original reports

Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy: Treatment Patterns From the PROXIMA Prospective Registry

abstract

Purpose There is a major clinical need to devise an optimal treatment sequence for the multiple therapy options available for patients with metastatic castration-resistant prostate cancer (mCRPC). In the absence of prospective clinical trials, sequencing information can be derived from large, real-world registry studies.

Patients and Methods PROXIMA (Treatment Patterns in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) is a large, global, prospective registry study evaluating real-world treatment patterns of patients with mCRPC who experience disease progression during or after docetaxel therapy. Patients were enrolled worldwide between 2011 and 2014. Treatments were determined by the treating physicians and recorded in categories of chemotherapy, hormonal therapy, targeted therapy, immunotherapy, and palliative therapy. Treatment sequencing patterns, response to treatment, and types of progression were recorded and analyzed. Progression-free survival and overall survival with different treatment modalities were analyzed using Kaplan–Meier method.

Results Treatment patterns were evaluated in 903 patients. Therapy selection was influenced by region. Hormonal therapy (57.5%) and taxane chemotherapy (26.4%) were the most frequently administered first subsequent treatments after docetaxel. Tumor responses to first subsequent treatment were observed in 22.6% of evaluable patients. Overall survival and progression-free survival did not differ significantly across different treatment modalities.

Conclusion Identifying an optimal treatment sequence is vital for improving the care of patients with mCRPC. The PROXIMA registry provided a representative sample of global data on real-world treatment patterns for patients with mCRPC previously treated with docetaxel. These data can be used to devise optimal therapy sequences and inform treatment decisions.

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INTRODUCTION

Prostate cancer is the most frequently diagnosed male malignancy and the fifth leading cause of cancer-related death in men worldwide.[1] Prostate cancer incidence varies > 25-fold worldwide; rates are highest in Australia and New Zealand, North America, and in western and northern Europe, but remain low in Asian populations. There is less variation in mortality rates worldwide, with the number of deaths from prostate cancer higher in less-developed regions.[1]

For most patients, early diagnosis is associated with good prognosis. Surgical or chemical castration is the standard treatment and up to 85% of patients respond initially. An estimated 10% to 50% of cases progress to metastatic castration-resistant prostate cancer (mCRPC) within 3 years of diagnosis. This aggressive form of the disease remains lethal despite recent therapeutic advances.[2,3]

Docetaxel was the first chemotherapy to demonstrate a survival benefit for men with mCRPC. Phase III studies published in 2004 showed

that docetaxel was superior to mitoxantrone in terms of overall survival (OS).[4,5] The results of the pivotal study, TAX 327 (Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer), led to the approval of docetaxel.[4,6] The first agent to demonstrate a survival benefit in the post-docetaxel setting was cabazitaxel, a second-generation taxane designed to overcome docetaxel resistance, which was approved as a second-line treatment of mCRPC in 2010.[6,7] Other agents currently available for post-docetaxel mCRPC include abiraterone acetate, enzalutamide, and radium-223.[6,8-10]

Currently, there is no standard sequence for these treatment options and treatment choices vary on the basis of patient and physician preference as well as patient characteristics. For example, treatment choices in Asia differ from those in the West because of various factors, including genetic background, living conditions, diet, and health care environments. In developed countries, medical castration is the commonly used option for androgen-deprivation therapy (ADT), whereas surgical castration is the favored option in developing countries.[11] Several retrospective studies provide little guidance on the optimal sequencing of agents.[12] Two ongoing studies (ClinicalTrials.gov identifiers: NCT02125357 and NCT02485691) are assessing treatment sequencing in mCRPC, with completion scheduled for 2018. Meanwhile, observational patient registries report real-world clinical outcomes and are an invaluable source of information on health care services, disparities in access to treatment, quality of care, and other factors affecting treatment decisions.[13,14] A unique registry study focusing on the use of primary ADT for the treatment of prostate cancer in Japan and the United States has been published.[15] However, there is a lack of large-scale registry data focusing on mCRPC and its clinical management.

PROXIMA (Treatment Patterns in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) is an international, multicenter, noninterventional, prospective registry study with patient participation of up to 24 months. The registry was designed to mirror real-life treatment patterns of patients with mCRPC who had disease progression during or after docetaxel-based chemotherapy. Treatment was determined by the treating physicians.

The primary objective of the study was to describe treatment patterns. Secondary objectives included comparison of treatment approaches across regions; evaluation of tumor response; disease progression during or after docetaxel treatment, subsequent treatments, and sequence of treatments; and assessment of progression-free survival (PFS) and OS with different treatment modalities.

PATIENTS AND METHODS

Study Design

PROXIMA is a prospective, observational study designed to examine real-world treatment patterns of patients with mCRPC whose disease progressed during or after a docetaxel-based regimen. Patients were enrolled in Asia (Hong Kong, Japan, South Korea, Thailand), Europe (Greece, Italy, Poland, Portugal, Slovenia, United Kingdom, Ireland), Latin America (Argentina, Brazil, Columbia, Venezuela), and other countries (Algeria, Iran, Pakistan, Saudi Arabia, Turkey, United Arab Emirates). To ensure the sample was representative, investigational sites were randomly selected in each country. The proposed sample size (10 to 300 patients [range of patients] proposed for the sample size across participating countries) depended on country-specific characteristics and site feasibility. Participating sites were asked to propose study participation to all consecutive eligible patients. Site data were collected using a questionnaire describing the potential implementation of a multidisciplinary team approach. Patient data were collected at baseline, 6 months (interim), and 12 to 15 months (end of study). Additional survival status was collected at 24 months.

