Optimizing outcomes for patients with metastatic prostate cancer: insights from South East Asia Expert Panel

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Abstract

Aims: Clinical decision making is challenging in men with metastatic prostate cancer (mPC), as heterogeneity in treatment options and patient characteristics have resulted in multiple scenarios with little or no evidence. The South East Asia Expert Panel 2019 addressed some of these challenges.

Methods: Based on evidence in the literature and expert interviews, 19 statements were formulated for key challenges in the treatment of men with castration-sensitive and -resistant prostate cancer in clinical practice. A modified Delphi process was used to reach consensus among experts in the panel and develop clinical practice recommendations.

Results: The majority of the panel preferred a risk-based stratification and recommended abiraterone or enzalutamide as first-line therapy for symptomatic chemotherapy naïve patients. Abiraterone is preferred over enzalutamide as a first-line treatment in these patients. However, the panel did not support the use of abiraterone in high risk lymph-node positive only (N+M0) or in non-metastatic (N0M0) patients. In select patients, low dose abiraterone with food may be used to optimize clinical outcomes. Androgen receptor gene splice variant status may be a useful guide to therapy. In addition, generic versions of approved therapies may improve access to treatment to a broader patient population. The choice of treatment, as well as sequencing are guided by both patient and disease characteristics, preferences, drug access, cost, and compliance.

Conclusion: Expert recommendations are key to guidance for the optimal management of mPC. Appropriate choice, timing, and sequence of treatment options can help to tailor therapy to maximize outcomes in men with mPC.

Keywords: abiraterone, chemotherapy, docetaxel, enzalutamide, metastatic prostate cancer

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Introduction

The South East Asian (SEA) Expert Panel convened a consensus conference to reflect on the management and outcomes with current strategies in patients with metastatic prostate cancer (mPC). The meeting was held in Bangkok, Thailand in June, 2019. The panel were invited to respond to a poll and anonymity was observed to capture the responses. Questions were drafted on idealized assumptions that all diagnostic procedures and management options were available.

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Methods

The panel

The panel for the SEA Consensus Conference 2019 meeting included 13 experts (11 medical oncologists, 2 urologists) from Thailand, Malaysia, and Vietnam. The meeting also included Fabio A. Schutz – a scientific expert from Brazil who was involved in the formulation of consensus recommendations for prostate cancer (PC) in Brazil (Table 1). The panel members were chosen for their vast experience and interest in PC.

Consensus process

A modified Delphi process was used to reach consensus and develop practice recommendations.[1,2] The Delphi method – an established means of determining consensus for a defined clinical problem – is based on systematic progression of repeated rounds of voting.[3–5] The iterative voting is effective for determining expert group consensus in areas that have little or no definitive evidence and where opinion is important.[6,7]

A comprehensive list of questions and possible answers was developed after reviewing available evidence in scientific literature and based on expert opinions. The modified Delphi method consisted of voting for a pre-validated list of questions in a face-to-face meeting followed by expert interactions to share viewpoints and enable discussions (Figure 1).[8] The modified Delphi method has been adopted in studies in the past and is reported to be effective and collaborative.[9,10] Respondents were instructed not to consider cost, access, or reimbursement, unless specifically asked to do so, to finalize an answer for voting. The same response from at least 66.6% of the participants was required for the formulation of consensus for a topic.

A total of 19 statements were formulated for the identified gaps and unmet needs of patients with mPC; 10 statements qualified for clear consensus in the first round of voting. Consensus was established for the remaining in subsequent voting and panel discussions.

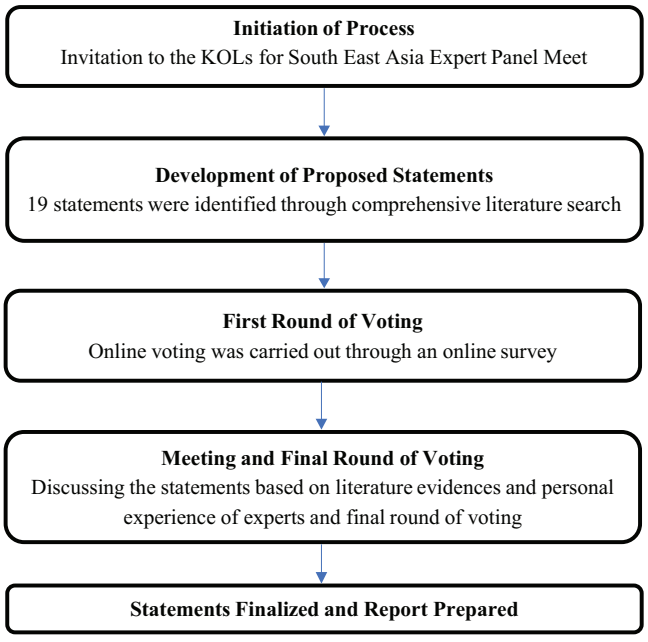

Figure 1. Modified Delphi method for development of expert recommendations.

