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

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Background

Metastatic hormone-sensitive prostate cancer (mHSPC) accounts for approximately 5–10% of all prostate cancer cases globally and is characterised by high mortality, contributing to 50% of prostate cancer-related deaths. Recent clinical trials have shown promising results with the triplet therapy combination of androgen deprivation therapy (ADT) + docetaxel (DOCE) + androgen receptor-targeted agent (ARTA). However, there is a lack of clarity on how to identify suitable patients for this triplet therapy. This study, based on the modified Delphi consensus, aimed to determine the clinical utility of the ADT + DOCE + ARTA triplet therapy in patients with mHSPC in the UK.

Methods

A steering group of eight UK healthcare professionals experienced in prostate cancer care discussed treatment challenges, developing 39 consensus statements across 4 topics. Agreement 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. The responses were analysed to establish a consensus for all statements. 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.

Conclusion

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.

KEYWORDS

- ADT
- ARTA
- Chemotherapy
- Docetaxel
- Prostate cancer
- Study, Delphi
- United Kingdom

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 4-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 underrepresentation 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 2016–2018[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]. Whilst 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]. Whilst 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 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 + DOCE compared to 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 was 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 utilise triplet therapy versus 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].

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.

METHODS

Initially in 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 search was conducted on PubMed and Cochrane. Search terms included but were not limited to "prostate cancer", "mHSPC", "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. 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.

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[28,29]. The study was not registered.

[PLACEHOLDER FOR FIGURE 1]

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

A. The role and utility of treatment intensification including the option of chemotherapy in triplet therapy
B. Identification of suitable patients to consider for treatment intensification including the option of chemotherapy in triplet therapy
C. The role of patient education and shared decision making
D. 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[30]. 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 two-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. 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 minutes 30 seconds), 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 seen further survey rounds were unnecessary. The group independently highlighted key statements from each topic, and these were used to form a series of actionable recommendations which were anonymously ratified by the group. Overall, four rounds of consensus development were undertaken.

RESULTS

Following ratification by the steering group, 39 statements were agreed upon 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 (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 (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 (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).

[PLACEHOLDER FOR 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 Figure S4.

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

No:	Statement:	Strongly Agree	Tend To Agree	Tend To Disagree	Strongly Disagree	Agreement
Topic A. The role & 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 co-morbidity 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 to 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 utilised in appropriate patients	32%	57%	11%	1%	**88%**
19	Triplet therapy should be considered in fitter patients e.g., 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%**
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 (e.g., 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 & 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%**

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 (Table S1). When analysed by region, 9

statements showed ≥10% variation in consensus (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 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 amongst respondents for ADT + ARTA over ADT + DOCE. This reflects EAU guidelines which recommend DOCE only be used in the context of triplet therapy[19]. Despite this, the steering group emphasised that there is a lag in clinical practice compared to 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[31]. 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 under treated[32]. 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[33]. 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[2,33].

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 to ADT + ARTA[34]. A meta-analysis of phase III RCTs suggests that ADT + ARTA also prolongs the time to first deterioration of pain/fatigue compared to ADT alone or ADT + DOCE[35]. 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[36–38]. 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[39]. However, there was a lack of consensus

regarding S22 (73%), and the use of triplet therapy in low volume disease with significant disease burden (e.g., 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 to low-volume patients without[40]. 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[40]. Systemic therapies can help to eradicate micro-metastases when the disease is not localised and help to prevent recurrence[41]. In a prospective phase II trial only 22% of patients achieved complete response of oligorecurrence through maximal localised therapy (radical prostatectomy and post-operative radiotherapy)[42]. Therefore, whilst 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%), whilst 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 to 86% for England (South). Scotland also showed consistently lower agreement across the majority of statements in this topic. Whilst 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[43], 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 & 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 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 co-ordinators 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[44,45]. S38 (90%) highlights there are currently inadequate levels of CNS to provide optimal patient support, which is acknowledged as a UK wide problem[46]. Whilst 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%).

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 (e.g., 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 to ADT + DOCE and should be considered in all patients, and is recommended (following assessment) in patients meeting *at least* one of the following criteria:
    a. Those whose life expectancy may be severely limited by their cancer

b. Those with high risk or high-volume disease

c. Those with no/few comorbidities

d. Those with visceral disease (e.g., lung or liver metastases)

e. 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 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.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The corresponding author can provide datasets used and/or analysed in the current study upon reasonable request.

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Conflicts of interest

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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.
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.
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JM has received honoraria from Astellas and Bayer.

Authors' contributions

All authors equally participated in developing the initial statements, contributing to the analysis and discussion of results, reviewing, and approving the final manuscript. Louisa Fleure, a lead uro-oncology nurse specialist from Guy's and St Thomas' NHS Foundation Trust, was also part of the steering group for this project and contributed to the development of the statements and the analysis and discussion of the results, but not to the development of the manuscript.

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BODY FIGURE LEGENDS

Figure 1. Modified Delphi study design

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%).

SUPPLEMENTARY INFORMATION

Supplementary Figure Legends

Figure S1. Occupational distribution of :

Figure S2. Distribution of respondents in the UK by time in role

Figure S3. Distribution of respondents based on the UK region

Figure S4. Agreement levels for each statement. For legibility all percentage labels below 5% have been removed.

Supplementary Tables

Table S1. Consensus statements which showed a difference of ≥10% variation above or below the overall agreement achieved, as analysed by role. Differences of +≥10% are highlighted in pink, and -≥10% are highlighted in blue

No:	Statement:	Total n=120	Medical Oncologist n=42	Clinical Oncologist n=31	Consultant Urologist n=16	Consultant Geriatrician n=15	Oncology Nurse Specialist n=11	Hospital Pharmacist n=5
3	The evidence for treatment intensification in mHSPC with ADT + ARTA + chemotherapy is based on ARASENS	89%	88%	94%	81%	73%	91%	100%
8	If a patient is offered treatment with docetaxel, then it should be in the context of triplet therapy (ADT + ARTA + Chemotherapy)	83%	83%	84%	56%	93%	100%	80%
11	Treatment intensification is not associated with significant impact to quality of life at 1 year in clinical trials compared to the comparator arms	73%	76%	68%	69%	60%	82%	60%
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	86%	79%	74%	94%	93%	82%	80%

22	Triplet therapy should be considered in patients with low volume disease that has a significant disease burden (e.g., with multiple lymph node involvement) who are suitable for chemotherapy	73%	64%	61%	93%	81%	55%	100%
25	All newly diagnosed mHSPC patients suitable for triplet therapy should be offered it	82%	74%	74%	87%	94%	64%	100%

Table S2. Consensus statements which showed a difference of ≥10% variation above or below the overall agreement achieved, as analysed by region. Differences of +≥10% are highlighted in pink, and -≥10% are highlighted in blue