The study evaluated the management of mCRPC (planned treatment and treatment actually received), tumor response (based on tumor imaging), prostate-specific antigen (PSA) response (a PSA decline of ≥ 50% from the PSA at progression), pain improvement, clinical symptoms other than pain improvement, types of disease progression (including PSA progression [a PSA increase of > 25% (≥ 2 ng/mL)], clinical progression, pain, other symptoms, new disease found by tumor assessment, and bone, visceral/other, or regional lymph node metastases) during or

after docetaxel-based treatment and subsequent lines of treatment, PFS at 12 months, and OS at 24 months, with different treatment modalities. PFS was a composite end point, comprising PSA, radiologically documented progression, and clinical progression.

Study Patients

Eligible patients had metastatic adenocarcinoma of the prostate that progressed during or after a docetaxel-based regimen received in the castration-resistant setting, were aged ≥ 18 years, and had provided written consent. Patients were excluded if they had started a new treatment line for mCRPC before the study, or if they were participating in a blinded clinical study.

Data collected at baseline included patient and disease characteristics, history of prostate cancer, details of and response to previous docetaxel-based chemotherapy, type of disease progression, and planned treatment. Data collected at interim and end-of-study visits included patient's health status, type of treatment received, relevant subsequent treatments, type of response or disease progression, and reasons for discontinuation. Patient's status (ie, alive, dead [of prostate cancer progression or other reasons], lost to follow-up) was recorded at each visit and at the 24-month survival status time point. A flow diagram showing the progress of patients through the PROXIMA registry is shown in Figure 1.

Study Treatment

Treatment was determined by the treating physicians and recorded in the following categories: chemotherapy (eg, taxane, anthracycline, anthracenedione, vinca alkaloid, nitrogen mustard/estrogen, topoisomerase 2 inhibitors, platinum salts, other), hormonal manipulations in addition to castration (ie, estrogen, glucocorticoids, antiandrogen [receptor blockage], antiandrogen [multiple actions], cytochrome P450 17A1 [CYP-17] inhibitor), targeted therapy, immunotherapy, monoclonal antibody, corticosteroids alone, palliative surgery (ie, spinal cord decompression, trans-urethral resection of the prostate, orthopedic surgery, urinary diversion, double-J stent insertion), palliative radiotherapy, radioisotopes, analgesics (ie, nonopioid, mild opioid, or strong opioid), bisphosphonates, or best supportive care.

Statistical Considerations

All statistical analyses were performed at the 5% significance level using two-sided tests or two-sided 95% CIs. Count of nonmissing data, means and standard deviations, median and range, and 95% CI of the mean were collected for quantitative variables. For categorical data, count and frequencies with 95% CI were collected.

For the time-to-event data, Kaplan-Meier estimates were calculated; 95% CIs were provided for median PFS and median OS. PFS and OS were calculated from the date when the informed consent form was signed to the date of progression or death, respectively. Patients lost to follow-up were censored at the time of last contact. Patients whose disease had not progressed at the time of the final analysis were censored at the cutoff. Associations between PFS and OS and demographic and clinical variables were assessed using univariate Cox proportional hazards model. Associations between event rates and demographic and clinical variables were assessed using a logistic regression model at the 5% significance level. Cox proportional hazards model and logistic regression were repeated in multivariate stepwise analyses, with variables having an entry threshold of 0.25 and a selection threshold of 0.1. Variables included age, weight loss, Charlson comorbidity index (CCI), PSA value at inclusion, ADT duration, first treatment strategy, timing from progression to inclusion, Eastern Cooperative Oncology Group performance status at inclusion, presence of visceral metastases at inclusion, and presence of bone metastases at inclusion.

RESULTS

Study Patients

Registry data were collected from November 10, 2011, to July 14, 2015. Treatment patterns were evaluated in 903 patients in Asia (n = 177), Europe (n = 444), Latin America (n = 126), and in other countries (n = 156). Median age was 71.0 years; median CCI at study inclusion was 4.0 (Table 1). At diagnosis, most patients had distant metastases in tumor, node, and metastases staging (67.8%) and were considered at high risk according to D'Amico staging (60.6%); Gleason score was 8 to 10 for 57.0% of patients. Median PSA level was 63 ng/mL at initial diagnosis and 100 ng/mL at inclusion; 80.1% of patients had PSA level ≥ 20 ng/mL at inclusion.

