabazitaxel ADT + pelvic RT + cabazitaxel ADT + prostate RT	ADT + prostate RT + cabazitaxel ADT + pelvic RT + cabazitaxel	m^2 for four cycles		
18-530 (NCT03777982)	n = 400 High-risk cN0M0 or cN1M0	EBRT plus >6 and <12 months ADT	LHRH agonist/antagonist LHRH agonist + apalutamide + abiraterone/prednisone	LHRH agonist or antagonist plus abiraterone plus prednisone plus apalutamide	LHRHA Abiraterone/ prednisone Apalutamide	MFS	12/2026
PREDICT-RT (NCT04513717)	n = 2478 high-risk (NCCN) cN1 ≥1.0 cm (conventional imaging) allowed for intensification study	Hormone naïve (LHRH agonist/antagonist allowed if started ≤60 days before registration)	De-intensification study (Decipher genomic risk (≤0.8)): RT plus ADT for 12 or 24 months Intensification study (Decipher genomic risk >0.8, or cN1): RT plus ADT for 24 months plus apalutamide plus abiraterone/ prednisone	RT + LHRH agonist/ antagonist for 12 months RT + LHRH agonist/ antagonist for 24 months plus apalutamide plus abiraterone/prednisone	LHRH agonist/ antagonist Apalutamide abiraterone/ prednisone	MFS	12/2033

Table 2b: Ongoing phase III trials in locally advanced PCa1 (exclusively pN1)

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Experimental treatment	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
PROPER (NCT02745587)	n = 330 pN+ in EPLND	Radical RP EBRT	ADT + high-dose EBRT limited to the prostate(bed) High-dose EBRT limited to the prostate(bed) and pelvic LN regions	ADT + high-dose EBRT limited to the prostate(bed)	2 years of ADT	Clinical relapse rate	04/2021 Data not yet reported
INNOVATE NRG-GU008 (NCT04134260)	n = 586 PCa after RP any T stage PSA > 0 ng/ml at least 30 days after RP negative mets on PET CT pN1 (pelvis only)	PCa nodal positive post-RP hormonal treatment naïve or <45 days of GnRH agonist/ antagonist	Active comparator: Arm I (hormone therapy per physician discretion for 24 months, standard of care RT) Experimental: Arm II (apalutamide, abiraterone acetate, prednisone): standard of care hormonal therapy and RT as in Arm I plus experimental drugs for max. 24 months	Active comparator: Arm I (hormone therapy per physician discretion for 24 months, standard of care RT) Experimental: Arm II (apalutamide, Abiraterone acetate, prednisone): standard of care hormonal therapy and RT as in Arm I plus experimental drugs for maximum of 24 months	2 years of ADT Apalutamide Abiraterone/ prednisone	MFS (assessment up to 7.5 years)	11/2026

PCa = prostate cancer; ADT = androgen deprivation therapy; RT = radiotherapy; OS = overall survival; PSA = prostate-specific antigen; EBRT = external beam radiotherapy; GnRH = gonadotropin-releasing hormone; PFS = progression-free survival; GS = Gleason score; LHRH = luteinising hormone releasing hormone analogue; NSSA = nonsteroidal antiandrogen; MFS = metastasis-free survival; RP = radical prostatectomy; LN = lymph node; RPLND = retroperitoneal lymph node dissection; pCR = pathologic complete response; LHRH = luteinising hormone releasing hormone; NCCN=National Comprehensive Cancer Center Network; EPLND = extended pelvic lymph node dissection; PET = positron emission tomography; CT = computed tomography.

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Most studies exclude patients with metastases on conventional or next-generation imaging but have not specified PSA thresholds for SRT initiation; an exception is the SPPORT trial, in which the upper limit is 1.0 ng/ml.

The optimal duration of adjuvant ADT remains unclear and has not been addressed in randomised trials. With regard to combination therapy, the GETUG-AFU 16 and RADICALS trials compared SRT at various radiation doses, with or without 6 months of ADT [18,19]. The addition of ADT to RT in the setting of biochemical relapse was shown to improve biochemical relapse-free survival (GETUG-AFU 16), freedom from progression (NRG Oncology/RTOG 0534 SPPORT) and also OS (RTOG 9601) [18–20]. The LOBSTER trial compares 5-year MFS among patients receiving high-dose stereotactic body radiation therapy (SBRT; 70 Gy to the prostate bed and seminal vesicles) plus 6 months of ADT, or 24 months of ADT alone.

PSMA PET/CT is the most accurate imaging method for patients with biochemical relapse [21–23]. The most common radiopharmaceuticals used in PSMA-PET/CT studies are 68Ga-PSMA-11 and 18F-labelled PSMA (PSMA-1007). Ongoing trials are directly comparing these tracers and evaluating newer radiopharmaceuticals (Table 3) [24–27]. One is ^{18}F-DCFPyL (PyL), a second-generation fluorinated PSMA-targeted PET agent that is more sensitive than conventional imaging and has recently been Food and Drug Administration (FDA) approved in the post-primary treatment setting [28–30]. PyL PET/CT was part of baseline imaging in the CONDOR trial and in two other studies (NCT03594760 and cohort B of NCT03459820).

Novel hormonal agents such as enzalutamide and apalutamide also are being tested in combination with LHRH agonists or antagonists plus SRT. Some of the phase III trials (NCT04423211, NCT04181203, NCT02319837 and NCT04134260) include patients with detectable oligometastases on modern imaging, for whom SBRT is an optional additive treatment. Patients in the comparator arms of most studies are receiving first-generation antiandrogen therapy, plus 6–24 months of ADT. The combination of ADT with/without abiraterone and apalutamide is being investigated in patients with detectable PSA after curative-intent radical prostatectomy (INNOVATE). The EMBARK trial has fully recruited more than 1000 patients with BCR randomised to ADT alone, ADT plus enzalutamide or enzalutamide alone. The ANZUP1801 (DASL-HiCaP) trial, high-risk patients with PSA persistence or PSA rise within 1 year after radical prostatectomy or who have very high-risk localised prostate cancer receive EBRT plus 96 weeks of an LHRH with or without darolutamide (more trials are listed in Table 3). The NRG-002 trial will assess the benefit of docetaxel as measured by improvement in freedom from progression (phase II) and subsequently MFS (phase III) when given in combination with radiation and androgen deprivation in the treatment of high-risk prostate cancer post-radical prostatectomy.

2.3. Outstanding gaps in knowledge

Unanswered questions about BCR include the optimal timing or PSA threshold at which to perform PSMA PET/CT imaging and/or to start treatment and the impact of local SRT and potential additional metastases-directed therapy (MDT) on long-term end-points, such as overall survival. The RADICALS-RT trial shows that selective delayed salvage is no worse than adjuvant therapy for all. Trials of timing salvage RT and systemic therapy are needed. Furthermore, clinical and genomic classifiers may help to identify patients that can be monitored compared with those who would benefit from active salvage therapy and to select patients who favour from addition systemic treatment and which systemic treatment to use and whether the treatment should be continuous or intermittent.

3. Management of the primary tumour in the metastatic setting

After the publication of the STAMPEDE and HORRAD trials [31,32], which assessed the addition of radiation therapy to the primary tumour only to standard care of, prostate RT has become standard treatment for patients with metastatic hormone-sensitive prostate cancer (HSPC) and low tumour burden disease.

3.1. Area of non-consensus

Overall, the panel agreed on the benefit of radiation therapy to the primary for patients with low burden M1 metastatic disease, but there was no consensus on whether radical prostatectomy should be considered in the same setting.

3.2. What is being done

Panellists concurred that in the setting of metastatic HSPC (mHSPC), existing data on radiotherapy should not be extrapolated to surgery. Currently, several relevant clinical trials of local treatment of the primary tumour in the metastatic setting are underway. The g-RAMPP study was terminated prematurely after the publication of the STAMPEDE data with radiotherapy. The TROMBONE pilot trial evaluated the feasibility and safety of radical prostatectomy among patients with newly diagnosed prostate cancer and up to three bone metastases. These studies will generate valuable information, but they are relatively small, and the results of each individually will likely not prove sufficient to support a new treatment standard. The results are expected in 2028 from the randomised phase III SWOG 1802

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Table 3
Ongoing phase III trials on biochemical recurrence after local therapy (not reported at time of APCCC 2019).

PET CT/MRI trials (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Primary end-point	Estimated primary completion date as per NCT
NCI-218-00040 (NCT03353740)	n = 345 BCR post-RP (AUA) or post-RT (Phoenix criteria)	Radical local treatment with either RP or RT	Ga-68 labelled PSMA-11 PET followed by PET/CT or PET/MRI	Sensitivity on per-patient basis of 68Ga-PSMA-11 PET of (1) tumour location in prostate bed, (2) In pelvis, (3) extrapelvic, (4) bone metastases confirmed by biopsy, clinical and conventional imaging follow-up	09/2020 Data reported[a]
ABX-CT-301 (NCT04102553)	n = 200 BCR after local treatment	Prior definitive local therapy	Experimental:^{18}F-PSMA-1007 PET-CT first, followed by ^{18}F-Fluorocholine PET/CT Active comparator: ^{18}F-Fluorocholine PET/CT followed by^{18}F-PSMA-1007 PET/CT	Detection rate of met. PCa lesions of ^{18}F-PSMA-1007 versus ^{18}F-Fluorocholine within 6 months after PET/CT	10/2020 Data not yet reported
CONDOR (NCT03739684)	n = 208 BCR after local treatment	PCa with subsequent definitive therapy negative or equivocal findings for PCa on conventional imaging within 60 days before day 1	^{18}F-DCFPyL PET/CT	Correct localisation rate (CLR): percentage of subjects with a one-to-one correspondence between localisation of at least one lesion identified on experimental imaging and the composite truth standard (within 60 days following^{18}F-DCFPyL PET/CT)	08/2019 Data reported[b]
SPOTLIGHT (NCT04186845)	n = 300 BCR after local treatment	PCa with prior curative-intent treatment potentially eligible for SRT	rhPSMA-7.3 (18F) PET CT	Positive predictive value of rhPSMA-7.3 (18F) PET on a patient level using histopathology or confirmatory imaging as a standard of truth (time frame 90 days)	01/2021 Data not yet reported
^{68}Ga-PSMA-11 PET (NCT03803475)	n = 475 a) Initial staging with intermediate to high risk PCa, b. BCR after local treatment	PCa after initial definitive local curative treatment	^{68}Ga PSMA-11 PET PSMA (PET/CT or PET/MRI)	Detection rate stratified by PSA level	08/2020 Data not yet reported
^{68}Ga -PSMA PET/CT in PCa (NCT03001869)	n = 1500 PCa a) BCR after local treatment	PCa high risk PCa after radical RP, curative-intent radiotherapy or other prostate-ablative	^{68}Ga-PSMA PET/CT	Safety of ^{68}Ga-PSMA PET/CT imaging (time frame 7 days) Efficacy of ^{68}Ga-PSMA	07/2024