No:	Statement:	Total n=120	England (North) n=34	England (South) n=70	Scotland n=13	Wales n=1	Northern Ireland n=2
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	92%	94%	94%	77%	100%	50%
18	Tools such as G8, Charlson comorbidity index (CCI), frailty scores should be utilised in appropriate patients	88%	88%	89%	92%	100%	50%
19	Triplet therapy should be considered in fitter patients e.g., ECOG 0-1	93%	100%	96%	69%	100%	50%
20	Triplet therapy should be considered in patients with high-risk disease	92%	97%	94%	62%	100%	100%
21	Triplet therapy should be the preferred option in patients with high volume disease who are suitable for chemotherapy, as defined by CHAARTED	94%	100%	99%	62%	100%	50%
22	Triplet therapy should be considered in patients with low volume disease that has a significant disease burden (e.g., with multiple lymph node involvement) who are suitable for chemotherapy	73%	76%	79%	38%	100%	50%
23	Triplet therapy should be the preferred option in patients with visceral disease (liver or lung metastases) who are suitable for chemotherapy	88%	88%	91%	69%	100%	100%
24	Approximately 30% of newly diagnosed mHSPC patients are potentially suitable for treatment intensification with triplet therapy	88%	97%	87%	69%	100%	50%
25	All newly diagnosed mHSPC patients suitable for triplet therapy should be offered it	82%	85%	86%	46%	100%	100%

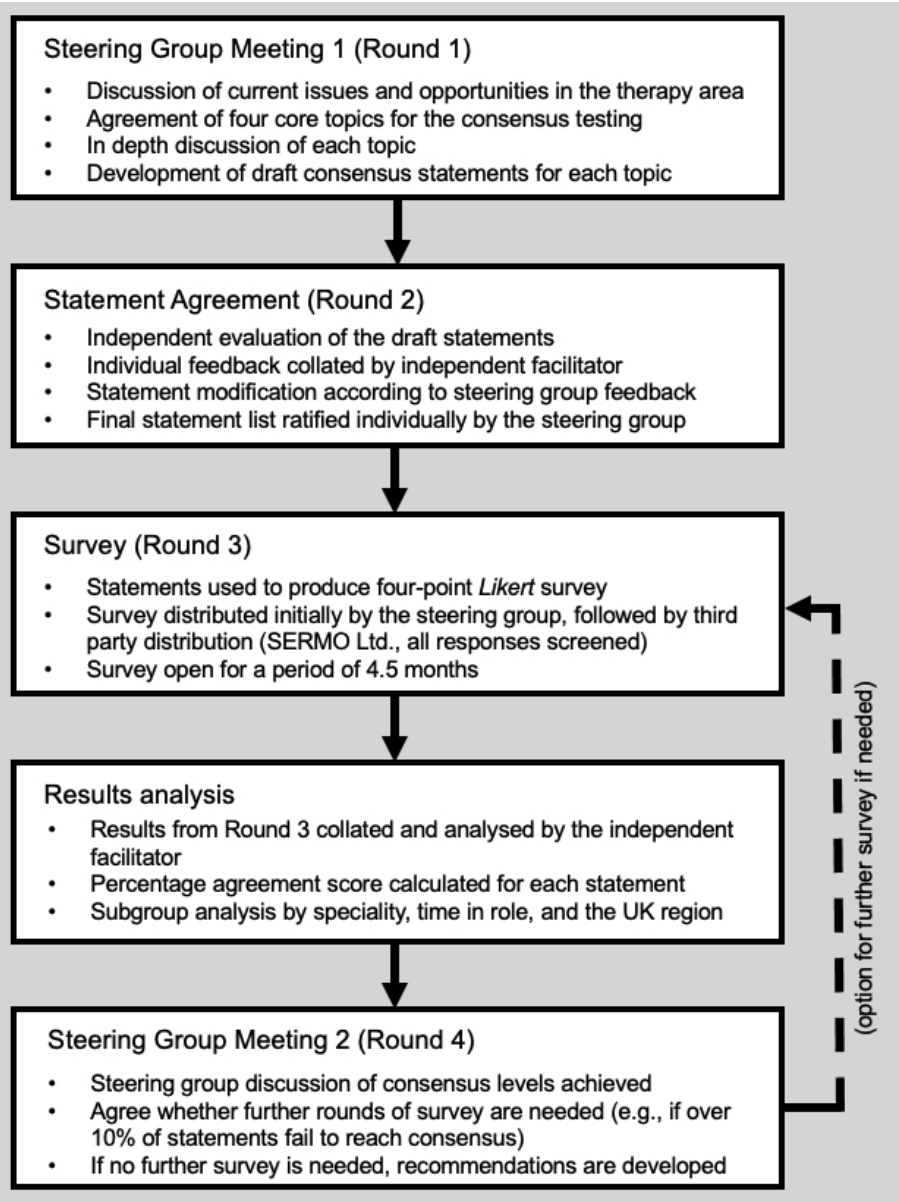

Figure 1. Modified Delphi study design

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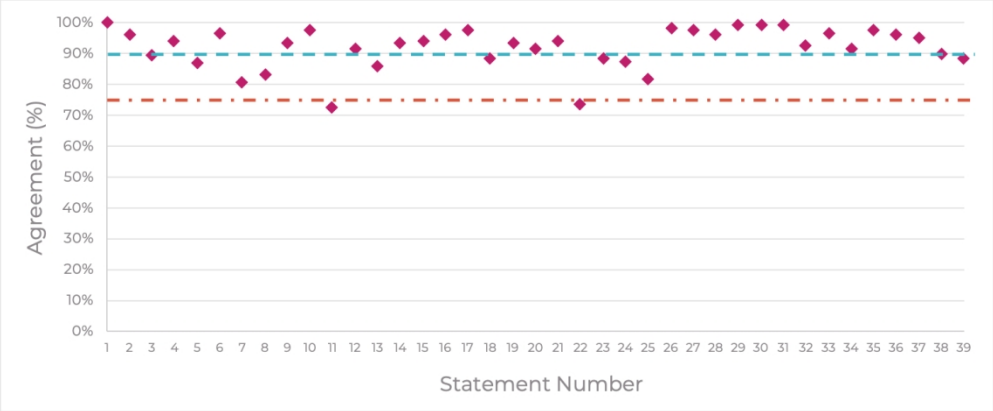

Figure 2. Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%).

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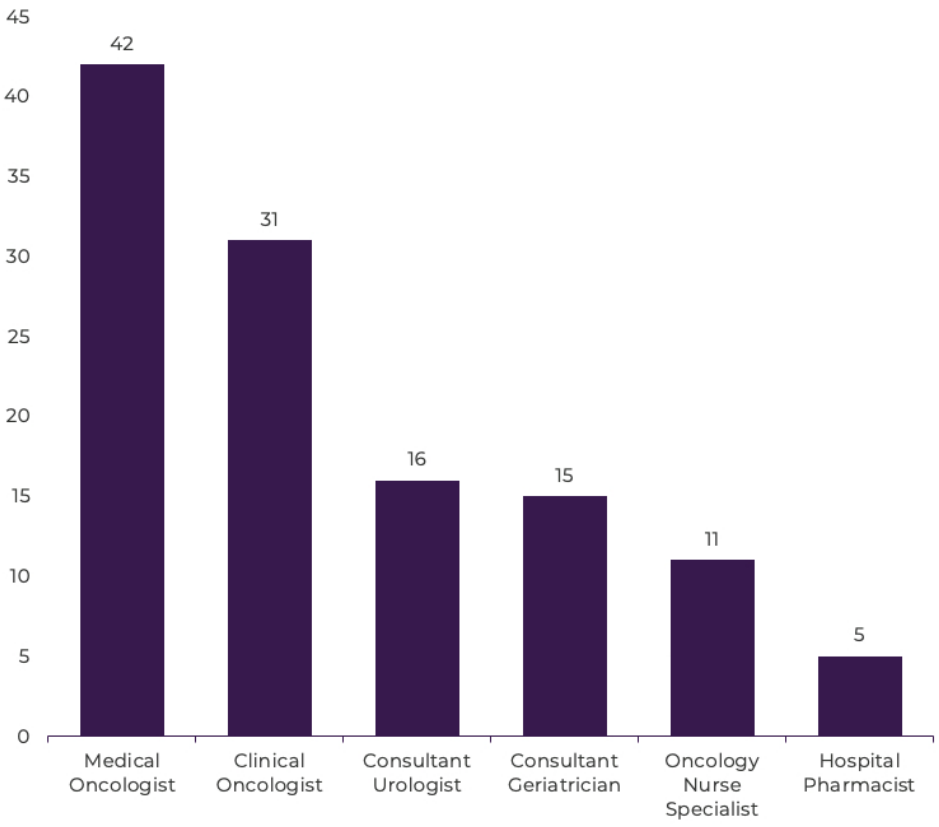