Results

Management of mPC in SEA

Androgen-deprivation therapy (ADT) is the backbone of treatment in metastatic castration-sensitive prostate cancer (mCSPC).[11] About 90% patients with mCSPC obtain an objective response to bone and soft tissue metastasis and prostate specific antigen (PSA) levels with initial ADT.[12] The panel deliberated upon the results of key clinical studies for abiraterone and docetaxel in mCSPC (Table 1).

Improved overall survival (OS) has been demonstrated with docetaxel plus ADT in the CHAARTED and STAMPEDE arm C studies.[13,14] Similar results for OS have been reported with abiraterone and prednisolone plus ADT in the LATITUDE and STAMPEDE arm G studies.[15,16] However the GETUG-AFU 15 study failed to demonstrate improvement in median OS with docetaxel in patients with mCSPC (Table 2).[17]

The expert panel consensus outcomes

Risk stratification in mPC. Patients with mCSPC can be stratified based on the volume or risk of the condition.[13,15] In the LATITUDE study, criteria for high-risk patients included the presence of two of the three high-risk factors, including a Gleason score of ⩾8, ⩾3 bone lesions, and the presence of measurable visceral metastasis.[15] On the other hand, the CHAARTED study defined high volume of metastases by the presence of visceral metastases or ⩾4 bone lesions with at ⩾1 beyond the vertebral bodies and pelvis.[13] The Gleason

Table 1. Expert panel for the SEA Consensus Conference 2019.

Country	Expert panelist	Institutional affiliation	Role and specialty
Brazil	Fabio A. Schutz	Beneficencia Portuguesa de Sao Paulo	Clinical Coordinator Department of Medical Oncology
Thailand	Ekaphop Sirachainan	Ramathibodi Hospital, Bangkok	Associate Professor/ Head of Division of Medical Oncology
Thailand	Thitiya Dejthevaporn	Ramathibodi Hospital, Bangkok	Assistant Professor. Medical Oncology
Thailand	Phichai Chansriwong	Ramathibodi Hospital, Bangkok	Medical Oncologist
Thailand	Napa Parinyanitikul	Chulalongkorn Hospital, Bangkok	Medical Oncologist
Thailand	Piyawan Tienchaiananda	Rajavithi Hospital, Bangkok	Medical Oncologist
Malaysia	Badrulhisham Bahadzor	Sunway Medical Centre, Selangor	Consultant Urologist
Malaysia	Ai Lian Tan	Hospital Pulau Pinang	Medical Oncologist
Malaysia	Adlinda Alip	University of Malaya Medical Centre, Kuala Lumpur	Head, Clinical Oncology Unit
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Việt Nam	Vu Quang Toan	National Cancer Hospital, Ha Noi	Vice Head of Department, Department of Medical Oncology
Việt Nam	Nguyen Thi Thai Hoa	National Cancer Hospital, Ha Noi	Head of Department, Medical Oncology
Việt Nam	Nguyen Thi Minh Hue	Cho Ray Hospital, HCMC	Department of Medical and Radiation Oncology
Việt Nam	Vu Dinh Khanh Hoang	Oncology Hospital, HCMC	HCMC Oncology Hospital

HCMC, Ho Chi Minh City; SEA, South East Asia.

score is a well-established prognostic factor for disease-specific survival in patients with PC, and higher scores are indicative of more aggressive disease.[18] The panel deliberated that patients with low volume disease, including patients with lymph-node negative and non-metastatic disease (N0M0), may have poor prognostic features such as high PSA and high Gleason score. There are possible overlaps between the risk- and volume-based stratification as it is difficult to categorize patients as low volume and low risk or high volume and high risk. Most clinicians (83.3%) adopt the risk-based criteria in clinical practice.

Consensus: The risk-based stratification of mCSPC has a broader scope for patient stratification and is more practical.

Extrapolation of LATITUDE results. The LATITUDE and Stampede (Arm G) trials have reported a survival advantage with abiraterone acetate plus prednisone in combination with ADT when compared with ADT and placebo in mCSPC (Table 1).