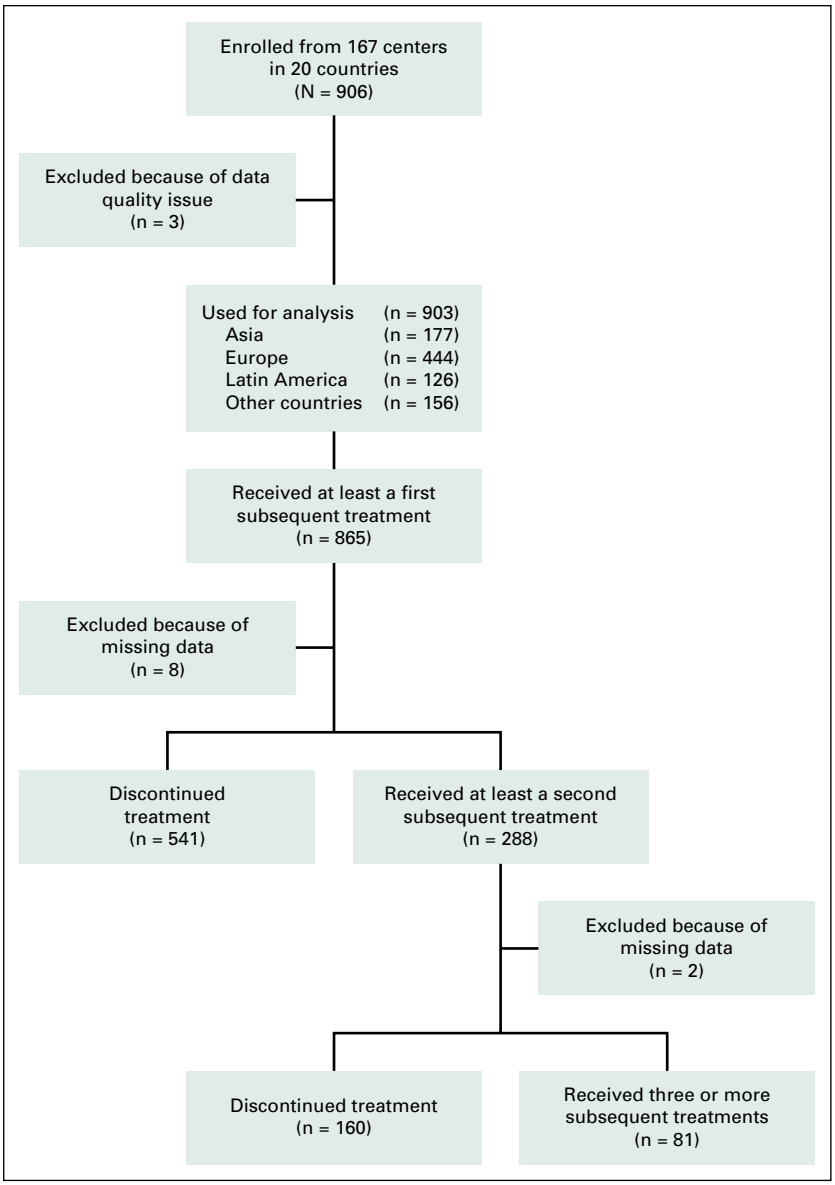

Fig 1. Patient flow diagram showing the progress of patients through the PROXIMA (Treatment Patterns in Patients With Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Regimen) registry.

There were no apparent differences in baseline disease characteristics across regions.

Duration of prior ADT was ≥ 24 months for 56.1% of patients, and ≥ 6 to < 24 months for 36.1% of patients. Duration of prior ADT was similar among regions, with 42.5% to 61.6% of patients receiving ≥ 24 months of ADT. Use of surgical castration only was more common in Asia than any other region (23.2% *v* 3.2% to 8.7%) but was highly variable among Asian countries. The last line of docetaxel was administered for a median of seven cycles (data not shown).

First Subsequent Treatment

Most patients (96.8%) received at least one subsequent treatment after inclusion. Hormonal therapy and chemotherapy were the most frequent first subsequent treatments (Fig 2A). Chemotherapy was the first subsequent treatment of 38.3% of patients; the most frequent were taxanes (26.4% of all patients). Hormonal therapy was the first subsequent treatment of 57.5% of patients; the most frequent were CYP-17 inhibitors (27.4% of all patients), multiple-action antiandrogen agents (14.6%), glucocorticoids (13.7%), and receptor blockage antiandrogen agents (11.8%). Immunotherapy was the first subsequent treatment of 0.9% of patients. Treatment decisions were not heavily influenced by physician specialty, duration of prior ADT, or CCI at inclusion (Fig 2B). Regional influences were detected: Chemotherapy was more frequently prescribed in Latin America and

in other countries (56.8% and 52.3%, respectively, *v* 27.1% in Europe), whereas a combination of chemotherapy and hormonal therapy was less frequently prescribed in Europe (6.6% *v* 20.0% to 20.9%). Targeted therapy was more frequently prescribed in Europe (10.7% *v* 0.6% to 1.7%; data not shown).

