BMJ Open

A modified Delphi consensus regarding the clinical utility of triplet therapy in patients with metastatic hormone-sensitive prostate cancer patients in the UK

Hilary Glen,[1] Amit Bahl,[2] Louisa Fleure,[3] Noel Clarke,[4,5] Suneil Jain,[6] Tania Kalsi,[7] Vincent Khoo,[8] Junaid Mobeen[9]

To cite: Glen H, Bahl A, Fleure L, *et al*. A modified Delphi consensus regarding the clinical utility of triplet therapy in patients with metastatic hormone-sensitive prostate cancer patients in the UK. *BMJ Open* 2024;**14**:e090013. doi:10.1136/bmjopen-2024-090013

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-090013).

Received 14 June 2024
Accepted 22 October 2024

For numbered affiliations see end of article.

Correspondence to
Dr Hilary Glen;
hilary.glen@ggc.scot.nhs.uk

ABSTRACT

Objectives This study aimed to determine the clinical utility of the androgen deprivation therapy (ADT)+docetaxel (DOCE)+androgen receptor-targeted agent (ARTA) triplet therapy in patients with metastatic hormone-sensitive prostate cancer (mHSPC) in the UK.

Design A modified Delphi method. A steering group of eight UK healthcare professionals experienced in prostate cancer care discussed treatment challenges, developing 39 consensus statements across four topics. Agreement with the statements was tested with a broader panel of professionals within this therapeutic area in the UK through an anonymous survey, using a four-point Likert scale. This was distributed by the steering group members and an independent third party. Following the survey, the steering group convened to discuss the results and formulate recommendations.

Setting The steering group convened online for discussions. The survey was distributed via email by the clinicians and the independent third party.

Participants Healthcare professionals involved in the provision of prostate cancer care, working in relevant professional roles (oncology, urology or geriatric consultant, oncology nurse specialist, and hospital pharmacist) within the UK. No patients or members of the public were involved within the study.

Interventions None.

Primary and secondary outcome measures Consensus was defined as high (≥75% agreement) and very high (≥90% agreement).

Results Responses were received from 120 healthcare professionals, including oncologists (n=73), urologists (n=16), geriatricians (n=15), nurse specialists (n=11) and hospital pharmacists (n=5). Consensus was reached for 37 out of 39 (95%) statements, and 27/39 (69%) statements achieved very high agreement ≥90%. Consensus was not reached for 2/39 (5%) statements.

Conclusions Based on the consensus observed, the steering group developed a set of recommendations for the clinical utility of ADT+DOCE+ARTA in treating patients with mHSPC in the UK. Following these recommendations enables clinicians to identify appropriate patients with mHSPC for triplet treatment, thereby improving patients' outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The key strength of this study is the very high consensus achieved across 120 responses from a diverse group of healthcare professionals working in multiple specialties.
⇒ The survey used a four-point Likert scale to avoid order and neutral response bias.
⇒ The fluctuations noted when analysed by subgroup indicate potential bias was minimal.
⇒ A limitation of the study is the bias towards responses from England, with under-representation of the devolved nations.
⇒ Regarding Scotland, having achieved reimbursement approval more recently than the other UK nations meant Scottish clinicians potentially have less experience using triplet therapy, which could explain the low levels of agreement from Scottish respondents.

BACKGROUND

Prostate cancer is a common form of cancer among males in the UK, constituting 27% of newly diagnosed cancer cases in 2016–18.[1] The incidence is higher in those aged ≥75 years, accounting for 34% of new cases annually in this group.[1] Approximately 19% of patients receive a diagnosis at the metastatic stage.[2] Newly diagnosed (de novo) metastatic hormone-sensitive prostate cancer (mHSPC) represents 5%–10% of all prostate cancer cases globally. It is characterised by high mortality, accounting for 50% of prostate cancer-related deaths.[3] While the introduction of novel therapeutic options has enhanced overall survival (OS) and quality of life (QoL),[4] mHSPC remains incurable.[5]

Metastatic prostate cancer can be categorised into several risk groups. Newly diagnosed advanced or metastatic disease is considered synchronous; whereas, patients

initially diagnosed and treated for local/non-metastatic prostate cancer are considered to have recurrent or metachronous disease.[6] Metastatic disease can be classified as either low or high volume, depending on the extent and type of metastases spread.[7] Treatment decisions are guided by factors such as level of risk (high or low), synchronous or metachronous nature, disease volume (high or low), the severity and type of symptoms experienced by patients, and patient characteristics such as age, comorbidities, current medications and treatment wishes.[3 5 8 9] The location of metastases can also be an important consideration.[10 11] While the disease may initially spread through the pelvic lymphatic pathways, in those with metachronous disease who have undergone lymphadenectomy or radiation therapy, nodal dissemination may be altered and metastases can develop in extrapelvic nodes.[11] Furthermore, those with visceral metastatic disease often have a worse prognosis, particularly those with liver or lung metastases.[12]

The standard-of-care treatment currently involves combining androgen deprivation therapy (ADT) with an androgen receptor-targeted agent (ARTA).[8] These combinations have been shown to improve OS, delay the onset of hormone resistance, reduce pain progression and/or alleviate symptomatic skeletal events.[5] Research is ongoing to try and identify patient biomarkers which can aid with diagnosis, prognosis and treatment decisions.[13–15] While some have been identified, there are still no robust biomarkers which predict patient response to doublet or triplet therapies.[3] Consequently, the selection of a suitable combination relies on various factors.[8]

Data from phase III randomised controlled trials (RCTs) (PEACE-1 and ARASENS) have shown a significant improvement in OS with the addition of an ARTA such as abiraterone (AAP, with prednisolone)[5] or darolutamide (DARO)[16] to ADT+docetaxel (DOCE) compared with ADT+DOCE alone. The results also demonstrated that intensification of treatment was generally well tolerated, with a safety profile consistent with ADT+DOCE.[17 18] ARASENS also showed that triplet therapy is effective in those with de novo, recurrent, high volume, and high and low risk disease.[17] There was also some evidence for effectiveness of triplet therapy in low-volume disease, but this was not significant.[17] Therefore, upfront triplet therapy presents a promising treatment option for a number of patients with prostate cancer, although research including more patients with low-volume metastatic disease is needed.[5 16]