In the LATITUDE study, addition of abiraterone acetate and prednisone (AAP) to ADT increased OS [not reached *versus* 34.7 months; hazard ratio (HR) for death: 0.62; 95% confidence interval (CI), 0.51–0.76; $p < 0.001$] and radiographic progression-free survival (PFS; 33.0 *versus* 14.8 months; HR for disease progression or death: 0.47; 95% CI: 0.39–0.55; $p < 0.001$) significantly when compared with placebo. However, the study included newly diagnosed patients with mCSPC.[15] On the other hand, the STAMPEDE trial included a broader patient population, including those with lymph node only disease (N+M0) and high-risk N0M0. In addition, the STAMPEDE trial included patients with newly

Table 2. Key studies for treatment options in mCSPC.

Clinical trial	Investigational agent and dose	Treatment assignment	OS	Median time to progression	Safety
CHAARTED [ClinicalTrials.gov identifier: NCT00309985] (Sweeney)[13] Median follow up: 28.9 months	Docetaxel: 75 mg/m^2 BSA IV every 3 weeks for 6 cycles	ADT + D (n = 397) and ADT alone (n = 393)	ADT + D: 57.6 months; ADT alone: 44.0 months (HR: 0.61; 95% CI: 0.47–0.80)	ADT + D: 20.2 months; ADT alone: 11.7 months (HR: 0.61; 95% CI: 0.51–0.72)	Any grade 3/4 AEs: 29.3% (ADT + D) Most common AEs: neutropenia (12.1%) and fatigue (4.1%).
GETUG-AFU 15 [ClinicalTrials.gov identifier: NCT00104715] (Gravis)[17] Median follow up 50 months (IQR 39-63)	Docetaxel: 75 mg/m^2 BSA IV every 3 weeks for up to 9 cycles	ADT plus docetaxel (n = 193) and ADT alone (n = 192)	ADT plus docetaxel: 58·9 months; ADT alone: 54·2 months (HR: 1·01, 95% CI: 0·75–1·36)	NR	72 SAEs in no SAEs in the ADT + D and ADT alone groups, respectively. Most common AEs: neutropenia (21%), febrile neutropenia (3%), abnormal liver function tests (2%), and neutropenia with infection (1%).
STAMPEDE Arm C [ClinicalTrials.gov identifier: NCT00268476] (James)[14] Median follow-up was 43 months (IQR 30–60)	Docetaxel: 75 mg/m^2 BSA IV every 3 weeks for 6 cycles with prednisolone 10 mg daily	ADT plus docetaxel (n = 592) and ADT alone (n = 1184)	(81 months vs. 71.3 months; HR 0.78; 95% CI, 0.66–0.93).	ADT plus docetaxel also improved median FFS compared with ADT alone (37 months *versus* 20 months; HR 0.61; 95% CI, 0.53–0.70)	Grade 3/4 AEs in the two groups: 39% *versus* 17%; one death in ADT + D group
LATITUDE [ClinicalTrials.gov identifier: NCT01715285] (Fizazi)[15] median follow-up of 30.4 months	AA: 1,000 mg daily with prednisolone 5 mg daily	ADT plus AA (n = 597) and ADT alone (n = 602)	ADT plus AA: not Reached; ADT alone: 34.7 months (HR: 0.62; 95% CI: 0.51–0.76)	Median radiographic PFS ADT plus AA: 33.0 months; ADT alone: 14.8 months (HR: 0.47; 95% CI: 0.39–0.55).	Grade 3/4 AEs in the two groups: 63% *versus* 48%. Most common AEs with AA: Mineralocorticoid-related hypertension (20%), hypokalemia (11%), and increased alanine aminotransferase levels (5%).
STAMPEDE Arm G* [ClinicalTrials.gov identifier: NCT00268476] (James)[16] Median follow up: 40 months	AA: 1,000 mg daily with prednisolone 5 mg daily	ADT plus AA (n = 960) and ADT alone (n = 957)	ADT plus AA: 83%; ADT alone: 76% (HR: 0.63; 95% CI: 0.52–0.76)	3-year FFS ADT plus AA: 75%; ADT alone: 45% (HR: 0.29; 95% CI: 0.25–0.34).	Grade ⩾3 AEs in the two groups: 47% *versus* 33%.

*941 men had newly diagnosed mCSPC; Results reported for overall population.
AA, abiraterone acetate; ADT, androgen-deprivation therapy; AE, adverse event; BSA, body surface area; CI, confidence interval; D, docetaxel; FFS, failure-free survival; HR, hazard ratio; IQR, interquartile range; mCSPC, metastatic castration-sensitive prostate cancer; NR: not reported; OS, overall survival; PFS, progression free survival; SAE, serious adverse event; STAMPEDE, systemic therapy for advanced or metastatic prostate cancer: evaluation of drug efficacy.

diagnosed (*de novo*) and relapsed disease after prior radical surgery and/or radiotherapy.[19] Survival benefits were seen with abiraterone in the STAMPEDE (Arm G) trial, which supports the use of abiraterone in a wider population of men with PC (Table 1).[16]

Consensus: the majority of panelists (69.2%) consider it acceptable to extrapolate the results of the LATITUDE trial to selected patients who subsequently develop metastases after failure of local therapy.