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Table 3 (*continued*)

PET CT/MRI trials (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Primary end-point	Estimated primary completion date as per NCT
	b) Staging of high-risk patients	definitive management		PET/CT imaging as measured by sensitivity and specificity versus CT on a per patient and per lesion basis (time frame 12 months)	
Imaging-guided SRT (NCT)	**Patient characteristic, planned number of patients**	**Pre-treatment**	**Study interventional method/ drug**	**Primary end-point**	**Estimated primary completion date as per NCT**
PSMA SRT (NCT03582774)	n = 193 Planned SRT for recurrence after primary RP PSA $\geq$ 0.1 ng/ml	RP	Standard of care SRT versus ^{68}GaPSMA-11-PET CT-guided SRT by discretion of treating radiation oncologist	Biochemical PFS after initiation of SRT	07/2023
18-002 (NCT03459820)	n = 1500 cohort A: High-risk PCa with inconclusive/equivocal conventional staging, clinical suspicion of advanced stage Cohort B: BCR after any treatment for PCa	A: treatment naïve high-risk PCa B: any prior radical curative local treatment for PCa	18F-DCFPyL PET/CT scan	Differences in optimal clinical management (time frame 30 days) as proposed by a panel of experts before and after 18F-DCFPyL PET/CT Secondary outcome measurement for BCR: Scan positivity fraction by PSA	06/2023
18.068 (NCT03594760)	n = 1000 PCa patients exclusively treated at single-centre Montréal for whom a PSMA-PET scan was requested	PCa patients for whom a PET-CT was requested	^{18}F-DCFPyL PET/CT scan	Overall survival (time frame 5 years) Images from ^{18}F-DCFPyL PET/CT scans will be combined with patient follow-up data in a deep learning algorithm to discover radiomics features predicting outcome	12/2023
SRT standard or hypofract. RT (NCT)	**Patient characteristic, planned number of patients**	**Pre-treatment**	**Study interventional method/ drug**	**Primary end-point**	**Estimated primary completion date as per NCT**
PERYTON (NCT04642027)	n = 538 BCR after RP with a PSA <1.0 ng/ml without evidence of LN or distant mets on PSMA PET CT <60 days	PCa post-RP	Arm A: conventional sEBRT 70 Gy total in 35 daily fractions of 2 Gy during 7 weeks Arm B: hypofractionated sEBRT 60 Gy total dose in 20 fractions of 3 Gy during 4 weeks	5-year PFS after treatment	09/2029

SHARE (NCT03920033)	n = 288 PCa intermediate or high risk BCR after RP non-metastatic nodal negative	PCa after RP with confirmed intermediate or high risk	Active comparator: SRT standard 66 Gy/33 fractions (fraction size 2 Gy) Experimental: SRT hypofractionated 65 Gy/26 fractions (fraction size 2.5 Gy)	Biochemical recurrence-free survival (time frame 5 years) PSA> 0.2 ng/ml followed by a repeat measurement >0.2 ng/ml	01/2022
Systemic treatment ± RT after curative-intent RP or RT (NCT)	**Patient characteristic, planned number of patients**	**Pre-treatment**	**Study interventional method/ drug**	**Primary end-point**	**Estimated primary completion date as per NCT**
ECOG-ACRIN EA8191 (NCT04423211)	n = 804 PCa with BCR (AUA definition) Negative or equivocal for extrapelvic metastases on conventional imaging	Post-RP	Active comparator Arm A: (EBRT, goserelin, leuprolide) STEP 0: fluciclovine F18 PET and SOC PET/CT baseline STEP 1: PET negative for extra pelvic metastasis SOC EBRT 6 months plus ADT for 6 months Experimental Arm B (EBRT, goserelin, leuprolide, apalutamide) STEP 0: as in arm A STEP 1: as in arm A plus apalutamide PO QD for 6 months Experimental Arm C (EBRT, goserelin, leuprolide, apalutamide) STEP 0: as in Arm A and B plus repeat fluciclovine F18 PET/CT at the time of second PSA recurrence or 12 months after the completion of enhanced systemic therapy STEP 1: PET pos for extrapelvic mets SOC EBRT, goserelin or leuprolide sc. as in Arm A and apalutamide as in Arm B. Experimental Arm D (ERBT, goserelin, leuprolide, apalutamide, RT)	PFS (conventional imaging assessed up to 10 years) PFS prolongation in patients without PET evidence of extrapelvic metastases PFS prolongation in patients with PET evidence of extrapelvic metastases	12/2027

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Table 3 (*continued*)

PET CT/MRI trials (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Primary end-point	Estimated primary completion date as per NCT
			STEP 0: as in other Arm C Step 1: as in Arms A and B plus SBRT or 3D-CRT, IMRT and IMPT over 3−5 fractions		
SPPORT (NCT00567580)	n = 1792 PCa after RP T3N0/Nx R0 or R1 M0 (conventional imaging) T2N0/Nx R0 or R1 M0 PSA post-RP at least 6 weeks after ≥0.1 and ≤1.0 ng/ml	PCa after RP with BCR	Arm I (active comparator): PBRT once daily, 5 days a week Arm II (experimental): PBRT and STAD (2 months before start PBRT antiandrogen flutamide or bicalutamide) for at least 4 months, LHRH agonist 4−6 months Arm III (experimental): PLNRT, PBRT and STAD	FFP	02/2008 data reported (no full publication)[c]
PRIMORDIUM (NCT04557059)	n = 412 PCa after RP and first postoperative PSA 0.1 ng/ml between weeks 6 and 13 BCR with high risk of developing metastasis (Gleason score ≥8, PSADT ≤ 12 months using at least three consecutive values ≥ 0.1 ng/ml from time of BCR (MSKCC online calculator) No evidence for metastasis on conventional imaging	PCa post-RP	Group 1 (active comparator): PSMA PET positive: RT (with or without optional SBRT) + LHRH agonist (6 months) Group 2 (experimental): PSMA PET positive: RT (with or without optional SBRT) + LHRH agonist (6 months) + Apalutamide (180 days) Group 3 (observational): PSMA PET negative at screening, data collected from routine clinical practice	ppMFS (time frame up to 7 years)	01/2028
CARLAHA-2 (NCT04181203)	n = 490 PCa treated with RP pT2, pT3 or pT4 N0 ECOG 0−1 metastasis excluded in 68Ga PSMA or 18FCH-PET CT Local relapse in PET CT allowed	PCa with primary RP and PSA ≤ 0.5 ng/ml within 3 months after surgery High-risk features: PSA at relapse >0.5 ng/ml or Gleason score >7 or tumour stage pT3b or PSA doubling time <6 months BCR (PSA ≥ 0.2 ng/ml and ≤2 ng/ml)	Active comparator: SRT + 6 months LHRH agonist (leuprorelin, goserelin or triptorelin acetate) Experimental: SRT + 6 months of LHRH agonist plus 6 months of Apalutamide	PFS (time frame 5 years)	09/2028

LOBSTER (NCT04242017)	n = 394 PCa after RP and ePLND pN0 asymptomatic PSA rise post-RP ≥ 0.2 ng/ml confirmed once ≥2 weeks PSA <0.4 ng/ml no additional staging required before inclusion	PCa treated with RP and ePLND BCR	Active comparator: salvage RT (70 Gy) + 6 months ADT Experimental: salvage RT (70 Gy) + 24 months ADT	MFS	02/2024 Not yet recruiting as of 06/2021
INNOVATE NRG-GU008 (NCT04134260)	n = 586 PCa after RP any T stage PSA > 0 ng/ml at least 30 days after RP negative mets on PET CT node-positive disease (pelvis only)	PCa nodal positive post-RP hormonal treatment naïve or <45 days of GnRH agonist/antagonist	Active comparator: Arm I (hormone therapy per physician discretion for 24 months, standard of care RT) Experimental: Arm II (apalutamide, Abiraterone acetate and prednisone): standard of care hormonal therapy and RT as in Arm I plus experimental drugs for a maximum of 24 months	MFS (assessment up to 7.5 years)	11/2026
EMBARK (NCT02319837)	n = 1068 PCa initially treated by RP or radiotherapy or both with curative intent PSADT ≤ 9 months absence of metastasis on conventional imaging	PCa initially treated in curative intend with rising PSA > 1 ng/ml after RP and >2 ng/ml above nadir after RT as primary treatment only	Active comparator: leuprolide plus placebo Experimental: leuprolide plus enzalutamide Experimental: enzalutamide monotherapy	MFS (time frame up to 67 months)	09/2023
SPCG14 (NCT03119857)	n = 349 PCa that received curative local treatment after RP: PSA > 10 or PSADT < 12 months and PSA > 0.5 ng/ml after RT: PSA > +2.0 above nadir and PSA > 10 or PSADT < 12 months and PSA > 0.5 OR locally advanced or not suitable for curative treatment: PSA<100, PSADT < 12 months or PSA > 20 or Gleason score 8−10 ECOG 0−1 between 18 and ≤ 80 years planned to receive bicalutamide 150 mg	PCa with initial curative treatment (RP or RT) with rising PSA non-metastatic (bone scan only assessment) prior ADT < 12 months total, stopped >12 months ago	Active comparator: antiandrogen (bicalutamide 150 mg) Experimental: antiandrogen (bicalutamide 150 mg) plus docetaxel 75 mg/m^2 q 3 weeks up to 8−10 cycles	PFS (assessed up to 60 months)	12/2023

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Table 3 (*continued*)

