Received: 23 October 2018 | Accepted: 12 February 2019 | Published on: 15 March 2019

DOI: 10.1111/ajco.13142

ORIGINAL ARTICLE

WILEY

A multicenter observational study of the real-world use of docetaxel for metastatic castration-resistant prostate cancer in China

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Abstract

Aim: To investigate the use of docetaxel for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in real-world clinical practice in China.

Methods: This single-arm, prospective, observational study was conducted at 32 study centers in China and included male patients aged ≥18 years with histologically confirmed prostate cancer who received ≥1 dose of docetaxel following failure of hormonal therapy (disease progression with serum testosterone <50 ng/dL). The primary aim was to investigate patterns of docetaxel treatment.

Results: Overall 403 patients were included between August 2011 and June 2016; patients initiated docetaxel after failure of first- (42.2% [170]), second- (31.0% [125]) and ≥third-line (12.7% [51]) hormonal therapy, estramustine (11.4% [46]) or other (2.7% [11]). The planned cycles of docetaxel therapy were completed by 30.8% of patients, and the mean (SD) number of cycles received was 4.4 (2.86). Median overall survival (mOS) was 22.4 (95% CI, 20.4–25.8) months and the prostate-specific antigen (PSA) response rate in patients with available data was 70.9% (168/237), with no differences in mOS and PSA response rates between treatment settings. Subgroup analysis revealed higher mOS in patients without visceral metastasis versus those with such metastases (22.9 vs. 17.4 months; $P = 0.022$). No new safety signals were observed and the most common adverse events associated with docetaxel were granulocytopenia (5%) and leukopenia (4.5%).

Conclusion: Data from this study showed that around three-quarters of Chinese patients with mCRPC treated with docetaxel initiated treatment following first- or second-line hormonal therapy and no new safety signals were observed.

KEYWORDS

castration-resistant prostate cancer, docetaxel, observational

1 | INTRODUCTION

In China, the incidence of prostate cancer has increased over the past 40 years, with current estimates citing 47 000 new cases annually, and is currently the seventh most frequently diagnosed cancer for men.[1–4] Furthermore, data collected in major cities including Beijing, Shanghai and Guangzhou suggest that around 68% of Chinese patients present with advanced prostate cancer at diagnosis.[5,6] Nearly 90% of all patients with metastatic prostate cancer initially respond to hormonal therapy; implemented surgically with bilateral orchiectomy, or medically with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists to maintain serum testosterone levels at castrate levels of <50 ng/dL.[7–9] However, most men with advanced prostate cancer eventually experience disease progression to castration-resistant prostate cancer (CRPC), in a median of 18–24 months; defined as castrate levels of serum testosterone with rising prostate-specific antigen (PSA) levels, progression of preexisting disease or appearance of new metastatic disease.[7–11] Until recently, metastatic CRPC (mCRPC) was associated with a very poor prognosis, and treatment was palliative only.

Based on the two landmark phase III trials TAX 327 and SWOG 9916 and subsequent studies the combination of docetaxel and prednisone every 3 weeks was established as a recommended first-line treatment for mCRPC.[12–17] A more recent Chinese Phase III study demonstrated that docetaxel-based treatment led to a significantly greater PSA response rate compared with mitoxantrone ($P = 0.021$), which supported the approval of docetaxel as a first-line therapy for mCPRC in China in 2010.[18] More recently, treatment options for mCRPC have expanded to include secondary hormonal therapy, abiraterone acetate, cabazitaxel, enzalutamide, radium-223 and sipuleucel-T,[7–9,16] however, of these only abiraterone is currently approved in China for the treatment of mCRPC.

In real-world clinical practice in China, the majority of patients with prostate cancer are treated in urology departments where urologists often prefer to re-use hormonal therapy rather than initiate chemotherapy; therefore, docetaxel is commonly used after second-, third- or subsequent-line hormonal therapy. In addition, the hormonal chemotherapy drug estramustine is used frequently due to the relatively late approval of docetaxel in China. However, data on the real-world use of docetaxel in mCRPC in China are scarce and since the approval of docetaxel for mCRPC in China, there has been no observational study to investigate its use in clinical practice. Such real-world data would provide valuable insights into adherence to clinical guideline recommendations as well as treatment patterns and real-world use of docetaxel, and help identify unmet clinical needs and areas for development. The present study was therefore conducted to evaluate the patterns of use, effectiveness and safety of docetaxel for treatment of mCRPC in real-life clinical practice in China.