Addition of docetaxel to hormonal therapy for metastatic hormone-sensitive PC. ADT plus docetaxel can also be considered as standard of care (SOC) for fit patients with high-volume mCSPC. Follow-up (53 months) data of the CHAARTED study demonstrated favorable benefits of OS for docetaxel therapy (3 weekly at 75 mg/m^2) in patients with high-volume disease (HR: 0.63; $n=513$) but no OS benefit for low-volume disease (HR: 1.04; $n=277$).[20] There was unanimous agreement (92%) amongst the panel for NOT recommending docetaxel in addition to ADT in metastatic castration-sensitive "low-volume" disease patients. A similar opinion was reported by the experts in advanced PC consensus meeting for the Asia Pacific Region.[21] *Post hoc* analyses of the GETUG-AFU15 study (median follow up: up to 7 years) was performed to assess the impact of metastatic burden on OS in patients with mCSPC. Treatment with docetaxel resulted in a non-significant 20% reduction in the risk of death in patients with high-volume disease. When compared with ADT alone, treatment with ADT and docetaxel improved OS in high-volume disease (35.1 months *versus* 39.8 months; HR: 0.78; 95% CI: 0.56–1.09) and no difference in OS was observed for low-volume disease (83.4 months *versus* not reached; HR: 1.02; 95% CI: 0.67–1.55).[22]

The panel (76.92%) reported toxicity as limiting factor for the use of docetaxel. Common safety concerns with the use of docetaxel in mPC include neutropenia, neutropenic fever, neuropathy, mucositis, and others.

There was clear consensus (85%) for choosing abiraterone and/or enzalutamide, depending on availability, over docetaxel as first-line therapy in addition to ADT in patients of metastatic castration-resistant prostate cancer (mCRPC) who are either asymptomatic or have minimal symptoms. There are no randomized controlled trials (RCTs) comparing abiraterone or enzalutamide with docetaxel in mPC. A network meta-analysis of three studies (LATITUDE, CHAARTED and GETUG-AFU-15), demonstrated that abiraterone, when added to prednisolone and ADT, was at least as effective as docetaxel and ADT in reducing the risk of death in patients with mCSPC. The findings from these studies suggest that Abiraterone was better than docetaxel at preventing disease progression and improving quality of life for at least one year of therapy with maximum benefit at 3 months.[23]

Consensus: When added to ADT in mCSPC, docetaxel has no benefits in patients with low-volume disease. Common safety concerns for the practical use of docetaxel in mPC include poor performance status and frailty of the patients, severe hepatic impairment, neutropenia, and neuropathy.

Note: Subsequent to this meeting, in September 2019, the results from long-term follow up of metastatic (M1) patients in the STAMPEDE trial were published.[24] There was no evidence of heterogeneity of docetaxel effect between metastatic burden sub-groups, in contrast to findings from the CHAARTED trial. Differences in baseline characteristics may account for differences in outcomes between the studies, for example, the proportion of patients with relapsed disease after prior local therapy in the low-volume mHNPC cohorts may explain the conflicting results. Less than 10% of men in the low-volume cohort of the STAMPEDE had relapsed after receiving prior local therapy, whereas, in the CHAARTED and GETUG-15 studies, more than 55% of men with low-volume disease received prior therapy.

Metastatic castration-resistant PC. Since 2010, clinical progress in treating PC patients in the castration-resistant setting has been remarkable; several novel therapeutics have demonstrated improved survival outcomes.[25]

Abiraterone has demonstrated beneficial outcomes in chemotherapy naïve patients with mCRPC who had no clinically significant cancer-related symptoms. In a phase III double-blind study [ClinicalTrials.gov identifier: NCT00887198], patients were randomized to receive abiraterone and prednisone ($n=546$) or placebo and prednisone ($n=542$). When compared with placebo, abiraterone improved radiographic PFS (8.3 months *versus* 16.5 months; HR: 0.53; 95% CI: 0.45–0.62; $p<0.001$) and showed a trend towards improved