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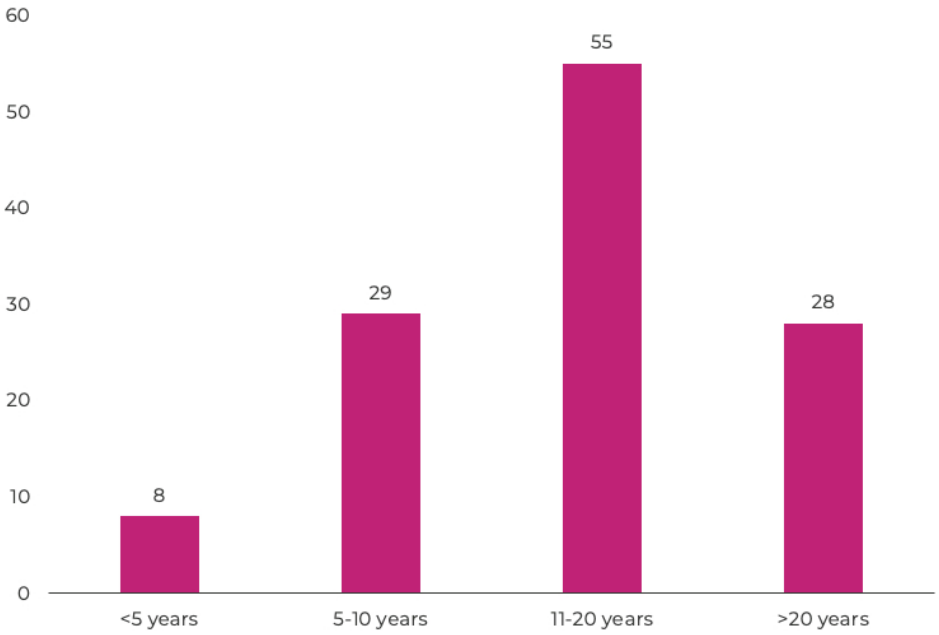

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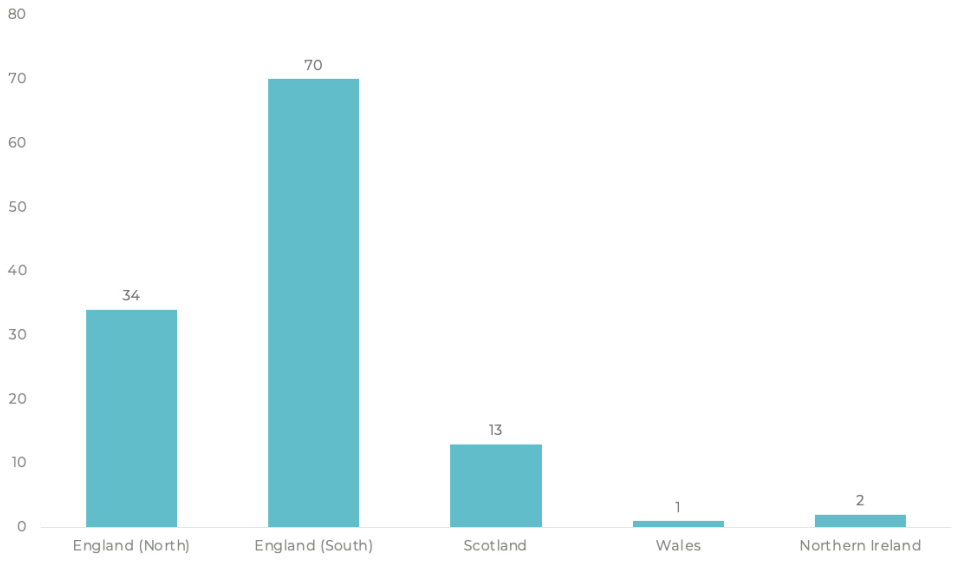

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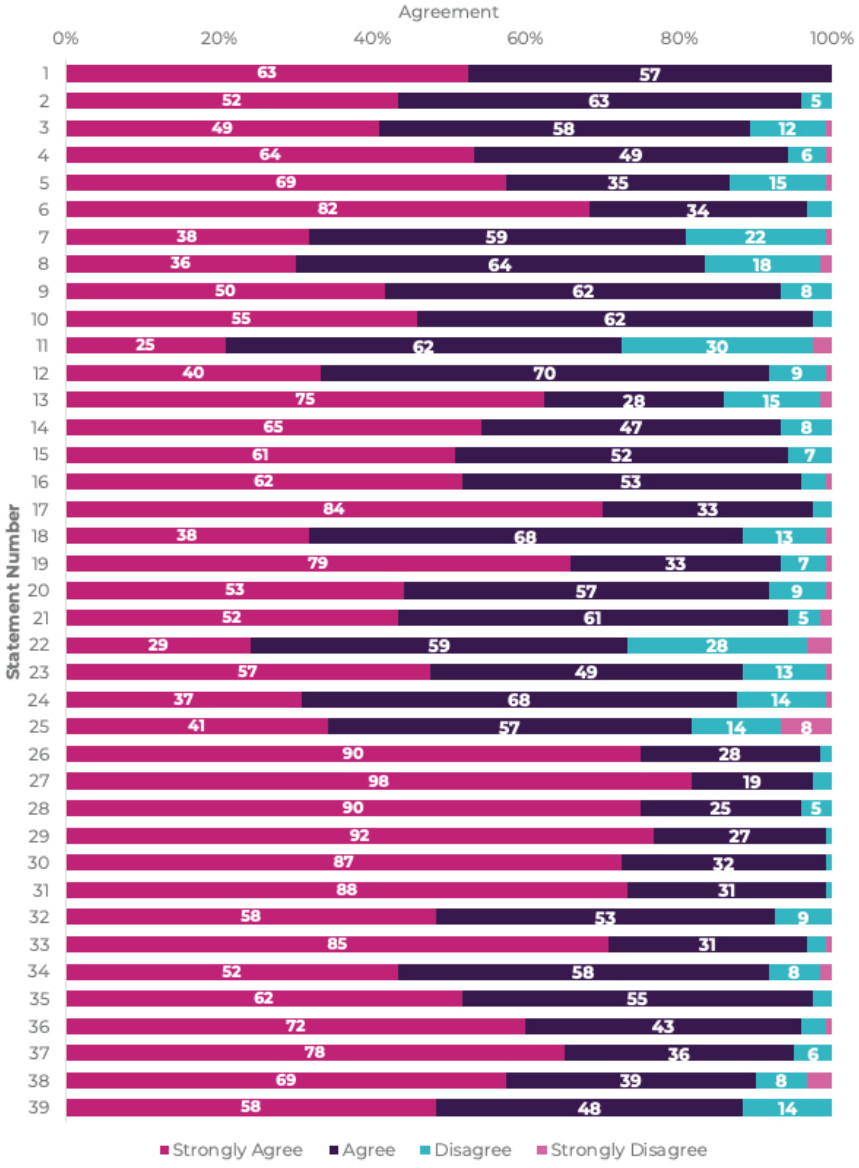

