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The effectiveness and safety of cabazitaxel (CBZ) in patients with metastatic castration-resistant prostate cancer (mCRPC) in routine clinical practice: Results of a prospective observational study (CAPRISTANA)

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Background

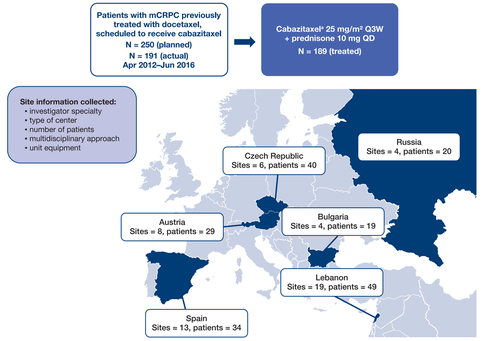
- Cabazitaxel (CBZ) is an approved treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) who have been previously treated with docetaxel (DOC).[1]
- CBZ was approved following the Phase III TROPIC study, where 25 mg/m^2 CBZ improved overall survival (OS) by 2.4 months versus mitoxantrone ($p < 0.0001$).[2]
- The Phase III PROSELICA study demonstrated the non-inferiority of 20 mg/m^2 versus 25 mg/mm^2 CBZ for OS.
- Real-world observational studies can validate effectiveness and safety results from large Phase III trials and identify unmet medical needs to improve patient care.
- CAPRISTANA was an international, multicenter, observational, prospective cohort, registry study examining the use of CBZ in routine clinical practice for the treatment of patients with mCRPC.

Methods

Study population and study design

- The observational study included patients with mCRPC treated with CBZ under routine conditions of use (25 mg/m^2 every 3 weeks plus oral prednisone or prednisolone 10 mg daily; **Figure 1**).

Figure 1. *Study design and international recruitment*



[a] Some patients also received a starting dose of 20 mg/m^2.
mCRPC, metastatic castration-resistant prostate cancer; Q3W, every 3 weeks; QD, once a day.

- Key inclusion criteria included:
  - patients with mCRPC, previously treated with DOC,
  - scheduled to receive at least one infusion of CBZ,
  - ≥ 18 years of age.
- Data were recorded using electronic case report forms at inclusion, every 3 months (± 15 days) throughout the observation period, and at the end of the study.
- Patients were followed until death or up to 1.5 years after initiation of CBZ treatment (whichever came first).

Outcomes

- Primary endpoint: to obtain routine clinical practice data on CBZ usage patterns for patients with mCRPC previously treated with DOC.
- Secondary endpoints included:
  - response rate,
  - progression-free survival (PFS; defined as time to disease progression or death due to any cause. Disease progression was defined as tumor progression, clinical progression or rising prostate-specific antigen),
  - time to treatment failure (TTF; defined as time to discontinuation of CBZ due to any cause),
  - OS (defined as time to death due to any cause),
  - safety (based on adverse events [AEs]),
  - health-related quality of life based on Functional Assessment of Cancer Therapy-Prostate and EQ-5D-3L questionnaire scores.

Statistical considerations

- The sample size for this study was chosen to permit the collection of sufficient data to fulfill post-reimbursement requirements. Consequently, the sample was assessed in terms of precision (95% confidence intervals) associated with event rate estimations.
- Analyses were descriptive in nature.
- All summaries and statistical analyses were generated using SAS version 9.2.

Results

Patient characteristics

- A total of 189 patients were treated with CBZ in 54 centers across six countries between April 2012 and June 2016.
- Baseline demographic and clinical characteristics are summarized in **Table 1**.
  - Patients had a median age of 69 years; 93.7% had an Eastern Cooperative Oncology Group performance status ≤ 1; 60.1% had a Gleason score ≥ 8; 58.7% had ≥ 1 comorbidity at baseline; and 87.3% had bone metastases.
  - The median time from diagnosis of prostate cancer to enrolment was 4.0 years, and 17.0 months from diagnosis of mCRPC.
  - All patients received at least one cycle of DOC before CBZ treatment (median number of DOC cycles was 6.0).

Table 1. *Patient baseline characteristics*

	N = 189
Median age, years (range)	69 (47–87)
< 65 years, %	29.1
65–75 years, %	47.1
≥ 75 years, %	23.8
ECOG PS, %	
0	38.6
1	55.0
2	5.8
3	0.5
Charlson Comorbidity Index, mean (range)	4.0 (1–35)
Total Gleason score at diagnosis, %[a]	
≤ 6	14.0
7	25.8
≥ 8	60.1
Median time from prostate cancer diagnosis to inclusion, years (Q1–Q3)	4.0 (2.1–6.0)
Median time from mCRPC diagnosis to inclusion, months (Q1–Q3)	17.0 (10.0–29.0)
Median time since last progression, months (Q1–Q3)[b]	0.5 (0.2–1.0)
Metastatic sites, %	
Bone	87.3
Regional lymph node	34.4
Visceral, other soft tissue	22.2
Other	6.3
Median number of docetaxel cycles (Q1-Q3)	6.0 (5.0–10.0)
Response to last line of docetaxel, %	
Complete response	4.2
Partial response	22.2
Stable disease	12.2
Progressive disease	60.3
Unknown or not evaluable	1.1

[a]n = 178; [b]n = 188.
ECOG PS, Eastern Cooperative Oncology Group performance score; Q1–Q3, interquartile range.