Second and Third Subsequent Treatments

Second subsequent treatments were reported for 288 of 903 patients. Most frequent second subsequent treatments were chemotherapy (44.8%, with 28.8% receiving only chemotherapy), hormonal therapies (44.4%, with 18.8%

Table 1. Patient and Disease Characteristics in the PROXIMA Study

Characteristic	Asia (n = 177)	Europe (n = 444)	Latin America (n = 126)	Other Countries (n = 156)	Total (N = 903)
Median age, years	71	71	71	68	71
< 70	71 (40.1)	183 (41.2)	55 (43.7)	84 (53.8)	393 (43.5)
≥ 70	106 (59.9)	261 (58.8)	71 (56.3)	72 (46.2)	510 (56.5)
Median time from initial diagnosis to inclusion, months	46	64	54	46	55
Median PSA value, ng/mL	159.8	85.6	121	99	100
Site of metastases					
Bone	156 (90.7)	390 (88.4)	119 (94.4)	146 (93.6)	811 (90.6)
Visceral, other soft tissue	19 (11.0)	97 (22.0)	21 (16.7)	37 (23.7)	174 (19.4)
Regional lymph nodes	44 (25.6)	166 (37.6)	24 (19.0)	38 (24.4)	272 (30.4)
ECOG PS ≤ 2 at inclusion	169 (95.5)	425 (95.7)	121 (96.0)	138 (88.5)	853 (94.5)
Charlson comorbidity index					
0	0	0	0	0	0
1–2	18 (10.2)	25 (5.7)	11 (8.8)	17 (10.9)	71 (7.9)
3–4	116 (65.5)	263 (59.5)	91 (72.8)	106 (67.9)	576 (64.0)
> 4	43 (24.3)	154 (34.8)	23 (18.4)	33 (21.2)	253 (28.1)
Symptoms at inclusion*	92 (52.0)	280 (63.1)	102 (81.0)	118 (75.6)	592 (65.6)
Analgesic use at inclusion	72 (40.7)	224 (51.0)	92 (73.0)	114 (73.0)	502 (55.9)
Treatment at diagnosis					
Prostactectomy	26 (14.9)	138 (32.3)	38 (30.9)	26 (16.7)	228 (25.9)
Chemotherapy	42 (24.0)	51 (11.9)	18 (14.6)	16 (10.3)	127 (14.4)
Radiation therapy	17 (9.7)	128 (30.0)	38 (30.9)	30 (19.2)	213 (24.2)
Brachytherapy	3 (1.7)	8 (1.9)	1 (0.8)	0	12 (1.4)
Type of prior castration†					
Chemical only	95 (53.7)	387 (87.4)	88 (69.8)	124 (79.5)	694 (76.9)
Surgical only	41 (23.2)	14 (3.2)	11 (8.7)	11 (7.1)	77 (8.5)
Chemical and surgical	41 (23.2)	42 (9.5)	27 (21.4)	21 (13.5)	131 (14.5)
Prior ADT duration, months					
< 6	15 (8.8)	30 (6.9)	10 (8.0)	14 (9.2)	69 (7.8)
≥ 6 and < 24	65 (38.0)	136 (31.5)	43 (34.4)	74 (48.4)	318 (36.1)
≥ 24	91 (53.2)	266 (61.6)	72 (57.6)	65 (42.5)	494 (56.1)
Chemotherapy lines, median No.‡	1.0	1.0§	1.0	1.0	1.0
Total chemotherapy lines in classes‡					
1	112 (63.3)	317 (71.6)	82 (65.1)	111 (71.2)	622 (69.0)
2	40 (22.6)	82 (18.5)	24 (19.0)	27 (17.3)	173 (19.2)
≥ 3	25 (14.1)	44 (9.9)	20 (15.9)	18 (11.5)	107 (11.9)

(Continued on following page)

Table 1. Patient and Disease Characteristics in the PROXIMA Study (Continued)

Characteristic	Asia (n = 177)	Europe (n = 444)	Latin America (n = 126)	Other Countries (n = 156)	Total (N = 903)
Response to previous docetaxel chemotherapy					
Complete	3 (2.2)	9 (2.5)	3 (2.8)	9 (6.8)	24 (3.3)
Partial	27 (19.4)	75 (21.1)	30 (27.8)	36 (27.1)	168 (22.8)
Stable disease	28 (20.1)	115 (32.3)	17 (15.7)	27 (20.3)	187 (25.4)
Progressive disease	81 (58.3)	157 (44.1)	58 (53.7)	61 (45.9)	357 (48.5)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: ADT, androgen-deprivation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PROXIMA, Registry of Treatment Patterns in Patients With Metastatic Castration-Resistant Prostate Cancer With Progression During or After Docetaxel-Based Regimen; PSA, prostate-specific antigen.

*Presence of symptoms (eg, cancer pain, fatigue, lymphedema) was assessed at inclusion.

†Percentages are calculated on the total of each column minus number of missing data.

‡Received for mCRPC before inclusion.

§One patient was not included from Europe.

receiving only hormonal therapy), palliative radiotherapy (8.7%), targeted therapies (6.3%, with 4.5% receiving only targeted therapy) and corticosteroids (6.3%). Immunotherapy was the second subsequent treatment of 0.7% of patients. For second subsequent chemotherapy and hormonal therapies, the most frequent were taxanes (27.1% of all patients with a second subsequent treatment), CYP-17 inhibitors (15.3%), multiple-action antiandrogen agents (14.9%), glucocorticoids (12.5%), and receptor blockage antiandrogen agents (10.4%; data not shown).