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A modified Delphi consensus regarding the clinical utility of triplet therapy in patients with metastatic hormone-sensitive prostate cancer patients in the UK

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

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ABSTRACT (WORD COUNT: 286)

Background

Metastatic hormone-sensitive prostate cancer (mHSPC) accounts for approximately 5-10% of all prostate cancer cases globally and is characterised by high mortality, contributing to 50% of prostate cancer-related deaths. Recent clinical trials have shown promising results with the triplet therapy combination of androgen deprivation therapy (ADT) + docetaxel (DOCE) + androgen receptor-targeted agent (ARTA). However, there is a lack of clarity on how to identify suitable patients for this triplet therapy. This study, based on the modified Delphi consensus, aimed to determine the clinical utility of the ADT + DOCE + ARTA triplet therapy in patients with mHSPC in the UK.

Methods

A steering group of eight UK healthcare professionals experienced in prostate cancer care discussed treatment challenges, developing 39 consensus statements across 4 topics. Agreement 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. The responses were analysed to establish a consensus for all statements. 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.

Conclusion

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.

KEYWORDS

- ADT
- ARTA
- Chemotherapy
- Docetaxel
- Prostate cancer
- Study, Delphi

- United Kingdom

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 4-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 underrepresentation 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 2016–2018[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]. Whilst 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]. Whilst 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 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 + DOCE compared to 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 was 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 utilise triplet therapy versus 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 it's results could not be used to develop the consensus statements. However, this found that DOCE + ADT benefits those with high volume disease most, compared to 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 7th–9th 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 search was conducted on PubMed and Cochrane. Search terms included but were not limited to "prostate cancer", "mHSPC", "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.

[PLACEHOLDER FOR FIGURE 1]

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

A. The role and utility of treatment intensification including the option of chemotherapy in triplet therapy
B. Identification of suitable patients to consider for treatment intensification including the option of chemotherapy in triplet therapy
C. The role of patient education and shared decision making
D. 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 two-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 was 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 minutes 30 seconds), 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 upon 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 (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 (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 (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).

[PLACEHOLDER FOR 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 Figure S4.

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

No:	Statement:	Strongly Agree	Tend To Agree	Tend To Disagree	Strongly Disagree	Agreement
Topic A. The role & 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 co-morbidity 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 to 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 utilised in appropriate patients	32%	57%	11%	1%	**88%**
19	Triplet therapy should be considered in fitter patients e.g., 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%**
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 (e.g., 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 & 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%**

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 (Table S1). When analysed by region, 9 statements showed ≥10% variation in consensus (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 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 amongst 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 to 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 under treated[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 to 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 to 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[40–42]. 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[43]. 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 (e.g., 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 to low-volume patients without[44]. 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[44]. Systemic therapies can help to eradicate micro-metastases when the disease is not localised and help to prevent recurrence[45]. In a prospective phase II trial only 22% of patients achieved complete response of oligorecurrence through maximal localised therapy (radical prostatectomy and post-operative

radiotherapy)[46]. Therefore, whilst 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%), whilst 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 to 86% for England (South). Scotland also showed consistently lower agreement across the majority of statements in this topic. Whilst 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[47], 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 & 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 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 co-ordinators 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[48,49]. S38 (90%) highlights there are currently inadequate levels of CNS to provide optimal patient support, which is acknowledged as a UK wide problem[50]. Whilst 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 4-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 underrepresentation 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 (e.g., 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 to ADT + DOCE and should be considered in all patients, and is recommended (following assessment) in patients meeting *at least* one of the following criteria:
    a. Those whose life expectancy may be severely limited by their cancer
    b. Those with high risk or high-volume disease
    c. Those with no/few comorbidities
    d. Those with visceral disease (e.g., lung or liver metastases)
    e. 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 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.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The corresponding author can provide datasets used and/or analysed in the current study upon reasonable request.

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Conflicts of interest

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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.
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JM has received honoraria from Astellas and Bayer.

Authors' contributions

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.

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BODY FIGURE LEGENDS

Figure 1. Modified Delphi study design

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%).

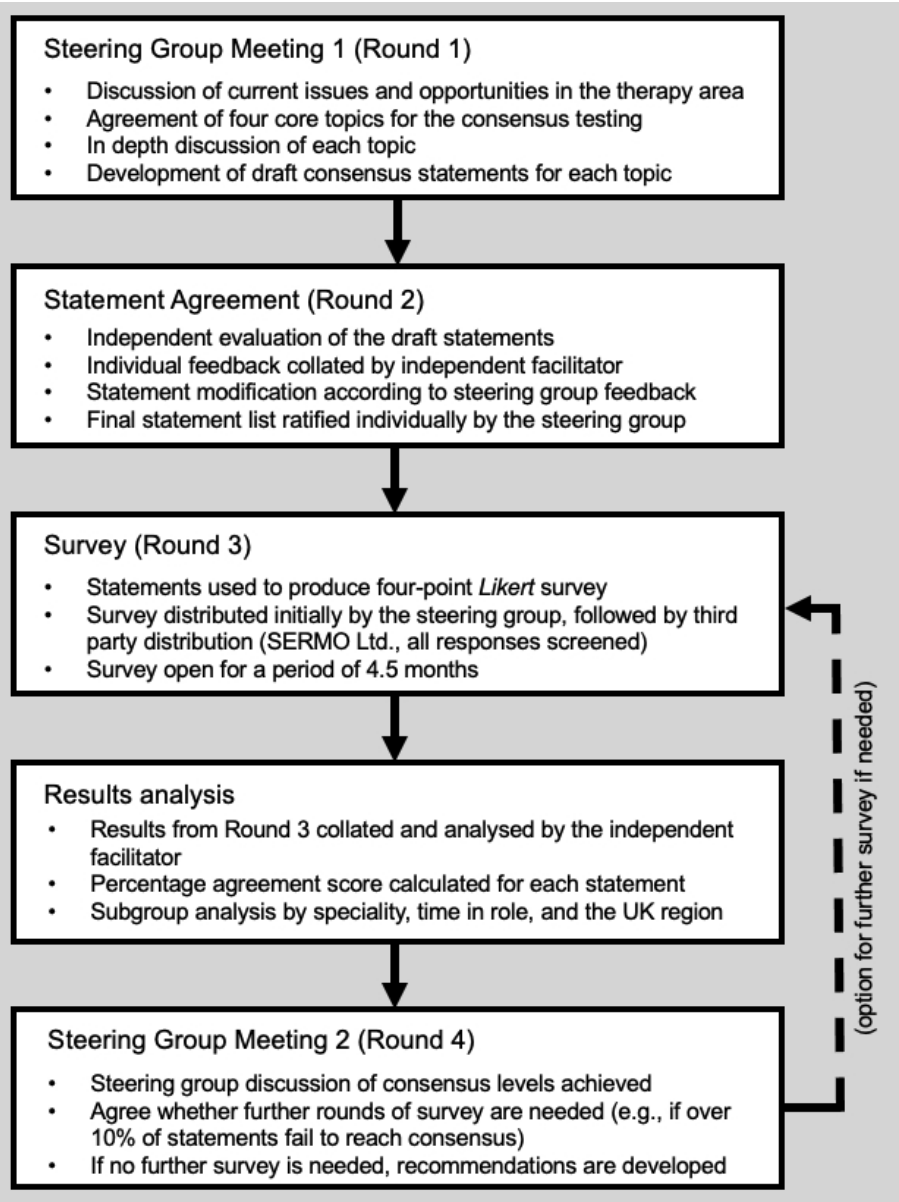

Figure 1. Modified Delphi study design

51x69mm (300 x 300 DPI)

