

## Research Article

Latif MF, et al. J Oncol Res Ther: JONT-162.

DOI: 10.29011/2574-710X. 000062

## Treatment versus Observation in Non-Metastatic Castrate Resistant Prostate Cancer, Results of United Kingdom Based Oncologists' Survey

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**Citation:** Latif MF, Azam F, Farooq A, Alshahrani S, Selwi WA, et al. (2018) Treatment versus Observation in Non-Metastatic Castrate Resistant Prostate Cancer, Results of United Kingdom Based Oncologists' Survey. J Oncol Res Ther: JONT-162. DOI: 10.29011/2574-710X. 000062

**Received Date:** 01 August, 2018; **Accepted Date:** 13 August, 2018; **Published Date:** 21 August, 2018

### Abstract

**Objectives:** Until recently there had been no clear guidelines for the management of non-metastatic castrate resistant prostate cancer. However, treatment paradigm is rapidly changing following the results of two phase 3 clinical trials in 2018. National Comprehensive Cancer Network has recently recommended Apalutamide in patients with non-metastatic castrate resistant prostate cancer with PSA-doubling-time of <10 months. The aim of this study was to find out oncologists' opinion regarding management of this group of patients.

**Methods:** We conducted an online survey of 120 Oncologists responsible for the management of prostate cancer in the UK. The survey asked the oncologists to select the management options for a 65 years old fit man with non-metastatic castrate resistant prostate cancer with rising PSA and shortening PSA doubling time.

**Results:** 96 (80%) of 120 oncologists responded. With PSA-doubling-time of <6 months and serum PSA of 18ng/ml, most oncologists (n=61, 64%) recommended systemic therapy as compared to active monitoring (n=35, 36%). On further progression with PSA-doubling-time of <3 months and serum PSA of 38ng/ml with no clinical and radiological evidence of metastases, 67 of 95 (71%) oncologists recommended systemic therapy as compared to active monitoring (n=28, 29%). Most oncologists preferred systemic therapy over observation on further PSA progression (p=0.001). 2nd generation hormones (Enzalutamide/Abiraterone) were preferred systemic treatment option selected by the oncologists.

**Conclusions:** Our study shows oncologists' preference and an unmet need for systemic treatment in non-metastatic castrate resistant prostate cancer. Majority of oncologists in UK recommend systemic therapy over active monitoring. They prefer second generation hormone therapy than systemic chemotherapy.

### Introduction

Prostate Cancer (PC) is more common in older men and it is estimated that 1 in 8 men in UK will develop prostate cancer in their lifetime [1]. Morphologically most prostate cancer are adenocarcinomas (95%). Other histological types include transitional cell cancers, small cell cancers and squamous cell cancers [2]. Standard treatments for localized prostate cancer include surgery and radiation therapy with or without Androgen

Deprivation Therapy (ADT). After curative treatment some patients develop recurrence usually detected by rising level of serum PSA. Many patients receive ADT after biochemical relapse with no evidence of metastases, although the evidence of early versus delayed ADT in this group of patients is inconclusive [3,4]. Around 10-20% of patients develop Castrate Resistant Prostate Cancer (CRPC) within 5 years of follow-up. 16% of these patients show no evidence of metastasis at the time of diagnosis of CRPC.