OS (27.2 months *versus* not reached; HR: 0.75; 95% CI: 0.61–0.93; $p=0.01$). There was also delay in clinical decline [⩾1 point decrease in Eastern Cooperative Oncology Group (ECOG) performance-status; 10.9 months *versus* 12.3 months; HR for decline: 0.82; 95% CI: 0.71–0.94; $p=0.005$], PSA progression (5.6 months *versus* 11.1 months; HR: 0.49; 95% CI: 0.42–0.57; $p<0.001$), and median time to initiation of cytotoxic chemotherapy (16.8 months *versus* 25.2; HR: 0.58; 95% CI: 0.49–0.69; $p<0.001$) and opiate use for cancer-related pain (23.7 months *versus* not reached; HR: 0.69; 95% CI: 0.57–0.83; $p<0.001$). However, this study excluded patients with visceral metastasis.[26] In another study in asymptomatic or mildly symptomatic men from China, Malaysia, Thailand and Russia ($n=313$; 24% with soft tissue or node metastasis), abiraterone significantly decreased the risk of PSA progression by 58% compared with prednisone alone (HR: 0.42; 95% CI: 0.27–0.65; $p<0.0001$).[27] Abiraterone is the preferred therapy in mCRPC patients who have visceral metastasis, as abiraterone has shown benefits in this population in the post-chemotherapy setting.[28,29]

Abiraterone versus enzalutamide. Both abiraterone and enzalutamide are optimal for symptomatic patients with mCRPC. The expert panel of the Advanced Prostate Cancer Consensus Conference (APCCC) 2017 recommended abiraterone or enzalutamide as first-line agents in symptomatic patients with mCRPC irrespective of prior use of chemotherapy.[30] In a retrospective study, African-American patients ($n=787$) with chemotherapy naïve mCRPC had better OS (910 days *versus* 784 days; HR: 0.887; 95% CI: 0.790–0.996) with abiraterone or enzalutamide when compared with white patients ($n=2123$).[31] There are no phase III trials with head-to-head comparisons for abiraterone or enzalutamide in mCRPC.

In the prospective observational multicentre phase IV study (AQUARiUS), abiraterone provided favorable outcomes for measures of fatigue and cognition over 6 months when compared with enzalutamide in patients with mCRPC.[32] In the Real-world Study of Enzalutamide and Abiraterone Acetate (with Prednisone) Tolerability (REAAcT), 100 patients with mCRPC were administered either abiraterone or enzalutamide. Fatigue (Functional Assessment of Cancer total score) and cognitive decline was reported in more numbers of patients who received enzalutamide.[33]

Non-metastatic PC. In a subgroup analysis of the STAMPEDE study [ClinicalTrials.gov identifier: NCT00268476], 915 patients with non-metastatic (N0M0 and N+M0) PC received SOC alone (ADT for 2+ years with or without radiotherapy) or SOC with abiraterone. In patients with N0M0 disease, abiraterone improved the 3-year failure-free survival (FFS) (98% *versus* 80%; HR: 0.14; 95% CI: 0.07–0.30).[34] In the phase II, proof-of-concept, open-label, single-arm IMAAGEN study in 131 men with high-risk (PSA ⩾10 ng/ml or PSA doubling time ⩽10 months) nmCRPC, treatment with abiraterone acetate (1000 mg) and prednisolone (5 mg) (28-day cycles; median follow up 40.0 months) demonstrated a significantly higher PSA response rate during cycles 1–6, with 86.9% and 59.8% patients achieving ⩾50% and ⩾90% reductions in PSA. Median time to PSA progression was 28.7 months (95% CI: 21.2–38.2) and the median time to radiological PFS was not reached (estimated to be 41.4 months, 95% CI: 27.6–NE, by sensitivity analysis, $n=15$). AEs, Grade ⩾3 AEs, and SAEs were reported in 96.2%, 61.1%, and 43.5% of patients, respectively.[35] However, there is no statistically significant improvement in long-term outcomes, such as OS, to support routine use of abiraterone for non-metastatic PC, and it is not supported by the National Comprehensive Cancer Network (NCCN) guidelines.[36]

Monitoring of abiraterone therapy. Patients receiving abiraterone should undergo careful clinical monitoring. It is usually recommended that patients undergo routine blood tests, including electrolytes and renal function tests, every 2–4 weeks initially and periodically thereafter. Liver function tests may be done every 2 weeks for the initial 3 months, every 4 weeks for 6 months, and as needed thereafter. Cardiac investigations, including echocardiography and biomarkers, may not be done routinely unless history is suggestive of cardiac risk factors in a patient. Frequent imaging (every 3 months) may not be necessary in patients without clinical signs of disease or PSA progression. It may be a rational choice to limit imaging to symptomatic patients. Close monitoring of PSA levels (every 3 weeks to 3 months) may be desirable to guide treatment in mCRPC.[29]

Consensus: All panellists agree that abiraterone or enzalutamide be recommended as first-line therapy for symptomatic chemotherapy naïve mCRPC patients. All panellists preferred abiraterone to enzalutamide as first-line treatment in patients with

mCRPC. A majority (66.7%) also recommended abiraterone or enzalutamide as first-line therapy for symptomatic chemotherapy naïve mCRPC patients with "visceral metastases".