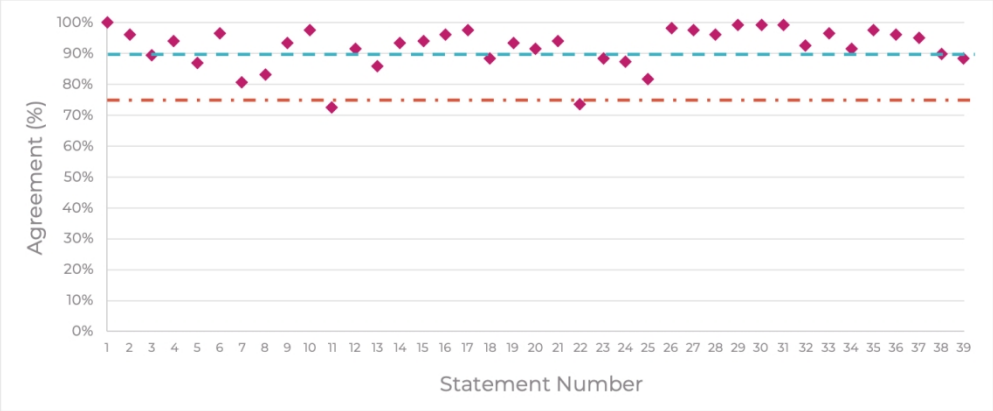

Figure 2. Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%).

131x54mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

Figure S1. Occupational distribution of respondents

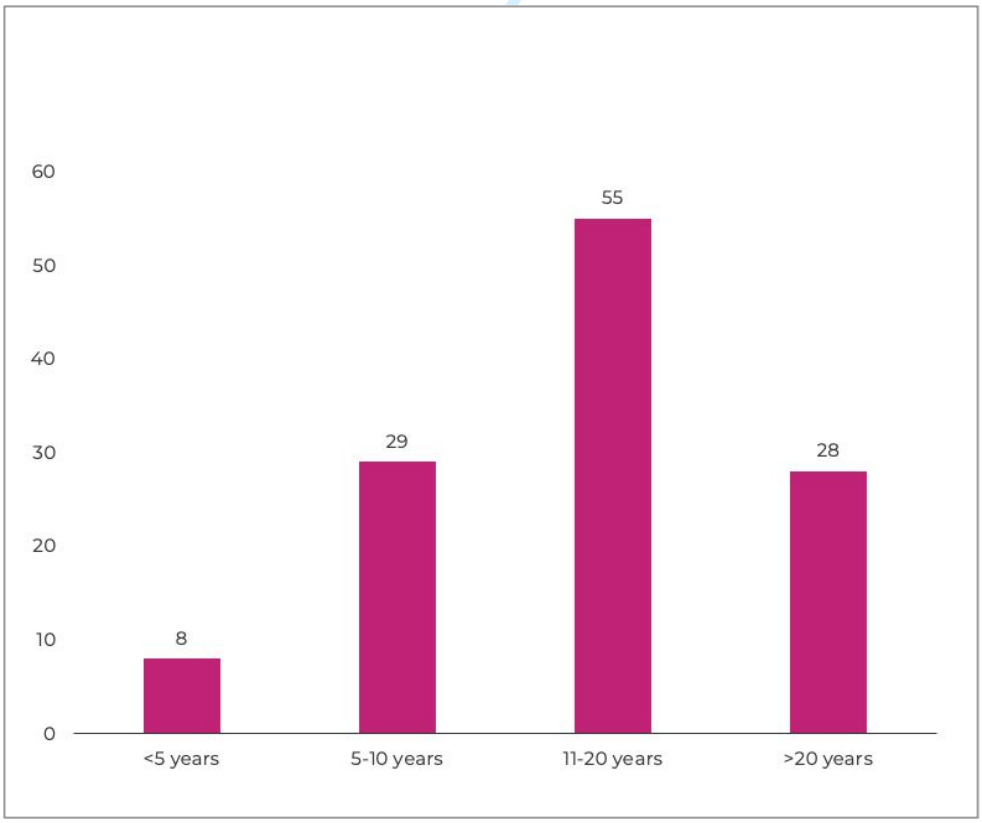

Figure S2. Distribution of respondents in the UK by time in role

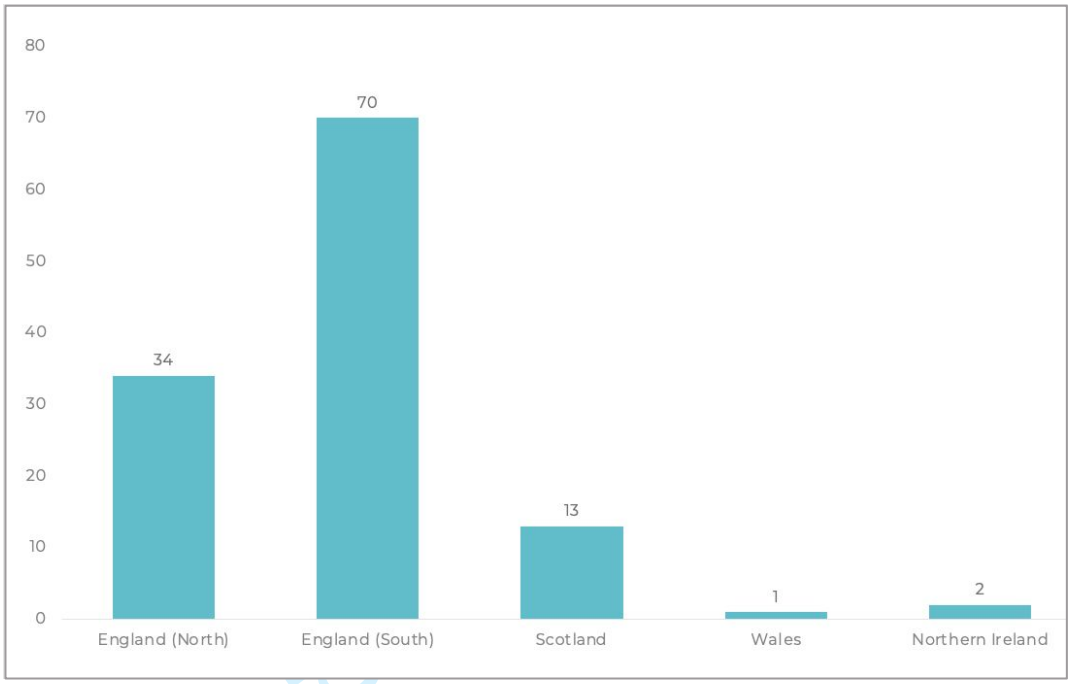

Figure S3. Distribution of respondents based on the UK region

Figure S4. Agreement levels for each statement. For legibility all percentage labels below 5% have been removed.