Of these patients, 33% develop bone metastasis within 2 years [5]. Non-Metastatic Castrate Resistant Prostate Cancer (NM-CRPC) is defined as rising level of serum PSA while on ADT with a castration level of testosterone in the absence of clinical and radiological evidence metastatic disease [6]. Some clinicians believe this definition of NM-CRPC is controversial as current imaging modalities might not be sensitive or reliable enough for detection of metastatic disease. A baseline serum PSA level of  $>10$  ng/ml, a high PSA velocity and PSA Doubling Time (PSA-DT) are reported to be predictors for shorter time to first bone metastasis and death [7]. Treatment is generally not recommended outside the context of clinical trial for NM-CRPC in most guidelines, however recently updated National Comprehensive Cancer Network (NCCN) guidelines recommend Apalutamide or secondary hormone therapy (antiandrogen, anti-androgen withdrawal, ketoconazole, Diethylstilbestrol, corticosteroids, other oestrogens), if PSA-DT is less than 10 months [8]. Systemic chemotherapy or immunotherapy is not recommended outside the context of a clinical trial. Due to limited clinical trials evidence in NM-CRPC, clinicians face challenges in management of these patients. However, there is strong evidence and consensus of systemic anticancer therapy in metastatic CRPC including second generation hormone therapy (Abiraterone, Enzalutamide), chemotherapy (Docetaxel, Cabazitaxel), vaccines and Radium 223 [9]. Clinicians usually take guidance from evidence of systemic therapy in metastatic CRPC while choosing treatment for NM-CRPC. We conducted a survey of UK based oncologists responsible for the management of PC. We aimed to identify the treatment trends for patients with NM-CRPC. There is no evidence based clear guidelines for treatment in this particular field. Our study also aimed to find out PSA related treatment decision factors including absolute PSA value, PSA velocity and PSA doubling time and other contributing clinical factors (age, performance status, time from diagnosis to development of castrate resistance, co morbidities).

## Methods

An online survey of Oncologists responsible for the management of PC in the United Kingdom was conducted.

Electronic invitations were sent from April 2015 till August 2015. The survey was designed as a questionnaire on Survey Monkey website and the participants were invited electronically. The participants were selected after an email correspondence with the managers of the oncology departments at different Oncology centres in UK. Managers were asked to provide the names and contact email addresses of the willing oncologists responsible for the management of prostate cancer at their hospital. After obtaining the contact information, the participants were invited electronically to complete a questionnaire with a clinical scenario of a patient with NM-CRPC via the survey monkey website. The survey asked the oncologists to select the management options for a 65-year-old fit man developing NM-CRPC 2 years after radical treatment with ADT and Radiation Therapy (RT) for intermediate risk localised prostate cancer (Gleason grade 7, PSA 12ng/ml and radiologically T2N0M0 disease). Serum PSA nadir of  $<0.1$  ng/ml was achieved 6 months after radiation therapy. On subsequent follow up visits, PSA started to rise approaching to 5ng/ml after 18 months of RT. Staging investigations including standard Computed Tomography (CT) scan of chest, abdomen & pelvis and bone scan demonstrated no evidence of disease and the patient was deemed unsuitable for local salvage therapy. This patient was then commenced on ADT and subsequently developed castrate resistant disease with PSA of 18 with doubling time of less than 6 months. Respondents were asked to select management option for the same patient of active monitoring or systemic therapy including estrogen, dexamethasone, docetaxel chemotherapy, second generation hormone therapy (Abiraterone, Enzalutamide) or other in 1<sup>st</sup> line, 2<sup>nd</sup> line and 3<sup>rd</sup> line setting with a PSA-DT of  $<6$  months,  $<3$  months and  $<2$  months respectively. PSA continued to rise despite selected treatments with no clinical or radiological evidence of metastases. Chi square test was used to compare active monitoring versus systemic therapy. P value of  $<0.001$  was considered statistically significant. They were also asked to select the factors influencing their treatment decision in this situation including absolute PSA value, PSA-DT both or other. Participants were also asked to choose clinical factors important to them influencing their decision in management of these patients Table 1.

1. A 65 years old fit man has developed castrate resistant prostate cancer 3 years after radical treatment with radiation therapy and androgen deprivation therapy. Staging investigations including CT scan and bone scan showed no evidence of disease recurrence. His most recent PSA is 18 ng/ml (PSA doubling time < 6 months).

How would you manage this patient (outside a clinical trial)?

- a) Active monitoring and initiation of systemic treatment on development of metastases
- b) Estrogens
- c) Dexamethasone
- d) Docetaxel chemotherapy
- e) 2<sup>nd</sup> Generation Hormone therapy (Enzalutamide/Abiraterone)
- f) Other (please specify)

2. Following your selected management option, PSA continues to rise with current value of 38 ng/ml (doubling time < 3 months). Repeat imaging shows no evidence of metastases.