Despite strong clinical data supporting the use of triplet therapy, there have currently been no clinical trials investigating the benefit of the addition of DOCE to ADT+ARTA.[19] Many indirect treatment comparisons have been published comparing treatments for mHSPC, but there is a lack of head-to-head clinical trials comparing efficacy.[20] In previous phase III RCTs (ARCHES, ENZAMET and TITAN), the efficacy and safety of ADT+ARTA in the treatment of mHSPC were evaluated. Within ARCHES and TITAN, patients were allowed to enrol regardless of previous DOCE therapy, as long as DOCE use was stopped before the new treatment was started.[21 22] In ENZAMET, some patients received up to two cycles of DOCE alongside ADT prior to initiation of enzalutamide/ARTA. The decision to initiate early docetaxel treatment was left up to the individual patient and their physicians.[23] The results indicate that sequential triplet therapy did not achieve prolongation of OS, possibly due to the limited number of patients within this subgroup.[5 21–23] As there remains a level of uncertainty regarding the addition of DOCE to ADT+ARTA, there is still a prevalence for use of doublet therapy with ADT+ARTA primarily based on concerns regarding increased toxicity of triplet therapy combination despite evidence of treatment tolerability.[16–18]

There is a lack of clear criteria in current guidelines on how and when to use triplet therapy vs doublet therapy, and how to determine suitability for DOCE. NICE guidelines recommend offering chemotherapy with DOCE to patients with newly diagnosed metastatic prostate cancer.[24 25] NHS England Clinical Commissioning Policy Statement for DOCE only says that an individual may not be suitable if they exhibit a poor overall performance status, pre-existing peripheral neuropathy, poor bone marrow function or a life-limiting illness.[26] EAU guidelines state DOCE should only be used in combination with ADT+ARTA.[19] These guidelines also state there is more evidence for the use of triplet therapy in synchronous disease, particularly those with high-volume disease, but acknowledge there are a variety of factors which will influence treatment choice. Factors to bear in mind when considering treatment intensification have been mentioned within the literature, including disease classification, treatment accessibility, toxicity profiles, and patient age, comorbidities and treatment preference.[3 27] The STOPCAP M1 meta-analysis was published after this study's initial literature review, while the survey was in field, therefore its results could not be used to develop the consensus statements. However, this found that DOCE+ADT benefits those with high-volume disease most, compared with those with metachronous low-volume disease.[6]

To date, there has been no clear consensus established on which patients are the ideal candidates for triplet therapy. Therefore, this project aimed to establish an expert consensus on the clinical utility of the triplet therapy of ADT+DOCE+ARTA in patients with mHSPC in the UK. The modified Delphi methodology was chosen for this project to examine areas of practice where there is limited empirical research and guidance.[28] This method provides a formal and recognised way to aggregate opinion data from healthcare professionals in a reliable manner.[29 30]

METHODS

Between 7 and 9 December 2022, a literature review was conducted to assess the current use of, and guidelines for, triplet therapy in the management of prostate cancer. The

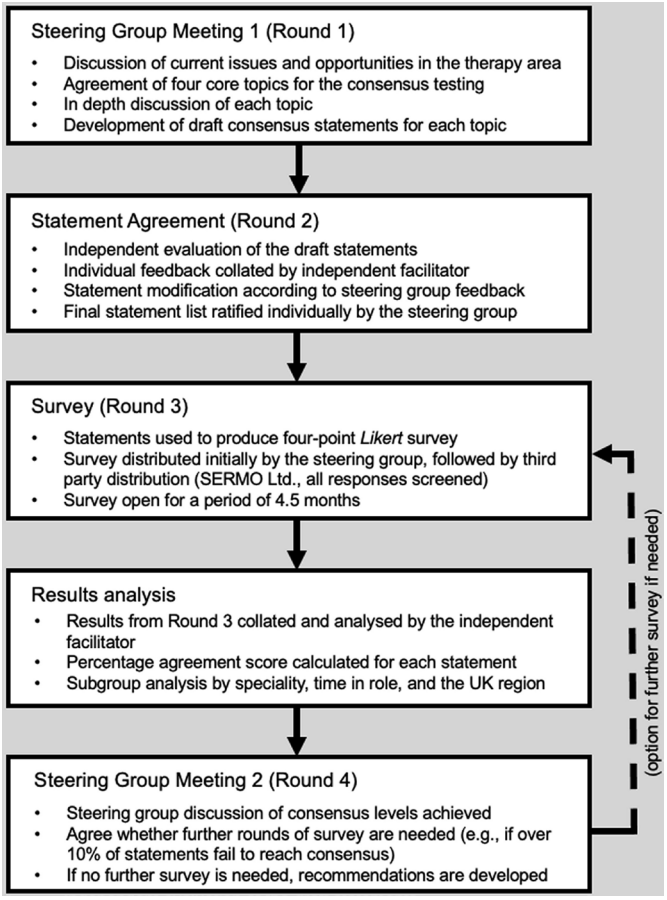

Figure 1 Modified Delphi study design.

search was conducted on PubMed and Cochrane. Search terms included but were not limited to 'prostate cancer', 'mHSPC' and 'mHSPC treatment options'. The searches were then filtered to include only literature from the past 5 years with the full text available, with further searches for UK-specific literature. This was used to develop the aim and scope of the project.

Following this, a specialist steering committee of UK healthcare professionals working in prostate cancer care provision were convened in March 2023 to discuss challenges and solutions within this evolving area of healthcare, including the utilisation of triplet therapy for mHSPC. These individuals were recruited based on previous publications and clinical experience in prostate cancer care, with the aim to gather a group from a variety of backgrounds, working across the UK. Overall, the group comprised four consultant clinical/medical oncologists, a consultant urologist, a consultant in geriatric medicine with expertise in geriatric oncology, a consultant pharmacist and a lead uro-oncology clinical nurse specialist. This steering group helped to develop the aim of the project and actively directed the project at each stage.

A modified Delphi methodology (figure 1) was employed throughout this project and was facilitated by an independent third party (Triducive Partners Ltd.). The technique used in this study was informed by Guidance on Conducting and REporting DElphi Studies (CREDES) and reporting follows the ACCORD guidelines.[31 32] The study was not registered.

During their initial meeting, the committee identified and agreed on four main topics for consideration:

1. The role and utility of treatment intensification including the option of chemotherapy in triplet therapy.
2. Identification of suitable patients to consider for treatment intensification including the option of chemotherapy in triplet therapy.
3. The role of patient education and shared decision making.
4. Multidisciplinary working.