A majority of the panel (84.62%) did not support the use of abiraterone in N0M0 PC with very high-risk features like Gleason score of 8–10 and very high PSA value.

Low dose abiraterone. Abiraterone is the first-line medication prescribed most widely for CRPC.[37] Registration studies for abiraterone have been conducted in fasting state though early clinical experience showed increased drug exposure when administered with food.[37,38] Further, higher drug concentrations have been achieved with higher fat content in food.[39] In a randomized phase II study in men with mCRPC ($n=72$), when administered with low-fat breakfast, low-dose AA was noninferior to the standard dosing with respect to PSA response (⩾50%) rate at 12 weeks (58% and 50% in the low and standard dosing groups, respectively) and median PFS (9 months in both groups).[40] However, these data may not be taken as conclusive for cost effectiveness for low dose abiraterone due to the limited sample size, lack of long-term outcomes and pharmacokinetics evaluation, and reasonably low PFS when compared with the landmark study.[26,41] Nevertheless, this strategy could be considered in regions of limited resources without access to fasting full dose of abiraterone.

Consensus: A majority of the panel (69.2%) agreed to a scientific rationale for use of low dose abiraterone with food in mCRPC (abiraterone 250 mg per day taken either concomitantly or within 30 min of a conventional low-fat breakfast).

ARv7 testing in mPC

Primary or secondary resistance to androgen signalling inhibition is reported in about 20–40% patients with PC.[42] In a prospective observational study in 37 mCRPC patients, ARv7, a splicing variant of the androgen receptor (AR) lacking the ligand-binding domain, showed a link with treatment failure. ARv7 was significantly associated with poorer radiological PFS, PSA-PFS, and OS in mCRPC treated with new hormonal agents.[43] Men with AR-V7-positive mCRPC had fewer confirmed prostate-specific antigen responses (0–11%) or soft tissue responses (0–6%), with similar results of shorter PFS and OS being reported in the PROPHECY study, a multicenter, prospective-blinded study of 118 men with high-risk mCRPC starting abiraterone acetate or enzalutamide treatment.[44] Though ARv7 is expressed in only about 10–20% patients with advanced PC, testing for ARv7 can guide targeted treatment in mCRPC.[45] Access and cost of ARv7 is an important limiting factor to adoption of ARV7 testing for treatment decisions in all patients.

Consensus: A majority of the panel (76.92%) recommended testing for ARv7, if and when available, before androgen receptor signaling inhibitors, abiraterone or enzalutamide, to predict outcomes in mCRPC.

Reimbursement decisions for abiraterone

Reimbursement of therapy is an important factor that influences access and uptake of therapy in PC.[46,47] Availability of generics can enable access to therapy, and bioequivalence has been established for generic and branded abiraterone.[48] Practical challenges in reimbursement include limitations to defined patient subsets and total fraction of cost of therapy.

Consensus: A majority (76.92%) of the panel considered abiraterone as an appropriate first-line treatment for men with mCSPC and supported recommendation for reimbursement of abiraterone. The entire panel favored the use of generic abiraterone, if available, as an appropriate treatment option in chemotherapy-naïve mCRPC patients, and 84.61% panellists agreed to support a recommendation for universal reimbursement.

Factors influencing choice of treatment in mHSPC

It is a common challenge to choose from ADT alone, ADT and docetaxel, and ADT and abiraterone for the management of mHSPC. There are no direct head-to-head prospective studies comparing ADT and docetaxel with ADT and abiraterone in mHSPC.[47,49] The efficacy of the two regimens in patients with metastatic hormone-sensitive PC (mHSPC) is reported to be similar in the available clinical evidence (Table 1). The STAMPEDE trial performed a direct, randomized comparative analysis of ADT plus abiraterone (1000 mg) and prednisolone (5 mg daily) ($n=377$) and ADT plus docetaxel (75 mg/m^2 3-weekly $\times$ 6) and prednisolone (10 mg daily) ($n=189$), and showed no evidence of a difference in OS (HR: 1.16; 95% CI

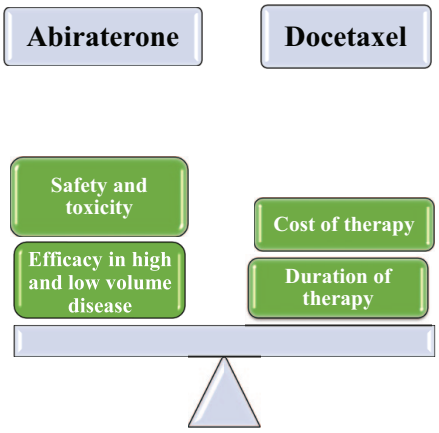

Figure 2. Abiraterone *versus* docetaxel in mCSPC.
mCSPC, metastatic castration-sensitive prostate cancer.