What would be your next management option (outside a clinical trial)?

- a) Active monitoring and initiation of systemic treatment on development of metastases
- b) Estrogens
- c) Dexamethasone
- d) Docetaxel chemotherapy
- e) 2<sup>nd</sup> Generation Hormone therapy (Enzalutamide/Abiraterone)
- f) Other (please specify)

3. Following your selected management option, PSA continues to rise with current value of 95 ng/ml (doubling time < 2 months) and no evidence of metastases radiologically.

What would be your next management option (outside a clinical trial)?

- a) Active monitoring and initiation of systemic treatment on development of metastases
- b) Estrogens
- c) Dexamethasone
- d) Docetaxel chemotherapy
- e) 2<sup>nd</sup> Generation Hormone therapy (Enzalutamide/Abiraterone)
- f) Other (please specify)

4. Following your selected management approach PSA continues to rise and no evidence of metastases.

What would be your next management option (outside a clinical trial)?

- a) Active monitoring and initiation of systemic treatment on development of metastases
- b) Estrogens
- c) Dexamethasone
- d) Docetaxel chemotherapy
- e) 2<sup>nd</sup> Generation Hormone therapy (Enzalutamide/Abiraterone)
- f) Other (please specify)

What would usually inform your decision making in this situation?

a) PSA doubling time  
b) Absolute PSA value  
c) Both of the above  
d) Other (please specify)

**Table 1:** Study questionnaire for the Oncologists.

## Results

A total of 120 oncologists were sent a questionnaire electronically. Ninety-six of 120 oncologists (80%) responded. All of the respondents were consultant oncologists responsible for the management of prostate cancer. In response to treatment options for a clinical scenario of a 65 years old patient with progressive NM-CRPC (rising serum PSA) and reducing PSA-DT, most oncologist opted to offer systemic treatments over active monitoring ( $p=0.001$ ).

In response to first question of rising serum PSA (PSA 18 ng/ml and PSA-DT <6 months), all of the 96 (100%) clinicians responded. Most of the oncologists ( $n=61$ , 64%) recommended systemic therapy as compared to active monitoring ( $n=35$ , 36%). The recommended systemic treatment options included second generation hormone therapy ( $n=16$ , 16.7%), Dexamethasone ( $n=14$ , 14.5%), docetaxel chemotherapy ( $n=10$ , 10.4%) and estrogen ( $n=5$ , 5.2%). Sixteen (16.7%) oncologists preferred systemic treatment options other than the above mentioned. After further PSA progression (PSA= 38 ng/ml) with PSA-DT of less than 3 months and no radiological evidence of metastases, 95 of 96 respondents replied. Sixty-seven (71%) of 95 oncologists again recommended

systemic therapy as compared to active monitoring ( $n=28$ , 29%). Second generation hormones and dexamethasone ( $n=22$ , 23.15% each) were both preferred treatments. Eleven (11.5%) oncologists suggested docetaxel chemotherapy and estrogen was suggested by 4 (4.2%) oncologists. Eight oncologists chose other treatments for this clinical situation Tables 2,3.

93 of 96 respondents replied to a question of PSA doubling time of less than 2 months (PSA=95 ng/ml) for the same patient. Majority of the oncologists ( $n=54$ , 59.1%) recommended systemic therapy as compared to active monitoring ( $n=39$ , 41.9%). Docetaxel chemotherapy, second generation hormones and other non-specified treatments were preferred equally by 13 (13.9%) oncologists. Dexamethasone and estrogen were other treatments chosen by 11 (11.8%) and 4 (4.3%) oncologists respectively.

Regarding the question of factors influencing treatment decision in NM-CRPC, forty-five (49%) oncologists consider both PSA absolute value and PSA-DT as the most important decision-making factor. PSA-DT only was considered as a main treatment decision factor by 18 (20%) oncologists and other factors (including symptoms and development of metastases) were considered as most important factors for the treatment initiation by 27 (30%) oncologists.