2 | METHODS

2.1 | Study design and patients

This was a single-arm, prospective, multicenter, observational study conducted in China. The study included adult patients (≥18 years) with histologically confirmed metastatic prostate adenocarcinoma who had received ≥1 dose of docetaxel (Taxotere®, Sanofi, France) following failure of hormonal therapy (disease progression and serum testosterone <50 ng/dL). Patients with a history of hypersensitivity to docetaxel, with neuroendocrine differentiation, or those who were participating or planning to participate in other clinical trials were excluded. During the study, docetaxel was administered in accordance with the local product label (docetaxel 75 mg/m^2 every 3 weeks IV, plus prednisone 5 mg twice a day) and at the discretion of the investigator. The study protocol was approved by the institutional review boards of Fudan University Shanghai Cancer Center (No. 110699-3). All patients provided written informed consent, and the study was conducted according to the principles of the Declaration of Helsinki. Analysis and reporting was guided by recommendations based on Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[19]

2.2 | Study endpoints

The primary goal of this study was to investigate the patterns of use of docetaxel in Chinese patients with mCRPC. Other endpoints included overall survival, PSA response rate (defined as a reduction in serum PSA of at least 50% maintained on two occasions at least 3 weeks apart, with transient increases in PSA in the first 12 weeks ignored, as per Working Group guidelines[20] and only including patients who had PSA ≥20 ng/mL at Baseline in-line with the Tax 327 study[14]), investigation of baseline factors that may influence patient survival and PSA response rate, reasons for docetaxel discontinuation, patterns of treatment selection following docetaxel failure and safety endpoints.

2.3 | Data collection

Patient data were collected at the enrollment visit, an end of treatment visit (<30 days from the last dose of docetaxel), and at follow-up visits every 6 ± 2 months after the end of treatment until patient death, discontinuation, or 2 years after enrollment of the last patient. Patients were grouped according to the following expected docetaxel treatment settings: docetaxel following failure of first-line hormonal therapy (i.e., patients treated with hormonal therapy who then experienced progression to mCRPC and subsequently received docetaxel), following failure of second- and third-line hormonal therapies, following failure of estramustine therapy and "other" settings. The "other" category was defined as all patients lacking sufficient information to classify the docetaxel treatment setting.

Subgroup analyses were performed to evaluate OS and PSA response of docetaxel therapy by treatment setting, Gleason score, age, evidence of metastasis to local lymph nodes, evidence of distant

metastasis, involvement of visceral metastasis in patients with distal metastasis and ECOG score.

2.4 | Statistical methods

The primary analysis population included all patients who received a docetaxel-based regimen after enrollment. The PSA population included all patients with a PSA level ≥20 ng/mL within 1 month prior to the use of docetaxel and excluded patients with lower levels or with missing data. The safety population included patients who received at least one dose of docetaxel.

Data were summarized and presented in frequency tables with frequency and percentage provided for categorical variables and mean (SD) for continuous variables, unless specified. Docetaxel treatment compliance was calculated as the actual total dose received as a percent of the scheduled dose. Kaplan–Meier curves were used to estimate rates of overall survival, and inter-subgroup differences in patient survival were assessed using the log-rank test; patients with missing data or lost to follow up were censored. All statistical tests were two-sided, and $P < 0.05$ was considered to be statistically significant. Type I errors were not corrected in this exploratory study.

Based on an assumed range of patients in each treatment setting of 15–40%, a <25% relative error for the proportion of patients in each treatment setting and a 95% confidence level, a sample size of 400 patients was calculated to provide a 95% CI of 11.5% to 18.5% for the calculation of the proportion of patients in each treatment setting.

3 | RESULTS

3.1 | Patients

A total of 403 patients were enrolled across 32 study centers in China from August 2011 to June 2016; 387 (96.0%) patients completed the end of treatment visit, and 392 (97.3%), 291 (72.2%), 204 (50.6%) and 139 (34.5%) patients completed the first, second, third and fourth follow-up visits. A total of 60 (14.9%) patients were alive at the end of the study, 255 (63.3%) had died and 88 (21.8%) patients prematurely withdrew from the study; comprised of 83 (20.6%) who were lost to follow-up, four (1.0%) due to voluntary withdrawal, and one (0.2%) due to a Grade 3 coagulopathy. Patient baseline characteristics are summarized in Table 1.