Table S1. Consensus statements which showed a difference of ≥10% variation above or below the overall agreement achieved, as analysed by role. Differences of +≥10% are highlighted in pink, and -≥10% are highlighted in blue

No:	Statement:	Total n=120	Medical Oncologist n=42	Clinical Oncologist n=31	Consultant Urologist n=16	Consultant Geriatrician n=15	Oncology Nurse Specialist n=11	Hospital Pharmacist n=5
3	The evidence for treatment intensification in mHSPC with ADT + ARTA + chemotherapy is based on ARASENS	89%	88%	94%	81%	73%	91%	100%
8	If a patient is offered treatment with docetaxel, then it should be in the context of triplet therapy (ADT + ARTA + Chemotherapy)	83%	83%	84%	56%	93%	100%	80%
11	Treatment intensification is not associated with significant impact to quality of life at 1 year in clinical trials compared to the comparator arms	73%	76%	68%	69%	60%	82%	60%
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	86%	79%	74%	94%	93%	82%	80%
22	Triplet therapy should be considered in patients with low volume disease that has a significant disease burden (e.g., with multiple lymph node involvement) who are suitable for chemotherapy	73%	64%	61%	93%	81%	55%	100%
25	All newly diagnosed mHSPC patients suitable for triple therapy should be offered it	82%	74%	74%	87%	94%	64%	100%

Table S2. Consensus statements which showed a difference of ≥10% variation above or below the overall agreement achieved, as analysed by region. Differences of +≥10% are highlighted in pink, and -≥10% are highlighted in blue

No:	Statement:	Total n=120	England (North) n=34	England (South) n=70	Scotland n=13	Wales n=1	Northern Ireland n=2
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	92%	94%	94%	77%	100%	50%
18	Tools such as G8, Charlson comorbidity index (CCI), frailty scores should be utilised in appropriate patients	88%	88%	89%	92%	100%	50%
19	Triplet therapy should be considered in fitter patients e.g., ECOG 0-1	93%	100%	96%	69%	100%	50%
20	Triplet therapy should be considered in patients with high-risk disease	92%	97%	94%	62%	100%	100%
21	Triplet therapy should be the preferred option in patients with high volume disease who are suitable for chemotherapy, as defined by CHAARTED	94%	100%	99%	62%	100%	50%

22	Triplet therapy should be considered in patients with low volume disease that has a significant disease burden (e.g., with multiple lymph node involvement) who are suitable for chemotherapy	73%	76%	79%	38%	100%	50%
23	Triplet therapy should be the preferred option in patients with visceral disease (liver or lung metastases) who are suitable for chemotherapy	88%	88%	91%	69%	100%	100%
24	Approximately 30% of newly diagnosed mHSPC patients are potentially suitable for treatment intensification with triplet therapy	88%	97%	87%	69%	100%	50%
25	All newly diagnosed mHSPC patients suitable for triple therapy should be offered it	82%	85%	86%	46%	100%	100%

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

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

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ABSTRACT (WORD COUNT: 290)

Objectives

This study aimed to determine the clinical utility of the ADT + DOCE + ARTA triplet therapy in patients with 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 4 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.

KEYWORDS

- ADT
- ARTA
- Chemotherapy
- Docetaxel
- Prostate cancer
- Study, Delphi

- United Kingdom

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 4-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 underrepresentation 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 2016–2018[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]. Whilst 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]. Whilst 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 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 + DOCE compared to 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 was 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 utilise triplet therapy versus 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 it's results could not be used to develop the consensus statements. However, this found that DOCE + ADT benefits those with high volume disease most, compared to 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 7th-9th 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 search was conducted on PubMed and Cochrane. Search terms included but were not limited to "prostate cancer", "mHSPC", "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.

[PLACEHOLDER FOR FIGURE 1]

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

A. The role and utility of treatment intensification including the option of chemotherapy in triplet therapy
B. Identification of suitable patients to consider for treatment intensification including the option of chemotherapy in triplet therapy
C. The role of patient education and shared decision making
D. 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 two-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 was 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 minutes 30 seconds), 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 upon 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 (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 (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 (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).

[PLACEHOLDER FOR 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 Figure S4.

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

No:	Statement:	Strongly Agree	Tend To Agree	Tend To Disagree	Strongly Disagree	Agreement
Topic A. The role & 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 co-morbidity 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 to 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 utilised in appropriate patients	32%	57%	11%	1%	**88%**
19	Triplet therapy should be considered in fitter patients e.g., 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%**
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 (e.g., 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 & 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%**

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 (Table S1). When analysed by region, 9 statements showed ≥10% variation in consensus (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 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 amongst 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 to 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 under treated[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 to 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 to 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[40–42]. 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[43]. 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 (e.g., 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 to low-volume patients without[44]. 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[44]. Systemic therapies can help to eradicate micro-metastases when the disease is not localised and help to prevent recurrence[45]. In a prospective phase II trial only 22% of patients achieved complete response of oligorecurrence through maximal localised therapy (radical prostatectomy and post-operative radiotherapy)[46]. Therefore, whilst 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%), whilst 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 to 86% for England (South). Scotland also showed consistently lower agreement across the majority of statements in this topic. Whilst 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[47], 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 & 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 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 co-ordinators 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[48,49]. S38 (90%) highlights there are currently inadequate levels of CNS to provide optimal patient support, which is acknowledged as a UK wide problem[50]. Whilst 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 4-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 underrepresentation 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 (e.g., 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 to ADT + DOCE and should be considered in all patients, and is recommended (following assessment) in patients meeting *at least* one of the following criteria:
    a. Those whose life expectancy may be severely limited by their cancer
    b. Those with high risk or high-volume disease
    c. Those with no/few comorbidities
    d. Those with visceral disease (e.g., lung or liver metastases)
    e. 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 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.

DECLARATIONS

Ethics approval and consent to participate

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.

Consent for publication

Not applicable

Availability of data and materials

The corresponding author can provide datasets used and/or analysed in the current study upon reasonable request.

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Conflicts of interest

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.

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Authors' contributions

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.

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BODY FIGURE LEGENDS

Figure 1. Modified Delphi study design

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%).