PET CT/MRI trials (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Primary end-point	Estimated primary completion date as per NCT
AFT-19 (NCT03009981)	n = 504 PCa after RP BCR PSADT ≤ 9 months (MSKCC calculation) screening PSA > 0.5 ng/ml Exclusion of metastases on conventional imaging LN < 2 cm abdominal or pelvic allowed	PCa prior RP prior adjuvant or salvage RT or not a candidate for both treatments ADT naïve or in adjuvant or neoadjuvant setting ≤36 months total duration and >9 months before randomisation	Active comparator Arm A: degarelix monotherapy OR leuprolide/bicalutamide Experimental Arm B: degarelix or leuprolide plus apalutamide Experimental Arm C: degarelix or leuprolide plus apalutamide plus Abiraterone/prednisone 52 weeks treatment in all arms	PSA PFS (time frame 36 months)	01/2023
PSA persistence (NCT)	**Patient characteristic, planned number of patients**	**Pre-treatment**	**Study interventional method/ drug**	**Primary end-point**	**Estimated primary completion date as per NCT**
DASL-HiCaP (ANZUP1801) (NCT04136353)	n = 1100 PCa after RP < 1 year, planned RT with persistent PSA (>0.1 ng/ml) or rising PSA > 0.1 ng/ml to be at very high risk for recurrence PCa planned primary RT and judged to be of very high-risk recurrence (Grade group 5 or 4 AND T2b-4 OR MRI with seminal vesicle invasion OR extracapsular extension OR PSA > 20 ng/ml OR pelvic nodal involvement)	PCa after RP (<1 year to randomisation) OR PCa planned for primary RT or at very high risk for recurrence M0 on conventional imaging	LHRH analogue 96 weeks plus EBRT plus placebo comparator: placebo for 96 weeks OR experimental: darolutamide for 96 weeks	MFS (time frame: an average 5 years)	01/2028
NRG-GU002 (NCT03070886)	n = 612 PCa after RP baseline Gleason ≥ 7 and baseline PSA before the start ADT, nadir ≥ 0.2 ng/ml (post-	PCa after RP (<1 year to randomisation)	Active comparator: ADT (leuprolide acetate, goserelin acetate, bicalutamide, flutamide, or nilutamide) for 6 months	FFP (phase II) MFS (phase III)	05/2026

	operative value is never undetectable) pN0 or pNx, cM0		plus EBRT for 7.5 weeks Experimental: ADT for 6 months plus EBRT for 7.5 weeks plus six cycles of docetaxel within 4–6 weeks after completion of EBRT		
Detectable PSA after curative RT to the prostate (NCT)	**Patient characteristic, planned number of patients**	**Pre-treatment**	**Study interventional method/ drug**	**Primary end-point**	**Estimated primary completion date as per NCT**
18-530 (NCT03777982)	n = 400 PCa high risk (NCCN) or N1 after definitive RT PSA > undetectable after RT at least six but <12 months of ADT	PCa high risk (NCCN) or cN1 after definitive RT with PSA > undetectable and prior ADT	Experimental 1: LHRH agonist or antagonist by SOC Experimental 2: LHRH agonist + apalutamide + abiraterone/prednisone	MFS (time frame 2 years)	12/2026

PET = positron emission tomography; CT = computed tomography, MRI = magnetic resonance imaging; BCR = biochemical recurrence; RP = radical prostatectomy; AUA = American urological association; RT = radiotherapy; Ga-68 = Gallium-68; PSMA = prostate-specific membrane antigen; PCa = prostate cancer; ^{18}F DCFPyL = 2-(3-{1-carboxy-5-[(6-[9180F]fluoro-pyridine-3-carbonyl)-amino]pentyl}-ureido)-pentanedioic acid; SRT = stereotactic radiotherapy; PSA = prostate-specific antigen; PFS = progression-free survival; LN = lymph node; sEBRT = stereotactic external body radiotherapy; Gy = grey; EBRT = external beam radiotherapy; SOC = standard of care; ADT = androgen deprivation therapy; PO = per os; QD = once daily; SBRT = stereotactic body radiotherapy; 3D CRT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy; IMPT = intensity-modulated proton therapy; PBRT = proton beam radiation therapy; STAD = standard androgen deprivation; LHRH = luteinising hormone releasing hormone; PLNRT = pelvic lymph node radiotherapy; FFP = freedom from progression; PSADT=PSA doubling time; MSKCC = Memorial Sloan Kettering Cancer Center; ppMFS = PSMA-PET metastasis-free survival; ECOG = Eastern Collaboration Oncology Group; ePLND = extended pelvic lymph = node dissection; MFS = metastasis-free survival; GnRH = gonadotropin-releasing hormone; NCCN = National Comprehensive Cancer Center Network

[a] Fendler WP et al. False positive PSMA PET for tumor remnants in the irradiated prostate and other interpretation pitfalls in a prospective multi-center trial. *Eur J Nucl Med Mol Imaging.* 2021 Feb; 48(2):501–508.

[b] Michael J. Morris et al. Diagnostic Performance of^{18}F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study- *Clin Cancer Res* July 1 2021 (27) (13) 3674–3682

[c] Pollack A et al. Short-term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiation therapy: The NRG Oncology/RTOG 0534 SPPORT Trial. ASTRO Annual Meeting 2018, LBA5.

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trial, in which approximately 1200 patients will receive systemic therapy with or without radical prostatectomy or radiation of the primary tumour. Until then, radical prostatectomy cannot be recommended as a standard treatment for patients with mHSPC outside of clinical trials. The ATLANTA trial is comparing HIFU versus RT versus surgery in 918 men with mHSPC and is currently recruiting in the United Kingdom.

The different radiation therapy schedules were not discussed at APCCC 2019. In addition, the optimal timing of radiation therapy remains unclear. In clinical practice, radiation oncologists frequently wait for systemic therapy to shrink the primary tumour to reduce the required radiation field and any accompanying toxicity. Non-randomised data from the STAMPEDE trial did not support this approach in mHSPC [31]. Data from the PEACE-1 trial will shed additional light on this question and the interaction of radiotherapy, docetaxel and abiraterone in this setting.

Another question is whether to irradiate not only the primary tumour but also pelvic lymph nodes that are detectable on imaging. Interestingly, despite a lack of supporting evidence from prospective trials, panellists concurred that patients with clinical nodal disease in the pelvis should have the nodes incorporated into the radiation field if the primary tumour was treated with radiation therapy. The phase III HORRAD and STAMPEDE trials used radiation to the prostate only and hence did not address this question [31,32]. Insights may come from the ongoing four-arm phase III PEACE-1 trial (NCT01957436), in which radiation to the pelvic node(s) was permitted at the investigators' discretion (Table 4). If the situation remains unclear, a dedicated head-to-head trial of the various permutations may be needed, although such a trial would take many years to report.

It is unknown whether adding local treatment of the primary tumour can benefit metastatic patients receiving treatment with ADT intensified with an AR pathway inhibitor or docetaxel. It may also be that patients with a larger burden of disease treated with intensified systemic therapy benefit from local therapy. In the STAMPEDE radiotherapy arm, 18% of patients also received docetaxel [3], and the effect sizes were similar with and without docetaxel. PEACE-1 will provide important information, pending its total sample size (1173 patients) is large enough to answer this question, given that the study includes patients with high-volume and low-volume disease. Also of interest is the SWOG 1802 trial, which randomises patients to receive guideline-recommended systemic therapies [33] with or without definitive surgery or radiation of the primary tumour.

3.3. Outstanding gaps in knowledge

The active trials in this setting will answer many of the open questions (Table 4). However, the question of 'what is low' in terms of volume of metastases and in relationship to benefit remains undefined, including the question of optimal end-points for clinical trials in this disease setting [34]. Remaining gaps relate mainly to the question of the impact of PSMA PET/CT-based imaging on patient selection and whether additional lymph node radiation may be beneficial and what is the optimal dose and schedule of radiation.

4. Management of mHSPC

The current standard systemic therapy for patients with mHSPC is ADT combined (intensified) with either an AR pathway inhibitor (abiraterone/prednisone, apalutamide and enzalutamide) or chemotherapy (docetaxel) if patients are generally fit.

4.1. Areas of non-consensus

Many questions in mHSPC remain unanswered, such as the clinical relevance of classifying disease by volume (extent of metastatic spread) versus risk (based on both metastatic volume and Gleason score only assessed in the synchronous metastatic setting); the distinction between metastatic disease that is synchronous (de novo) versus metachronous (relapsing after radical local treatment); how to best manage low-volume/risk mHSPC; how best to manage aggressive-variant disease; and whether an AR pathway inhibitor provides added benefit to docetaxel (ENZAMET, PEACE 1 and ARASENS) [35,36] or sequentially (TITAN and ARCHES) [37,38]. There is now evidence that apalutamide or enzalutamide provide benefit for metachronous low-volume mHSPC, although this remains controversial for docetaxel [39].

4.2. What is being done

Some of the previously mentioned questions will be answered by ongoing trials or by secondary analysis of individual trials or meta-analyses existing data sets, that is, STOPCaP and ICECaP [40]. PEACE-1 provided evidence that the combination of ADT, abiraterone, and docetaxel led to improved clinical progression-free survival (PFS), results that were very similar to those of the interim analysis for ENZAMET with enzalutamide in place of abiraterone [35,36]. Further follow-up of PEACE-1 will provide important overall survival data on the combination of docetaxel and abiraterone and radiation of the primary tumour (±pelvis; see Section 3). STAMPEDE will report on the addition of both abiraterone and enzalutamide to standard of care (SOC) and, separately, the addition of metformin to SOC. This study's diverse disease categories and some the use of standard-of-care docetaxel in some arms should generate a rich set of additional data in coming years.