The first round of consensus involved in-depth discussion of each topic, followed by the generation of consensus statements in line with the themes of these topics. Following the meeting, the statements were consolidated before being reviewed independently and anonymously by the group. All statements were assessed on the basis of 'accept', 'remove' or 'reword' (along with suggested changes). Changes were then made based on these comments, as determined by a simple majority. This constituted the second round of consensus.

The ratified statements were then used to develop a four-point Likert survey ('strongly disagree', 'tend to disagree', 'tend to agree' and 'strongly agree'). Distribution of this was the third round of consensus and gathered the opinions of a broader range of healthcare professionals. The consensus threshold was defined a priori as 75%, a widely accepted standard.[33] Additionally, consensus was categorised as 'high' at ≥75% and 'very high' at ≥90%. The survey was anonymous, and the personal data of respondents were unknown to both the steering group and the independent facilitator, although some demographic data was captured (respondent role, time in role and UK region). A consent statement was placed at the beginning of the survey. Each respondent indicated their agreement to participate by completing and submitting the questionnaire. Since the study was conducted anonymously, ethical approval was not required.

Stopping criteria were established a priori as a 2-month survey window, a target of 100 responses, and 90% of statements passing the threshold for consensus. These criteria were established to gain the required number of responses while accounting for time pressures within the healthcare system. If the target number of responses and number of statements over the threshold were achieved, it was agreed that no further rounds of survey would be needed. Initially, the survey was distributed by the steering group, however, due to low response rates, the survey window was extended, and an independent agency (SERMO Ltd.) was used to generate responses through convenience sampling of their panel of UK healthcare professionals. All respondents were screened to ensure they were involved in the provision of prostate cancer care, working in relevant professional roles (oncology, urology or geriatric consultant, oncology nurse specialist, and hospital pharmacist) and were working within the UK.

For the online survey, there was also a time to completion requirement (minimum 4 min 30 s), which along with pattern recognition was used to ensure genuine engagement by responders. Respondents received a nominal fee for completing the survey.

Completed surveys were analysed to generate an overall arithmetic agreement score for each statement. This was determined from the percentage of respondents expressing agreement ('tend to agree' or 'strongly agree') with each statement. Survey results were discussed at a series of steering group meetings in November and December 2023. It was agreed that due to the high levels of consensus, and that the stopping criteria were met, no further survey rounds were necessary. The group independently highlighted key statements from each topic based on the levels of consensus and the discussions had by the group. This took into consideration the mean consensus level and the distribution of agreement across the Likert scale. Key statements were used to form a series of actionable recommendations which were anonymously ratified by the group. The statements selected and the recommendations developed were considered in line with the literature and aimed to provide practical ways to address care needs for patients or educational needs for healthcare practitioners. Overall, four rounds of consensus development were undertaken.

Patient and public involvement

As the aim of the study was to gather opinion data from clinicians, no members of the public or patients were involved in the design or completion of this work.

RESULTS

Following ratification by the steering group, 39 statements were agreed on and used for the survey. A total of 120 responses were received, 16 through steering group distribution and 104 through the third-party agency. All responders were healthcare specialists with experience in the management of patients diagnosed with prostate cancer and were based in the UK. They included the following professional roles (online supplemental figure S1):

- Medical oncologist (n=42).
- Clinical oncologist (n=31).
- Consultant urologist (n=16).
- Consultant geriatrician (n=15).
- Oncology nurse specialist (ONS) (n=11).
- Hospital pharmacist (n=5).

Among the participants, the majority (n=54) had 11–20 years of experience in role (online supplemental figure S2). Most respondents (n=70) were located in England (South), with 34 participants from England (North) and 13 from Scotland. Furthermore, 2 professionals were from Northern Ireland and 1 was from Wales (online supplemental figure S3).

Consensus was reached for 37 statements (95%), with 27 statements achieving agreement levels of ≥90%. Consensus was not reached for 2/39 statements (5%) (figure 2).

The list of statements and their overall consensus scores is presented in table 1. The distribution of consensus scores on the four-point Likert scale, provided by respondents, is illustrated in online supplemental figure S4.

When analysed by roles, some statements demonstrated marked differences in the levels of agreement achieved. Six statements showed ≥10% variation from the overall level of consensus across roles (online supplemental table S1). When analysed by region, 9 statements showed ≥10% variation in consensus (online supplemental table S2). Scotland (n=13 responders) showed the lowest levels of agreement with the statements, particularly in those pertaining to the use of triplet therapy.

DISCUSSION

The analysis of the results revealed a strong consensus regarding the majority of statements. This enabled the formulation of a set of guiding principles for the clinical utility of ADT+DOCE+ARTA in the treatment of patients with mHSPC. Results and implications are discussed by

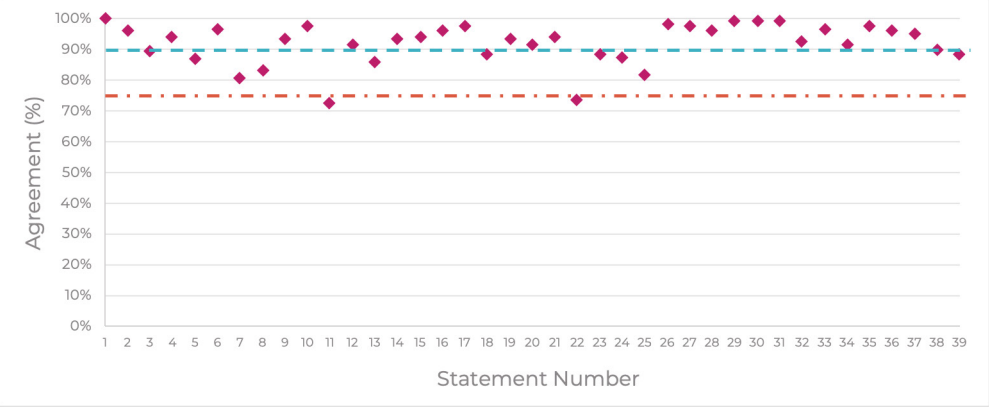

Figure 2 Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%).