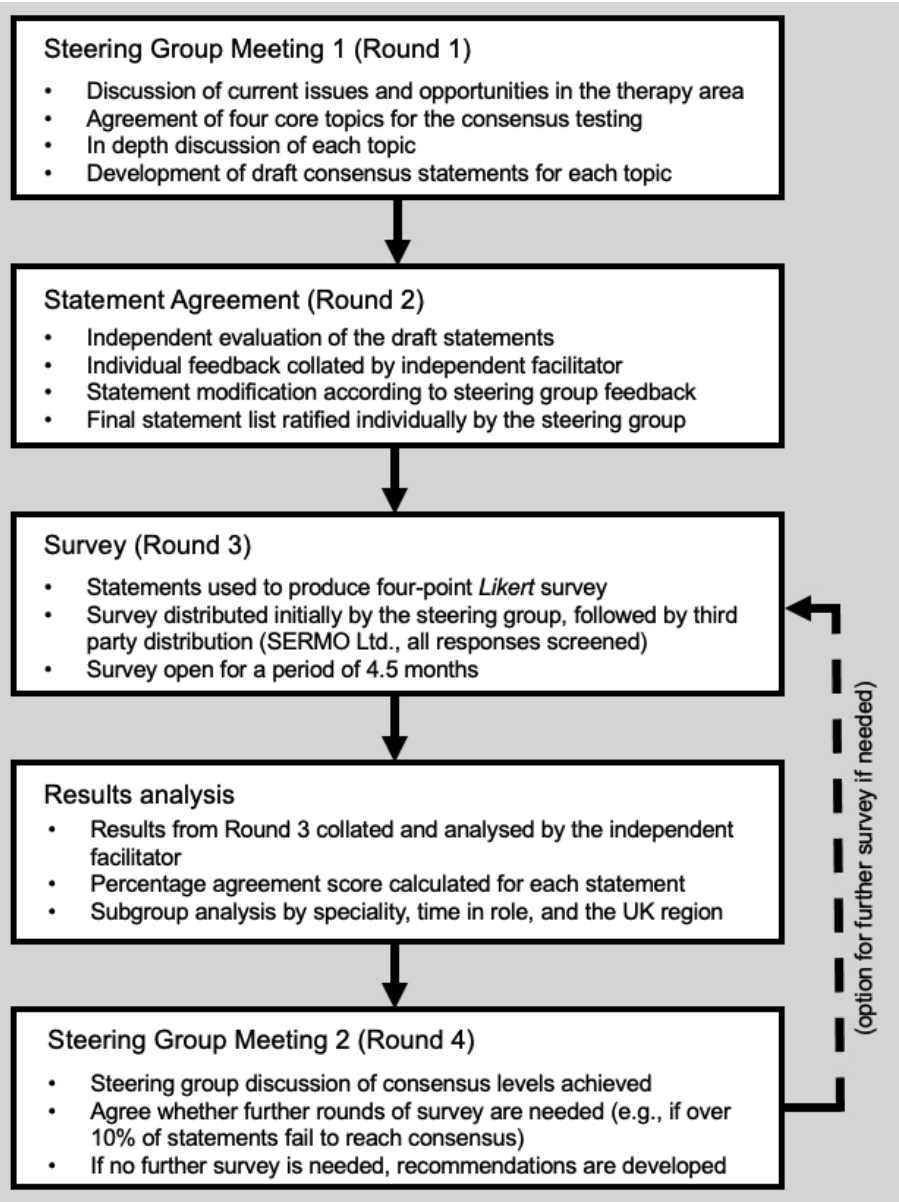

Figure 1. Modified Delphi study design

51x69mm (300 x 300 DPI)

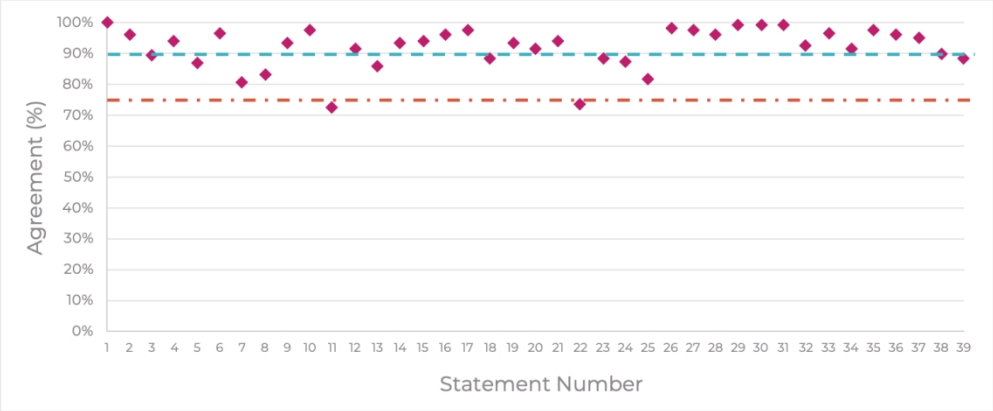

Figure 2. Consensus agreement levels by statement. The threshold for consensus is depicted by the green line (75%). The blue line signifies the threshold for very strong agreement (90%).

131x54mm (300 x 300 DPI)