0.82–1.65), prostate cancer-specific survival (HR: 1.02; 95% CI: 0.70–1.49), or symptomatic skeletal events (HR: 0.83; 95% CI 0.55–1.25) in patients with advanced PC or mPC. However, when evaluating short-term outcomes including FFS, usually directed by PSA progression, and radiological PFS, abiraterone was superior to docetaxel. This study reported 60% patients with M1, 76% with Gleason 8–10; and 79% with World Health Organization (WHO) performance status 0.[50] Another meta-analysis and indirect comparison by Wallis *et al.* ($n=6067$ patients; five RCTs) failed to demonstrate any significant difference in OS between abiraterone and docetaxel in the treatment of mCSPC (HR: 0.84, 95% CI: 0.67–1.06); the abiraterone-ADT combination showed better performance in younger patients (HR, 0.77, 95% CI, 0.60–1.004).[51] Similarly, relatively better efficacy, without significant differences in OS, has been reported for abiraterone-ADT when compared with docetaxel-ADT in another network meta-analysis ($n=6204$).[52] The choice of abiraterone *versus* docetaxel is governed by risk stratification, comorbidities, safety concerns, access, cost, and quality of life considerations.[46,47,53]

Disease and patient characteristics can guide the choice of therapy. Factors that drive the choice of chemotherapy instead of other survival-prolonging agents like abiraterone in mCSPC include high volume disease, visceral metastasis, cost of treatment, treatment duration, rapidly progressive disease, comorbidities, ECOG performance status, severe symptomatic patients, safety, and compliance. Cost of therapy and access to therapy are key factors that influence treatment decisions in patients with mCSPC (Figure 2).

In recent studies, patients with mPC have received early docetaxel followed by enzalutamide (ENZAMET; about 50% patients) or apalutamide (TITAN; about 10% patients).[54,55] However, subgroup analysis results do not support use of sequential or concomitant docetaxel and enzalutamide/apalutamide. ARASENS is a phase III trial ongoing and randomizing mCSPC patients to receive ADT + docetaxel *versus* ADT +docetaxel+darolutamide.[56]

Factors influencing choice of therapy in mCRPC

Clinically important factors that drive the choice of chemotherapy instead of other survival prolonging agents like Abiraterone or Enzalutamide in mCRPC patients are: visceral metastasis, symptomatic disease, rapid progression, patient preferences, drug availability, short response to ADT, patient age, performance status, comorbidities, how the patient is responding during treatment, biomarkers, cost, and compliance.

Short response to ADT, that is, rise in PSA levels within a year of ADT, is a common clinical challenge. These patients may not be good responders to abiraterone or enzalutamide. Early castration resistance is a generally poor prognostic sign that may translate to shorter duration of mCRPC therapies. In mCRPC patients with ADT response of <12 months, first-line treatment can be chemotherapy if patients have symptoms and abiraterone if patients are asymptomatic or mildly symptomatic.[29] In patients who received abiraterone in a castration-sensitive setting, chemotherapy should be preferred to enzalutamide for progression to castration resistance.

Switch and sequence of therapy in mCRPC

Head-to-head comparisons to guide the switch or sequence of treatment with abiraterone, enzalutamide, or docetaxel in mCRPC are lacking.[29] Radiological and clinical progression should warrant a switch in therapy. Patients with PSA progression should be monitored closely for radiological or clinical progression, as changing therapy based solely on biochemical progression after initial response is not recommended.[57]

Both abiraterone and enzalutamide have shown survival benefits in mCRPC patients who progressed after treatment with docetaxel. In the phase III COU-AA-301 study, abiraterone showed a longer median OS (15.8 months, 95%