Questions	Responses	Active monitoring	Systemic therapy n (%)	Preferred treatment
		n (%)	n (%)	
1. How would you manage this patient with PSA of 18 (PSA <sub>DT</sub> of <6 months)?	96 (100)	35 (36)	61 (64)	2 <sup>nd</sup> gen HT
2. How would you manage this patient, following selected management option, PSA continued to rise to 38 with PSA <sub>DT</sub> of < 3months. No evidence of metastases	95 (99)	28(29)	67(71)	2 <sup>nd</sup> gen HT & Dexamethasone
3. How would you manage after further rise in PSA to 95 with PSA <sub>DT</sub> of 2 months and no metastases	93(97)	39(42)	54(59)	2 <sup>nd</sup> gen HT & Docetaxel

**Table 2:** Preferred Management options for Non-metastatic castrate resistant prostate cancer by Oncologists 2<sup>nd</sup> gen hormones= Enzalutamide or Abiraterone + Prednisolone, HT=Hormone Therapy.

Systemic treatment options for NMCRPC	Number of responses for PSA of 18 & PSAdT of <6 months	Number of responses for PSA of 38 & PSAdT of <3months	Number of responses for PSA of 95 & PSAdT of 2 months
Enzalutamide or Abiraterone + Prednisolone	16	12	13
Docetaxel	10	11	13
Dexamethasone	14	22	11
Estrogen	5	4	4
Other treatment	16	8	13
Total (systemic therapy)	61	67	54
Active Monitoring	35	28	39

**Table 3:** Preferred Systemic treatment options by oncologists.

## Discussion

Androgen-Deprivation Therapy (ADT) is the standard first line treatment for advanced prostate cancer [10]. Rising serum PSA is sometimes the first and only sign of progressive disease in otherwise asymptomatic men [11,12]. Approximately 85% of men with NM-CRPC will develop metastatic disease, most commonly in bones. Prognosis of metastatic CRPC is poor with median survival of only 16-18 months in most studies. Aim of treatment in NM-CRPC is to delay the development of metastases, reduce disease related morbidity, improvement in overall survival and quality of life. Evidence for active systemic treatment in NM-CRPC has been limited until recently. The results of our study show oncologists' preference and an unmet need for systemic treatment in NM-CRPC. Majority of oncologists in UK recommend systemic therapy over active monitoring in patients with progressive NM-CRPC and short PSA-DT. Experience in the use of different systemic treatment agents for metastatic CRPC was the only real time guidance to manage patients with NM-CRPC. However, data presented in ASCO GU 2018 showed benefits with Enzalutamide and Apalutamide in this setting. PROSPER study investigated Enzalutamide and SPARTAN study investigated Apalutamide in NM-CRPC. PROSPER a multinational, Phase 3, Double-blinded, Placebo-controlled study that randomised 1401 patients to Enzalutamide plus ADT or placebo plus ADT. The primary end point of metastases free survival was significantly better with Enzalutamide (36.6 v 14.7 months). Secondary endpoints including time to PSA progression and time to subsequent therapy were in favour of Enzalutamide [13]. A multicentre, Double-Blind, Placebo-Controlled, phase 3 SPARTAN study randomised 1207 patients with NM-CRPC to Apalutamide plus ADT versus placebo plus ADT. The primary endpoint of metastases free survival was significantly in favour of Apalutamide (40.5 vs 16.2 months). Secondary endpoints including time to metastases, time to PSA progression, time to symptomatic progression and progression

free survival were significantly better with Apalutamide [14]. Apart from these 2 trials the evidence in the medical literature is limited. Reports from clinical trials have suggested mixed results with possible benefit of systemic therapy in some while no significant benefit in others. Positive clinical activity was seen with Atrasentan (endothelin A receptor antagonist) in phase 2 and 3 trials of metastatic CRPC but its use in NM-CRPC did not show similar clinical activity in phase 3 trial. Improved PSA progression, progression-free survival (PFS) and serum alkaline phosphatase in metastatic CRPC were reported but not in a phase 3 study of NM-CRPC. A phase 3 randomized, double-blind, placebo-controlled trial of Atrasentan in 941 patients with NM-CRPC reported 93 days delay in median time to progression as compared to placebo which was not statistically significant. The median survival was 1477 days with Atrasentan as compared to 1403 days with placebo [15-18].