TABLE 1 Patient demographics and baseline characteristics

Variable[a]	*N* = 403
Age, years	69.5 (8.26)
Duration of prostate cancer[b], years	2.9 (2.41)
Gleason score ≤7, *n* (%)	213 (52.9)
Gleason score >7, *n* (%)	190 (47.1)
PSA level, ng/mL	
Median (range)	61.0 (0.0–5000.0)
Clinical staging, *n* (%)	
I	7 (1.7)
II	26 (6.5)
III	42 (10.4)
IV	301 (74.7)
Unknown	27 (6.7)
ECOG score, *n* (%)	
0	144 (35.7)
1	203 (50.4)
2	48 (11.9)
3	6 (1.5)
4	2 (0.5)
Distant metastasis, *n* (%)	
Nonlocal lymph node metastases	24 (6.0)
Bone	338 (83.9)
Liver	11 (2.7)
Lung	35 (8.7)
Adrenal gland	2 (0.5)
Other	20 (5.0)
Docetaxel used at enrolment, *n* (%)	399 (99.0)
Mean cycles, number (SD)	2.0 (1.97)
Mean dose, mg (SD)	239.7 (239.40)
Mean dose, mg/m^2 (SD)	67.2 (11.57)

Abbreviations: ECOG, Eastern Co-Operative Oncology Group; PSA, prostate-specific antigen.
[a]Mean (SD) unless otherwise stated.
[b]Time from first diagnosis.

3.2 | Patterns of docetaxel use

The majority of patients initiated treatment with docetaxel after failure of first-line (42.2%) or second-line hormonal therapy (31.0%), with a minority initiating docetaxel after failure of ≥third-line hormonal therapy (12.7%) or estramustine therapy (11.4%; Figure 1A).

Among the 170 patients who initiated docetaxel after failure of first-line hormonal therapy, the majority (94.7%) had received pharmaceutical hormonal therapies, with bicalutamide (79.4%), goserelin (43.5%) and flutamide (23.5%) the most common (Figure 1B). Hormonal therapy with surgical and medical procedures was received by 33.5% of patients, including bilateral orchidectomy (note that patients may have received ≥1 hormonal therapies; Figure 1C). Almost all (99.2%) of the 125 patients who received docetaxel after failure of second-line hormonal therapy had also been treated with pharmaceutical hormonal therapies, the most common of which were bicalutamide (95.2%), flutamide (71.2%) and goserelin (28.4%). An additional 58 (46.4%) patients received hormonal therapy with surgical and medical procedures.

3.3 | Docetaxel exposure, reasons for discontinuation and concomitant medications

The median number of docetaxel cycles received following enrollment was 4.0 (range: 1–18), the mean total dose was 66.9 mg/m^2 (SD = 9.12), and the median dose by body surface area was 67.7 mg/m^2 (26.7–133.3; Table 2). The rate of treatment compliance in terms of total docetaxel dose received versus planned total dose was 94%.