Clinical use

- Patients received a median of six cycles of CBZ (range 1–24); median cumulative dose 140.52 mg/m^2 (**Table 2**).
- Most patients (84.7%) received CBZ as a second-line therapy, with the remaining as third line or later (15.3%).
- Over half of patients received granulocyte-colony stimulating factor (G-CSF) at Cycle 1 (56.6%), with 52.9% receiving G-CSF as a prophylactic and 3.7% therapeutically.
- Half of patients required dose delay (50.8%).
- Dose reductions occurred in 14.3% of patients.
- CBZ was discontinued due to disease progression in 58.7% of patients; and due to AEs in 11.6%.
- After discontinuing CBZ, 39.2% of patients received an androgen receptor-targeted agent or next-generation hormonal therapy and 14.8% received chemotherapy.

Table 2. *Clinical use of cabazitaxel*

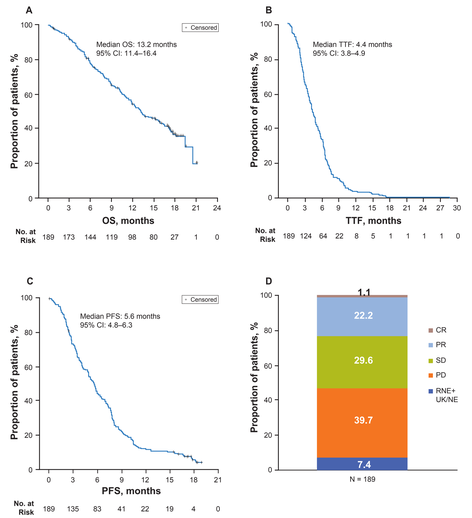
	N = 189
Line of cabazitaxel therapy during the study, %	
2	84.7
3	12.2
4	2.1
6	1.1
Median total cumulative dose, mg/m^2 (Q1–Q3)	140.52 (89.05–204.87)
Median duration of exposure, weeks (Q1–Q3)	18.60 (12.00–30.90)
Median number of cycles, (Q1–Q3) [range]	6 (4–9) [1–24]
Symptomatic overdose, %	0.0
G-CSF use during Cycle 1 of cabazitaxel therapy, %	56.6
Analgesic use associated with cabazitaxel therapy, %	46.6
At least one dose delay, %	50.8
Hematologic toxicity	7.4
Non-hematologic toxicity	3.7
Both hematologic and non-hematologic toxicity	0.5
Other reason	42.9
At least one dose reduction, %	14.3
Hematologic toxicity	4.2
Non-hematologic toxicity	5.3
Both hematologic and non-hematologic toxicity	1.6
Other reason	3.7
Reasons for cabazitaxel discontinuation, %	
Progressive disease	58.7
Patient's decision	14.8
Other reason	14.8
Adverse event	11.6
Patients receiving treatment after cabazitaxel, n (%)	
Chemotherapy	28 (14.8)
Hormonal therapy	74 (39.2)

G-CSF, granulocyte-colony stimulating factor; Q1–Q3, interquartile range.

Efficacy

- Median OS was 13.2 months, median PFS was 5.6 months and median TTF was 4.4 months (**Figure 2**).
- Disease control was seen in 52.9% of patients; 1.1% achieved a complete response (CR), 22.2% achieved a partial response (PR) and 29.6% achieved stable disease (SD).

Figure 2. *Efficacy*



CI, confidence interval; CR, complete response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RNE, response not evaluated; SD, stable disease; TTF, time to treatment failure; UK, unknown.

Table 3. *Safety*

Possibly related TEAEs occurring in ≥ 2% of patients, %	N = 189	
	All grades	Grade ≥ 3
Any class	37.6	13.8
Anemia	10.6	2.1
Neutropenia	9.5	7.9
Diarrhea	8.5	1.1
Asthenia	7.9	0.5
Nausea	5.3	0.5
Fatigue	5.3	0
Decreased appetite	4.8	0
Vomiting	3.7	1.1
Constipation	2.1	0
Stomatitis	2.1	0
Peripheral neuropathy	2.1	0
Possibly related serious TEAEs occurring in ≥ 2% of patients, %		
Any class	12.2	9.0
Neutropenia	5.8	4.8
Diarrhea	2.6	1.1
Anemia	2.1	1.6

TEAE, treatment-emergent adverse event.

Safety

- Treatment-emergent adverse events (TEAEs) of any grade possibly related to CBZ were reported in 37.6% of patients; the most frequent TEAEs were anemia (10.6%), neutropenia (9.5%), diarrhea (8.5%) and asthenia (7.9%; **Table 3**).
- Grade ≥ 3 TEAEs occurred in 13.8% of patients, the most frequent of which was neutropenia (7.9%).
- Serious AEs possibly related to CBZ were reported in 12.2% of patients, the most frequent of which was neutropenia (5.8%).
- No new safety signals were identified.

Conclusions

- This international, observational study documented use of CBZ in patients with mCRPC previously treated with a DOC-containing regimen.
- Patients had similar baseline characteristics to those in the TROPIC and PROSELICA studies.[2,3]
- CBZ was received by most patients (84.7%) as a second-line therapy.
- Patients received a median of six cycles of CBZ (comparable to the median number of cycles in the TROPIC and PROSELICA studies) and the most frequent reason for treatment discontinuation was disease progression.[2,3]
- Best overall response: CR: 1.1%, PR: 22.2%, SD: 29.6%.
- OS in CAPRISTANA was comparable with the TROPIC and PROSELICA studies.[2,3]
- The safety profile was consistent with previous reports; rate of clinical Grade ≥ 3 neutropenia (7.9%) was lower than in TROPIC (21.3%) and PROSELICA (9.6%; Sanofi data on file). This may be because G-CSF was allowed from Cycle 1 in CAPRISTANA.
- In summary, this observational study supports the effectiveness and safety of CBZ reported in TROPIC and PROSELICA, using a diverse "real life" patient population.

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