Table 1 Defined consensus statements and corresponding levels of agreement (percentages have been rounded to the nearest decimal place)

No.	Statement	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Agreement
Topic A. The role and utility of treatment intensification including the option of chemotherapy in triplet therapy						
1	There is level 1 evidence that treatment intensification in newly diagnosed mHSPC including doublet therapy (ADT+ARTA) improves PFS and OS vs ADT alone	53%	48%	0%	0%	**100%**
2	There is level 1 evidence that triplet therapy and early treatment intensification in the form of ADT+docetaxel+ARTA benefits mHSPC patients vs doublet therapy of ADT+docetaxel	43%	53%	4%	0%	**96%**
3	The evidence for treatment intensification in mHSPC with ADT+ARTA + chemotherapy is based on ARASENS	41%	48%	10%	1%	**89%**
4	The evidence for treatment intensification in mHSPC with ADT+ARTA is based on TITAN, ENZAMET, LATITUDE, ARCHES and STAMPEDE	53%	41%	5%	1%	**94%**
5	ADT monotherapy is no longer acceptable standard of care for patients with mHSPC apart from patients in whom ARTA or docetaxel is contraindicated, if the patient is elderly/frail/unfit due to comorbidity or if the patient declines additional treatment	58%	29%	13%	1%	**87%**
6	Ensuring equity of access across the UK to treatment intensification in appropriate patients is a priority	68%	28%	3%	0%	**97%**
7	In newly diagnosed mHSPC, the preferred doublet is ADT+ARTA rather than ADT+docetaxel	32%	49%	18%	1%	**81%**
8	If a patient is offered treatment with docetaxel, then it should be in the context of triplet therapy (ADT+ARTA + chemotherapy)	30%	53%	15%	2%	**83%**
9	The inclusion of docetaxel to ADT+ARTA provides better overall free survival vs ADT+docetaxel	42%	52%	7%	0%	**93%**
10	There is evidence that treatment intensification significantly delays time to castration resistance. This is an important consideration in the management of mHSPC	46%	52%	3%	0%	**98%**
11	Treatment intensification is not associated with significant impact to quality of life at 1 year in clinical trials compared with the comparator arms	21%	52%	25%	3%	**73%**
Topic B. Identification of suitable patients to consider for treatment intensification including the option of chemotherapy in triplet therapy						
12	In metastatic disease, a patient's prostate cancer is likely to be a determining factor of reduced life expectancy, and treatment intensification with triplet therapy should be considered	33%	58%	8%	1%	**92%**
13	Most patients should be assessed with a comprehensive multidisciplinary assessment (such as the comprehensive geriatric assessment) to identify suitability for treatment intensification with triplet therapy	63%	23%	13%	2%	**86%**
14	If a patient's life expectancy is significantly limited due to comorbidities (<1–2 years), then treatment intensification with triplet therapy may not be appropriate	54%	39%	7%	0%	**93%**
15	Patients' fitness should be assessed with treatment intensification of triplet therapy in mind, and optimised in readiness where appropriate and required	51%	43%	6%	0%	**94%**
16	Age alone is not a criterion for denying treatment intensification with triplet therapy	52%	44%	3%	1%	**96%**
17	Assessment for frailty and vulnerability is important in determining suitability for treatment intensification	70%	28%	3%	0%	**98%**
18	Tools such as G8, Charlson Comorbidity Index (CCI), frailty scores should be used in appropriate patients	32%	57%	11%	1%	**88%**
19	Triplet therapy should be considered in fitter patients for example, ECOG 0–1	66%	28%	6%	1%	**93%**
20	Triplet therapy should be considered in patients with high-risk disease (as defined by LATITUDE with having at least two of the three following high-risk factors: a Gleason score of 8 or more (on a scale of 2 to 10, with higher scores indicating more aggressive disease), at least three bone lesions, and the presence of measurable visceral metastasis)	44%	48%	8%	1%	**92%**

Continued

Table 1 Continued

No.	Statement	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Agreement
21	Triplet therapy should be the preferred option in patients with high-volume disease who are suitable for chemotherapy, as defined by CHAARTED (presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis)	43%	51%	4%	2%	**94%**
22	Triplet therapy should be considered in patients with low-volume disease that has a significant disease burden (eg, with multiple lymph node involvement) who are suitable for chemotherapy	24%	49%	23%	3%	**73%**
23	Triplet therapy should be the preferred option in patients with visceral disease (liver or lung metastases) who are suitable for chemotherapy	48%	41%	11%	1%	**88%**
24	Approximately 30% of newly diagnosed mHSPC patients are potentially suitable for treatment intensification with triplet therapy	31%	57%	12%	1%	**88%**
25	All newly diagnosed mHSPC patients suitable for triplet therapy should be offered it	34%	48%	12%	7%	**82%**
Topic C. The role of patient education and shared decision making						
26	Identifying and understanding patient goals is critical to the shared decision-making process	74%	23%	2%	0%	**98%**
27	Shared decision making is vital for decisions regarding treatment intensification in mHSPC	82%	16%	3%	0%	**98%**
28	Shared decision making improves compliance and adherence to treatment	75%	21%	4%	0%	**96%**
29	Shared decision making is important in minimising a patient's post-treatment regret	77%	23%	1%	0%	**99%**
30	Patient education is important to provide the tools for patients to mitigate or respond to side effects during treatment	73%	27%	1%	0%	**99%**
31	Patient understanding of the disease and their treatments is important	73%	26%	1%	0%	**99%**
Topic D. Multidisciplinary working						
32	Categorisation of patients by volume and risk should be done for all patients by the MDT	48%	44%	8%	0%	**93%**
33	The prostate cancer MDT pro-forma should contain all relevant patient details including all comorbidities and functional status	71%	26%	3%	1%	**97%**
34	Physical and psychological prehabilitation should be an integral part of management of patients with mHSPC	43%	48%	7%	2%	**92%**
35	Education is an ongoing process of the prostate cancer team and should be integrated into the work programme	52%	46%	3%	0%	**98%**
36	Multidisciplinary working has been shown to improve outcomes in cancer patients	60%	36%	3%	1%	**96%**
37	All patients with mHSPC should have a named CNS throughout their prostate cancer journey	65%	30%	5%	0%	**95%**
38	CNS staffing levels are currently inadequate to provide optimal patient support in prostate cancer	58%	33%	7%	3%	**90%**
39	Lack of chemotherapy suite capacity should not be a reason in decision making regarding triplet therapy	48%	40%	12%	0%	**88%**

ADT, androgen deprivation therapy; ARTA, androgen receptor-targeted agent; CNS, clinical nurse specialists; MDT, multidisciplinary team; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival.

topic below (N.B. in the discussion below statements are referred to as S1, S2, etc).