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Table 4
Ongoing phase II/III trials addressing the management of the primary tumour in the metastatic setting (not reported at time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Experimental treatment	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
g-RAMPP (NCT02454543)	n = 452 planned, stopped after 131 incl. mHSPC, max. five bone metastases, PSA ≤200	ADT; docetaxel allowed	Operation of the primary tumour	BST plus radical RP with extensive lymphadenectomy versus BST	ADT; docetaxel allowed	Prostate cancer−specific survival	12/2019 Data not yet reported
SWOG-S1802 (NCT03678025)	n = 1273 mHSPC	BST	Local treatment of the prostate	BST versus BST plus surgery or RT of the prostate	BST	OS	04/2028
PEACE I (NCT01957436)	n = 1173 mHSPC	ADT	Systemic therapies, RT treatment of the prostate	Arm A: ADT + docetaxel Arm B: ADT + docetaxel plus Abiraterone Arm C: ADT plus docetaxel plus RT of the primary tumour Arm D: ADT plus docetaxel plus abiraterone plus RT of the primary tumour	See prior column experimental treatment	OS	08/2021 rPFS 1 data reported[a]
IP-2 ATLANTA (NCT03763253) large phase II	n = 918 mHSPC$_2$ diagnosed <6 months	ADT < 4 months	Local treatment of the prostate	Intervention arm 1: minimally invasive ablative therapy (cryotherapy or HIFU), in addition to SOC systemic treatment Interventional arm 2: radical therapy (RP or EBRT in radical dose) in addition to SOC systemic treatment	Control Arm: SOC: ADT with or without docetaxel, abiraterone, enzalutamide or any other proven agent treatment as determined by treating physician	PCa on post-SOC prostate biopsy Safety (adverse events) PFS	03/2023

PCa = prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; PSA = prostate-specific antigen; ADT = androgen deprivation therapy; BST = best standard treatment; RT = radiotherapy; RP = radical prostatectomy; OS = overall survival; rPFS = radiographic progression-free survival; HIFU = high-intensity focused ultrasound; EBRT = external beam radiotherapy; SOC = standard of care; PFS = progression-free survival.

[a] Fizazi, K et al. A phase 3 trial with a 2 × 2 factorial design of abiraterone acetate plus prednisone and/or local radiotherapy in men with de novo metastatic castration-sensitive prostate cancer (mCSPC): First results of PEACE-1. J Clin Oncol 2021 39:15_suppl, 5000-5000.

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Table 5
Ongoing phase III trials in metastatic hormone-sensitive PCa (not reported at time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug Experimental treatment	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
GETUG-AFU 21/ PEACE-1 (NCT01957436)	n = 1173 Newly diagnosed mHSPC Patients with prior local treatment of the primary are excluded	Maximum 3 months of ADT	ADT plus docetaxel ADT plus docetaxel plus abiraterone ADT plus docetaxel plus RT of the primary tumour ADT plus docetaxel plus abiraterone plus RT of the primary tumour	See prior column	OS and PFS	rPFS data reported[a]
STAMPEDE (NCT00268476)	n = 12,200 Newly diagnosed N0M0 (2 of 3: T3/4, PSA ≥40 ng/ml or Gleason 8−10) Newly diagnosed N + M0 (Stage T any N + M0) Newly diagnosed M1 = de novo M1 Previously treated M0 (PSA ≥4 ng/ml and DT ≤ 6 months or PSA ≥20 ng/ml) Previously treated M1 = M1 after local therapy (RT or OP)	Maximum 3 months of ADT	ADT plus abiraterone plus enzalutamide ADT plus standard of care (including abiraterone) plus metformin ADT plus standard of care plus transdermal oestrogen	See prior column	OS	09/2024 (depending on arm)
ARASENS (NCT02799602)	n = 1303 Newly diagnosed mHSPC, candidates for ADT plus docetaxel	Maximum 3 months of ADT	ADT plus docetaxel versus ADT plus docetaxel plus darolutamide	See prior column	OS	06/2021 Data not yet reported
ARANOTE (NCT04736199)	N = 555 Newly diagnosed mHSPC	Maximum 3 months of ADT	ADT plus darolutamide versus ADT plus placebo		rPFS	03/2024
S1216 (NCT01809691)	n = 1313 Newly diagnosed	Maximum 3 months of ADT	ADT plus orteronel versus ADT plus bicalutamide	See prior column	OS	03/2022

	mHSPC					
Keynote-991 (NCT04191096)	n = 1232 Newly diagnosed mHSPC at least two bone metastases	Maximum 3 months of ADT, prior docetaxel allowed	ADT plus enzalutamide versus ADT plus enzalutamide plus pembrolizumab	See prior column	rPFS and OS	07/2026
CAPItello (NCT04493853)	n = 1000 Newly diagnosed mHSPC with PTEN deficiency	Maximum 3 months of ADT	ADT plus abiraterone/ prednisone ± Capivasertib	See prior column	rPFS	11/2024
SHR-3680-III-HSPC (NCT03520478)	n = 572 Newly diagnosed PCa	NA	SHR3680 (AR antagonist) versus Bicalutamide (50 mg)	NA	rPFS and OS	04/2023
ESTO2 (NCT04026230)	n = 400 PCa with an indication for definitive ADT	NA	Atorvastatin (80 mg) versus placebo	NA	Time to CRPC	12/2025
PRONOUNCE (NCT02663908)	n = 545 PCa with an indication for definitive ADT	None	Degarelix versus leuprolide	See prior column	Time to first major cardiovascular event	03/2021 data reported[b]
PSMAddition (NCT04720157)	n = 1126 Newly diagnosed mHSPC Metastatic to bone and/or soft tissue/visceral sites PSMA-PET positive on 68Ga-PSMA-11 PET/CT scan	Maximum of 45 days of ADT and novel hormonal agent	7.4 GBq (±10%)^{177}Lu-PSMA-617, once every 6 weeks (± 1 week) for planned 6 cycles, in addition to SOC (ARDT +ADT) administered per the physician's order versus SOC (ARDT + ADT) administered per the physician's order	See prior column	rPFS	08/2024

PCa = prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; ADT = androgen deprivation therapy; RT = radiotherapy; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; DT = doubling time; OP = operation; rPFS = radiographic progression-free survival; PTEN = phosphatase and tensin homolog; NA = not applicable; CRPC = castration-resistant prostate cancer; PSMA = prostate-specific membrane antigen; PET = positron-emission tomography; Ga = gallium;CT = computed tomography; GBq = gigabecquerel; SOC = standard of care; ARDT = androgen-receptor directed therapy.

[a] Fizazi, K et al. A phase 3 trial with a 2x2 factorial design of abiraterone acetate plus prednisone and/or local radiotherapy in men with de novo metastatic castration-sensitive prostate cancer (mCSPC): First results of PEACE-1. J Clin Oncol. 2021 39:15_suppl,5000-5000.

[b] Lopes, RD et al. Cardiovascular Safety of Degarelix versus Leuprolide in Patients with Prostate Cancer: The Primary Results of the PRONOUNCE Randomized Trial. *Circulation. 2021,* Aug 30. Online ahead of print.

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The phase III placebo-controlled ARASENS trial evaluates the safety and efficacy of darolutamide among patients with newly diagnosed mHSPC receiving ADT plus docetaxel (Table 5). Additional trials are investigating adding agents to ADT: orteronel (S1216), pembrolizumab plus enzalutamide (KEYNOTE-991), capivasertib plus abiraterone (CAPItello) or atorvastatin (ESTO2), abiraterone ± niraparib (AMPLITUDE), enzalutamide ± talazoparib (TALAPRO), and ADT + any novel ARPI ± ^{177}Lu-PSMA-617 (PSMA addition; see Table 5).

Many agents targeting the AR pathway are associated with an increased risk of cardiovascular events, especially among patients with a history of cardiovascular disease; this risk is becoming increasingly relevant as the population ages and as PC patients are exposed to a longer duration of androgen-receptor axis targeting therapies and prednisone. The recently published HERO trial reported a favourable safety profile for the oral GnRH antagonist (relugolix) compared with leuprolide, not as a primary or prespecified secondary end-point but rather as a result of a prespecified safety analysis [41], and currently, only short-term data are available. The reduced incidence of cardiovascular events was particularly striking in patients with a prior history of such an event. PRONOUNCE, another important large ongoing trial, addresses this issue by randomising patients to receive degarelix or leuprolide with the primary end-point of time to first major cardiovascular event (NCT02663908). Unfortunately, the study was terminated prematurely and showed no relevant difference in major adverse cardiovascular events [42]. A meta-analysis of all published trials is conducted by Duke University.

4.3. Outstanding gaps in knowledge

The main gaps in mHSPC concern patients at the either very high or very low risk end of the scale to either deintensify or intensify therapy as needed. For frail/vulnerable patients or for patients who responded very well to ADT in combination with an ARPI, de-escalation strategies such as intermittent use of either ADT + an ARPI, or just of the ARPI alone, can be used to decrease cumulative toxicity. By contrast, escalation strategies for patient with aggressive or minimally hormone-responsive disease and treatment monitoring, especially the identification of tumour lesions with discordant response to systemic therapy and the early identification of resistant clones especially treatment-emergent aggressive/neuroendocrine variants require investigation. In addition, improved patient selection, potentially with molecular signatures, needs to be prospectively investigated, including targeted agents that have been shown to be active in selected populations of mCRPC.

5. Management of synchronous, metachronous, oligometastatic and oligoprogressive disease

For oligometastatic prostate cancer, whether synchronous or metachronous, there is not yet a standard definition and treatment recommendations, and approaches vary from systemic therapy alone to MDT or MDT in combination with systemic therapy.

5.1. Area of non-consensus

There was no consensus on most questions about the definition and management of oligometastatic disease. For example, there was disagreement about the maximum number of metastases (3 versus 5) that would constitute oligometastatic disease, whether the category of oligometastatic disease should include patients with a limited number of visceral metastases and whether these patients should be considered for metastasis-directed treatment. There was also no consensus on the nature, timing or duration of systemic therapy for synchronous and metachronous oligometastatic prostate cancer, nor on the concept of and management options for oligoprogressive disease. It is also not known whether oligometastatic disease is best defined by conventional or next-generation imaging.

5.2. What is being done

A small number of clinical trials that may help classify oligometastatic patients and guide imaging and treatment are underway. The ongoing phase III PRESTO trial (the GETUG-AFU-36 study) aims to randomise 350 patients with hormone-sensitive oligometastatic (synchronous or metachronous, a maximum of five lesions [bone and/or lymph node]) prostate cancer to receive standard therapy with or without stereotactic body radiotherapy (SBRT) for lesion ablation. The primary end-point is time to development of castration-resistant prostate cancer (CRPC; Table 6).

The randomised multiarm phase II/III CORE trial evaluates whether adding SBRT to standard care improves progression-free survival (PFS) among patients with prostate, breast or non−small cell lung cancer and ≤3 extracranial metastases. Enrolled patients can have either mHSPC or mCRPC. This trial has completed enrolment.