SUPPLEMENTARY INFORMATION

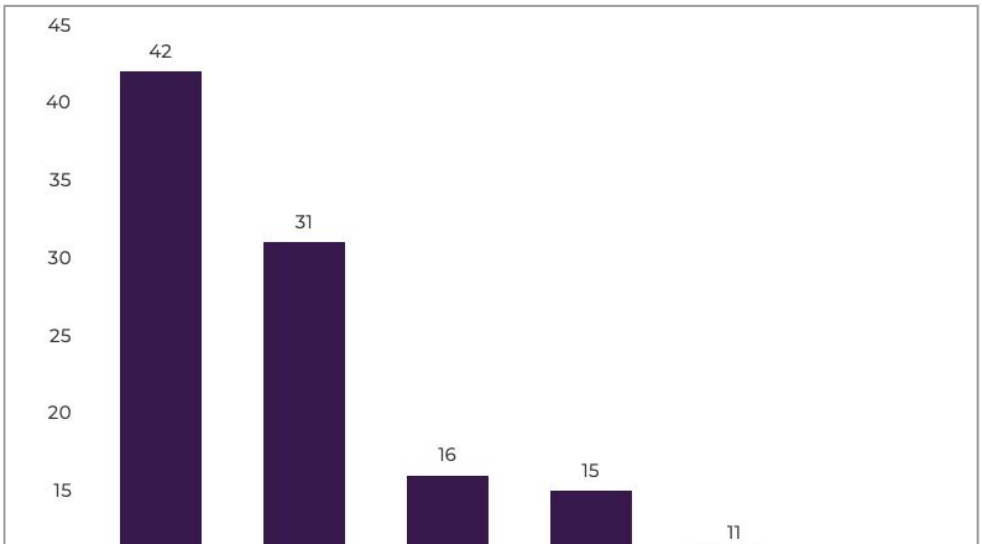

Figure S1. Occupational distribution of respondents

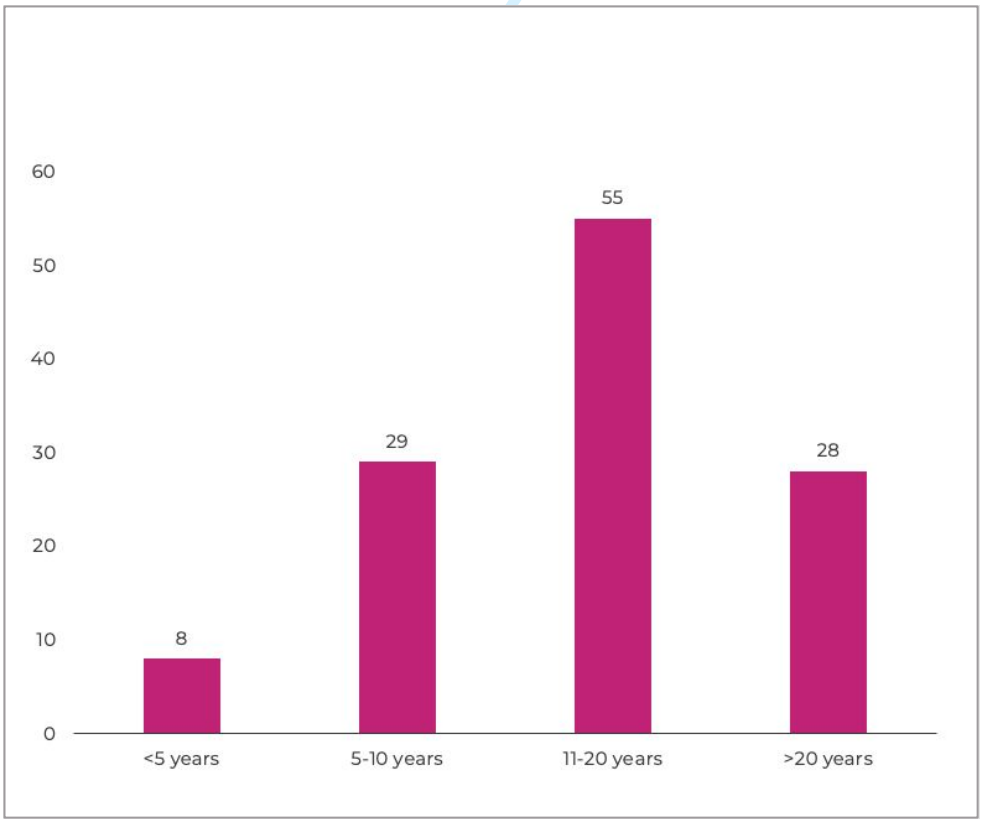

Figure S2. Distribution of respondents in the UK by time in role

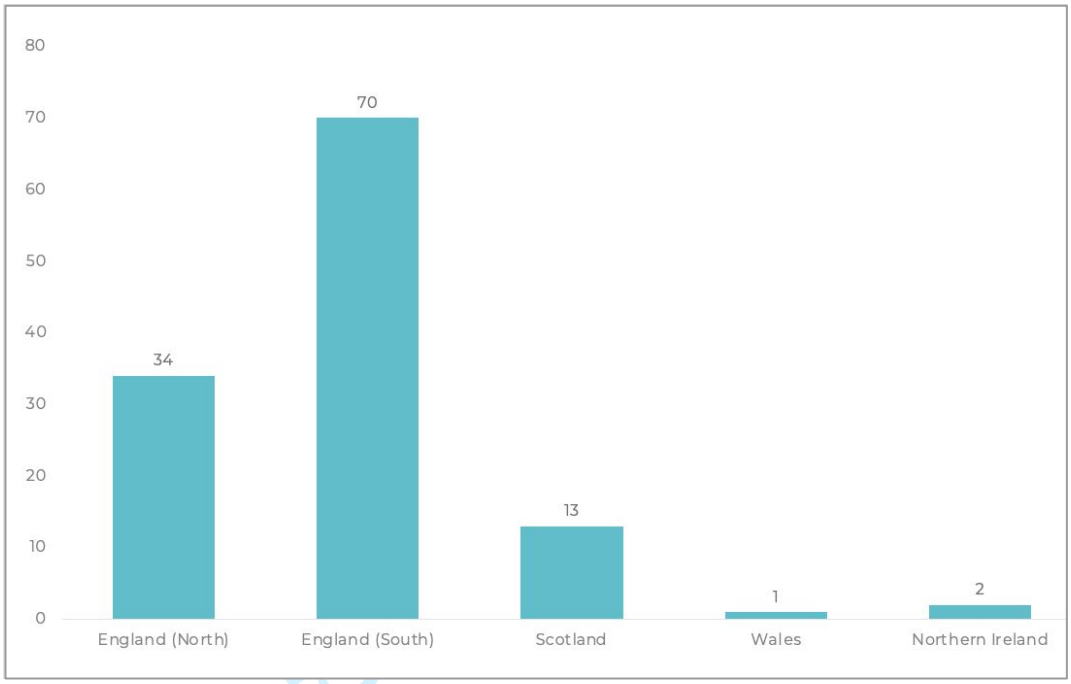

Figure S3. Distribution of respondents based on the UK region

Figure S4. Agreement levels for each statement. For legibility all percentage labels below 5% have been removed.

Table S1. Consensus statements which showed a difference of ≥10% variation above or below the overall agreement achieved, as analysed by role. Differences of +≥10% are highlighted in pink, and -≥10% are highlighted in blue

No:	Statement:	Total n=120	Medical Oncologist n=42	Clinical Oncologist n=31	Consultant Urologist n=16	Consultant Geriatrician n=15	Oncology Nurse Specialist n=11	Hospital Pharmacist n=5
3	The evidence for treatment intensification in mHSPC with ADT + ARTA + chemotherapy is based on ARASENS	89%	88%	94%	81%	73%	91%	100%
8	If a patient is offered treatment with docetaxel, then it should be in the context of triplet therapy (ADT + ARTA + Chemotherapy)	83%	83%	84%	56%	93%	100%	80%
11	Treatment intensification is not associated with significant impact to quality of life at 1 year in clinical trials compared to the comparator arms	73%	76%	68%	69%	60%	82%	60%
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	86%	79%	74%	94%	93%	82%	80%
22	Triplet therapy should be considered in patients with low volume disease that has a significant disease burden (e.g., with multiple lymph node involvement) who are suitable for chemotherapy	73%	64%	61%	93%	81%	55%	100%
25	All newly diagnosed mHSPC patients suitable for triple therapy should be offered it	82%	74%	74%	87%	94%	64%	100%

Table S2. Consensus statements which showed a difference of ≥10% variation above or below the overall agreement achieved, as analysed by region. Differences of +≥10% are highlighted in pink, and -≥10% are highlighted in blue

No:	Statement:	Total n=120	England (North) n=34	England (South) n=70	Scotland n=13	Wales n=1	Northern Ireland n=2
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	92%	94%	94%	77%	100%	50%
18	Tools such as G8, Charlson comorbidity index (CCI), frailty scores should be utilised in appropriate patients	88%	88%	89%	92%	100%	50%
19	Triplet therapy should be considered in fitter patients e.g., ECOG 0-1	93%	100%	96%	69%	100%	50%
20	Triplet therapy should be considered in patients with high-risk disease	92%	97%	94%	62%	100%	100%
21	Triplet therapy should be the preferred option in patients with high volume disease who are suitable for chemotherapy, as defined by CHAARTED	94%	100%	99%	62%	100%	50%

22	Triplet therapy should be considered in patients with low volume disease that has a significant disease burden (e.g., with multiple lymph node involvement) who are suitable for chemotherapy	73%	76%	79%	38%	100%	50%
23	Triplet therapy should be the preferred option in patients with visceral disease (liver or lung metastases) who are suitable for chemotherapy	88%	88%	91%	69%	100%	100%
24	Approximately 30% of newly diagnosed mHSPC patients are potentially suitable for treatment intensification with triplet therapy	88%	97%	87%	69%	100%	50%
25	All newly diagnosed mHSPC patients suitable for triple therapy should be offered it	82%	85%	86%	46%	100%	100%