Topic A. The role & utility of treatment intensification including the option of chemotherapy in triplet therapy

All statements in this topic, with the exception of S11, achieved consensus. The high agreement between respondents shows there is an appreciation of the benefit triplet therapy can provide patients, over the use of ADT plus DOCE (S2, 96%; S9, 93%; S10, 98%). It is also clear that ADT monotherapy is no longer standard of care and should not be offered unless the patient is unfit or declines treatment (S1, 100%; S5, 87%). The strong consensus among professionals on the use of doublet treatment regimens for patients with mHSPC is supported by results from the phase III RCTs and guideline recommendations.[5 8 16–19]

When considering doublet therapy, there is clear preference among respondents for ADT+ARTA over

ADT+DOCE. This reflects EAU guidelines which recommend DOCE only be used in the context of triplet therapy.[19] The agreement is also comparable to a consensus study undertaken by Gillessen *et al* (2023), in which ADT+ARTA was seen to be the preferable treatment option in the majority of cases.[34] Despite this, the steering group emphasised that there is a lag in clinical practice compared with guidelines. As of 2020, approximately two-thirds of patients with mHSPC in the UK receive ADT monotherapy, potentially due to the lack of availability of ADT+ARTA.[35] More recently, the National Prostate Cancer Audit found that 28% of patients in Wales (English data was not available for analysis) with high-risk locally advanced disease were placed on ADT monotherapy and potentially undertreated.[36] The use of DOCE in treating mHSPC decreased during the COVID-19 pandemic, from 37.3% of patients receiving this treatment in 2019 to just 11.6% and 11.2% in 2020 and 2021 respectively.[37] More recent audit data from England shows that across all patients with prostate cancer, the use of DOCE has increased since 2022;[2] however, there is still significant underutilisation of treatment intensification.[2 37]

Agreement with S11 (73%) shows the majority of responders concur that at 1-year post-treatment, there is no detriment to QoL with treatment intensification. However, not achieving a strong agreement reflects that there is still a potential lack of understanding in how treatment intensification impacts quality of life, with some healthcare professionals believing additional therapies increase toxicity, thereby reducing quality of life. Though there is impact over the short term, STAMPEDE results show in the long term (approximately 1 year, as stated in S11) there is no significant negative impact to quality of life from ADT+DOCE compared with ADT+ARTA.[38] A meta-analysis of phase III RCTs suggests that ADT+ARTA also prolongs the time to first deterioration of pain/fatigue compared with ADT alone or ADT+DOCE.[39] Furthermore, triplet therapy offers increased rates of overall survival, alongside longer time to pain progression, and first symptomatic skeletal event than ADT alone or ADT+DOCE.[4 40 41] When analysed by role, ONS (82%) and medical oncologists (76%) showed the highest levels of agreement with S11, demonstrating that those who have the greatest contact with patients, and potentially a greater understanding of how treatments affect QoL, generally agree with this statement. The lack of consensus with S11 could also be due to confusion over the negative wording ('is not associated'), and the lack of specificity regarding whether the 'significant impact' was positive or negative.

Topic B. Identification of suitable patients to consider for treatment intensification including the option of chemotherapy in triplet therapy

All statements in topic B, except S22, reached consensus. The levels of agreement seen across this topic suggest an outline for the appropriate patient population for triplet therapy, including:

- Those with reduced life expectancy due to their cancer and *not* due to comorbidities (S12, 92%; S14, 93%).
- Those deemed fit for therapy following comprehensive multidisciplinary assessment including geriatric assessments, G8, Charlson Comorbidity Index score, frailty score, and ECOG score (S13, 86%; S15, 94%; S17, 98%; S18, 88%; S19, 93%).
- Those with high-risk disease (S20, 92%).
- Those with high-volume disease as defined by CHAARTED (S21, 94%).
- Those with visceral disease (S23, 88%).

Patients who are ineligible for triplet therapy are those whose life expectancy is significantly limited due to comorbidities (<1–2 years), and those who are considered frail. Disease volume is also a key deciding factor. Survey respondents and the steering group felt that triplet therapy should be the preferred treatment for those with high-volume disease. This is defined by CHAARTED as disease with visceral metastases or ≥4 bone lesion with ≥1 beyond the vertebral bodies and pelvis.[42] Of the respondents to the survey by Gillessen *et al* (2023), 61% stated preference for triplet therapy, while 33% preferred ADT+ARTA. Only 6% preferred ADT+DOCE.[34]

There was a lack of consensus regarding S22 (73%), and the use of triplet therapy in low-volume disease with significant disease burden (eg, multiple lymph node involvement). The group agreed with this level of consensus but stress that patients with extra-pelvic lymph node involvement may potentially benefit from treatment intensification with triplet therapy. A retrospective study of 224 mHSPC patients found that in patients with low-volume disease, the presence of concomitant extra-pelvic metastases was a sign of poor prognosis when compared with low-volume patients without.[43] This research suggests non-regional lymph node metastases should be considered high-volume, especially when they occur with bone metastases, and could benefit from more intense treatment.[43] Systemic therapies can help to eradicate micrometastases when the disease is not localised and help to prevent recurrence.[44] In a prospective phase II trial, only 22% of patients achieved complete response of oligorecurrence through maximal localised therapy (radical prostatectomy and postoperative radiotherapy).[45] Therefore, while there has been no study directly testing triplet therapy in those with low-volume disease and extra-pelvic lymph node involvement, there may be a basis for its use in this patient population.

From the consensus observed, respondents agree that all newly diagnosed mHSPC patients who are suitable should be offered triplet therapy (S25, 82%). However, there was some disagreement between roles and regions with this statement. This is potentially due to how broad the statement is and could reflect different approaches to decision making. For example, ONS had the lowest agreement (64%) followed by medical and clinical oncologists (74%). These respondents may have allowed the consideration of wider factors like patient comorbidities

and treatment needs to influence their response, even though S25 relates specifically to patients eligible for the treatment. In contrast, geriatricians (94%) and urologists (87%), while cognisant of patient needs, agree it is appropriate to offer patients all treatments which they are eligible for.