Third subsequent treatments were reported for 81 of 903 patients; most frequent were hormonal therapies (50.6%, with 25.9% receiving only hormonal therapies), chemotherapy (32.1%, with 21.0% receiving only chemotherapy), palliative radiotherapy (18.5%), and targeted therapies (7.4%, with 4.9% receiving only targeted therapy). The most frequent were taxanes (17.3% of all patients with a third subsequent treatment), receptor blockage antiandrogen agents (17.3%), multiple-action antiandrogen agents (17.3%), CYP-17 inhibitors (11.1%), glucocorticoids (9.9%), and estrogen (8.6%; data not shown). Immunotherapy was the third subsequent treatment of 1.2% of patients.

Tumor Response

Overall, 90 of 399 evaluable patients (22.6%) had a tumor response with the first subsequent treatment (Fig 3). Ten patients had a complete response (2.5%)—patients who received hormonal therapy without chemotherapy (n = 8), patients who received hormonal therapy plus taxane (n = 1), and patients who received taxane chemotherapy without hormonal therapy (n = 1). Eighty patients had a partial response (20.1%); the majority had received hormonal therapy without chemotherapy (n = 38) or taxane chemotherapy with or without hormonal therapy (n = 37). No complete responses were reported during the second or third subsequent treatments. Partial responses were seen in 18 patients (17.8%) and five patients receiving second subsequent therapy and third subsequent therapy, respectively (data not shown). Response rates (complete plus partial responses) for patients receiving chemotherapy versus hormonal therapies without chemotherapy, and taxanes versus hormonal therapies without chemotherapy, as first subsequent treatment, did not differ significantly ($P = .9970$ and $P = .0868$, respectively).

PFS and OS During First Subsequent Treatment

PFS and OS did not differ significantly between treatment modalities. Median PFS for all patients was 7.6 months (95% CI, 6.8 to 8.3). In the taxane treatment group, 70% of patients were progression free at 6 months, compared with 58% to 65% for other treatments. Median PFS for patients who received chemotherapy versus hormonal therapies without chemotherapy as first subsequent treatment was 7.7 months (95% CI, 6.7 to 9.1) versus 8.0 months (95% CI, 6.8 to 9.4), respectively ($P = .243$). Median PFS for patients who received taxanes versus hormonal therapies without chemotherapy was 9.0 months (95% CI, 7.7 to 10.1) versus 8.0 months (95% CI, 6.8 to 9.4), respectively ($P = .672$; Fig 4). Multivariate analyses identified age, baseline