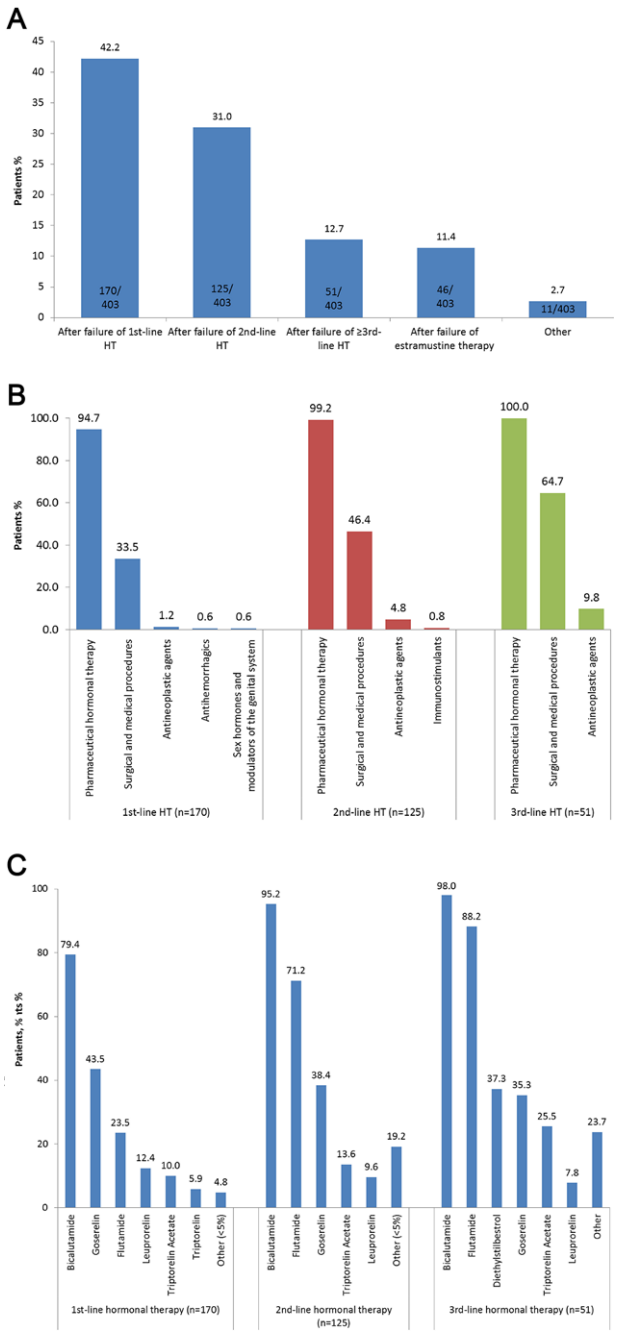

FIGURE 1 Patterns of use of docetaxel for treatment of metastatic castration-resistant prostate cancer in China (A). The most common hormonal therapies[a] (B) and pharmaceutical hormonal therapies (C) used in first-, second- and third-line treatment of Chinese patients with metastatic castration resistant prostate cancer who later receive docetaxel-based treatment. a, Patients may have received ≥1 hormonal therapy. HT, hormonal therapy [Colour figure can be viewed at wileyonlinelibrary.com]

The most common reasons for discontinuation of docetaxel treatment included "other reasons" (94 [23.3%]), followed by inability to afford medical expenses (91 [22.6%]), tumor progression (57 [14.1%]), AEs other than disease progression (20 [5%]) and death (6 [1.5%]; Table S1).

During the course of the study, a total of 108 (26.8%) patients received concomitant medications. The most frequently used class of drug was immunostimulants (41 [10.2%], mainly granulocyte colony stimulating factor [n = 33]), followed by drugs for acid-related disorders (31 [7.7%]).

TABLE 2 Docetaxel treatment during the study

Docetaxel treatment	N = 403
Mean total cycles of docetaxel (SD)	4.4 (2.86)
Median total cycles of docetaxel (range)	4.0 (1–18)
Mean cumulative docetaxel dose, mg (SD)	516.2 (343.22)
Median cumulative docetaxel dose, mg (range)	412.5 (80–1500)
Mean docetaxel dose, mg/m^2 (SD)	66.9 (9.12)
Median docetaxel dose, mg/m^2 (range)	67.7 (26.7–133.3)
Treatment compliance[a], % (SD)	94.0 (10.94)

Abbreviation: SD, standard deviation.
[a]Treatment compliance = total dose × 100/scheduled total dose.

3.4 | Docetaxel effectiveness

There were 256 patients with evaluable survival data, for whom mOS was 22.4 months (95% CI: 20.4–25.8; Table 3). No significant differences in mOS were observed between patients receiving docetaxel in the different treatment settings, with similar mOS for patients treated after failure of first-, second- and third-line hormonal therapy. The results of a subgroup analysis revealed that patients without visceral metastases had a longer mOS compared with patients with visceral metastases (22.9 months vs. 17.4 months, P = 0.019). However, no further significant differences in mOS were observed for the other subgroups investigated (Table 4).

A PSA response was achieved by 70.9% of the 237 patients with evaluable PSA data and there were no significant differences in PSA response rate between patients receiving docetaxel in the different treatment settings (Table 3). There was marked decline of the PSA response rate in the first few months of treatment from 93.2% at month 1 to 49.4% at month 15. Subgroup analysis revealed that patients positive for lymph node metastasis achieved a significantly higher PSA response rate with docetaxel treatment compared with those without lymph node metastasis (80.7% vs. 68.1%, P = 0.041). No differences in PSA response rate were observed for the other subgroups investigated (Table 4).

3.5 | Treatment patterns following docetaxel treatment failure

There were 31 (7.7%) patients who received at least one dose of anticancer therapy after docetaxel treatment failure, with hormonal therapies (n = 14), antineoplastic agents (n = 11) and drugs for treatment of bone disease being the most common. Following docetaxel failure, the most frequently used hormonal therapies were prednisone (n = 3) and triptorelin (n = 3) and the most common antineoplastic agent was docetaxel (n = 5).