When considering region, Scotland only showed 46% agreement with S25 compared with 86% for England (South). Scotland also showed consistently lower agreement across the majority of statements in this topic. While it could be due to lower response rate (n=13), disparity here could also be due to the differences in reimbursement. DARO+ADT+DOCE has been reimbursed in England since November 2022 but only since September 2023 in Scotland. Therefore, it could be that clinicians in England have more experience using triplet therapy and are more agreeable to using it in practice. Interestingly, it was a noted trend across all statements that those with the most experience in treatment decision making (oncologists) and patient follow-up (ONS) were more likely to agree with evidence and statements supporting the use of triplet therapy but less likely to agree with broad blanket statements that did not consider the complexities of patient assessment and treatment.

Overall, it must be emphasised that patient eligibility must be assessed in a holistic manner, considering a wide range of factors, and that treatment should be tailored to each patient. In general, assessments should consider the balance between the disease risk, the treatment risk to the patient and the potential benefits to the patient. It must also be emphasised that age alone is not an appropriate criterion for denying treatment (S16, 96%). Although the safety of triplet therapy has been found to be comparable to ADT+DOCE,[18] it may be important to consider triplet therapy as a front-line treatment when patients are at their fittest to ensure they are able to tolerate potential side effects.

Topic C. The role of patient education and shared decision making

Very high consensus was seen within this topic, with all six statements achieving ≥96%. It is clear that respondents value the goals of their patients and see shared treatment decision making as vital (S26 and S27, 98%). Patient education is crucial for decision making and allows individuals to understand and report side effects during their treatment (S31, 99%). The steering group highlight that this is especially true for novel therapies, and it is important that patients have access to resources which can help explain their treatment options to facilitate informed decision-making.

While pharmaceutical companies have various tools to inform patients, there is a need for independently developed resources to provide objective lay information. For example, Macmillan and Prostate Cancer UK provide an array of resources. However, it is hard to keep up to date with current treatment options in light of ongoing research and new data. Patients with prostate cancer presently lack a source of information pertaining to triplet therapy. Mobile health applications may provide options to engage and educate patients, but there is often insufficient funding to introduce these into wider practice. Development of patient materials is key to patient support, and the current lack of up-to-date information on the latest treatment options must be remedied. Addressing the barriers to patient education within the UK will require nationwide investment to ensure there is equitable access.

Topic D. Multidisciplinary working

All eight statements achieved ≥88% agreement, showing a broad base of support for the importance of multidisciplinary teams in decision making. The majority of statements, such as S35 (98%), S36 (96%), S37 (95%) and S39 (88%), are not specific to prostate cancer and can be related to all cancer patients and the NHS as a whole. Of particular note is the role of the prostate cancer multidisciplinary team (MDT) pro-forma (S33, 97%). The steering group highlight the need for consistency in patient assessments in order to provide a comprehensive evidence base for decision making. This relates to the points discussed in Topic B, ensuring that treatment can be properly tailored to the patient and that fitness for therapy is established. Due to the evolving treatment landscape within prostate cancer, continuous education for clinical staff must be undertaken (S36, 96%) so that the MDT can make informed decisions based on up-to-date standards of care.

The steering group also highlighted the significance of S37 (95%) and the crucial role of clinical nurse specialists (CNS) in coordinating MDT services. CNS not only act as care coordinators but help educate patients and support them throughout their treatment journey. Having a named CNS during cancer care has been found to be associated with higher survival rates, better symptom management, and more cost-effective and streamlined services.[46 47] S38 (90%) highlights there are currently inadequate levels of CNS to provide optimal patient support, which is acknowledged as a UK-wide problem.[48] While it may not be a prostate cancer-specific concern, greater numbers of CNS would help realise more aspirational goals of care such as the development of physical and psychological rehabilitation (S34, 92%).

Strengths and limitations of this study

The key strength of this study is the very high consensus achieved across a diverse group of healthcare professionals from multiple specialties. A total of 120 responses were collected. The survey used a four-point Likert scale to avoid order and neutral response bias. It is acknowledged that some responders may have felt genuinely neutral about certain statements and were forced to select opinion answers. However, responder groups were chosen as they were believed to have the required knowledge base to answer the survey and the fluctuations noted when analysed by subgroup indicate trends in responses,

suggesting minimal bias. Recommendations were based on the levels of consensus achieved and developed by the steering group. This group was comprised of specialists from a variety of backgrounds in healthcare across the UK, who were chosen for their high levels of experience in managing prostate cancer.

A limitation of the study is the bias towards responses from England, with under-representation of the devolved nations. Higher responses from other regions would have enabled more in-depth comparison of professional opinions across the UK. Regarding Scotland, having achieved reimbursement approval more recently than the other UK nations meant Scottish clinicians potentially had less experience using triplet therapy. This could explain the low levels of agreement from Scottish respondents. The growing experience and confidence in using triplet therapy might alter the opinion of healthcare providers on some statements going forward. The stunted response rate from survey dissemination by the steering group caused the study to rely on a clinical panel. This may have introduced selection bias, as not all clinicians in the UK are registered to the panel. However, this did mean the survey had a wider reach and responses were not biased towards colleagues of the steering committee. Finally, the wording of some statements may have been ambiguous, which could have influenced agreeability.

RECOMMENDATIONS

Based on the survey findings and agreement by the steering group, the following recommendations for achieving the optimal approach for the treatment of patients with mHSPC within the UK are suggested:

1. All patients should be assessed for frailty and vulnerability when considering treatment options, taking into account life expectancy, comorbidities, age, and personal circumstances, as well as patient goals and preferences.
2. ADT monotherapy is no longer the accepted standard of care for mHSPC, and should not be offered unless the patient is unfit for, or declines other treatments (eg, ARTA etc).
3. ADT+ARTA is the preferred doublet therapy, and docetaxel should not be offered to patients unless in the context of triplet therapy (ADT+ARTA+Chemotherapy).
4. All patients should have their fitness for treatment intensification with triplet therapy assessed, and this should be optimised in readiness where appropriate and required.
5. Triplet therapy improves overall survival compared with ADT+DOCE and should be considered in all patients, and is recommended (following assessment) in patients meeting *at least* one of the following criteria:
    1. Those whose life expectancy may be severely limited by their cancer.
    2. Those with high risk or high-volume disease.
    3. Those with no/few comorbidities.
    4. Those with visceral disease (eg, lung or liver metastases).
    5. Those with low-volume disease with extra-pelvic lymph node involvement.
6. Shared decision making is key when considering treatment intensification, clinicians must consult with the patient and ensure they are educated on their treatment options with the relative risks and benefits.
7. Information provided to MDTs for treatment decision making must be consistent and comprehensive to ensure that decisions are made using the broadest base of evidence possible.