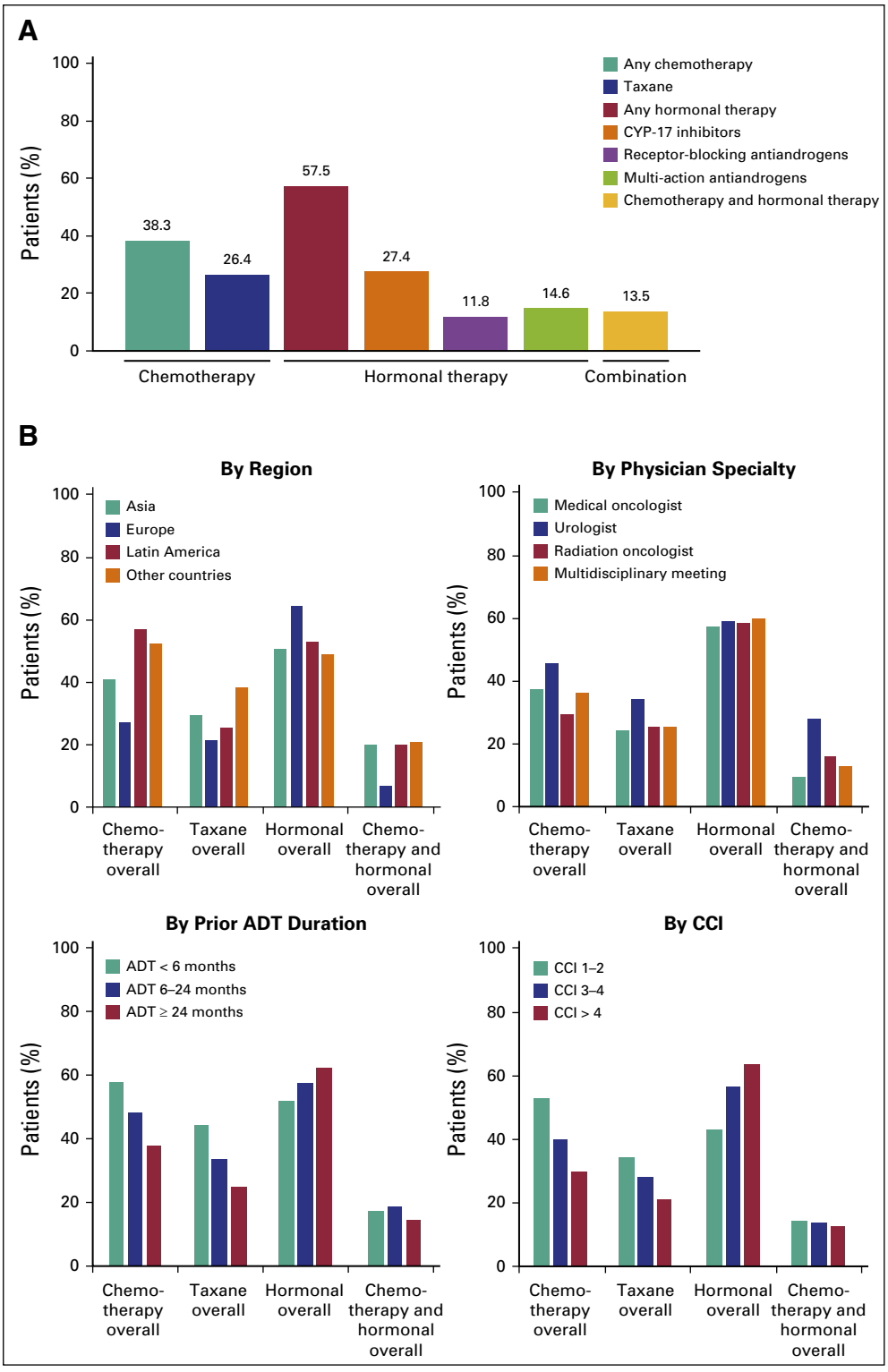

Fig 2. First subsequent treatment on study. (A) Treatment classes assignment overall, and (B) by region, physician specialty, ADT duration, and CCI. ADT, androgen-deprivation therapy; CCI, Charlson comorbidity index; CYP-17, cytochrome P450 17A1.

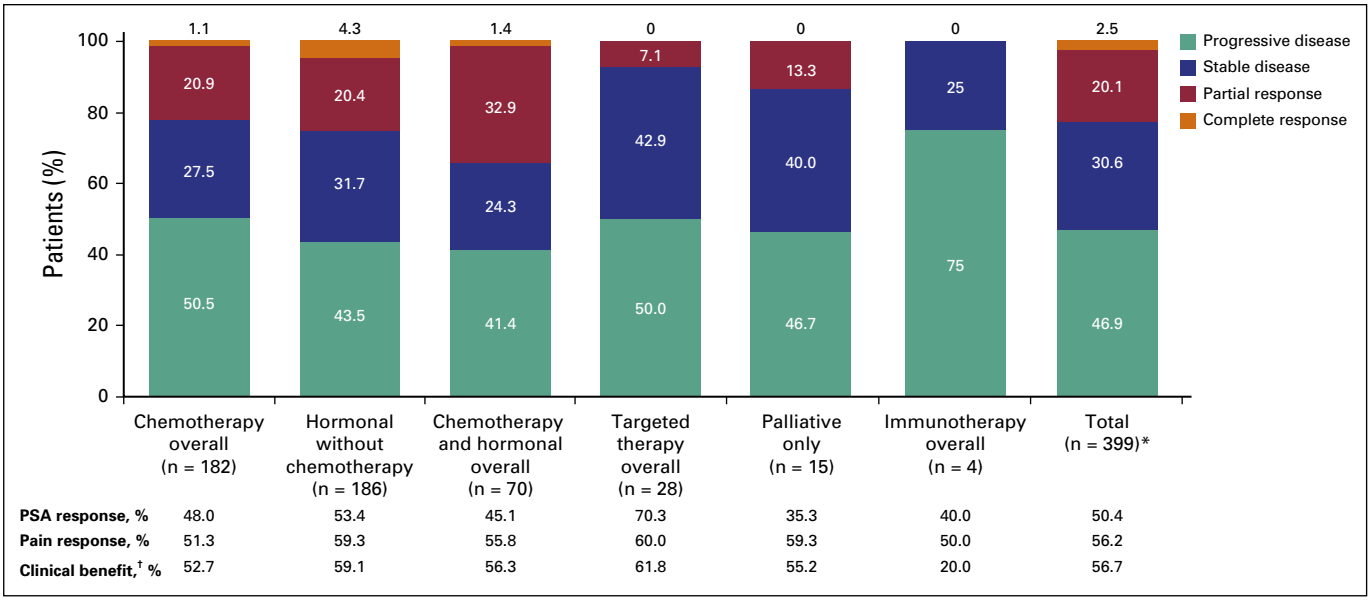

Fig 3. Tumor response by first subsequent treatment in evaluable patients. (*) Includes responses across all treatment types. (†) Improvement on the basis of cancer pain, analgesic consumption, and performance status. This benefit may not be correlated to any PSA decrease or objective response. PSA, prostate-specific antigen.

PSA level, visceral metastases, and weight loss at 6 months as significant factors affecting PFS (data not shown).

Median OS for all patients was 15.1 months (95% CI, 14.0 to 17.6). In the taxane group, 89% of patients were alive at 6 months, compared with 80% to 84% for other therapies. At 12 months, 68% of patients in the taxane group and 71% of patients in the antiandrogens (multiple actions) without taxanes group were alive, compared with 60% to 63% in other groups. The trend was similar at 18 and 24 months. Median OS for patients who received chemotherapy versus hormonal therapies without chemotherapy as first subsequent treatment was 16.3 months (95% CI, 13.9 to 18.5) versus 16.6 months (95% CI, 14.1 to 19.0), respectively (P = .655). Median OS for patients who received taxanes versus hormonal therapies without chemotherapy was 18.7 months (95% CI, 16.7 to 21.3) versus 16.6 months (95% CI, 14.1 to 19.0), respectively (P = .263; Fig 4). Multivariate analyses identified baseline PSA level, visceral metastases, weight loss at 6 months, and prior ADT duration as significant factors affecting OS at 24 months (Table 2).