Abiraterone plus prednisolone were also investigated in a phase 2 multicentre study of NM-CRPC. Results of this trial were reported by Ryan et al. as median time to PSA progression of 28.7 months and a median time to radiographic disease progression of 41.4 months in 131 patients with high risk (PSA  $\geq$  10ng/mL or PSA doubling time  $\leq$  10 months at screening) disease [19]. STRIVE trial is another randomised double-blind phase 2 study investigated the efficacy of Enzalutamide in patients with NM-CRPC and metastatic CRPC. 139 of 396 patients had NM-CRPC. At the time of analysis in patients with NM-CRPC, median PFS was not reached with Enzalutamide compared with 8.6 months with Bicalutamide. The study concluded that Enzalutamide significantly reduced risk of prostate cancer progression or death compared with Bicalutamide in patients with NM-CRPC or metastatic CRPC [20]. Although the evidence for the use of systemic treatment in NM-CRPC is still new but there is strong clinical trial evidence of benefit of active systemic therapy in metastatic CRPC. Clinical efficacy of Abiraterone was demonstrated in two phase 3 clinical

trials. COU-AA-301 study reported improvement in median overall survival (14.8 vs 10.9 months), PSA progression (10.2 vs 6.6 months) and progression-free survival (5.6 vs 3.6 months) with Abiraterone plus prednisolone as compared to placebo plus prednisolone in metastatic CRPC after chemotherapy [21]. COU-AA-302 study in chemotherapy naïve metastatic CRPC patients reported improved median radiographic progression-free survival (16.5 vs 8.3 months) and overall survival (median not reached vs 27.2 months) in favour of Abiraterone plus prednisolone as compared to placebo plus prednisolone [22]. Enzalutamide is also an established treatment option for chemotherapy naïve and post chemotherapy metastatic CRPC. A phase 3 randomised AFFIRM trial reported significantly improved median overall survival (18.4 v 13.6 months) in favour of Enzalutamide in patients with metastatic CRPC after chemotherapy. It also met all the secondary endpoint of the trial including reduction in the PSA level by 50% or more, soft-tissue response rate, quality-of-life response rate, time to PSA progression, radiographic progression-free survival, and time to the first skeletal-related event [23]. In PREVAIL study, 1717 chemotherapy naïve men with metastatic CRPC were randomised to receive enzalutamide (n=872) or placebo (n= 845). An interim analysis after 540 deaths demonstrated a statistically significant improvement in overall survival and radiographic progression free survival in patients with metastatic CRPC [24]. Positive results from the above trials in metastatic chemotherapy naïve and post chemotherapy CRPC have led to initiation of clinical trials in NM-CRPC. PROSPER and SPARTAN trials have already reported positive outcome in NM-CRPC. ARAMIS trial is an on-going randomized, double-blind, placebo-controlled phase 3 study in high risk NM-CRPC and is expected to recruit 1500 patients at 450 sites in 33 countries. This study will investigate efficacy and safety of ODM-201 with a primary endpoint of metastasis-free survival. The study is expected to complete recruitment by June 2020 [25].

## Conclusion

Our study shows oncologists' preference and an unmet need for systemic treatment in NM-CRPC. Majority of oncologists in UK recommend systemic therapy over active monitoring in patients with progressive NM-CRPC and short PSA-DT. They prefer second generation hormone therapy than systemic chemotherapy. Further development of evidence-based guidelines will help clinicians choose appropriate treatment for this group of patients. However, with the emerging evidence of role of second generation anti androgens, the treatment paradigm is likely to change in this group of patients.

## Acknowledgements

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