CONCLUSION

Based on the consensus achieved, the steering group was able to develop a set of recommendations regarding treatment of patients with mHSPC, particularly the clinical utility of ADT+DOCE+ARTA. Implementing these recommendations has the potential to support the prompt identification of the most suitable patients with mHSPC for triplet treatment, as well as help to guide optimal decision-making practices within the MDT. It is believed that taking a more holistic and comprehensive patient centric approach to assessment and optimisation will improve treatment of mHSPC and improve patient outcomes.

Author affiliations
[1]Beatson West of Scotland Cancer Centre, Glasgow, UK
[2]University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[3]Guy's and Saint Thomas' NHS Foundation Trust, London, UK
[4]Clinical Effectiveness Unit, Royal College of Surgeons of England, London, UK
[5]The Christie NHS Foundation Trust, Manchester, UK
[6]Queen's University Belfast, Belfast, UK
[7]Guy's and St Thomas' NHS Foundation Trust, London, UK
[8]Department of Oncology, Royal Marsden NHS Foundation Trust, London, UK
[9]Nottingham University Hospitals NHS Trust, Nottingham, UK

Acknowledgements The authors would like to thank Dal Singh and Dr Katie Larner from Triducive Partners Limited for their assistance in facilitating the steering group meetings, gathering the data, analysing the results, writing the manuscript and reviewing the final draft.

Contributors All authors equally participated in developing the initial statements, contributing to the analysis, discussion of results and formulation of recommendations. All authors, apart from LF, contributed to the development of the manuscript. HG is the guarantor for this work.

Funding This project was initiated and funded by Bayer.

Competing interests All authors received funding from Bayer while undertaking this study. Client commissioned Triducive Partners Limited to facilitate the project and analyse the responses to the consensus statements in line with the Delphi methodology. HG has received honoraria from ACCORD, Astellas, AstraZeneca, Bayer, Ferring, Janssen, and Pfizer. AB has received honoraria, and undertaken advisory boards and meeting sponsorships for ACCORD, Astellas, Bayer, BMS, Janssen, and Novartis. AB has received institutional research grants from Bayer, Janssen, and Regeneron. LF has received honoraria from ACCORD, Astellas, AstraZeneca, Bayer, Ipsen, and Novartis. NC has received honoraria, and undertaken advisory boards and lectures for Astellas, AstraZeneca, Bayer, Ipsen, Janssen, Merck and Pfizer. NC has received research funding via the STAMPEDE Trial from Astellas, Janssen, and Novartis. NC reports academic conflicts from STAMPEDE, Radicals, Propel, and Patch trials. SJ has received honoraria for advisory boards, speaker fees, consultancy, and travel from ACCORD, Accuray, Astellas, AstraZeneca, Bayer, Boston Scientific, BXT Nanotherapy, Janssen, and Pfizer. TK has received honoraria from AstraZeneca, Bayer, ESMO, and Janssen for educational events and

expert consensus work. VK has received honoraria and non-financial support for advisory, speaker forums and conferences from Accuray, Astellas, Astra Zeneca, Bayer, Bristol Myers Squibb, Boston Scientific, Janssen, Merck Serono, Merck Sharp & Dohme, and Novartis. JM has received honoraria from Astellas and Bayer.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study did not require registration because neither the assigned interventions nor the outcomes assessed were related to the health of participants. The study was not considered human research and as such, Research Ethics Board review was not required. All respondents involved in the survey within study were informed of the research purpose and that their data would remain anonymous. Their consent to was assumed through the completion and submission of their survey responses.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