DISCUSSION

Several therapies are available for patients with mCRPC; however, there is a lack of consensus regarding the optimal sequencing and duration of treatments. The mCRPC treatment paradigm is influenced by various international and national treatment guidelines and by the clinical judgement of treating physicians and experience with available therapies.[16]

The PROXIMA registry provided real-world global data on the clinical management of mCRPC in patients who experienced disease progression during or after prior docetaxel-based therapy. The registry included data from 903 patients from 20 countries primarily in Europe, Asia, and Latin America. No region-specific trends were observed in baseline patient and disease characteristics; however, there were regional differences for prior treatments received, number of subsequent treatments, and preferred treatment type. The regional differences may have various underlying causes; the higher use of chemotherapy in Latin America and other countries may have been due to the unavailability of other agents. Conversely, targeted therapy may be more widely available in Europe than in other countries. Treatment choices in the presented study were influenced by region and sometimes showed intraregional variation. The wide intraregional variation in treatment patterns observed for the Asia region in PROXIMA has been noted before; Western treatment guidelines do not reflect Asian demography of prostate cancer, but no region-specific guidelines are available.[11]

Of note, patient enrollment in the PROXIMA registry commenced in November 2011, when the treatment options for post-docetaxel mCRPC

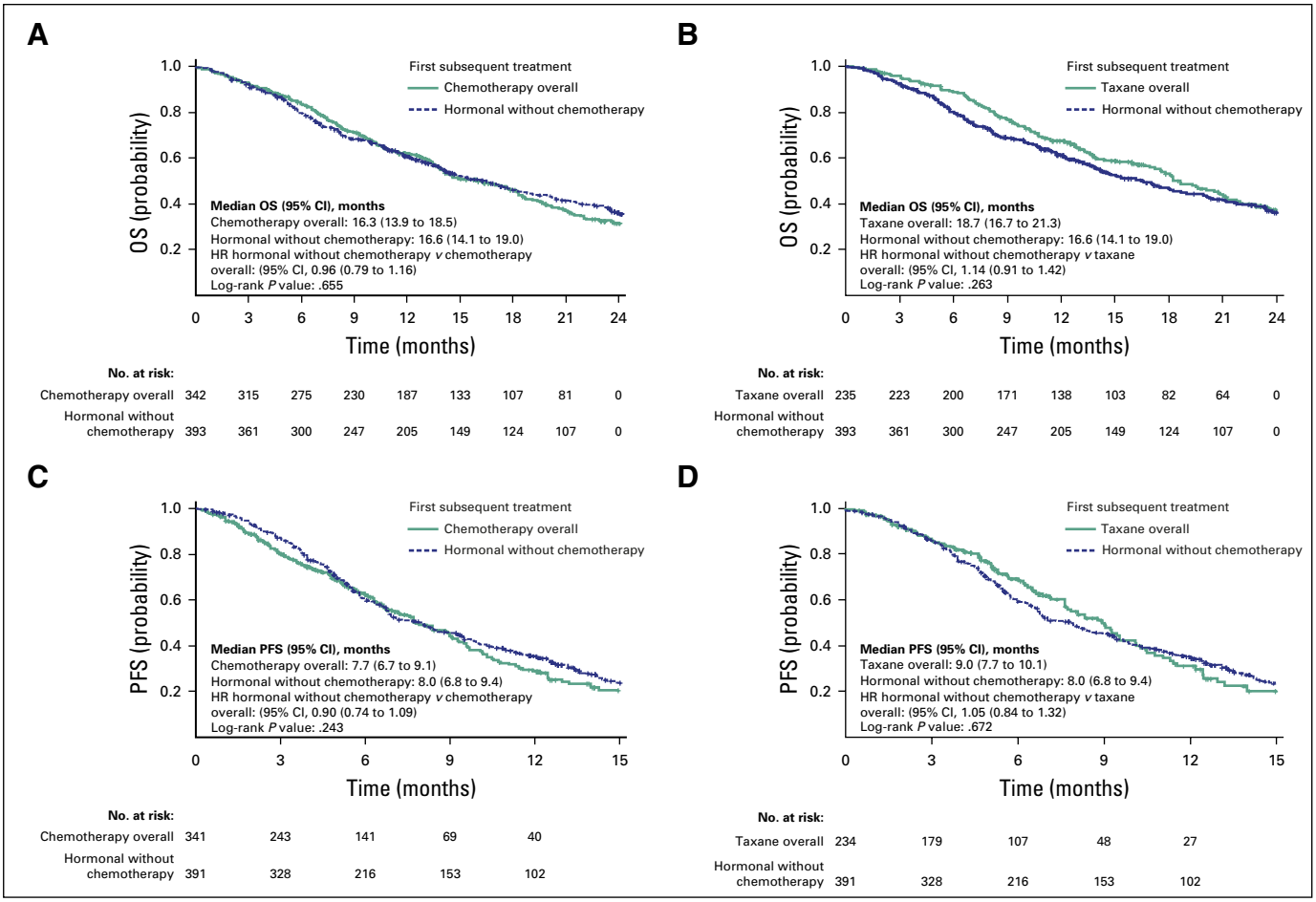

Fig 4. Overall survival (OS) and progression-free survival (PFS) by first subsequent treatment of (A, C) chemotherapy versus hormonal therapy; (B, D) taxane therapy versus hormonal therapy. ADT, androgen-deprivation therapy; HR, hazard ratio.