The phase III ADOPT trial evaluates whether adding ADT to SBRT improves progression-free survival (mPFS) among patients with oligometastatic prostate cancer. Participants have BCR after local radical treatment, 1−4 lesions on imaging and no evidence of visceral metastases.

The randomised, adaptive phase II/III PCS-IX study assesses whether adding SBRT to systemic treatment with ADT plus enzalutamide delays disease progression and postpones the need for second-line systemic therapy

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Table 6
Ongoing phase III trials in the different settings of oligometastatic disease (not reported at time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Baseline imaging	Number of lesions	Local treatment	Systemic treatment	Primary end-point	Comments	Estimated primary completion date as per NCT
PRESTO (NCT04115007)	n = 350 mHSPC Synchronous Metachronous metastases	previous RP or RT to the prostate and/or pelvic LN	PET CT (either F-, Choline- or PSMA) or WB MRI and contrast CT	≤5 asymptomatic or oligosymptomatic bone and/or LN metastasis, visceral metastases excluded	SRBT	SOC (long-term ADT, abiraterone or docetaxel)	CRPC-free survival	30 Gy (3 × 10 Gy) for axial and appendicular bones and LN metastases or 35 Gy (5 × 7 Gy)	01/2023
PLATON (NCT03784755)	n = 410 mHSPC Synchronous or metachronous oligometastatic	Systemic treatment naïve, prior RP or RT with curative intent	CT and/or MRI and bone scan	≤5 metastases (≤3 non-bony metastases), no brain metastases	SRBT to prostate if untreated and low volume (arm 1 experimental) plus all sites of disease + SOC (arm 2 experimental)	SOC	FFS	Ablative RT has to start ≤6 weeks of randomisation	07/2025
CORE trial (NCT02759783)	n = 245 mHSPC or mCRPC Metachronous Non-prostate: breast, NSCLC	No prior systemic treatment despite adjuvant, if treatment switch due to PD to metachronous oligometastatic status, ≤8 weeks before study start	contrast CT	≤3 extracranial	SRBT	SOC	PFS		10/2024
PSMA-PETgRT (NCT03525288)	N = 130 phase II/III mHSPC Metachronous Oligometastatic high risk or recurrent	No prior ADT ≤ 12 months	DCFPyL/ PSMA-PET/ CT	<6 lesions (for N1: per region), site: N1, M1a/b (<4)/c	PSMA-PET gRT versus non-PSA-guided RT to prostate and oligometastates	SOC	FFS (5 years)	Arm A: PSMA PET/CT guided RT prostate and SBRT oligometastases (>5 metastases: RT prostate only) Arm B: standard RT to prostate (no PSMA-PET imaging pre-treatment)	05/2024
ADOPT trial (NCT04302454)	n = 280 mHSPC Oligorecurrent, metachronous	No prior systemic treatment, biochemical recurrence after RP or RT	PSMA-PET	1−4 lesions bone or LN, no visceral metastases	MDRT	MDRT + ADT (leuprorelin)	MPFS	PSA < 10 ng/ml, PSA doubling time ≤3 months excluded	12/2022
PCS-IX (NCT02685397)	n = 374 mCRPC Oligorecurrent	Local treatment curative intent, ADT	CT, bone scan and/or MRI	≤5 lesions	SRBT	Enzalutamide + ADT	rPFS	Experimental arm: SRBT + ADT + enzalutamide	04/2025

mHSPC = metastatic hormone-sensitive prostate cancer; RP = radical prostatectomy; RT = radiotherapy; LN = lymph node; ; PET = positron-emission tomography; CT = computed tomography; PSMA = prostate-specific membrane antigen; WB = whole body; MRI = magnetic resonance imaging; SBRT = stereotactic body radiotherapy; SOC = standard of care; ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; Gy = Grey; FFS = failure-free survival; mCRPC = metastatic castration-resistant prostate cancer; NSCLC = non−small cell lung cancer; PD = progressive disease; PFS = progression-free survival; gRT = guided radiotherapy; F-DCFPyL = 2-(3-{1-carboxy-5-[(6-[9180F]fluoro-pyridine-3-carbonyl)-amino]pentyl}-ureido)-pentanedoioic acid; PSA = prostate-specific antigen; MDRT = metastasis-directed radiotherapy; MPFS = metastasis progression-free survival; rPFS = radiographic progression-free survival.

among patients with oligometastatic recurrence (≤5 lesions) after local treatment with curative intent.

5.3. Outstanding gaps in knowledge

The main gap for oligometastatic prostate cancer is the need for better evidence on the management impact of next-generation imaging on relevant oncological outcomes. Many of the ongoing trials are either small to medium sized or have short-term end-points that are not yet a surrogate for overall survival. In oligometastatic mHSPC defined by next-generation imaging, the question as to whether radical local treatment of the primary and all sites of metastatic disease improves outcomes needs to be addressed. With the rapid developments in next-generation imaging, the impact of the imaging modality and/or tracer on test accuracy and management strategies needs to be prospectively tested, and ultimately, the development of predictive biomarkers that can be used for treatment selection may be of primary importance.

6. Non-metastatic CRPC

Addition of a next-generation androgen receptor (AR) antagonist (enzalutamide, apalutamide and darolutamide) has become standard for patients with non-metastatic CRPC (nmCRPC), defined by conventional imaging, having a PSA-DT ≤10 months and a total PSA of ≥2 [43–46].

6.1. Areas of non-consensus

There was no consensus on the question whether the data from the approved AR antagonists can be extrapolated to abiraterone or to patients with a PSA doubling time of >10 months; nor on the management options for patients with nmCRPC who had no radical treatment of the primary, or at what time point systemic therapy should be changed in the nmCRPC setting.

6.2. What is being done

Currently, no large phase III clinical trials in nmCRPC are ongoing.

6.3. Outstanding gaps in knowledge

The integration of next-generation imaging in the nmCRPC space merits further research, especially the question of the added value of MDT identified by next-generation imaging with or without systemic therapy [47]. Limited data are available, but in a recent analysis of 200 patients with nmCRPC, PSMA-PET with the 68Ga-PSMA-11 radiotracer detected disease in 98% of patients with nmCRPC and who would have been eligible for one of the pivotal studies [48]. Nevertheless, these patients shared the characteristics of those patients who benefited from the addition of a next-generation AR antagonist, including improved metastasis-free and overall survival. This suggests that these findings should not alter management, but it is not known whether alternative management strategies would yield improved outcomes remains unknown.

In the SPARTAN study [49], 77% of patients had received local treatment of the prostate; in ARAMIS [45], 25% had undergone prostatectomy; in PROSPER [43], these data were not reported, and none of the three trials reported data on prior salvage radiation therapy. These gaps raise questions about the role of local treatment (prostate and/or pelvis) in nmCRPC, especially when next-generation imaging confirms the presence of disease in the pelvis.

The question of how best to determine the response or progression of disease also needs to be addressed. In the three pivotal trials, CT and ^{99m}Tc bone scans were performed every 16 weeks [43,45,50]. In clinical practice, however, this seems excessive, especially considering the median time to first detected metastasis, which is in the range of 40 months. However, monitoring by PSA alone can fail to detect progression in the absence of a concurrent PSA rise; note that in the PREVAIL trial, 25% of patients fell into this category [51].

7. Management of metastatic CRPC

Most of the pivotal phase III trials that have defined the treatment approach to men with metastatic CRPC (mCRPC) were undertaken before the advent of intensified ADT. The use of docetaxel and ARPIs together with ADT in the hormone-sensitive setting has made the subsequent treatment of mCRPC particularly challenging, with little evidence available to support decision-making.

7.1. Areas of non-consensus

There was no consensus on the question of treatment change because of PSA rise alone or in the case of progression on next-generation imaging (whole body, diffusion-weighted MRI or PET/CT). In addition, no consensus was reached on the sequential administration of the endocrine therapies, especially for enzalutamide after abiraterone; however, the CARD study prospectively demonstrated the limited value of sequencing of endocrine therapies compared with cabazitaxel [52]. Further areas of debate were whether AR-V7 testing is recommended for treatment selection or on the routine use of bicalutamide or dexamethasone in the mCRPC setting. Concerning Lutetium-PSMA therapy, there was little clinical trial data available in 2019 and no consensus on when to use this treatment nor on patient selection by imaging or on treatment monitoring.

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Table 7
Ongoing phase III trials focusing on the management of metastatic CRPC (mCRPC) (not reported at time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study drug/ intervention	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
PROCADE (NCT03850795)	n = 430 Progressing mCRPC Asymptomatic or mildly symptomatic	No prior CHT No prior novel hormonal agent No prior Radium-223	HC-1119 versus enzalutamide	ADT	ORR (RECIST 1.1) week 24	11/2022
IPATential150 (NCT03072238)	n = 1101 mCRPC Asymptomatic or mildly asymptomatic Valid PTEN IHC result	Previously untreated No prior CHT or AR-targeted agent allowed	Abiraterone/ prednisone plus placebo versus abiraterone/ prednisone plus ipatasertib	ADT	rPFS PTEN-loss tumours (IHC) against ITT population	03/2020 Data reported[a]
PRESIDE (NCT02288247)	n = 690 mCRPC Asymptomatic or minimally symptomatic	Previously untreated Open label period 1 enzalutamide until week 13 assessment Confirmed PD → period 2	Period 2 continued enzalutamide after adding docetaxel plus prednisone versus continued placebo plus docetaxel plus prednisone	ADT	PFS	04/2020 Data not yet reported
KEYNOTE-641 (NCT03834493)	n = 1200 mCRPC	Previously untreated or progressed on/or intolerant to abiraterone	Enzalutamide plus placebo versus enzalutamide plus pembrolizumab 200 mg q21	ADT	OS rPFS	11/2023
CR105505, ACIS (NCT02257736)	n = 983 mCRPC	Treatment naïve	Abiraterone/ prednisone plus placebo versus abiraterone/ prednisone plus apalutamide	ADT	rPFS	03/2018 Data reported[b]
CRPC-EVE (NCT03580239)	n = 120 mCRPC with PI3K-AKT-mTOR signalling pathway deficiency by NGS	Conventional treatment failed (including docetaxel, AR-targeted agent)	Everolimus 10 mg/d + BSC versus placebo + BSC	ADT	PFS OS	01/2023
SPLASH (NCT04647526)	n = 415 mCRPC PSMA-PET scan positive	Progressed on one of the novel hormonal agents: abiraterone/ prednisone or enzalutamide or darolutamide in either mCRPC or mHSPC	Arm A: 6.8 GBq (±10%) of [Lu-177]-PNT2002 every 8 weeks for four cycles Arm B: enzalutamide or abiraterone/ prednisone	ADT	rPFS	03/2023
PSMAfore (NCT04689828)	n = 450 mCRPC ≥1 metastatic lesion ^{68}Ga-PSMA-11 PET/CT scan positive No prior	Progressed on one of the novel hormonal agents: abiraterone/ prednisone, enzalutamide, darolutamide or apalutamide	Active comparator: Androgen receptor-directed therapy (ARDT) of physician's choice Experimental: 7.4	ADT	rPFS	05/2023