1 Cancer Research UK. Prostate cancer statistics, 2024. Available: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer
2 National Prostate Cancer Audit. NPCA State of the Nation Report - An audit of the care received by people with prostate cancer in England and Wales from 01/01/2019 to 31/01/2023. 2024.
3 Piombino C, Oltrecolli M, Tonni E, *et al*. De Novo Metastatic Prostate Cancer: Are We Moving toward a Personalized Treatment? *Cancers (Basel)* 2023;15:4945.
4 Hamid AA, Sayegh N, Tombal B, *et al*. Metastatic Hormone-Sensitive Prostate Cancer: Toward an Era of Adaptive and Personalized Treatment. *Am Soc Clin Oncol Educ Book* 2023.
5 Oing C, Bristow RG. Systemic treatment of metastatic hormone-sensitive prostate cancer-upfront triplet versus doublet combination therapy. *ESMO Open* 2023;8:101194.
6 Vale CL, Fisher DJ, Godolphin PJ, *et al*. Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials. *Lancet Oncol* 2023;24:783–97.
7 Verzoni E, Pappagallo G, Alongi F, *et al*. Achieving Consensus for Management of Hormone-Sensitive, Low-Volume Metastatic Prostate Cancer in Italy. *Curr Oncol* 2022;29:4578–86.
8 Parker C, Castro E, Fizazi K, *et al*. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31:1119–34.
9 Lowrance W, Dreicer R, Jarrard DF, *et al*. Updates to Advanced Prostate Cancer: AUA/SUO Guideline (2023). *J Urol* 2023;209:1082–90.
10 Vinjamoori AH, Jagannathan JP, Shinagare AB, *et al*. Atypical metastases from prostate cancer: 10-year experience at a single institution. *AJR Am J Roentgenol* 2012;199:367–72.
11 Tanaka T, Yang M, Froemming AT, *et al*. Current Imaging Techniques for and Imaging Spectrum of Prostate Cancer Recurrence and Metastasis: A Pictorial Review. *Radiographics* 2020;40:709–26.
12 Gosein M, Mohammed L, Chan A, *et al*. A pictorial review of the less commonly encountered patterns of metastatic prostate carcinoma. *Ecancermedicalscience* 2020;14:1159.
13 Meehan J, Gray M, Martínez-Pérez C, *et al*. Tissue- and Liquid-Based Biomarkers in Prostate Cancer Precision Medicine. *J Pers Med* 2021;11:664.
14 Nakamura N, Rogers P, Eggerson R, *et al*. Translational Research for Identifying Potential Early-stage Prostate Cancer Biomarkers. *Cancer Genomics Proteomics* 2023;20:1–8.
15 Gadade DD, Jha H, Kumar C, *et al*. Unlocking the power of precision medicine: exploring the role of biomarkers in cancer management. *Futur J Pharm Sci* 2024;10:5.
16 Hack J, Crabb SJ, Southampton Clinical Trials Unit, University of Southampton, Southampton General Hospital, Southampton, UK, *et al*. Is Triple Therapy the New Standard for Metastatic Hormone-sensitive Prostate Cancer? *Oncol & Haematol* 2022;18:120.
17 Hussain M, Tombal B, Saad F, *et al*. Darolutamide Plus Androgen-Deprivation Therapy and Docetaxel in Metastatic Hormone-Sensitive Prostate Cancer by Disease Volume and Risk Subgroups in the Phase III ARASENS Trial. *J Clin Oncol* 2023;41:3595–607.
18 Jian T, Zhan Y, Hu K, *et al*. Systemic triplet therapy for metastatic hormone-sensitive prostate cancer: A systematic review and network meta-analysis. *Front Pharmacol* 2022;13:955925.
19 Mottet N, Cornford P, Bergh R, *et al*. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer, 2023. Available: https://uroweb.org/guidelines/prostate-cancer
20 Shore ND, Morgans AK, Paracha N, *et al*. A systematic review: Are the findings of indirect treatment comparisons (ITCs) in metastatic hormone-sensitive prostate cancer (mHSPC) consistent? *J C O* 2024;42:324.
21 Armstrong AJ, Szmulewitz RZ, Petrylak DP, *et al*. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. *JCO* 2019;37:2974–86.
22 Chi KN, Chowdhury S, Bjartell A, *et al*. [Phase III TITAN Study] Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, 2021.
23 Sweeney CJ, Martin AJ, Stockler MR, *et al*. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023;24:323–34.
24 National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management (ng131). 2021.
25 National Institute for Health and Care Excellence. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer. 2023.
26 NHS England. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer [B15/PS/a]. 2016.
27 Zattoni F, Rajwa P, Gandaglia G, *et al*. Optimal combination therapy for metastatic hormone-sensitive prostate cancer: new evidence, challenges and unanswered questions. *Curr Opin Urol* 2023;33:445–51.
28 Shang Z. Use of Delphi in health sciences research: A narrative review. *Medicine (Abingdon)* 2023;102:e32829.
29 Kurvers RHJM, Herzog SM, Hertwig R, *et al*. Boosting medical diagnostics by pooling independent judgments. *Proc Natl Acad Sci U S A* 2016;113:8777–82.
30 Woolley AW, Chabris CF, Pentland A, *et al*. Evidence for a Collective Intelligence Factor in the Performance of Human Groups. *Science* 2010;330:686–8.
31 Jünger S, Payne SA, Brine J, *et al*. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliat Med* 2017;31:684–706.
32 Gattrell WT, Logullo P, van Zuuren EJ, *et al*. ACCORD (ACcurate COnsensus Reporting Document): A reporting guideline for consensus methods in biomedicine developed via a modified Delphi. *PLoS Med* 2024;21:e1004326.
33 Diamond IR, Grant RC, Feldman BM, *et al*. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol* 2014;67:401–9.
34 Gillessen S, Bossi A, Davis ID, *et al*. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. *Eur J Cancer* 2023;185:178–215.
35 National Institute for Health and Care Excellence. Abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer (ta721). 2021.
36 National Prostate Cancer Audit. Annual Report 2022 - Prostate Cancer services during the COVID-19 Pandemic. 2022.

37 Dodkins J, Cook A, Nossiter J, *et al*. 1790P Utilisation rates of treatment intensification for metastatic hormone sensitive prostate cancer (mHSPC) in England, UK. *Ann Oncol* 2023;34:S967.
38 Rush HL, Murphy L, Morgans AK, *et al*. Quality of Life in Men With Prostate Cancer Randomly Allocated to Receive Docetaxel or Abiraterone in the STAMPEDE Trial. *J Clin Oncol* 2022;40:825–36.
39 Afferi L, Longoni M, Moschini M, *et al*. Health-related quality of life in patients with metastatic hormone-sensitive prostate cancer treated with androgen receptor signaling inhibitors: the role of combination treatment therapy. *Prostate Cancer Prostatic Dis* 2024;27:173–82.
40 Smith MR, Hussain M, Saad F, *et al*. Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer. *N Engl J Med* 2022;386:1132–42.
41 Fizazi K, Foulon S, Carles J, *et al*. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2×2 factorial design. *Lancet* 2022;399:1695–707.
42 Sweeney CJ, Chen Y-H, Carducci M, *et al*. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med* 2015;373:737–46.
43 Jiang Z, Fan J, Gan C, *et al*. Impact of non-regional lymph node metastases accurately revealed on ^{18}F-PSMA-1007 PET/CT in the clinical management of metastatic hormone-sensitive prostate cancer. *EJNMMI Res* 2023;13:64.
44 Zappulla P, Calvi V. Gastrointestinal Bleeding and Direct Oral Anticoagulants among Patients with Atrial Fibrillation: Risk, Prevention, Management, and Quality of Life. *TH Open* 2021;5:e200–10.
45 Glicksman RM, Metser U, Vines D, *et al*. Curative-intent Metastasis-directed Therapies for Molecularly-defined Oligorecurrent Prostate Cancer: A Prospective Phase II Trial Testing the Oligometastasis Hypothesis. *Eur Urol* 2021;80:374–82.
46 Alessy SA, Davies E, Rawlinson J, *et al*. Clinical nurse specialists and survival in patients with cancer: the UK National Cancer Experience Survey. *BMJ Supp Palliat Care* 2022.:bmjspcare-2021-003445.
47 Kerr H, Donovan M, McSorley O. Evaluation of the role of the clinical Nurse Specialist in cancer care: an integrative literature review. *Eur J Cancer Care* 2021;30.
48 Macmillan Cancer Support. Addressing the gap - Highlighting the need for growing the specialist cancer nursing workforce. 2020.