3.6 | Safety

Overall, 156 (38.7%) patients reported a total of 274 AEs and 80 (19.9%) patients prematurely discontinued the study due to AEs

TABLE 3 Docetaxel treatment effectiveness by treatment setting

Pattern of use of docetaxel in Chinese patients with mCRPC	Median overall survival, months (95% CI), $n^a = 256$	PSA response rate, % (n/n^b)
All patients	22.4 (20.4, 25.8)	70.9 (168/237)
By line of therapy		
After failure of first-line hormonal therapy	22.5 (19.2, 29.5)[c]	73.6 (64/87)
After failure of second-line hormonal therapy	23.3 (18.1, 26.5)[c]	67.1 (55/82)
After failure of ≥third-line hormonal therapy	22.4 (19.0, 36.5)	65.4 (17/26)
After failure of estramustine therapy	20.2 (16.6, 27.7)	69.7 (23/33)
Other	28.6 (17.5, not evaluable)	100.0 (9/9)
Intergroup *P*-value[d]	0.781	0.490

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.
[a]Patients with available survival data.
[b]Denominator is the number of patients in each category who had PSA ≥20 ng/mL at baseline.
[c]$P = 0.781$ for the difference in median overall survival with initiation of docetaxel following failure of first- and second-line hormonal therapy.
[d]Chi-squared test.

TABLE 4 Subgroup analysis of docetaxel treatment effectiveness

Subgroup	Median OS, months (95% CI)	*P*-value[a]	PSA response rate, % (n/n^b)	*P*-value[a]
Gleason score				
≤7	24.8 (20.6, 27.7)	0.328	69.9 (86/123)	0.733
>7	20.8 (18.3, 25.1)		71.9 (82/114)	
Age, years				
<70	23.3 (20.6, 29.4)	0.057	73.3 (96/131)	0.367
≥70	21.5 (18.4, 25.9)		67.9 (72/106)	
Lymph node metastasis				
Positive	22.2 (19.0, 27.4)	0.885	80.7 (67/83)	0.041
Negative	22.4 (19.2, 27.7)		68.1 (47/69)	
Unknown	22.9 (19.8, 27.8)		63.5 (54/85)	
Distant metastasis				
Positive	22.3 (19.9, 25.1)	0.182	71.5 (148/207)	0.484
Negative	27.7 (16.6, NE)		57.1 (8/14)	
Unknown	24.9 (13.2, 31.0)		75.0 (12/16)	
Visceral metastasis				
Positive	17.4 (11.6, 25.9)	0.022	70.0 (21/30)	0.844
Negative	22.9 (20.4, 26.5)		71.8 (127/177)	
ECOG score				
≤1	22.4 (20.2, 25.8)	0.927	70.0 (142/203)	0.439
>1	22.4 (17.0, 31.8)		76.5 (26/34)	

Abbreviation: ECOG, Eastern Co-operative Oncology Group.
[a]Inter-subgroup differences were presented by using log-rank test.
[b]Denominator is the number of patients in each category who had PSA ≥20 ng/mL at Baseline.

(Table S2). Treatment-related AEs were reported by 20.8% of patients, the majority of which were Grade 1 (24 [28.6%]) or Grade 2 (32 [38.1%]). The most frequently reported treatment-related AEs were leukopenia (22 [5.5%]) and a decreased white blood cell count (18 [4.5%]). Treatment-related serious AEs (Grade >3) were reported in 24 (6.0%) patients. The most common SAEs were leukopenia (8 [2.0%]) and lung infection (4 [0.9%]). Overall, nine (2.2%) patients died due to SAEs, including six patients who died due to treatment-related SAEs: respiratory failure, lung infection, acute hepatic failure, multiorgan failure, cardiac failure.

4 | DISCUSSION

Prostate cancer has emerged as a major health problem worldwide, particularly in China where its incidence is increasing and is associated with more advanced disease, poorer prognosis and shorter survival compared with patients in Western countries.[1,2,4] Although docetaxel is recommended as a first-line therapy for the treatment mCRPC in international and Chinese guidelines,[15–17] this observational study addresses a critical gap in the understanding of the real-world clinical use of docetaxel for mCRPC in China, revealing that the

majority of patients receive first-line (42.2%) or second-line (31.0%) treatment with hormonal therapy before initiating docetaxel. Furthermore, a significant minority of patients received docetaxel-based treatment after failure of ≥third-line hormonal therapy or following estramustine. Of the patients with available data, docetaxel was effective in a real-world setting, providing a mOS of 22.4 months and a PSA response rate of 70.9%.