(continued on next page)

Table 7 (*continued*)

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study drug/ intervention	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
	treatment with docetaxel		GBq (200 mCi) ± 10% ^{177}Lu-PSMA-617 once every 6 weeks for 6 cycles			

PCa = prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; CHT = chemotherapy; ADT = androgen deprivation therapy; ORR = overall response rate; RECIST = response evaluation criteria in solid tumours; PTEN = phosphatase and tensin homolog; IHC = immunohistochemistry; AR = androgen receptor; rPFS = radiographic progression-free survival; ITT = intention to treat; PD = progressive disease; PFS = progression-free survival; OS = overall survival; PI3K/AKT/mTOR = phosphatidylinositol 3-kinase/protein kinase B (PKB/AKT), and mammalian target of rapamycin; NGS = next-generation sequencing; BSC = best supportive care; PSMA = prostate-specific membrane antigen; PET = positron-emission tomography; mHSPC = metastatic hormone-sensitive prostate cancer; GBq = gigabecquerel; Lu = lutetium; Ga = gallium; CT = computed tomography; mCi = millisievert.

[a] Sweney, C et al. Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multi-centre, randomised, double-blind, phase 3 trial *The Lancet*. Volume 398, Issue 10295, 131−142.

[b] Rathkopf, DE et al. Final results from ACIS, a randomized, placebo (PBO)-controlled double-blind phase 3 study of apalutamide (APA) and abiraterone acetate plus prednisone (AAP) versus AAP in patients (pts) with chemo-naive metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2021, 39:6_suppl, 9-9.

7.2. What is being done

Investigators are exploring regimens that combine distinct mechanisms of action, such as AR blockade together with immune checkpoint inhibition. In the randomised, double-blind PRESIDE trial, patients who have developed mCRPC while on enzalutamide start on docetaxel and either remain on enzalutamide or switch to placebo; the primary end-point is PFS (Table 7). In addition, the large phase III KEYNOTE-641 (NCT03834493) trial evaluates rPFS and OS among patients with mCRPC who receive enzalutamide plus pembrolizumab or enzalutamide alone. This study includes a cohort of patients who previously received abiraterone, which was not prespecified but will nonetheless provide insights on sequencing insights. Previously, a similarly designed study (IMBassador250) showed no evidence that adding atezolizumab to enzalutamide after abiraterone delayed disease progression or improved overall survival [53]. The EORTC-1333 PEACE 3 trial [54] compares the combination of enzalutamide and Ra223 and enzalutamide alone in patients with bone metastatic asymptomatic or minimally symptomatic CRPC. A similar study with abiraterone, ERA223, has been halted for excess of fracture, resulting most likely at least partly from a low use of bone-protecting agents [55].

Most experts at APCCC 2019 supported ^{177}Lu-PSMA theranostic treatment only for patients with mCRPC who had exhausted all standard treatment options. The phase III VISION trial investigating the efficacy of ^{177}Lu-PSMA-617 in patients whose PSMA PET-positive mCRPC has progressed on at least one AR-targeted agent, and one or two lines of taxane chemotherapy met both of its alternate end-points of OS and rPFS and will be a new standard treatment option for patients with mCRPC after chemotherapy [56].

In mCRPC, many phase III trials are ongoing, including combination endocrine therapies, targeted agents, immunotherapy, or alternate PSMA targeting agents (details in Tables 7 and 9).

7.3. Outstanding gaps in knowledge

Prospective randomised trials are missing for patients who received ADT intensification treatments in the hormone-sensitive setting and for the optimal sequence for the use of the different treatment options. The very concept of an 'optimal sequence' may indeed be illusory. Concerning imaging, the question of how to monitor treatment response and when to change treatment needs to be better defined, particularly in the advent of next-generation imaging that is increasingly used in the advanced prostate cancer disease setting [47]. Also validation studies are still required to determine the utility of AR-V7 testing as predictive biomarker.

8. Bone health and bone metastases

Bone health is important and mainly involves two settings: prevention/treatment for ADT-induced bone loss and prevention of skeletal-related events (SREs) in patients with mCRPC and bone metastases.

8.1. Area of non-consensus

No consensus was reached for patients starting long-term ADT on the question of routine bone mineral density measurement, the start of osteoclast-targeted therapy without bone mineral density (BMD) measurement nor in patients starting ADT plus abiraterone/prednisone in the mHSPC setting. In patients with mCRPC, although there is general agreement to the

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importance of the use of osteoclast-targeted therapy to reduce the risk of SREs, no consensus was reached on the timing of the initiation of this therapy nor on the treatment duration and frequency of application.

8.2. What is being done

With regard to protection from ADT-induced bone loss, the ERA-223 trial reported an increased fracture rate among patients who received abiraterone/prednisone in combination with radium-223 [55], and the cumulative fracture rate in PEACE 3 patients was also high, if no bone-protecting agents were used demonstrating the need for bone-protecting agents in these patients [54]. The optimal timing and type of osteoclast-targeted therapy to accomplish this goal remain undefined. Furthermore, when starting treatment with denosumab or a bisphosphonate, it remains unclear whether and when to switch patients to the higher dose and more frequent schedule that are used to reduce the risk of SRE, or whether to use a less intense schedule aimed at prevention of osteoporosis.

In mCRPC, neither of the two approved bone-directed agents, zoledronic acid or denosumab has shown improvement in OS [57–59]. However, questions regarding frequency of administration, schedule and overall duration of osteoclast-targeted therapy remain unresolved. The risk of side effects, particularly osteonecrosis of the jaw, increases with the duration of osteoclast-targeted therapy.

Two trials are addressing the question of schedule of bone-targeting agents. A large, randomised, phase III non-inferiority trial (REDUSE) of patients with mCRPC as well as those with bone metastatic breast cancer is investigating a reduced frequency schedule of denosumab after an initial monthly run-in phase (Table 8). The primary end-point is time to first symptomatic SRE. A smaller trial (REaCT-BTA) also randomises patients with mCRPC or metastatic breast cancer to 4 or 12 weekly deliveries of denosumab, pamidronate or zoledronic acid. A randomised non-inferiority trial including metastatic breast cancer but also mCRPC was recently published [60]. Patients were randomised to 4-weekly versus 12-weekly bone-targeted agents (zoledronate, pamidronate and denosumab) with a primary end-point of change in health-related quality of life -physical function by the European Organisation for Research and Treatment of Cancer (EORTC-QLQ-C30). The primary end-point was met, and there was no difference in SRE- and SSE-free survival.

8.3. Outstanding gaps in knowledge

It is unknown which patients starting on long-term ADT should receive a bone-protecting agent from the start of treatment or when under treatment and which algorithm should be used to define initiation. For the bone-protecting agents for mCRPC, the optimal dose, schedule and duration of therapy are unknown.

9. Molecular characterisation of tissue and blood

Based on the approval of olaparib and rucaparib for patients with DNA repair gene alterations, tumour genomic profiling should be performed in patients with advanced prostate cancer. There is no standard as to when to perform the testing in the treatment sequence.

9.1. Areas of non-consensus

There was no consensus on when to recommend tumour genomic profiling in the disease course, nor regarding which tests to use nor on the specific question whether all mCPRC patients should have tumour genomic profiling for BRCA1/2 and/or mismatch repair defects (MSI high). For either patients with MSI-high tumours, or patients with biallelic CDK12 loss, there was no consensus on when to use a checkpoint inhibitor in the disease course. In addition, no consensus was reached on PARP inhibitor or platinum-based treatment in patients with a strong family history but no documented somatic and/or germline aberration. Although a large percentage of panellists regarded a biallelic alteration as mandatory for PARPi treatment, there was no consensus that a monoallelic BRCA1/2 alteration was sufficient. The experts did not reach consensus on PARP inhibitor therapy after platinum-based treatment or the reverse sequence in patients with a pathogenic BRCA1/2 aberration. The role of maintenance PARP inhibitor after platinum-based therapy is not known.

9.2. What is being done

Clinically, the marked heterogeneity of the clinical course of prostate cancer has frustrated efforts to improve prognostication and treatment selection by means of molecular characterisation [61,62]. Current trials of molecularly targeted prostate cancer therapies focus on mCRPC, rather than earlier points in the disease trajectory, and no trials have investigated the optimal time point at which to initiate genetic or molecular testing. For the small subset of patients with MSI-high prostate cancer, checkpoint inhibitor treatment may be available in some countries based on a tumour agnostic approval.

Ongoing phase III trials in molecularly selected patients with prostate cancer focus on checkpoint inhibitors and novel agents, such as PARPi. Recent data from the PROfound study have underlined the benefit of the PARPi olaparib for patients with BRCA1/2 alterations including monoallelic alterations [63,64]; this drug is now approved by the European Medicines

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Table 8
Ongoing phase III trials addressing bone health and bone metastases (not reported at time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Experimental treatment	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
REDUSE (NCT02051218)	n = 1380 mBC mCRPC ≥3 bone metastases	NA	Denosumab	3× denosumab 120 mg sc. q4w followed by denosumab 120 mg sc. q12w versus denosumab 120 mg sc. q4w	Standard of care	Time to first on-trial symptomatic skeletal event	12/2021
REaCT-BTA (NCT02721433)	n = 250 mCRPC mBC	NA	Denosumab, pamidronate, zoledronic acid	4-weekly versus 12-weekly denosumab, pamidronate, zoledronic acid	Standard of care	Health-related quality of life scores measured with EORTC QLQ-C30 functional domain (physical subdomain)	09/2019 Data reported[a]

PCa = prostate cancer; mBC = metastatic breast cancer; mCRPC = metastatic castration-resistant prostate cancer; NA = not applicable; q4w = every four weeks; q12w = every twelve weeks; sc = subcutaneous; EORTC = European Organization for Research and Treatment of Cancer; QLQ = quality of life questionnaire.