CI: 14·8–17.0) when compared with placebo (11.2 months, 95% CI: 10.4–13.1) (HR: 0.74, 95% CI: 0.64–0.86; $p < 0.0001$) at a median follow up of 20.2 months in 1195 patients with mCRPC.[58] Similar results for median OS were reported with enzalutamide in a phase III study in 1199 men (AFFIRM Trial) with mCRPC after chemotherapy (18.4 months, 95% CI: 17.3 to not yet reached *versus* 13.6 months, 95% CI: 11.3–15.8HR: 0.63; 95% CI: 0.53–0.75; $p < 0.001$).[59] However, optimal sequencing of abiraterone and enzalutamide is important to maximize clinical and biochemical benefits in mCRPC. When administered to mCRPC patients who have progressed after enzalutamide ($n = 30$), abiraterone produced only modest response in PSA progression and OS and no objective radiographic responses.[60] In a retrospective review, the sequence of therapy did not significantly impact clinical outcomes in patients who received abiraterone followed by enzalutamide ($n = 50$) or the reverse ($n = 47$). In the two sequence groups, there were no significant differences in median PFS (HR: 0.71; 95% CI: 0.46–1.08; log-rank $p = 0.105$) or median OS (HR: 0.98; 95% CI: 0.64–1.52; log-rank $p = 0.834$). Though the PSA response rate to first-line treatment was not significantly different between patients who initially received abiraterone (48%) and those who initially received enzalutamide (51%) ($p = 0.840$), there was a significant difference in the PSA response rate to second-line treatment in the two groups (6.4% *versus* 30%; $p = 0.004$).[61]

Progression of disease should be monitored with PSA, radiological assessments, and clinical signs. Rare instances of an isolated rise in PSA progression should not necessitate a switch in therapy. In this case, switch from prednisolone to dexamethasone may be beneficial.[62–64]

Consensus: The panel was asked to opine as to the appropriate order in which to stagger abiraterone, docetaxel, and enzalutamide therapies. None of the experts supported enzalutamide as first-line treatment in mCRPC. Most (77.8%) preferred the sequence of abiraterone, docetaxel, and enzalutamide, whereas 22.2% supported the sequential use of abiraterone, enzalutamide, and docetaxel in mCRPC. Cabazitaxel was not discussed as a potential option for treatment. A majority (91.7%) agreed that PSA progression alone, without clinical or radiological progression, should not trigger switch in treatment.

Switch in steroid treatment. In patients with castration resistance, switch from prednisolone to dexamethasone may help to check PSA progression.[62–64] In the single-arm, open-label, phase II SWITCH study, 36 patients with mCRPC who had PSA and/or limited radiographic progression after at least 12 weeks on abiraterone and prednisolone were switched over to abiraterone and dexamethasone (0.5 mg daily). In these patients, the proportion of patients achieving a PSA decline of $\geqslant$30% from baseline after 6 weeks PSA30 (primary end point) and PSA response rate at 12 weeks-PSA50 (secondary end point) were 46.2% and 34.6%, respectively. Median time to biochemical and radiological progression and OS was 5.3, 11.8, and 20.9 months, respectively.[63]

Consensus: Most panelists (83.3%) considered steroid switch from prednisolone to dexamethasone as a safe and non-expensive way of obtaining response to abiraterone in selected patients with mCRPC.

Conclusion

This first consensus statement of experts from SEA provides valuable guidance for real-life management of mPC. Addition of abiraterone or docetaxel to ADT in patients with newly diagnosed, non-castrate mPC has an established survival benefit over ADT alone. Men with *de novo* mCSPC with high-risk features (LATITUDE criteria) or low-volume or high-volume (CHAARTED criteria in STAMPEDE analysis) should be offered treatment with abiraterone in addition to ADT. Majority of the panel supported recommendation for reimbursement of abiraterone as first line treatment for mCSPC. The panel favored the use of generic abiraterone, if available, as an appropriate treatment option in chemotherapy-naïve mCRPC and for universal reimbursement. Panel recommendations are based on existing literature and current practices. Though the results may have been influenced by availability, cost, or physician preferences, the conclusions shall facilitate clinical decision-making for optimizing outcomes in mPC patient management across the region.

Note to readers

The treatment landscape of PC is changing rapidly; this brings both opportunities and challenges for physicians. Subsequent to this expert group

meeting, Enzalutamide was approved by the United Stated Food and Drug Administration (FDA) for patients with metastatic castration-sensitive prostate cancer. The approval is based on results from the ARCHES trial [ClinicalTrials.gov identifier: NCT02677896] – a randomized phase III study that evaluated 1150 men with mCSPC and met its primary endpoint of radiographic progression-free survival (rPFS). Another AR targeting agent, apalutamide, has received approval in the mCSPC space based on results from the TITAN trial [ClinicalTrials.gov identifier: NCT02489318]. Similarly for CRPC, Sipuleucel-T, the first immunotherapy product approved by the FDA, addition of radium-223 to SOC leading to OS benefit demonstrated in the ALSYMPCA trial, have also contributed to changes in treatment paradigms. Radiation to the primary tumor is also poised to become a new SOC. However, these were not discussed in this expert meeting as they were not uniformly available across the region, consequently these were not included in detail in the manuscript. However, we would like to draw the attention of readers to these aspects and advise that they evaluate them for optimizing therapy selection and improving outcomes.

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Supplemental material

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