were limited; cabazitaxel gained US approval in June 2010, and abiraterone and enzalutamide were not approved in the United States until 2011 and 2012, respectively.[6] The regional availability of these treatments varied considerably in the first years after approval. Hormonal therapies and taxane chemotherapy (with or without concomitant hormonal therapy) were the most frequently administered treatments for patients with mCRPC whose disease progressed while receiving or after receiving a docetaxel-based regimen. Although the PROXIMA registry did not differentiate between taxanes, the majority of taxane chemotherapy was administered at a dose of 20 to 25 mg/m^2, which suggests that most taxane-treated patients received cabazitaxel,

Table 2. Multivariate Stepwise Cox model of OS

Variable	Factor	*P*	HR (95% CI)
Age, years	< 70 *v* ≥ 70	.009	1.42 (1.09 to 1.84)
Weight loss at 6 months, %, *v* weight gain	0 to 5	< .001	1.37 (0.97 to 1.93)
	5 to 10		1.96 (1.30 to 2.96)
	10 to 20		2.32 (1.50 to 3.60)
	≥ 20		2.94 (1.32 to 6.58)
PSA level at inclusion, ng/mL	< 10 *v* ≥ 20	< .001	0.40 (0.26 to 0.61)
	10 to 20 *v* ≥ 20		0.74 (0.45 to 1.22)
ADT duration, months	< 6 *v* ≥ 24	< .001	1.80 (1.12 to 2.91)
	≥ 6 and < 24 *v* ≥ 24		1.80 (1.38 to 2.35)
Visceral metastases at inclusion	Yes *v* no	< .001	2.69 (1.77 to 4.10)

NOTE. Included population received a first subsequent treatment.
Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen.

and not docetaxel (usually administered as a 75 mg/m^2 dose).[17,18]

Tumor responses to first subsequent treatment were recorded in 22.6% of patients. The highest response rate was observed in patients who received a combination of chemotherapy and hormonal therapy. Although comparable to the response rate recorded for the prior docetaxel therapy, this response rate warrants further evaluation of the different therapy sequences in mCRPC.

In this study, PFS and OS were similar for chemotherapy or taxane chemotherapy compared with other treatment strategies. Baseline PSA level, visceral metastases, weight loss at 6 months, and prior ADT duration were associated with OS in multivariate analyses.

Recent studies reporting the use of docetaxel in metastatic hormone-sensitive prostate cancer have led to a change in clinical practice, with docetaxel being administered with ADT earlier.[12,19,20] This paradigm change may lead to a refinement in the sequencing of docetaxel. However, this change may potentially result in more patients' cancer becoming resistant to docetaxel at the time of progression to mCRPC. The data from the PROXIMA registry indicate that different treatment modalities do not differ significantly in terms of OS. These results should contribute to the shifting prostate cancer treatment landscape, particularly when the use of taxanes is discussed in the context of metastatic hormone-sensitive prostate cancer versus mCRPC.

This study has several limitations. In the absence of a breakdown of subsequent treatments received within each of the different treatment groups, the specific treatment received is unknown. For example, it is difficult to ascertain if the patients who received taxane received cabazitaxel or were rechallenged with docetaxel; we can only assume from the dosing information that most patients received cabazitaxel (most received 20 to 25 mg/m^2, the recommended dose[s] of cabazitaxel). Furthermore, in certain countries, the more expensive treatments may not have been readily accessible. Other common limitations of registry studies include suboptimal data availability, presence of potential confounding, and under-reporting of outcomes for patients who left the registry or did not receive adequate follow-up. As in any comparative registry study of patient outcomes across different regions, there may have been a patient sampling bias. Only selected patients who received standard treatment and had regular follow-up may have been included, and thus the sample may not be fully representative of all patients in the region.

The mCRPC treatment landscape has changed since the start of patient enrollment in the PROXIMA registry, and soon other therapeutic options are likely to become available for mCRPC. This underlines the urgent need for devising an optimal treatment sequence for the currently available treatment options. More prospective clinical studies assessing different treatment sequences are urgently needed. Meanwhile, the PROXIMA registry data reflect a large sample of international, real-world treatment settings and, therefore, may be used to inform the current and future treatment landscape.

DOI: https://doi.org/10.1200/JGO.18.00009
Published online on jgo.org on September 27, 2018.

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: Takeda (Inst), Novartis (Inst), Astellas Pharma (Inst)

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ACKNOWLEDGMENT

We thank the participating patients, investigators, research nurses, and data managers involved in the study. Editorial support was provided by Olga Ucar of MediTech Media, funded by Sanofi.

This study was sponsored by Sanofi.

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Prior Presentation

Presented at European Society for Medical Oncology 2014 (poster 792P), Madrid, Spain, September 26-30, 2014; and at European Cancer Congress 2015 (poster P040), Vienna, Austria, September 25-29, 2015.

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