[a] Clemons, M et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. *Eur J of Cancer* 142 (2021) 132−140

Table 9
Ongoing phase III trials addressing molecular characterisation of tissue and blood (not reported at time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
MAGNITUDE (NCT03748641)	n = 1000 mCRPC Cohort 1: HRR gene alteration Cohort 2: no HRR gene alteration Cohort 3: open label	No prior abiraterone in mHSPC or mCRPC, No novel hormonal agents or docetaxel in mCRPC	Cohort 1, 2 niraparib 200 mg plus abiraterone 1000 mg/prednisone 10 mg versus niraparib plus placebo Cohort 3: niraparib plus abiraterone plus prednisone	ADT	cohort 1 and 3: rPFS	07/2022
PROpel (NCT03732820)	n = 720 mCRPC ECOG 0−1 availability of either an archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue sample, or a new biopsy taken during the screening	Treatment naïve in mCRPC setting and no prior abiraterone	Olaparib 300 mg BID plus abiraterone plus prednisone versus abiraterone plus prednisone plus placebo	ADT	rPFS	07/2021
TRITON 3 (NCT02975934)	n = 400 mCRPC Deleterious mutation in a BRCA1/2 or ATM gene	1 novel hormonal agent for mCRPC No prior chemotherapy for mCRPC	Rucaparib versus abiraterone or enzalutamide or docetaxel	ADT	rPFS	02/2022
KEYLYNK-010 (NCT03834519)	n = 780 randomised mCRPC Unselected for homologous recombination repair defects	mCRPC Failed prior treatment with one NHA and chemotherapy No prior enzalutamide or apalutamide in mHSPC No prior enzalutamide or Darolutamide	Pembrolizumab 200 mg plus olaparib 600 mg versus abiraterone or enzalutamide	ADT	OS rPFS	04/2022
TALAPRO-2 (NCT03395197)	n = 1037 Asymptomatic or mildly symptomatic mCRPC Life expectancy ≥12 months part 2: DDR mutation status	Treatment naïve in mCRPC (only abiraterone allowed) Chemotherapy in mHSPC allowed No prior enzalutamide, apalutamide or darolutamide in any setting Exclusion: LN metastasis below aortic bifurcation only	Talazoparib 0.5 mg plus enzalutamide versus enzalutamide plus placebo	ADT	Confirm the dose of talazoparib (part 1) rPFS (part 2)	08/2021

PCa = prostate cancer; mCRPC = metastatic castration-resistant prostate cancer; HRR = homologous recombination repair; mHSPC = metastatic hormone-sensitive prostate cancer; ADT = androgen deprivation therapy; rPFS = radiographic progression-free survival; ECOG = eastern collaborative oncology group; FFPE = formalin-fixed paraffin-embedded; BID = twice daily; BRCA1/2 = breast cancer gene 1/2; ATM = ataxia telangiectasia mutated; NHA = next-generation hormonal agent; OS = overall survival; DDR = DNA damage response and repair; LN = lymph node.

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Agency (EMA) and FDA. The results are awaited from the TRITON 3 trial, in which patients with mCRPC who have BRCA1/2 or ATM alterations receive either the PARPi rucaparib or physician's choice of standard of care, with a primary end-point of rPFS (Table 9).

Of note, almost no molecularly targeted phase III studies in prostate cancer have included platinum-based therapies. Retrospective case series support the activity of platinum, especially in molecularly selected mCRPC patients with DNA repair gene alterations [65]. Hopefully, data from ongoing phase II trials will help confirm this finding and pave the way for phase III studies of this therapy. So far, one of the only relevant phase III trials is ProBio, in which patients with mCRPC receive prespecified treatments based on biomarker signatures in their free circulating tumour DNA; carboplatin is being administered to individuals with alterations in DNA repair genes. For a list of key phase III studies, please see Table 9.

Combination treatments that include PARPi also are of interest in mCRPC and are the subject of several ongoing phase III trials, including MAGNITUDE, PROpel, TALAPRO-2 and KEYLYNK-010. A prior randomised phase II study suggested that rPFS may be longer with olaparib plus abiraterone compared with abiraterone alone [66]. Treatment benefits occurred irrespectively of DNA damage repair gene alteration status, suggesting potential synergy between PARPi and AR-targeted treatment.

9.3. Outstanding gaps in knowledge

While ongoing phase III trials will generate copious information on patients with DNA repair gene alterations, there is a lack of trials specifically for patients with prostate cancer with other pathogenic alterations, for example, defective mismatch repair protein (dMMR) status or MSI high, with CDK12 alterations, ATM alterations or SPOP mutations.

10. Health status assessment in older patients and special populations

The International Society for Geriatric Oncology recommends that patients with prostate cancer who are >75 years receive a health status assessment before undergoing treatment [67].

10.1. Area of non-consensus

At APCCC 2019, the panel did not reach consensus on the question of a health status assessment in patients aged >70 years with advanced prostate cancer nor on which assessments to use.

10.2. What is being done

The results of ongoing studies may eventually improve consensus by clarifying how older age/frailty affects outcomes and management considerations (Table 10). One large trial (PRISM NCT03516110) stratified patients receiving ADT by quality of life and age, but the results are not yet available. Another large phase III trial (PREPARE NCT02704832), which is currently enrolling, will perform baseline geriatric screening using the G8 tool. Vulnerable patients identified by G8 (G8 $\leq$ 14 points) will be randomised to receive either standard care or an enhanced care protocol that includes a geriatric assessment, ongoing case management and supportive care interventions prescribed by geriatricians. In addition, the PEACE-6 trial soon plans to open a cohort of elderly or frail patients with mHSPC, who will be randomised to receive ADT with or without additional next-generation endocrine therapy.

10.3. Outstanding gaps in knowledge

Dedicated clinical trials in advanced prostate cancer that integrate information on health status assessment into the treatment concept (dose of anticancer therapy and specific treatment monitoring in older patients with a view of adverse events of special interest) are not being performed currently. Based on trial data in other oncological areas the main question is whether a modified treatment regimen in older/frail patients will result in less adverse events without significantly impacting oncological outcomes.

11. Side effects of hormonal treatments and their management

Although hot flushes are one of the most common and bothersome side effects of ADT (and may be even more common when combined endocrine therapies are used), and there exist a number of behavioural and pharmacological treatment options, there are no high evidence level data and no clear recommendation in international guidelines for their management.

11.1. Areas of non-consensus

There was no consensus on the best management option for patients with bothersome hot flushes on ADT, nor on the preferred management strategy for patients experiencing significant fatigue on enzalutamide or apalutamide therapy.

11.2. What is being done

Many therapeutic strategies to improve hot flushes have been investigated [68,69], but the management of those induced by ADT has been significantly under-researched

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Table 10
Ongoing phase III trials addressing health status assessment in elderly patients (not reported at time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Experimental treatment	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
PREPARE (NCT02704832)	Locally advanced or metastatic (n = 1500): breast, colorectal, lung, PCa, bladder, ovarian, lymphoma	NA	G8 screening	If G8 $\leq$ 14: randomised according to Arm A: Usual care (treatment according to on-going regimens in oncology) or Arm B: Case management (assessment of the patient by the nurse and the geriatrician with interventions as prescribed by the geriatrician)	Standard	1. OS at 1 year 2. HR-QoL by 3 EORTC QLQ-C30 at 1 year	02/2019 Recruitment status unknown since 2017
PRISM (NCT03516110)	PCa (n = 831): $\geq$60 years, eligible to start GnRH agonist therapy	NA	QLQ-ELD-14 in cohorts aged 60 to <70 years, 70 to <75 years, $\geq$75 years	None	ADT	QLQ-ELD-14 at 6 months	02/2020 Data reported[a]
GIVE (NCT02785887)	Any solid tumours (n = 223) $\geq$70 years	NA	Arm A: routine oncological care plus geriatric intervention Arm B: routine oncological care	In addition to routine oncological care, patients will be reviewed by a geriatrician and may receive intervention if CGA deficits are found	Standard	RDI is defined as the ratio (in percentage) of the total administered dose of chemotherapy to the standard dose of the same chemotherapy regimen, as defined by the treating centre	09/2018 Data not yet reported

PCa = prostate cancer; NA = not applicable; G8 = geriatric 8 score; OS = overall survival; HR-QOL = health-related quality of life; EORTC = European Organization for Research and Treatment of Cancer; QLQ = quality of life questionnaire; GnHR = gonadotropin hormone releasing hormone; ELD = elderly; ADT = androgen deprivation therapy; CGA = comprehensive geriatric assessment; RDI = Relative dose intensity.

[a] Francois Rozet et al. Quality of life of prostate cancer (PCa) patients aged 60 years and older: Changes in QLQ-ELD14 dimensions after a six-month gonadotropin-releasing hormone agonist (GnRHa) therapy, according to age groups—Primary analysis of PRISME study. *J Clin Oncol* 2021 39:6_suppl, 55-55.

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Table 11
Ongoing pilot or phase II trials addressing the side effects of hormonal treatments and their management (no phase III currently ongoing; not reported at the time of APCCC 2019).