The results of this study confirm the effectiveness of docetaxel in Chinese patients with mCRPC; the mOS of 22.4 months is consistent with the 21.9 months reported for the docetaxel arm in the recent Chinese registration study[18] and is longer than results from the pivotal TAX327 and SWOG 9916 phase III studies (19.2 and 17.5 months, respectively).[12,13] In addition, the PSA response rate of 70.9% was twice as high as reported in the Chinese registration study (35.1%)[18] and noticeably higher than the 25.7–50% response rates reported for patients in the docetaxel arms of other phase II and III trials, although it should be noted that the PSA response rate in this study was calculated only for patients with available PSA data.[13,14,21,22] In contrast, a similar PSA response rate of 69.5% was previously reported in the CALGB 90401 study, with the addition of bevacizumab to docetaxel and prednisone.[23] However, it should be noted that the median PSA level at Baseline was comparatively lower in this study than in these previous studies in Chinese and Caucasian patients (61.0 ng/mL vs. 70.9–168 ng/mL), which may explain the relatively higher rate of patients who attained a ≥50% reduction in serum PSA in this study.[13,14,18,21]

Subgroup analyses revealed that mOS and PSA response rate were not associated with docetaxel treatment setting, Gleason score, age group, ECOG score or evidence of distant metastasis. The mOS and PSA responses observed in this study and key phase III trials suggest that docetaxel-based treatment is beneficial in patients with mCRPC who have received up to and beyond three previous lines of hormonal therapy.[15–17] This is important as most international and local guidelines recommend continuing hormonal therapy as one of the first-line treatment options and, more recently, second-line hormonal therapies have shown effectiveness for mCRPC.[7–9] These results have clinical implications in China where primary treatment is typically hormonal therapy initiated by urologists.

Although treatment compliance was high at 94.0%, the overall docetaxel exposure (4.4 (2.86) cycles of docetaxel at a mean dose of 66.9 mg/m^2) was below the recommended dosage of docetaxel 75 mg/m^2 every 3 weeks for up to 10 cycles.[15–17] The number of treatment cycles received was also lower than reported in previous phase III studies (median 8–9.5).[14,18,23] The main reasons reported for early treatment discontinuation in this study were "inability to afford medical expenses" (22.6%) followed by disease progression (14.1%). These results reflect the real-world challenges faced by patient and clinicians when making treatment decisions, particularly in developing countries like China.

This study has several limitations which deserve mention. First, the observational design of the study is associated with potential biases from the process of patient recruitment and data collection, particularly because survival and PSA data were not available for all patients and a number of patients were lost to follow-up. In addition, although subgroup analyses suggest that particular patient and disease characteristics may be associated with docetaxel treatment outcomes, causal inferences cannot be reliably drawn. Finally, the study also did not assess the influence of the neutrophil-to-lymphocyte ratio on survival, which has been regarded as an important prognostic factor in patients with mCRPC.[24,25]

This study provides important information on the patterns of docetaxel use in patients with mCRPC in real-world clinical practice in China, and provides evidence of its safety and effectiveness in this setting. However, it must be noted that the treatment landscape for mCRPC has evolved rapidly over the past 5 years and first-line treatment options are no longer limited to docetaxel-based chemotherapy.[8,9] New AR-targeted agents, such as abiraterone and enzalutamide, have demonstrated clinical benefit in chemotherapy refractory mCRPC patients.[26,27] Other new therapies, including cabazitaxel, radium-223, and sipuleuce-T, have also been approved by regulatory authorities,[7–9,16] although only abiraterone is currently approved in China (it should also be noted that abiraterone was only approved in China in 2015 and entered clinical use in 2016). Treatment decisions for patients with mCRPC are therefore often based on multiple factors, including patient health status, tumor status, tolerability, and responses to individual treatment, and health economic factors. The data generated in this study provide valuable real-world insights which can inform clinician decision-making regarding the clinical application of docetaxel and associated outcomes in Chinese patients with mCRPC.

ACKNOWLEDGEMENTS

Writing support for this manuscript was paid for by Sanofi and provided by Jake Burrell PhD (Rude Health China). This study was funded by Sanofi (China).

CONFLICTS OF INTEREST

All contributing authors claimed they did not have any conflicts of interest.

DATA AND PROTOCOL ACCESS

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies and process for requesting access can be found at: https://www.clinicalstudydatarequest.com/.'

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: He D, Sun Z, Guo J, et al. A multicenter observational study of the real-world use of docetaxel for metastatic castration-resistant prostate cancer in China. *Asia-Pac J Clin Oncol*. 2019;15:144–150. https://doi.org/10.1111/ajco.13142