Trial (NCT)	Patient characteristic, planned number of patients	Pre-treatment	Study interventional method/drug	Local experimental treatment	Systemic treatment for PCa	Primary end-point	Estimated primary completion date as per NCT
(SGB) in Men Treated for PCa Improve Hot Flashes (NCT03796195)	n = 20 Single group assignment, Interventional, <65 years, >28 hot flushes/week	Metastatic or non-metastatic PCa under ADT No current CHT or radium-223	Guided right-sided SGB	5% bupivacaine (5 mL)	ADT planned for ≥2 months	Hot flush frequency (weekly until 6 months)	01/2023
Vitamin B6 in Reducing Hot Flashes in Patients With PCa undergoing ADT (NCT03580499)	n = 40 Single group assignment	PCa under ADT	Vitamin B6 daily for 12 weeks		ADT planned for ≥13 months	Median change in response to 10-point hot flush scale (baseline to 8 weeks)	02/2022
Oxybutynin Versus Placebo for the Treatment of Hot Flashes in Men Receiving ADT (NCT04600336)	n = 87 Placebo controlled, two dose levels >28 hot flushes/ week	PCa under ADT for 1 month Novel hormonal agents allowed	Low-dose oxybutynin chloride (2.5 ml twice daily) PO BID on days 8 −49 (6 weeks) or high-dose oxybutynin chloride (5.0 ml twice daily) PO BID same schedule		ADT planned >42 days after randomisation	Patient reported hot flush scores up to 6 weeks	02/2023
REDOSE (NCT03927391)	n = 50 Randomised mCRPC frail (G8 assessment ≤14 points or ≥grade 1 for CNS disorders (CTCAE) one of the following: fatigue, concentration impairment, cognitive disturbance, amnesia, depressed level of consciousness, memory impairment, hypersomnia)	mCRPC under ADT No prior treatment with enzalutamide	Enzalutamide standard dose (160 mg) versus enzalutamide reduced dose (120 mg)		Enzalutamide planned within label	Change in the CNS side effect fatigue (FACIT-fatigue questionnaire versus 4) Reduced dose of enzalutamide compared with standard dose after 6 weeks of treatment	12/2021

Cognitive Effects of AR Directed Therapies for Advanced PCa (NCT03016741)	n = 100 Two arms non-randomised PCa under ADT	At least 1 month ADT mHSPC <2 weeks abiraterone or enzalutamide CHT > 12 months <6 months CHT for mHSPC	Enzalutamide for mCRPC Abiraterone/ prednisone for mHSPC or mCRPC within label	Cognitive function (Cogstate score and Cogstate module scores) baseline, 3, 6 and 12 months	08/2022
ARACOG (NCT04335682)	n = 132 Two-arm randomised cross-over design nmCRPC mCRPC	No prior CHT for CRPC, no prior CHT < 6 months for mHSPC	Darolutamide 600 mg BID or enzalutamide 160 mg QD	Change in the maximally changed cognitive domain (24 weeks)	04/2023

PCa = prostate cancer; SGB = stellate ganglion block; ADT = androgen deprivation therapy; PO = per os; BID = twice daily; mCRPC = metastatic castration-resistant prostate cancer; G8 = geriatric 8; CNS = central nervous system; CTCAE = Common Terminology Criteria of Adverse Events; FACIT = the functional assessment of chronic illness therapy; AR = androgen receptor; mHSPC = metastatic hormone-sensitive prostate cancer; nmCRPC = non-metastatic castration-resistant prostate cancer; CRPC = castration-resistant prostate cancer; QD = once daily.

and is in need of clinical trials. Only a few relevant studies are underway, and none are phase III (Table 11). Most ongoing studies of interventions for ADT-induced hot flushes focus on stellate ganglion blockade with 5% bupivacaine, oxybutynin (an antimuscarinic agent drug that works by blocking the effects of acetylcholine on smooth muscle) and vitamin B6. These early-phase studies include a single-group assessment of hot flush frequency (NCT03796195), and a placebo-controlled trial using a standardised hot flush score (NCT02295163). Another phase II trial (NCT03580499) compares hot flush score among patients receiving oral vitamin B6 (without bupivacaine or oxybutynin) or placebo. In addition, a randomised, double-blind, placebo-controlled trial (NCT04600336) is investigating the efficacy of two different doses of oral oxybutynin, administered for six weeks.

Another key but often underestimated side effect of prostate cancer therapy is central nervous system (CNS) side effects, primarily with enzalutamide and apalutamide [70]. The mechanism for these is not yet fully understood, but the results of murine studies suggest that both enzalutamide and its active metabolite penetrate the CNS. The recently presented ODENZA phase II trial randomised 249 patients to darolutamide (1200 mg daily) for 12 weeks followed by enzalutamide 160 mg daily for 12 weeks or the reverse sequence with enzalutamide followed by darolutamide with a primary end-point of patient preference. Fatigue was a key factor influencing patient's preference and numerically a greater number of patients preferred darolutamide, but statistically the difference was not significant [71]. Cognitive impairment, in particular, seems to be a class effect and was addressed at APCCC 2019 but did not lead to a consensus on management (i.e. a dose reduction or a switch to abiraterone). ODENZA should soon report cognitive function data evaluated by Cogstate [72] in men randomly receiving darolutamide or enzalutamide. Two ongoing trials are focused on enzalutamide dosing in frail patients. The phase II REDOSE trial compares fatigue with standard-dose versus reduced-dose (120 mg) enzalutamide in patients with CRPC and baseline frailty, defined as G8 score $\leq$14 in addition to one predefined CNS disorder of Common Toxicity Criteria Adverse Event grade $\geq$1. The second trial is a non-randomised two-arm study (NCT03016741) of cognitive function, as assessed by Cogstate at different time points during up to 1 year of treatment with abiraterone (for mHSPC or mCRPC) or enzalutamide (for mCRPC). ARACOG is a phase II randomised cross-over trial that compares darolutamide and enzalutamide in patients with CRPC. The primary end-point is changed at week 24 in cognitive domain as measured by the Cambridge Neuropsychological Test Automated Battery. The DaroAcT trial (NCT04157088) randomises patients with mCRPC to enzalutamide or darolutamide with a

primary end-point of Time Up and Go time at 6 months.

11.3. Outstanding gaps in knowledge

With the introduction of potent endocrine treatment combinations, especially in mHSPC, the evaluation and impact of specific side effects on quality of life as well as management strategies for these side effects should be addressed in dedicated clinical trials. With very prolonged survival with metastatic disease now possible with intensified ADT, the question of intermittent therapy for good responders may need to be revisited.

12. Discussion

Experts at APCCC 2019 identified many clinically important areas in advanced prostate cancer that are beset by low level of evidence and/or conflicting interpretation of the available clinical data. The international panel of clinical experts did not reach consensus, with a single round of voting, on 88% of questions concerning disease management. It is important to take into consideration that for the consensus questions at APCCC, unless specified otherwise, answers were based on the hypothetical scenario that all diagnostic procedures and treatments were readily available, that there were no contraindications to treatment and that there was no option to enrol the patient in a clinical trial, and there was no second round of voting after hearing the opinions of other panel members. For some questions, the lack of agreement may be explained by answer options that were similar but not identical. For the interpretation, combination of answer options was not performed. The difference in the level of consensus was more pronounced by different specialities (urology versus medical oncology versus radiation/clinical oncology) rather than regions of practice (Europe versus North America versus rest of the world) [2]. Since APCCC 2019, several clinical trials have addressed some of these topics, but our review of clinical trial databases revealed that many questions remain either entirely uninvestigated or understudied.

In the management of locally advanced prostate cancer, the novel and highly efficacious AR pathway inhibitors that are used in a number of trial and the genomic classifiers may lead to new standards of management. Furthermore, the growing use of PSMA PET-based imaging will create new disease categories of cN0 and cN1 disease, as well as cM0/cM1.

The three pivotal trials selected patients based on PSA criteria (both absolute level and doubling time). Considering the heterogeneity of nmCRPC, however, incorporating both PSA thresholds and genomic plus clinical variables might help best select the patients at greatest risk for near-term progression to symptomatic metastatic disease, who might benefit most from additional treatment. Relevant data on the Decipher test have been presented for a subset of SPARTAN participants, showing that patients with high Decipher scores may have greater benefit from apalutamide therapy [73], but no ongoing phase III trials are investigating genomic testing for risk stratification in nmCRPC.

Concerning treatment monitoring, imaging in clinical trials has almost always has been limited to conventional CT and technetium-99m (^{99m}Tc) bone scans, while in practice, clinicians in many regions are increasingly using more sensitive and precise imaging, such as PSMA PET/CT or whole-body diffusion-weighted MRI. The growing use of next-generation imaging to stage high-risk 'localised' prostate cancer will heighten the identification of synchronous metastatic disease. To date, the clinical significance and treatment implications of this stage of migration remain unknown. Should patients with low-volume metastatic disease receive intensified systemic therapy and/or the addition of systemic ADT to radiation therapy? Or would the burden and side effects of intensified treatment in these patients outweigh potential benefits?

Another key area of uncertainty is how best to define, manage and monitor oligometastatic prostate cancer. Unfortunately, the widespread use of SBRT in many countries (despite an absence of definitive data on its benefits) will make randomisation of clinical trial participants quite difficult. An additional gap is the sparse data on bone health agents for osteoporosis prevention among patients with locally advanced or mHSPC who are starting on long-term ADT. Current guidelines on cancer treatment-induced bone loss reflect a lack of high-level evidence, and currently, no trials are being performed in the mHSPC setting. In older studies, monthly dosing of bone health agents was shown to prevent SREs in mCRPC but not in mHSPC. However, many patients now are living much longer in the mHSPC setting, and their prolonged hypogonadism and exposure to abiraterone and prednisone presumably increase their osteoporotic fracture risk.

Finally, hormonal treatments are the backbone of care for many patients with advanced prostate cancer. It induces a considerable burden of adverse effects, which greatly impairs most patients' quality of life. There is a concerning lack of phase III trials assessing how to reduce, or even just better manage, this key issue. One reason for this mismatch is that it is difficult to sponsor large, randomised, controlled studies of clinically relevant questions if pharmaceutical companies are unmotivated to provide support; in many cases, national government tax-funded programmes or foundation grants are insufficient. The same is true for de-escalation trials: It is almost impossible to find funding for this kind of trial and ironically; in most countries, the administrative hurdles for safety will be not

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less even if a lower dose is used, and mostly, the drug has to be paid by the trial even if it would be a standard treatment. Thus, it is critically important that academics prioritise clinical questions that urgently need answering through dedicated research and advocate for patients and investigators to dedicate themselves to answering these important questions. In addition, regulators are encouraged to try to find alternative rules for academic trials testing a lower dose intensity of a standard treatment.

Authors' contributions

U.V., S.G. and A.O. contributed to study concept and design. All authors contributed to acquisition of data, analysed and interpreted the data and critically revised the article for important intellectual content. U.V., S.G. and A.O. drafted the article.

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